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Alcohol intake and risk of rheumatoid arthritis: a Mendelian randomization study

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00393-018-0537-z) includes supplementary data. The data is available at http://www.springermedizin.de/zeitschrift-fuer-rheumatologie. It can be found at the end of the article under "Supplementary material".

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial joint inflammation that leads to disability and a decreased quality of life. Although the etiology of RA is not fully understood, environmental factors likely play an important role in the development of RA in genetically susceptible individuals [9, 18].

Many environmental factors have been suspected of inducing RA, but their role remains poorly understood. Among these, alcohol intake has been identified as a preventive factor, but the findings regarding its effect on RA development have been inconsistent [15, 22]. Alcohol contains components such as ethanol and antioxidants, which suppress the immune response and decrease the synthesis of proinflammatory cytokines, such as tumor necrosis factor, interleukin-6 (IL-6), and IL-8 [28]. Previous meta-analyses of observational studies have shown that alcohol consumption was inversely associated with the risk of RA [15, 22]. However, observational studies are prone to bias, such as reverse causation and residual confounding, thereby precluding a clear understanding of the effect of alcohol intake on RA [14, 19].

Mendelian randomization (MR) is a technique that uses genetic variants as instrumental variables (IVs) to assess whether an observational association between a risk factor and an outcome is consistent with a causal effect [6]. A two-sample MR estimates causal effects where data on the exposure and outcome have been measured in different samples [17]. This approach is very useful in situations where it is difficult to measure the exposure and outcome in the same set of individuals [17]. No previous study has used the MR approach to test the causal effect of alcohol intake on the risk of RA. Thus, the aim of this study was to examine whether alcohol intake is causally associated with occurrence of RA using a two-sample MR analysis.

Materials and methods

Data sources and selection of genetic variants

We searched the MR Base database (http://www.mrbase.org/), which houses a large collection of summary statistic data from hundreds of genome-wide association studies (GWASs). We used the publicly available summary statistics datasets of GWASs for alcohol intake frequency (increase) from the 500,000 individuals included in the UK Biobank ($n = 336{,}965$; https://github.com/Nealelab/UK_Biobank_GWAS) as the exposure. A two-sample MR study of genetic variants associated with alcohol intake was used as the IV to improve inference based on linkage disequilibrium (LD) R^2 of 0.001, clumping distance of 10,000 kb, and p-value threshold of 5.00E-08 (genome-wide significance). We obtained summary statistics (beta coefficients and standard errors) for 24 single-nucleotide polymorphisms (SNPs) associated with alcohol intake frequency as the IVs from GWASs from the UK Biobank. We used a GWAS meta-analysis of 5539 autoantibody-positive individuals with RA and 20,169 controls of European descent [25] as the outcome.

Statistical analysis for Mendelian randomization

MR analysis requires genetic variants to be related to, but not potential confounders of an exposure [5]. First, we assessed the independent association of SNPs with alcohol intake frequency. Second, we examined the association between each SNP and risk of RA. Third, we combined these findings to estimate the uncompounded causal association between alcohol intake frequency and risk of RA using MR analysis. We performed two-sample MR, a method used to estimate the causal effect of an exposure (alcohol intake) on outcomes (RA) using summary statistics from different GWASs [11], to assess the causal relationships between alcohol intake frequency and risk of RA, using summary data from alcohol intake frequency and RA GWASs with 24 SNPs as IVs (**Table 1**).

