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Tea intake and non-alcoholic fatty liver disease risk: A two-sample Mendelian randomization study

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a major global health problem due to its great disease and economic burdens. Tea is a popular beverage consumed by billions of people.
globally owing to its health benefits. However, the evidence regarding the association between tea intake and NAFLD risk is inconsistent.
Objective: To examine the genetically predicted causal association between tea intake and NAFLD risk using the two-sample Mendelian randomization (MR) method.
Methods: Single-nucleotide polymorphisms (SNPs) strongly associated with tea intake were obtained from a large dataset (N = 447,485) in the UK biobank, and summary-level genetic data for NAFLD (2,275 cases and 375,002 controls) were collected from the FinnGen consortium. The two-sample MR method was used to investigate the causal association between tea intake and NAFLD risk. The random-effects inverse-variance weighted (IVW) was used as the primary approach for estimating the causal effect, and MR Egger, weighted median, simple mode, and weighted mode were used to verify the robustness of the primary results.
Results: Twenty-four valid SNPs were selected as the instrumental variables for tea intake. The IVW results indicated that tea intake was not causally associated with NAFLD risk (Odds ratio: 1.48; 95 % confidence interval: 0.64, 3.43; $p = 0.364$); moreover, the results from other methods were consistent with this finding. A leave-one-out analysis further demonstrated the robustness of our results. No evidence of heterogeneity, outliers, or horizontal pleiotropy was found.
Conclusion: Our results do not support tea intake being causally associated with a decreased risk of NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome and is thought to result from the complex interactions among dysregulated metabolism, imbalanced gut microbiota, and pathological immune responses [1]. NAFLD includes a range of liver diseases, from pure non-alcoholic fatty liver and non-alcoholic steatohepatitis to the associated fibrosis and cirrhosis; some patients even progress to end-stage liver disease and hepatocellular carcinoma [2,3]. NAFLD comes with heavy disease and economic burdens and has become a major global health problem worldwide [4–6]. According to the most recent epidemiological data [4], NAFLD affects 20–25 % of the general global population. A recent study [2] found that NAFLD occurs in approximately 30 % of the general population in China, making it the

Abbreviations: **CI**, Confidence interval; **GWAS**, Genome-wide association studies; **IVW**, Inverse-variance weighted; **MR**, Mendelian randomization; **NAFLD**, Non-alcoholic fatty liver disease; **MAFLD**, Metabolic dysfunction-associated fatty liver disease; **MASLD**, Metabolic dysfunction-associated steatotic liver disease; **OR**, Odds ratio; **RCT**, Randomized controlled trial; **SNP**, Single-nucleotide polymorphism.

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leading cause of chronic liver disease in the country. Moreover, NAFLD is often associated with multiple chronic diseases (notably, obesity and type 2 diabetes), and in some cases, patients with NAFLD have a poor prognosis [6,7]. One prospective study [7] demonstrated that NAFLD was associated with all-cause mortality in adult patients and was increased with the fibrosis stage. In addition, a recent systematic review reported high direct medical and societal burdens for non-alcoholic steatohepatitis [6]. In fact, the national direct annual medical costs of NAFLD are estimated to be $103 billion in the United States and £5.24 billion in the United Kingdom [7].

Tea is a popular beverage worldwide that has been around for thousands of years. Some of the ingredients in tea, such as catechins and polyphenols, have pharmacological properties and are often used as health food supplements [8,9]. Several studies [10–14] suggested that tea intake is associated with improvements in various health outcomes such as hypertension, diabetes, NAFLD, and cognitive function. A meta-analysis of randomized controlled trials (RCTs) reported the beneficial effects of black tea on systolic blood pressure and a reduction in the incidence of diabetes by green tea [12]. Moreover, mechanistic studies [10,14] have shown that the catechins in green tea can alleviate NAFLD incidence and progression due to their antioxidant, hypolipidemic, thermogenic, and anti-inflammatory actions. However, a recently published cross-sectional study [15] found that daily tea consumption was not associated with newly diagnosed NAFLD in Chinese adults. Given that the results on the association between tea intake and NAFLD risk are conflicting, while concurrently traditional observational studies are often susceptible to confounding effects and reverse causality [16,17]. When using observational data [18], it is necessary to use reliable methods to determine the causal effects of tea drinking on NAFLD risk.

