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Is alcohol consumption related to likelihood of reporting chronic widespread pain in people with stable consumption? Results from UK Biobank

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Abstract:	Studies have suggested alcohol consumption is strongly related to reduced reporting of chronic widespread pain (CWP) and level of disability in people with CWP or fibromyalgia. Direction of causality has not been established, that is whether the association is due to people's health influencing their alcohol consumption or vice versa. UK Biobank recruited over 500,000 people aged 40-69 years registered at medical practices nationwide. Participants provided detailed information on health and lifestyle factors including pain and alcohol consumption. Total units consumed per week was calculated for current drinkers. Information was also collected on changes in alcohol consumption and reasons for such changes. Analysis was by logistic regression expressed as odds ratios (ORs) with 95% confidence intervals (CIs), then adjusted for a large number of potential confounding factors (adjORs). In males who reported drinking the same as 10 years previously, there was a U-shaped relationship between amount drunk and odds of reporting CWP (non-drinkers CWP prevalence 2.4%, 19.1-32.1 units/wk 0.4%, >53.6 units/wk 1.0%; adjORs 2.53 95% CI [1.78-3.60] vs 1 vs 1.52 [1.05-2.20]). In females there was a decrease in proportion reporting CWP up to the modal category of alcohol consumption with no further change in those drinking more (non-drinkers CWP prevalence 3.4%, 6.4-11.2 units/wk 0.7%, >32.1 units/wk 0.7%; adjORs 2.11 [1.67-2.66] vs 1 vs 0.86 [0.54-1.39]). This large study has shown a clear relationship between alcohol consumption and reporting of pain even in people who had not reported changing consumption due to health concerns, after adjustment for potential confounding factors.

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Dear editors of PAIN,

We would like to resubmit the manuscript entitled 'Is alcohol consumption related to likelihood of reporting chronic widespread pain in people with stable consumption? Results from UK Biobank', authored by myself (MB), Tatiana Macfarlane (TM), and Gary Macfarlane (GM). All authors have read and approved the paper. We have revised the manuscript and the version submitted has tracked changes.

Author contributions were as follows:

Study conception and design: MB, TM, GM

Analysis and interpretation of data: MB, TM, GM

Drafting of manuscript: MB

Critical revision: MB, TM, GM

Please find below our responses to reviewers' comments on our previous version of the manuscript (reviewers' comments in **bold** and our replies are in *italic*).

We believe that attention to these has improved the manuscript and hope that PAIN may accept it for publication.

Sincerely,

Marcus Beasley

Response to Reviewers' Comments

Reviewer #1: Beasley and colleagues have adequately referred to all my previous points, with one exception. The discussion of the mechanisms by which alcohol mediates pain has simply been moved from the introduction to the discussion. While I agree that it fits much better there, I still think that their explanation does not explain things very well. First, the study by Kim et al. (2013) examines the relationship between alcohol consumption and fibromyalgia and does not examine the mechanisms (i.e. GABA). The reported review by Enna et al. (2006) talks about animals (i.e. relationship between GABA and pain) and the study by Foerster et al. (2012) provides only evidence of altered GABA concentrations in the insula of fibromyalgia patients and does not link those to alcohol consumption. Thus a clear explanation of how GABA reduces pain sensitivity and why insula is still missing.

I would suggest not talking about "mechanisms" but rather more broadly, about "previous studies have shown".

We have removed the paragraph talking about mechanisms.

Reviewer #2: In my primary review, I commented that the data in this paper speak for themselves: that of course remains the case, but the revision does ease the task of the reader to make sense of them. Overall the authors' responses to the comments of both reviewers have enhanced the paper, in terms of flow of argument and qualifications regarding inferences that can be made.

There remains scope for improving grammar and syntax, which I expect can be rectified in the proofing process.

We've read through the manuscript again to check for grammatical/syntactical errors, and made some changes.

The abstract would be enhanced by explicit expression of the main finding - a clear relationship between the consumption of alcohol and experience of pain even among those who had not reported changing alcohol consumption due to health concerns.

We've rewritten the final sentence of the abstract to try and make the expression of the main finding more explicit as suggested.

Reviewer #3: Review of revised manuscript PAIN-D-14-14682R1

I have read the manuscript, and comments and proposed changes from reviewers.

The authors have considered comments from reviewers and adjusted the text in, what I consider, a relevant way. In cases where reviewers' suggestions have not been fully adopted the authors have argued for their case in a relevant and valid way (for examples: the comment on multicollinearity, the speculative reasoning about the effect of alcohol on pain).

Comments and suggestions from reviewers have made hypotheses more clear and the discussion more relevant than in the previous version of the manuscript.

Thank you to all the reviewers for the time taken to review this manuscript. Note also, that there has been one minor alteration to the heading for Figure 2d with the addition of the word 'illness'.

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Abstract

Studies have suggested alcohol consumption is strongly related to reduced reporting of chronic widespread pain (CWP) and level of disability in people with CWP or fibromyalgia. Direction of causality has not been established, that is whether the association is due to people's health influencing their alcohol consumption or vice versa. UK Biobank recruited over 500,000 people aged 40-69 years registered at medical practices nationwide. Participants provided detailed information on health and lifestyle factors including pain and alcohol consumption. Total units consumed per week was calculated for current drinkers. Information was also collected on changes in alcohol consumption and reasons for such changes. Analysis was by logistic regression expressed as odds ratios (ORs) with 95% confidence intervals (CIs), then adjusted for a large number of potential confounding factors (adjORs). In males who reported drinking the same as 10 years previously, there was a U-shaped relationship between amount drunk and odds of reporting CWP (non-drinkers CWP prevalence 2.4%, 19.1-32.1 units/wk 0.4%, >53.6 units/wk 1.0%; adjORs 2.53 95% CI [1.78-3.60] vs 1 vs 1.52 [1.05-2.20]). In females there was a decrease in proportion reporting CWP up to the modal category of alcohol consumption with no further change in those drinking more (non-drinkers CWP prevalence 3.4%, 6.4-11.2 units/wk 0.7%, >32.1 units/wk 0.7%; adjORs 2.11 [1.67-2.66] vs 1 vs 0.86 [0.54-1.39]). This large study has shown a clear relationship between alcohol consumption and reporting of pain even in people who had not reported changing consumption due to health concerns, after adjustment for potential confounding factors.

