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ORIGINAL ARTICLE

Association between Tea Intake and Alcohol Consumption and Diabetes Complications: A Two Sample Mendelian Randomization Study

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Abstract

Background: Studies have indicated that there is a relationship between tea drinking, alcohol consumption, and a reduced risk of diabetes and its complications. However, there is currently no consensus on the potential relationships between tea drinking, alcohol consumption, and diabetes as well as its complications. In this study, we employed a two-sample Mendelian randomization (MR) analysis for the first time to systematically explore the causal relationships between tea intake, alcohol consumption, and diabetes as well as its complications.

Methods: Genetic instruments for tea drinking were identified from a genome-wide association study (GWAS) involving 447,485 individuals. Genetic instruments for alcohol intake were identified from a GWAS involving 462,346 individuals. Summary data for diabetes and its complications were obtained from various GWAS meta-analyses. Causal effects between tea drinking, alcohol consumption, and diabetes as well as its complications were examined. Inverse variance-weighted Mendelian randomization (MR) analysis was conducted as the primary method for causal inference. Further sensitivity analyses were performed to ensure the robustness of the results.

Results: The IVW assessment showed a causal relationship between alcohol intake and three diabetic complications. Type 2 diabetes with other specified/multiple/unspecified complications , Type 2 diabetes with ophthalmic complications and Type 2 diabetes with renal complications indicated an association with alcohol intake. However, there was horizontal pleiotropy in the study of alcohol intake and three diabetic complications, making the conclusions unreliable. The IVW assessment showed a causal relationship between tea intake and two diabetic complications. Type 1 diabetes with neurological complications, Type 1 diabetes with peripheral circulatory complications showed an association with tea intake.

Conclusion: Our research shows that tea and alcohol consumption have a protective effect against diabetic complications.This research contributes to a deeper understanding of dietary influences on diabetes, offering potential directions for future research and public health advocacy.

Keywords: tea; alcohol;diabetes complication; diabetes mellitus; type 1 diabetes; type 2 diabetes; Mendelian randomization.

Introduction

Diabetes is a serious metabolic disorder with an increasing incidence rate. It is estimated that by 2030, there will be over 578 million people worldwide affected by diabetes(1). As the diabetes progresses, patients may gradually develop various vascular complications, including macrovascular diseases such as cerebrovascular disease, cardiovascular disease, and peripheral vascular disease, as well as microvascular diseases such as diabetic nephropathy, retinopathy, and neuropathy(2). Among adults (aged 20-79) with diabetes worldwide, diabetic

vascular complications are the leading cause of death(2).Among the numerous complications associated with diabetes, diabetic neuropathy caused by damage to the peripheral and autonomic nervous systems is the most common (3). According to the International Diabetes Federation, it is estimated that by 2050, half of the individuals with type 2 diabetes will develop some form of neuropathy without effective intervention (4, 5). The main types of nerve damage in diabetic neuropathy include distal symmetric polyneuropathy, small-fiber-predominant neuropathy, radiculoplexopathy, and mononeuropathy (6). These syndromes lead to a high incidence of morbidity, increased mortality, and pain in patients (7).Peripheral artery disease (PAD) is a chronic arterial occlusive disease of the lower limbs, and it is particularly closely associated with diabetes. Approximately 20-30% of individuals with PAD also have diabetes(8). The incidence of PAD is 2 to 4 times higher in patients with type 2 diabetes compared to non-diabetic individuals(9). As the duration of diabetes progresses, the prevalence of PAD also increases(10). Furthermore, diabetes exacerbates the severity of PAD, augmenting the risk of severe complications such as amputation(11-12).

Epidemiological studies have shown that the global prevalence of diabetic retinopathy (DR) among diabetes patients is 22.27%. It is estimated that in 2020, there were approximately 103.12 million adults worldwide with DR, and this number is projected to increase to 165 million by 2045 (13). Almost all individuals with type 1 diabetes (T1D) and 60% of those with type 2 diabetes (T2D) will develop diabetic retinopathy within 20 years of having diabetes (14). DR can lead to progressive visual impairment and is one of the leading causes of preventable blindness among working-age populations. Additionally, DR increases the risk of severe systemic vascular complications such as stroke and coronary heart disease (15). Diabetic nephropathy (DN) is characterized by persistent albuminuria and subsequent decline in glomerular filtration rate. Ultimately, diabetic patients may progress to develop end-stage renal disease (ESRD) (16). Approximately 30% of individuals with type 1 diabetes and about 40% of those with type 2 diabetes will develop diabetic nephropathy (17, 18). Diabetic nephropathy has become a major cause of end-stage renal disease globally and is also a risk factor for cardiovascular disease (19). Multiple studies have shown that DN patients have a significantly increased risk of adverse cardiovascular events, infections, and mortality (20).

