



# Habitual consumption of alcohol with meals and lung cancer: a Mendelian randomization study

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**Background:** The objective of this study was to determine the causal relationship between habitual alcohol consumption with meals and lung cancer.

**Methods:** Public genetic summary data from two large consortia [the Neale Lab and the International Lung Cancer Consortium (ILCCO)] were used for analysis. As the instrumental variables of habitual alcohol consumption with meals, data on genetic variants were retrieved from Neale Lab. Additionally, genetic data from other consortia [Global Lipid Genetics Consortium (GLGC), Tobacco, Alcohol and Genetics (TAG), Genetic Investigation of Anthropocentric Traits (GIANT)] were utilized to determine whether alcohol could causally alter some general risk factors for lung cancer. The primary outcome was the risk of lung cancer (11,348 cases and 15,861 controls in the ILCCO). The R package TwoSampleMR was used for analysis.

**Results:** Based on the inverse variance weighted method, the results of the two-sample Mendelian randomization (MR) analyses indicated that commonly consuming alcohol with meals was a protective factor, reducing lung cancer risk [odds ratio (OR) 0.175, 95% confidence interval (CI): 0.045–0.682,  $P=0.012$ ]. The heterogeneity analysis revealed that the causal relationship analyses of different types of lung cancer all had low heterogeneity ( $P>0.05$ ). The horizontal pleiotropic study showed that major bias was unlikely. The MR assumptions did not seem to be violated. The causal relationship analyses between habitual alcohol consumption with meals and some risk factors for cancers showed that this alcohol consumption habit was a beneficial factor for reducing body mass index (BMI) and the number of cigarettes smoked per day.

**Conclusions:** Habitual appropriate alcohol consumption with meals is a protective factor for the development of lung cancer.

**Keywords:** Mendelian randomization; alcohol; lung cancer

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## Introduction

Conventionally, alcohol consumption has been thought to cause many risk factors towards various diseases, such as obesity; however, a study conducted by Arif *et al.* (1) indicated that an appropriate alcohol consumption habit (fewer than 5 drinks per week) could decrease the incidence of obesity. Furthermore, for various diseases, several studies have shown that appropriate alcohol consumption (light-to-moderate, less than 30 g/d) is beneficial for patients' health and can not only reduce the risk of type 2 diabetes (2), arterial hypertension (3), and cardiovascular diseases (4) but can also decrease patient mortality (5).

It is estimated that lung cancer, as the first leading cause of cancer death in the USA, will result in more than 130 thousand patient deaths in 2020 (6), with a total 5-year survival rate of 19% (6). It is crucial to clarify modifiable risk factors and beneficial factors to improve the prevention of lung cancer because of the increasing burden (7). Regarding risk factors, smoking has been identified as the most frequent cause of lung cancer (8), and because of tobacco control policies, lung cancer mortality has significantly decreased (6,9,10). In addition, regarding beneficial factors, the study by Zhou *et al.* (11) showed that education was one of the protective factors for lung cancer, which was proposed by Mendelian randomization (MR).

Worldwide interest in MR has greatly increased over the last 10 years; this method uses genome-wide association study (GWAS) data to demonstrate the exact causal relationship between A and B (using instrumental variable analysis with genetic instruments), which can avoid the influences of other exposure factors on the outcomes (12). Previously, several observational studies have shown that appropriate alcohol consumption (amount per day and frequency per week) could prevent lung cancer (13,14). Among these studies, the study by Brenner *et al.* (13) demonstrated that alcohol intake of less than 20 g/d was a beneficial factor for the prevention of lung cancer. Moreover, Li *et al.* (14) indicated that occasionally consuming alcohol throughout the week was a favorable factor for the survival of Chinese men with lung cancer. Therefore, we conducted an MR study to confirm the causal relationship between the habitual consumption of alcohol with meals and lung cancer. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3063>).