Is alcohol consumption related to likelihood of reporting chronic widespread pain in people with stable consumption? Results from UK Biobank

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Abstract

Studies have suggested alcohol consumption is strongly related to reduced reporting of chronic widespread pain (CWP) and level of disability in people with CWP or fibromyalgia. Direction of causality has not been established, that is whether the association is due to people's health influencing their alcohol consumption or vice versa. UK Biobank recruited over 500,000 people aged 40-69 years registered at medical practices nationwide. Participants provided detailed information on health and lifestyle factors including pain and alcohol consumption. Total units consumed per week was calculated for current drinkers. Information was also collected on changes in alcohol consumption and reasons for such changes. Analysis was by logistic regression expressed as odds ratios (ORs) with 95% confidence intervals (CIs), then adjusted for a large number of potential confounding factors (adjORs). In males who reported drinking the same as 10 years previously, there was a U-shaped relationship between amount drunk and odds of reporting CWP (non-drinkers CWP prevalence 2.4%, 19.1-32.1 units/wk 0.4%, >53.6 units/wk 1.0%; adjORs 2.53 95% CI [1.78-3.60] vs 1 vs 1.52 [1.05-2.20]). In females there was a decrease in proportion reporting CWP up to the modal category of alcohol consumption with no further change in those drinking more (non-drinkers CWP prevalence 3.4%, 6.4-11.2 units/wk 0.7%, >32.1 units/wk 0.7%; adjORs 2.11 [1.67-2.66] vs 1 vs 0.86 [0.54-1.39]). This large study has shown a clear~~strong~~ relationship between alcohol consumption and ~~likelihood of~~ reporting of pain~~CWP exists~~ even in people ~~reporting unchanged consumption~~who had not reported changing consumption due to health concerns, ~~and~~ after adjustment for ~~a large number of~~ potential confounding factors.

Introduction

Chronic widespread pain (CWP) or multi-site pain have been included as essential criteria in classification and diagnostic criteria for fibromyalgia, respectively [26,27]. CWP is defined as pain that is present above and below the waist, on the left and right hand sides, and in the axial skeleton. Epidemiological studies have identified a number of characteristics which might be considered risk factors for the development of CWP [9]. These include sleep problems, psychological distress, and certain beliefs about health and illness. Estimates for the prevalence of fibromyalgia range from around 1% to around 5% [10], while a recent meta-analysis estimated the pooled prevalence of CWP at 10.6% [18].

Among the lifestyle factors that have been identified as having an association with CWP is the consumption of alcohol. One population-based UK study has shown pain reporting and pain-related disability is associated with the amount of alcohol usually consumed [15]. In this study of 13,574 people, those who said they had never druank alcohol regularly were 50% more likely to report CWP than those who said they drank 11-35 units/week. Among people with CWP, those that had never druank regularly were more than twice as likely to have pain that was disabling than those drinking 11-35 units/week. A further US clinic study of patients with fibromyalgia found reduced symptoms and better quality of life in those drinking low to moderate amounts of alcohol than those not drinking [11].

That pain is less common among people who drink alcohol does not mean that the reason they are less likely to have pain is because they drink alcohol. A number of problems with making such causal inferences from observational studies of the relationship between alcohol and health outcomes have been noted, including, dependent misclassification of exposure and outcome [2]; unmeasured confounding [12]; the inappropriate selection of referent group [12]; classification biases counting occasional drinkers in abstainer reference group [22]; and, selection biases [12,23]. For the alcohol–pain relationship a major issue is whether the observed relationship is due to people reducing or stopping their alcohol consumption because of ill-health [7].

Among criteria for causality that seem to be satisfied by observational evidence of the association between alcohol and pain are strength of relationship, and biological gradient, i.e. dose-response relationship [15]. It has however been noted that the positive effect of alcohol was not restricted to pain reporting but could also be shown with other health outcomes [6] and this lack of specificity would be evidence against a causal effect on pain. One criterion missing from currently reported observational studies is temporality, which would indicate whether drinking precedes relief from

chronic pain, or alternatively whether experiencing chronic pain leads people to reduce their alcohol consumption.

Using data from a very large "Biobank", which provides information on a comprehensive set of possible confounders and which allows us to identify people with long-term stable alcohol consumption, we wished to test whether we could confirm a previous observation of a ' reversed J-shaped' relationship between alcohol consumption and pain reporting , i.e. that the lowest and highest categories of alcohol consumption had higher levels of pain reporting than those in the 'moderate' category of alcohol consumption.

Methods

The UK Biobank is a large cohort study which recruited more than 500,000 people between the ages of 40 and 69 registered with a National Health Service general practitioner in the UK. Participants attended assessment centres in 22 cities in England, Scotland and Wales where they completed touchscreen questionnaires on health and lifestyle. The activities under UK Biobank are governed by an Ethics and Governance Framework, overseen by an Ethics and Governance Council (www.egcukbiobank.org.uk). The core scientific protocol and operational procedures of the UK Biobank resource, as well as proposed used of it, have approval from appropriate ethics committees.

Pain

Participants were asked if they had any pain in the last month in regional body sites, or to indicate if they had pain all over the body. For each site indicated they were asked whether pain had last for 3 months or more. For the current analysis, if a participant answered they had pain all over the body that had lasted for 3 months or more, they were classed as someone with CWP.

Alcohol consumption

Participants were first asked '"About how often do you drink alcohol?'". If a current non-drinker they were then asked whether they previously drank and if so, to select their reason for stopping from a list: 'Illness or ill health', 'Doctor's advice', 'Health precaution', 'Financial reasons', 'Other reason', 'Do not know', or 'Prefer not to answer'. For analysis the first three options were combined as 'Illness or Health Precaution', and the remainder as 'Other reasons'. Those who said they were currently drinking were asked if they currently drank more, less or the same compared to 10 years ago. Those who said they had reduced their drinking were asked their reason for reducing consumption from the same list given to those who had stopped drinking. The same classification of categories for those reducing consumption were used as those giving up drinking. Current drinkers were asked how much they drank per week, or per month if drinking less frequently than weekly, of white wine, red wine, beer or

cider, spirits or liquers, and fortified wine, in appropriate measures, i.e., how many glasses or pints. Typical value in units were chosen for each alcohol-type and an overall consumption level was calculated for current drinkers. (For example, 1 glass of red wine was equal to 125 ml, and at 13% alcohol by volume was taken to be 1.625 units of alcohol). One was added to the number of units consumed per week (so that non-drinkers would have a value of 1, to give a natural log of 0) and natural logarithms were taken (so that a dose-response relationship between CWP and alcohol could be plotted). Categories of these value were calculated in increments of 0.5. For the stratified analyses, categories were combined where total numbers in a category were low.

