Educational attainment causally impacts drinking behaviors and risk for alcohol dependence: results from a two-sample Mendelian randomization study in ~ 780,000 study participants

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ABSTRACT

Background

Observational studies suggest that lower educational attainment may be associated with risky alcohol consumption behaviors. However, these findings may be biased by confounding and reverse causality. Using two-sample Mendelian randomization (MR), we can determine whether education is causally related to alcohol consumption behaviors and alcohol dependence (AD).

Methods

We performed two-sample MR using summary statistics from recent genome-wide association studies (GWAS) in 784,726 study participants to assess the causal effects of educational attainment on alcohol consumption behaviors, including intake frequency, total weekly drinks, beverage preferences, whether alcohol is consumed with meals, as well as AD risk. Of 53 independent (linkage disequilibrium R^2=0.001, kb distance<10,000) nucleotide polymorphisms (SNPs) that predict educational attainment, and after removal of palindromes with intermediate allele frequency, 51 were present in the alcohol consumption behaviors, and 44 were present in the AD GWAS. Complementary MR techniques accommodating different assumptions about genetic pleiotropy (inverse variance weighted (IVW), Egger, weighted median, and weighted mode MR) tested the sensitivity of our results.

Results

We found strong evidence of a causal effect between years of education and alcohol consumption behaviors generally. Higher educational attainment decreased alcohol intake frequency (IVW odds ratio (OR_{IVW}), 0.718, 95% CI, 0.673-0.765, P_{IVW}=4.62E-24), as well as weekly distilled spirits intake (OR_{IVW}, 0.874, 95% CI, 0.833-0.917, P_{IVW}=3.91E-08), and weekly beer plus cider intake (OR_{IVW}, 0.837, 95% CI, 0.805-0.869, P=5.58E-20), but increased weekly white wine ($OR_{IVW,}$ 1.220, 95% CI, 1.172-1.269, P_{IVW}=7.96E-23), red wine (OR_{IVW}, 1.227, 95% CI, 1.174-1.282, P_{IVW}=6.67E-20), and fortified wine intake (OR_{IVW}, 1.051, 95% CI, 1.027-1.075, P_{IVW}]=1.87E-07). We also found evidence educational attainment reduced AD risk (OR_{IVW} .508, 95% CI, .315-.819, P_{IVW}=5.51E-03). We found no evidence for total weekly consumption (OR_{IVW} .508, 95% CI, .315-.819, P_{IVW}=5.51E-03). Consistency of results across complementary MR methods strengthens our causal inferences.

Conclusions

Our findings show low educational attainment is causally associated with increased alcohol consumption frequency, increased preference for beer, cider, and spirits, and AD risk, indicating a potential mechanism explaining reported associations between educational attainment and adverse health outcomes, including cardiovascular disease. These findings suggest increased educational attainment might be a useful prevention strategy to reduce risky alcohol behaviors and AD.

INTRODUCTION

Alcohol consumption is a major risk factor exhibiting a complex relationship with death and disability in the United States and worldwide with the World Health Organization estimating alcohol is responsible for 139 million disability- adjusted life-years globally [1-3]. For example, acute intoxication may result in injuries, poisoning, and interpersonal violence [3,4], while longer-term alcohol consumption contributes to chronic diseases, including multiple types of cancer [5-7], cardiovascular disease [8-10], type 2 diabetes [6], and dependent drinking leading to psychiatric comorbidities, self-harm, or other impairments [2,11-13]. The complex relationship between alcohol, morbidity, and morality is due, in part, to the pattern of its use and the beverage type consumed [14,15] with beer and hard liquor consumption associated with riskier drinking patterns and increased risk for alcohol-related problems [16,17].

The seriousness of the acute and chronic diseases linked with problematic/risky alcohol consumption indicates identifying causal risk factors related to how alcohol is consumed is imperative to develop and improve intervention and treatment strategies. Among various social determinants associated with health disparities (age, gender, race, ethnicity, etc.) and mortality, educational attainment has been identified as a prominent risk factor [18]. For example, at age 25, the average life expectancy of U.S. adults without a high school diploma is 9 years shorter than college graduates [19]. The impact of education on alcohol consumption behaviors may be an important pathway mediating these effects. Observational studies have demonstrated educational attainment influences drinking patterns, beverage preferences, and alcohol-related outcomes [15,20-22]. Higher educational