Evaluating the genetically predicted causal association between exposure factors and outcomes has become possible due to the rapid development of *-omics* technology and the publication of large-sample genome-wide association studies (GWAS) [18]. For instance, there is a plethora of GWAS that have observed a statistical association between specific genetic polymorphisms and the consumption of certain aliments and drinks, such as tea consumption [19]. In that context, Mendelian randomization (MR) is a method that uses genetic variants, such as single nucleotide polymorphisms (SNPs), as instrumental variables to examine causal associations between exposure factors and outcomes [20,21]. According to the Mendelian laws of inheritance, alleles from parents are assigned randomly to offspring when gametes are formed; thus, the relationship between genetic variation and disease is not generally affected by traditional confounding factors, such as the growth environment, socioeconomic status, or behavioral factors [21,22]. In addition, genetic variation comes from the parents and remains unchanged after birth. Genotype determines phenotype, and genotype is associated with a disease through phenotype; therefore, causal temporality is reasonable [17]. In recent years, this approach has been widely adopted and applied to investigate the causal relationships between different exposure factors and health outcomes [23–25]; of note, using "*'Mendelian randomization' [Title/Abstract]*" as a search strategy, more than 6,000 relevant publications have been published in PubMed until August 17, 2023. For example, Jin et al. [23] used the MR method and found no causal association between tea intake and migraine risk. To the best of our knowledge, no studies have used the MR method to investigate the causal association between tea intake and NAFLD risk. Thus, this study aims to investigate the causal effect of tea intake on NAFLD risk using the two-sample MR method to provide new insights into the prevention and treatment of NAFLD.

2. Material and methods

2.1. Study design

To investigate genetically predicted causal associations between tea intake and NAFLD risk, this study utilizes a two-sample MR design based on publicly available summary statistics from large-scale GWAS. For this MR analysis, tea intake was considered the exposure, and NAFLD risk was the outcome. Genetic variants (i.e., SNPs) that were significantly associated with exposure were used as instrumental variables to examine the potential causal effects of tea intake on NAFLD risk. Our selection of instrumental variables strictly adhered to the requirements of an MR analysis [20,26] (Fig. 1). Specifically, the instrumental variables fulfilled the following three critical assumptions: (1) relevance assumption: the genetic variant must be significantly associated with the exposure; (2) independence assumption: the genetic variant must not be associated with any confounders of the exposure-outcome association; (3) exclusion assumption: the genetic variant can affect the outcome only through the exposure [20,26]. Ethical approval was waived because only GWAS summary data from publicly available databases were used.

2.2. Data sources

Tea intake was considered the exposure in this study, and summary statistics ("ukb-b-6066", https://gwas.mrcieu.ac.uk/) were obtained from the UK biobank. This dataset was published in 2018, and contains a total of 447,485 males and females of European ancestry, and it includes nearly ten million (i.e., 9,851,867) SNPs. Information regarding tea intake was obtained from a specific food frequency questionnaire, based on which the participants were asked to answer the following question: "*How many cups of tea do you drink each day? (Include black and green tea)*," while the intake was treated as a continuous measurement using cups/day [23]. NAFLD risk was considered an outcome for this study. To avoid sample overlap, a key aspect should be considered when conducting a two-sample MR analysis, between the exposure and the outcome, we obtained the genetic associations of NAFLD risk from FinnGen database (https://www.finngen.fi/fi). The dataset used in our study was the from the FinnGen R9 release, and this dataset contains 2,275 cases and 375,002 controls of European ancestry [27].

2.3. Selection of genetic instruments for tea intake

Valid SNPs were selected based on the following steps: (1) to select SNPs strongly associated with tea intake, the genome-wide significance level was set at $p < 5 \times 10^{-8}$ [28]; this step was utilized to meet the first assumption of the MR approach; (2) linkage disequilibrium clumping ($r^2 < 0.001$, region size = 10,000 kb) was conducted to guarantee the independence of different SNPs. Additionally, the exposure and outcome data were harmonized; (3) *F*-statistics were calculated to evaluate the strength of the SNPs as instrumental variables, for which the *F*-statistics < 10 of the SNPs were considered as weak instrumental variables and were removed, and for which the following calculation formula was used [25]: $F = \text{beta}^2/\text{se}^2$, where *beta* is the effect size of the SNP on the exposure, and *se* is the standard error of the genetic effect; (4) SNPs that were associated directly with the outcome at $p < 5 \times 10^{-8}$ were excluded to meet the exclusion assumption [28]; (5) using default