Adjusting variables

Factors were chosen which were known to be risk factors for pain and were likely to be associated with alcohol consumption. These were: age (years) [21]; Body Mass Index (BMI) [25]; education (having a university degree or not) [19]; deprivation (Townsend Index [24]) [17]; social networks (frequency of visits by family and friends) [3]; mood ('Do you ever feel miserable for no reason?', and 'Do you often feel fed-up?') [16]; loneliness ('Do you often feel lonely?') [4]; smoking (Never smoker/Tried once or twice/Previous occasional smoking/Previous smoking most days/Current occasional smoker/Current smoker most days) [20]; ethnicity (White/Mixed/Asian or Asian British/Black or Black British/Chinese/Other ethnic group) [16]; and employment status [16]. Adjustment was also made for assessment centre.

Statistical Analysis

As prevalence of CWP has consistently been shown to be more common in females, and because levels of exposure to alcohol differed between males and females, analyses were conducted separately by gender. The proportion of people reporting CWP was calculated in each category of drinking status (i.e. drinker/non-drinker and change compared to 10 years ago). Logistic regression was used to calculate ORs, and adjORs for CWP in each category compared to current drinkers with no change in consumption. As prevalence of CWP is low, odds ratios are a good approximation for risk ratios. The proportion of people reporting CWP was then calculated for each level of alcohol consumption (and logistic regression used to calculate ORs and 95% Confidence Intervals (CIs)). The reference category in males was log units plus one between (males 3 and 3.5 (, corresponding to 19.1-32.1 units/wk), and in females between 2 and 2.5 (, corresponding to 6.4-11.2 units/wk). These were chosen as they were the modal consumption categories. The analysis was then stratified by change in alcohol consumption since 10 years ago, and reasons for change in consumption. ORs were plotted on graphs at the midpoint of a consumption category to show the dose-response relationship [13]. A sensitivity analysis was carried out including those who had missing data on the adjusting variables. Among

drinkers, weekly consumption of red wine, white wine, beer or cider, and spirits was categorised and ORs and adjORs of CWP were calculated and plotted.

Results

502,656 people completed the UK Biobank recruitment questionnaire. After removing those with missing data (~~i.e.~~ missing pain status n=4,610, missing adjusting variables n=44,473, drinking monthly but not asked alcohol consumption n=64,807, not providing alcohol consumption n=13,489) 375,277 participants were included in the analysis. The median age was 58 years (interquartile range (IQR) 50 to 63), 51.7% were female, and 1.2% reported having CWP. Of those included in the analysis, 83.3% said they drink at least once a week, 7.4% drank less frequently, 4.3% were current non-drinkers but had previously drank, and 5.0% had never drank. Median weekly consumption among males and females drinking weekly was 20.4 units (IQR 11.8-34.2), and 10.7 units (IQR 6.5-17.7) respectively.

CWP and changes in drinking habits

Reporting of CWP was least in those currently drinking and reporting no change in drinking habits (males 0.5%, females 0.8%) (**Table 1**) and greatest in those currently not drinking but reporting having been drinkers before (males 3.7%, females 4.9%). The excess remained after adjusting for potential confounding factors - adjOR 2.59 (95% CI 2.17-3.09) in males and 2.77 (95% CI 2.41-3.19) in females.

The dose-response relationship between alcohol and CWP in males

Among all males, the proportion reporting CWP (**Table 2**) was greater in those not drinking (3.2%) compared to those in the reference category (0.7%) - adjOR 2.16 (95% CI 1.84-2.55). Proportions were at similar levels in all those drinking low to moderate amounts (**Figure 1a**). There was an increase in CWP in those drinking more than 53.6 units per week compared to the reference category, but this was non-significant after adjustment (1.2% with CWP in those drinking over 53.6 units per week, adjOR 1.07 95% CI 0.88-1.29). A similar dose-response pattern – either U-shaped or reversed-J-shaped - was also seen in those drinking more, the same, or less due to illness or as a health precaution, as 10 years previously (**Figures 1b-d**). Specifically in those drinking the same as 10 years ago odds of reporting CWP was significantly elevated in non-drinkers (adjOR 2.53, 95% CI 1.78-3.60) and in those with the highest consumption (adjOR 1.52, 95% CI 1.05-2.20).

The dose-response relationship between alcohol and CWP in females

Among females there was a decrease in proportion reporting CWP (**Table 3**) with increasing categories of consumption from non-drinkers (4.0%) through to the reference category of those drinking 6.4 to 11.2 units per week (0.9%) - adjOR 2.30 (95% CI 2.02-2.63). Proportions of those reporting CWP were also similar for increasing levels of consumption above the reference category (**Figure 2a**). This same

pattern was seen in those drinking the same amount as 10 years previously (non-drinkers vs reference category adjOR 2.11, 95% CI 1.67-2.66) (**Figure 2c**) and those who had changed their consumption (**Figures 2b,2d,2e**). Sensitivity analysis looking at the dose-response relationship of CWP with alcohol consumption including those participants for whom full adjusting data was not available did not alter the results (**Table 6**).

The dose-response relationship between consumption of different alcohol types and CWP among drinkers

In both male and female drinkers the strongest associations were with red wine consumption. There were increased odds of reporting CWP (**Tables 4 and 5**) in those not drinking red wine compared to those drinking 11.2-19.1 units per week (males: 1.3% vs 0.4%, adjOR 1.74 95% CI 1.28-2.35; females: 1.3% v. 0.6% adjOR 1.44 95% CI 1.12-1.85). There were increases in CWP with increasing amounts of beer/cider or spirits consumed but these were not significant after adjustment.

Discussion

This very large population-based study found that non-drinkers are more likely to report CWP than those drinking moderate amounts of alcohol. In males, the classic U- or J-shaped relationship was found with increased reporting of CWP in the very lowest and highest categories of consumption. In females there were reduced odds of reporting CWP across increasing categories of consumption. Furthermore similar dose-response patterns were shown when looking at sub-groups of people based on changes in drinking habits, specifically those who had the same consumption as 10 years previously, which might suggest that the observed pattern is not due to people changing their drinking habits due to a change in pain/health status. Examination of specific sources of alcohol showed that the dose-response relationship was mainly observed for red wine.

