



Beasley, M., Freidin, M. B., Basu, N. , Williams, F. M.K. and Macfarlane, G. J. (2019) What is the effect of alcohol consumption on the risk of chronic widespread pain? A Mendelian randomisation study using UK Biobank. *Pain*, 160(2), pp. 501-507.  
(doi:[10.1097/j.pain.0000000000001426](https://doi.org/10.1097/j.pain.0000000000001426))

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**What is the effect of alcohol consumption on the risk of chronic widespread pain? A Mendelian randomisation study using UK Biobank – Version 2**

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Number of pages of manuscript: 21

Number of tables: 4

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## **Abstract**

Studies have shown that moderate alcohol consumption is strongly associated with reduced reporting of chronic widespread pain (CWP). The study designs used however are prone to confounding and are not able to establish the direction of causality. The current study overcomes these problems by using the Mendelian randomisation design to determine the effect of alcohol consumption on the likelihood of reporting CWP. The UK Biobank recruited 500,000 participants aged between 40 and 69 years. Data collected included questions on chronic pain and alcohol consumption, and biological samples providing genotypic information. Alcohol consumption was categorised as 'weekly consumption' or 'non or infrequent'. Participants were classified by genotype according to alleles of the rs1229984 SNP, either 'GG' or 'AA/AG'. CWP was defined as pain all over the body for more than 3 months that interfered with activities. Associations between genotype, CWP and alcohol consumption were tested by logistic regression. Instrumental variable analysis was used to calculate the causal effect of weekly alcohol consumption on CWP. Persons with 'GG' genotype had an increased risk of CWP (odds ratio, OR 1.17, 99% confidence interval CI 1.01-1.35) and were more likely to consume alcohol weekly (OR 1.76, 1.70-1.81) compared to those with 'AA/AG' genotype. Weekly consumption of alcohol was associated with reduced risk of CWP (OR 0.33, 0.31-0.35), but instrumental variable analysis did not show a causal effect of alcohol consumption on reducing CWP (OR 1.29, 0.96-1.74). An interpretation of observational population studies as showing a protective effect of alcohol on CWP is not supported.

**Keywords:** alcohol, drinking, chronic widespread pain, epidemiology, Mendelian randomisation

## INTRODUCTION

A defining feature of fibromyalgia is chronic pain all over the body, or chronic widespread pain (CWP) [23,24]. One estimate of global fibromyalgia prevalence is 2.7% [20] but estimates can range from 1.1 to 6.4% depending on criteria used [11,22]. Meta-analyses have estimated CWP prevalence at 9.8% globally [1] and 14.2% within the UK [7]. Among lifestyle factors associated with fibromyalgia and CWP is alcohol consumption. One study among fibromyalgia patients found moderate alcohol consumption was associated with reduced symptom severity compared to abstinence [13]. The authors suggested ethanol-enhanced production of  $\gamma$ -Aminobutyric Acid (GABA) [12] as a mechanism for effects of alcohol in people with fibromyalgia, among whom studies have shown decreased levels of GABA [9]. Population studies have found CWP is less common among persons with moderate alcohol consumption, even among those who had not reduced drinking due to ill health [3]. In one study, those drinking 11 to 35 units a week were a third less likely to report CWP as those who had never drunk regularly, while among people with CWP, moderate alcohol consumption was associated with less disability [15].

There are limits to inferences that can be drawn from observational studies [8]. It is conceivable that alcohol has analgesic effects, and that is why moderate drinkers report less pain. However, these studies are prone to confounding and 'reverse causation'. A confounded relationship would mean a third variable associated with alcohol consumption but is not its consequent, though it may be its antecedent, has an effect on pain. 'Reverse causation' could mean that people reduce their alcohol intake because they have chronic pain. Both explanations would produce the associations described in previous studies.

One study design that overcomes some of these problems is Mendelian randomisation [2]. Mendelian randomisation is particularly useful when a randomised trial is not feasible, as when studying effects of alcohol consumption. In this design, genetic variants strongly associated with a particular behaviour, such as a single genetic base or single-nucleotide polymorphism (SNP), are chosen as proxy measures for the behaviour [14]. Their distribution throughout a population is assumed random, so

their influence is assumed to be distributed randomly and not influenced by confounders. One SNP that affects alcohol consumption is rs1229984 on chromosome 4, in the gene *ADH1B* for alcohol dehydrogenase. The common variant of this SNP is the guanine (G) nucleotide, while a smaller number of people carry one or two copies of the adenine (A) allele (global minor allele frequency between 0.0628 and 0.159 [19]). Among people with the rare variant, increased production of alcohol dehydrogenase converts ethanol to acetaldehyde more rapidly so unpleasant effects are experienced after consuming alcohol [4]. Because of ill effects of alcohol, people manifesting AA or AG at rs1229984 consume less.

