The triangular association of ADH1B genetic polymorphism, alcohol consumption and the risk of depression in older men

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ABSTRACT

Alcohol use, particularly alcohol abuse and dependence, are associated with increased risk of depression. Current diagnostic criteria suggest that the relationship is causal, but the evidence has only been derived from observational studies that are subject to confounding and bias. Given the logistic and ethical constraints that would be associated with a trial of alcohol use to prevent depression, we aimed to complete a Mendelian randomisation study to determine if a genetic polymorphism associated with alcohol abuse and dependence (*ADH1B* rs1229984 G→A) contributed to modulate the risk of depression in a community-derived cohort of older men. This retrospective analysis of a cohort of 3873 community-dwelling men aged 65-83 years living in the metropolitan region of Perth, Western Australia, investigated the triangular association between the rs1229984 G→A polymorphism and alcohol use and, after 3.2 to 8.2 years, the presence of current depression of history of depression. The mean number of standard drinks consumed per week (n; standard deviation; range) according to genotype was AA 1.8 (17; 2.7; 0 to 7), GA 5.9 (262; 7.5; 0 to 35), GG 8.5 (3594; 10.9; 0 to 140) (GG>AA, GG>GA; $p<0.001$). Consumption of 1 or 2 drinks per day decreased the odds of depression (n=610) by 30% and 40%, whereas consumption of more than 6 daily drinks more than doubled the odds of depression (odds ratio: 2.12, 95% confidence interval: 1.02, 4.40). The *ADH1B* rs1229984 G→A polymorphism was not associated with current or past depression ($p=0.857$). In addition, the presence of the A allele did not interact with alcohol use to modulate the risk of depression ($p=0.725$). These results suggest that alcohol consumption does not cause or prevent depression in older men.

INTRODUCTION

Alcohol consumption is an increasingly important modifiable factor associated with poor health outcomes, representing the 3rd leading cause of years of life lost due to disability worldwide.[1] Excessive use of alcohol has been linked to numerous health problems, such as cancers of the digestive system, liver and breasts, as well as trauma.[2] Whether alcohol use is causally linked to the onset and perpetuation of mental disorders such as depression is not yet clear. Over the past 25 years, several studies have reported a 'J' shape association between alcohol use and depression, with abstainers and heavy drinkers experiencing more severe depressive symptoms than light or moderate drinkers.[3-5]

Data from the National Longitudinal Alcohol Epidemiologic Survey showed that the odds of major depression was 4 times higher among adults with past alcohol dependence (n=836) than people with no such history (n=5214), suggesting that the past regular consumption of large amounts of alcohol might contribute to the onset or perpetuation of depressive symptoms.[6] Similarly, data from a New Zealand birth cohort study found that alcohol abuse and dependence were associated with the presence of major depression between ages 17 and 25 years, and that the pattern of association was consistent with a causal effect of alcohol on the onset of depression.[7] An analysis of a large cohort of 3755 US twin pairs showed that alcoholism and depression have overlapping but not identical causes, and only a small fraction of the vulnerability to these disorders could be attributed to heritable factors.[8] Taken together, the findings of observational studies published to date are generally supportive of the hypothesis that the regular consumption of large amounts of alcohol contributes to cause depression. However, bias and confounding could plausibly explain these results.

The best way to demonstrate that alcohol consumption is causally associated with depression is to show, by means of sufficiently powered randomized controlled trials, that lowering (or increasing) alcohol use reduces (or increases) the incidence and severity of depressive symptoms. However, such a trial would be difficult to justify from a logistic and ethical point of view. Traditionally, the next best form of evidence for causality is a systematic review of observational studies, which has proven difficult because of the significant heterogeneity of the research published in this area.[9]