There are a number of limitations of cross-sectional observational surveys with self-report measures. Firstly, there may be some reporting bias and respondents may underestimate the amount of alcohol they drink, perhaps for reasons of social desirability. However, the reported levels of alcohol consumption were in the normal range. Before exclusions for missing data the proportion of males drinking over 21 units per week was 37%, and over 50 units was 9%. The proportions given for these categories in males between 45 and 64 in the General Lifestyle Survey (GLF) of 2010 [5] were 30% and 9%. In females in the UK Biobank, the proportion drinking over 14 units a week was 22% and the proportion over 35 units a week was 3%, in comparison to 20% and 4% in the GLF. The design of this study also relies on the accurate reporting of change in drinking status from 10 years previously, although interestingly the results observed in this group were similar to all subjects included. A selection bias may have also be an issue given that an important proportion of participants were

excluded for incomplete data. This is only a problem if the association is only found in those who provide full data, but similar results were found in the sensitivity analysis which included those with missing adjusting variables. In the statistical analysis a large number of adjusting variables were used. These were used for adjustment as they are presumed confounders. However, it is possible that some of these third variables may actually be mediators of the observed effect in which case they should not have been used in adjustment and the observed relationship will have been underestimated [1].

There are more general problems with drawing causal inferences from observational studies, and observational~~indeed~~ findings often fail to replicate in randomised controlled trials (RCTs) [14]. A trial of alcohol use ~~for chronic pain~~ however, would not be ethically or methodologically feasible. A study design which can be used when RCTs are impracticable is Mendelian randomisation [28]. For example,~~In a~~ Mendelian randomisation was used in a study on the effect of alcohol on cardiovascular disease in which the~~the~~ findings of observational studies were reversed [8]. Mendelian randomisation studies could be used to assess the relationship between alcohol and chronic pain using variants of genes for enzymes involved in the metabolism of alcohol, and this approach seems the most promising to understand if the relationship is causal or not.

The results of this study confirm and build on those of previous studies which have found that pain-reporting is higher in non-drinkers than in drinkers. As a much larger study with similar prevalance estimates as other cohorts [16] this allows for more precise estimates of effect. It also provides information on a much greater number of potential confounders. One purpose of the study was to look at criteria that might help to support or oppose the causal relationship between alcohol and reduced risk of pain, particularly the biological gradient. A linear monotonic dose-response relationship was found in females but not in males although it was not strong. The gradient in females was not greatly different in drinkers who had reduced their drinking because of illness and those who had not changed their drinking. This suggests the observed relationship is not explained by people reducing consumption due to pain. This is the first time the relationship has been examined by type of alcohol consumed and the relationship found when looking at total consumption was only clearly observed with red wine. This result goes against a general effect of alcohol and suggests that some unmeasured factors might confound the observed relationship between red wine drinking and pain. In our sample, red wine drinkers were different to those drinking other types of alcohol. For example, in males drinking between 19.1 and 32.1 units per week, those who drank any red wine were more likely to have a university degree than those that did not drink red wine at all (44% vs 18%), less likely to be unemployed (1% vs 3%), and less likely to report smoking most days (5% vs 13%).

~~If there were a general effect of alcohol on chronic pain then mechanisms would have to be considered. It has been suggested that the acute effects of alcohol on pain are through its action on~~

~~gamma-Aminobutyric acid (GABA) neurons in the central nervous system. GABA is an inhibitory neurotransmitter that has a role in the mediation of pain and has also been found to have altered concentrations in the insular cortex of fibromyalgia patients. Other mechanisms have been proposed for the action of alcohol on pain that do not involve directly its effect on neurotransmission but instead its psychosocial effects which are known risk markers for chronic pain, including reduction of fear-avoidance mechanisms, social integration, and stress-relief. If it was established that alcohol consumption was effective in preventing chronic pain, prospective studies would be required to determine whether mediators of the effect were neurobiological or psychosocial.~~

There is a strong, clear association between drinking alcohol and reduced likelihood of reporting pain. There is however still no convincing evidence that drinking alcohol causes people to be less likely to have pain. This study provides evidence that the~~-~~ association is not explained by people in poor health reducing their alcohol consumption, and that the association is most clear for red wine consumption. Similar relationships of low to moderate alcohol consumption are seen with a wide range of outcomes [6] and avoidance of alcohol might be considered a (non-causative) risk marker for poor general health, of which pain is one feature. If however, alcohol consumption does affect pain, or if people who are at risk of having chronic pain are found to process alcohol differently resulting in them reducing their consumption, then these findings could be used to inform new ~~pathways as~~ targets for~~of~~ treatment in~~for~~ chronic pain syndromes.

Acknowledgements

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Figures and Tables

Alcohol consumption was associated with lowered reporting of chronic widespread pain in a large biobank. The association remained when looking at those without changed consumption.