The current analysis aimed to examine the association of variants of the rs1229984 SNP with reporting of CWP in a large population sample from the UK, and to use the variants as an instrumental variable for estimating the causal effect of alcohol consumption on CWP.

## **METHODS**

### **UK Biobank**

The UK Biobank recruited over 500,000 participants aged between 40 and 69 years from among patients registered at general medical practitioners within the UK National Health Service [21]. Around 9.2 million people were invited to take part in the study, making a participation rate of 5.5% [16]. Participants attended assessment centres across the UK where they completed by touchscreen electronic questionnaires that included questions on health and lifestyle. Physical measures and biological samples were also collected at assessment centre visits. The UK Biobank is overseen by the UK Biobank Ethics and Governance Council, and has received approval from appropriate ethics committees.

### **Pain questions**

Participants were asked by touchscreen questionnaire 'In the last month have you experienced any of the following that interfered with your usual activities?' They were provided with a list of options to choose from: headache, facial pain, neck or shoulder pain, back pain, stomach or abdominal pain, hip pain, knee pain, pain all over the body, none of the above, prefer not to answer. Participants who chose 'pain all over the body' were not offered the option of choosing any other pain sites. For each pain selected or for 'pain all over the body', they were then asked if they had the pain for more than 3 months. Participants were classified as having CWP if they answered they had 'pain all over the body', and that they had experienced this for more than 3 months. This definition of CWP has been used in a number of previous studies [3,16,17]

### **Alcohol questions**

Participants were also asked 'About how often do you drink alcohol?', and given a number of options from which to choose. If participants answered 'once or twice a month', 'special occasions only', or 'never' they were classified as 'non or infrequent' drinkers of alcohol for this analysis. If their answer was 'once or twice a week', '3 or 4 times a week', or 'daily', they were classed as 'weekly consumers' of alcohol.

### **Other chronic pain risk markers**

A number of other risk markers for CWP were collected at the assessment centre visit and used as adjusting factors: age at time of visit in whole number of years, BMI calculated from height and weight measured at visit, and Townsend Deprivation index derived from a participant's postcode. The following were also collected by touchscreen questionnaire: employment (classified for this analysis as employed/self-employed, retired, unable to work because of sickness/disability, unemployed, or none of the above/other); smoking (never, tried once or twice, previous occasional smoker, previous smoking most days, current occasional smoker, or current smoker most days); self-reported ethnic group (classed as white or non-white ethnic background for this analysis); university degree or not; measures of mood (ever felt miserable, often felt fed-up); and frequency of visits with friends and family (2 or more a week versus 1 or less).

### **Genotyping information**

Genotyping information was available for UK Biobank participants. Variants of rs1229984 were used as markers for exposure to alcohol consumption. This SNP lies in exon 3 of the *ADH1B* gene which codes for an alcohol dehydrogenase. The reference allele is guanine (G) and carriers of one or two copies of the adenine (A) allele have faster metabolism of alcohol. These people are more likely to have unpleasant effects from drinking and so drink less and are at lower risk for alcoholism [4]. For this analysis, participants were classed as either carrying the 'GG' or 'AA/AG' variants of rs1229984. Those with 'AA' and 'AG' variants were combined into one group because of the lower minor allele frequency for rs1229984 [4].

### **Analysis**

Stata/SE 13.0 was used to examine associations between alcohol consumption, CWP, and genotype. First, the association between reporting CWP and variants of the rs1229984 SNP was examined. The percentage of those having CWP in each genotype ('AA/AG' and 'GG') was calculated. Logistic regression was used to calculate the odds ratio (OR) with 99% confidence interval (CI) for reporting CWP in those with the 'GG' genotype compared to those with 'AA/AG'. Analyses were performed

separately for males and females, and in those of self-reported white and non-white ethnicity. Analyses were stratified by gender and ethnicity since gender is associated with both CWP and alcohol consumption, and self-reported ethnicity is associated with CWP and genotype. ORs adjusted for age, gender, and chronic pain risk markers, were calculated

In order to confirm the association of the rs1229984 SNP with alcohol consumption, the proportion of weekly consumers of alcohol and those not consuming or consuming infrequently was calculated for each genotype. Logistic regression was used to calculate ORs of weekly consumption of alcohol in those with the 'GG' genotype compared to those with 'AA/AG'. This was repeated separately for those of each gender, and for those of self-reported white and non-white ethnicity.