More recently, genetic epidemiologists have proposed that Mendelian randomisation can be used to infer causality between an exposure and a clinical outcome.[10] The rationale, in this case, is that genetic polymorphisms that modify the efficiency of enzymes involved in the metabolism of alcohol should also modify the consequences of alcohol use. For example, the rs1229984 G→A (Arg→His) variant of the alcohol dehydrogenase 1B (*ADH1B*) gene can reduce the ability of the enzyme to oxidise ethanol by as much as 80-fold.[11] The odds of alcohol dependence or abuse is 3 times higher among adults with the GG than with the AA genotype (i.e., more efficient metabolisers have greater odds of alcohol-related disorders).[12] In addition, a recent investigation of European and African-American cohorts demonstrated that a greater proportion of people with the GG genotype develop alcohol dependence with increasing age compared with carriers of the A allele.[13] Consequently, the *ADH1B* rs1229984 G→A polymorphism produces a natural (Mendelian) randomisation, with individuals allocated to a higher (GG) or lower (GA/AA) probability of alcohol abuse or dependence according to a random assortment of alleles during gamete production and fertilization. These groups should not differ systematically in any other way. For example, those with the GG genotype should not be no more likely to be smokers or married or have lower education than individuals with the GA/AA genotypes (i.e., the distribution of confounding variables is expected to be random).

The aim of the present study was to determine if alcohol consumption is causally related to current or past clinically significant depression in later life. To address this question, we used two complementary approaches to explore the triangular association between exposure to *ADH1B* rs1229984 G→A polymorphism, alcohol use and depression. Firstly, we investigated the cross-sectional association between *ADH1B* rs1229984 genotypes and alcohol use in a large cohort of older adults recruited as part of the Health In Men Study (HIMS). The idea was to confirm that this genotypic variation is associated with a pattern of alcohol use in later life that is similar to that reported for younger adults.[13] Secondly, we followed these men for up to 8 years to ascertain whether exposure to alcohol at the time of study entry and to the *ADH1B* rs1229984 G→A polymorphism were associated with prevalent depression at the follow up assessment. Consistent with a causal role of alcohol on the onset and maintenance of clinically significant depressive symptoms, we hypothesised that participants with the *ADH1B* rs1229984 G→A polymorphism would have lower risk of depression than men with the GG genotype.

METHODS

Ethics statement

The study was conducted in accordance to 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 paper arises from a retrospective cohort analysis of 3873 community-dwelling older men living in the metropolitan region of Perth, Western Australia. Details about the recruitment of participants and study procedures have been described elsewhere.[14]

Baseline assessment

During the 1996-1998 assessment, men completed a questionnaire that contained information about the date of the assessment, the participant's date of birth, highest level of education attained, marital status and lifestyle practices (including questions about physical activity, smoking and alcohol use).

We assessed physical activity with the following question: *In a usual week do you do any vigorous exercise that makes you breathe harder of 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 then 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 a "never a regular smoker", "past smoker", "current smoker". We also asked men whether they had drunk alcohol during the last year (yes/no). Those who answered yes were then asked to indicate how may standard drinks of alcohol they consumed each day of a usual week (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. We added the total number of drinks consumed during a usual week and divided the result by 7 to calculate the average number of standard drinks consumed per day. For the purposes of presentation of the data, we ascribed the value zero to those who indicated that in a usual week they did not consume any alcohol, 1 to those who indicated that they consumed on average more than zero but no more than 1 standard drink per day, and so on until 7+ to indicate that men in this group consumed on average more than 6 standard drinks per day.

We used standard procedures to measure participant's height (to 0.5 cm) and weight (to 0.2 Kg) and calculated the body mass index (BMI) in Kg/m^2. Men with BMI<18.5 were classified as underweight, between 18.5 and 24.9 normal, 25 and 29.9 overweight, and 30 or above 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 that our men had cardiovascular disease if they answered 'yes' to any of these questions.