attainment is associated reduced odds of reporting high-risk drinking [1,21], or at least one episode of heavy episodic drinking within the past 12 months [15,19,23]. Moreover, men and women with less education are more likely to report higher single occasion quantity consumed and alcohol-related harm [19,20]. While education is associated with differences alcohol consumption behaviors, these observational studies are subject to reverse causation, or residual confounding [24-27], Further, inferring causality from correlations and multivariable adjusted regression models is often unreliable [28,29]. Mendelian randomization (MR) analysis uses randomly inherited genetic markers (single nucleotide polymorphisms (SNPs)) associated with a risk factor (e.g., education) as proxies for environmental exposures to assess causal inferences about the effect of the exposure on an outcome (e.g., alcohol consumption patterns and AD risk). MR is analogous to randomized control trials (RCTs) since genetic variants are not modifiable and free from confounding [26,27,30,31] and is an important strategy for establishing causal relationships where RCTs are impractical [26]. MR relies on three main assumptions: (1) the instrument is significantly associated with the exposure (i.e., genome-wide level statistical significance); (2) the instrument does not affect the outcome via pathways other than the exposure of interest (termed "horizontal pleiotropy"); and (3) the instrument is not associated with confounders [32]. MR analysis has traditionally been performed using individual-level single datasets containing both the exposure and outcome(s) of interest which often do not have enough statistical power to examine horizontal pleiotropy. However, the increasing availability of summary-level data from genome-wide association studies (GWAS) can be used to perform MR analyses where gene exposure and gene outcome measures are derived from two separate GWAS [33]. These "two-

sample MRs" benefit from increased statistical power and enable sensitivity analyses to test the robustness of the MR findings.

Recent two-sample MR studies have shown inverse relationships between education and both smoking and coronary heart disease [34,35]. However, to our knowledge, MR has not been applied to examine the effects of educational attainment on alcohol consumption patterns, DSM-IV alcohol dependence (AD), or alcohol-related diagnoses. In this study we use two-sample MR in the largest available GWAS data for educational attainment (N = 293,723) [36], AD (N = 28,657) [37], and alcohol consumption pattern variables (alcohol consumption frequency, total consumption [38], and whether alcohol is consumed with meals), and beverage-specific preferences (cider and beer, red wine and white wine, and hard liquor) from UK Biobank participants (N ≤ 462,346) to assess causal associations between education and alcohol consumption patterns, alcohol dependence, and alcohol-related disease diagnoses.

METHODS

DATA SOURCES

Contributing genome-wide association study (GWAS) consortiums are described in Table 1. We selected the GWAS with the largest sample sizes consisting of similar populations of European ancestry and avoiding sample overlap. All summary statistics are publicly available online. All studies included rigorous quality control, imputation to the 1000 Genomes Project panel and adjustments for age and population structure. Details on the GWAS, including quality control of the genetic data, are available in the

supplementary material. All studies have existing ethical permissions from their respective institutional review boards and include participant informed consent. The exposure in the present study was educational attainment as measured by years of schooling; the outcomes were the risks of alcohol consumption behaviors and alcohol related diagnoses.

GENETIC INSTRUMENTS FOR EXPOSURE: EDUCATIONAL ATTAINMENT

We extracted summary association statistics for the 74 genome-wide significant (P < 5E-08) single nucleotide polymorphisms (SNPs) previously demonstrated to be associated with educational attainment defined as years of schooling [36], measured in standard deviation (SD) units (mean=14.33 years, SD=3.61 years), ascertained in up to 293,723 persons from 64 discovery cohorts. Twenty-one of the 74 variants were excluded (linkage disequilibrium (LD) R^2=0.001, > 10,000 kb) leaving 53 independent SNPs for the two sample Mendelian randomization analysis (Supplementary Table 1).

GENETIC INSTRUMENTS FOR OUTCOMES

Alcohol consumption behaviors

We used summary association statistics from the MRC-IEU UK Biobank (UKB) GWAS Pipeline [39] on six alcohol consumption behaviors assessed as ordered categorical responses: (1) alcohol intake frequency, *i.e.* daily or almost daily, three or four times a week, once or twice a week, one to three times a month, special occasions only, or never (N=432,346); and for UKB respondents who indicated they drank at least once or twice a week, (2) average weekly spirits intake in increments of one pub measure of alcohol

(N=326,565); (3) average weekly beer plus cider intake in increments of one pint (N = 327,634); (4) average weekly red wine intake in increments of one glass (N=327,026); (5) average weekly white wine plus champagne in increments of one glass (N=326,801); and (6) average weekly fortified wine intake in increments of one glass (N=327,563). We also used summary association statistics from the MRC-IEU UK Biobank GWAS Pipeline on an additional alcohol consumption behavior assessed as a binary response: (7) alcohol usually taken with meals (cite UKB data field 1618), ascertained in 235,645 persons (number of cases=159,104, number of controls=75,541). Out of the 53 possible independent SNPs associated with education years, 52 were present in the GWASs, 1 SNP was identified in high linkage disequilibrium (LD) as a proxy for the missing SNP, and 2 SNPs were removed for being palindromic with intermediate allele frequencies, giving a total of 50 SNPs for analysis (Supplementary Table 1).