Diabetes and its complications not only significantly impact individuals and families but also have a profound economic impact on society (22). Therefore, it is crucial to explore innovative methods for early prevention and intervention of these complications.

Tea is one of the most widely consumed beverages in the world.It has numerous health benefits, including antioxidant, anticancer, liver protection, heart health, anti-obesity, gut microbiota improvement, and anti-diabetic effects(22-29). It contains many bioactive compounds, which may reduce the risk of diabetes and its complications(30). A clinical case-control study showed that regular consumption of green tea can lower the risk of diabetic retinopathy by 50% compared to non-consumers(31). Several studies have demonstrated the protective effects of tea intake against diabetic nephropathy(32-34).A randomized controlled trial has demonstrated the therapeutic value of green tea extract in the treatment of diabetic peripheral neuropathy (35). Animal experimental results suggest that Epigallocatechin-3-O-gallate, a bioactive compound in green tea, has beneficial effects in lowering blood glucose, reducing blood lipids, and exhibiting antioxidative and anti-inflammatory properties. This may prevent the occurrence and development of diabetic neuropathic pain (36). Additionally, observational studies have found that drinking more than 150 milliliters of tea per day for at least one year may reduce arterial stiffness compared to non-tea drinkers (37). This may contribute to the alleviation of peripheral artery disease .

Nevertheless, the research results regarding the causal relationship between tea consumption and vascular complications of diabetes are inconsistent. A longitudinal study conducted in Iran revealed that high consumption of tea leaves was not associated with an increased risk of chronic kidney disease (38). Another study also suggested that there was no significant correlation between tea intake and changes in estimated

glomerular filtration rate (eGFR) (39). Furthermore, the results of a prospective cohort study further indicated that tea intake was unrelated to the risk of end-stage renal disease (40).A cohort study involving 12,428 older adults did not find a significant association between green or black tea consumption and glomerular filtration rate(41).A cross-sectional study found no significant correlation between tea drinking frequency, type, and the risk of DR (42). A recent Mendelian randomization study did not provide genetic evidence for causality between tea intake and type 2 diabetes or several glycemic traits, including HbA1c, FPG, and HOMA-IR levels. Therefore, evidence supporting tea consumption as a preventive measure for T2D remains insufficient (43).

The causal relationship between alcohol and complications of diabetes is also subject to debate. In the Mediterranean population, moderate alcohol consumption has been associated with a lower prevalence of peripheral artery disease (PAD) compared to non-drinkers. However, heavy alcohol consumption is associated with an increased risk of PAD (44). Yang et al. suggest that alcohol consumption may be a risk factor for lower limb arterial disease in patients with type 2 diabetes (45). On the other hand, a cross-sectional study found a negative correlation between alcohol consumption and peripheral artery disease in non-smoking men and women (46). A prospective study found that moderate alcohol consumption is negatively correlated with the risk of neuropathy and proliferative retinopathy in patients with type 1 diabetes (47). Another cross-sectional study found a significant association between moderate alcohol consumption and a reduced incidence of diabetic retinopathy in patients with type 2 diabetes compared to non-drinkers (48). However, a meta-analysis revealed no significant association between alcohol intake and the risk of diabetic retinopathy (49). Another observational study reported an increased risk of visual impairment associated with alcohol consumption in patients with type 2 diabetes but found no association with retinopathy (50). A cross-sectional study found that alcohol drinkers have a higher risk of diabetic nephropathy and severe retinopathy in patients with type 1 diabetes (51). Consequently, comprehending the causal relationship between tea, alcohol, and complications of diabetes is crucial for directing lifestyle interventions designed to mitigate diabetes-related complications in diabetic patients.

Mendelian randomization (MR) is a statistical technique that uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to infer causal relationships between exposures and outcomes. Since genetic variations are randomly allocated during gamete formation and are largely unaffected by environmental or lifestyle factors, MR can mitigate confounding factors and reverse causality in causal inference. In this study, a two-sample Mendelian randomization method was employed, utilizing publicly available large-scale genome-wide association study (GWAS) databases, to explore the causal relationships between tea consumption, alcohol intake, and diabetes, as well as its complications.