Next, the association between alcohol consumption and CWP in the population was confirmed. The percentage of those with CWP in consuming alcohol weekly, and in those not consuming or consuming infrequently was calculated. ORs for reporting of CWP in 'weekly consumers' compared to 'non or infrequent' consumers were calculated with 99% confidence intervals (CI) by logistic regression. Adjusted odds ratios (AORs) with 99% CIs were then calculated using logistic regression. Analyses were repeated in those of white and non-white ethnicity, and in both genders.

Instrumental variable analysis by the inverse-variance weighting (ratio) method [5] was used to calculate the causal effect of weekly consumption of alcohol on CWP, using variants of the rs1229984 SNP as an instrumental variable and 'non or infrequent' as the reference category. In this method, the ratio of the coefficient of CWP regressed on genotype (adjusted for covariates) to the coefficient of alcohol regressed on genotype (also adjusted) gives the causal estimate of the effect of alcohol on CWP. The coefficients were obtained from logistic regression models, and odds ratios were obtained by exponentiation of the ratio of the coefficients. The standard error estimates for the risk ratios were adjusted for the observed correlation between CWP and alcohol consumption. ORs with 99% CIs are reported overall and separately for each category of gender and ethnicity.

## RESULTS

Alcohol consumption information was available for 501,098 participants of whom 344,656 (68.9%) reported consuming alcohol weekly. Pain information was available for 500,410 participants of whom 7,130 (1.4%) reported CWP. Genotype was available for 486,321 participants of whom 28,511 (5.9%) were 'AA/AG'. The number of participants who had alcohol, pain, and genotype information available was 484,178. Characteristics of participants by genotype are given in **Table 1**. Those with 'GG' genotype tended to have higher BMI and greater deprivation than those of 'AA/AG' genotype, and were less likely to be of non-white ethnicity. There were also differences in employment status and number of those with a university degree. Differences in smoking behaviour and other characteristics were small.

### Genotype and CWP

Participants of 'GG' genotype were slightly more likely to report CWP than those with 'AA/AG' (**Table 2**) (1.4 vs. 1.2%, OR 1.17, 99% CI 1.01-1.35)). The estimate of effect did not exclude the null in the 99% CI after adjustment for other risk markers (aOR 1.14, 0.97-1.33). Higher prevalence of CWP was also seen among those with the 'GG' genotype when looking separately at those of white ethnicity and non-white ethnicity (1.3 vs. 1.1%, OR 1.25, 1.06-1.48, and 3.4 vs. 2.1%, OR 1.64, 1.24-2.20 respectively). The size of these effects were attenuated and failed to exclude the null from the 99% CI when adjusted for CWP risk markers.

### Genotype and alcohol consumption

Among participants for whom information on alcohol consumption and genotype was available, there were differences in alcohol consumption among those of the 'GG' and 'AA/AG' genotypes (**Table 3**). Among males, those of 'GG' genotype were more likely to consume alcohol weekly compared to those with 'AA/AG' (77.8 vs. 67.1%, OR 1.71, 1.63-1.80, aOR 1.60, 1.52-1.69). Among females the same patterns were observed with 62.9% of those of 'GG' genotype consuming alcohol weekly compared to 47.8% of those drinking none or infrequently (OR 1.85, 1.77-1.93, aOR 1.77, 1.69-1.86). The same

pattern was observed in both those of white and non-white ethnicities, with a greater proportion among those of 'GG' genotype consuming alcohol weekly.

#### **Association between alcohol consumption and CWP in the population**

Participants who reported consuming alcohol weekly were less likely to report CWP compared to those drinking none or infrequently (**Table 4, Figure 1**) (0.9 vs 2.6%, OR 0.33, 0.31-0.35, aOR 0.56, 0.53-0.61). This was observed among those of white and non-white ethnicity and in both genders.

