Association between alcohol consumption and Alzheimer's disease: A Mendelian Randomization Study

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Abstract

Observational studies have suggested that a U-shaped relationship exists between alcohol consumption and Alzheimer's disease, with light-moderate drinkers at lower risk of developing Alzheimer's disease. A two-sample Mendelian randomization approach was used to examine whether alcohol consumption causally effects the risk of developing Alzheimer's disease. We used summary level genome-wide association data for alcohol consumption from the UK biobank, alcohol dependence from the Netherlands Twin Register (NTR) and the Netherlands Study of Depression and Anxiety, and Alzheimer's disease from the International Genomics of Alzheimer's Project. Variants associated with alcohol consumption were combined using an inverse variance weighted fixed-effects approach. We found no evidence of a causal association between genetically predicted alcohol consumption (β = 0.078; SE = 0.354; 95% CI = -0.617, 0.772; p = 0.826) or alcohol dependence (β = -0.011; SE = 0.026; 95% CI = -0.062, 0.039; p = 0.666) with Alzheimer's disease. A causal relationship was observed between genetically predicted alcohol consumption and γ-glutamyltransferase levels (β = 0.159; SE = 0.062; 95% CI = 0.037, 0.282; p = 0.011), which was used as a positive control. The findings from this Mendelian randomization study do not find evidence of a causal association between alcohol consumption and Alzheimer's disease. These findings contrast with those of recent systematic reviews of observational studies.

Keyworkds: Alcohol Consumption; Alcohol dependence; Alzheimer's disease; Mendelian randomization

Introduction

The projected prevalence of dementia is expected to reach 131.5 million in 2050 [1]. This will have major implications for national health and social services, with the cost of caring for individuals living with dementia expected to rise from USD $818 billion in 2015 to USD $2 trillion in 2030 [1]. In the absence of any therapeutic interventions for dementia, successful intervention strategies that target modifiable risk factors to promote disease prevention is currently the only available approach that can have an impact on the projected rates of dementia.

Alcohol consumption is a modifiable behaviour that has emerged as a potential protective factor for dementia. A recent overview of systematic reviews that investigated the association between alcohol consumption and dementia or cognitive decline, identified three high quality systematic reviews that meet their inclusion criteria [2]. Two of the three systematic reviews conducted a meta-analysis and concluded that light-moderate alcohol consumption in contrast to abstainers was correlated with a 25-38% reduction in risk of Alzheimer's disease (AD), vascular dementia (VaD) and all cause dementia (ACD) [3,4]. In contrast the third review, performed a qualitative analysis and concluded that the literature did not provide a concrete evidence of a causal association between alcohol consumption and AD [5]. A more recent meta-analysis found light-moderate alcohol consumption to be protective [6]. Light alcohol consumption corresponding to either 4 drinks/week, 6g/day or 1 times/week provided the greatest risk reduction in ACD, while excessive alcohol consumption of 23 drinks/week or 12.5g/day significantly increased risk of ACD. Furthermore, qualitative analysis indicated that the protective effects only existed for wine consumption [6]. Observational studies however may underestimate the detrimental effects of long-term excessive alcohol consumption, which is associated with the development alcohol-

related dementia (ARD), due to participants with ARD not been recruited or lost to follow-up [7].

Several mechanisms have been proposed that may underlie the observed protective effects of moderate alcohol consumption on dementia. First, moderate alcohol consumption has been associated with increased levels of circulating high-density lipoprotein cholesterol, apolipoprotein AI and adiponectin and decreased fibrinogen levels [8]. The cardio protective effects of these biomarkers decrease cardiovascular disease risk, thus reducing the risk of cerebrovascular injury. Second, moderate alcohol consumption is associated with an anti-inflammatory effect that could moderate the neuroinflammatory response observed in Alzheimer's disease [9,10]. Finally, in red wine resveratrol is proposed to have both neuroprotective effects and anti-oxidant properties that reduce neuronal cell death [11].

