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Meta-analyses

A systematic review and a dose–response meta-analysis of coffee dose and nonalcoholic fatty liver disease

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SUMMARY

Objective: Nonalcoholic fatty liver disease (NAFLD) is the most predominant chronic liver disease worldwide. Effect of coffee on NAFLD risk and its potential dose–response patterns were explored in the study.
Design: PubMed, Web of Science, MEDLINE, Cochrane and Embase were searched up to 10 April 2018. We performed pair-wise meta-analysis of <1 cup per day vs. 1–2 cups per days or >2 cups per day to pool the relative risks (RRs) and corresponding 95% confidence intervals (CIs). And dose–response analysis was used to estimate relationship of NAFLD occurrence with coffee intake.
Results: Seven articles were included with 4825 cases and 49,616 non-cases. Compared with <1 cup, 1–2 cups or >2 cups of coffee consumption per day were not significantly associated with NAFLD occurrence, and RR were 0.97 (95% CI: 0.85–1.11) and 0.88 (95%CI: 0.72–1.06). However, the summary RR of the highest versus lowest coffee consumption was 0.94 (95% CI: 0.92–0.97). Dose–response meta-analysis presented a non-linearity curve relationship of coffee and NAFLD occurrence while coffee consumption >3 cups per day reduced NAFLD significantly.
Conclusion: Coffee intake level more than 3 cups was observed lower risk of NAFLD than <2 cups per day. Although the risk of NAFLD was inversely associated with coffee consumption, while relevance may not be very close and more observational studies would be needed to verify the relationship of coffee and NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a growing cause of chronic liver disease characterized by excessive fat deposition in the liver, which affects 15%–30% of the general population worldwide [1–3]. The most common risk factors of NAFLD are involved with obesity, insulin resistance and the features of metabolic syndrome, and it's more prevalent (about 50%–90%) in these patients [4]. Evidence suggests that 68% of adults are overweight in the United States, evaluating that 75 to 100 million people may have NAFLD and it is now the second-most common indication for performing liver transplantation [5,6]. NAFLD is categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) histologically. And NAFL is defined as the existence of hepatic steatosis without hepatocellular injury, while NASH is based on NAFL accompanied by hepatocellular ballooning injury with or without fibrosis, which can progress to cirrhosis and hepatocellular carcinoma (HCC) [7,8]. With high rates of obesity and diabetes mellitus, NAFLD related liver disease such as decompensated cirrhosis, liver failure and HCC will increase mortality and society burden extremely [4]. Although a number of pharmacological treatments improving histological features of NAFLD have been reported with undergoing evaluation [9]. Lifestyle intervention still is the main treatment of NAFLD, including diet control, physical activity and behavioral modification [7].

Abbreviations: NAFLD, Nonalcoholic fatty liver disease; RRs, relative risks; CIs, confidence intervals; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma.

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Coffee is the world's most popular beverage only second to water and has been large-scale consumption every day worldwide [10]. Coffee has been suggested to be beneficial to health in various diseases and lowered risk of several cancers like colorectal, liver, renal, ovarian, pancreatic, oesophageal, endometrial, and pharyngeal cancer [10]. Besides coffee consumption significantly reduce risk of type 2 diabetes mellitus and metabolic syndrome [11,12]. And emerging evidence support that coffee has a hepatoprotective effect in different liver disease conditions ranging from elevation of serum enzymes from the liver to liver fibrosis and hepatocellular carcinoma [13]. In a large population-based study, among persons at high risk for liver injury, coffee drinkers have lower levels of aminotransferases activity compared to non-coffee drinkers [14]. And regular coffee consumption can relieve hepatic fibrosis in patients with NAFLD [15]. Therefore, coffee is regarded as a non-pharmacological tool of primary and secondary prevention of NAFLD [16]. However, there were also many studies indicated that coffee intake was not associated with hepatic steatosis in non-alcoholic or serum ALT concentrations [17,18]. It is not clear that whether amount of coffee consumption per day influences on NAFLD occurrence. Hence, a comprehensive meta-analysis was performed to determine the link between coffee intake and NAFLD risk, and to evaluate the dose–response relationship of coffee consumption levels with NAFLD.

Methods

Search strategy

We conducted a comprehensive literature search on PubMed, Web of Science, MEDLINE, Cochrane and Embase databases of all English language articles published up to 10 April 2018. The search terms used for the study selection were “coffee” or “caffeine” combined with “nonalcoholic fatty liver disease”, “NAFLD”, “fatty liver, nonalcoholic”, “nonalcoholic fatty liver”, “nonalcoholic steatohepatitis” or “steatohepatitis, nonalcoholic”. Reference lists of included manuscript and published meta-analyses or reviews were also examined additionally.