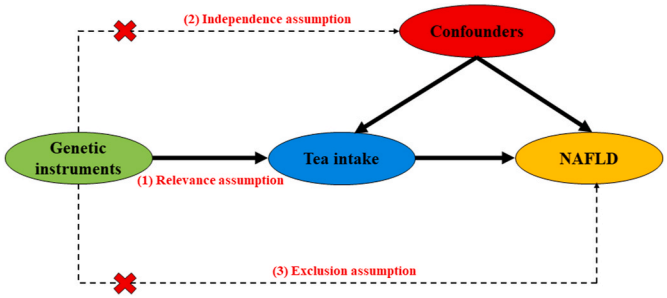

Fig. 1. Analysis model of the Mendelian randomization analysis.

parameters ($r^2 > 0.8$, $p < 1 \times 10^{-8}$, and genome build by GRCh37), PhenoScanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/) was searched to exclude SNPs that were significantly related to potential confounding factors such as body mass index, body weight, hip/waist circumference, and hypertension [28], and in so doing, in order to meet the independence assumption of the MR approach.

2.4. Statistical analysis

First, the Wald ratio method was used to evaluate the genetically predicted causal effects of single SNPs on NAFLD [29]. Then, five mainstream statistical methods were used to pool the effects of the individual SNPs. Of these, the random-effect inverse variance-weighted (IVW) method is widely recognized as the most effective when SNPs are valid and lack horizontal pleiotropy [25,28]. Therefore, IVW was used as the main method for our study, and the MR Egger, weighted median, simple mode, and weighted mode methods were used to verify the results of the analysis. The weighted median method can provide effective estimates when at least 50 % of the SNPs are valid [25,28]. MR-Egger was used to evaluate horizontal pleiotropy [30]; when the intercept is close to 0, no pleiotropy is indicated [27]. Importantly, MR-Egger can provide unbiased estimates, even if all SNPs are invalid because of horizontal pleiotropy [25]. To identify potential pleiotropic outliers, the MR-PRESSO test was used, and heterogeneity across different SNPs was checked using Cochran's Q statistics. In addition, a leave-one-out analysis was performed to evaluate the effects of single SNPs on the overall estimate to assess the robustness of the analysis results. MR analysis results are presented as the odds ratio (OR) with 95 % confidence interval (CI). "TwoSampleMR 0.5.7" and "forestplot 3.1.1" were run in R 4.2.3 (R Foundation for Statistical Computing) to analyze the data and construct graphs. Two-sided p values less than 0.05 were considered statistically significant.

3. Results

After screening steps (1) and (2), 33 SNPs were identified as significantly associated with tea intake. Steps (3) and (4) did not exclude any SNPs, but step (5) excluded 9 SNPs (rs10741694, rs12591786, rs1481012, rs2279844, rs2472297, rs2478875, rs4410790, rs4808193, and rs9937354) that were possibly closely related to potential confounders. Finally, 24 SNPs were included as instrumental variables for tea intake, and the *F*-statistics ranged from 30.02 to 136.84, indicating no weak instrumental variable bias. Detailed information for the SNPs included is presented in the **Supplementary File**.

The primary analysis results indicated that genetically predicted tea intake was not associated with NAFLD risk (OR: 1.48; 95 % CI: 0.64, 3.43; $p = 0.364$), as shown in Fig. 2. Four other methods also indicated that tea intake was not associated with NAFLD risk and further verified the IVW method results. As shown in Fig. 3, a leave-one-out analysis demonstrated that no single SNP significantly affected the MR results. The results of Cochran's Q test did not indicate significant heterogeneity (IVW: Q = 21.88, p = 0.527; MR-Egger: Q = 21.45, $p = 0.493$). The MR-Egger intercept was very close to 0 (−0.013, $p = 0.519$), indicating no horizontal pleiotropy. MR-PRESSO analysis did not reveal any outliers, and this was also indicated by the symmetrical distribution of the SNPs shown in Fig. 4.

4. Discussion

In the present study, we used the two-sample MR method to examine the genetically predicted causal effects of tea intake on NAFLD risk. The primary analysis demonstrated no causal association between tea intake and decreased NAFLD risk, and this finding was further validated by the results of other analytical methods.

