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Impact of Alcohol Consumption on Lifespan: a Mendelian randomization study in Europeans

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Alcohol is widely used but recognized as a risk factor for several adverse health outcomes based on observational studies. How alcohol affects lifespan remains controversial, with no trial to make such an assessment available or likely. We conducted a Mendelian randomization (MR) to assess the effect of alcohol on lifespan in men and women, including a possible role of smoking and education. Strong ($p < 5e^{-8}$), independent ($r^2 < 0.001$) genetic predictors of alcohol consumption in 2,428,851 participants of European ancestry from the Sequencing Consortium of Alcohol and Nicotine use (GSCAN) consortium genome wide association study (GWAS) were applied to sex-specific GWAS of lifespan (paternal and maternal attained age) and age at recruitment to the UK Biobank. We used multivariable MR to allow for smoking and education, with systolic and diastolic blood pressure as control outcomes. Inverse variance weighted was the primary analysis with sensitivity analysis. Alcohol consumption decreased lifespan overall (− 1.09 years (logged alcoholic drinks per week), − 1.89 to − 0.3) and in men (− 1.47 years, − 2.55 to − 0.38), which remained evident after adjusting for smoking (− 1.81 years, − 3.3 to − 0.32) and education (− 1.85 years, − 3.12 to − 0.58). Estimates from sensitivity analysis were similar, and when using the genetic variant physiologically associated with alcohol use. Alcohol consumption was associated with higher blood pressure as expected. Our study indicates that alcohol does not provide any advantages for men or women but could shorten lifespan. Appropriate interventions should be implemented.

Keywords Alcohol consumption, Mendelian randomization, Lifespan, Sex differences

Abbreviations

CI	Confidence interval
HR	Hazard ratio
SD	Standard deviation
MR	Mendelian Randomization
IV	Instrument variable
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
BMI	Body mass index
BOLT-LMM	Bolt liner mixed model
IVW	Inverse variance weighting
GWAS	Genome-wide association study
GSCAN	GWAS and Sequencing Consortium of Alcohol and Nicotine use
GLGC	Global Lipids Genetics Consortium
ICBP	International Consortium of Blood Pressure
SSGAC	Social Science Genetic Association Consortium
WM	Weighted median

Alcohol, as a psychoactive drug, has a long history of use in human culture. Globally alcohol consumption varies considerably with cultural norms, alcohol tolerance and gender. Alcohol consumption is one of the four target behaviors proposed by the World Health Organization (WHO) in 2014 as harmful to health and in need of change [1]. Nevertheless, controversy remains about the role of alcohol [2] particularly at older ages, where alcohol appears to protect against all-cause mortality, despite being harmful at younger ages [3]. No trials of the

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effects of use of alcohol on mortality have been conducted or are likely to be conducted given alcohol is a known carcinogen [4] although a large-scale trial would be definitive [5].

Observational evidence has expanded our knowledge about the role of alcohol in all-cause mortality [6], but is open to confounding and selection bias. Confounding is pervasive and pernicious, particularly for behaviours which may be strongly socially patterned, such as physical activity, alcohol consumption, smoking and diet. For example, observationally moderate alcohol consumption is associated with better health, however people who alcohol drink moderately may have many other moderate and possibly health-giving habits [7]. Notably, the benefits of moderate alcohol consumption sometimes extend to occasional drinkers, suggesting the benefits could be due to the attributes of the drinkers rather than of the alcohol [8]. Moreover, associations changing with age, such as the effect of alcohol appearing beneficial at specifically older ages [3], could be a manifestation of survival bias [9]. With age participants are increasingly strongly selected survivors of lifelong habits, such as alcohol consumption, leading to depletion of the susceptibles, which can make harmful exposures look protective in old age because the study is missing all those who have already died because of the exposure [10]. Finally, alcohol consumption tends to be greater in men than women [11–13], whether alcohol consumption is a modifiable contributor to shorter lives in men than women has rarely been considered.

Mendelian randomization (MR) studies, which use genetic variants (typically single nucleotide polymorphisms (SNPs) to reduce confounding [14]), have provided valuable insights about disease specific effects of alcohol [15–17]. MR studies have rarely addressed the effect of alcohol consumption on all-cause mortality, when the key question is whether benefits for cardiovascular disease outweigh the known harms of alcohol [18]. Moreover, all-cause mortality as an outcome is open to selection bias because it misses those who died early (i.e., before recruitment) which can exaggerate the benefits of alcohol [19]. Instead, we used parental lifespan which may reduce such selection bias [19]. Lifespan was based on parental attained age, as previously [20], because it has more power than participant lifespan. Using parental attained age has much more variability because there is a greater range in parental current age or age at death. In addition, to address selection bias further we also assessed death before recruitment from alcohol use, by examining effects on early deaths using a longevity design, as previously [21,22]. Given, men and women differ in alcohol consumption and lifespan we considered them separately and adjusted for possible confounders, such as education and smoking. Finally, we used well-established consequences of alcohol consumption as positive control outcomes, i.e., systolic blood pressure (SBP) and diastolic blood pressure (DBP) [23].