## Methods

### *Genetic variants associated with lung cancer*

The exposure factor data (habitual alcohol consumption with meals) in this study were based on the Neale Lab. The outcome data (incidence of lung cancer, lung adenocarcinoma, and lung squamous cell cancer) were retrieved from the International Lung Cancer Consortium (ILCCO) (15), and the data for small cell lung cancer were obtained from the UK BioBank. In terms of other risk factors, the data of triglycerides and total cholesterol were obtained from the Global Lipid Genetics Consortium (GLGC) (16); the data of smoking habits (including cigarettes smoked per day, former *vs.* current smoker, age of smoking initiation, and ever *vs.* never smoker) were obtained from the Tobacco, Alcohol and Genetics (TAG) consortium (17); and the data of obesity class 1–3, waist circumference (adjusted by body mass index, BMI), hip circumference (adjusted by BMI), and waist-to-hip ratio (adjusted by BMI) were retrieved from the Genetic Investigation of Anthropocentric Traits (GIANT) (18,19). (Table 1).

### *Statistical analyses*

To determine MR estimates of habitual alcohol consumption with meals for lung cancer, we used several MR approaches. In our study, habitual consumption of alcohol meant appropriate alcohol consumption habit (light-to-moderate, less than 30 g/d). We conducted a random effect inverse variance weighted (IVW) meta-analysis of the Wald ratio for individual single nucleotide polymorphisms (SNPs). Other statistical tests (the weighted median and MR-Egger regression methods) were used to estimate the effects. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Three assumptions were the basis of the MR method: (I) the instrumental variables are strongly associated with the habitual consumption of alcohol with meals; (II) the instrumental variables influence lung cancer only through their effect on habitual alcohol consumption with meals; and (III) the instrumental variables are independent of any confounder (20). We assessed the directional pleiotropy based on the intercept obtained from the MR-Egger analysis (21).

The common risk factors for lung cancer were identified in previous studies (22,23). Analyses were performed by

**Table 1** Details of studies included in Mendelian randomization analyses

Variable	Consortium	PMID	Population	Gender
Lung cancer	ILCCO	24880342	11,348	European
Habitual consumption of alcohol with meals	Neale Lab	UK BioBank	–	–
Obesity 1–3 (waist circumference, hip circumference, waist-to-hip ratio)	GIANT	23563607, 25673412;	European (for obesity 1–3); mixed (waist circumference, hip circumference, waist-to-hip ratio)	Mixed
Triglycerides, total cholesterol	GLGC	24097068	Mixed	Mixed
Cigarettes smoking	TAG	20418890	European	Mixed

ILCCO, International Lung Cancer Consortium; TAG, Tobacco, Alcohol and Genetics; GLGC, Global Lipids Genetics Consortium; GIANT, Genetic Investigation of Anthropocentric Traits.

**Table 2** Results from two sample MR

Cancer	Method	Numbers of SNPs	P value	OR	95% CI
Lung cancer	MR-Egger	14	0.375	0.002	2.01E–09 to 1,355.308
	Weighted median	14	0.034*	0.201	0.046–0.885
	Inverse variance weighted	14	0.012*	0.175	0.045–0.682
Small cell lung cancer	MR-Egger	14	0.777	0.998	0.985–1.012
	Weighted median	14	0.796	1.000	0.998–1.002
	Inverse variance weighted	14	0.900	1.000	0.999–1.001
Lung adenocarcinoma	MR-Egger	14	0.887	3.108	7.18E–07 to 13,449,061.81
	Weighted median	14	0.059	0.139	0.018–1.079
	Inverse variance weighted	14	0.078	0.247	0.052–1.169
Squamous cell lung cancer	MR-Egger	14	0.149	2.36E–06	1.64E–13 to 33.966
	Weighted median	14	0.016*	0.065	0.007–0.605
	Inverse variance weighted	14	0.004*	0.075	0.013–0.429

\*, P value <0.05. MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidential index.

using the package TwoSampleMR (version 0.3.4) in R (version 3.4.2).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