NAFLD is a complex systemic disease that occurs as a result of the combination of multiple metabolic, genetic, and microbiome-related

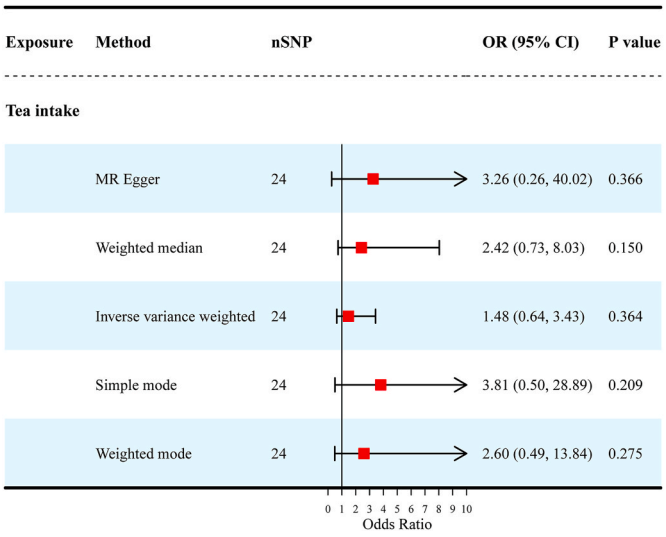

Fig. 2. Forest plot of the Mendelian randomization analysis.

factors; however, the specific mechanisms of NAFLD remain incompletely understood [1,3]. NAFLD currently poses huge medical and societal burdens to countries around the world, especially in western countries [1,31]. Fortunately, most risk factors for NAFLD, including obesity, type 2 diabetes, lipid abnormalities (e.g., high triglyceride concentrations), and hypertension, are modifiable, and healthy lifestyles can prevent NAFLD occurrence and delay its progression [1,3]. In response to this major global health problem, a global Delphi study report was recently released to provide a consensus and recommendations on multiple aspects of the epidemiology, prevention, and treatment of NAFLD [31].

Previous studies have suggested that tea intake can potentially reduce NAFLD risk and disease progression. For example, Xu et al. [32] recently reviewed the regulatory effects and molecular mechanisms of teas and their active compounds (e.g., catechin and flavonoids) on NAFLD, suggesting that these compounds offer potentially beneficial effects against NAFLD and providing research directions for future research. Based on the rats' experiments, Kobayashi et al. [10] reported that green tea catechin can improve experimentally induced liver damage owing to its antioxidant and antifibrotic effects. In addition, in 2021, Mao et al. [33] evaluated the effects of 12 tea extracts on NAFLD in mice that fed high-fat diets, and the results revealed that the effect varied with different teas. In particular, histopathological results showed that several teas can improve hyperlipidemia-induced hepatic steatosis and adipocytic hypertrophy. For example, Qing Brick tea can prevent NAFLD by significantly mitigating the increase in liver triglyceride levels [33]. Furthermore, a meta-analysis of four observational studies indicated that green tea intake is associated with a low risk of fatty liver disease (Risk ratio: 0.65; 95 % CI: 0.44, 0.98; $p = 0.039$) [34].

However, unlike these lines of evidence, our results did not indicate that tea intake can reduce NAFLD risk. This difference may be due to the following reasons. First, the significant differences between human and animal models often lead to positive findings in preclinical studies that are not fully reflected in humans; this phenomenon is very common in drug development [35]. Second, the positive results reported in previous observational studies and the associated meta-analysis may be attributed to residual confounding factors or reverse causation [23]. Interestingly, our results are supported by a novel Chinese cross-sectional study reporting that daily tea consumption is not associated with newly diagnosed NAFLD [15]. In addition, it is worth mentioning that Cai et al. [36] reported no causal association between tea intake and seven common cardiovascular diseases: angina, atrial fibrillation, acute myocardial infarction, hypertension, coronary atherosclerosis, peripheral vascular disease, and heart failure. Considering that the