Methods

Study design

We used an MR study to assess causal effects of alcohol consumption on lifespan based on mother's and father's attained age (current age or age at death) in the UK Biobank, and age at recruitment to the UK Biobank in men and women (Fig. 1). The UK Biobank is a study of > 500,000 adults recruited at 22 centers in Great Britain in 2006-10, average age ~ 57 years with slightly more women than men [24,25]. Two types of closely related genotyping arrays were used in the UK Biobank: UK BiLEVE and UK Biobank Axiom [26]. We obtained genetic predictors of alcohol consumption in logged alcoholic drinks per week (mean number of alcoholic drinks per week: 1.93, SD: 3.41) from a genome wide association study (GWAS) from the Sequencing Consortium of Alcohol and Nicotine use (GSCAN) study. GSCAN is a meta-analysis of GWAS of substance use (including smoking and alcohol consumption) among participants mostly of European ancestry (79%) [27], and among those of European descent, approximately 70% are from 23andme and 17% from the UK Biobank. We used all GSCAN participants of European descent ($n = 2{,}428{,}851$) in univariable MR and UK Biobank participants only in multivariable analysis allowing for confounding by smoking and education. Given the possibility of bias from overlapping samples for exposure and outcome we compared univariable estimates using all GSCAN and GSCAN excluding 23andme and GSCAN excluding both 23andme and UK Biobank. Additionally, we used one SNP physiologically linked to alcohol use (rs1229984 (*ADH1B*)) which was identified independent of the UK Biobank [28,29]. Detailed information about the studies used is shown in Table 1.

MR studies rely on the assumptions of instrumental variable (IV) analysis, i.e., relevance, independence and exclusion restriction. Relevance requires that the IV predicts the exposure, which was addressed by only using independent genome wide significant genetic predictors. Independence requires no instrument outcome confounding which was addressed by using genetic predictors of the exposure given genetics are much less confounded than observed exposures [30]. We also allowed for potential confounding by adjusting for smoking and socio-economic position. Exclusion restriction requires that the IV is independent of the outcome, given the exposure, which was addressed by sensitivity analysis for genetic pleiotropy and use of lifespan and survival to recruitment to address selection bias.

Exposures

We used strong (p-value $< 5 \times 10^{-8}$), independent ($r^2 < 0.001$, distance < 10000 kb) genetic instruments for alcohol consumption (logged number of alcoholic drinks per week) from several GSCAN based on different combinations of underlying studies (Table 1), sometimes including the UK Biobank. Since alcohol consumption is socially patterned, to give a comprehensive understanding of alcohol use, we also used a genetic variant physiologically related to alcohol consumption in Europeans (rs1229984 in *ADH1B*) as a single genetic instrument, with the association of rs1229984 with alcohol consumption obtained from the corresponding GSCAN. To assess potential bias from overlapping samples we replicated the analysis for alcohol on lifespan using GSCAN excluding 23andme as well as using the version excluding both 23andme and the UK Biobank.