We used summary association statistics from the SSGAC GWAS of alcohol consumption using the UKB cohort of 414,343 persons, measured as “drinks per week” constructed from responses about average weekly intake for types of alcohol, defined (by pictures) as “glasses” for red wine, fortified wine, and champagne and white wine; “pints” for beer and cider; and “measures” for spirits. For purposes of the GWAS, the “drinks per week” phenotype was the sum of “pints,” “glasses” and “measures” (“drinks per week” mean=8.92 drinks, SD= 9.30 drinks) [38]. For persons who had indicated (in the alcohol intake frequency question) drinking “one to three times a month”, the number of drinks (sum total of pints of beer or cider, glasses of wine, and measures of spirits) consumed per month was divided by 4 to construct the phenotype. Out of the 53 possible SNPs

associated with years in school, 51 were present in the GWASs, and 1 SNP was removed for being palindromic with intermediate allele frequencies, giving a total of 50 SNPs for analysis (Supplementary Table 1).

Alcohol dependence

We used summary association statistics from the PGC on AD in 28,657 (number of cases=8,485, number of controls=20,657) persons, defined as meeting criteria for a DSM-IV (or DSM-IIIR in one instance) diagnoses of AD [37]. Out of the 53 possible SNPs associated with years in school, 53 were present in the GWASs, no SNPs were identified in high linkage disequilibrium (LD) as a proxy for the missing SNPs, and 9 SNPs were removed for being palindromic with intermediate allele frequencies, giving a total of 44 SNPs for analysis (Supplementary Table 1).

SAMPLE OVERLAP

Participant overlap between the samples used to estimate genetic associations between exposure and outcome in two sample MR can bias results [40]. We used only genetic variants and summary statistics from the 64 samples (N=293,723) used in the discovery analysis and did not use summary statistics from the replication analysis using the UKB cohort, so as to avoid overlap with the UKB sample used in 12 of the 13 alcohol related outcomes. As regards the thirteenth outcome, AD, a careful comparison of the cohorts included in the PGC AD GWAS and SSGAC educational attainment GWAS showed 2 common cohorts (N=11,096) (Minnesota Center for Twin and Family Research (MCTFR); Swedish Twin Registry (STR)), which accounted for 38.7% of participants in

the PGC but only 3.8% of participants in SSGAC; the percentage overlap for purposes of determining weak instrument bias (WIB) here is taken with respect to the larger data set, because only participants in both studies leads to correlation in estimates, and additional participants in the exposure data set attenuates the correlation that leads to WIB. Based on a simulation study of the association between sample overlap and the degree of WIB, considerable WIB bias would not be expected [40].

STATISTICAL ANALYSIS

Two-sample Mendelian randomization

Analyses were carried out using TwoSampleMR, version 4.16 [32], and MR-PRESSO, version 1.0 [41], in the R environment, version 3.5.1 (2018-07-02).

We used four complementary methods – inverse variance-weighted (IVW) MR, MR Egger, weighted median, and weighted mode MR – to determine the causal effects of education years on alcohol behaviors and alcohol related diagnoses and discern sensitivity to different patterns of violations of IV assumptions. Consistency of results across these methods (each making different assumptions about pleiotropy) strengthens causal inference; significant divergent results may indicate bias from genetic pleiotropy. IVW MR implements a weighted regression of the exposure SNP effects against the outcome SNP effects (*i.e*. meta-analyses SNP-specific Wald estimates from exposure and outcome GWASs), with the regression constrained to pass through the origin, and the weights derived from the inverse of the variance of the outcome effects. We used multiplicative random effects IVW MR, allowing SNPs to have different mean effects, allowing for heterogeneity due, *e.g*., to horizontal pleiotropy. Unbiased estimates of a

causal effect are returned so long as horizontal pleiotropy is balanced [42,43].

MR Egger extends IVW MR by not constraining the intercept to pass through the origin, allowing the net-horizontal pleiotropic effect across all SNPs to be unbalanced or directional (i.e. some SNPs could be acting on the outcome through a pathway other than through the exposure) [43,44]. MR Egger thus relaxes the assumption of "no horizontal pleiotropy" (IV assumption 2, introduction, above) and assumes only that the horizontal pleiotropic effects are not correlated with the SNP-exposure effects. MR Egger returns unbiased causal effect estimates even if the assumption is violated for all SNPs, but causal effect estimates in MR Egger are less precise (wider confidence intervals expected) than those in IVW MR. The MR Egger intercept provides an estimate of the directional pleiotropic effect [43].

