Alcohol consumption and cognitive impairment in older men

A mendelian randomization study

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ABSTRACT

Objective: To determine whether alcohol consumption is causally associated with cognitive impairment in older men as predicted by mendelian randomization.

Methods: Retrospective analysis of a cohort study of 3,542 community-dwelling men aged 65 to 83 years followed for 6 years. Cognitive impairment was established by a Mini-Mental State Examination score of 23 or less. Participants provided detailed information about their use of alcohol during the preceding year and were classified as abstainers, occasional drinkers, and regular drinkers: mild (<15 drinks/wk), moderate (15–27 drinks/wk), heavy (28–34 drinks/wk), and abusers (≥ 35 drinks/wk). We genotyped the rs1229984 G $\rightarrow$ A variant of the alcohol dehydrogenase 1B (*ADH1B*) gene, which is associated with lower prevalence of alcohol abuse and dependence. Other measures included age, education, marital status, smoking and physical activity, body mass index, diabetes, hypertension, and cardiovascular diseases.

Results: At study entry, rs1229984 G $\rightarrow$ A polymorphism was associated with lower prevalence of regular use of alcohol and decreased consumption among regular users. Six years later, 502 men (14.2%) showed evidence of cognitive impairment. Abstainers and irregular drinkers had higher odds of cognitive impairment than regular drinkers (odds ratio [OR] = 1.23, 95% confidence interval [CI] = 1.00–1.51, after adjustment for other measured factors). The rs1229984 G $\rightarrow$ A polymorphism did not decrease the odds of cognitive impairment (AA/GG OR = 1.35, 95% CI = 0.29–6.27; GA/GG OR = 1.05, 95% CI = 0.71–1.55).

Conclusions: Alcohol consumption, including heavy regular drinking and abuse, is not a direct cause of cognitive impairment in later life. Our results are consistent with the possibility, but do not prove, that regular moderate drinking decreases the risk of cognitive impairment in older men. *Neurology*® 2014;82:1038–1044

GLOSSARY

ADH1B = alcohol dehydrogenase 1B; **CI** = confidence interval; **DSM-V** = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; **HIMS** = Health in Men Study; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **SNP** = single nucleotide polymorphism.

Alcohol intoxication impairs attention, psychomotor speed, tracking ability, working memory, and cognitive flexibility,^{1,2} but the cognitive consequences of chronic use are less well established.³ *DSM-V* criteria suggest that alcohol consumption can cause both minor and major cognitive disorders (the latter is consistent with the diagnosis of dementia), and specific criteria for alcohol-related dementia have been proposed.⁴ However, contrasting evidence from several observational studies suggests that moderate alcohol use lowers rather than increases the risk of cognitive impairment.^{5–9}

Mendelian randomization could be a potentially useful strategy to determine whether alcohol is causally linked to cognitive impairment.¹⁰ The rationale, in this case, is that genetic polymorphisms that modify the efficiency of enzymes involved in the metabolism of alcohol should

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Go to *Neurology*.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

also modify the consequences of alcohol consumption. The rs1229984 G → A (Arg → His) variant of the alcohol dehydrogenase 1B (*ADH1B*) gene reduces the ability of the enzyme to oxidize ethanol by approximately 80-fold.¹¹ For this reason, the risk of alcohol-related disorders is 3 times higher among adults with the GG than with the AA genotype (i.e., efficient metabolizers have higher risk).^{12,13} Consequently, individuals are assigned to higher (GG) or lower (GA/AA) probability of alcohol abuse according to the random assortment of *ADH1B* alleles during gamete production and fertilization (i.e., the distribution of confounding is random). Thus, if alcohol causes cognitive impairment, carriers of the *ADH1B* rs1229984 G → A polymorphism should have lower risk of cognitive impairment than their counterparts with the GG genotype. We designed this longitudinal study to test this hypothesis.

METHODS **Standard protocol approvals, registrations, and patient consents.** The study was conducted in accordance with the principles expressed in the Declaration of Helsinki for Human Rights. The Human Research Ethics Committee of the University of Western Australia approved the study protocol, and all men provided written informed consent to participate.