While accumulating of evidence suggests that light-moderate alcohol consumption is associated with a reduced risk of dementia, there are several limitations within the literature that temper the positive interpretation of these results. First, selection effects may bias results, with heavy drinkers who already show signs of cognitive impairment screened out of studies [3]. Second, alcohol consumption is associated with an increased mortality risk, potentially resulting in participants been lost to follow-up out of a study prior to a dementia diagnosis. This would result in an underestimate of dementia incidence and biasing estimates of relative risk [12]. Third, the abstainer comparison groups within studies are often composed of life-time abstainers and former drinkers who may have reduced or quite drinking because of other detrimental health outcomes [13,14]. As such it is possible that confounding health factors increase dementia risk in non-drinkers. Fourth, the apparent protective association between alcohol consumption and dementia may be confounded by other health/lifestyle characteristics, such as lower cardiovascular risk factors, that are associated with a reduced incidence of dementia [3,4]. In particular, socioeconomic status and prior intelligence both

influence the amount and type of alcohol consumed, and as such may play an important confounding role in the alcohol-dementia relationship [15].

As such, the current observational studies are limited by issues of confounding and reverse causality. In the absence of a randomized control trials, a novel method for estimating causal effects of risk factors in observational studies using genetic variants is Mendelian Randomization.

Mendelian Randomization uses genetic variants as proxies for environmental exposures to provide an estimate of the causal association between an intermediate exposure and a disease outcome (Figure 1) [16]. Mendelian randomization is similar to a 'genetic randomized control trial' due to the random allocation of genotypes from parents to offspring and are thus not affected by reverse causation and are independent of confounding factors that may influence disease outcomes (Figure 3) [16]. The genetic variants used in Mendelian randomization act as an instrumental variable (IV) under the following assumptions: 1) it is associated with exposure (non-zero effect assumption); 2) it is independent of measured or unmeasured confounders (independence assumption) and; 3) it is associated with the outcome via the causal effect of the exposure (exclusion restriction assumption) [16]. If the assumptions hold for the genetic variant, any association between the genetic variants and the disease outcome must come via the variants association with the exposure. This implies that the exposure is causally related to the outcome.

Recently, a two-sample Mendelian Randomization method was developed that uses data on gene-exposure and gene-outcomes associations from different samples to estimate causal associations [17]. This method takes advantage of the increasing abundance of publicly available summary statistics from genome wide associations studies of disease and

risk factors, leveraging the increasing sample sizes and therefore power to detect causal associations [18].

In this study, we perform a two-sample Mendelian randomization analysis to assess the causal effect of alcohol consumption and alcohol dependence on the risk of developing Alzheimer's disease. Additionally, we also perform a two-sample MR analysis with alcohol consumption and γ-glutamyl transferase (GGT) as a positive control, were the causal effects between GGT and alcohol intake have been strongly established [19].

Methods

Data sources

Genetically predicted alcohol consumption and alcohol dependence: Single nucleotide polymorphisms strongly associated with alcohol consumption or alcohol dependence at genome wide significance ($P < 5 \times 10^{-8}$) were obtained from genome wide association studies (GWAS). We assessed correlations (linkage disequilibrium) between the selected SNPs using LDlink [20], when SNPs were in strong linkage disequilibrium ($r^2 > 0.9$) they were discarded to retain the SNPs with the smallest *p*-value. SNPs that were moderately correlated ($r^2 < 0.9$) were accounted for using a correlation matrix. Whether any of the SNPs were directly related to Alzheimer's disease and GGT (pleiotropic effects), rather than via their effect on alcohol consumption was determined by obtaining their known traits/phenotypes from a genotype to phenotype cross-reference database, the NHGRI-EBI GWAS Catalogue [21]. The β coefficients (or log odds ratio for binary outcomes) and standard errors for the selected SNPs were recorded (Table 1 & 2).

Genetic risk for Alzheimer's disease: Association of the selected alcohol consumption and alcohol dependence associated SNPs with late-onset Alzheimer's disease were extracted

from a GWAS performed by the International Genomics of Alzheimer's Project (IGAP) [22]. IGAP is a meta-analysis of 4 previously published GWAS datasets: the European Alzheimer's Disease Imitative (EADI), the Alzheimer Disease Genetics Consortium (ADGC), Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), and Genetic and Environmental Risk in AD (GERAD) and includes a sample of 17,008 LOAD cases and 37,154 cognitively normal elder controls. SNPs that were not available in the LOAD GWAS were replaced with proxy SNPs that were in strong linkage disequilibrium ($r^2 > 0.8$).