Weighted median MR uses the median effect of all available SNPs, so that only half the SNPs need to be valid instruments (*i.e.* no horizontal pleiotropy, no association with confounders, and robust association with the exposure) to return an unbiased causal effect estimate. Stronger SNPs contribute more towards the causal estimate, with the contribution of each SNP weighted by the inverse variance of its association with the outcome [33]. Weighted mode MR clusters the SNPs into groups based on similarity of causal effects and returns the causal effect estimate based on the cluster that has the largest number of SNPs. Weighted mode-based MR returns unbiased causal effects so long as the SNPs within the largest cluster are valid instruments. Weighted mode MR weights each SNP's contribution to the clustering by the inverse variance of its outcome

effect. Assuming the most common causal effect is consistent, the estimated causal effects would be unbiased even if all other instruments are invalid [25].

Sensitivity analyses and diagnostics

To evaluate heterogeneity in genetic instruments effects, indicating potential violations of the IV assumptions, i.e. of no horizontal pleiotropy [45], we used the MR Egger intercept test [45], the Cochran Q heterogeneity test [46], and the MR pleiotropy residual sum and outlier (MR-PRESSO) test [47]

MR-Egger regression provides a test for average pleiotropy: the MR Egger regression intercept can be interpreted as the average pleiotropic effect across all IVs. As pleiotropy can induce heterogeneity of the individual ratio estimates, the Cochran Q test used to identify outliers has been applied in the context of MR to detect pleiotropy [47]. MR-PRESSO extends the principal of the Q test, performing IVW meta-analysis using the MR linear regression of the variant's effect sizes on the exposure and outcome, and implementing a "global" test comparing the observed distance of the variants to the regression line with the distance expected under the null hypothesis of no pleiotropy (all variants should reside on the line) [47]. Thus, MR-PRESSO identifies potential bias from horizontal pleiotropy. We used MR-PRESSO to identify variants that exhibit pleiotropy, removed the outlier variants, reran Mendelian randomization analyses, and retested to determine whether outlier removal resolved the detected heterogeneity. We present the outlier adjusted causal estimates in Figures 1 and 2, and full MR results before and after outlier correction in Supplementary Table 2.

Directionality

We used the Steiger directionality test to test the causal direction between the hypothesized exposure and outcomes [48].

RESULTS

OVERVIEW

We regard as results those causal estimates (1) agreeing in direction and magnitude across MR methods, exceeding nominal significance ($P < 0.01$) in IVW MR, (2) not indicating bias from horizontal pleiotropy (MR-PRESSO global $P > 0.01$ or MR-PRESSO distortion $P < 0.01$, plus MR Egger intercept $P > 0.01$), and (3) indicating true causal effect directionality (Steiger directionality test $P < 0.001$). We present full MR results with test statistics in Supplementary Table 2. We compare the IVW and Egger MR estimates against the causal effect as estimated using each of the SNPs in Supplementary Table 3 (we used the Wald ratio to perform single SNP MR). We present individual genetic variant associations in Supplementary Table 1. Causal effects estimates may be expressed as odds ratios (OR) with 95% confidence interval (CI) per standard deviation increment in years of education (SD=3.61 years). We present herein the results and Figures 1 and 2 only the outlier corrected causal estimates.

EFFECTS OF EDUCATIONAL ATTAINMENT ON ALCOHOL CONSUMPTION BEHAVIORS

We found strong evidence of a causal effect between years of education and alcohol consumption behaviors generally, after outliers had been identified and removed (in the event both MR PRESSO global and distortion tests indicated significant outliers), heterogeneity resolved (Q_{IVW} $P > 0.01$), except where otherwise noted, no pleiotropy indicated (MR-PRESSO global $P > 0.01$ and an insignificant MR Egger intercept $P > 0.01$), and direction of causal effect true (Steiger test $P < 0.001$).

Alcohol intake frequency and pattern

Genetically increased educational attainment decreased alcohol intake frequency (OR_{IVW}, .718, 95% CI, 0.673-0.765, P_{IVW}= 4.62E-24, Q_{IVW} P=.084, MR-PRESSO P=0.041, MR Egger Intercept P=.545, 9 outlier variants identified and removed). Given that each category of alcohol intake frequency approximately doubles intake frequency (*e.g.* from 1-2 times per week to 3-4 times per week), then a one SD decrease in educational attainment (SD=3.61 years) increases the odds of approximately doubling intake frequency by 39.2%. Causal estimates were broadly consistent in magnitude and direction across MR methods.

At the same time, higher educational attainment increased the odds of taking alcohol with meals by 19.1% (OR_{IVW},1.191, 95% CI, 1.151-1.231, P_{IVW}=1.63E-24), although, even after all significant outliers were identified and removed, we found strong evidence of residual heterogeneity (Q_{IVW} P=1.48E-05) and contrary evidence of pleiotropy (MR-PRESSO significant P<.001, but MR Egger intercept not significant P=.642).