Study design, setting, and participants. The data reported in this article arose from a retrospective cohort analysis of 3,542 community-dwelling older men living in the metropolitan region of Perth, Western Australia.¹⁴

Baseline assessment. Between 1996 and 1998, participants underwent an assessment that recorded their date of birth, highest level of education attained, marital status, and lifestyle practices (including questions about physical activity, smoking, and alcohol use). Physical activity was assessed by asking men, “In a usual week, do you do any vigorous exercise that makes you breathe harder or puff and pant, such as fast walking, jogging, aerobics, vigorous swimming, vigorous cycling, tennis, football, squash, etc.?” Men who indicated that they engaged in vigorous activity for 150 minutes or more per week were considered physically active. We also asked participants, “Have you ever smoked cigarettes, cigars, or a pipe regularly (yes/no)?” Men who acknowledged having smoked regularly before were then asked, “How often do you smoke now (every day/not every day/not at all)?” We used the answers of participants to classify them as “never a regular smoker,” “past smoker,” or “current smoker.” We then asked men whether they had drunk alcohol during the last year (yes/no). Those who answered yes were required to indicate how many standard drinks of alcohol they consumed each usual day (from Monday to Sunday). A standard drink was defined as 285 mL of full-strength beer (5%) or the corresponding volume of reduced-alcohol beer; 1 pub measure of spirits, sherry, or port; or 1 glass of wine (equivalent to approximately 10 g of alcohol). We used this information to calculate the total number of drinks participants consumed during a usual week (sum of the number of drinks consumed during usual days of the week).

We considered that participants were abusing alcohol if they consumed 28 or more drinks per week.

We used standard procedures to measure participants' height (to 0.5 cm) and weight (to 0.2 kg) and calculated the body mass index. Men with a body mass index <18.5 kg/m² were classified as underweight, between 18.5 and 24.9 as normal, 25 to 29.9 as overweight, and 30 or above as obese.

Finally, we asked participants, “Have you ever been told by a doctor that you had a stroke/heart attack/angina?” (yes/no for each question). We considered cardiovascular diseases to be present if men answered yes to any of these questions. Men answered similar questions about the presence of diabetes and hypertension.

Primary outcome: Cognitive impairment. During the 2001 and 2004 wave of HIMS (Health in Men Study), which took place 3 to 8 years after baseline, participants underwent a cognitive assessment with the Mini-Mental State Examination (MMSE).¹⁵ The MMSE is a scale that assesses orientation for time and place, repetition and short-term recall of a list of 3 words, calculation, language (repetition, comprehension, naming, and written expression), and visuospatial construction. Scores range from 0 to 30, and a total score of 23 or less indicates the presence of clinically significant cognitive impairment.^{16,17}

***ADH1B* rs1229984 genotype.** We extracted DNA from blood samples collected during the 2001 to 2004 assessment of HIMS and used the TaqMan Drug Metabolism Genotyping assay to determine the allelic distribution at the single nucleotide polymorphism (SNP) rs1229984, which was associated with a call rate of 98.5% (Life Technologies Corporation, Carlsbad, CA). This procedure allowed us to determine the frequency of the common G and of the minor A alleles.

Statistical analyses. Data were managed and analyzed with the statistical package Stata release 12.1 (StataCorp, College Station, TX). We used descriptive statistics (mean, SD of the mean, proportions) to summarize the data, and Pearson χ^2 statistic to compare the distribution of various risk factors according to participants' rs1229984 genotypes and cognitive status. We also used Mann-Whitney ranked test to compare the number of standard drinks consumed per week by men with the GG genotype and carriers of the minor A allele, followed by the Cuzick nonparametric test for trend. The Hardy-Weinberg test determined whether the distribution of alleles at SNP rs1229984 was in equilibrium.

We used logistic regression to investigate the crude association between baseline exposures and cognitive status at follow-up, as estimated by the odds ratio (OR) and respective 95% confidence interval (CI). The α was set at 5% and all tests reported were 2-tailed.