Genetically predicted γ-glutamyl transferase (GGT): Association of alcohol consumption and dependence related SNPs on liver function were extracted from a GWAS performed in 61,089 research patients on γ-glutamyl transferase blood concentration ($\log_{10}$ transformed IU/L) [23]. The β-coefficients and standard errors for the selected SNPs were recorded (Table 1 & 2).

Mendelian Randomization Analysis

The SNP-exposure (alcohol consumption and alcohol dependence) and SNP-outcome coefficients (Alzheimer's disease and GGT) were combined in a fixed-effects meta-analysis using an inverse-variance weighted approach to give an overall estimate of causal effect [17]. This is equivalent to a weighted regression of the SNP-outcome coefficients on the SNP-exposure coefficients with the intercept constrained to zero. This method assumes that all variants are valid instrumental variables based on the Mendelian randomization assumptions. Moderate correlations ($r^2 < 0.9$) between the exposure SNPs were accounted for in the analysis using a correlation matrix. This extends the inverse variance weighted method to a generalized weighted regression model. The causal estimate of the IVW analysis expresses

the causal increase in the outcome (or log odds of the outcome for a binary outcome) per unit change in the exposure. For the Alcohol consumption – GGT MR analysis, rs1260326 was excluded due to potential pleiotropic effects.

All statistical analyses was conducted using R version 3.4.0 [24], with the Mendelian Randomization analysis performed using the 'MendelianRandomization' package [25].

Ethics approval: Each study from which GWAS summary data was collected had been specifically approved by the Ethical Committees of the original studies and all the participants provided a written informed consent. This analysis did not require ethics approval as it used publicly available summary data.

Results

Alcohol Consumption and Alzheimer's Disease: Table 1 shows that 14 loci (11 single nucleotides polymorphism (SNPs), 3 indels) that were associated with alcohol consumption (drinks per week adjusted for sex, age and weight) in a large GWAS of alcohol consumption performed in 112,117 individuals from the United Kingdom [26]. Of these 14 loci, the 3 indels were excluded and only seven SNPs were available in the LOAD GWAS, with an additional SNP, rs283413 ($r^2 = 0.87$) used to replace rs29001570.

Table 3 shows the results of the Mendelian Randomization analysis. Genetically predicted alcohol consumption was not causally associated with Alzheimer's disease.

Alcohol Dependence and Alzheimer's Disease: SNPs associated with alcohol dependence were extracted from a large GWAS of alcohol dependence ascertained via the Alcohol Use Disorder Identified Test (AUDIT) in a sample of 1,374 cases and 6,468 controls from the Netherlands [27]. We extracted 40 SNPs that were nominally associated ($P < 10^{-5}$) with alcohol dependence as no SNPs reached genome wide significance ($P < 5 \times 10^{-8}$). 25

SNPs were further excluded due to high linkage disequilibrium, giving a total of 15 SNPs (Table 2). Of these 15, only 12 were available in the LOAD GWAS, and no proxies were available to use as replacements.

Table 3 shows the results of the Mendelian Randomization analysis. Genetically predicted alcohol dependence was not associated with Alzheimer's disease.

γ-glutamyl transferase Positive Control: For the SNPs associated with alcohol consumption, only 2 SNPs was available in the GGT GWAS, with proxies available for, rs29001570 (rs283413: r^2 = 0.87), rs9991733 (rs7674434: r^2 = 0.99), and rs9841829 (rs9851444: r^2 = 1). For the SNPs associated with alcohol dependence, 6 SNPs were available in the GGT GWAS, with a proxy available for rs55768019 (rs5009513: r^2 = 0.99).