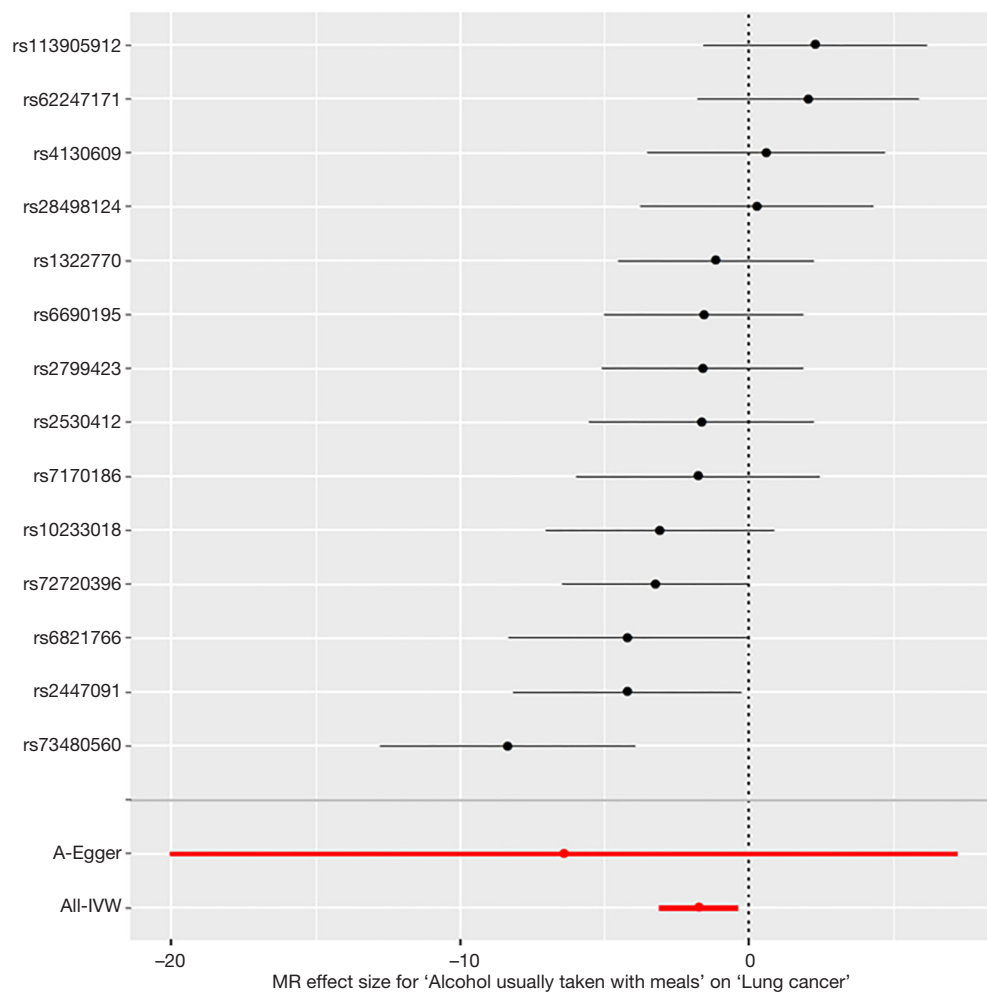
## Results

### *Causal relationships between appropriate alcohol consumption and lung cancer*

The IVW analysis results indicated that habitual appropriate alcohol consumption with meals was a protective factor for lung cancer (OR 0.175, 95% CI: 0.045–0.682, P=0.012)

and lung squamous cell cancer (OR 0.075, 95% CI: 0.013–0.429, P=0.004). However, the two-sample MR results of habitual appropriate alcohol consumption with meals and lung adenocarcinoma (OR 1.000, 95% CI: 0.999–1.001, P=0.900), as well as small cell lung cancer (OR 0.247, 95% CI: 0.052–1.169, P=0.078), did not show causal relationships (Table 2, Figures 1–5).

The heterogeneity study showed that the heterogeneity in the causal relationship analysis between habitual appropriate alcohol consumption with meals and the incidence of lung cancer was high (P=0.033 for Egger, P=0.039 for IVW); however, the heterogeneities in different types of lung cancer were low (P>0.05 for MR-Egger, and



**Figure 1** Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on lung cancer. MR, Mendelian randomization.

IVW) (Table 3). The horizontal pleiotropy study showed that habitual appropriate alcohol consumption with meals did not have multiple effects on other factors of lung cancer ( $P > 0.05$ ) (Table 4). The direction of the causal relationship of all MR analyses showed forward causal relationships ( $P < 0.05$ ) (Table 5).