RESULTS Of the 12,203 men assessed for the first time between 1996 and 1998, 2,301 (18.9%) died before the 2001–2004 assessment and another 4,348 (35.6%) declined or were unable to complete the new survey. Of the remaining 5,554 participants, 4,247 (76.5%) agreed to donate a blood sample, and genotyping of SNP rs1229984 was completed for 3,873 (69.7%) of them. Of the latter, 3,542 (63.8%) underwent assessment with the MMSE and constitute the study sample. A slightly larger proportion of regular alcohol users than abstainers or irregular drinkers completed the subsequent assessment of cognitive function with the MMSE

(40.6% vs 37.7%; $\chi^2 = 7.85$, $df = 1$, $p = 0.005$). The average time between the first and second assessments was 5.7 years (SD = 0.9, range 3.2–8.2).

Cross-sectional association between *ADH1B* genotypes and alcohol use at baseline. Two hundred twenty-two men (6.3%) carried the *ADH1B* rs1229984 G → A polymorphism (estimated disequilibrium coefficient $D = 0.002$; likelihood ratio $\chi^2 = 9.81$, $df = 1$, $p = 0.002$), although the distribution of alleles was in equilibrium among men with cognitive impairment given controls without cognitive impairment (likelihood ratio $\chi^2 = 2.35$, $df = 2$, $p = 0.309$). These results seem consistent with selective mating (i.e., regular GG/A drinkers may be

more likely to mate other GG/A drinkers, whereas AA nondrinkers may be more likely to mate other AA nondrinkers). The demographic, lifestyle, and clinical characteristics of participants are summarized in table 1. More participants with the AA than the GG or GA genotypes were physically active, and a lower proportion of those carrying the A allele were regular drinkers ($\chi^2 = 12.80$, $df = 2$, $p = 0.002$). One hundred fourteen men (3.2%) reported consuming 35 or more drinks during a usual week, of whom only 2 carried the G → A polymorphism (none with the AA genotype). The mean number of drinks consumed per week was 2.1 (SD = 3.0, range 0–7), 5.8 (SD = 7.8, range 0–35), and 8.4 (SD = 10.9, range 0–140) for men with the

Table 1 Demographic, lifestyle, and clinical characteristics of participants at the time of enrollment according to their rs1229984 genotype

	Genotype (rs1229984)			χ^2 (df)	p Value
	GG (n = 3,320), n (%)	GA (n = 211), n (%)	AA (n = 11), n (%)		
Age group, y					
65-69	1,510 (45.5)	98 (46.4)	6 (54.5)	8.73 (6)	0.190
70-74	1,144 (34.5)	62 (29.4)	3 (27.3)		
75-79	546 (16.4)	36 (17.1)	2 (18.2)		
80+	120 (3.6)	15 (7.1)	0		
High school completed	1,655 (49.9)	111 (52.9)	8 (72.7)	2.96 (2)	0.227
Married	2,840 (85.6)	177 (83.9)	10 (90.9)	0.73 (2)	0.695
Physically active	772 (23.2)	50 (23.7)	7 (63.6)	9.98 (2)	0.007 ^a
Smoking history					
Never	1,192 (35.9)	78 (37.0)	4 (36.4)	0.94 (4)	0.919
Past	1,882 (56.7)	121 (57.3)	6 (54.5)		
Current	246 (7.4)	12 (5.7)	1 (9.1)		
Alcohol use					
Nondrinker	444 (13.4)	37 (17.5)	1 (9.1)	21.56 (10)	0.018 ^a
Irregular	626 (18.9)	51 (24.2)	6 (54.5)		
<15 drinks/wk	1,630 (49.1)	98 (46.4)	4 (36.4)		
15-27 drinks/wk	370 (11.1)	17 (8.1)	0		
28-34 drinks/wk	138 (4.2)	6 (2.8)	0		
≥35 drinks/wk	112 (3.4)	2 (0.9)	0		
Body mass index					
Normal	1,066 (32.1)	67 (31.9)	6 (54.5)	2.74 (6)	0.841
Underweight	1 (0.3)	1 (0.5)	0		
Overweight	1,748 (52.7)	112 (53.3)	4 (36.4)		
Obese	493 (14.9)	30 (14.3)	1 (9.1)		
Hypertension	1,182 (37.4)	77 (38.7)	6 (54.5)	1.49 (2)	0.475
Diabetes	251 (7.6)	18 (8.5)	1 (9.1)	0.30 (2)	0.861
Cardiovascular diseases	757 (24.0)	39 (19.6)	3 (27.3)	2.05 (2)	0.359