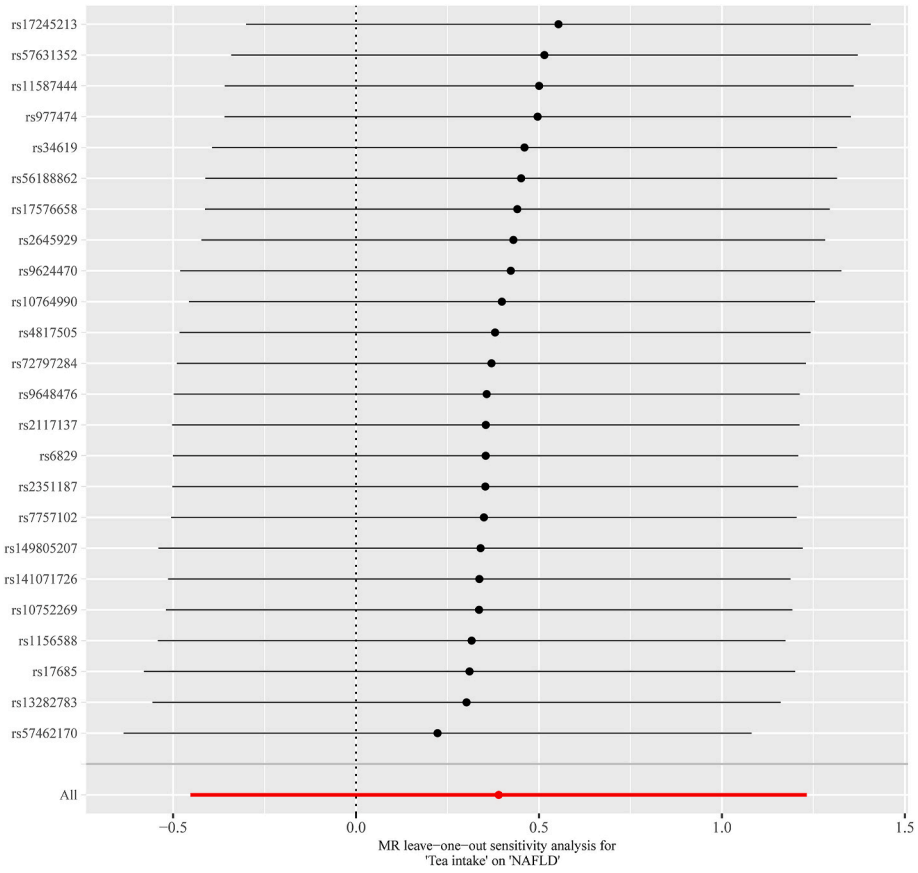

Fig. 3. Forest plot of the leave-one-out analysis.

interpretation and application of the scientific evidence should be based on the triangulation principle [37], that is, to consider the evidence from different sources comprehensively. Therefore, high-quality, large--sample RCTs should be conducted in future to further clarify the causal relationship (if any) between specific tea intake and NAFLD risk.

This study has several strengths. First, to the best of our knowledge, this is the first MR study to investigate the causal effects of tea intake on NAFLD risk. Our use of the MR method reduced the confounders and reverse causation commonly occurring in classical observational epidemiological studies. Second, the SNPs included are all valid, as proven by a lack of evidence regarding weak instrument variables, heterogeneity, and horizontal pleiotropy. Notably, horizontal pleiotropy has a significant impact on the accuracy of MR estimates. Third, the GWAS data for tea intake and the risk of NAFLD were obtained separately from different cohorts, thus avoiding the bias from sample overlap. Lastly, five critical methods with different statistical assumptions were used to estimate the causal association between tea intake and risk of NAFLD, and they provide basically consistent results, thus increasing the robustness of our findings.