2. Materials and Methods

2.1 Data Collection

GWAS data for Diabetic Nephropathy (DN), Diabetic Retinopathy (DR) and different subtypes of the disease based on previous studies were used as the outcome factors for this study, which can be found in the table below. The ending factors mainly include diabetes complicating peripheral circulatory system complications, diabetes complicating peripheral neuropathy, DN, DR and diabetes complicating various other complications. SNPs associated with alcohol intake were screened as instrumental table sizes using genome-wide association studies (GWAS) published in the https://gwas.mrcieu.ac.uk/ , Finland database as a reference. Both exposure and outcome cohorts were restricted to subjects of European ancestry to minimize population stratification bias. All original studies included in this MR have been approved by the ethics committees of their institutions, respectively. In addition, informed consent was already obtained from relevant participants in the original studies. Therefore, no further ethical approval was required for the present MR analysis.

Table 1 Publicly available exposure data

Disease categories	Phenocode	Ancestry	num_cases	num_controls

Proliferative diabetic retinopathy	finngen_R9_DM_RETINA_PROLIF	European	9511	362581
Diabetes endpoints	finngen_R9_DM_RETINOPATHY_EXMORE	European	10413	308633
Type 1 diabetes with other specified/multiple/ unspecified complications	finngen_R9_E4_DM1NASCOMP	European	6234	308280
Type 1 diabetes with neurological complications	finngen_R9_E4_DM1NEU	European	1077	308280
Type 1 diabetes with ophthalmic complications	finngen_R9_E4_DM1OPTH	European	5202	308280
Type 1 diabetes with peripheral circulatory complications	finngen_R9_E4_DM1PERIPH	European	669	308280
Type 1 diabetes with renal complications	finngen_R9_E4_DM1REN	European	1579	308280
Type 2 diabetes with other specified/multiple/unspecified complications	finngen_R9_E4_DM2NASCOMP	European	46373	308280
Type 2 diabetes with neurological complications	finngen_R9_E4_DM2NEU	European	1894	308280
Type 2 diabetes with ophthalmic complications	finngen_R9_E4_DM2OPTH	European	4172	308280
Type 2 diabetes with peripheral circulatory complications	finngen_R9_E4_DM2PERIPH	European	2179	308280
Type 2 diabetes with renal complications	finngen_R9_E4_DM2REN	European	2684	308280
Diabetic background retinopathy	finngen_R9_H7_RETINOPATHYDIAB_BKG	European	4011	344569

2..2 Study Design

As shown in Figure 1, we used MR analysis to examine the causal relationship between alcohol intake and DN, DR, and different subtypes of the disease. The instrumental variables for MR analysis needed to fulfill three assumptions: i) causally related to exposure, ii) independent of confounders, and iii) affecting outcomes only through exposure (54). Instrumental variables were extracted from alcohol intake according to harmonized criteria set at a genome-wide significance level of $p < 5 \times 10\text{-}8$ (55). The 71 SNPs were included in the alcohol intake dataset. Next, we performed linkage disequilibrium (LD) clustering analyses using the 1000 Genomes Project Phase III (EUR) as a reference panel to identify independent SNPs ($r2 < 0.001$ in the 10,000 kb range). The exposure dataset and the outcome dataset were harmonized by the R "harmonise_data" function and paired SNPs with intermediate allele frequencies were excluded. For SNPs that were not present in the outcome dataset, no substitution SNPs were sought. The F-statistic was used to assess the strength of the instrumental variables for each species, and instrumental variables were considered to be sufficiently strong if F was greater than 10 (56,57). None of the instrumental variables included in this study were "weak" instrumental variables (F statistic greater than 10).