Mean age of participants was 71.3 years (SD = 4.1, range 65.0–83.4). χ^2 : Pearson χ^2 statistic. The odds ratio of being a regular drinker among carriers of the A allele was 0.64 (95% confidence interval = 0.48–0.84).

^aStatistically significant.

AA, GA, and GG genotypes, respectively (Cuzick nonparametric test for trend, $z = 4.12$, $p < 0.001$).

Prevalence of cognitive impairment at follow-up. Table 2 shows the characteristics of participants at the time of entry into the study according to whether they showed evidence of cognitive impairment 5.7 years later. Men showing evidence of cognitive impairment (14.2%) were older than their counterparts at the time of

enrollment. High school completion and being married were associated with lower odds of cognitive impairment, whereas the reverse was true for men with history of coronary heart disease or stroke.

Longitudinal association between alcohol exposure and cognitive impairment. Consumption of 15 to 27 drinks per week was associated with lower odds of cognitive impairment compared with no drinking (OR = 0.60,

Table 2 Sociodemographic, lifestyle, clinical, and genetic characteristics of participants 5.7 years before the assessment of cognitive status

	No cognitive impairment (n = 3,040), n (%)	Cognitive impairment (n = 502), n (%)	OR	95% CI
Age group, y				
65-69	1,409 (46.3)	205 (40.8)	1	Reference
70-74	1,048 (34.5)	161 (32.1)	1.06	0.85-1.32
75-79	481 (15.8)	103 (20.5)	1.47	1.14-1.91 ^a
80+	102 (3.4)	33 (6.6)	2.22	1.46-3.38 ^a
High school completed	1,609 (52.9)	165 (32.9)	0.44	0.36-0.53 ^a
Married	2,618 (86.2)	409 (81.5)	0.71	0.55-0.90 ^a
Physically active	726 (23.9)	103 (20.5)	0.82	0.65-1.04
Smoking				
Never	1,100 (36.2)	174 (34.7)	1	Reference
Past	1,717 (56.5)	292 (58.2)	1.08	0.88-1.32
Current	223 (7.3)	36 (7.2)	1.02	0.69-1.50
Alcohol use				
Nondrinker	399 (13.1)	83 (16.5)	1	Reference
Irregular	577 (19.0)	106 (21.1)	0.88	0.64-1.21
<15 drinks/wk	1,495 (49.2)	237 (47.2)	0.76	0.58-1.00
15-27 drinks/wk	344 (11.3)	43 (8.6)	0.60	0.40-0.89 ^a
28-34 drinks/wk	123 (4.0)	21 (4.2)	0.82	0.49-1.38
≥35 drinks/wk	102 (3.4)	12 (2.4)	0.57	0.30-1.08
BMI group				
Normal	979 (32.2)	160 (31.9)	1	Reference
Underweight	9 (0.3)	3 (0.6)	2.04	0.55-7.61
Overweight	1,608 (52.9)	256 (51.0)	0.97	0.79-1.20
Obese	441 (14.5)	83 (16.5)	1.15	0.86-1.54
Hypertension	1,081 (85.7)	184 (38.2)	1.03	0.85-1.26
Diabetes	226 (7.4)	44 (8.8)	1.20	0.85-1.68
Cardiovascular diseases	661 (22.9)	138 (28.6)	1.35	1.09-1.68 ^a
Genotype (rs1229984)				
GG	2,851 (93.8)	469 (93.4)	1	Reference
GA	180 (5.9)	31 (6.2)	1.05	0.71-1.55
AA	9 (0.3)	2 (0.4)	1.35	0.29-6.27

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

Cognitive impairment was defined by a score of 23 or less on the Mini-Mental State Examination. The OR of cognitive impairment among carriers of the A allele compared with the GG genotype was 1.03 (95% CI = 0.70-1.52, after adjustment for age and physical activity). Median and interquartile range of Mini-Mental State Examination scores for noncarriers and carriers of the A allele: 27 (25-28) and 27 (25-28); Mann-Whitney test adjusted for ties: $z = 0.16$, $p = 0.870$.

