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1 **Alcohol use and cognitive functioning in young adults: improving causal inference**

2

3 Liam Mahedy<sup>1,2,3</sup> (Ph.D.), Steph Suddell<sup>1,2,3</sup> (MSc), Caroline Skirrow<sup>1,4</sup>, (Ph.D.), Gwen S.

4 Fernandes<sup>5</sup> (Ph.D.), Matt Field<sup>6</sup> (Ph.D.), Jon Heron<sup>5</sup> (Ph.D.), Matthew Hickman<sup>5</sup> (Ph.D.),

5 Robyn Wootton<sup>1,2,3</sup> (Ph.D.), Marcus R. Munafò<sup>1,2,3</sup> (Ph.D.)

6

7 **Affiliations**

8 <sup>1</sup>School of Psychological Science, University of Bristol, Bristol, UK.

9 <sup>2</sup>MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK.

10 <sup>3</sup>National Institute for Health Research Biomedical Research Centre at the University

11 Hospitals Bristol NHS Foundation Trust and the University of Bristol, Bristol, UK.

12 <sup>4</sup>Cambridge Cognition, Cambridge, UK.

13 <sup>5</sup>Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

14 <sup>6</sup>Department of Psychology, University of Sheffield, Sheffield, UK.

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16 All authors meet authorship criteria.

17

18 **Corresponding author:** Liam Mahedy, School of Psychological Science, University of Bristol,

19 12a Priory Road, Bristol, UK, BS8 1TU.

20 Tel: +44 (0) 117 33 10616; Email: liam.mahedy@bristol.ac.uk

21

22 **Running head:** Alcohol and cognition in young adults

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24 **Conflict of interest:** CS is employed by Cambridge Cognition Ltd. MRM is co-director of  
25 Jericoe Ltd, which produces software for the assessment and modification of emotion  
26 recognition. LM, RW, SS, MF, JH, & MH report no conflicts of interest.

27 **Abstract**

28 **Background and Aims:** There have been few longitudinal studies of association between  
29 alcohol use and cognitive functioning in young people. We aimed to examine whether alcohol  
30 use is a causal risk factor for deficient cognitive functioning in young adults.

31 **Design:** Linear regression was used to examine the relationship between longitudinal latent  
32 class patterns of binge drinking and subsequent cognitive functioning. Two-sample  
33 Mendelian randomisation (MR) tested evidence for the causal relationship between alcohol  
34 use and cognitive functioning.

35 **Setting:** South West England.

36 **Participants:** The observational study included 3,155 adolescents and their parents (fully  
37 adjusted models) from the Avon Longitudinal Study of Parents and Children (ALSPAC). Genetic  
38 instruments for alcohol use were based on almost 1,000,000 individuals from the GWAS &  
39 Sequencing Consortium of Alcohol and Nicotine use (GSCAN). Genome-wide association  
40 studies for cognitive outcomes were based on 2,500 individuals from ALSPAC.

41 **Measurements:** Binge drinking was assessed at approximately 16, 17, 18, 21, and 23 years.  
42 Cognitive functioning comprised working memory, response inhibition, and emotion  
43 recognition assessed at 24 years of age. Ninety-nine independent genome-wide significant  
44 SNPs associated with 'number of drinks per week' were used as the genetic instrument for  
45 alcohol consumption. Potential confounders were included in the observational analyses.

46 **Findings:** Four binge drinking classes were identified: 'low-risk' (41%), 'early-onset monthly'  
47 (19%), 'adult frequent' (23%), and 'early-onset frequent' (17%). The association between  
48 early-onset frequent binge drinking and cognitive functioning: working memory ( $b=0.09$ ,  
49  $95\%CI=-0.10$  to  $0.28$ ), response inhibition ( $b=0.70$ ,  $95\%CI=-10.55$  to  $11.95$ ), and emotion  
50 recognition ( $b=0.01$ ,  $95\%CI=-0.01$  to  $0.02$ ) in comparison to low-risk drinkers were

51 inconclusive as to whether a difference was present. Two-sample MR analyses similarly  
52 provided little evidence that alcohol use is associated with deficits in working memory using  
53 the inverse variance weight ( $b=0.29$ , 95%CI=-0.42 to 0.99), response inhibition ( $b=-0.32$ ,  
54 95%CI=-1.04 to 0.39), and emotion recognition ( $b=0.03$ , 95%CI=-0.55 to 0.61).

55 **Conclusions:** Binge drinking in adolescence and early adulthood may not be causally related  
56 to deficiencies in working memory, response inhibition, or emotion recognition in youths.

57

## 58 INTRODUCTION

59 Alcohol use during adolescence, when the brain is still developing and undergoing  
60 considerable structural and functional changes (1) is a major public health concern. The  
61 association between binge drinking and cognitive functioning (i.e., working memory,  
62 response inhibition, and emotion recognition) has received particular attention because some  
63 cognitive functions do not peak until early adulthood (2–5) in parallel with maturation of the  
64 prefrontal cortex (6,7).

65 There is a wealth of evidence from animal (8,9), neuroimaging (10–12), twin (13,14),  
66 and cognitive neuroscience (15,16) studies suggesting that adolescent binge drinking is  
67 negatively associated with cognitive functioning. However, the direction of this association  
68 remains unclear as many of these results are based on evidence from small cross-sectional  
69 studies. Studies that have examined this association using prospective data have largely  
70 revealed mixed findings. For example, some studies have found that alcohol use preceded  
71 deficits in domains of cognitive functioning (17–20), while other studies have provided  
72 support for the opposite direction (21–23). One possible way to overcome reverse causation  
73 is to use Mendelian randomisation (24). This approach uses genetic variants to proxy for an  
74 exposure in an instrumental variable analysis to estimate the causal effect on the outcome  
75 (25). One previous study examining the association between alcohol use and cognition in mid-  
76 to late-adulthood using observational and MR approaches (26), found that having consumed  
77 ‘any versus no’ alcohol was associated with better immediate recall, delayed recall, verbal  
78 fluency, and processing speed in the observational study, however these findings were not  
79 supported by the MR analyses.