#### **Causal effect of weekly alcohol consumption on risk of CWP**

The estimate of the causal effect of alcohol consumption on risk of CWP using instrumental variable analysis did not show a decreased risk with weekly consumption of alcohol (**Table 4, Figure 1**) (OR 1.29, 0.96-1.74). Effect estimates were similar for males and females, and those of white and non-white ethnicity, ranging from ORs of 1.28 to 1.49, apart from among non-white males which showed a small decreased risk of OR 0.96. None of the effect estimates excluded the null in their 99% confidence intervals.

## DISCUSSION

We did not find evidence for a protective effect of weekly alcohol consumption on the reporting of CWP. Those participants with a genetic predisposition to avoid alcohol were less likely to report CWP, not more. The results of the instrumental variable analysis suggest there could be a small harmful effect of alcohol on CWP.

The main strength of the study is that of the Mendelian randomisation method. To the extent that variants of the rs1229984 SNP are distributed randomly among the population, they are not confounded with other factors that may have an effect on the outcome. This method also deals with the problem of so-called 'reverse causation'. While in traditional observational studies the direction of causality between two associated variables is difficult to ascertain, in our study, it is not possible that being less likely to report pain *caused* people to carry the A allele. Additional strengths of this study include its large sample size, the availability of a number of other CWP risk markers, and similar levels of alcohol consumption as found in other surveys in the UK population [6]. Also, the definition of CWP used (chronic pain all over the body that has interfered with activities and experienced for more than 3 months) gave prevalence estimates consistent with that of fibromyalgia, indicating that we were likely considering a phenotype at the same extreme end of the pain spectrum.

There are however limitations to our study. One is that rare variants of the SNP may not be randomly distributed throughout the population. Carriers of the rs1229984 A allele are more likely to be of non-white ethnicity. In the sample studied here, ethnicity is itself associated with socio-demographic factors, and with the reporting of pain [16]. However, the observed associations between the SNP variant and CWP held when looking at those of self-reported white ethnic background alone. Furthermore, for our analysis all those of non-white ethnic background were included in the same category. This was not in order to make any inferences about this group of people, as we would expect it to be quite heterogeneous, but only included for completeness. Another limitation of the method is

that the SNP used may have pleiotropic effects, that is, effects of the variants on CWP other than through their effects on alcohol consumption. In our instrumental variable analysis we dealt with this by adjusting for a number of common risk markers for CWP. This however makes the assumption that these risk markers were not on the casual pathway between alcohol consumption and CWP. For some of these covariates, for example gender and ethnicity, this was a reasonable assumption. It is possible however, that some of these covariates are pathway variables mediating the effect of alcohol on CWP in which case our estimate of the effect could be biased [5]. The direction of this potential bias could mean we have underestimated the effect of alcohol on pain so would not alter the conclusion that alcohol does not have a positive effect on pain.

Previous studies have found that CWP reporting was greater in non-drinkers compared to those drinking alcohol moderately [3,15], and the current study confirmed that association. The current study also concluded that, using variants of SNPs as a marker for alcohol consumption, alcohol consumption does not prevent CWP. While previous studies were observational and could only make a comment about associations between alcohol consumption and CWP, the current study used a method that allows an estimate of the causal effect of alcohol on CWP. We can conclude that the previous results were not due to moderate alcohol consumption causing people to have less pain. The results of those observational studies could instead be due to the effect of having pain on alcohol consumption, that is, people with pain being more likely to reduce their consumption. Our study did not have the power to examine small effects of alcohol consumption on CWP, and we cannot rule out the null hypothesis that there was no effect. However, the direction of effect means it is possible that alcohol consumption has a small harmful effect on CWP. It may be that at the population level, people with CWP reduce their consumption of alcohol *because* of the harmful effect on their symptoms.

In this study, the best estimate of the effect of weekly alcohol consumption on risk of CWP was small (risk ratio of about 1.3). For a condition with a low prevalence (1.5%), this represents an absolute

increase in risk of about 4 people per thousand. A randomised trial designed to assess this size of difference at 5% significance level with 90% power, and 100% treatment compliance, would require a sample size of over 67,000 participants. However, this estimate effect of alcohol on CWP has been adjusted for covariates. Some of these are among possible consequences of drinking alcohol (higher BMI, worse mood, lower levels of education) and could be regarded as potential mediators of its influence on CWP. In that case, it is possible that the true effect is larger than this. It is also possible that these covariates are colliders, consequences of both alcohol consumption and CWP, which would also influence the estimate of effect.