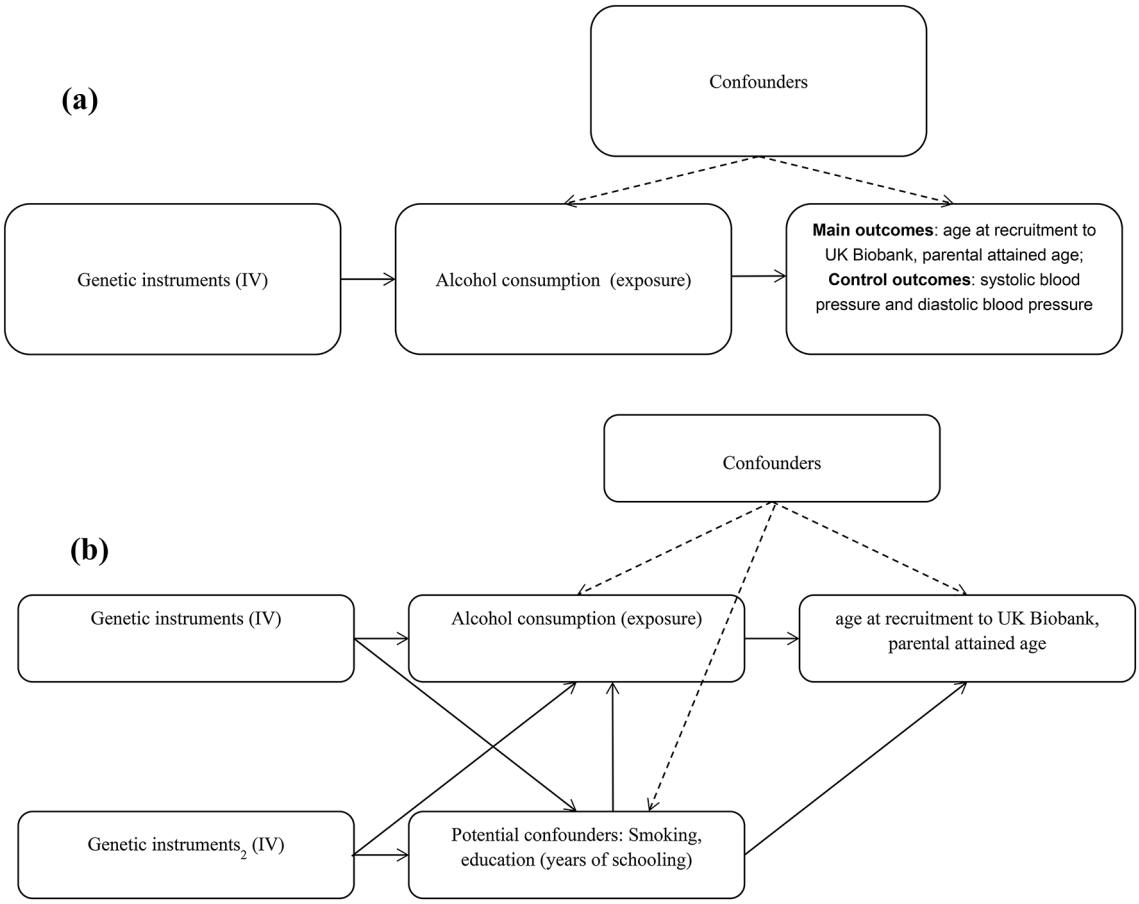

Fig. 1. **a** Using control outcomes to test the validity of the SNPs used in this study. **b** Analytic model of MR analysis in this study.

Outcomes

We obtained quality controlled genetic associations with paternal attained age (317,652 with age at death and 97,659 with current age) and maternal attained age (246,941 with age at death and 165,996 with current age) from the UK Biobank as a measure of lifespan (Table 1) [31], given the heritability of lifespan [32]. To focus on natural deaths mothers/fathers who died before 57/46 years were excluded (due to different age of natural death for men and women). Participants who reported being adopted were also excluded [31]. We converted the log protection ratios into years of life lost by multiplying by -10 and then multiplying by 2.5863 for mothers and 2.2869 for fathers to account for the fact that children only inherit half of each parent's genetic makeup [33]. We obtained quality controlled genetic associations with age at recruitment to the UK Biobank in men and women from the Neale Lab (http://www.nealelab.is/uk-biobank) (Table 1).

Smoking

We assessed the associations of smoking initiation with alcohol consumption, which suggested smoking initiation might confound the relation of alcohol with lifespan (**Supplementary Fig. 1**); so, we adjusted for smoking. Smoking initiation and cigarettes per day were also obtained from several GSCAN ($n = 607,291$ and $n = 249,752$) [34], as shown in Table 1. Some GSCANs include UK Biobank participants.

Potential confounders

We also assessed potential confounding by key socio-economic attributes, taken from the UK Biobank. Alcohol consumption was not confounded by total household income but was by education (**Supplementary Fig. 1**), as expected [35–37]. So, we also adjusted for years of schooling, obtained from the Social Science Genetic Association Consortium (SSGAC) ($n = 766,345$, age older than 30) (Table 1) [38].

Control outcomes

Genetic associations with diastolic blood pressure (DBP) and systolic blood pressure (SBP) ($n = 757,601$; (54.7% women, 61% UK Biobank)) are from the International Consortium of Blood Pressure (ICBP) adjusted for sex, age, age^2 and body mass index (BMI) [39]. Given, adjustment for BMI may bias towards the null if the genetic instruments affect BMI [40], we also used DBP and SBP from the UK Biobank, which provides the largest GWAS without adjustment for BMI (Table 1).

Traits	Data source	UK Biobank overlap	Author, year	Sample size	Ethnicity	Sex	Covariates	Univariable mean F-statistics
Exposures								
Alcohol consumption (logged alcoholic drinks per week)	GSCAN	Yes	Saunders, 2022 [27]	2,428,851	European	Men and women	Principal components	73.5
Alcohol consumption (logged alcoholic drinks per week) (excluding 23andme)	GSCAN	Yes	Liu M, 2019 [34]	335,394	European	Men and women	Principal components	76.2
Alcohol consumption (logged alcoholic drinks per week) (excluding 23andme)	GSCAN	Yes	Saunders, 2022 [27]	666,978	European	Men and women	Principal components	57.5
Alcohol consumption (logged alcoholic drinks per week) (excluding 23andme and UK Biobank)	GSCAN	No	Saunders, 2022 [27]	304,322	European	Men and women	Principal components	59.1
Outcomes								
Age at recruitment	Neale Lab UK Biobank			167,020	White British	Men		
Age at recruitment	Neale Lab UK Biobank			194,174	White British	Women		
Father's attained age	UK Biobank		Pilling LC, 2017 [31]	415,311	European	Men	Age, sex, indicators of assessment center, array type	
Mother's attained age	UK Biobank		Pilling LC, 2017 [31]	412,937	European	Women	Age, sex, indicators of assessment center, array type	
Systolic blood pressure	ICBP		Evangelou E, 2018 [39]	757,601	European	Men and women	Sex, age, age^2, and body mass index (BMI)	
Systolic blood pressure	UK Biobank		Ben Elsworth, 2018	436,419	European	Men and women	Sex and genotyping array (BOLT-LMM) *	
Diastolic blood pressure	ICBP		Evangelou E, 2018 [39]	757,601	European	Men and women	Sex, age, age^2, and body mass index (BMI)	
Diastolic blood pressure	UK Biobank		Ben Elsworth, 2018	436,424	European	Men and women	Sex and genotyping array (BOLT-LMM) *	
Potential confounders								
Cigarettes smoked per day	GSCAN		Liu M, 2019 [34]	249,752	European	Men and women	Principal components	100.2
Smoking initiation	GSCAN		Liu M, 2019 [34]	607,291	European	Men and women	Principal components	42.1
Education (Years of schooling)	SSGAC		Lee JJ., 2018 [38]	766,345	European	Men and women	Principal components	49.0
Household income before tax	UK Biobank		Ben Elsworth, 2018	397,751	European	Men and women	Sex and genotyping array (BOLT-LMM) *	40.8