Articles were included if they met all the following criterions: (1) case–control, cross-sectional or prospective design studies, (2) at least three categories (including the reference group) of coffee consumption inrelation to nonalcoholic fatty liver disease or elevated serum alanine aminotransferase (ALT) activity, and (3) adjusted RRs (Risk Ratios), HRs (Hazard Ratios), or ORs (Odds Ratios) with corresponding 95 CIs were noted or other informations were sufficient for their calculation. We excluded studies without sufficient statistics. Two reviewers independently screened articles according to title and abstract. Articles that were unsure eligibility were obtained in full-text. If there was any disagreement, which would be resolved by a third reviewer.

Data extraction

Data were extracted from identified articles by using a standardized extraction form

The following information were collected: (1) author name; (2) country; (3) year of publication; (4) sex of participants; (5) age range of the study population; (6) study design; (7) NAFLD cases/no-cases and total number of participants; (8) coffee consumption category; (9) coffee evaluation (10) participants excluded. The quality of each article was evaluated according to the Newcastle–Ottawa Quality Assessment Scale (NOS) [19]. The following contents were assessed: selection of participants and measurement of exposure (0–4 points), the comparability of the design and analysis (0–2 points), evaluation of methodological quality outcome (0–3 points). The process was independently performed by two reviewers and any discrepancies were resolved by discussion.

Data synthesis and statistical analysis

In our study, all OR and HR were roughly regarded as RR [20]. For articles that reported only multiple dose of coffee with distributions of cases and noncases, unadjusted effect estimates with 95% CIs were calculated directly [21]. In our studies, three articles reported RR and adjusted effect estimates with 95% CIs, and the RRs (95% CI) of other four articles were calculated. Besides in one study we counted “seldom/rarely” as “0 cup coffee per day”, “less than monthly” and “less than weekly” as “<1 cup per day”, “daily” as “1–2 cups per day”, “more than once a day” as “>2 cups per day” [17]. In an article which did not report exact number of different coffee consumption in control group, we regarded group 1, 2, 3 as 30, 63, 60 according to other information and this would not cause a significant impact on result because author did not reply emails [22]. The effect size of articles were evaluated by relative risks (RRs) and incident cases of classified: <1 cup per day, 1–2 cups per day and >2 cups per day. The meta-analysis of <1 cup per day vs. 1–2 cups per days and <1 cup per day vs. >2 cups per day were performed. Heterogeneity between the articles was assessed by I^2 statistic [23]. A sensitivity analysis was performed by omitting each study from the overall analysis. Bias of publication was examined by the tests of Egger [24]. The median or mean coffee consumption not resported was the mean of the upper and lower boundaries. If the highest dose was not provided, we assigned the mean was 25% larger than the lower boundary. If the lowest dose was not provided, we assigned the mean was half of the upper boundary [11]. To perform a dose–response meta-analysis, the correlated natural logs of the RRs with their standard error (SE) were used, which were across all coffee intake categories. To conduct the dose–response curve, the restricted cubic splines including 4 knots at the 5%, 35%, 65%, and 95% percentiles of the distribution were used to assess the curvilinear relations [25]. All statistical analyses were performed by Stata 13.0 and Review Manager 5.3.

Results

Article selection

Total 214 articles were identified after removing duplicates in our initial search. After screening titles and abstracts, the remaining 60 were reading with full text. According to our inclusive criterions and exclusive criterions, seven articles were included in our meta-analysis [14,17,22,26–29]. The detailed flow diagram of eligible literature was presented in Fig. 1. Characteristics of our articles were shown in Table 1. Among of seven articles consisting of one case–control, four cross-sectional and two prospective studies, four researchs were from US while others were from Japan, Germany and Israeli. A total of people were included with 4825 cases and 49,616 non-cases. The coffee consumption categories ranged from 0 cup per day to >5 cups per day. Five articles were not included hepatitis B or hepatitis C patients and four articles excluded alcoholic fatty liver participants according to different alcohol consumption criterion. One article did not report the excluding criterion of participants.