Figure 1

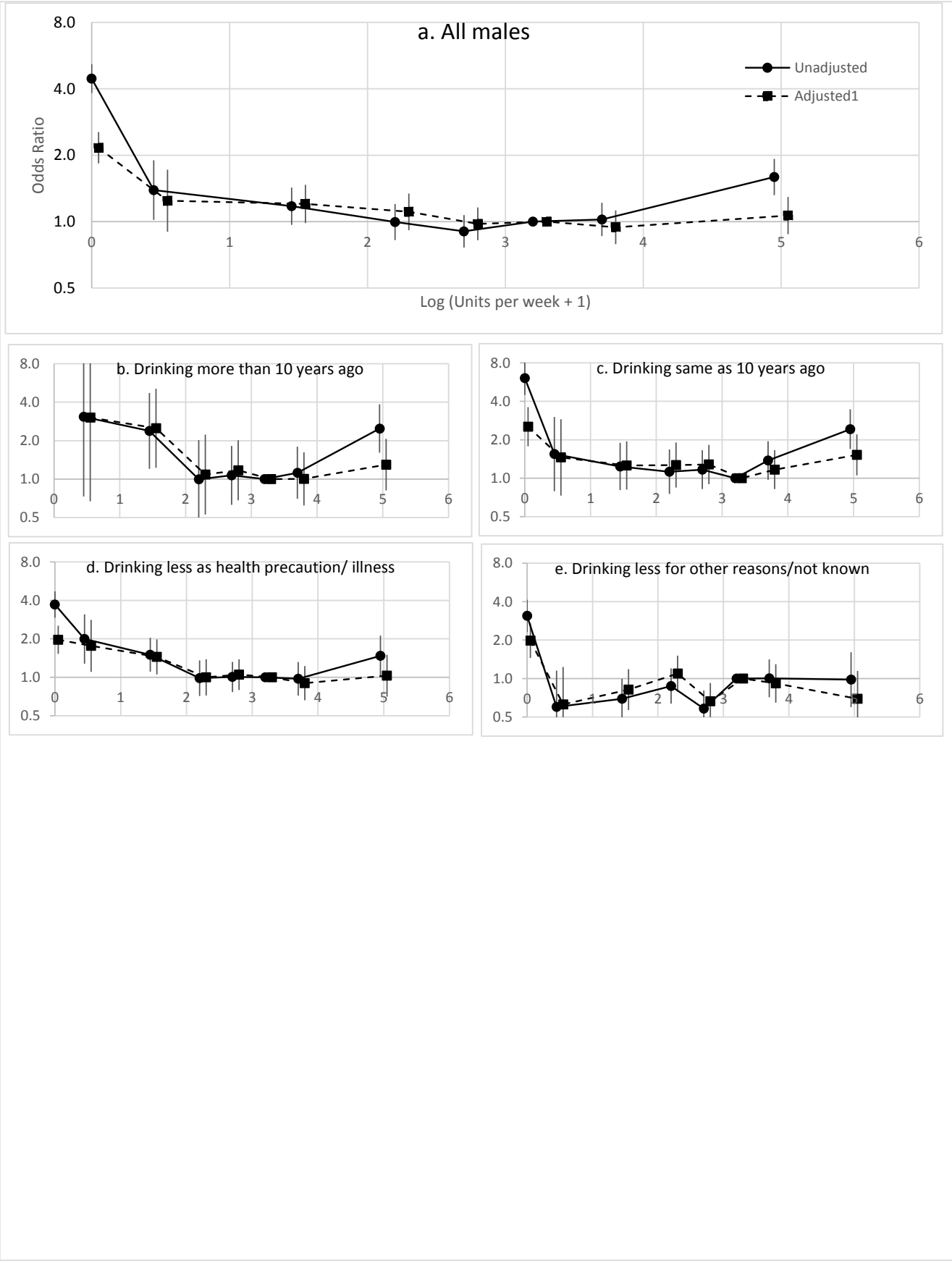
a. All males
Unadjusted
Adjusted1
Odds Ratio
Log (Units per week + 1)
b. Drinking more than 10 years ago
c. Drinking same as 10 years ago
d. Drinking less as health precaution/ illness
e. Drinking less for other reasons/not known

Figure 2

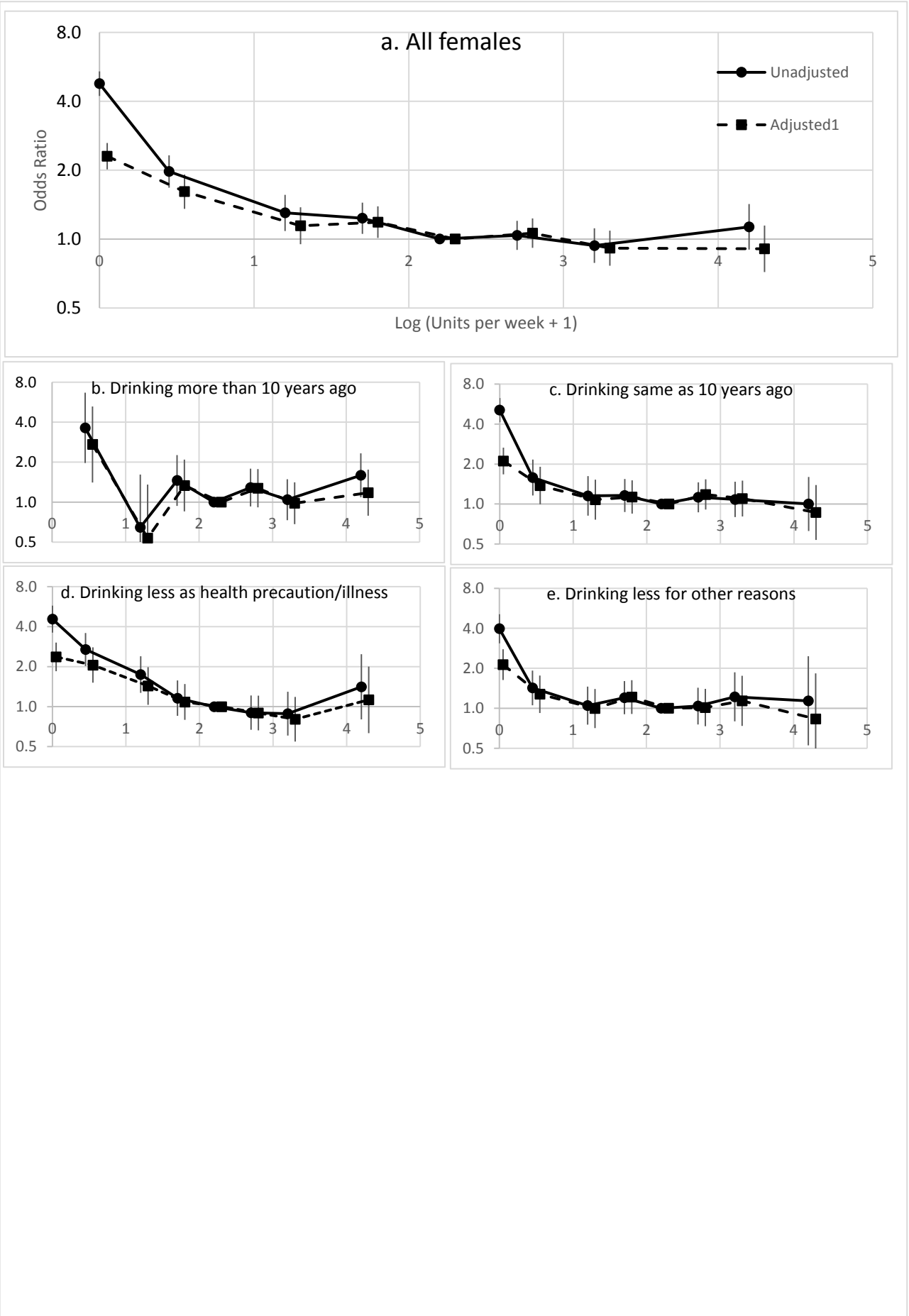
a. All females
Unadjusted
Adjusted1
Odds Ratio
8.0
4.0
2.0
1.0
0.5
0
1
2
3
4
5
Log (Units per week + 1)
b. Drinking more than 10 years ago
c. Drinking same as 10 years ago
d. Drinking less as health precaution/illness
e. Drinking less for other reasons