Table 1 Instrumental SNPs associated with alcohol intake and RA GWASs

Instrumental SNP	Gene	Chromosome loci	Effect allele	Exposure (alcohol intake)			Outcome (RA)		
				Beta	SE	*p*-value	Beta	SE	*p*-value
rs11039429	NUP160	11	T	–0.025	0.004	1.67E-12	–0.041	0.021	0.061
rs11787216	AC138647.1	8	T	0.025	0.004	1.70E-11	0.039	0.025	0.099
rs11940694	KLB	4	G	–0.043	0.004	1.75E-32	–0.010	0.043	0.820
rs1260326	GCKR	2	C	–0.048	0.004	7.60E-40	0.030	0.026	0.213
rs13102973	PABBPC4L	4	C	–0.021	0.004	1.59E-08	0.010	0.026	0.700
rs13231886	ZM1Z2	7	A	–0.020	0.004	4.92E-08	–0.020	0.026	0.427
rs13390019	ANKRD36	2	C	0.029	0.005	3.33E-08	–0.030	0.045	0.493
rs17097556	ZRANB2-AS2	1	G	–0.025	0.005	4.19E-08	–0.010	0.021	0.637
rs17690703	MAPT-AS1	17	T	0.027	0.004	3.64E-11	–0.010	0.021	0.656
rs1788030	TCF4	18	T	0.020	0.004	1.29E-08	0.030	0.027	0.279
rs1893659	C180rf8	18	A	–0.031	0.004	1.27E-17	–0.051	0.027	0.056
rs2159935	KZT	4	A	–0.021	0.004	5.74E-09	–0.051	0.024	0.031
rs363096	HTT	4	C	–0.023	0.004	8.58E-11	0.010	0.021	0.608
rs4726481	MGAM	7	T	0.022	0.004	7.89E-10	–0.010	0.021	0.621
rs540606	SZX3	2	G	–0.023	0.004	2.14E-10	0.030	0.024	0.197
rs571312	MC4R	18	A	0.027	0.004	1.78E-10	–0.030	0.032	0.311
rs58905411	CBX5	12	A	–0.030	0.004	9.32E-17	–0.010	0.039	0.793
rs6016781	SAMHD1	20	T	–0.022	0.004	1.77E-09	–0.020	0.021	0.336
rs650558	MLX	17	T	0.023	0.004	1.04E-08	–0.020	0.026	0.455
rs7428430	SEMA3F-AS1	3	T	–0.023	0.004	7.94E-11	0.010	0.038	0.795
rs838145	IZUMD1	19	A	0.024	0.004	2.39E-11	0.020	0.026	0.403
rs9372625	MMS22L	6	A	–0.028	0.004	4.33E-14	–0.041	0.027	0.131
rs9842406	FOXP1	3	G	–0.025	0.004	3.36E-12	0.010	0.025	0.709
rs9923768	RBFOX1	16	A	–0.021	0.004	7.14E-09	0.020	0.031	0.498

SNP single nucleotide polymorphism, *GWAS* genome-wide association study, *Beta* beta coefficient, *SE* standard error, *RA* rheumatoid arthritis

Table 2 The MR estimates from each method of assessing the causal effect of alcohol intake on the risk of rheumatoid arthritis (RA)

MR method	Number of SNPs	Beta	SE	95% confidence interval	Association *p*-value	Cochran Q statistic	I^2	Heterogeneity *p*-value
Inverse variance weighted	24	0.218	0.213	–0.221 to 0.657	0.306	24.7	0.069	0.367
MR Egger	24	–0.778	0.947	–2.737 to 1.181	0.420	24.5	0.061	0.321
Weighted median	24	–0.286	0.302	–0.911 to 0.339	0.344	25.8	0.109	0.311[a]

MR Mendelian randomization, *SNP* single nucleotide polymorphism, *Beta* beta coefficient, *SE* standard error
[a]Maximum likelihood method, $I^2 = (Q - df) / Q$ [13]

The IVW method uses a meta-analysis approach to combine the Wald ratio estimates of the causal effect obtained from different SNPs and provide a consistent estimate of the causal effect of the exposure on the outcome when each of the genetic variants satisfies the assumptions of an instrumental variable [21]. Although the inclusion of multiple variants in an MR analysis results in increased statistical power, it has the potential to include pleiotropic genetic variants that are not valid IVs [11]. To explore and adjust for pleiotropy, i. e., the association of genetic variants with more than one variable, the weighted median and MR-Egger regression methods were utilized. MR-Egger regression analysis, which is robust to invalid instruments, tests and accounts for the presence of unbalanced pleiotropy by introducing a parameter for this bias by incorporating summary data estimates of causal effects from multiple individual variants [1]. MR-Egger applies a weighted linear regression of the gene-outcome coefficients on the gene-exposure coefficients [1]. The slope of this regression represents the causal effect estimate, and the intercept can be interpreted as an estimate of the average horizontal pleiotropic effect across the genetic variants [8]. The weighted median estimator provides a consistent estimate of the causal effect, even when up to 50% of the information contributing to the analysis comes from genetic variants that are invalid IVs [2]. The weighted median estimator has the advantage of retaining greater precision in the estimates compared to the MR-Egger analysis [2]. Tests were considered statistically significant at $p < 0.05$. All

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Alcohol intake and risk of rheumatoid arthritis: a Mendelian randomization study