Table 1. Detailed information on data sources and variables in this study. Abbreviations: GWAS, genome-wide association study; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; GLGC: Global Lipids Genetics Consortium; ICBP: International Consortium of Blood Pressure; SSGAC: Social Science Genetic Association Consortium; BOLT-LMM: Bolt Linear Mixed Model. * account for both relatedness and population stratification.

Statistical analysis

We calculated the univariable F-statistics ($\beta^2/var(\beta)$) as a measure of instrument strength [41] and used the Sanderson–Windmeijer multivariable F-statistic [42]. An F-statistic > 10 is usually taken as adequate [43]. R^2 was estimated as 2*EAF*(1-EAF) *beta^2, where beta is the genetic association with the exposure in SD units and EAF is effect allele frequency [44]. We estimated power using the approximation that the sample size for an MR study is the sample size for exposure on outcome divided by the r^2 for instruments on exposure, using a t-test for continuous outcomes [45], i.e., age at recruitment, and a binomial test [46] for dichotomous outcomes. We also estimated heterogeneity between SNPs from the Cochran's Q statistic [42].

We aligned genetic variants for exposure and outcome across studies and excluded or replaced palindromic variants that could not be unequivocally aligned. Inverse variance weighting (IVW) was the main analysis, complemented by the weighted median and MR-Egger. The weighted median uses the majority of genetic variants to test for a causal effects, and is valid as long as more than 50% of the weight comes from valid genetic variants [47]. The MR-Egger intercept assesses the exclusion restriction assumption due to genetic pleiotropy, assuming the Instrumental Strength Independent of Direct Effect (InSIDE) assumption is fulfilled. Although, we used very large samples, sample overlap could bias the estimates, particularly MR-Egger estimates, towards the confounded estimate when I^2_{GX} is low [48], which we also reported. In addition, we used MRlap to assess any potential bias from using overlapping samples for exposure and outcome.

We used the R packages "TwoSampleMR" (version: 0.5.6), "Mendelian Randomization" (version: 0.7.0), "MVMR" (version: 0.4), "MRlap" (version 0.0.3) to facilitate the MR analysis, "metafor" (version: 3.8-1) to assess

differences by sex and "forestplotter" (version: 1.0.0) in R (4.3.0, 2023-04-21 ucrt) to create graphics. We only used publicly available data in this study, therefore no ethics approval was needed.

Results

Genetic instruments

After aligning the genetic instruments across studies, we obtained 242 independent genome-wide SNPs for alcohol. The minimum F statistic was above 10. The variance of alcohol consumption explained by the instruments was 0.89%. The study at 80% power and 5% alpha could detect a difference for the IVW estimates using all instruments of about 1.06 and 0.83 years in men and women respectively, and around 0.71 years difference for lifespan overall and 0.58 and 0.54 years for age at recruitment in men and women separately, and 0.4 years overall. Three assumptions (i.e., relevance, independence and exclusion restriction) should be met for a valid MR study. The F-statistics met the rule-of-thumb criterion of >10 addressing relevance. To ensure independence, we also adjusted for the potential confounders, i.e., smoking and education. The MR-Egger intercepts did not suggest violations of the exclusion restriction assumption.

Associations of alcohol consumption with the control outcomes

As expected, alcohol consumption was positively associated with the control outcomes of SBP (1.08 mmHg, 95% CI: 0.14 to 2.01 for all SNPs and 3.76 mmHg, 95% CI: 3.02 to 4.49 for rs1229984 from *ADH1B*) and DBP (0.55 mmHg, 95% CI: 0.01 to 1.09, for all SNPs and 0.58 mmHg, 95% CI: 0.16 to 1.00 for rs1229984) after meta-analyzing estimates from ICBP and UK Biobank (Fig. 2), with generally consistent estimates from sensitivity analysis (WM and MR-Egger), particularly when using rs1229984.