Similar to other MR studies [23,27,28,36], our study has several limitations that need to be considered. First, the summary statistics of GWAS data for tea intake and the risk of NAFLD are all obtained from individuals of European descent, thus limiting the generality of our results; therefore, careful interpretation is required when applying the results to populations from other ethnic or racial ancestries. Second, other in-depth analyses could not be conducted because we could not access the data for different tea types (e.g., black and green teas) or detailed individual characteristics (e.g., age and sex) of the GWAS participants. In addition, our findings may be affected by the bias (e.g., measurement error) [38] existed in the original studies of the summary statistics that we used in this MR study. Third, the population under study in the UK Biobank has been criticized for not being representative of the sampling population to the extent that a *"healthy volunteer"* selection bias appears to exist [39]. However, the extensive body of research stemming from the UK biobank and the accompanying wide assessment of associations between risk factors and disease could add to how generalizable its findings can be, not least for the Caucasian populations [39]. Fourth, this study would have benefited from a more granular analysis of specific liver outcomes, such as measurements for steatosis (fat accumulation) and fibrosis through appropriate tools such as FibroScan. To this end, similarly to existing studies [40], future approaches could assess how tea intake might influence these NAFLD-related processes to increase the clinical relevance of the findings, as to whether tea consumption affects the progression of liver disease, rather than just NAFLD as a general diagnosis. Moreover, the possibility of potential nonlinear effects, where varying levels of tea consumption could have distinct impacts on health outcomes, cannot be excluded because in this study, tea intake was considered as a continuous variable, and not a categorical one (i.e., low, moderate, and high intake). More broadly, the definitions of the disease have evolved from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) [41] and most recently to metabolic dysfunction-associated steatotic liver disease (MASLD) [42] and, as a result, our study cannot achieve 100 % consistency. However, several studies suggest that there is over 90% overlap in population among these definitions [43], which in every case is going to affect all studies derived from the UK biobank and focusing on liver pathology. Last, whether the GWAS-derived associations between tea consumption and specific genetic variants is more of statistical nature or whether there is a so far undeciphered biological underpinning remains to be explored in future studies.

5. Conclusion

In conclusion, this MR study demonstrates that genetically predicted

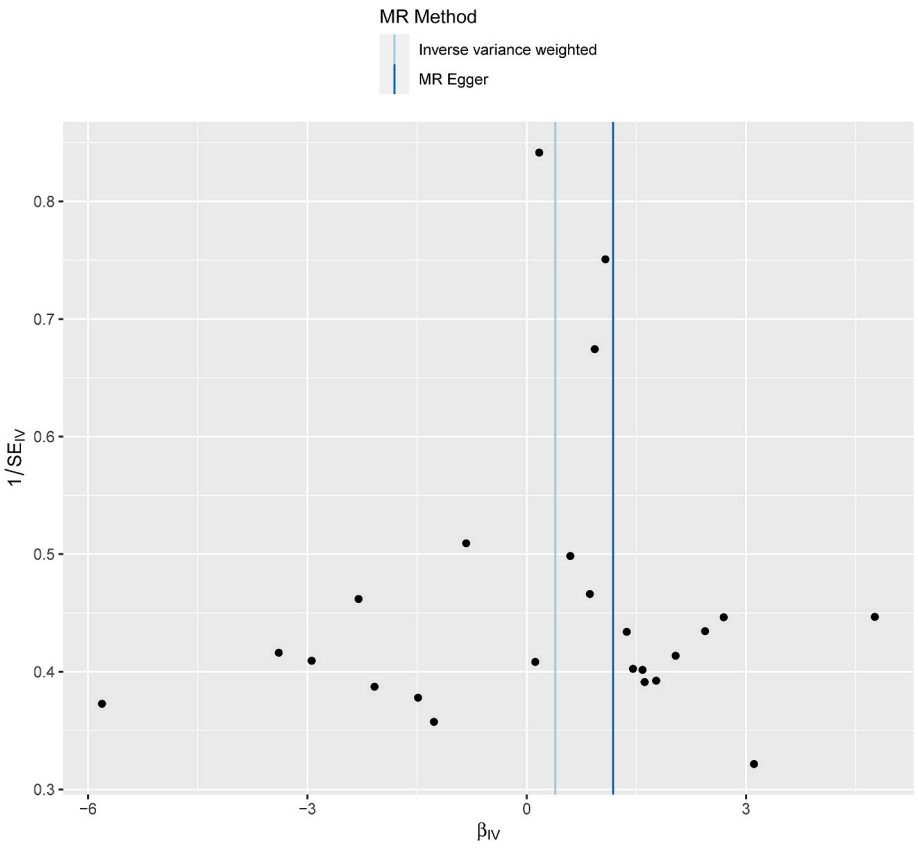

Fig. 4. Funnel plot of the Mendelian randomization analysis.

tea intake is not associated with decreased NAFLD risk. Our study provides new insight to better understand the relationship between tea intake and NAFLD occurrence and development. However, the results of this MR study should be further verified in non-European populations.

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Data availability statement

The survey data can be obtained from https://gwas.mrcieu.ac.uk/ and https://www.finngen.fi/fi, and they are publicly available for researchers globally.