^aStatistically significant.

95% CI = 0.40–0.89). The reduced odds of cognitive impairment associated with consumption of 15 to 27 drinks per week remained even after the exclusion of abstainers from the analyses (OR = 0.68, 95% CI = 0.47–0.99; reference: irregular drinkers). The observed benefits associated with moderate consumption of alcohol (15–27 drinks per week) were no longer statistically significant when the analyses were adjusted for age, education, marital status, and prevalent cardiovascular diseases (OR = 0.73, 95% CI = 0.49–1.10, $p = 0.133$). However, the adjusted odds of cognitive impairment was higher among irregular drinkers and abstainers than regular drinkers (any amount) (OR = 1.23, 95% CI = 1.00–1.51, after statistical adjustment for age, education, marital status, and prevalent cardiovascular diseases). Time between recruitment and the assessment of cognitive function was similar for men with and without cognitive impairment (mean = 5.7, SD = 1.0, and mean = 5.7, SD = 0.9, respectively; $t = 1.15$, $p = 0.251$).

Longitudinal association between the *ADH1B* rs1229984 G→A polymorphism and cognitive impairment. The allelic distribution of the *ADH1B* rs1229984 G→A polymorphism among men with cognitive impairment was under Hardy-Weinberg equilibrium given controls: likelihood ratio $\chi^2 = 2.35$ ($df = 2$), $p = 0.309$. Compared with the GG genotype, AA carriers had a nonsignificant increased odds of cognitive impairment (OR = 1.35, 95% CI = 0.29–6.27). The odds of cognitive impairment among men with the AA genotype increased, albeit not significantly, when we excluded abstainers from the analyses: OR = 1.58, 95% CI = 0.34–7.49; reference: irregular drinkers. Given the prevalence of genotypes among participants, we calculated the sample size that would be required to declare as significant an increase in the odds of cognitive impairment of 35% associated with the AA/GG genotype: 196,595 men (this would be consistent with a decrease in the odds of cognitive impairment associated with regular alcohol consumption).

DISCUSSION The results of this study confirmed that the *ADH1B* rs1229984 G→A polymorphism is associated with decreased regular intake of alcohol, amount of alcohol consumed, and less-frequent alcohol abuse.^{13,18} We also found that, compared with abstainers, moderate alcohol use (15–27 drinks per week) is associated with less cognitive impairment 6 years later, and that the regular consumption of large amounts of alcohol (28 or more drinks per week) does not increase the risk of cognitive impairment at follow-up. The apparent protective effect of moderate alcohol use on cognitive function was no longer statistically significant after adjustment for potential confounders (age, education, marital

status, and prevalent cardiovascular diseases), although, as a group, regular drinkers had lower adjusted odds of cognitive impairment than abstainers or irregular drinkers 5.7 years later. Furthermore, our data revealed that the *ADH1B* rs1229984 G→A polymorphism does not decrease the risk of cognitive impairment, as would have been expected if alcohol abuse was a direct cause of it. Indeed, our genetic findings are consistent with the possibility that regular alcohol use decreases the medium- to long-term risk of cognitive impairment in older men.