Average weekly alcohol intake

We also found strong evidence of a causal effect between increased educational attainment and average weekly intake of categories of alcohols, with outliers identified and removed. Higher educational attainment decreased the risk average weekly spirits intake (OR_{IVW}, .874, 95% CI, 0.833-0.917, P_{IVW}=3.91E-08; Q_{IVW} P=.135; MR-PRESSO P=.08, 1 outlier identified; MR Egger intercept P=.934). Higher educational attainment also decreased the risk of average weekly beer plus cider intake, although with strong evidence of heterogeneity remaining (OR_{IVW}, .837, 95% CI, 0.805-0.869, P=5.58E-20; Q_{IVW} P=.006), and contrary evidence of pleiotropy (MR-PRESSO significant P=.009; but MR Egger intercept not significant P=.190), even after all significant outliers were identified and removed.

In contrast, higher educational attainment increased the risk of average weekly champagne plus white wine intake (OR_{IVW}, 1.220, 95% CI, 1.172-1.269, P_{IVW}=7.96E-23; Q_{IVW} P=.066; MR-PRESSO P=.143, MR Egger intercept P=.463, no outliers identified); as well as the risk of average weekly fortified wine intake (OR_{IVW}, 1.051, 95% CI, 1.027-1.075, P_{IVW}=1.87E-07; Q_{IVW} P=.022; MR-PRESSO P=.038, MR Egger intercept P=.427, no outliers identified); and average weekly red wine intake (OR_{IVW}, 1.227, 95% CI, 1.174-1.282, P_{IVW}=6.67E-20; Q_{IVW} P=.022; MR-PRESSO P=.083, MR Egger intercept P=.419, 6 outliers identified).

We found no evidence of a causal effect between increased educational attainment and average weekly intake of drinks overall (OR_{IVW}=1.031, 95% CI, 0.985-1.079, P_{IVW}=.189; Q_{IVW} P=0.049; MR-PRESSO P=.064, MR Egger intercept P=.154, 3 outliers identified and removed).

EFFECTS OF EDUCATIONAL ATTAINMENT ON ALCOHOL DEPENDENCE

We found evidence of a causal effect between increased educational attainment and AD (DSM-IV or DSM-III diagnoses) (Figure 2). Increased educational attainment decreased the risk of AD, with outliers identified and removed and heterogeneity resolved, by almost 50% (per unit SD=3.61 years education) (OR_{IVW}, 0.508, 95% CI, 0.315-0.819, P_{IVW}=5.52E-03; Q_{IVW} P=.044; MR-PRESSO P=.059, MR Egger intercept P=.045). While magnitude and direction of the causal estimates were consistent across IVW, weighted median, and weighted mode MR, the MR Egger point estimate was directionally opposite, although not significantly different from 0 ($P_{MREgger}$=.163).

DISCUSSION

Using the largest summary-level GWAS data available and complementary two-sample MR methods, we found strong genetic evidence that educational attainment is a causal determinant of alcohol consumption behavior, drink preferences, and risk for AD. More specifically, higher educational attainment reduced intake frequency, beer, cider, and spirits intake, and AD risk, while increasing wine and champagne intake, and the likelihood of drinking with meals, all indicating educational attainment an important factor responsible for variation in alcohol consumption behavior. We found weak

contrary evidence that our results may be driven by genetic pleiotropy in only two of the eight alcohol consumption behaviors (average weekly beer plus cider intake and alcohol usually taken with meals). Consistency of results across MR methods (accommodating different assumptions about genetic pleiotropy) strengthens the causal inference. Educated persons generally have healthier lifestyle habits, fewer comorbidities, and live longer than their less educated counterparts [49,50] and our results suggest it is causally associated with different likelihoods of belonging to variegated alcohol consumer typologies, with more educated individuals consuming wine at meals compared to less educated individuals drinking more often, without accompanying meals, and preferring beer, cider, or spirits. We found an additional 3.61 years of education reduced the risk of AD by approximately 50%, which is consistent with results from small community samples [51,52], nationally-representative surveys [53], and the most recent (published) AD GWAS that found a strong inverse genetic correlation with education [37]. Notably, compared to wine drinkers, beer and spirit drinkers are at increased risk of becoming heavy or excessive drinkers [54,55], and AD [55-57], and beer and spirits account for the majority of hazardous [58]. Furthermore, drinkers who prefer beer and spirits are at increased risk for alcohol-related problems and illicit drug use [17,59-61]. Beer and spirit consumption without meals increases blood alcohol concentration rapidly; Ashton et al., 2017 recently found that emotions elicited by drinking beer and spirits – *i.e.* feeling energized, confident, and sexy [62] – are also reported among drinkers with lower educational attainment [62], which suggests a pattern of alcohol consumption motivated primarily to reduce negative emotions or getting drunk [16,62,63]. Similarly, a growing body of research indicates that stressors, chronic strain, and trauma – which can precede or

follow from low educational attainment – are associated with stronger alcohol and drug use as coping strategies [64-66], which may, in turn, increase the risk of AD [67].