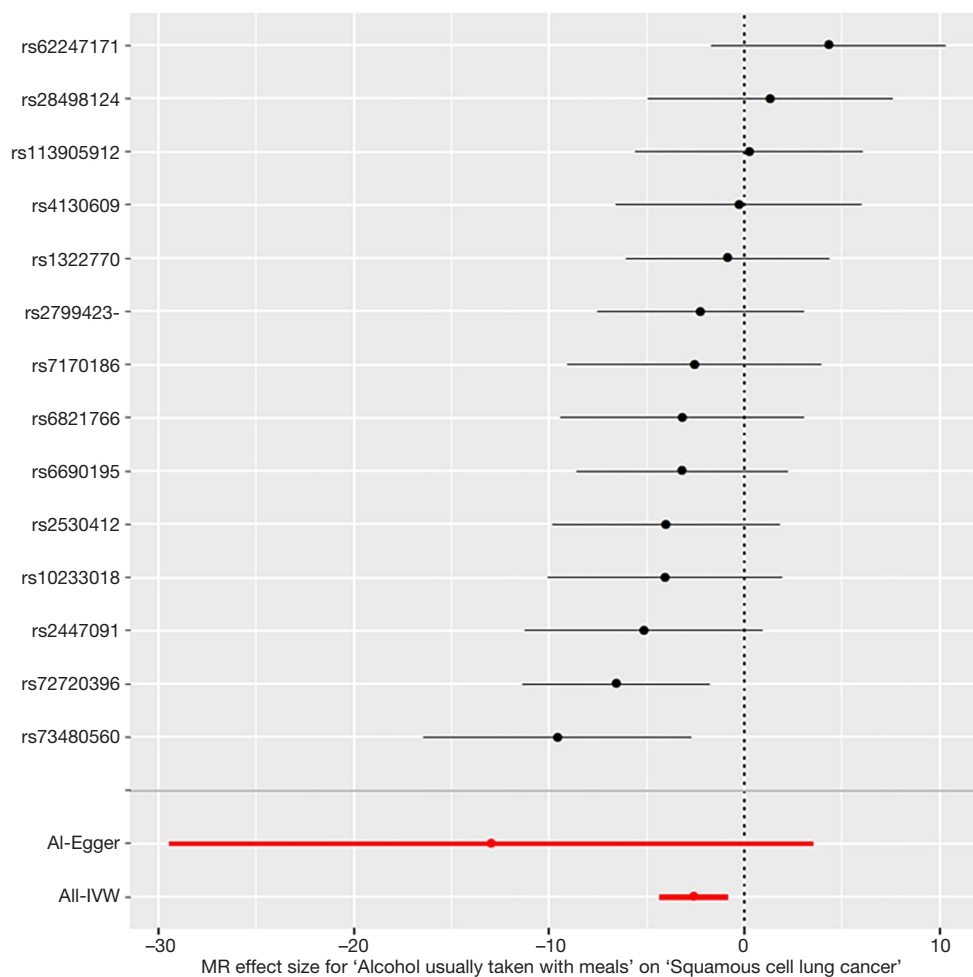
#### **Causal relationship between appropriate alcohol consumption and risk factors**

The MR analyses between habitual appropriate alcohol consumption with meals and other risk factors for lung cancers showed that the former was a protective factor associated with reduce BMI (OR 0.701, 95% CI: 0.577–

0.852,  $P < 0.001$ ) and fewer cigarettes smoked per day (OR 0.002, 95% CI: 3.500E–06 to 0.901,  $P = 0.046$ ). However, other risk factors, including age of smoking initiation (OR 1.140, 95% CI: 0.961–1.354,  $P = 0.133$ ), former *vs.* current smoker (OR 1.778, 95% CI: 0.532–5.949,  $P = 0.350$ ), total cholesterol (OR 0.707, 95% CI: 0.420–1.189,  $P = 0.192$ ), and triglycerides (OR 0.762, 95% CI: 0.542–1.072,  $P = 0.119$ ), did not show significant causal relationships with habitual appropriate alcohol consumption with meals (Table 6).