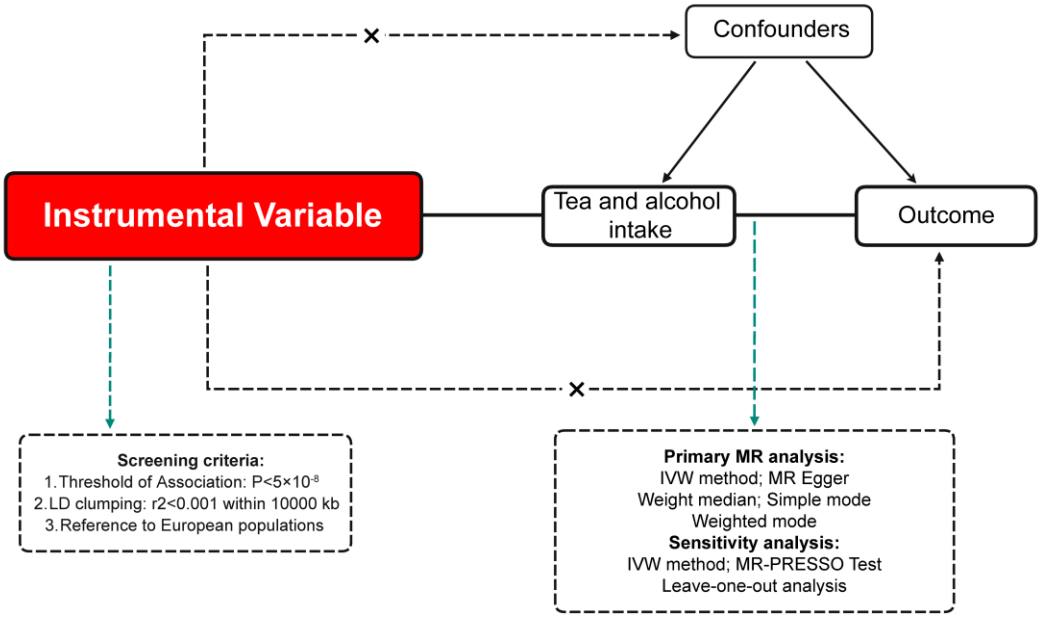

Figure 1 Flow chart

2.3 Statistical Analysis

Multiple methods have been used to assess whether there is a causal relationship between alcohol intake and DN, DR, and different subtypes of the disease, including the MR Egger method, the weighted median method, the inverse variance weighting method, the simple model method, and the weighted model method. The IVW method uses a meta-analysis approach to combine the Wald estimates of each SNP to derive an overall estimate of the effect of alcohol intake on disease (58). This method relies on all SNPs and is efficient in estimation which was chosen as the main method for this study (56). However, the results of IVW are stable only when there is no horizontal pleiotropy. Based on the assumption that instrumental strength is independent of direct effect (InSIDE), MR-Egger can utilize the intercept to assess horizontal pleiotropy (59). The MR egger method is preferred when horizontal pleiotropy is present. If more than 50% of the instrumental variables are invalid, the weighted median method is used to assess causality (60). The weighted median method was preferred when heterogeneity existed. In addition, these five methods must be oriented in the same direction. the MR-PRESSO analysis method assesses and reduces horizontal multidimensionality by detecting and excluding outliers (61). Cochran's IVW Q statistic is used to assess heterogeneity of instrumental variable (62).

To identify potentially heterogeneous SNPs, we performed a "leave-one-out" analysis (63). By excluding each instrumental variable in turn, we observed stable results for the MR analysis.For dichotomous variables, the odds ratio was used as the outcome. For continuous variables, β values were used as the results. F statistical formula: F=beta^2/se^2. For each statistical test, we consider an overall significance level of $P < 0.05$ to be satisfactory. The data were analyzed using the R software (version 4.1.3). MR analyses were performed using the "TwosampleMR" R software package (64).

3. Result

3.1 Causal relationship between tea and alcohol intake and disease

Alcohol intake was found to be causally associated with Type 2 diabetes with other specified/multiple/unspecified complications, Type 2 diabetes with ophthalmic complications and Type 2 diabetes with renal complications. A causal relationship was found between tea intake and Type 1 diabetes with neurological complications and Type 1 diabetes with peripheral circulatory complications (Figure 2). IVW method to assess the existence of the causal relationship between Type 2 diabetes with other specified/multiple/unspecified complications (odds ratio = 0.80, 95% confidence interval: 0.66 - 0.97), Type 2 diabetes with ophthalmic complications (odds ratio = 0.62, 95% confidence

interval: 0.43 -0.88), Type 2 diabetes with renal complications (odds ratio = 0.52, 95% confidence interval: 0.35 -0.78) and alcohol intake. IVW method to assess the existence of the causal relationship between Type 1 diabetes with neurological complications (odds ratio = 0.26, 95% confidence interval: 0.07 -0.90), Type 1 diabetes with peripheral circulatory complications (odds ratio = 0.22, 95% confidence interval: 0.05 -0.91) and tea intake. And there is no causal relationship between other diabetic complications and alcohol and tea intake.