Table 1 CWP by changes in alcohol consumption

Males, n=181,112

	Drinking status	Total	Number with CWP (%)	OR	Adj OR
Current Drinkers	No change	63599	330 (0.5)	1 [Ref]	1 [Ref]
	Drinking more than 10 years ago	25197	167 (0.7)	1.28 (1.06-1.54)	1.09 (0.90-1.32)
	Drinking less than 10 years ago	80088	807 (1.0)	1.95 (1.72-2.22)	1.33 (1.17-1.52)
Current non-drinkers	No change	5137	123 (2.4)	4.70 (3.82-5.80)	2.36 (1.87-2.98)
	Previous drinker	7091	263 (3.7)	7.38 (6.27-8.70)	2.59 (2.17-3.09)

Females, n=194,165

	Drinking status	Total	Number with CWP (%)	OR	Adj OR
Current Drinkers	No change	65284	510 (0.8)	1 [Ref]	1 [Ref]
	Drinking more than 10 years ago	42108	326 (0.8)	0.99 (0.86-1.14)	0.92 (0.80-1.06)
	Drinking less than 10 years ago	64295	884 (1.4)	1.77 (1.59-1.98)	1.37 (1.23-1.54)
Current non-drinkers	No change	13521	463 (3.4)	4.50 (3.97-5.11)	2.06 (1.79-2.38)
	Previous drinker	8957	442 (4.9)	6.59 (5.79-7.50)	2.77 (2.41-3.19)

Note: AdJOR is adjusted for age, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status, and assessment centre

Table 2

Table 2 CWP in males by alcohol consumption

		Current weekly consumption (units)	Total	Number with CWP (%)	OR (95% CI)	Adj OR (95% CI)
All (n=181,112)		0	12228	386 (3.2)	4.45 (3.83-5.18)	2.16 (1.84-2.55)
		0-1.7	4564	46 (1.0)	1.39 (1.02-1.90)	1.24 (0.90-1.72)
		1.7-6.4	17935	153 (0.9)	1.17 (0.97-1.43)	1.20 (0.99-1.47)
		6.4-11.2	23341	169 (0.7)	1.00 (0.82-1.20)	1.11 (0.91-1.340
		11.2-19.1	36639	241 (0.7)	0.90 (0.76-1.07)	0.98 (0.82-1.16)
		19.1-32.1	42495	309 (0.7)	1 [Ref]	1 [Ref]
		32.1-53.6	29437	219 (0.7)	1.02 (0.86-1.22)	0.94 (0.79-1.12)
		More than 53.6	14473	167 (1.2)	1.59 (1.32-1.93)	1.07 (0.88-1.29)
	Drinking more (n=25,197)	0-1.7	134	2 (1.5)	3.07 (0.73-12.92)	3.30 (0.67-13.72)
		1.7-6.4	947	11 (1.2)	2.38 (1.20-4.72)	2.50 (1..23-5.10)
		6.4-11.2	2047	10 (0.5)	1.00 (0.49-2.02)	1.09 (0.53-2.23)
		11.2-19.1	4384	23 (0.5)	1.07 (0.63-1.82)	1.17 (0.68-2.01)
		19.1-32.1	6930	34 (0.5)	1 [Ref]	1 [Ref]
		32.1-53.6	6547	36 (0.5)	1.12 (0.70-1.79)	1.00 (0.62-1.62)
		More than 53.6	4208	51 (1.2)	2.49 (1.61-3.85)	1.30 (0.82-2.07)
Compared to 10 years ago	Drinking same (n=68,736)	0	5137	123 (2.4)	6.08 (4.48-8.25)	2.53 (1.78-3.60)
		0-1.7	1615	10 (0.6)	1.54 (0.79-3.02)	1.45 (0.73-2.89)
		1.7-6.4	6449	32 (0.5)	1.24 (0.81-1.89)	1.26 (0.81-1.94)
		6.4-11.2	8633	39 (0.5)	1.12 (0.75-1.68)	1.27 (0.85-1.90)
		11.2-19.1	13446	63 (0.5)	1.17 (0.82-1.66)	1.28 (0.90-1.82)
		19.1-32.1	15680	63 (0.4)	1 [Ref]	1 [Ref]
		32.1-53.6	11782	65 (0.6)	1.38 (0.97-1.95)	1.17 (0.82-1.66)
		More than 53.6	5994	58 (1.0)	2.42 (1.69-3.46)	1.52 (1.05-2.20)

Drinking less because of illness or as health precaution (n=37,087)	0	3857	175 (4.5)	3.71 (2.93-4.17)	1.97 (1.53-2.53)
	0-1.7	964	24 (2.5)	1.99 (1.28-3.11)	1.76 (1.10-2.82)
	1.7-6.4	3497	66 (1.9)	1.50 (1.11-2.04)	1.44 (1.05-1.98)
	6.4-11.2	4501	56 (1.2)	0.98 (0.71-1.36)	1.00 (0.72-1.38)
	11.2-19.1	7548	96 (1.3)	1.01 (0.77-1.32)	1.05 (0.79-1.38)
	19.1-32.1	9173	116 (1.3)	1 [Ref]	1 [Ref]
	32.1-53.6	5439	67 (1.2)	0.97 (0.72-1.32)	0.90 (0.66-1.22)
	More than 53.6	2108	39 (1.9)	1.47 (1.02-2.12)	1.03 90.71-1.50)
Drinking less for other reasons/ not known (n=50,092)	0	3234	88 (2.7)	3.09 (2.31-4.14)	1.98 (1.45-2.70)
	0-1.7	1851	10 (0.5)	0.60 (0.31-1.15)	0.63 (0.32-1.23)
	1.7-6.4	7042	44 (0.6)	0.70 (0.49-0.99)	0.82 (0.57-1.18)
	6.4-11.2	8160	64 (0.8)	0.87 (0.64-1.20)	1.09 (0.79-1.51)
	11.2-19.1	11261	59 (0.5)	0.58 (0.42-0.81)	0.66 (0.48-0.92)
	19.1-32.1	10712	96 (0.9)	1 [Ref]	1 [Ref]
	32.1-53.6	5669	51 (0.9)	1.00 (0.71-1.410	0.92 (0.65-1.29)
	More than 53.6	2163	19 (0.9)	0.98 (0.60-1.61)	0.69 (0.42-1.15)

Note: AdJOR is adjusted for age, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status, and assessment centre. The log likelihood chi-square from model for all males including all covariates was 2761.56 with 45 degrees of freedom and $p<0.0001$ and pseudo R-square was 0.1441).