#### **Discussion**

The results of our MR study verified the causal relationship between habitual appropriate alcohol consumption with



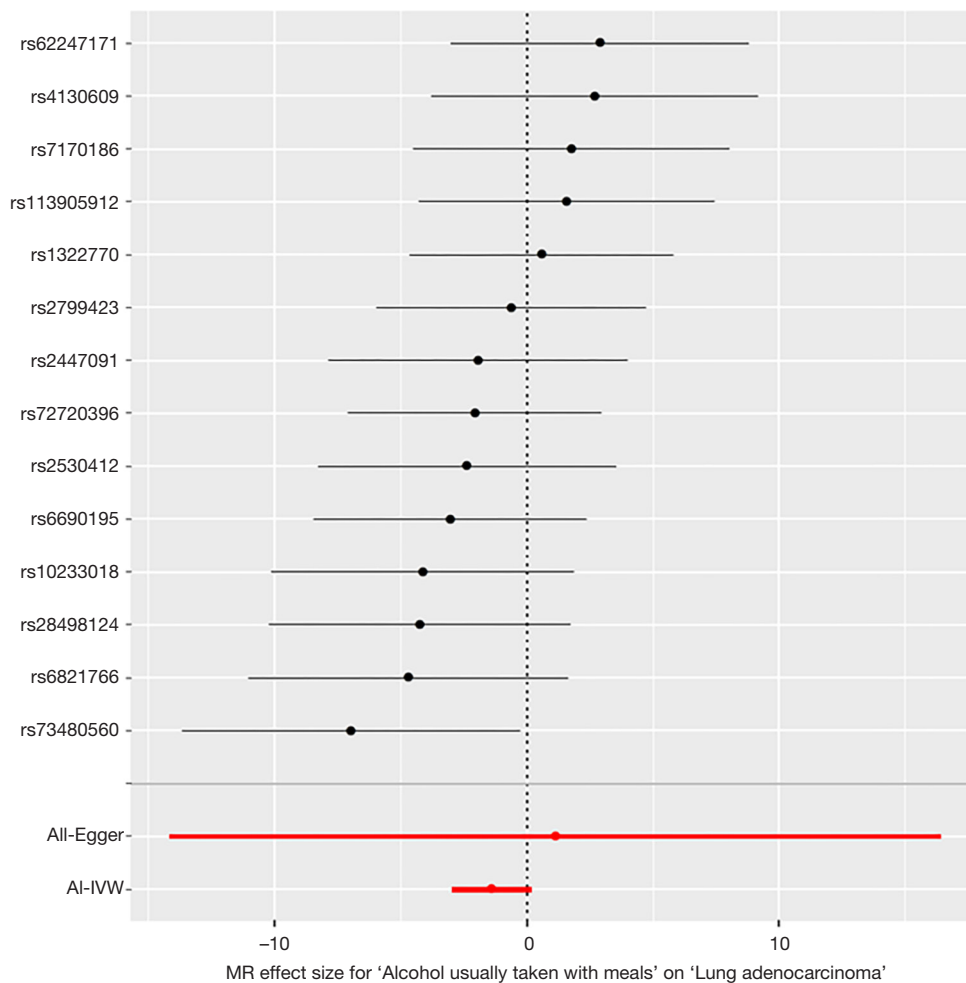
**Figure 2** Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on lung squamous cell cancer. MR, Mendelian randomization.

meals and lung cancer. Several studies have supported the idea that light-to-moderate alcohol consumption could not only decrease the incidence of lung cancer (13,24), but could also benefit lung cancer patients' prognosis. Additionally, light-to-moderate alcohol consumption showed benefits in the studies of many different diseases, including type 2 diabetes (2), arterial hypertension (3), and cardiovascular diseases (4). In this case, we are inclined to conclude that appropriate alcohol consumption is important for health (13,25).