Alcohol consumption and lifespan

Overall alcohol consumption based on all 242 genetic instruments was consistently associated with shorter lifespan using the IVW estimate and in sensitivity analysis (Fig. 3) [27] as was alcohol consumption only using rs1229984 from *ADH1B*. Scatterplots also suggested that rs1229984 was the key determinant of a possibly understated IVW estimate (Fig. 4) [27]. Results were similar using instruments from a smaller GSCAN excluding 23andme **(Supplementary Fig. 2**) [27]. MRlap suggested the IVW estimate was slightly under-estimated and should be closer to the estimate from only using rs1229984 (**Supplementary Table 1**) [27]. Results were slightly more marked using instruments from a GSCAN [27] excluding 23andme and UK Biobank (Fig. 5**)**. Estimates were also similar using the previous, smaller GSCAN excluding 23andme (**Supplementary Fig. 3**) [34]. Findings were also similar after adjusting for smoking and/or years of schooling, with adequate multivariable F-statistics (i.e. F statistics for alcohol consumption were 9.1 and 18.9 when adjusting for education and smoking respectively) (**Supplementary Fig. 4 and Supplementary Fig. 5) [34].**

Alcohol consumption was also associated with shorter lifespan in men with a directionally similar association in women using IVW and sensitivity analysis or only using rs1229984 from *ADH1B* (Fig. 3) [27]. Scatterplots suggested that rs1229984 was the key determinant of a possibly understated IVW estimate (Fig. 4) [27]. Estimates were similar using instruments from smaller GSCANs excluding 23andme **(Supplementary Fig. 2 and Supplementary Fig. 3**) [27,34]. Again MRlap suggested a slight under-estimate (**Supplementary Table 1**) [27]. Results were similar using instruments from a GSCAN [27] excluding the 23andme and UK Biobank but were more marked only using rs1229984 from *ADH1B***(**Fig. 5**)**. Some estimates were attenuated by adjusting for smoking and/or years of schooling (**Supplementary Fig. 4 and Supplementary Fig. 5) [34**].

Alcohol consumption and age at recruitment to UK Biobank

Using the IVW estimate based on all 242 genetic instruments higher alcohol consumption was not clearly associated with survival to UK Biobank recruitment (Fig. 3) but was using sensitivity analysis or only using rs1229984 from *ADH1B* (Fig. 3) [27]. Scatterplots suggested rs1229984 was the key determinant of a possibly understated IVW estimate (Fig. 6) [27]. Estimates were similar in men and women (Fig. 3) [27]. Results were similar using instruments from a GSCAN [27] excluding the 23andme (**Supplementary Fig. 2**). MRlap gave similar estimates (**Supplementary Table 1**) [27]. Alcohol was clearly associated with worse survival excluding 23andme and UK Biobank (Fig. 5) [27]. Estimates were also similar when using instruments from a smaller GSCAN excluding 23andme (**Supplementary Fig. 3**) [34]. After adjusting for smoking and/or years of schooling, alcohol consumption was unrelated to survival to UK Biobank recruitment (**Supplementary Fig. 4 and Supplementary Fig. 5) [34].**

Discussion

As expected, alcohol consumption was positively associated with blood pressure. We add by showing alcohol consumption was consistently associated with shorter lifespan, which was particularly evident for men even after allowing for smoking and education.

A recent meta-analysis of observational studies found no benefits of alcohol consumption at any level, with no harm at low levels and higher risk at higher levels [49], whilst others have found U shaped relations [50,51]. However, the included studies recruited across the age range [49–52]. As such, they are open to selection bias attenuating the estimates because studies recruiting older people are inevitably missing deaths from alcohol consumption at younger ages [3,53], when alcohol consumption tends to track throughout life from early adulthood [54,55]. Here, we assessed alcohol consumption on lifespan at younger ages, proxied by survival to recruitment, and at older ages, proxied by parental lifespan, and found no benefits. We add by showing harms at older ages, particularly for men, unlike previous studies [56–58].