Table 3 shows the results of the Mendelian Randomization analysis for both alcohol consumption and alcohol dependence. Genetically predicted alcohol consumption was positively associated with GGT blood concentrations, though alcohol dependence was not associated with GGT blood concentrations. A heterogeneity test to assess for the presence of pleiotropy was non-significant for both genetically predicted alcohol consumption (Q = 1.784, p = 0.618) and genetically predicted alcohol dependence (Q = 4.55, p = 0.602)

Discussion

This is the first Mendelian randomization study to examine the causal association between alcohol consumption and AD. The results of this study do not support a possible causal effect between alcohol intake on risk of developing AD, with neither genetically predicted alcohol consumption or alcohol dependence causally associated with Alzheimer's disease. Genetically predicted alcohol consumption was associated with levels of γ-glutamyltransferase, confirming that the instrumental variable was a suitable proxy for

alcohol consumption in the Mendelian randomization analysis. No association between the alcohol dependence and GGT was observed, likely due to relaxing the p-value threshold for inclusion of SNPs into this study (nominally significant, rather than genome-wide significant). This can introduce more weak instruments into the analysis, and in the context of two-sample MR analysis, bias results towards the null [17]. Furthermore, the SNPs for Alcohol dependence were selected from a GWAS that used AUDIT, rather than the DSM-IV clinical diagnosis, to assess alcohol dependence. While this can reduce the power to detect an association by introducing noise into the phenotype, AUDIT is considered one of the most accurate screening tools for alcohol dependence [28]. Therefore, the lack of associations is likely due its small sample size (7,842). As such, the results from this study suggest that light-moderate alcohol consumption is unlikely to be casually related to a reduced risk of Alzheimer's disease, but further evaluation of the effect of excessive alcohol consumption on risk of Alzheimer's is needed.

The findings from this study contrast with those of recent meta-analyses and systematic reviews [2,6], which have suggested that light-moderate alcohol consumption is protective against dementia. However, all prior findings have been conducted in observational studies that assume no confounders influence the reported results and are limited by selection bias, an underlying illness-death structure, and the heterogeneous nature of the abstainer comparison group. Like randomized control trials, Mendelian randomization analyses reduces confounding and reverse causality due to the random allocation of genotypes from parents to offspring. This can allow for more robust inference of causal effects. As such the results from this study provides further support for the cautious interpretation of the proposed cognitive health benefits of alcohol [14], and further highlights that future observational studies need to account for potential confounding factors.

Despite cautious interpretation of the protective effects of alcohol intake, moderate alcohol consumption has been recognised by 8.1% of 20-39 year olds in a national survey of Australiana's as reducing dementia risk [29]. Furthermore, a second survey indicated that 18.6%, 33.3% and 31.9% of 20-44, 45-64 and 65+ year olds reported drinking wine improves cognitive health [30]. As 5.9% of all global deaths are attributable to alcohol, with over 200 disease linked to alcohol consumption [31], further clarification of the role of alcohol intake is required to further align national drinking guidelines with optimal health outcomes.

While, these results suggest that alcohol consumption is not causally linked to the development of Alzheimer's disease, a causal relationship could exist between other dementia subtypes. One proposed mechanisms for the protective effect of light-moderate alcohol consumption on dementia is a reduction in cardiovascular disease due the cardio protective effects of increased levels of circulating high-density lipoprotein cholesterol, apolipoprotein AI and adiponectin and decreased fibrinogen levels [8]. As such, alcohol consumption could have protective effects on vascular dementia, which is characterised by cerebrovascular disease and ischemic or haemorrhagic brain injury [32]. Observational studies however have found conflicting evidence for an association between alcohol consumption and VaD, though only a limited number of studies have investigated this association [3,4]. Unfortunately, a Mendelian randomization study would be underpowered to examine the causal link between alcohol intake and VaD, with the largest GWAS of VaD consisting of 67 cases and 5,700 controls, which identified a single significant locus. As such, as future studies should further investigate the genetic architecture of VaD, Mendelian randomization analysis should revisit the alcohol consumption — VaD relationship.