CRediT authorship contribution statement

Cuncun Lu: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Lixin Ke:** Writing – review & editing, Investigation, Formal analysis. **Alexios-Fotios A. Mentis:** Writing – review & editing, Methodology. **Qiang Zhang:** Writing – review & editing. **Ziyi Wang:** Writing – review & editing. **Zhifei Wang:** Writing – review & editing, Supervision.

Declaration of Generative AI and AI-assisted technologies in the writing process

None.

Declaration of competing interest

We have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2024.100322.

References

[1] Tilg H, Adolph TE, Dudek M, Knolle P. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. Nat Metab 2021;3:1596–607.
[2] Lu R, Liu Y, Hong T. Epidemiological characteristics and management of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis in China: a narrative review. Diabetes Obes Metabol 2023;25:13–26.
[3] Powell EE, Wong VW-S, Rinella M. Non-alcoholic fatty liver disease. Lancet 2021;397:2212–24.
[4] Díaz LA, Fuentes-López E, Ayares G, Idalsoaga F, Arnold J, Márquez-Lomas A, et al. The establishment of public health policies and the burden of non-alcoholic fatty liver disease in the Americas. Lancet Gastroenterology. Hepatology 2022;7:552–9.
[5] Haigh L, Kirk C, El Gendy K, Gallacher J, Errington L, Mathers JC, et al. The effectiveness and acceptability of Mediterranean diet and calorie restriction in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. Clin Nutr 2022;41:1913–31.
[6] Witkowski M, Moreno SI, Fernandes J, Johansen P, Augusto M, Nair S. The economic burden of non-alcoholic steatohepatitis: a systematic review. Pharmacoeconomics 2022;40:751–76.
[7] Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 2021;385:1559–69.
[8] Bilia AR, do Céu Costa M. Medicinal plants and their preparations in the European market: why has the harmonization failed? The cases of St. John's wort, valerian, ginkgo, ginseng, and green tea. Phytomedicine 2021;81:153421.
[9] Singh A. Herbal-based nutraceuticals in management of lifestyle diseases: experience from Indian population. Future Inte. Med. 2024;3:106–15.