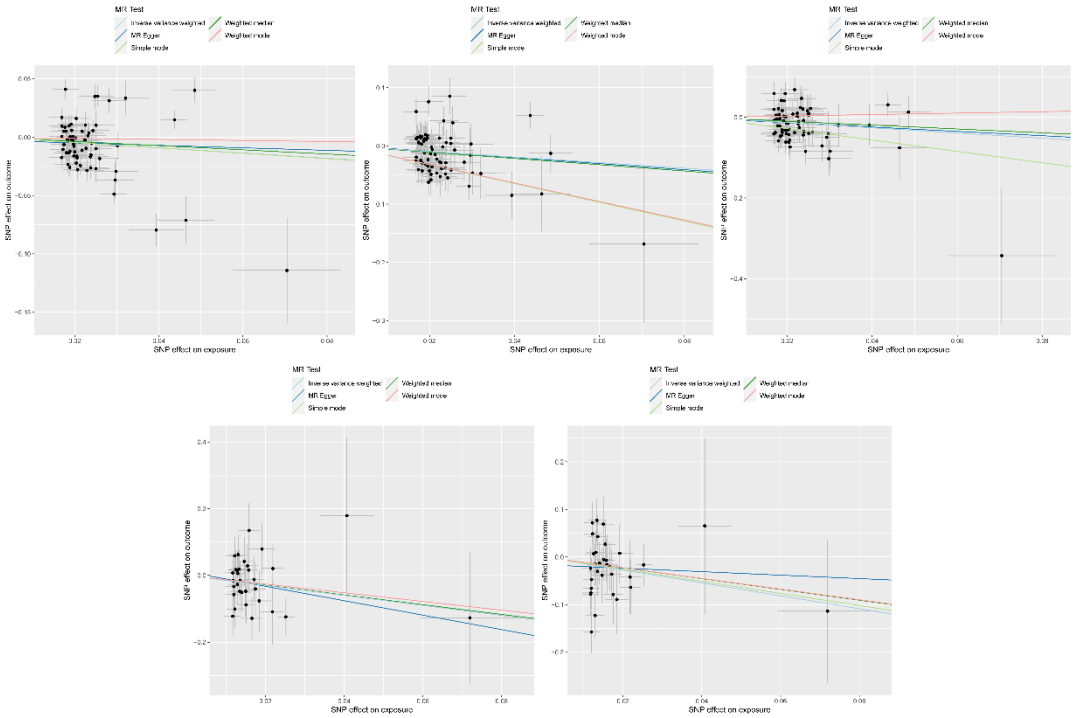

Figure 2. Scatterplot of the causal relationship between tea and alcohol consumption and diabetes mellitus. **(A)** Scatterplot of MR analysis of alcohol intake and type 2 diabetes mellitus with other specified/multiple/unspecified comorbidities. **(B)** Scatterplot of MR Analysis of Alcohol Intake and Type 2 Diabetes Mellitus with Ocular Complications. **(C)** Scatterplot of MR Analysis of Alcohol Intake and Type 2 Diabetes Mellitus with Renal Complications. **(D)** Scatterplot of MR analysis of tea intake and type 1 diabetes mellitus with neurological complications. (**E)** Scatterplot of MR analysis of tea intake and type 1 diabetes mellitus with peripheral circulatory complications.

3.2 Sensitivity analysis

First, Cochran's Q test (P > 0.05) as well as the funnel plot suggested that there was no heterogeneity (Figure3). Leave-one-out assay reveals aberrant SNP loci for causal analysis of alcohol intake and type 2 diabetes with other specified/multiple/unspecified complications (Figure4). Meanwhile, the MR-PRESSO test found horizontal pleiotropy for both alcohol intake and all three exposure factors. Leave-one-out assay reveals aberrant SNP loci for causal analysis of tea intake and Type 1 diabetes with neurological complications, Type 1 diabetes with peripheral circulatory complications. However, the MR-PRESSO test and MR Egger's intercept analysis revealed no horizontal pleiotropy except for Type 1 diabetes with neurological complications and Type 1 diabetes with peripheral circulatory complications. Therefore, it was considered that there was no pleiotropy between Type 1 diabetes with neurological complications, Type 1 diabetes with peripheral circulatory complications, and tea intake.