The results from this study should be interpreted in conjunction with some limitations. First, we cannot be certain the selected SNPs do not violate the exclusion-restriction assumption. While we investigated potential pleiotropic effects for the selected SNPs, we could only identify known effects based on our current understanding of their underlying mechanisms. Second, given the use of separate samples, we were unable to test whether the association with AD varied by level of alcohol consumption or by other covariates such as age or gender. Given the proposed dose-response relationship between alcohol consumption and dementia, a causal relationship could be expected between excessive alcohol consumption and increased risk of dementia. Nevertheless, the use of alcohol dependence as an instrumental variable should address this issue. Third, the GWAS for IGAP and UK Biobank were conducted in participants of European ancestry, limiting the interpretation these results to other ethnic groups.

Despite these limitations, this study has a number of strengths. First, this study takes advantage of publically available datasets to gain more precise estimates and greater statistical power due to the large sample sizes associated with the GWAS for alcohol consumption (n = 112,117), alcohol dependence (n = 7,842), and Alzheimer's disease (n = 74,046). Second, MR is less prone to the bias of observational studies, particularly in relation to reverse causation and confounding, providing a more robust estimate of causal relationships between exposures and outcomes.

In conclusion, this Mendelian randomization study did not find evidence of a causal relationship between alcohol consumption and Alzheimer's disease. This contrasts with recent findings from systematic reviews which have suggested that light-moderate alcohol consumption is associated with a reduced risk of dementia outcomes. This discrepancy could be due to limitations in the methodology of observational studies including, selection effects,

study attrition, the heterogeneous nature of abstainer groups or confounding. As such our results reiterate that abstainers should not initiate alcohol consumption to improve 'cognitive health' and further suggests that alcohol consumption should be reduced considering alcohols overall harmful effects.

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Conflicts of interest

The authors have no conflict of interest to report

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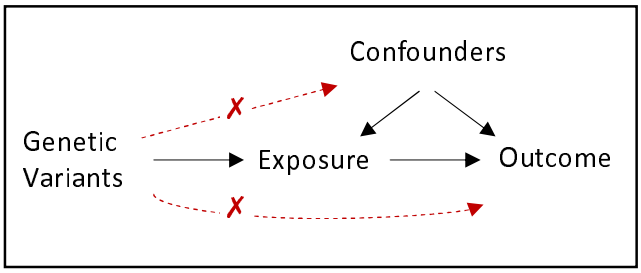

Figure 1: Model for a Mendelian randomization study. Genetic variants known to be associated with the exposure (Non-zero effect assumption) are used to estimate if the exposure causally influences the outcome. The genetic variable is assumed not to be associated with confounders (Independence assumption) or the outcome (exclusion restriction assumption).

Table 1: SNPS associated with Alcohol Consumption and considered for Mendelian Randomization analysis with Alzheimer's Disease & GGT

Alcohol Consumption				Alzheimer's Disease				GGT				Pleiotropy[a]
SNP	β	SE	*p*	Proxy	β	SE	*p*	Proxy	β	SE	*p*	
rs145452708	-0.034	0.003	$1.15x10^{-30}$	-	0.0107	0.058	0.8534	-	-	-	-	-
rs193099203	-0.031	0.003	$3.79x10^{-25}$	-	-	-	-	-	-	-	-	-
rs1260326	-0.028	0.003	$1.34x10^{-21}$	-	-8.00E-04	0.0161	0.9608	rs1260326	0.0138	0.0023	8.02E-14	Blood Metabolites Cardiovascular Traits Metabolic Traits Inflammatory bowel disease Gout Blood Proteins Coffee Consumption Liver Enzymes
rs11940694	-0.027	0.003	$8.40x10^{-19}$	-	-0.0363	0.0167	0.02941	-	-0.0039	0.0023	0.07313	-