The MR analyses between habitual alcohol consumption with meals and some risk factors for lung cancer demonstrated that this causal relationship probably resulted from the phenomenon that people with this habit care more

about their health by avoiding some risk factors, such as smoking (fewer cigarettes smoked per day) and so on. On the one hand, the deduced effect above seems reasonable when patients are smokers. On the other hand, for non-smoking lung cancer patients, the study conducted by Fehring *et al.* (26) indicated that light-to-moderate alcohol consumers (less than 20 g per day) had lower lung cancer risk than non-drinkers. Furthermore, Garcia Lavandeira *et al.* (27) suggested that the consumption of almost all kinds of alcohol, except spirits, posed no risk to lung cancer patient survival.

To explore the mechanism, we hypothesized that flavonoids found in wine may reduce the risk of some cancers. Support for a beneficial role of flavonoids is



**Figure 3** Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on lung adenocarcinoma. MR, Mendelian randomization.

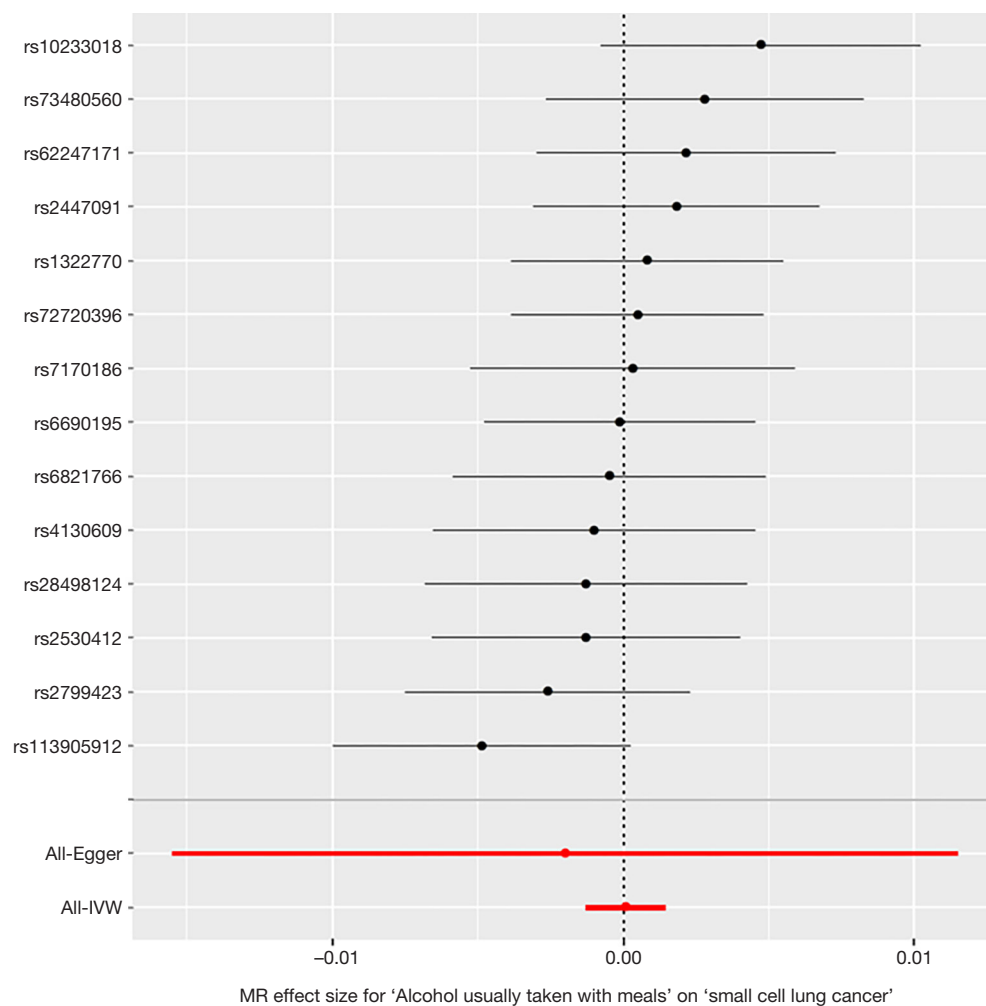
provided by several studies where higher dietary intake of flavonoids (including flavonols, flavanones and quercetin) was inversely associated with lung cancer risk (28).