Quality assessment and publication bias

Five articles had a score of 7–8 stars and two articles were 6 stars by NOS. Coffee consumption in all articles were measured by self-administration. The diagnosis of NAFLD or NASH in four articles were based on ultrasonography, one article was elevated serum alanine aminotransferase (ALT) activity, one article was based on

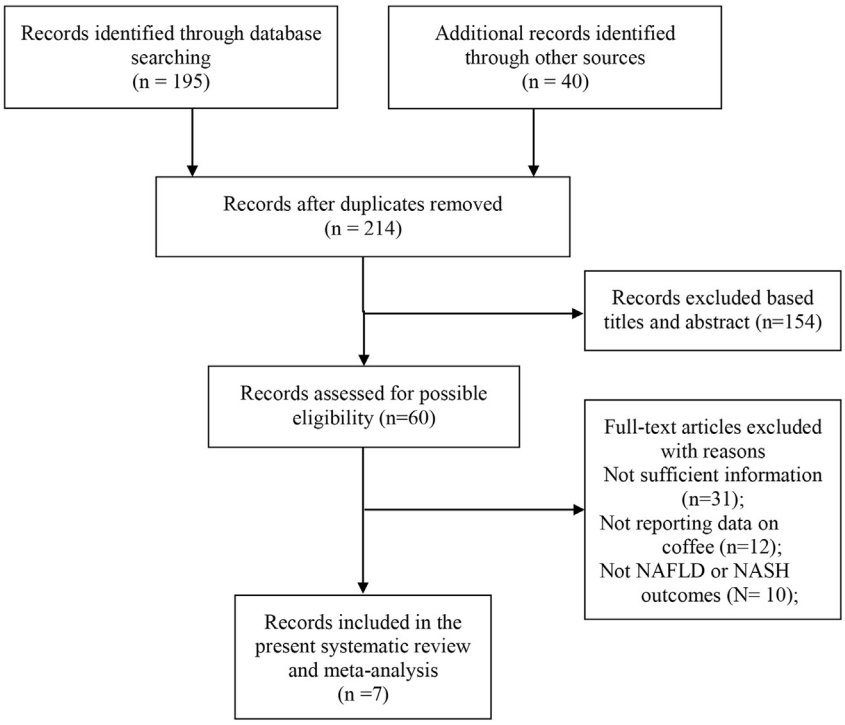

Fig. 1. A flow diagram of literature search process in the present study.

liver histology and one article was based on serum alanine aminotransferase and liver histology. Egger's linear regression test was performed to examine the publication and there was not evident publication bias ($p = 0.127$).

Coffee consumption and the occurrence of NAFLD or NASH

A sensitivity analysis showed the result of the overall analysis was not affected after omitting each study. Figure 2 showed the

Table 1
Main characteristics of the studies included in this meta-analysis. NOS, Newcastle–Ottawa Quality Assessment Scale. NA, no reported in article.

The Author	Country, Publication Year	Sexs	Age (years)	Study Design	Cases/Non-cases, Total number	Coffee consumption	Coffee evaluation	Participants excluded	NOS
T Imatoh	Japan, 2015	Male 1030	48.5	Cross-sectional study	270/760, 1030	0 cup/day, 1–2 cups/day, ≥3 cups/day.	self-reported questionnaire	HBV or HCV	8
T Graeter	Germany, 2015	Male 663, Female 789	42.3	Cross-sectional study	381/1071, 1452	Seldom/rarely, Less than monthly, Less than weekly, Daily, More than once a day.	standardized questionnaire	HBV or HCV, alcoholic liver disease.	7
K Bambha	US, 2014	Male 295, Female478	48	Cross-sectional study	616/166, 782	0 cup/day, <1 cup/day, 1–<2 cups/day, ≥2 cups/day.	validated dietary questionnaire	chronic liver disease (autoimmune,drug-induced) alcoholic liver disease,	7
D Catalano	US, 2010	Male 147, Female 163	48.7	Case-control	157/153, 310	0 cup/day, <3 cups/day, >3 cups/day.	Calculate average of coffee cups/day	liver steatosis, diabetes, alcoholic liver disease, HBV or HCV	7
S Zelber	Israeli, 2014	Male185, Female 162	50.68	Cross-sectional study	107/240, 347	<1 cup/day, 1–2 cups/day, 3–5 cups/day, >5 cups/day.	specific questionnaire	alcoholic liver disease HBV or HCV and hepatotoxic drugs	7
V Wendy	US 2017	NA	61	Prospective study	2786/41790, 44576	0 cup/day, <1 cup/day, 1 cup/day, 2–3 cups/day, ≥4 cups/day.	standardized questionnaire	NA	6
C RUHL	US 2005	NA	>20	Prospective study	508/5436 5944	0 cup/day, <1 cup/day, 1–2 cups/day, >2 cups/day.	self-reported questionnaire	type 1 diabetes mellitus, current pregnancy, missing data on serum ALT activity or coffee consumption	6