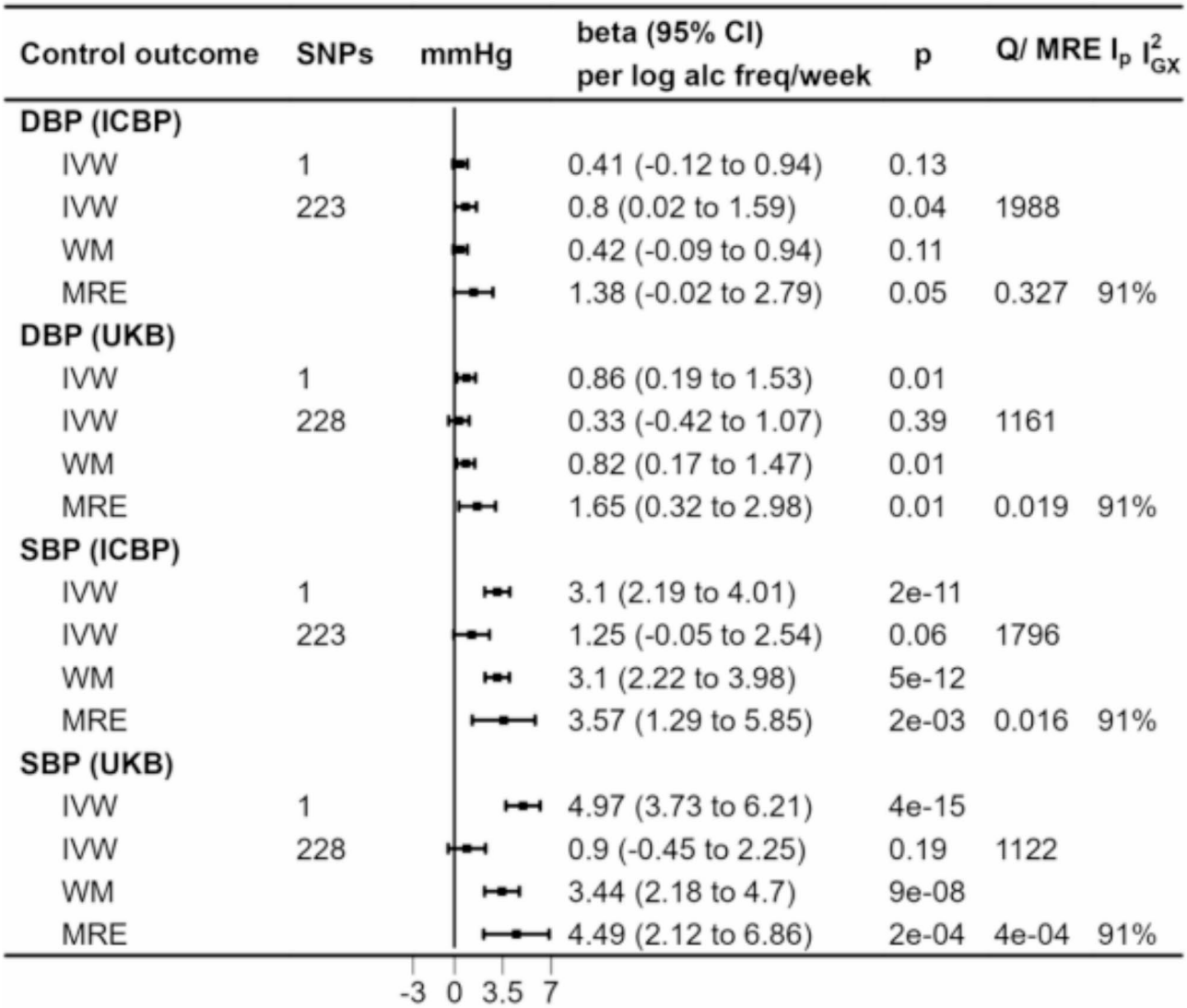

Fig. 2. MR estimates for the causal effects of alcohol consumption (logged alcoholic drinks per week) from GSCAN ($n = 2{,}428{,}851$) [27] on the control outcomes of DBP and SBP from ICBP [39] and UK Biobank. Note: IVW: Inverse variance weighting; WM: Weighted median; MRE: MR-Egger; Ip: p-value for intercept; DBP: diastolic blood pressure; SBP: systolic blood pressure. 1 SNP is rs1229984 from the full GSCAN.

Alcohol is metabolized differently by sex, such that after consuming the same amount of alcohol, the concentration is higher in women [59,60], suggesting alcohol consumption should be more detrimental in women than men [61]. However, alcohol drinking is often heavier in men [62], perhaps because it is often related to masculinity identity and male bonding, especially among youth [63], in many settings (e.g. night life, parties) across the globe [64,65]. So, the same frequency of alcohol consumption likely corresponds to higher alcohol consumption in men than women. Alternatively, men may be more susceptible to the long-term consequences of alcohol than women.

Any benefits of alcohol consumption are likely driven by cardiovascular disease, because alcohol is known to cause cancer [66,67], liver disease [68], injuries [69], mental health issues [70–72] and cognitive impairment [73]. Cardiovascular benefits of alcohol have been attributed to alcohol raising HDL-cholesterol, reducing coronary artery plaque, reducing coagulation and anti-oxidant properties [74–76]. Recent evidence from trials suggests little relevance to cardiovascular disease of HDL-cholesterol [77] or anti-oxidants [23]. Whether the well-established detrimental effect of alcohol on blood pressure [78,79] is outweighed by beneficial effects of alcohol on cardiovascular disease via plaque and coagulation factors is moot.

Our study has some strengths worth mentioning. First, we used an IV study design with a large sample size from the most recent GSCAN study to obtain less confounded estimates with outcomes that reduce survival bias, ascertained that any bias from overlapping samples likely slightly understates the magnitude of any effect, replicated using an instrument physiologically related to alcohol onsumption (rs1229984) and replicated using different instruments. Second, we used control outcomes to assess the validity of the instruments for alcohol. Third, the MR design allows investigation of lifelong effects of alcohol on lifespan instead of relatively acute