Primary outcome: depression status

During the 2001-2004 wave of HIMS, which took place 5.7 years after the baseline assessment, we asked participants to indicate whether they had *ever received treatment for an emotional or nervous illness such as depression (yes/no)* or if they had been *told by a doctor for the first time in the last 5 years that you had depression (yes/no)*. Men who answered 'yes' to either of these questions were considered to have experienced depression in the past. We also used the Western Australian Data Linkage System (WADLS) to determine if participants had a recorded diagnosis of depression before this follow up assessment. WADLS connects death records, acute hospital admissions, hospital movements, cancer registry and psychiatric outpatient contacts for all Western Australian residents.[15,16] The following codes from the International Classification of Diseases (ICD) were used to investigate the presence of 'past depression': 296.2, 296.3, 300.4, and 311 according to ICD-9 coding, and F06.32, F32, F33, F34.1, F43.20, F43.21, and F43.22 according to ICD-10. In addition, participants completed the rating of the 15-item Geriatric Depression Scale.[17] For the purposes of this study, we considered that men were experiencing clinically significant symptoms at the time of assessment if they scored 7 or more on the 15-item Geriatric Depression Scale (GDS-15).[17] The outcome of interest of this study was the presence of current

(GDS-15≥7) or history of past depression (as ascertained by WADLS or by direct questioning) at the follow up assessment.

Determining the *ADH1B* rs1229984 genotype

We extracted DNA from blood samples collected during the 2001-2004 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, California, USA). This procedure allowed us to determine the frequency of the common G allele and of the minor A allele.

Statistical analyses

Data were managed and analyzed with the statistical package Stata release 12.1 (StataCorp, College Station, TX). We used descriptive statistics (mean, standard deviation of the mean [SD], proportions) to summarize our data, Pearson's chi-square statistic ($|^2$) to compare the distribution of various exposures according to participant's rs1229984 genotype and depressive status, or oneway analysis of variance (followed by Scheffé correction for multiple comparisons) and t-tests to contrast the age of participants according to genotype and depression 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. The Hardy-Weinberg test determined if the distribution of alleles at SNP rs1229984 was in equilibrium.

We used logistic regression to investigate the crude association between various exposures present at the baseline assessment and depression status 5.7 years later. This analysis was followed by a stepwise multivariate logistic regression to establish a parsimonious explanatory model of depression for the cohort. The odds ratio (OR) and respective 95% confidence interval

(95%CI) of the OR are reported for the crude and parsimonious associations. We used the Hosmer-Lemeshow goodness of fit χ^2 test to evaluate the adequacy of the parsimonious logistic regression model. We calculated the probability of depression using the Stata postestimation command "predict" following the most parsimonious logistic regression model to explain the presence of depression in this cohort. We then plotted the adjusted probability of depression according to number of daily drinks of alcohol stratified by the presence of the rs1229984 A allele. Alpha was set at 5% and all tests reported are two-tailed.

RESULTS

Three thousand eight hundred and seventy-three men provided valid information on relevant exposures at the baseline assessment. The age of participants ranged from 65 to 83 years. The frequency of the *ADH1B* rs1229984 A allele in our sample was 3.8% and the estimated disequilibrium coefficient (D) 0.003 (Pearson $\chi^2(1)=24.60$, $p<0.001$). A lower proportion of carriers than non-carriers of the rs1229984 A allele were regular drinkers (59.1% vs 68.2%; OR=0.68, 95%CI=0.53, 0.87), and 17.6% of carriers compared with 13.8% of non-carriers reported that they had not consumed any alcohol during the preceding 12 months ($\chi^2(1)=2.94$, $p=0.086$). Of the 2615 regular drinkers, the 165 carriers of the A allele consumed on average 3 standard drinks less than non-carriers per week (Mann-Whitney test $z=3.01$, $p=0.003$). Men with the AA genotype consumed no more than 7 standard drinks per week (average of 1 or less per day). This number increased to a maximum of 35 and 140 standard drinks per week for those with the GA and GG genotypes, respectively. Table 1 summarises the sociodemographic, lifestyle and clinical characteristics of men at the baseline assessment. Apart from alcohol consumption, the distribution of sociodemographic factors, lifestyle variables and cardiovascular diseases were similar across the 3 rs1229984 genotypes.