This results of this and previous studies leave some unanswered questions. Here, we estimated a small negative effect of alcohol consumption on CWP but could not rule out sampling error. If drinking alcohol does increase the risk of CWP we would have to consider by what mechanism. A general question for epidemiological researchers is how such a strong relationship as seen in the population between moderate levels of alcohol consumption and decreased CWP might come about given that that alcohol consumption does not lower the risk of CWP. The population-level effect may be behavioural, that is to say people who are at higher risk of CWP actively change their behaviour to avoid drinking. Possible reasons for avoidance of alcohol among patients with CWP are the use of medications for which alcohol consumption is proscribed, or that alcohol may be exacerbating symptoms, but this is an area for future research.

In conclusion, this study found those participants that had a genetic predisposition to avoid alcohol consumption reported less CWP not more. An instrumental variable analysis showed that weekly alcohol consumption does not cause the risk of CWP to be decreased. The interpretation of observational population studies as showing a protective effective of alcohol against pain is not supported.

## **Acknowledgements**

This research has been conducted using the UK Biobank resource, application no. 1144, and was funded by the University of Aberdeen. MF is funded by the EU FP7 project PainOmics (contract #602736). The authors have no conflicts of interest to declare.

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**Table 1 Participant characteristics by genotype**

	<b>AA/AG</b>	<b>GG</b>	<b>OR (99% CI)</b>	<b>Difference (99% CI)</b>	<b>n</b>	
<b>Age, mean (SD), years</b>	56.1 (8.16)	56.6 (8.09)	-	0.44 (0.32-0.57)	486,306	
<b>Gender, Female (%)</b>	15,412 (54.1)	248,218 (54.2)	1.01 (0.98-1.04)	-	486,306	
<b>Ethnicity, Non-white (%)</b>	4,464 (15.6)	21,190 (4.7)	0.26 (0.25-0.27)	-	484,007	
<b>BMI, mean (SD)</b>	27.0 (4.64)	27.4 (4.80)	-	0.48 (0.40-0.55)	484,335	
<b>Townsend Index, mean (SD)</b>	-1.16 (3.175)	-1.32 (3.083)	-	-0.16 (-0.21- -0.11)	485,708	
<b>Employment status</b>	<b>Employed or self-employed</b>	16,767 (59.4)	261,454 (57.4)	1 [Ref]	-	
	<b>Retired</b>	8,703 (30.8)	153,272 (33.6)	1.13 (1.09-1.17)	-	
	<b>Unable to work</b>	801 (2.8)	15,223 (3.3)	1.22 (1.11-1.34)	-	483,819
	<b>Unemployed</b>	548 (1.9)	7,406 (1.6)	0.87 (0.77-0.97)	-	
	<b>None of above</b>	1425 (5.1)	18,220 (4.0)	0.82 (0.76-0.88)	-	
<b>Smoking</b>	<b>Never</b>	11,547 (40.8)	182,851 (40.1)	1 [Ref]	-	
	<b>Tried once or twice</b>	4,175 (14.8)	66,273 (14.6)	1.00 (0.96-1.05)	-	
	<b>Previous, occasional</b>	3,230 (11.4)	52,223 (11.5)	1.02 (0.97-1.08)	-	
	<b>Previous, most days</b>	6,389 (22.6)	106,055 (23.3)	1.05 (1.00-1.09)	-	483,805
	<b>Current, occasionally</b>	857 (3.0)	12,373 (2.7)	0.91 (0.83-1.00)	-	
<b>Current, most days</b>	2,098 (7.4)	35,734 (7.8)	1.08 (1.01-1.15)	-		
<b>University degree, Yes (%)</b>	10,836 (38.7)	146,423 (32.4)	0.76 (0.73-0.78)	-	480,062	
<b>Miserable, Yes (%)</b>	11,570 (41.7)	192,214, (42.8)	1.05 (1.02-1.08)	-	476,645	
<b>Fed up, Yes (%)</b>	10,711 (38.81)	181,903 (40.7)	1.08 (1.05-1.12)	-	474,587	
<b>Frequent family/friend visits, Yes (%)</b>	11,243 (40.0)	193,367 (42.6)	1.11 (1.08-1.15)	-	482,210	

OR, odds ratio or multinomial odds ratio; CI, confidence interval; n, number of participants used for calculation; BMI, body mass index

