Research Square

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Coffee and the risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis of 11 observational studies

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Abstract

BACKGROUND Nonalcoholic fatty liver disease (NAFLD) is a common metabolic disorder. According to some epidemiological studies and different meta-analysis, it is not clear that whether the relevance of the occurrence and progression of NAFLD and coffee consumption is very close. So we conducted the present article to make it clear.

METHODS The PubMed, Cochrane library and Embase were searched up to December 1, 2022. We performed the meta-analysis of not regular coffee vs. regular coffee drinking and coffee drinking vs. the progression of NAFLD, and conducted subgroup analysis of participants, kinds of coffee, methods of diagnosis to verify that relationship. The pooled odds ratio (ORs) and corresponding 95% confidence intervals (CIs) and pooled standardized mean difference (SMD) IV. Random and 95% CIs were calculated by random-effects model.

RESULTS Eleven articles were included, including 7093 cases and 20625 non-cases. Whether regular coffee drinking or not was not significantly associated with NAFLD occurrence, and OR were 0.84 (95% CI: 0.43–1.62). Moreover, the pooled SMD IV. Random. from the comparison of coffee drinking vs. the progression of NAFLD was − 0.12(95%CI :-0.31-0.07), showing not statistical significance. What's more, subgroup analysis of people being obese or not, methods of diagnosis of NAFLD, types of coffee, suggested non beneficial efficacy of coffee drinking on NAFLD.

CONCLUSIONS The existing evidence showed coffee drinking did not significantly decrease the occurrence and progression of NAFLD. In addition, different kinds of coffee failed to show any beneficial efficacy on NAFLD. Thus, coffee is not recommended for people to decrease the occurrence and slow the progression of NAFLD. As we were unable to assess the components of coffee on NAFLD, the results of this meta-analysis should be interpreted with caution. Further study is needed to assess the influence of main ingredient of coffee, caffeine, on NAFLD.

Background

Nonalcoholic fatty liver disease (NAFLD) is a common metabolic disorder ranging from liver steatosis to nonalcoholic steatohepatitis (NASH) [1]. And liver steatosis is defined as the existence of hepatic steatosis without hepatocellular injury, while NASH is based on liver steatosis accompanied by hepatocellular ballooning injury with or without fibrosis, which can progress to cirrhosis and hepatocellular carcinoma (HCC) [2–3]. With high rates of obesity, NAFLD related liver disease such as cirrhosis, liver failure and HCC will extremely increase mortality and society burden [4]. Lifestyle intervention still is the main treatment of NAFLD, including physical activity, diet control and behavioral modification, although a number of pharmacological treatments improving histological features of NAFLD have been reported with undergoing evaluation [5]. Coffee is the most consumed beverage worldwide[6] and is produced from the bean of an evergreen shrub belonging to the family of Rubiaceae, genus coffee. Therefore, coffee is regarded as a nonpharmacological tool of primary and secondary prevention of NAFLD [7]. Different epidemiologic studies have suggested a certain association between coffee drinking and NAFLD. Recently, case-control and cross-sectional studies have suggested that consumption of coffee is a protective factor for NAFLD or hepatic fibrosis[8–13], while there are also many studies indicate an inverse association of coffee consumption with liver damage in patients with NAFLD[14–18]. And a meta-analysis performed by Shen el[19] in 2015 suggested that although total caffeine intake is not associated with the prevalence or hepatic fibrosis of NAFLD, regular caffeine consumption may significantly reduce hepatic fibrosis in patients with NAFLD. but another meta-analysis[20] by Chen in 2018 showed coffee intake level more than 3 cups was observed lower risk of NAFLD than < 2 cups per day. In other words, according to those epidemiological studies and different meta-analysis, it is not clear that whether the relevance of coffee consumption and NAFLD is very close. Therefore, we conducted a systematic review and meta-analysis of the association of the occurrence and progression of NAFLD and coffee consumption to make the relationship of them clear with more studies and statistical analysis technique.