TABLE 1

Six hundred and ten men reported or had health records consistent with past or current depression 5.7 years after joining the study (range: 3.2 to 8.2 years). The mean age of participants with and without depression at the baseline assessment was 71.9 (SD=4.2) and 71.3 (SD=4.1) years (t=3.24, p=0.001). Compared with participants who denied having ever received a diagnosis of depression, men with depression were more frequently not married (p=0.012), past or current smokers (p=0.001), obese (p=0.001), abstainers or occasional drinkers (p=0.001), or were afflicted by cardiovascular diseases (p<0.001). The rs1229984 A allele was present in 45 (7.4%) and 234 (7.2%) of men with and without current or past history of depression ($|^2$(1)=0.03, p=0.857). Table 2 outlines the distribution of baseline exposures according to the depression status at follow up. The results of the analyses did not change noticeably when the outcome was limited to current depression (i.e., GDS-15 ≥ 7, n=200) at the follow-up assessment (16 and 263 men with and without depression were A carriers; $|^2$(1)=0.19, p=0.659).

TABLE 2

Logistic regression showed that the presence of current or past depression was not associated with the presence of the rs1229984 A allele (p=0.946), nor was there an interaction between presence of the A allele and alcohol consumption (p=0.725). A parsimonious multivariate logistic regression model of depression retained the following significant factors: age group 75-79 (OR=1.33, 95%CI=1.06, 1.67), past smoking (OR=1.29, 95%CI=1.11, 1.50), being underweight (OR=1.11, 95%CI=1.02, 1.20), cardiovascular diseases (OR=1.57, 95%CI=1.29, 1.91), and consuming an average of 1 (OR=0.70, 95%CI=0.57, 0.85) or 2 alcoholic drinks per day (OR=0.58, 95%CI=0.45,

0.76). Hosmer-Lemeshow test showed that the model had robust goodness of fit ($|^2$(8)= 4.28, p=0.831).

Finally, we calculated the probability of depression according to the number of standard drinks consumed per day 5.7 years earlier, and stratified our estimates by the presence of the *ADH1B* rs1229984 A allele. Figure 1 shows a quadratic fit of the probabilistic estimates, with similar "J" curves for carriers and non-carriers of the rs1229984 A allele. The probability of depression decreased with increasing consumption of alcohol up to about 2 standard drinks per day, after which the probability of depression increased rapidly in an almost linear fashion with increasing alcohol use.

FIGURE 1

DISCUSSION

The results of this study show that older men with the G→A variation on the rs1229984 *ADH1B* gene consume less alcoholic beverages than those carrying the common G allele or, alternatively, that carriers of the GG genotype consume significantly more alcohol than carriers of the A allele. As predicted by Mendelian randomisation, this discrete pattern of alcohol use according to genotype could not be explained by other measured factors such as age, education, marital status, smoking, physical activity, body mass or cardiovascular morbidity. We also found that the regular consumption of 1 to 2 drinks per day decreased the risk of depression, while consuming more than 6 daily drinks increased the risk. However, the presence of current or past depression was not associated with the rs1229984 *ADH1B* genotype, and the A allele of the rs1229984 *ADH1B gene* did not modify the association between alcohol consumption and the probability of depression.

Taken together, these findings suggest that alcohol use is unlikely to be causally related to the presence of current of past clinically significant depressive symptoms in older men.