Abstract

Objective. To examine whether alcohol intake is causally associated with rheumatoid arthritis (RA).
Methods. We performed a two-sample Mendelian randomization (MR) analysis using the inverse-variance weighted (IVW), weighted median, and MR-Egger regression methods. We used the publicly available summary statistics of alcohol intake frequency from the UK Biobank genome-wide association studies (GWASs; $n = 336{,}965$) as the exposure and a GWAS meta-analysis of 5539 autoantibody-positive RA patients and 20,169 controls as the outcome.
Results. We selected 24 single nucleotide polymorphisms (SNPs) associated with alcohol intake frequency at genome-wide significance as instrumental variables (IVs) to improve inference, 16 of which were inversely associated with RA. The IVW method showed no evidence of a causal association between alcohol intake and RA (beta = 0.218, SE = 0.213, $p = 0.306$). The MR-Egger regression revealed that directional pleiotropy was unlikely to bias the result (intercept = 0.027, $p = 0.292$). The MR-Egger analysis and the weighted median approach showed no causal association between alcohol intake and RA (beta = –0.778, SE = 0.947, $p = 0.420$ and beta = –0.286, SE = 0.302, $p = 0.344$, respectively). Cochran's Q test did not indicate heterogeneity between IV estimates based on the individual variants, and results from a "leave-one-out" analysis demonstrated that no single SNP was driving the IVW point estimate.
Conclusion. The MR analysis does not support a causal inverse association between alcohol intake and RA occurrence.

Keywords

Alcohol intake · Rheumatoid arthritis · Mendelian randomization · Genetic predisposition to disease · Genome-wide association study

Alkoholkonsum und Risiko der rheumatoiden Arthritis: eine Mendel-Randomisierungsstudie

Zusammenfassung

Ziel. In der vorliegenden Studie wurde untersucht, ob Alkoholkonsum kausal mit der rheumatoiden Arthritis (RA) zusammenhängt.
Methoden. Es wurde eine Zwei-Stichproben-Mendel-Randomisierungs(MR)-Analyse mit Inverse-Varianz-Gewichtung (IVG), gewichtetem Median und MR-Egger-Regression durchgeführt. Dafür herangezogen wurden die öffentlich zugänglichen statistischen Kennzahlen zur Häufigkeit des Alkoholkonsums aus den genomweiten Assoziationsstudien (GWAS) der UK Biobank ($n = 336.965$) für die Exposition sowie eine GWAS-Metaanalyse von 5539 Autoantikörper-positiven Patienten mit RA und 20.169 Kontrollpersonen für das Outcome.
Ergebnisse. Insgesamt 24 Einzelnukleotid-polymorphismen (SNP), die mit genomweiter Signifikanz mit der Häufigkeit des Alkoholkonsums assoziiert waren, wurden als Instrumentvariablen (IV) ausgewählt, um bessere Schlussfolgerungen zu ermöglichen. Von diesen waren 16 invers mit RA assoziiert. Die IVG-Methode ergab keinen Hinweis auf einen kausalen Zusammenhang zwischen Alkoholkonsum und RA (beta = 0,218, SE = 0,213, $p = 0{,}306$). Die MR-Egger-Regression zeigte, dass eine Verzerrung des Ergebnisses durch eine gerichtete Pleiotropie unwahrscheinlich war (Achsenabschnitt =0,027, $p = 0{,}292$). Die MR-Egger-Analyse und der Ansatz mit gewichtetem Median ergaben keinen kausalen Zusammenhang zwischen Alkoholkonsum und RA (beta = –0,778, SE = 0,947, $p = 0{,}420$ bzw. beta = –0,286, SE = 0,302, $p = 0{,}344$). Der Cochran-Q-Test wies nicht auf eine Heterogenität zwischen IV-Schätzungen auf Grundlage der individuellen Varianten hin, und eine Leave-one-out-Analyse zeigte, dass nicht ein einzelner SNP die IVG-Punktschätzung bestimmte.
Schlussfolgerung. Die MR-Analyse stützt eine kausale inverse Assoziation zwischen Alkoholkonsum und dem Auftreten einer RA nicht.

Schlüsselwörter

Alkoholkonsum · Rheumatoide Arthritis · Mendel-Randomisierung · Genetische Krankheitsdisposition · Genomweite Assoziationsstudie

MR analyses were performed in the MR Base platform (App version: 1.2.1 e646be (27 June 2018), R version: 3.5.0; ESM 1, Supplementary data: Analysis R code for two-sample MR.; [12]).