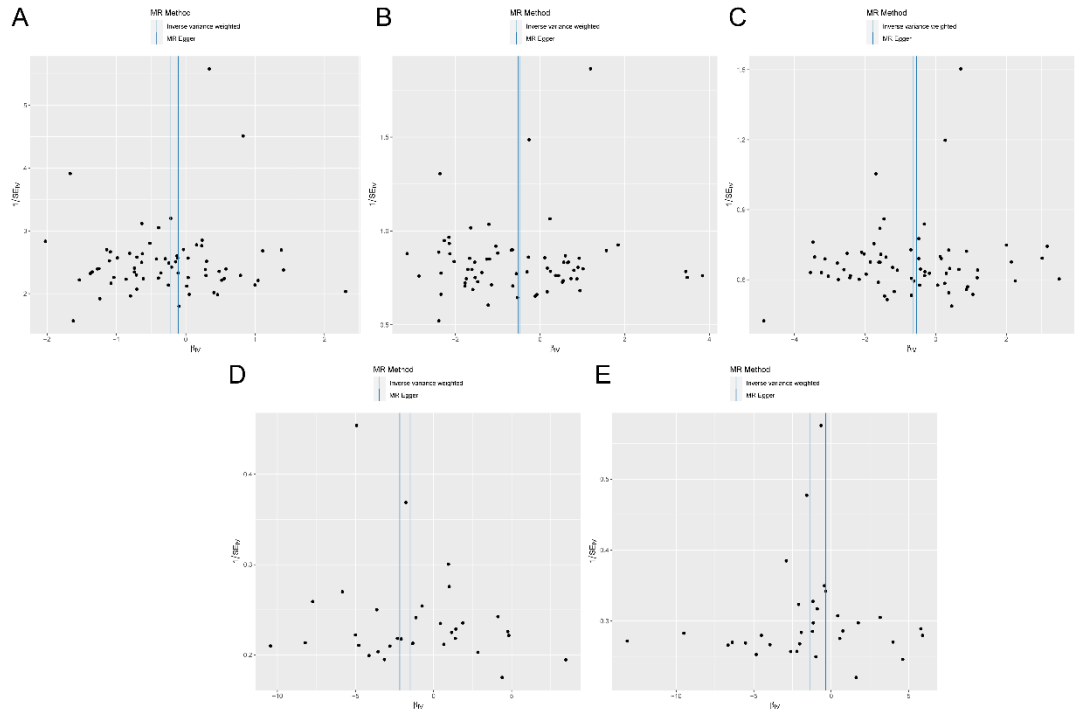

Figure 3. Funnel plots for assessing the degree of bias in instrumental variables. (A) Funnel plots of alcohol intake and type 2 diabetes mellitus with other specified/multiple/unspecified comorbidities. **(B)** Funnel plots of Alcohol Intake and Type 2 Diabetes Mellitus with Ocular Complications. **(C)** Funnel plots of Alcohol Intake and Type 2 Diabetes Mellitus with Renal Complications. **(D)** Funnel plots of tea intake and type 1 diabetes mellitus with neurological complications. **(E)** Funnel plots of tea intake and type 1 diabetes mellitus with peripheral circulatory complications.