In contrast to the often-reported positive relationship between educational attainment and total consumption reported from observational studies [21,68,69], we found no evidence of a causal relationship. Results from previous observational studies may be explained by other socioeconomic factors also been linked to differences in total alcohol consumption [15]. Our null finding does support similar results from Davies et al., 2016, who used the 1972 mandated increase in school-leaving age in the UK as a natural experiment instrumental variable design to investigate the causal effects of staying in school on total alcohol consumption (from individuals in the UKB database who turned 15 in the first year before and after the schooling age increased (N=22,138)) [50]. Davies et al. may have found a significant effect of staying in school had they included the disaggregated behavioral dimensions of alcohol consumption. Nevertheless, even if no educational attainment-total alcohol consumption relationship exists, studies have reported that both the specific alcoholic beverage and the pattern with which it is consumed, controlling for total consumption, independently contribute to risky health behaviors [70-72].

PATHWAYS AND POLICY IMPLICATIONS

Recent large Mendelian randomization studies demonstrating inverse relationships between educational attainment on smoking behaviors [35], and coronary heart disease (CHD) risk [34], as well as natural experiments [50,73,74] and twin studies finding that differences in educational attainment, even after controlling for shared environmental

factors such as parental behaviors, housing conditions, and access to schooling, still significantly impact mortality risk [75-77], represent the growing body of literature suggesting a causal effect of increased educational attainment on health and mortality. Other observational studies have linked alcohol consumption patterns to health, disease, and mortality risk [78-80]. It is possible that the impact of educational attainment on both alcohol consumption patterns and alcoholic beverage preference may be significant pathways or mediators in the relationship between educational attainment and health outcomes. Our findings, along with the results from these other studies, suggest that increasing educational attainment may achieve substantial health benefits.

STRENGTHS & LIMITATIONS

We note several strengths. We have analyzed multiple alcohol-related behavioral phenotypes which serve as a check on the consistency of our results. We have implemented multiple complementary MR methods (IVW, Egger, weighted median, and weighted mode MR) and diagnostics. Consistency of results across MR methods (accommodating different assumptions about genetic pleiotropy) strengthens our causal interpretation of the estimates [81]. We also used the largest GWASs published to date for our exposure and outcome samples; large summary datasets employed are important for MR and other genetic analysis investigating small effect sizes [82]. We also note limitations and future directions. The datasets are from Anglophone countries, where beer is the preferred drink [83]; therefore, applicability to other countries with different alcohol preferences may be limited. There may be selection bias from in the datasets. It has been reported the UK Biobank sample population is more educated, have healthier lifestyles,

and fewer health problems than the UK population [84], which selection bias could bias the MR estimates [85]. Further, while we included multiple alcohol consumption behaviors, GWASs for binge drinking (defined as consuming more than 5 drinks per occasion for men and 4 drinks per occasion for women [86]) and high-intensity binge drinking (HIBD) consuming 2- and 3- times the binge thresholds [23] are not currently available. Observational studies show a positive relationship of educational attainment on binge drinking [87], but a negative relationship on HIBD [23]. Our null finding (no significant causal effect of educational attainment on total weekly alcohol consumption) may be reconciled with these observational studies of binge and high-intensity binge drinking, as well as observational studies of total consumption, abstracting from confounding factors, to the effect that alcohol consumption behavior (frequency, alcohol taken with meals, alcohol drink preferences) as well as, or instead of, total consumption, may be the main alcohol related pathway to health and mortality. Binge and high-intensity binge drinking are important behaviors to examine in the future.

Further still, we were unable to analyze the effect of educational attainment on alcohol-related disease diagnoses, e.g. alcoholic liver disease, alcoholic cardiomyopathy, alcoholic cirrhosis of the liver, alcoholic hepatitis, degeneration of the nervous system due to alcohol; the only available GWASs were population based (MRC-IEU UKB GWAS Pipeline), with case-control ratios ranging from .00432% (cardiomyopathy) to .0745% (alcoholic liver disease). Finally, educational attainment measured years of completed schooling; determining how various aspects of education differentially impact alcohol consumption was impossible but should be a topic of future work.

CONCLUSIONS

Our findings support the notion that lower educational attainment causally affects alcohol consumption patterns, beverage preferences, and AD risk. Educational attainment may also affect drinking motives. In contrast to observational studies, we found no evidence educational attainment causally impacts total consumption, suggesting heretofore reported findings may be due to confounding. However, through its effect on alcohol consumption behaviors, educational attainment may have significant indirect effects on health outcomes: the effect of educational attainment on both alcohol consumption patterns and alcoholic beverage preference may be significant pathways or mediators in the relationship between educational attainment and health outcomes. In conjunction with the evidence demonstrating the causal role of education on other health behaviors, our findings suggest that increasing educational attainment may be a useful target for prevention programs against problematic alcohol use and its consequences.