Materials and Methods

Search strategy

Two authors (youchun Lei, xiaodong Lai) independently searched the PubMed, Cochrane library and Embase databases for all available studies that evaluated the association between coffee consumption and NAFLD risk. The search terms used for the study selection were "caffeine" or "coffee" combined with "nonalcoholic fatty liver","fatty liver, nonalcoholic","nonalcoholic fatty liver disease", "NAFLD", "liver steatosis, nonalcoholic", "steatohepatitis, nonalcoholic"or "nonalcoholic steatohepatitis". Our search was limited to population-based studies, and articles written in English. In addition, the reference lists of identified studies were checked manually to include other potentially eligible studies. This process was performed iteratively until no additional articles could be identified. No restrictions on publication year were imposed. And the search was completed on June 1, 2022.

Articles were included if they met all the following criterions: (a) population: general population and clinic patients; (b) intervention: daily coffee drinking (regardless of general and espresso coffee); (c) comparison: the association between coffee intake and occurrence of NAFLD and advanced fibrosis; (d) outcome: occurrence of NAFLD and advanced fibrosis; (e) design:case-control, cross-sectional and prospective design studies; (f) adjusted Odds Ratios (ORs) with corresponding 95 CIs were noted or other information were sufficient for their calculation. We excluded studies without sufficient statistics. Two reviewers screened articles independently 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 by two authors (youchun-Lei,xiaodong-Lai) independently from identified articles by using a standardized extraction form. The following information were collected: (1) first author, (2) country, (3) year of publication, (4)study design, (5) NAFLD diagnosis criteria, (6) NAFLD cases and total number of participants; (7) participants characteristics, (8) coffee consumption, (9) adjustments, (10) outcome. Extracted data were entered into a

standardized excel file and were checked by another author (yongsheng Liu). Any disagreements were resolved by discussion and consensus. The quality of each article was evaluated according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [21]. The following contents were assessed: selection of participants and determination of control group (0–4 points), the comparability of the design and analysis (0–2 points), measurement of exposure and evaluation of methodological quality outcome (0–3 points). The process was performed independently by two reviewers and any discrepancies were resolved by discussion.

Data synthesis and statistical analysis

Differences were shown as ORs with 95% CIs for dichotomous outcomes, and standardized mean differences (SMDs) with 95% CIs for continuous outcomes. In the present study, four studies reported ORs and adjusted effect estimates with 95% CIs, and the SMDs with 95% CI of other seven articles were calculated. Besides we counted “<1 cup per day, less than monthly, less than weekly, seldom/rarely” as “not regular coffee drinking”, and regard “1-2cup per day, > 2 cups per day, daily, more than once a day” as “regular coffee drinking”. The meta-analysis of not regular coffee vs. regular coffee drinking and coffee drinking vs. the progression of NAFLD were performed. Heterogeneity between the articles was assessed by I^2 statistic [22]. A random-effects model was used regardless of heterogeneity[20]. Due to study design, NAFLD diagnosis criteria, participants characteristics, coffee consumption, adjustments, and other confounding factors were not coincident among studies, we further performed sensitivity analyses to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall pooled estimate. The sensitivity analyses were conducted for participants characteristics, types of coffee, stages of NAFLD. We also examined the impact of a single study on the overall pooled estimate by omitting one study in each turn. And publication bias of articles were assessed by visually inspecting funnel plots and exact Egger tests. A *P* value <0.05 was judged as statistically significant, except where otherwise specified. All statistical analyses were performed by Stata 12.0 and Review Manager 5.3.