Limitations of the study design

HIMS is a well established community derived sample of older men for whom a wealth of clinical, sociodemographic, lifestyle and genetic data are available.[14] We concede, however, that the present study used a fraction of the inception cohort because blood samples were only collected at the follow up assessment. We have previously published data showing that men who did not donate a blood sample had worse physical health.[18] This would have biased our sample towards a healthier sample and would have decreased our ability to investigate the effects of alcohol on the mood of people whose lifestyle led to a more severe deterioration of physical health. If men with the rs1229984 *ADH1B* GG genotype who drank more heavily were preferentially lost to the follow up assessment, then a bias favouring the selection of carriers of the A allele could have been introduced. Our sample had 3594 men with the GG genotype, while the expected number under the assumptions of Hardy-Weinberg equilibrium would have been 3583. Hence, there is no evidence that our selection procedures biased the sample towards a smaller than expected number of men with the rs1229984 *ADH1B* GG genotype. We also recognise that our definition of depression does not necessarily equate to a diagnosis of major depression according to DSM-IV or ICD-10 criteria, but our approach to the definition of 'caseness' by means of self-report, record linkage and direct assessment is most likely indicative of clinically significant depression.[17] In addition, as our study was limited to older men, we cannot be confident that our findings would apply equally to women or to other age groups, although the results of previous investigations that included women and younger adults would suggest that there is no reason to believe they would not.[13] We limited our analysis to a single SNP of the alcohol dehydrogenase enzyme, but acknowledge that several other polymorphisms of this and of other genes could interfere with the

metabolism of alcohol.[11] Nonetheless, given the constraints of our research design and budget, we selected the SNP that is most robustly associated with alcohol-related disorders,[11-13] although we concede that we examined associations with alcohol consumption rather than disorders (such as abuse or dependence). One may also argue that a study with 3873 people could be underpowered to investigate these types of associations, although we were able to demonstrate that the relevant G→A rs1229984 polymorphism had the expected impact on alcohol use, but showed no hint of an effect on the outcome depression. Hence, our negative results regarding association with depression cannot be easily attributed to lack of power. Finally, we acknowledge that the consumption of alcohol might have changed during the follow up period and, indeed, there is evidence that people who drink heavily tend to decrease consumption with increasing older age (changes among light to moderate drinkers are minimal).[19] Consequently, we would expect a lower number of heavy drinkers at the follow up compared with the baseline assessment. If we accept that heavy alcohol use causes depression, then less people would become depressed with increasing age. This does not seem to be the case. In addition, we would have expected the association between heavy alcohol use and depression to decrease with increasing age, which we were unable to demonstrate with our data.

Interpretation of the findings

Our analyses of non-genetic data are consistent with those from other observational studies showing a 'J' curve association between alcohol consumption and the risk of depression: men who reported consuming 1 or 2 standard drinks per day had the lowest risk of depression.[3] However, the distribution of the probabilities of depression according to alcohol use did not seem to vary substantially among carriers and non-carriers of the A allele of the rs1229984 *ADH1B* gene. If alcohol use were a direct cause of depression, we would have expected to observe a clear shift of the probability curve to the left (i.e., lower consumption would be associated with greater risk

because A-allele carriers are poorer metabolisers of alcohol) and a decrease in the prevalence of depression in men with the GA and AA compared with GG genotype. That was not the case. Therefore, we have rejected our initial hypothesis and concluded that alcohol consumption does not cause or prevent depression, at least not in older men.

If our results are valid, how can we explain the association between significant alcohol use and depression reported by other observational studies? Nearly 20 years ago, Lipton[20] argued that alcohol drinking is a marker for a spectrum of behaviours that modulate response to stress and risk of depression, such as financial strain, negative life events, social isolation and physical ill health.[21] Other lifestyle practices, such as physical inactivity and smoking, are also more frequent among heavy regular alcohol users[22,23] and could conceivably create a spurious association between alcohol and depression. There is also some evidence that people prone to depression or with depressive disorder might use alcohol more frequently to alleviate their low mood.[24,25] In other words, previously reported associations between alcohol use and depression could have arisen as a result of confounding, bias or reverse causality.

In conclusion, the results of our study do not support the hypothesis that alcohol consumption (as ascertained 5 years earlier) associated with polymorphisms of the ADH1B gene causes or prevents depression in older men. Future studies should now seek to determine if any other forms of alcohol use are causally related to depression.

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Table 1. Demographic, lifestyle and clinical characteristics of participants at the baseline assessment according to their rs1229984 genotype.