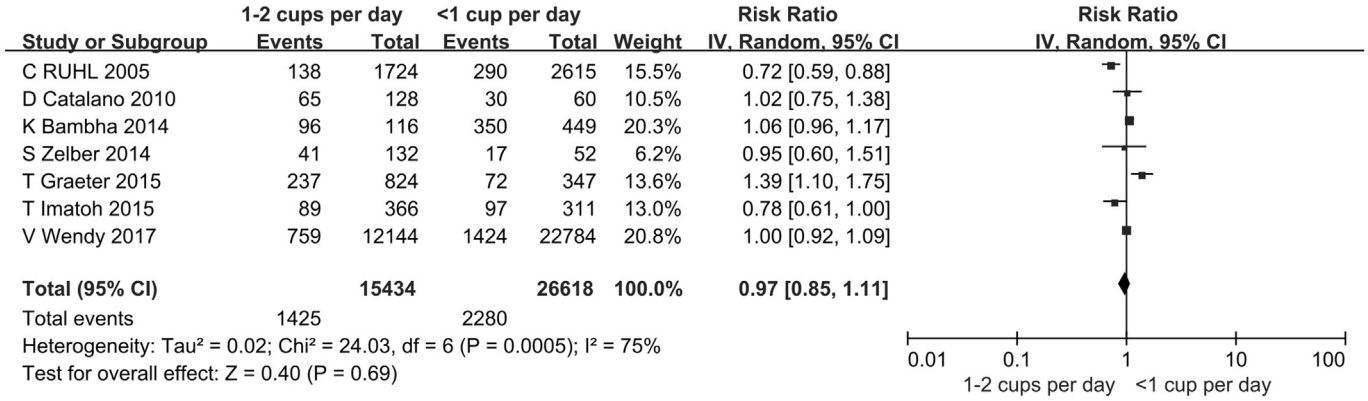

Fig. 2. Forest plot for the relationship of coffee intake (<1 cup per day vs. 1–2 cups per day) with the risk of incident NAFLD.

forest plot of RRs (95 CIs) for the relation of coffee intake with the occurrence of NAFLD. In comparision of <1 cup per day vs.1–2 cups per day, the heterogeneity ($p < 0.001$, $I^2 = 75\%$) was significant and a random-effect model was chosen. The pooled RRs was 0.97 (95% CI: 0.85–1.11), suggesting not a significant association in occurrence of NAFLD between <1 cup per day and 1–2 cups per day. As shown in Fig. 3, a random-effect model was available in comparision of <1 cup per day vs.>2 cups per day with heterogeneity ($p < 0.001$, $I^2 = 87\%$). The pooled RRs was 0.88 (95%CI 0.72–1.06), which also showed not statistical significance.

Dose–response meta-analysis

Figure 4 showed the total coffee intake and NAFLD risk. The summary RR of seven articles for the highest versus lowest coffee consumption was 0.94 (95% CI: 0.92–0.97), suggesting the relative risk of NAFLD was decreased 0.06 with increment of one cup coffee intake per day. To determine the relationship between coffee intake and NAFLD risk, a dose–response analysis was conducted. The P value for the test of non-linearity was significant ($p < 0.05$). The non-linearity model was chosen and the relationship of coffee intake with occurrence of NAFLD was presented in Fig. 5. As result shown, RR was inversely associated with coffee consumption, while more than 3 cups per day coffee intake, NAFLD risk was decreased significantly.

Discussion

The present meta-analysis included 7 articles involving a total 54,441 participants. Compared with <1 cup, coffee consumption of 1–2 cups or >2 cups per day were not significant different in occurrence of NAFLD and the overall analysis results were not affected though sensitivity analysis was performed. But result of the highest versus lowest coffee consumption in occurrence risk of NAFLD showed statistical significance, and NAFLD relative risk was decreased 0.06 with increment of one cup coffee intake per day. And a dose–response association was shown between NAFLD risk and coffee consumption, and analysis indicated a non-linearity curve relationship, suggesting coffee consumption was inversely associated with coffee NAFLD occurrence.