For these SNPs included in our MR study, rs4130609 reflected single nucleotide variation in *SOX5* gene, which reduced expression by alcohol exposure (29). Moreover, rs113905912 represented single nucleotide variation in *KMT2E* gene, and the mutation of this gene was associated with various diseases, such as some intellectual disability disorders (30), leukemia (31), and vasculopathy (32). Besides, rs62247171 meant Single nucleotide variation in *FOXP1* gene, which could be also related to multiple sclerosis (33), and ischemic stroke (33).

The MR results showed that habitual alcohol

consumption with meals had an inverse effect on BMI. The study conducted by Arif *et al.* (1) also demonstrated that compared with nondrinkers, subjects with moderate alcohol consumption (fewer than 5 drinks per week) had a lower BMI. One interesting MR study (34) indicated that regular light-to-moderate alcohol consumption could increase high-density lipoprotein and reduce total glycerides, total cholesterol, and low-density lipoprotein, and according to previous studies, these lipid indicators were associated with lung cancer (35,36).

Randomized controlled trials (RCTs) are widely accepted to verify causality, but they are associated with a high cost. Because of the consistently long latency between the exposures and the occurrence of diseases, it is impractical



**Figure 4** Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on small cell lung cancer. MR, Mendelian randomization.

and impossible to investigate all these causal associations through RCTs. However, in MR, genetic markers are used as variables of exposure instead of the exposure itself to facilitate causal inference (37). This method is rarely affected by confounding, reverse causality, and measurement error (38). Additionally, we can implement MR design by using two-sample MR analysis based on published summary data from large-scale GWASs, which greatly increases the scope and statistical power of MR studies (39,40).

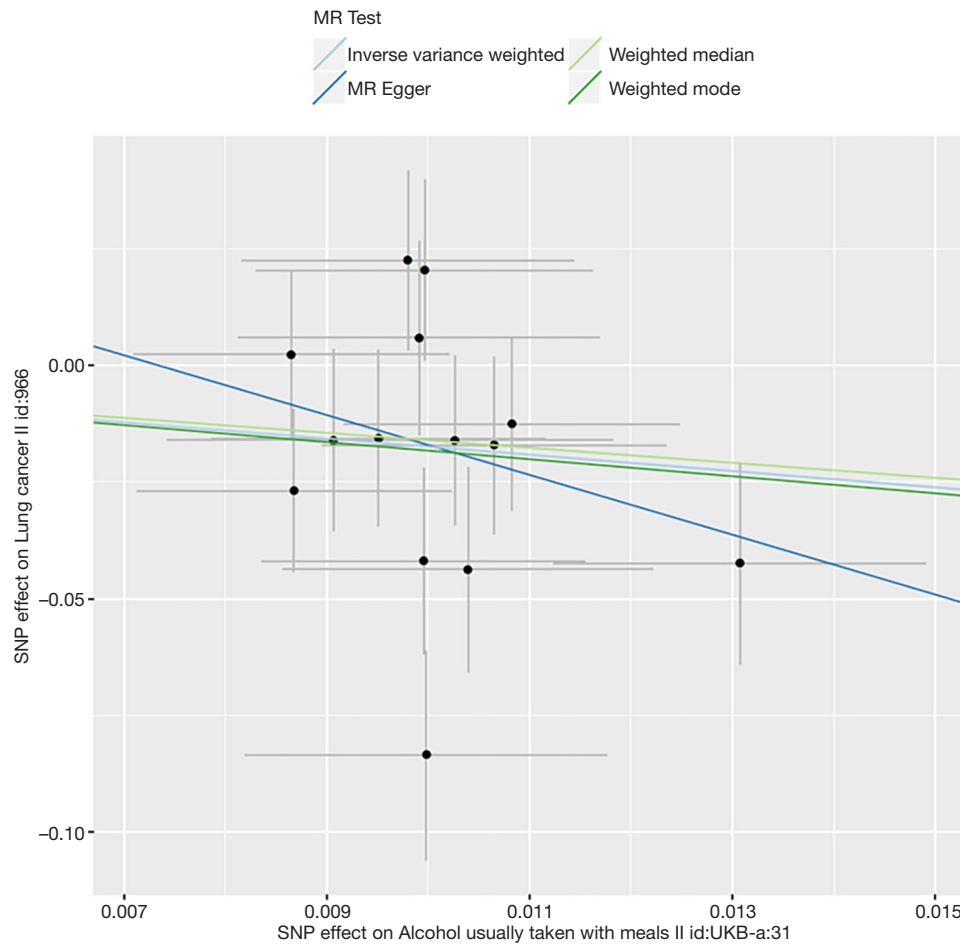
Our study is the first MR study about alcohol consumption habits (alcohol habitually consumed with meals) and lung cancer. Participants were grouped based on their randomly allocated genotype, mimicking an RCT. However, limitations still exist in our study. First, all the