Results

3.1 study selection

A total of 433 studies were identified by the initial database search, and 98 studies were excluded because of duplicate studies. After screening titles and abstracts, the remaining 16 were reading with full text. According to the inclusive criterion and exclusive criterion, eleven articles were included in our meta-analysis [8–18]. The detailed flow diagram of eligible literature was displayed in Fig. 1. Three case-control and eight cross-sectional studies consisted of the selected studies, among them 4 researches reported dichotomous outcomes, while 7 gave continuous outcomes. Coffee consumption in all articles were measured by questionnaires. The diagnosis of NAFLD or liver fibrosis in six articles were based on ultrasonography, four articles was based on liver biopsy, one article was evaluated by serum aminotransferase activity. And six studies were not included patients with viral, autoimmune, drug-induced, alcoholic liver diseases, four articles were with adjustments of metabolic syndrome, exercise, smoking, tea, sugar intake, and one study did not report the excluding criterion of participants. In addition, 9 studies were general population, and 2 studies were obese patients. And the characteristics of those included studies were showed in Table 1. In our meta-analysis, a total of people were included with 7093 cases and 20625 non-cases.

Table 1
Main characteristics of the studies included in this meta-analysis

The author	Country publication year	Study design	Diagnosis criteria	Cases/Total number	Participants	Coffee consumption	Outcome	Adjustments	N
R Anty	France 2012	Cross-sectional study	liver biopsies	68/195	severely obese European patients	g/week	NASH fibrosis(≥stage2 versus <stage2)	AST,HOMA-IR, Metabolic syndrome	6
A Birerdinc	USA 2011	Case-control	elevated serum aminotransferases	1782/18550	U.S. population	mg/d continuous	Caffeine intake is independently associated with a lower risk for NAFLD	age, gender, ethnicity and metabolic syndrome components	5
D Catalano	Italy 2010	Case-control	clinic diagnosis	157/310	general population	cups/d	No difference in coffee intake beteween cases and controls. more coffee drinking was inversely associated with bright liver score	diabetes, alcohol history ,previous HBV and/or HCV infections.	4
K Funatsu	Japan 2011	Cross-sectional study, following up study	ultrasonography	376/1612; 164/492	healthy middle-aged men	cups/d	In both 1999 and 2004, the subjects with fatty liver reported a lower volume of daily coffee intake compared with those without fatty liver	age, BMI, exercise, alcohol, green tea smoking	6
Gutiérrez-Grobe	Mexico 2012	Case-control	ultrasonography	73/130	Mexican population	mg/d continuous	A high intake of coffee has a protective effect against nonalcoholic fatty liver disease however there was no significant difference in the antioxidant variables analyzed.	alcohol intake of > 20 g/d, tested positive for hepatitis B antigen or hepatitis C antibody and viral, genetic, autoimmune or drug-induced liver disease	6
W Molloy	USA 2012	Cross-sectional study	US and liver biopsy	180/306 presence	clinic patients	mg/d	NASH fibrosis(≥stage2 versus <stage2)	other liver disease and excess alcohol consumption	6
N Veronese	Italy 2018	Cross-sectional study	ultrasonography	2428/2819	middle-aged population living in South Italy	cups/d	Coffee intake was not associated with any lower odds of hepatic steatosis in either non-alcoholic or alcoholic forms in this large cohort of South Italian individuals.	active chronic hepatitis (hepatitis B (HBV) or hepatitis C (HCV)), acute forms, autoimmune hepatitis, cirrhosis, or hemochromatosis	8
Zelber-Sagi	Israel 2014	Cross-sectional study, prospective	Ultrasonography Steato Test, Fibr Test	107/347;	general population	cups/d	Coffee consumption was not associated with NAFLD on US	current smoking, sugar intake, and physical activity	7