Table 3 CWP in females by alcohol consumption

		Current weekly consumption (units)	Total	Number with CWP (%)	OR (95% CI)	Adj OR (95% CI)
All (n=194,165)		0	22478	905 (4.0)	4.78 (4.22-5.40)	2.30 (2.02-2.63)
		0-1.7	14611	249 (1.7)	1.97 (1.68-2.32)	1.61 (1.36-1.91)
		1.7-3.5	15397	174 (1.1)	1.30 (1.08-1.56)	1.14 (0.95-1.38)
		3.5-6.4	26130	280 (1.1)	1.23 (1.05-1.44)	1.19 (1.01-1.39)
		6.4-11.2	41227	359 (0.9)	1 [Ref]	1 [Ref}
		11.1-19.1	40490	366 (0.9)	1.04 (0.90-1.20)	1.06 (0.92-1.23)
		19.1-32.1	24382	199 (0.8)	0.94 (0.79-1.11)	0.91 (0.77-1.09)
		More than 32.1	9450	93 (1.0)	1.13 (0.90-1.42)	0.91 (0.72-1.15)
	Drinking more (n=42,108)	0-1.7	578	13 (2.2)	3.63 (1.97-6.67)	2.72 (1.41-5.25)
		1.7-3.5	1227	5 (0.4)	0.65 (0.26-1.61)	0.54 (0.21-1.36)
		3.5-6.4	3388	31 (0.9)	1.46 (0.94-2.26)	1.34 (0.85-2.09)
		6.4-11.2	8886	56 (0.6)	1 [Ref}	1 [Ref]
		11.1-19.1	12585	102 (0.8)	1.29 (0.93-1.79)	1.27 (0.91-1.77)
		19.1-32.1	10346	68 (0.7)	1.04 (0.73-1.49)	0.98 (0.68-1.41)
		More than 32.1	5098	51 (1.0)	1.59 (1.09-2.33)	1.18 (0.79-1.76)
Compared to 10 years ago		0	13521	463 (3.4)	5.09 (4.13-6.28)	2.11 (1.67-2.66)
		0-1.7	5779	63 (1.1)	1.58 (1.16-2.16)	1.38 (1.00-1.91)
	Drinking same as 10 years ago (n=78,805)	1.7-3.5	5910	47 (0.8)	1.15 (0.82-1.62)	1.08 (0.76-1.53)
		3.5-6.4	10368	83 (0.8)	1.16 (0.87-1.54)	1.13 (0.85-1.51)
		6.4-11.2	15910	110 (0.7)	1 [Ref]	1 [Ref}
		11.1-19.1	15467	120 (0.8)	1.12 (0.87-1.46)	1.18 (0.91-1.53)
		19.1-32.1	8815	66 (0.7)	1.08 (0.80-1.47)	1.10 (0.81-1.50)
		More than 32.1	3035	21 (0.7)	1.00 (0.63-1.60)	0.86 (0.54-1.39)
		0	4103	261 (6.4)	4.55 (3.60--5.76)	2.37 (1.85-3.03)

Drinking less because of illness or as health precaution (n=29,509)	0-1.7	2412	93 (3.9)	2.69 (2.02-3.58)	2.06 (1.51-2.79)
	1.7-3.5	2526	64 (2.5)	1.74 (1.27-2.39)	1.43 (1.03-1.98)
	3.5-6.4	4182	71 (1.7)	1.16 (0.85-1.57)	1.08 (0.79-1.48)
	6.4-11.2	6805	100 (1.5)	1 {Ref}	1 [Ref]
	11.1-19.1	5960	79 (1.3)	0.90 (0.67-1.21)	0.89 (0.66-1.21)
	19.1-32.1	2841	37 (1.3)	0.88 (0.61-1.29)	0.80 (0.55-1.18)
	More than 32.1	680	14 (2.1)	1.41 (0.80-2.48)	1.12 (0.63-2.00)
Drinking less for other reasons/not known (n=43,743)	0	4854	181 (3.7)	3.97 (3.08-5.11)	2.13 (1.63-2.78)
	0-1.7	5842	80 (1.4)	1.42 (1.05-1.92)	1.28 (0.92-1.76)
	1.7-3.5	5734	58 (1.0)	1.05 (0.75-1.46)	1.00 (0.71-1.40)
	3.5-6.4	8192	95 (1.2)	1.20 (0.90-1.60)	1.22 (0.91-1.63)
	6.4-11.2	9626	93 (1.0)	1 [Ref]	1 [Ref}
	11.1-19.1	6478	65 (1.0)	1.04 (0.76-1.43)	1.01 (0.73-1.40)
	19.1-32.1	2380	28 (1.2)	1.22 (0.80-1.87)	1.14 (0.74-1.76)
	More than 32.1	637	7 (1.1)	1.14 (0.53-2.47)	0.83 (0.38-1.83)

Note: AdJOR is adjusted for age, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status, and assessment centre. The log likelihood chi-square from model for all females including all covariates was 3800.34 with 45 degrees of freedom and $p<0.0001$ and pseudo R-square was 0.1367.

Table 4 CWP by consumption of different alcohol types in male drinkers (n=168,884)