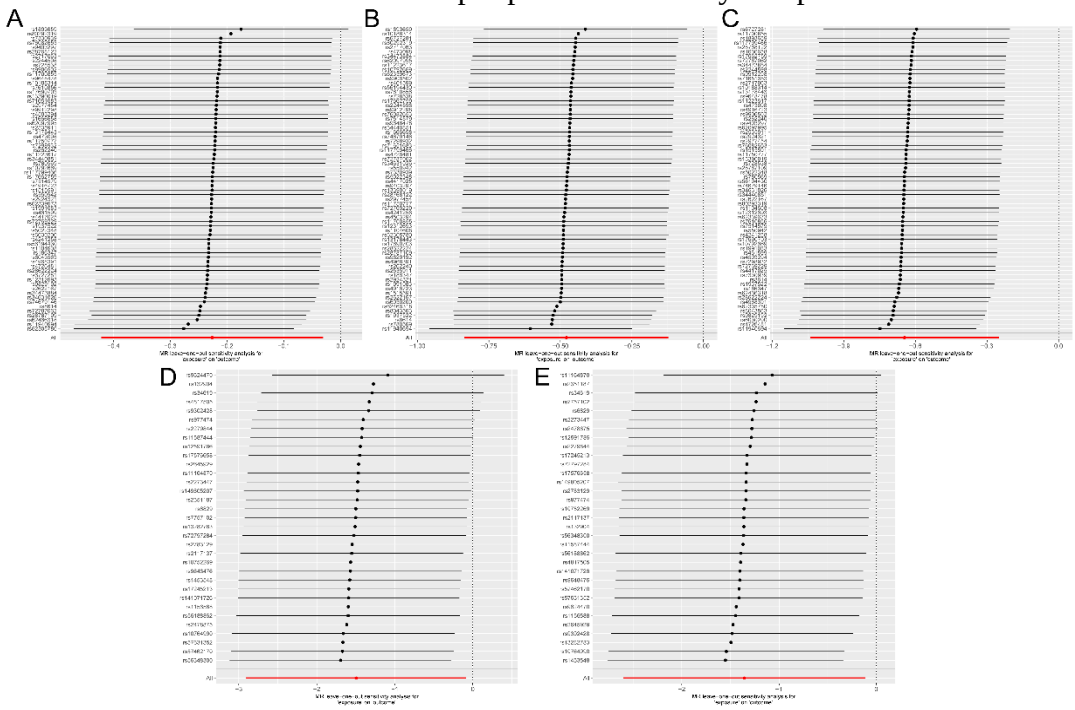

Figure 4. Evaluating MR results for the remaining instrumental variables after removing SNPs from the instrumental variables one by one. (A) Tree diagrams for alcohol intake and type 2 diabetes mellitus with other specified/multiple/unspecified comorbidities. **(B)** Tree diagrams for Alcohol Intake and Type 2 Diabetes Mellitus with Ocular Complications. **(C)** Tree diagrams for Alcohol Intake and Type 2 Diabetes Mellitus with Renal Complications. **(D)** Tree diagrams for tea intake and type 1 diabetes mellitus with neurological complications. **(E)** Tree diagrams for tea intake and type 1 diabetes mellitus with peripheral circulatory complications.

Discussion

To the best of our knowledge, this study represents the inaugural application of Mendelian randomization (MR) to evaluate the causal links between tea and alcohol consumption and the risk of diabetic complications.Our analysis revealed a causal association between alcohol consumption and various complications of T2D, including specified/multiple/unspecified, ocular, and renal complications.On the other hand, a causal link was observed between tea consumption and type 1 diabetes mellitus, specifically regarding neurological and peripheral circulatory complications.These findings suggest protective effects of tea intake.Furthermore, this Mendelian randomization study exhibited no evidence of selection bias or instrumental weaknesses.

Resveratrol constitutes the primary bioactive compound present in wine.Studies have shown that treating animals with resveratrol can reduce hyperglycemia and hyperlipidemia, improve the integrity of kidney structure, and enhance renal function in diabetic nephropathy.Administration of resveratrol has been found to lower urinary albumin and serum creatinine levels in diabetic nephropathy mice, indicating an improvement in renal function.Additionally, the administration of resveratrol has been shown to decrease oxidative stress, reduce inflammatory cell infiltration, lower cytokine production, and diminish malondialdehyde (MAD) levels in the kidneys.Moreover, it enhances the activity of antioxidant enzymes and upregulates the expression of SIRT1.These results indicate that resveratrol treatment may exert protective effects against diabetic nephropathy (63-65).Diabetic retinopathy is characterized by an enhanced inflammatory response, ischemia, advancing degeneration of retinal pigment epithelial cells, blood-retinal barrier dysfunction, and subsequent vision loss (15).Studies on animals indicate that resveratrol potentially inhibits retinal neuronal apoptosis in diabetic rats (66).Supplementation with resveratrol significantly lowers blood glucose levels and reduces body weight in diabetic rats.Additionally, it elevates oxidative indices and superoxide dismutase activity in both blood and retina, ameliorates increased NF-κB activity and the rate of cell apoptosis in the retina (67), thereby offering protective effects against diabetic retinopathy (DR).Furthermore, resveratrol is capable of decelerating the progression of diabetic cataracts by mitigating oxidative damage to lens proteins (68).