The author	Country publication year	Study design	Diagnosis criteria	Cases/Total number	Participants	Coffee consumption	Outcome	Adjustments	N
T Graeter	Germany 2015	Cross-sectional study	ultrasonography	381/1452	general population	cups/d	Relationship between hepaticsteatosis and caffeine consumption could not be shown	chronic hepatitis B or C;alcohol abuse	7
K Barros	Brazil 2015	Cross-sectional study	liver biopsy	82/103	morbid obese patients	ml/week	Progressively higher CC percentages of individuals with normal liver histology were observed .Obese individuals with eleva ted CC exhibited lower frequencies of NASH, although with no statistical significance in this sample.	NOT mention	7
K Bambha	USA 2014	Cross-sectional study	Liver biopsy	616/782	US adults	cups/d	Coffee intake is inversely associated with advanced fibrosis among NAFLD patients with lower HOMA-IR.	chronic liver disease (viral, autoimmune, drug-induced, cholestatic, genetic)	7

NOS, Newcastle-Ottawa Quality Assessment Scale, BMI: body mass index; HOMA: homeostasis model-insulin resistance index; NAFLD: non-alcoholic fatty liver disease;NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis..

3.2 Quality assessment and publication bias

Five articles had a score of 7–8 stars, four articles were 6 stars and two studies had 4–5 stars by NOS. Egger's linear regression test was performed to examine the publication bias of binary outcome and continuous outcome, and there was not evident publication bias (P = 0.839) for the forme, while obvious publication bias (P = 0.047) for the latter. The study by Birerdinc el[9] with skew distribution was excluded through funnel plots, then publication bias (P = 0.362) of continuous studies was not evident in Egger test.

3.3 Coffee consumption and the NAFLD

A sensitivity analysis showed the result of the overall analysis was not affected after omitting each study. Figure 2 showed the forest plot of ORs (95 CIs) for the relation of coffee consumption with the occurrence of NAFLD. In comparison of not regular coffee vs. regular coffee drinking, the heterogeneity ($p < 0.001$, $I^2 = 93\%$) was significant and a random-effect model was chosen. The pooled ORs was 0.84 (95% CI: 0.43–1.62), suggesting not a significant relationship between occurrence of NAFLD and regular coffee drinking. As indicated in Fig. 3, a random-effect model was selected in comparison of coffee drinking vs. the progression of NAFLD with heterogeneity ($p < 0.001$, $I^2 = 100\%$). The pooled standardized mean difference IV. Random. was − 0.69(95%CI :-2.61-1.23), which also showed not statistical significance. Moreover, eliminating the study by Birerdinc el [9] with publication bias had not influenced on the results, and the pooled standardized mean difference IV. Random. Was − 0.12(95% CI :-0.31-0.07) showed by Fig. 4. In addition, different kinds of coffee failed to show any beneficial efficacy on NAFLD.What's more, subgroup analysis of people being obese or not, methods of diagnosis of NAFLD, suggested non beneficial efficacy of coffee drinking on NAFLD.

Discussion

This is a further meta-analysis of eleven observational studies to evaluate the effect of coffee on the occurrence and progression of NAFLD. The present meta-analysis suggested that coffee did not significantly decrease the occurrence and progression of NAFLD in the participants being obese or general. In addition, different kinds of coffee failed to show any beneficial efficacy on NAFLD.

The main finding of our meta-analysis, seems to contradict the end points of previous meta-analysis [20], which was performed to appraise the influence of the amount of coffee consumption on NAFLD occurrence. The previous meta-analysis included seven articles, resulting in 4825 cases, and revealed that coffee intake level more than 3 cups was observed lower risk of NAFLD than < 2 cups per day, in other words, the risk of NAFLD was inversely associated with coffee consumption. Our analysis did not contain three studies[23–25], included in the previous meta-analysis, because one of them provided data on chronic liver disease not NAFLD[23], and the data in the study [24] was inconsistent, as well as other one study[25], was just an abstract from a meeting, which did not give sufficient information to calculate. Besides, the present meta-analysis comprised other seven studies [8, 9, 11–14, 17]. In addition, compared with the previous meta-analysis, the diagnosis of NAFLD in the present meta-analysis was made by liver biopsy in four additional articles, which was more exact than

ultrasonography. What's more, more statistical methods were used in the present meta-analysis. The data was analyzed by binary variables and continuous variables.