Heterogeneity and sensitivity test

We assessed heterogeneities between SNPs using Cochran's Q-statistics [10] and I^2 statistic [3, 13]. We also performed a "leave-one-out" analysis to investigate the possibility that the causal association was driven by a single SNP.

Results

Studies included in the meta-analysis

Instrumental variables for Mendelian randomization

We selected 24 independent SNPs from alcohol intake GWASs as the IVs. All of them are associated with alcohol intake frequency at genome-wide significance (**Table 1**; **Fig. 1**). Sixteen of the 24 SNPs were inversely associated with RA, and the association with rs2159935 was statistically significant (**Table 1**; ESM 2, Supplementary data: Original and harmonized datasets). In all, 0.5% of variance in the exposure (value of R^2 statistic) was explained by the genetic variants serving as IVs.

Mendelian randomization results

The IVW method found no evidence to support a causal association between alcohol intake and RA (beta = 0.218, SE = 0.213, $p = 0.306$; **Table 2**; **Figs. 1 and 2**). The intercept represents the average pleiotropic effect across the ge-

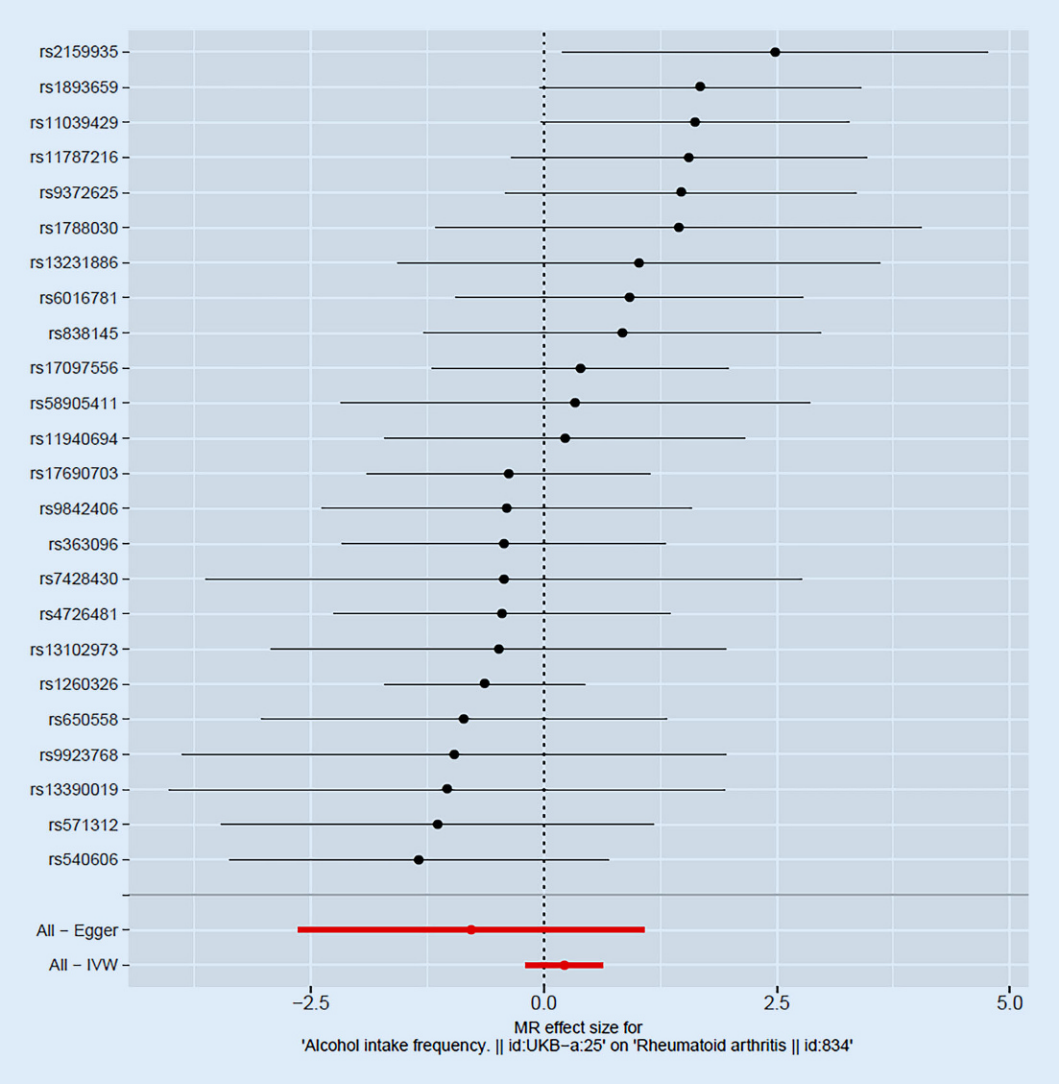

Fig. 1 ◀ Forest plot of the causal effects of alcohol intake-associated single nucleotide polymorphisms (SNPs) on rheumatoid arthritis (RA)

netic variants, i. e., the average direct effect of a variant with the outcome. If the intercept is not zero (the MR-Egger test), there is evidence of directional pleiotropy. The MR-Egger regression revealed that directional pleiotropy was unlikely to be biasing the result (intercept = 0.027, $p = 0.292$). The MR-Egger analysis found no causal association between alcohol intake and RA (beta = –0.778, SE = 0.947, $p = 0.420$; **Table 2**; **Fig. 2**). The weighted median approach did not provide evidence of a causal association between alcohol intake and RA either (beta = –0.286, SE = 0.302, $p = 0.344$; **Table 2**; **Fig. 2**). IVW was positive, while the more robust estimates were negative. However, they did not still differ significantly between each other based on the confidence intervals (**Table 2**).