[10] Kobayashi H, Tanaka Y, Asagiri K, Asakawa T, Tanikawa K, Kage M, et al. The antioxidant effect of green tea catechin ameliorates experimental liver injury. Phytomedicine 2010;17:197–202.
[11] Lin Y, Shi D, Su B, Wei J, Găman MA, Sedanur Macit M, et al. The effect of green tea supplementation on obesity: a systematic review and dose–response meta-analysis of randomized controlled trials. Phytother Res 2020;34:2459–70.
[12] Liu W, Wan C, Huang Y, Li M. Effects of tea consumption on metabolic syndrome: a systematic review and meta-analysis of randomized clinical trials. Phytother Res 2020;34:2857–66.
[13] Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: a systematic review. Phytomedicine 2017;34:26–37.
[14] Masterjohn C, Bruno RS. Therapeutic potential of green tea in nonalcoholic fatty liver disease. Nutr Rev 2012;70:41–56.
[15] Xia Y, Wang X, Zhang S, Zhang Q, Liu L, Meng G, et al. Daily tea drinking is not associated with newly diagnosed non-alcoholic fatty liver disease in Chinese adults: the Tianjin chronic low-grade systemic inflammation and health cohort study. Nutr J 2019;18:1–8.
[16] Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002;359:248–52.
[17] Wallach JD, Serghiou S, Chu L, Egilman AC, Vasiliou V, Ross JS, et al. Evaluation of confounding in epidemiologic studies assessing alcohol consumption on the risk of ischemic heart disease. BMC Med Res Methodol 2020;20:1–10.
[18] Pagoni P, Dimou NL, Murphy N, Stergiakouli E. Using Mendelian randomisation to assess causality in observational studies. BMJ Ment Health 2019;22:67–71.
[19] Furukawa K, Igarashi M, Jia H, Nogawa S, Kawafune K, Hachiya T, et al. A genome-wide association study identifies the association between the 12q24 locus and black tea consumption in Japanese populations. Nutrients 2020;12:3182.
[20] Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafò MR, et al. Mendelian randomization. Nature Reviews Methods Primers 2022;2:6.
[21] Teumer A. Common methods for performing Mendelian randomization. Frontiers in cardiovascular medicine 2018;5:51.
[22] Smith GD, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? BMJ 2005;330:1076–9.
[23] Jin C, Tu S, Sun S, Zhang Z, Wang X. Noncausal effects between tea intake and migraine risk: a Mendelian randomization study. Sci Rep 2023;13:12898.
[24] Swerdlow DI, Kuchenbaecker KB, Shah S, Sofat R, Holmes MV, White J, et al. Selecting instruments for Mendelian randomization in the wake of genome-wide association studies. Int J Epidemiol 2016;45:1600–16.
[25] Xie J, Huang H, Liu Z, Li Y, Yu C, Xu L, et al. The associations between modifiable risk factors and nonalcoholic fatty liver disease: a comprehensive Mendelian randomization study. Hepatology 2023;77:949–64.
[26] Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018;362.
[27] Tao M, Zhou G, Liu J, He M, Wang C, Luo X, et al. Visceral adipose tissue and risk of nonalcoholic fatty liver disease: a Mendelian randomization study. Clin Endocrinol 2023;99:370–7.
[28] Zhang X, Chen K, Yin S, Qian M, Liu C. Association of leisure sedentary behavior and physical activity with the risk of nonalcoholic fatty liver disease: a two-sample Mendelian randomization study. Front Nutr 2023;10:1158810.
[29] Boehm FJ, Zhou X. Statistical methods for Mendelian randomization in genome-wide association studies: a review. Comput Struct Biotechnol J 2022;20:2338–51.
[30] Cho Y, Haycock PC, Sanderson E, Gaunt TR, Zheng J, Morris AP, et al. Exploiting horizontal pleiotropy to search for causal pathways within a Mendelian randomization framework. Nat Commun 2020;11:1010.
[31] Lazarus JV, Mark HE, Anstee QM, Arab JP, Batterham RL, Castera L, et al. Advancing the global public health agenda for NAFLD: a consensus statement. Nat Rev Gastroenterol Hepatol 2022;19:60–78.
[32] Xu J, Wei Y, Huang Y, Wei X. Regulatory effects and molecular mechanisms of tea and its active compounds on nonalcoholic fatty liver disease. J Agric Food Chem 2023;71:3103–24.
[33] Mao QQ, Li BY, Meng JM, Gan RY, Xu XY, Gu YY, et al. Effects of several tea extracts on nonalcoholic fatty liver disease in mice fed with a high-fat diet. Food Sci Nutr 2021;9:2954–67.
[34] Yin X, Yang J, Li T, Song L, Han T, Yang M, et al. The effect of green tea intake on risk of liver disease: a meta analysis. Int J Clin Exp Med 2015;8:8339.
[35] Kummer B, Löck S, Gurtner K, Hermann N, Yaromina A, Eicheler W, et al. Value of functional in-vivo endpoints in preclinical radiation research. Radiother Oncol 2021;158:155–61.
[36] Cai D, Chen J, Wu Y, Jiang C. No causal association between tea consumption and 7 cardiovascular disorders: a two-sample Mendelian randomization study. Front Genet 2022;13:989772.
[37] Hanson-DeFusco J. What data counts in policymaking and programming evaluation–Relevant data sources for triangulation according to main epistemologies and philosophies within social science. Eval Progr Plann 2023;97:102238.
[38] VanderWeele TJ, Tchetgen EJT, Cornelis M, Kraft P. Methodological challenges in mendelian randomization. Epidemiology 2014;25:427–35.
[39] Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 2017;186:1026–34.
[40] Schneider CV, Hamesch K, Gross A, Mandorfer M, Moeller LS, Pereira V, et al. Liver phenotypes of European adults heterozygous or homozygous for Pi* Z variant of AAT (Pi* MZ vs Pi* ZZ genotype) and noncarriers. Gastroenterology 2020;159:534–548. e11.
[41] Gofton C, Upendran Y, Zheng M-H, George J. MAFLD: how is it different from NAFLD? Clin Mol Hepatol 2023;29:S17.
[42] Ramírez-Mejía MM, Jiménez-Gutiérrez C, Eslam M, George J, Méndez-Sánchez N. Breaking new ground: MASLD vs. MAFLD—which holds the key for risk stratification? Hepatology International 2024;18:168–78.
[43] EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81:492–542.