	Weekly consumption (units)	Total	Number with CWP (%)	OR (95% CI)	Adj OR (95% CI)
Red Wine	0	55798	718 (1.3)	3.35 (2.63-4.75)	1.74 (1.28-2.35)
	0-6.4	49142	287 (0.6)	1.59 (1.17-2.17)	1.39 (1.02-1.90)
	6.4-11.2	31502	144 (0.5)	1.24 (0.90-1.73)	1.09 (0.78-1.52)
	11.2-19.1	12788	47 (0.4)	1 [Ref]	1 [Ref]
	19.1-32.1	13793	74 (0.5)	1.46 (1.01-2.11)	1.25 (0.87-1.81)
	More than 32.1	5861	34 (0.6)	1.58 (1.02-2.46)	1.26 (0.81-1.96)
White Wine	0	92042	910 (1.0)	1.77 (1.26-2.48)	1.10 (0.78-1.55)
	0-6.4	55588	280 (0.5)	0.90 (0.63-1.28)	0.90 (0.63-1.29)
	6.4-11.2	11043	55 (0.5)	0.89 (0.58-1.36)	0.87 (0.56-1.33)
	11.2-19.1	6242	35 (0.6)	1 [Ref]	1 [Ref]
	19.1-32.1	2670	15 (0.6)	1.00 (0.55-1.84)	0.91 (0.49-1.68)
	More than 32.1	1299	9 (0.7)	1.24 (0.59-2.58)	0.94 (0.45-1.97)
Beer/Cider	0	33121	192 (0.6)	0.67 (0.55-0.83)	0.89 (0.72-1.10)
	0-6.4	50231	318 (0.6)	0.74 (0.61-0.88)	0.99 (0.82-1.20)
	6.4-11.2	26539	183 (0.7)	0.80 (0.65-0.99)	0.93 (0.75-1.14)
	11.2-19.1	21465	184 (0.9)	1 [Ref}	1 [Ref]
	19.1-32.1	21125	209 (1.0)	1.16 (0.95-1.41)	0.98 (0.80-1.20)
	More than 32.1	16403	218 (1.3)	1.56 (1.28-1.90)	1.04 (0.85-1.28)
Spirits	0	102190	781 (0.8)	0.68 (0.49-0.95)	1.02 (0.72-1.44)
	0-6.4	53714	370 (0.7)	0.61 (0.43-0.87)	0.94 (0.66-1.33)
	6.4-11.2	5947	57 (1.0)	0.86 (0.56-1.30)	0.98 (0.64-1.50)
	11.2-19.1	3220	36 (1.1)	1 [Ref]	1 [Ref]
	19.1-32.1	2942	35 (1.2)	1.06 (0.67-1.70)	0.92 (0.57-1.48)
	More than 32.1	871	25 (2.9)	2.61 (1.56-4.38)	1.63 (0.95-2.79)

Note: AdJOR is adjusted for age, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status, and assessment centre

Table 5 CWP by consumption of different alcohol types in female drinkers (n=171,687)

	Weekly consumption (units)	Total	Number with CWP (%)	OR (95% CI)	Adj OR (95% CI)
Red Wine	0	61612	820 (1.3)	2.17 (1.70-2.77)	1.44 (1.12-1.85)
	0-6.4	58346	520 (0.9)	1.45 (1.13-1.86)	1.26 (0.98-1.62)
	6.4-11.2	29340	223 (0.8)	1.23 (0.94-1.61)	1.14 (0.87-1.50)
	11.2-19.1	11503	71 (0.6)	1 [Ref]	1 [Ref]
	19.1-32.1	8525	67 (0.8)	1.28 (0.91-1.78)	1.13 (0.81-1.59)
	More than 32.1	2361	19 (0.8)	1.31 (0.79-2.17)	0.96 (0.57-1.60)
White Wine	0	59685	747 (1.3)	1.64 (1.32-2.05)	1.17 (0.94-1.47)
	0-6.4	74137	690 (0.9)	1.22 (0.98-1.52)	1.08 (0.86-1.35)
	6.4-11.2	18863	137 (0.7)	0.95 (0.73-1.24)	0.89 (0.68-1.16)
	11.2-19.1	11754	90 (0.8)	1 [Ref]	1 [Ref]
	19.1-32.1	5609	45 (0.8)	1.05 (0.73-1.50)	0.99 (0.69-1.43)
	More than 32.1	1639	11 (0.7)	0.88 (0.47-1.64)	0.64 (0.34-1.21)
Beer/Cider	0	130029	1228 (0.9)	0.56 (0.42-0.75)	0.87 (0.64-1.18)
	0-6.4	31043	335 (1.1)	0.64 (0.47-0.87)	0.93 (0.68-1.290
	6.4-11.2	5944	74 (1.2)	0.74 (0.51-1.07)	0.86 (0.58-1.26)
	11.2-19.1	2812	47 (1.7)	1 [Ref]	1 [Ref]
	19.1-32.1	1291	26 (2.0)	1.21 (0.75-1.96)	1.05 (0.63-1.75)
	More than 32.1	568	10 (1.8)	1.05 (0.53-2.10)	0.68 (0.33-1.38)
Spirits	0	112072	1017 (0.9)	0.59 (0.42-0.83)	0.92 (0.64-1.31)
	0-6.4	51354	581 (1.1)	0.73 (0.52-1.04)	0.98 (0.68-1.40)
	6.4-11.2	4495	56 (1.2)	0.81 (0.53-1.24)	0.86 (0.55-1.33)
	11.2-19.1	2217	34 (1.5)	1 [Ref]	1 [Ref]
	19.1-32.1	1304	23 (1.8)	1.15 (0.68-1.97)	0.86 (0.50-1.49)
	More than 32.1	245	9 (3.7)	2.45 (1.16-5.17)	1.29 (0.59-2.83)

Note: AdJOR is adjusted for age, BMI, education, deprivation, social networks, mood, loneliness, smoking, ethnicity, employment status, and assessment centre

Table 6 Sensitivity analysis, CWP by alcohol consumption including those with missing adjusting variables

Males (n=196,529)

Weekly consumption (units)	Total	Number with CWP (%)	OR (95% CI)
0	14346	500 (3.5)	4.69 (4.09-5.39)
0-1.7	5036	60 (1.2)	1.57 (1.19-2.06)
1.7-6.4	19539	177 (0.9)	1.19 (0.99-1.42)
6.4-11.2	25145	199 (0.8)	1.04 (0.87-1.23)
11.2-19.1	39426	273 (0.7)	0.91 (0.77-1.06)
19.1-32.1	45711	349 (0.8)	1 [Ref]
32.1-53.6	31617	241 (0.8)	1.00 (0.85-1.18)
More than 53.6	15709	188 (1.2)	1.57 (1.32-1.88)

Females (n=209,708)

Weekly consumption (units)	Total	Number with CWP 9%)	OR (95% CI)
0	25651	1104 (4.3)	4.81 (4.29-5.40)
0-1.7	15909	282 (1.8)	1.93 (1.66-2.25)
1.7-3.5	16618	193 (1.2)	1.26 (1.06-1.49)
3.5-6.4	28115	307 (1.1)	1.18 (1.02-1.37)
6.4-11.2	44175	409 (0.9)	1 [Ref]
11.1-19.1	43244	406 (0.9)	1.01 (0.88-1.16)
19.1-32.1	25939	211 (0.8)	0.88 (0.74-1.04)
More than 32.1	10057	101 (1.0)	1.09 (0.87-1.35)