In an attempt to produce robust results, we formulated rigorous inclusion criteria and included studies that clearly stated the amount of coffee consumption and specifically diagnosed of NAFLD or liver fibrosis in our meta-analysis. Using four articles from the previous meta-analysis as a base, we included seven other studies. According to 7093 cases and 20625 non cases, the present meta-analysis suggested that coffee drinking did not significantly decrease the occurrence and the progression of NAFLD. Binary variables including four articles showed the pooled ORs: 0.84 (95% CI: 0.43–1.62), suggesting not a significant relationship between occurrence of NAFLD and regular coffee drinking. Subgroup analysis of obese patient and general population showed the same result in the binary meta-analysis. It was consistent with the conclusion of Shen et al [19]. Also the continuous variables including seven articles illustrated the pooled Std. Mean difference IV. Random. was − 0.12(95%CI :-0.31-0.07), which showed not statistically significant connection between coffee drinking and the progression of NAFLD. And subgroup analysis of progression of NAFLD, liver fibrosis, revealed the pooled SMD IV. Random. was − 0.11(95%CI :-0.47-0.24), showing the same result. In the continuous meta-analysis, other subgroup analysis of methods of diagnosis of NAFLD, liver biopsy and ultrasonography, types of coffee, regular coffee and espresso coffee, suggested non beneficial efficacy of coffee drinking on NAFLD. That was different from the finding of Shen et al and Chen et al, while supported by Veronese et al, Graeter et al. Moreover, exclusion of any single study and sensitivity analyses based on various exclusion criteria did not materially alter the pooled results, which adds robustness to our main finding.

Although there were many different aspects, they had some similarities. The occurrence of NAFLD was the primary outcome and was consistently reported in many of the included studies in both the previous meta-analysis and our meta-analysis. These two meta-analyses showed not a significant association between the occurrence of NAFLD and coffee drinking within 2 cups per day. This was the same with the outcome form Shen et al[19], demonstrating that total caffeine intake is not associated with the prevalence or hepatic fibrosis of NAFLD. In addition, people in the two analysis did not the same race, from different regions. So the outcome was more creditable for clinic recommendation.

Some epidemiologic studies do not have the same suggestion, and different authors in meta-analysis have inconsistent conclusions, although coffee is regarded as a nonpharmacological tool of primary and secondary prevention of NAFLD [7]. In other words, it is not clear that whether the relevance of coffee consumption and NAFLD is very close.Therefore, we performed the further meta-analysis with more studies and statistical analysis technique to verify the relationship of coffee and NAFLD. And the present meta-analysis suggested that coffee did not significantly decrease the occurrence and progression of NAFLD in the participants being obese or general. In addition, different kinds of coffee failed to show any beneficial efficacy on NAFLD. Therefore, coffee is not recommended for people to decrease the occurrence and slow the progression of NAFLD.

One potential limitation of the present meta-analysis was the various diagnostic criteria of NAFLD used among studies, liver biopsy and ultrasonography. Another limitation was that we were unable to assess the components of coffee on NAFLD, such as caffeine, sugar. Then, further studies should focus on the following points. Firstly, it is necessary to pay more attention on components, timing, and duration of coffee for the occurrence and progression of NAFLD; to date, a great variability exists in the literature. Secondly, early diagnosis is crucial for the the occurrence and progression of NAFLD, so the liver biopsy is essentially used to diagnose NAFLD.

In conclusion, the emerging evidence showed coffee drinking did not significantly decrease the occurrence and progression of NAFLD in the participants. In addition, different kinds of coffee failed to show any beneficial efficacy on NAFLD. Thus, coffee is not recommended for people to decrease the occurrence and slow the progression of NAFLD. Moreover, the results of this meta-analysis should be interpreted with caution because we unable to assess the components of coffee on NAFLD. Further study is needed to assess to the influence of main ingredient of coffee, caffeine, on NAFLD.

Declarations

Acknowledgements

Not applicable.