Heterogeneity and sensitivity test

Cochran's Q test and the funnel test indicated no evidence of heterogeneity between IV estimates based on the individual variants (**Table 2**). Heterogeneity is the variability in the causal estimates obtained for each SNP (i. e. how consistent is the causal estimate across all SNPs). Low heterogeneity suggests increased reliability of MR estimates. Our results of I^2 values showed low heterogeneity, indicating increased reliability of MR estimates (**Table 2**). Results from the "leave-one-out" analysis demonstrated that no single SNP was driving the IVW point estimate. The MR estimates generated using IVW, weighted median, and MR-Egger regression analyses were consistent. Therefore, the MR analysis results do not support a causal association between alcohol intake and RA.

Discussion

We used three different estimation methods for the MR analyses: the inverse variance weighting method, the weighted median method, and MR-Egger regression. The MR estimates using all three methods were consistent; they do not support a causal inverse association between alcohol intake and occurrence of RA.

The findings of previous meta-analyses have reported a protective effect of alcohol on RA. An inverse relationship between alcohol intake and RA risk is bio-

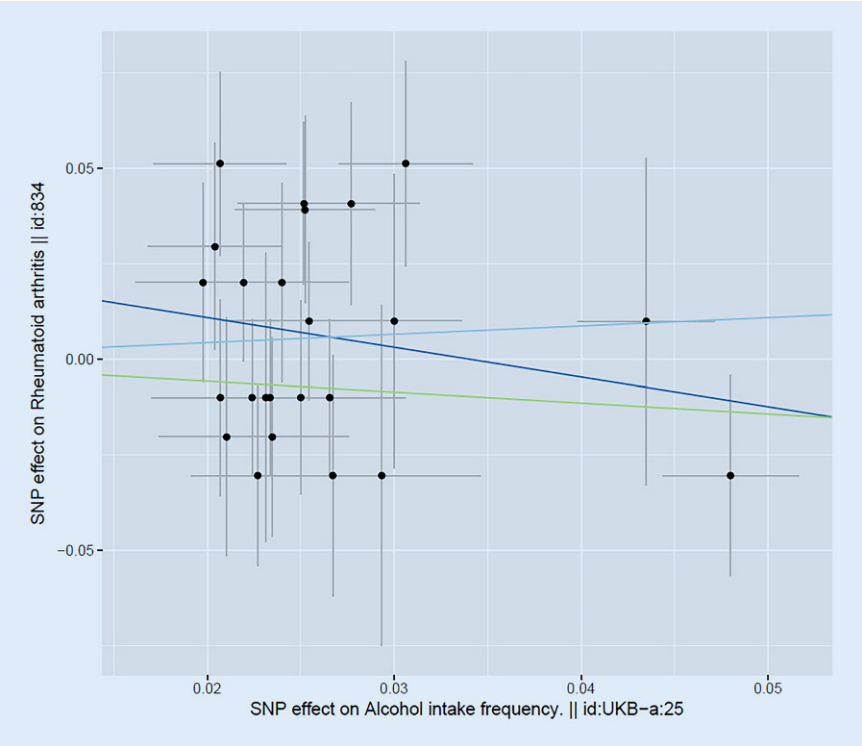

Fig. 2 ▲ Scatter plots of genetic associations with alcohol intake against the genetic associations with rheumatoid arthritis (RA). The slopes of each line represent the causal association for each method. The *blue line* represents the inverse-variance weighted (IVW) estimate, the *green line* represents the weighted median estimate, and the *dark blue line* represents the MR-Egger estimate. *SNP* single nucleotide polymorphism