Flavonoids represent the primary phenolic compounds present in red wine.The flavonoid content in red wine encompasses flavanols (like catechins), flavonols (such as quercetin and myricetin), and anthocyanins (notably malvidin-3-glucoside) (69).In STZ-induced diabetic rats, treatment with different flavonoid compounds has been shown to improve the oxidative-reductive status of the retina, promoting an increase in glutathione and a decrease in lipid peroxidation.Observations also reveal that flavonoids can boost the levels of antioxidant enzymes, including SOD and CAT (70).Experimental findings suggest that flavanols exert a positive impact on retinal lesions and cataracts in diabetic rats.The underlying mechanisms are likely linked to the antioxidant properties of flavanols and their ability to inhibit VEGF, ERK1/2, p38MAPK, and aldose reductase (71).In conclusion, there is a notable potential for flavonoids present in red wine to offer protective effects against retinopathy in diabetic rats.A recent observational study has shown that increased consumption of flavonoids correlates with a lower risk of diabetic nephropathy (72).Studies have demonstrated that anthocyanins enhance kidney function in diabetic nephropathy patients by modulating amino acid metabolism (73).A systematic review and meta-analysis of animal research indicates that quercetin could enhance kidney function in diabetic nephropathy animal models, attributed to its antioxidant, anti-inflammatory, anti-fibrotic properties, and the regulation of renal lipid accumulation.This compound has the capability to diminish oxidative stress and inflammatory responses in the kidneys (74).Taken together, these studies suggest that flavonoids have protective effects against diabetic nephropathy.These findings provide potential candidates for the development of new therapeutic approaches for diabetic nephropathy.

Prior research has suggested that tea consumption provides protective benefits against complications related to diabetes.A randomized controlled trial has established the efficacy of green tea extract (GTE) intake in the treatment of mild to moderate diabetic peripheral neuropathy (DPN) (35).The flavonoids present in tea possess potent

antioxidant properties and are capable of enhancing apoptotic and neurotrophic factors. They alleviate oxidative stress, thus safeguarding neurons from damage and potentially preventing diabetic retinopathy (75-82).Research has demonstrated that both pu-erh tea and green tea exert protective effects against diabetic nephropathy. These benefits may be attributed to various mechanisms, such as the reduction of advanced glycation end-product (AGE) accumulation, enhancement of energy metabolism, and mitigation of oxidative stress(83-89).These findings offer promising avenues for potential pharmaceutical agents in the development of novel treatments for diabetic nephropathy.

The varying impacts of tea and alcohol on complications in type 1 and type 2 diabetes can be attributed to the distinct pathogenic mechanisms of T1DM and T2DM.T1DM results from the extensive destruction of pancreatic beta cells, culminating in an absolute insulin deficiency.Conversely, T2DM primarily stems from insulin resistance and the progressive deterioration of insulin secretion (90).Owing to these divergent pathogenic mechanisms, the effects of tea and alcohol on complications may vary between these diabetes subtypes.Furthermore, in contrast to T2DM, which predominantly affects middle-aged and elderly individuals, T1DM typically develops in children and adolescents, who generally have limited exposure to tea and alcohol.This factor might also play a role in elucidating the disparities in their impacts across the different subtypes.

Indeed, Mendelian randomization (MR) studies have yielded results that are inconsistent with those of prior observational studies.Several factors may account for this discrepancy.Firstly, the issues of reverse causality and residual confounding cannot be entirely ruled out in prior observational studies.Secondly, data in previous studies were derived from self-reported tea consumption, potentially leading to misclassification errors due to habitual tea drinking patterns.Consequently, the assessment of long-term tea consumption in observational studies may lack precision.Lastly, the demographic of habitual tea drinkers is not randomly distributed, being somewhat influenced by regional differences in tea consumption and closely linked to variables like age and gender.All these elements could potentially impact the outcomes of previous observational studies.

5 Conclusion:

In conclusion, our study elucidates the causal relationship between alcohol and tea consumption and the development of diabetes and its complications, as determined through Mendelian randomization (MR) analysis.This insight offers fresh perspectives for subsequent mechanistic research and promotes advocacy for healthier lifestyles.

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Institutional Review Board Statement:

The UK Biobank and FinnGen R9 projects were approved by the Ethical Review Board and all

participants signed an informed agreement. The study was conducted in accordance with the

guidelines of the Declaration of Helsinki, and the utilization of summary level statistics did not

require additional ethical review and approval.

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Availability of data and materials:

Exposure data were acquired from the GWAS summary dataset of the UK Biobank project incorporated by the MRCIEU GWAS database (https://gwas.mrcieu.ac.uk/) . Outcome data were obtained from the FinnGen R9 repository (https://r9.finngen.fi/). All data is publicly available.

Contributions:

M.J. independently completed the experimental design, data collection and manuscript writing.All author have read and agreed to the published version of the manuscript.

Conflicts of Interest:

The authors declare no competing interests.

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