**Table 2** Association of CWP with variants of rs1229984

Ethnicity	Gender	Variant	No CWP	CWP	OR (99% CI)	n	AOR (99% CI)	n
All	All	AA/AG	27973 (98.8)	344 (1.2)	1 [Ref]	484,575	1 [Ref]	454,400
		GG	449807 (98.6)	6451 (1.4)	1.17 (1.01-1.35)		1.14 (0.97-1.33)	
	Male	AA/AG	12876 (99.0)	125 (1.0)	1 [Ref]	221,873	1 [Ref]	207,436
		GG	206517 (98.9)	2355 (1.1)	1.17 (0.93-1.49)		1.11 (0.86-1.44)	
	Female	AA/AG	15097 (98.6)	219 (1.4)	1 [Ref]	262,702	1 [Ref]	246,964
		GG	243290 (98.3)	4096 (1.7)	1.16 (0.97-1.39)		1.15 (0.95-1.40)	
White	All	AA/AG	23511 (98.9)	250 (1.1)	1 [Ref]	457,553	1 [Ref]	432,962
		GG	428084 (98.7)	5708 (1.3)	1.25 (1.06-1.48)		1.14 (0.95-1.36)	
	Male	AA/AG	11009 (99.2)	90 (0.8)	1 [Ref]	209,237	1 [Ref]	197,702
		GG	196027 (98.9)	2111 (1.1)	1.32 (1.00-1.74)		1.14 (0.85-1.54)	
	Female	AA/AG	12502 (98.7)	160 (1.3)	1 [Ref]	248,316	1 [Ref]	235,260
		GG	232057 (98.5)	3597 (1.5)	1.21 (0.98-1.49)		1.14 (0.91-1.42)	
Non-white	All	AA/AG	4317 (97.9)	92 (2.1)	1 [Ref]	25,390	1 [Ref]	21,438
		GG	20269 (96.6)	712 (3.4)	1.65 (1.24-2.20)		1.16 (0.84-1.61)	
	Male	AA/AG	1801 (98.2)	34 (1.9)	1 [Ref]	11,713	1 [Ref]	9,734
		GG	9648 (97.7)	230 (2.3)	1.26 (0.78-2.04)		0.99 (0.56-1.74)	
	Female	AA/AG	2516 (97.7)	58 (2.3)	1 [Ref]	13,677	1 [Ref]	11,704
		GG	10621 (95.7)	482 (4.3)	1.97 (1.37-2.83)		1.23 (0.82-1.85)	

CWP, chronic widespread pain; OR, odds ratio; CI, confidence interval; n, number of participants used for individual calculation; AOR, adjusted odds ratio

**Table 3** Association of alcohol consumption with variants of rs1229984

<b>Ethnicity</b>	<b>Gender</b>	<b>Variant</b>	<b>Non or infrequent</b>	<b>Weekly consumption</b>	<b>OR (99% CI)</b>	<b>n</b>	<b>AOR (99% CI)</b>	<b>n</b>
All	All	AA/AG	12304 (43.3)	16097 (56.7)	1 [Ref]	485,227	1 [Ref]	454,758
		GG	138480 (30.3)	318346 (69.7)	1.76 (1.70-1.81)		1.69 (1.63-1.76)	
	Male	AA/AG	4290 (32.9)	8753 (67.1)	1 [Ref]	222,143	1 [Ref]	207,549
		GG	46519 (22.3)	162581 (77.8)	1.71 (1.63-1.80)		1.60 (1.52-1.69)	
	Female	AA/AG	8014 (52.2)	7344 (47.8)	1 [Ref]	263,084	1 [Ref]	247,209
		GG	91961 (37.1)	155765 (62.9)	1.85 (1.77-1.93)		1.77 (1.69-1.86)	
White	All	AA/AG	9031 (38.0)	14762 (62.0)	1 [Ref]	458,029	1 [Ref]	433,273
		GG	124252 (28.6)	309984 (71.4)	1.53 (1.47-1.58)		1.69 (1.63-1.76)	
	Male	AA/AG	3087 (27.8)	8029 (72.2)	1 [Ref]	209,414	1 [Ref]	197,798
		GG	40760 (20.6)	157538 (79.4)	1.49 (1.40-1.57)		1.60 (1.51-1.70)	
	Female	AA/AG	5944 (46.9)	6733 (53.1)	1 [Ref]	248,615	1 [Ref]	235,475
		GG	83492 (35.4)	152446 (64.6)	1.61 (1.53-1.69)		1.76 (1.68-1.85)	
Non-white	All	AA/AG	3189 (71.6)	1265 (28.4)	1 [Ref]	25,533	1 [Ref]	21,485
		GG	13614 (64.6)	7465 (35.4)	1.38 (1.26-1.52)		1.65 (1.48-1.84)	
	Male	AA/AG	1171 (63.1)	685 (36.9)	1 [Ref]	11,786	1 [Ref]	9,751
		GG	5456 (54.9)	4474 (45.1)	1.40 (1.22-1.60)		1.61 (1.38-1.88)	
	Female	AA/AG	2018 (77.7)	580 (22.3)	1 [Ref]	13,747	1 [Ref]	11,734
		GG	8158 (73.2)	2991 (26.8)	1.28 (1.11-1.46)		1.70 (1.45-1.98)	