rs29001570	-0.026	0.003	$9.58x10^{-19}$	rs283413	0.0747	0.0976	0.444	rs283413	-0.0873	0.1339	0.5123	-
rs3114045	-0.02	0.003	7.98x 0^{-12}	-	0.0446	0.0224	0.04582	-	-	-	-	-
rs140280172	-0.02	0.003	$2.89x10^{-11}$	-	-	-	-	-	-	-	-	-
rs9841829	0.019	0.003	$3.36x10^{-10}$	-	-0.0191	0.0185	0.3032	-	$-1.0x10^{-4}$	0.0033	0.482	-
rs35081954	0.018	0.003	$2.14x10^{-09}$	-	-	-	-	-	-	-	-	-
rs375507729	0.018	0.003	$3.19x10-^{09}$	-	-	-	-	-	-	-	-	-
rs9991733	0.018	0.003	$3.80x10^{-09}$	-	0.0126	0.0179	0.4807	rs7674434	-0.0049	0.0026	0.01637	-
rs149127347	-0.018	0.003	$4.42x10^{-09}$	-	-	-	-	-	-	-	-	-
rs145329623	-0.017	0.003	$5.68x10^{-09}$	-	0.059	0.0951	0.5347	-	-	-	-	-

[a]Pleitropy was identified using Ensemble (Homo sapiens – phenotype)

Table 2: SNPS associated with Alcohol Dependence and considered for Mendelian Randomization analysis with Alzheimer's Disease & GGT

Alcohol Dependence				Alzheimer's Disease				GGT				Pleiotropy[a]
SNP	β	SE	*p*	Proxy	β	SE	*p*	Proxy	β	SE	*p*	
rs117557854	-0.73	0.15	$1.55x10^{-6}$	-	-	-	-	-	-	-	-	-
rs2400954	-0.21	0.04	$3.90x10^{-6}$	-	-0.008	0.0158	0.6127	-	-4.00E-04	0.0023	0.8597	-
rs2400955	-0.22	0.04	$6.88x10^{-6}$	-	-0.0124	0.0167	0.4567	-	-0.0016	0.0024	0.46250	-
rs7199896	-0.46	0.09	$4.87x10^{-6}$	-	-	-	-	-	-	-	-	-
rs75433892	-1.31	0.27	$1.56x10^{-6}$	-	-	-	-	-	-	-	-	-
rs57126985	-0.56	0.12	$6.43x10^{-6}$	-	0.0027	0.0679	0.9679	-	-	-	-	-
rs79978308	-0.58	0.12	$4.69x10^{-6}$	-	-0.0517	0.0519	0.3186	-	-	-	-	-
rs145441266	-0.69	0.14	$2.05x10^{-6}$	-	-0.0407	0.1246	0.7442	-	-	-	-	-
rs2253612	-0.36	0.07	$8.25x10^{-7}$	-	0.0042	0.0269	0.8767	-	-3.00E-04	0.0036	0.4109	-
rs62191099	-0.22	0.04	$5.23x10^{-6}$	-	0.0116	0.0178	0.5158	-	-	-	-	-
rs12632235	-0.78	0.16	$5.31x10^{-6}$	-	-0.0256	0.0634	0.6861	-	-9.00E-04	0.0063	0.8677	-
rs55768019	-0.22	0.04	$7.58x10^{-7}$	-	-0.0111	0.0158	0.4815	rs5009513	0.0036	0.0021	0.1328	-
rs74745534	-0.92	0.18	$1.40x10^{-6}$	-	-0.0203	0.1045	0.8459	-	-	-	-	-
rs1479432	-0.24	0.05	$5.65x10^{-6}$	-	-0.0176	0.0189	0.3504	-	-3.00E-04	0.0029	0.7641	-
rs17688247	-0.29	0.01	$6.01x10^{-6}$	-	0.0412	0.0225	0.06703	-	0.0031	0.0031	0.4798	-

[a]Pleitropy was identified using Ensemble (Homo sapiens – phenotype)

Table 3: Estimations of the causal associations of alcohol consumption & alcohol dependence with Alzheimer's disease or *γ-glutamyltransferase*.

Exposure	Outcome	*n* SNPs	β	SE	95% CI	*p*
Alcohol Consumption	Alzheimer's disease	8	0.078	0.354	-0.617, 0.772	0.826
Alcohol Dependence	Alzheimer's Disease	12	-0.012	0.026	-0.062, 0.039	0.654
Alcohol Consumption	GGT	5	0.159	0.062	0.037, 0.282	0.011
Alcohol Dependence	GGT	7	0.004	0.004	-0.004, 0.012	0.355