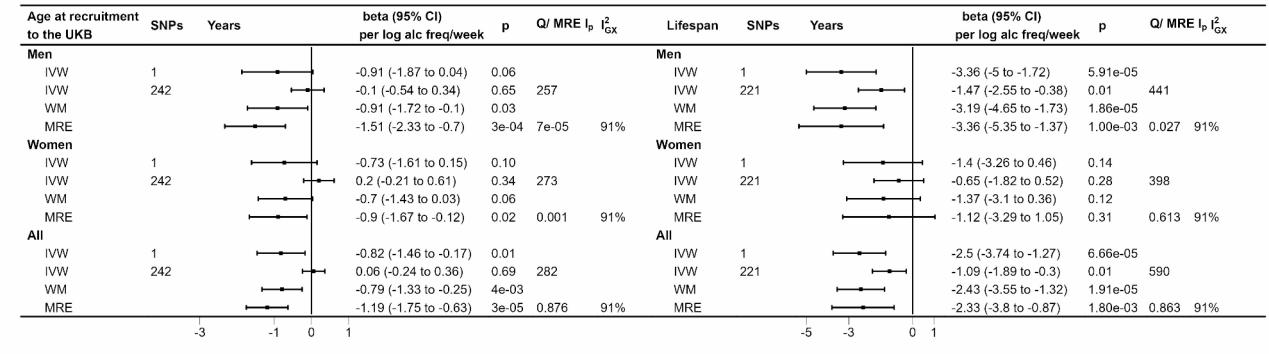

Fig. 3. MR estimates for the causal effects of alcohol consumption (logged alcoholic drinks per week; $n = 2{,}428{,}851$) from GSCAN [27] on lifespan (maternal $n = 412{,}937$, and paternal $n = 415{,}311$)and age at recruitment (men=167,020, women=194,174) from the UK Biobank [31]. Note: IVW: Inverse variance weighting; WM: Weighted median; MRE: MR-Egger; Ip: p-value for intercept; 1 SNP is rs1229984 from full GSCAN.

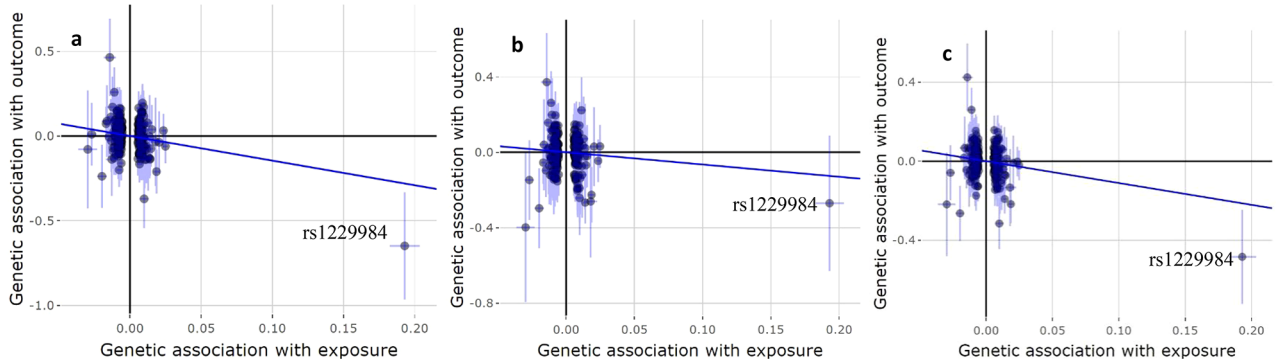

Fig. 4. Scatterplots for inverse variance weighting estimates of alcohol consumption (logged alcohol drinks per week) from the full GSCAN (Saunders et al., 2022; $n = 2{,}428{,}851$) and parental attained age (Pilling et al. 2017) in men (a; n = $n = 415{,}311$), women (b; $n = 412{,}937$) and overall (c; $n = 828{,}248$) from the UK Biobank. [The outlier is rs1229984 from *ADH1B*].

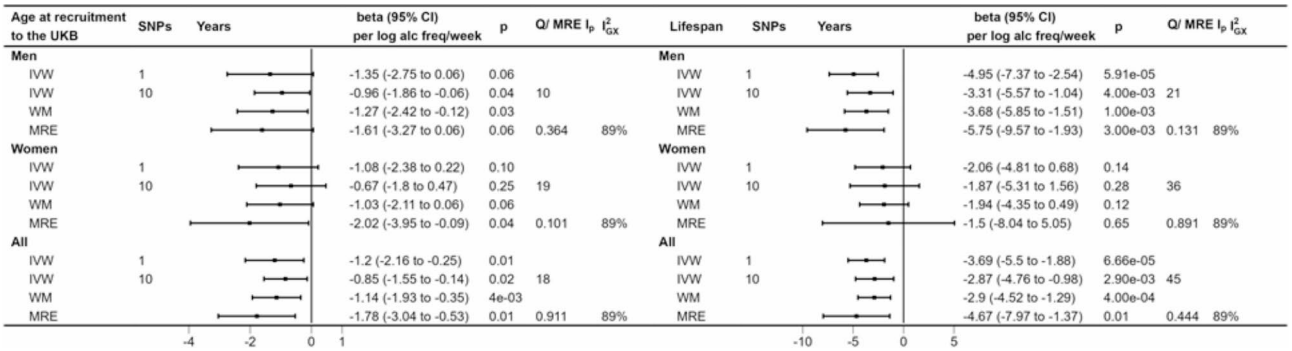

Fig. 5. MR estimates for the causal effects of alcohol consumption (logged alcoholic drinks per week; $n = 304{,}322$) excluding 23andme and UK Biobank [27] from GSCAN on lifespan (maternal $n = 412{,}937$, and paternal $n = 415{,}311$) and age at recruitment (men=167,020, women=194,174) from the UK Biobank [31]. Note: IVW: Inverse variance weighting; WM: Weighted median; MRE: MR-Egger; Ip: p-value for intercept; 1 SNP is rs1229984 from full GSCAN excluding 23andme and UK Biobank.