OR, odds ratio; CI, confidence interval; n, number of participants used for individual calculation; AOR, adjusted odds ratio

**Table 4** Association of weekly alcohol consumption and CWP, and causal effect of weekly consumption on CWP

Ethnicity	Gender	Consumption	Association in the population					Estimated causal effect		
			No CWP	CWP	OR (99% CI)	n	AOR (99% CI)	n	OR (99% CI)	n
All	All	None	151739 (97.4)	4077 (2.6)	1 [Ref]	499,988	1 [Ref]	465,150	1 [Ref]	454,178
		Weekly	341132 (99.1)	3040 (0.9)	0.33 (0.31-0.35)		0.56 (0.53-0.61)		1.29 (0.96-1.74)	
	Male	None	51048 (97.8)	1150 (2.2)	1 [Ref]	227,901	1 [Ref]	211,352	1 [Ref]	207,324
		Weekly	174272 (99.2)	1431 (0.8)	0.36 (0.33-0.40)		0.61 (0.54-0.69)		1.28 (0.73-2.23)	
	Female	None	100691 (97.2)	2927 (2.8)	1 [Ref]	272,087	1 [Ref]	253,798	1 [Ref]	262,507
		Weekly	166860 (99.0)	1609 (1.0)	0.33 (0.31-0.36)		0.54 (0.49-0.59)		1.29 (0.91-1.82)	
White	All	None	134234 (97.6)	3327 (2.4)	1 [Ref]	471,633	1 [Ref]	442,840	1 [Ref]	432,779
		Weekly	331181 (99.1)	2891 (0.9)	0.35 (0.33-0.38)		0.57 (0.53-0.62)		1.31 (0.93-1.84)	
	Male	None	44106 (98.0)	923 (2.0)	1 [Ref]	214,785	1 [Ref]	201,349	1 [Ref]	197,612
		Weekly	168396 (99.2)	1360 (0.8)	0.39 (0.35-0.43)		0.63 (0.55-0.71)		1.37 (0.73-2.57)	
	Female	None	90128 (97.4)	2404 (2.6)	1 [Ref]	256,848	1 [Ref]	241,491	1 [Ref]	235,167
		Weekly	162785 (99.1)	1531 (0.9)	0.35 (0.32-0.38)		0.54 (0.49-0.59)		1.28 (0.86-1.89)	
Non-white	All	None	16828 (95.9)	721 (4.1)	1 [Ref]	26,657	1 [Ref]	22,310	1 [Ref]	21,399
		Weekly	8968 (98.5)	140 (1.5)	0.36 (0.29-0.46)		0.52 (0.39-0.68)		1.35 (0.69-2.63)	
	Male	None	6617 (96.9)	214 (3.1)	1 [Ref]	12,155	1 [Ref]	10,003	1 [Ref]	9,712
		Weekly	5257 (98.7)	67 (1.3)	0.39 (0.27-0.57)		0.49 (0.32-0.75)		0.96 (0.30-3.13)	
	Female	None	10211 (95.3)	507 (4.7)	1 [Ref]	14,502	1 [Ref]	12,307	1 [Ref]	11,687
		Weekly	3711 (98.1)	73 (1.9)	0.40 (0.29-0.55)		0.52 (0.36-0.75)		1.49 (0.68-3.28)	

CWP, chronic widespread pain; OR, odds ratio; CI, confidence interval; n, number of participants used for individual calculation; AOR, adjusted odds ratio