logically plausible. Alcohol inhibited the onset of collagen-induced inflammatory arthritis through downregulating leukocyte migration and reducing nuclear factor-κB (NF-κB) activation [16]. Alcohol was also shown to have anti-inflammatory effects in humans through reducing NF-kB-driven inflammatory mediator production by monocytes, which is a key cellular pathway in RA [20].

A meta-analysis demonstrated that low to moderate alcohol consumption may reduce the risk of developing RA in a dose-dependent manner, indicating the existence of a J-shaped nonlinear trend between alcohol consumption and risk of RA [15]. However, individuals with low to moderate alcohol intake have healthier lifestyles compared with complete abstainers, and RA could therefore result from confounding lifestyle factors. Another meta-analysis found that alcohol intake is inversely associated with anti-citrullinated protein antibody (ACPA)-positive RA [22]. However, this result was obtained only from retrospective case–control studies, which are subject to both selection and recall bias; thus, there is a high possibility the finding was affected by bias.

MR minimizes the possibility of bias inherent to observational studies due to residual confounding or reverse causality [23]. However, MR studies are susceptible to bias from pleiotropy (association of genetic variants with more than one variable) [27]. Although the inclusion of multiple variants in MR analysis typically leads to increased statistical power, it also results in the potential inclusion of pleiotropic genetic variants that are not valid IVs [24]. To eliminate pleiotropy, we employed a weighted median estimator, which provides valid estimates even if 50% of the SNPs are not valid instruments [2], and we used MR-Egger regression to provide a test for unbalanced pleiotropy and a causal estimate of the influence of the exposure on the outcome in its presence [1]. The MR-Egger approach showed no evidence of unbalanced pleiotropy, as indicated by the intercept *p*-value. The MR-Egger analysis results in a loss of precision and power, but our weighted median estimator results were similar to the IVW estimator, providing additional confidence in these associations. Our data do not support a causal association between alcohol intake and RA risk. Previously reported associations between alcohol intake and occurrence of RA may be the result of bias or confounding factors inherent to observational studies, such as misclassification of alcohol consumption, reverse causation, a small number of studies of small sizes, recall bias, and selection bias.

The present study has several limitations. First, our analysis included a relatively small number of SNPs as IVs and might have had limited power to detect an association. The statistical power can be increased, and a more precise causal estimate can be obtained by combining multiple genetic variants together [7]. Second, most genetic variants only have a modest effect on a given exposure, because genetic variants might only explain a very small proportion of variance in a particular exposure [26]. Explaining 0.5% of variance in the exposure is a small value, as also the number of 24 SNPs we used as IVs is quite small. We estimated study power to test whether our study was adequately powered to detect clinically relevant changes in RA risk [4]. The power of the MR analysis had a limited power (0.6). This means that very large numbers of cases are required to detect a causal relationship for the outcome of interest. Third, the RA studies were based on participants of European ancestry. As causality may depend on ethnicity and selection bias, further MR studies involving other populations are needed to account for this. Fourth, only autoantibody-positive individuals with RA were included in this MR analysis. Thus, the causal association between alcohol intake and RA risk should also be explored in autoantibody-negative RA patients. Nevertheless, this meta-analysis has its strengths. Although alcohol has been studied as a potential protective factor for RA, an MR has never been performed. This is the first such study on the causal relationship between alcohol intake and RA.

In conclusion, the MR analysis results do not support a causal association between alcohol intake and RA risk. Epidemiological evidence for an inverse association of alcohol intake with a lower risk of RA does not appear to be causal. However, well-designed epidemiological studies and MR studies using more variants that account for a larger proportion of alcohol consumption are warranted to confirm or rule out causality.

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Compliance with ethical guidelines

Conflict of interest. S.-C. Bae and Y. H. Lee declare that they have no competing interests.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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