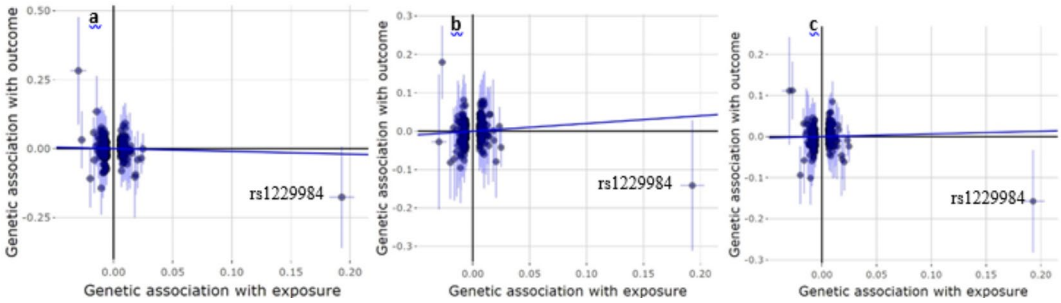

Fig. 6. Scatterplots showing association of genetic instruments with alcohol consumption (logged alcoholic drinks per week) from the full GSCAN (Saunders et al., 2022; $n = 2{,}428{,}851$) against associations with age at recruitment in men (a; $n = 167{,}020$), women (b; $n = 194{,}174$) and overall (c; $n = 361{,}194$) from the UK Biobank. [The outlier is rs1229984 from *ADH1B*].

effects. Fourth, we only included participants of European descent, limiting heterogeneity but avoiding possible confounding at the population level. Finally, the effect of alcohol consumption is given in years of life lost per logged alcoholic drinks per week, which may be more easily interpretable than relative risk.

There are several limitations in this study. First, the UK Biobank recruited volunteers, which could introduce bias. However, associations found in the UK Biobank are similar to those obtained from population representative studies [80]. Second, the outcomes concern only white British/European participants, limiting transportability to other groups. However, causes should be consistent but are not always relevant [81], for example to people who do not use alcohol. Third, alcohol was self-reported, participants may have underreported their alcohol consumption, however, consistent underestimates still indicate the trend. Fourth, the measure of alcohol consumption may exclude never drinkers [34], although interpretations vary [82]. However, the percentage of lifetime abstainers in men in the UK is low [80,82], and a similar interpretation was obtained using a single genetic variant (rs1229984) physiologically determining alcohol use in the whole population (Fig. 3). Fifth, some potential participants might not have survived to be recruited, and the measure of lifespan excluded early parental deaths, which we addressed by including age at recruitment to the UK Biobank as an outcome. Sixth, some potential participants may have been too ill to participate in the UK Biobank, so age at recruitment may be more like quality-adjusted years than years of life, however, the estimates remain directionally informative. Seventh, some non-paternity is possible, but is unlikely related to alcohol consumption, so any bias for lifespan is likely towards the null. Eighth, in order to be conservative, we used all SNPs for alcohol as well as a single physiologically relevant SNP (rs1229984). Similar to estimates from MRlap those from the single SNP analysis suggested slightly greater harms of alcohol on lifespan. Ninth, we did not conduct non-linear MR in this study, so we cannot rule out the possibility of a U-shaped association of alcohol consumption with lifespan. However, MR studies are increasingly indicating that the association of alcohol with cardiovascular disease, which was thought to be non-linear, is linear [83]. Similarly, a recent observational study also suggested harms of any level of regular (rather than occasional) alcohol use [84]. Tenth, we may have underestimated the effect of alcohol on lifespan, because early deaths, possibly due to non-natural causes, were excluded [31]. Eleventh, we conducted a partly one-sample study using two sample methods, which could bias particularly the MR-Egger estimates [48]. However, our large sample size and high I^2_{GX} reduces this possibility. In addition, we used MRlap to quantify any possible bias, as well as repeating the univariable analysis using genetic instruments from different samples with more or less overlap which gave similar estimates (Fig. 3 compared with Fig. 5). Finally, the GWAS of lifespan only included deaths from natural causes, excluding parents who died before the ages of 57 years (mothers) and 46 years (fathers). This exclusion criterion may inadvertently exclude some deaths related to alcohol consumption, which might bias towards the null.

From a public health perspective our findings highlight the importance of a reduction in alcohol consumption particularly by men. Men are heavier alcohol drinkers than women [3,62], and the harmful effects of alcohol consumption on lifespan are greater in men than women, so it is important to emphasize that alcohol is harmful for both men and women. Given, the relationship of alcohol consumption, gender, and lifespan is complex and multifaceted, these findings suggest that there are important social and metabolic differences that need to be considered when developing public health strategies and recommendations around alcohol consumption. As policymakers seek to handle the negative effects of alcohol on public health, they should prioritize measures that target men.

Conclusion

Our findings have important implications for policy making regarding alcohol consumption. They support the WHO guidelines for treating alcohol consumption as a behavior that should be changed and suggest recommendations for alcohol consumption should be tailored to the needs of men and women.

Data availability

This study used data from the MR-base plat form (https://www.mrbase.org/), UK Biobank (http://www.nealelab.is/uk-biobank/) and Neale lab (https://www.nealelab.is/uk-biobank).

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All participants were consent for publication.

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We only used publicly available data in this study, therefore no ethics approval was needed.

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