	Genotype (rs1229984)			
	GG N=3594 n (%)	GA N=262 n (%)	AA N=17 n (%)	p
Age group in years	1595 (44.4)	116 (44.3)	11 (64.7)	0.106
65-69	1274 (35.4)	83 (31.7)	4 (23.5)	
70-74	592 (16.5)	45 (17.2)	2 (11.8)	
75-79	133 (3.7)	18 (6.9)	0	
80+				
High school education	1728 (48.1)	123 (47.1)	9 (52.9)	0.880
Marital status married	3075 (85.6)	221 (84.3)	16 (94.1)	0.516
Physically active	811 (22.6)	56 (21.4)	7 (41.2)	0.167
Smoking history: never	1260 (35.1)	94 (35.9)	6 (35.3)	0.988
past	2053 (57.1)	146 (55.7)	10 (58.8)	
current	281 (7.8)	2 (8.4)	1 (5.9)	
Daily alcohol consumption* 0	1144 (31.8)	104 (39.7)	10 (58.8)	0.010
1	1125 (31.3)	82 (31.3)	7 (41.2)	
2	655 (18.2)	50 (19.1)	0	
3	296 (8.2)	15 (5.7)	0	
4	210 (5.8)	6 (2.3)	0	
5	76 (2.1)	5 (1.9)	0	
6	54 (1.5)	0	0	
7+	34 (0.9)	0	0	
Body mass index normal	1129 (31.4)	79 (30.3)	6 (35.3)	0.957
underweight	12 (0.3)	1 (0.4)	0	
overweight	1888 (52.6)	138 (52.9)	10 (58.8)	
obese	563 (15.7)	43 (16.5)	1 (5.9)	
Cardiovascular diseases	840 (24.5)	47 (18.8)	4 (23.5)	0.124

Note: The Odds ratio (OR) of being a regular drinker among carriers of the A allele was 0.68 (95%CI=0.53, 0.87).
*Mean number of standard drinks consumed per week (SD; range): AA 1.8 (2.7; 0 to 7), GA 5.9 (7.5; 0 to 35), GG 8.5 (10.9; 0 to 140); F=10.45 (2), p<0.001 (GG>AA, GG>GA).

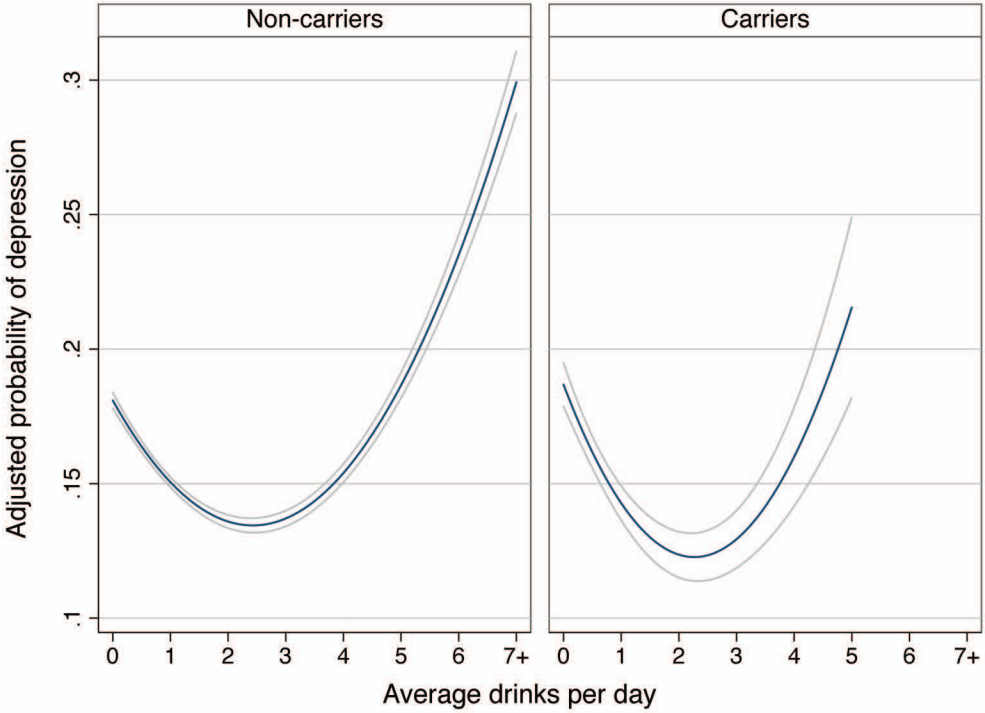
Table 2. Sociodemographic, lifestyle, clinical and genetic characteristics of participants 6 years before the assessment of their depression status.