There had been numerous researches about association of coffee consumption and liver disease, most of which supported coffee had a beneficial impact on liver [14,30–32]. A high consumption of coffee played a protective role on nonalcoholic fatty liver disease and were associated with a significant reduction in risk of fibrosis among NASH patients [31,33]. In a US multiethnic cohort, those who drank more than 2 cups per day coffee were associated with lower risk of incident HCC and chronic liver disease mortality significantly [34]. And for patients with preexisting liver disease, coffee intake more than 2 cups per day reduced incidence of fibrosis and cirrhosis, lowed hepatocellular carcinoma rates, as well as decreased mortality [35]. Besides a retrospective cross-sectional study showed coffee consumption relieved liver stiffness suggesting less fibrosis and inflammation in a variety of liver disease such as NAFLD, HBV and HCV [36]. A result of systematic review and meta-analysis showed coffee drinkers had low risk of NAFLD and patients with NAFLD drinking coffee had a lower risk of liver fibrosis, but this meta-analysis just included 3 articles and no more than 2500 participants [37]. Due to limitation of articles or participants, the conclusion should be more conservative. In our study,

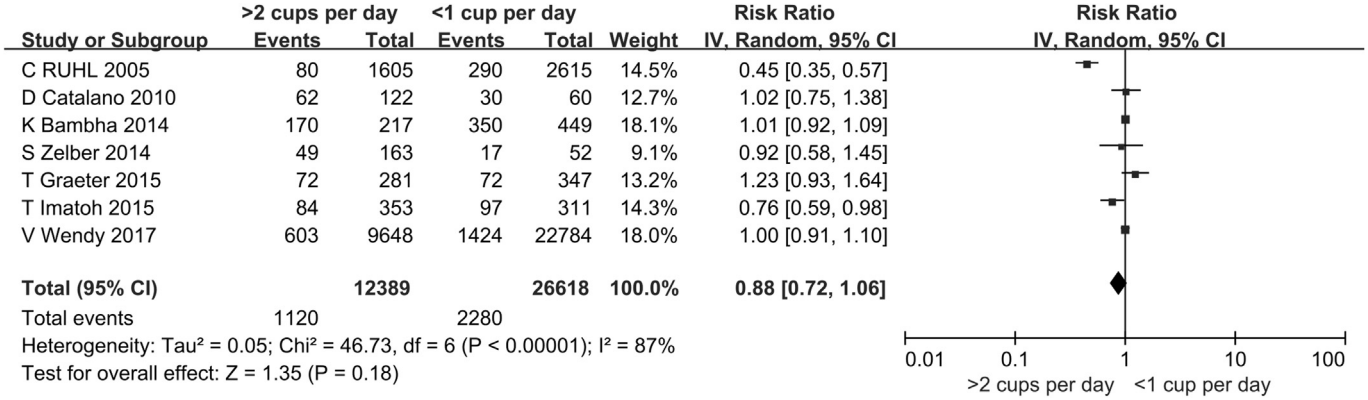

Fig. 3. Forest plot for the relationship of coffee intake (<1 cup per day vs. >2 cups per day) with the risk of NAFLD incident.

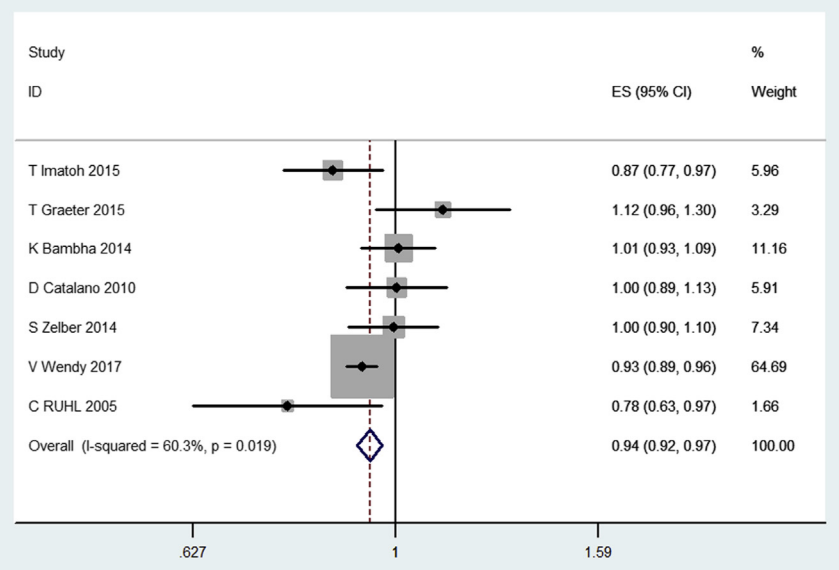

Fig. 4. Forest plot for risk of NAFLD due to increase intake of one-cup of coffee per day.