Data for this study were derived from a well-established cohort of older Australians.¹⁴ We acknowledge, however, that our analyses were limited to a fraction of surviving men who were healthier than those who did not return for assessment.¹⁹ The consequent healthy-participant bias would have favored the selection of men without cognitive impairment, leading to an underestimation of the true prevalence of cognitive impairment and decreasing the power of analyses designed to investigate this outcome. Similarly, heavy drinkers taking part in the study might have been healthier than those who did not participate, which would have decreased our ability to investigate the negative consequences of drinking. However, we found that our regular alcohol users had greater chance of completing the second assessment than abstainers or irregular users, which suggests that our results cannot be easily attributed to healthy-participant bias among regular drinkers (i.e., sicker regular drinkers leaving the study earlier). Moreover, we have shown before that regular drinkers have lower mortality than nondrinkers and that the amount and frequency of alcohol use is not associated with increased general mortality or mortality due to dementia.²⁰ Hence, our results are unlikely to be attributable to differential censoring caused by alcohol use.

Our definition of cognitive impairment relied entirely on the performance of participants on the MMSE, which may not equate to a diagnosis of dementia. Nonetheless, our approach has acceptable face validity and is used widely to assess the cognitive abilities of older people.^{15,16} We cannot be certain that our study did not include prevalent cases of cognitive impairment, although our inclusion criteria required men to be living independently in the community and to survive 6 years, making the presence of prevalent cases less likely. Nevertheless, the lack of objective cognitive data at the baseline assessment is a limitation. Our assessment of alcohol consumption was based on self-report rather than objective measures, although current evidence suggests that this is a reliable and valid approach to measure alcohol use.²¹ We measured alcohol use only at study entry and acknowledge that the pattern of consumption may have changed during the follow-up period or might

have been different earlier in life. There is evidence that heavy, but not light or moderate, drinkers decrease consumption with increasing age,²² leading to a decrease in the prevalence of heavy drinking at follow-up. If heavy alcohol use was a cause of cognitive impairment, there would be a decrease in the prevalence of cognitive impairment as people get older, which is certainly not the case.²³ Furthermore, we limited our genetic analysis of the *ADH1B* gene to a single SNP, although various other polymorphisms of this and other genes have a role in the metabolism of alcohol.¹¹ However, the rs1229984 G → A SNP was chosen because of its marked effect on alcohol dehydrogenase activity and robust association with alcohol-related disorders.^{11–13} At present, it is unclear whether this polymorphism could potentially affect other metabolic pathways that contribute to modulate cognitive function (i.e., pleiotropy).

This study was limited to older men and it is unclear whether the results can be generalized to other age groups or to women. We also concede that our findings on cognitive impairment are limited to 3 to 8 years and that different associations could potentially occur over more extended periods of time. We conducted analyses to clarify whether the length of follow-up had affected the risk of cognitive impairment, but found no supportive evidence. Finally, we recognize that the *ADH1B* rs1229984 G → A polymorphism has low prevalence and that a study with 3,542 men may have been underpowered to detect the expected differences between the groups. However, the association observed was in opposition to what would have been expected if heavy alcohol use caused cognitive impairment, a finding that is consistent with a protective effect of alcohol on cognition in later life.^{5,7,24}

Our results indicate that alcohol consumption is not a direct cause of cognitive impairment in later life. Thus, the concept of alcohol-related dementia, which has currency as a clinical entity, may lack validity. Our data suggest that the supposed cognitive benefits of regular moderate alcohol consumption are partly explained by age, education, marital status, and prevalent comorbidities,²⁵ but they are consistent with the possibility that moderate alcohol use is associated with a small decrease in the risk of cognitive impairment in later life. A large mendelian randomization study is now required to establish whether this association is truly causal.

AUTHOR CONTRIBUTIONS

O. Almeida conceived and designed the experiments, analyzed the data, and drafted the manuscript. All authors performed the experiments, reviewed the manuscript for important intellectual content, and approved its submission for publication.

STUDY FUNDING

Supported by competitive research grants from the National Health and Medical Research Council of Australia, numbers 279408, 379600, 403963, 513823, and 634492. The sponsors had no role in

the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

DISCLOSURE

O. Almeida, G. Hankey, and B. Yeap report no disclosures relevant to the manuscript. J. Golledge is partly funded by the Health and Medical Research Office of Queensland. He has received consultancy fees from Remedy Health Care Australia. L. Flicker reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 13, 2013. Accepted in final form December 9, 2013.

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