		Never depressed N=3263 n (%)	Past or current depression N=610 n (%)	Crude OR (95%CI) of depression*
Age group in years	65-69	1479 (45.3)	243 (39.8)	1
	70-74	1141 (35.0)	220 (36.1)	1.17 (0.96, 1.43)
	75-79	517 (15.8)	122 (20.0)	1.44 (1.13, 1.82)
	80+	126 (3.9)	25 (4.1)	1.21 (0.77, 1.89)
High school education		1566 (48.0)	294 (48.2)	1.01 (0.85, 1.20)
Marital status married		2810 (86.2)	502 (82.3)	0.75 (0.59, 0.94)
Physically active		754 (23.1)	120 (19.7)	0.81 (0.66, 1.01)
Smoking history:	never	1184 (36.3)	176 (28.8)	1
	past	1834 (56.2)	375 (61.5)	1.38 (1.13, 1.67)
	current	245 (7.5)	59 (9.7)	1.62 (1.17, 2.24)
Daily alcohol consumption*	0	1026 (31.4)	232 (38.0)	1
	1	1048 (32.1)	166 (27.2)	0.70 (0.56, 0.87)
	2	621 (19.0)	84 (13.8)	0.60 (0.46, 0.78)
	3	260 (8.0)	51 (8.4)	0.87 (0.62, 1.21)
	4	169 (5.2)	47 (7.7)	1.23 (0.86, 1.75)
	5	69 (2.1)	12 (2.0)	0.77 (0.41, 1.44)
	6	47 (1.4)	7 (1.1)	0.66 (0.29, 1.48)
	7+	23 (0.7)	11 (1.8)	2.12 (1.02, 4.40)
Body mass index	normal	1039 (31.8)	175 (28.8)	1
	underweight	13 (0.4)	0	-
	overweight	1727 (52.9)	309 (50.8)	1.06 (0.87, 1.30)
	obese	483 (14.8)	124 (20.4)	1.52 (1.18, 1.97)
Cardiovascular diseases		702 (22.6)	189 (32.2)	1.63 (1.34, 1.98)
Genotype (rs1229984)	GG	3029 (92.8)	565 (92.6)	1
	GA	221 (6.8)	41 (6.7)	0.99 (0.70, 1.40)
	AA	13 (0.4)	4 (0.7)	1.65 (0.54, 5.08)

*Multivariate parsimonious logistic regression model retained the following significant factors: age group 75-79 (OR=1.33, 95%CI=1.06, 1.67), past smoking (OR=1.29, 95%CI=1.11, 1.50), being underweight (OR=1.11, 95%CI=1.02, 1.20), cardiovascular diseases (OR=1.57, 95%CI=1.29, 1.91), and consuming an average of 1 (OR=0.70, 95%CI=0.57, 0.85) or 2 alcoholic drinks per day (OR=0.58, 95%CI=0.45, 0.76).

FIGURE LEGEND

Figure 1. Probability of depression according to the number of standard drinks consumed 6 years earlier according to *ADH1B* genotype (A-allele carriers: right panel versus GG genotype: left panel). The dark blue line indicates the mean probability of depression and the surrounding grey lines the 95% confidence limits. The analyses were adjusted for age, smoking history, presence of cardiovascular diseases and body mass index group.


Non-carriers
Carriers
Adjusted probability of depression
.1
.15
.2
.25
.3
0
1
2
3
4
5
6
7+
Average drinks per day