NAFLD risk could be reduced only when coffee intake more than 3 cups per day. Furthermore what levels of coffee consumption played the greatest protection role on NAFLD should be quantitatively elucidated.

It is biologically supported that appropriate coffee consumption can decrease the occurrence of NAFLD, which might be effective for people while more than 3 cups per day. Coffee contains various chemical components such as coffeine, diterphenoci alcohols, potassium, niacin and the antioxidants like chlorogenic acid (CGA) [38]. These compounds have anti-oxidative and anti-fibrotic properties and may attenuate a range of liver diseases such as fibrosis, cirrhosis and hepatocellular carcinoma [16,35]. Coffee with high CGA concentrations plays an important role on modulating glucose intolerance and improving NAFLD in obese rats [39]. Besides caffeine improves liver fibrosis by antagonism of adenosine receptor A2a, which inhibits hepatic stellate cells [40,41]. In rats model, coffeine attenuates thioacetamide-induced liver inflammation and fibrosis and its antifibrotic effects may via down-regulating expression of transforming growth factor-β and connective tissue growth factor [30,42]. In alcohol-induced liver injury, caffeine also has a protective role on liver fibrosis via dampening the cAMP/PKA/CREB pathways [32]. Similarly, other components in coffee such as cafestol and kehweol can protect liver by antioxidant effect by preventing inflammatory reaction down-regulation of immune and inflammatory markers [35].

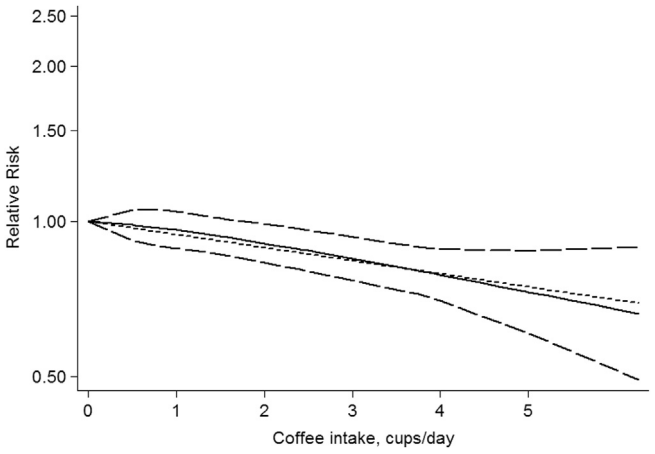

Fig. 5. Dose–response relationship of coffee intake (cups per day) with the risk of occurrence of NAFLD. Solide line, best-fitting restricted cubic spine; dotted line, 95% confidential interval.

Compared with precious meta-analysis about association of coffee intake and occurrence of nonalcoholic fatty liver disease [37], our study included more articles and more participants as well as multi-dose coffee consumption. We obtained an important finding of non-linear relationship of coffee intake and NAFLD risk. Additionally, combined use of pair-wise meta-analysis and dose–response meta-analysis further provided us with data to examine the link of NAFLD and coffee intake. Protective role on NAFLD was evident when coffee consumption was more than 3 cups per day but not less than 2 cups. High coffee consumption was usually associated with an unhealthy lifestyle like smoking, a less healthy diet and less frequency of physical activity [11]. Thus, the association between coffee and NAFLD risk might be stronger than observed. However, our meta-analysis still have limitations as follows. Firstly, the relevant information of coffee consumption such as coffee type, method of brewing, coffee components and drinking time were not stated in detail in articles. Different coffee type like caffeinated coffee or decaffeinated coffee may be different influence on the protection efficacy on NAFLD [30,35]. Secondly, the size of coffee cups may have increased the measurement error and affected the results. A study showed the volume of a standard coffee cup was different between America and Europe [43]. Thirdly, our study did not focus on the association of coffee consumption dose and liver fibrosis among NAFLD patients, which should be explored further. Fourth, our conclusions were based to observational articles, relationship of coffee consumption and NAFLD could not be confirmed just according to current date alone.

In conclusion, our meta-analysis provided evidence of non-linear relationship between coffee intake and occurrence of NAFLD. Coffee intake level more than 3 cups was observed lower risk of NAFLD than <2 cups per day. Although the risk of NAFLD was inversely associated with coffee consumption, while relevance may not be very close and this trend was still remained to be further explored.

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Conflicts of interest

None declared.

Acknowledgements

The authors declare that there is no actual or potential conflict of interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.11.030.

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