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CODE AVAILABILITY

The analysis code in R is available on request and all data displayed in the figures are available in the Supplementary Tables.

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TABLES & FIGURES

Table 1. Contributing GWAS Consortiums

Phenotype	First author (year)	Consortium	Sample Size	Availability
EXPOSURE:				
Educational attainment (SD=3.61y)[a]	Okbay (2016)	SSGAC	293,723	www.thessgac.org/data [2]
OUTCOMES:				
Alcohol intake frequency[b]	Elsworth (2018)	MRC-IEU	462,346	www.mrbase.org [4]
Weekly intake (drinks)[c]	Karlsson Linnér (2019)	SSGAC	414,343	www.thessgac.org/data [3]
Weekly intake:				
Spirits (measure)[b]	Elsworth (2018)	MRC-IEU	326,565	www.mrbase.org [4]
Beer plus cider (pint)[b]	Elsworth (2018)	MRC-IEU	327,634	www.mrbase.org [4]
Red wine (glass)[b]	Elsworth (2018)	MRC-IEU	327,026	www.mrbase.org [4]
Champagne plus white wine (glass)[b]	Elsworth (2018)	MRC-IEU	326,801	www.mrbase.org [4]
Fortified wine (glass)[b]	Elsworth (2018)	MRC-IEU	327,563	www.mrbase.org [4]
Alcohol dependence (AD)[d]	Walters (2018)	PGC	28,657	www.med.unc.edu/pgc/results-and-downloads [5]

[1] Variable types: (a) Continuous (units=SD); (b) Categorical ordered; (c) Integer; (d) Binary
[2] EduYears_Discovery_5000.txt
[3] DRINKS_PER_WEEK_GWAS.txt
[4] MRC-IEU UKB GWAS Pipeline through the MR-BASE database and analytical platform for Mendelian randomization
[5] AlcDep August 2018

Abbreviations: SSGAC = Social Science Genetics Association Consortium; PGC = Psychiatric Genomics Consortium; MRC-IEU = Medical Research Council Integrative Epidemiological Unit, University of Bristol; SD = standard deviation