participants included in our study were of European origin. Thus, whether the results can be generalized to other populations still needs to be studied and verified. Moreover, the summary data we used for two-sample MR did not allow for stratified analyses by covariates of interests, such as age and smoking status.

## Conclusions

Habitual alcohol consumption with meals has a causal relationship with lung cancer. Furthermore, more work is needed to elucidate the potential mechanisms that mediate the associations between habitual alcohol consumption with meals and lung cancer.





**Figure 5** Scatter plots of genetic associations with alcohol usually taken with meals against the genetic associations with lung cancer. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

**Table 3** Heterogeneity tests

Cancer	Method	Q	Q_df	P value
Lung cancer	MR-Egger	22.379	12	0.033*
	Inverse variance weighted	23.229	13	0.039*
Small cell lung cancer	MR-Egger	10.322	12	0.588
	Inverse variance weighted	10.414	13	0.660
Lung adenocarcinoma	MR-Egger	12.042	12	0.442
	Inverse variance weighted	12.148	13	0.516
Squamous cell lung cancer	MR-Egger	14.548	12	0.267
	Inverse variance weighted	16.411	13	0.228

\*, P value <0.05. MR, Mendelian randomization.



**Table 4** Test for directional horizontal pleiotropy

Cancer	Egger_intercept	SE	P value
Lung cancer	0.047	0.070	0.512
Small cell lung cancer	2.10E-05	6.91E-05	0.766
Lung adenocarcinoma	-0.025	0.078	0.750
Squamous cell lung cancer	0.105	0.084	0.239

\*, P value <0.05. SE, standard error.

**Table 5** Test that the exposure is upstream of the outcome

Cancer	Snpr2. exposure	Snpr2. outcome	Correct_causal_direction	Steiger_P value
Lung cancer	0.003	0.001	True	0.007*
Small cell lung cancer	0.003	2.31E-05	True	<0.001*
Lung adenocarcinoma	0.003	0.001	True	0.001*
Squamous cell lung cancer	0.003	0.001	True	0.026*

\*, P value <0.05. SNPs, single nucleotide polymorphisms.

**Table 6** Two sample MR of alcohol consumption and risk factors

Risk factors	Numbers of SNPs	P value	OR	95% CI
Age of smoking initiation	8	0.133	1.140	0.961–1.354
BMI	14	<0.001*	0.701	0.577–0.852
Total cholesterol	8	0.192	0.707	0.420–1.189
Triglycerides	8	0.119	0.762	0.542–1.072
Cigarettes smoked per day	8	0.046*	0.002	3.50E-06 to 0.901
Former vs. current smoker	8	0.350	1.778	0.532–5.949

\*, P value <0.05. MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidential index; BMI, body mass index.

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**Conflicts of Interest:** All authors have completed the ICMJE

uniform disclosure form (available at: <http://dx.doi.org/10.21037/atm-20-3063>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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