Author contributions

YL consulted literature and wrote the manuscript; YW and JG designed the review; YL and XL assisted with writing and revising the manuscript; WF, CW, TY and JY collecting and correcting data. All authors contributed to the article and approved the submitted version.

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Ethics approval and consent to participate

This study collected data from published articles by others for reporting, so no ethics statement was required.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted without any commercial or fnancial relationships that could be construed as a potential confict of interest.

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Figures

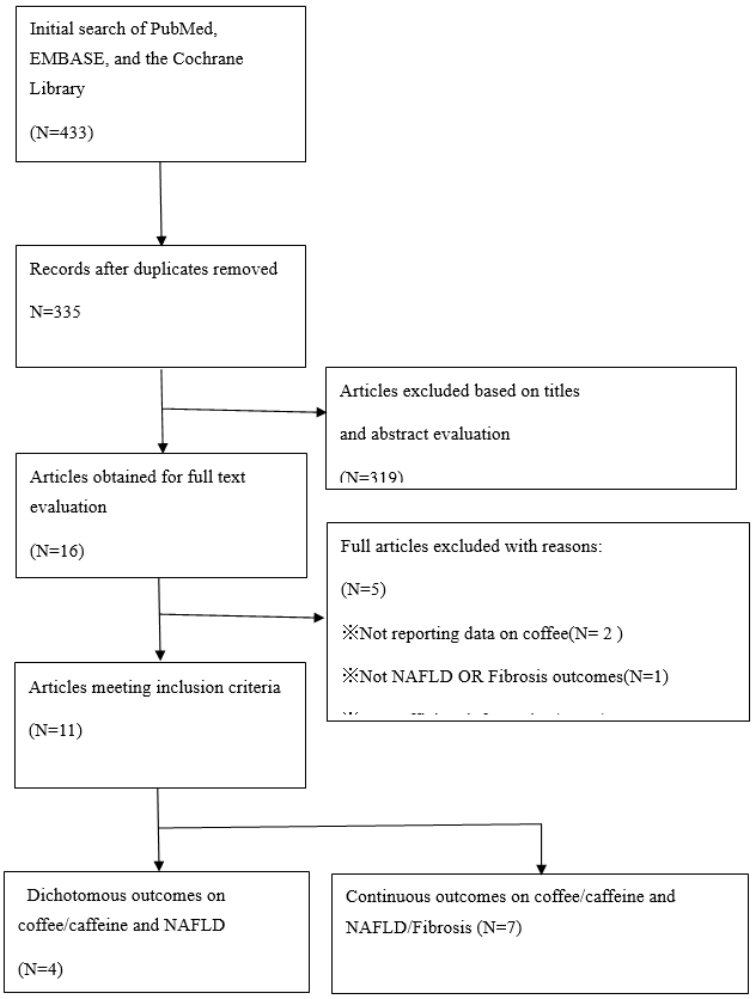


Figure 1

A flow diagram of literature search process in the present study

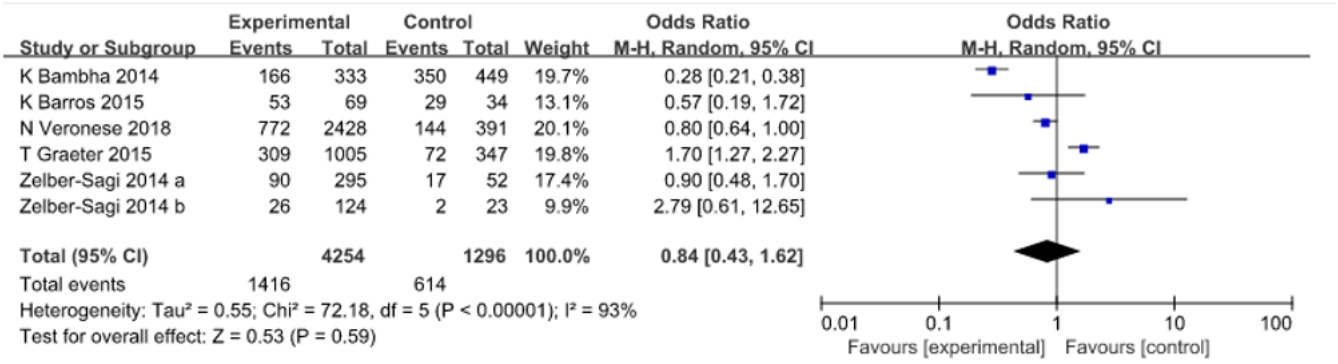


Figure 2

Forest plot of ORs for the relation of coffee consumption with the occurrence of NAFLD

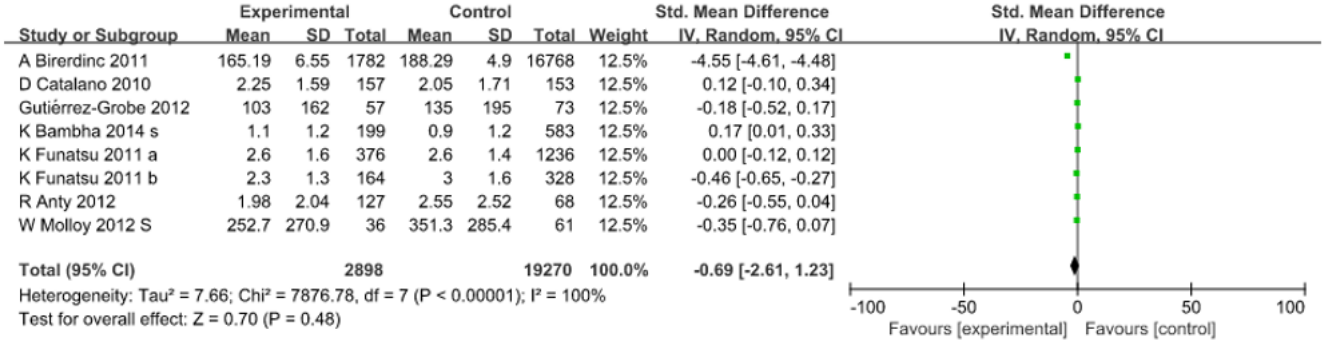


Figure 3

Forest plot of the relation of coffee drinking with the progression of NAFLD

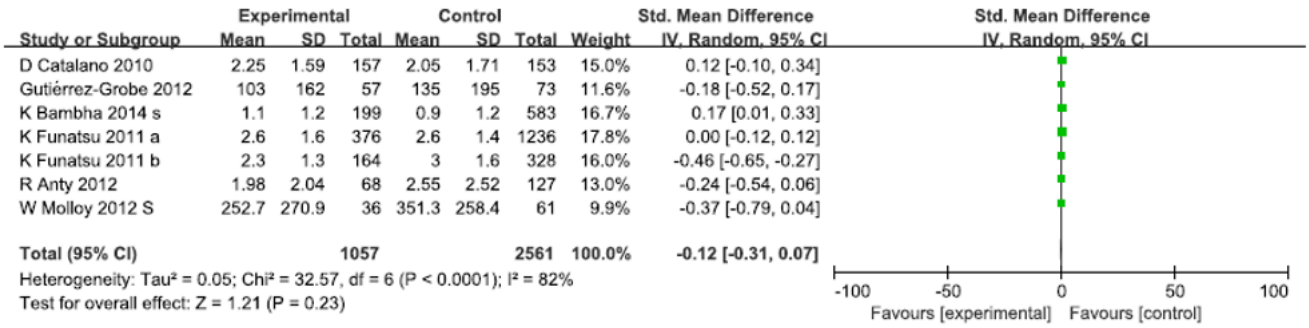


Figure 4

Forest plot of the relation of coffee drinking with the progression of NAFLD eliminating the study with publication bias