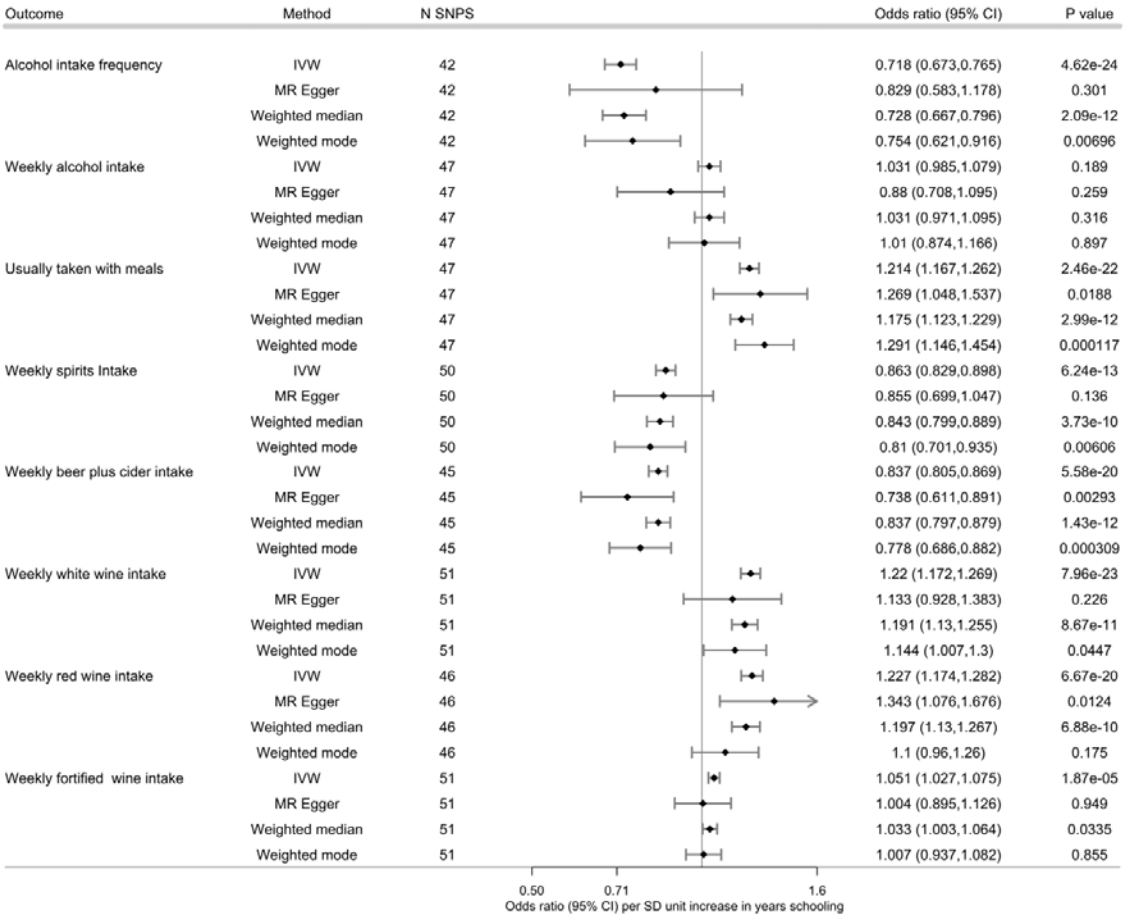

Figure 1. Causal estimates of educational attainment on risk of alcohol consumption behaviors using genome wide significantly associated (P < 5E-08) independent ((LD R^2 = 0.001, LD distance < 10,000 kb) single nucleotide polymorphisms (SNPs) as instrumental variables for educational attainment. Results from inverse variance-weighted (IVW) and 3 complementary methods (Egger, weighted median, weighted mode) two sample Mendelian randomization (MR), following removal of outlier variants (P < 0.15 in MR-PRESSO) are shown. Causal estimates express the change in odds ratio (OR) per standard deviation (SD=3.61 years) increment in educational attainment. Error bars indicate 95% confidence intervals.

Abbreviations: MR= Mendelian randomization; IVW=Inverse Variance Weighted MR;

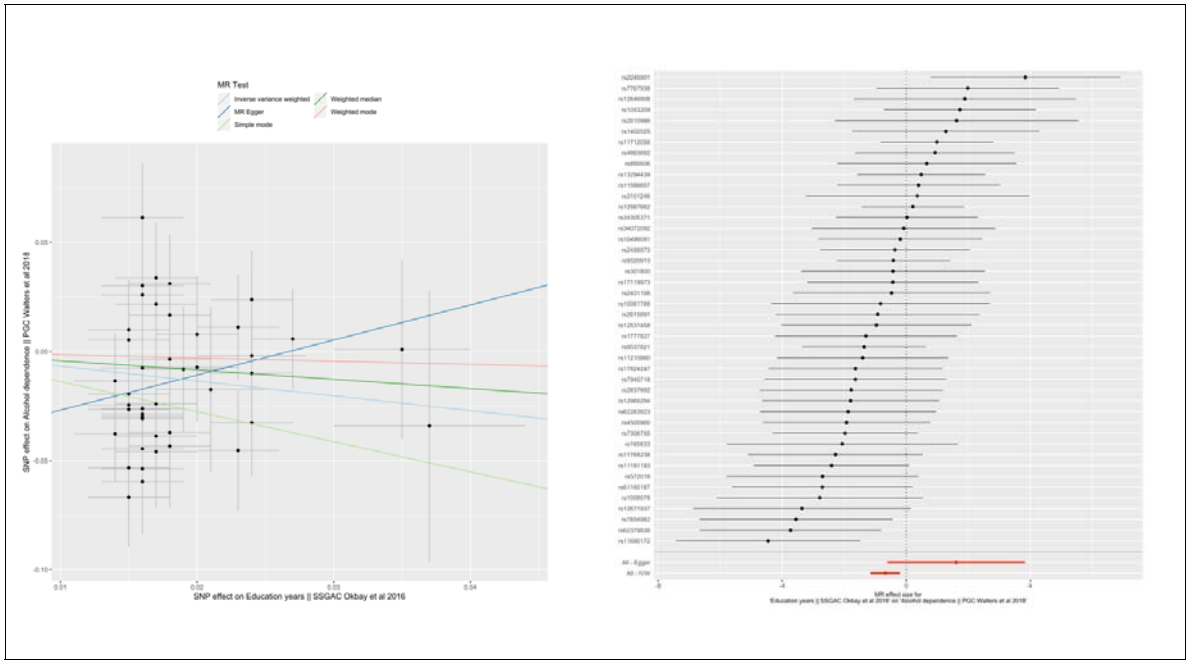

Figure 2. Genetic associations of educational attainment with likelihood of alcohol dependence (DSM-IV diagnoses). Analysis of 28,657 individuals (number of cases=8,485, number of controls=20,657) of European ancestry. (Left) Scatter plot showing correlation of genetic associations of educational attainment with genetic associations of alcohol dependence. Lines represent the slopes of the different regression analyses. (Right) Forest plot comparing the MR estimates using the inverse variance weighted (IVW) MR and MR Egger methods against the single SNP tests (Wald ratios).