80 In an effort to strengthen the evidence we used a triangulation approach with  
81 observational and genetic epidemiological methods to better understand the causal

82 relationships between drinking patterns and cognitive functioning in young adults using data  
83 from Avon Longitudinal Study of Parents and Children (ALSPAC). The aims were to investigate  
84 (1) whether patterns of binge drinking (assessed between 16 to 23 years) were associated  
85 with working memory, response inhibition, and emotion recognition assessed at age 24, and  
86 (2) whether alcohol use was associated with cognitive functioning using two-sample  
87 Mendelian randomisation (MR) (27). MR can reduce bias from residual confounding and  
88 reverse causation by using genetic variants that are known to be associated with the exposure  
89 (25). We expected to find that more frequent binge drinking would be associated with  
90 deficient cognitive functioning, and that this association would be supported by the MR  
91 analyses.

92

## 93 **METHODS**

### 94 *Design*

95 Longitudinal latent class analysis was used to derive heterogenous patterns of binge  
96 drinking from ages 16 to 23 years. Linear regression was used to examine the relationship  
97 between patterns of binge drinking and subsequent cognitive functioning. The young person  
98 provided self-reported information on binge drinking and cognitive functioning. The clear  
99 temporal ordering of exposure, confounders and outcome helps to rule out the possibility of  
100 reverse causality. Two-sample MR tested evidence for the causal relationship between  
101 alcohol use and cognitive functioning.

### 102 **Observational analyses**

#### 103 *Participants and Procedure*

104 We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), an  
105 ongoing population-based study that contains a wide range of phenotypic and environmental

106 measures, genetic information and linkage to health and administrative records. A fully  
107 searchable data dictionary is available on the study's website  
108 <http://www.bristol.ac.uk/alspac/researchers/our-data/>. Approval for the study was obtained  
109 from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.  
110 Informed consent for the use of data collected via questionnaires and clinics was obtained  
111 from participants following recommendations of the ALSPAC Ethics and Law Committee at  
112 the time. Consent for biological samples has been collected in accordance with the Human  
113 Tissue Act (2004). All pregnant women residing in the former Avon Health Authority in the  
114 south-west of England and had an estimated date of delivery between 1 April 1991 and  
115 December 1992 were eligible for the study (Phase I consisted of  $N=14,541$ ). Of the 13,988  
116 offspring alive at one year, a small number of participants have withdrawn fully from the  
117 study ( $n=41$ ), leaving an eligible sample of 13,947. Of these, 9,299 offspring were invited to  
118 attend the 24-year clinic assessment. Detailed information about ALSPAC is available online  
119 [www.bris.ac.uk/alspac](http://www.bris.ac.uk/alspac) and in the cohort profiles (28–30). A detailed overview of our study  
120 population, including attrition at the different measurement occasions is presented in  
121 Supplementary Material Figure S1.

## 122 **Measures**

123 A timeline of data collection is presented in Supplementary Material Figure S2.

### 124 *Exposure: Binge drinking*

125 Information on binge drinking was collected on five occasions via a questionnaire (Q)  
126 or during attendance at a study clinic (C). Mean ages at response were: 16y 7m (Q), 17y 9m  
127 (C), 18y 6m (Q) 20y 11m (Q), and 22y 11m (Q) using the following question reflecting drinking  
128 over the past year “How often do you have six or more drinks on one occasion?”. One drink  
129 was specified as ½ pint (568 ml) average strength beer/lager, one glass of wine, or one single



130 measure (25ml) of spirits. Responses at each time point were used to derive a repeated 3  
131 level ordinal variable with categories “Never/Occasional” (comprising of “Never” and “Less  
132 than monthly”), “Monthly” and “Weekly”. Daily or almost daily was collapsed into the  
133 “Weekly” group.

#### 134 *Outcome variables*

135 At 24 years of age ( $M=24.0$  years;  $SD=9.8$  months) participants attended a clinic-based  
136 assessment which included computerised cognitive assessments as part of a broader  
137 assessment battery of mental and physical health and behaviour. Data collection for the  
138 online questionnaires was collected and managed by REDcap electronic data capture tools  
139 (31,32).

#### 140 *Working memory*

141 The  $N$ -back task (2-back condition) was used to assess working memory. The  $N$ -back  
142 task (33) is widely used to measure working memory (17,34,35). A measure of discriminability  
143 ( $d'$ ) was chosen as the primary outcome measure given it is an overall performance estimate.  
144 Of the participants assessed with cognitive tasks at age 24 ( $n=3,312$ ),  $n=182$  did not provide  
145 any data on the task;  $n=70$  were omitted due to negative  $d'$  scores and/or not responding to  
146 over 50% of the trials, leaving a sample of  $n=3,242$  ( $M=2.75$ ,  $SD=0.81$ ).

#### 147 *Response inhibition*

148 The Stop Signal Task (36) was used to assess response inhibition – the ability to  
149 prevent an ongoing motor response. The task consisted of 256 trials, which included a 4:1  
150 ratio of trials without stop signals to trials with stop signals. Mean response times were  
151 calculated. An estimate of *stop signal reaction time* (SSRT) was calculated and used as the  
152 primary outcome as it is a reliable measure of inhibitory control, with shorter SSRT's indicating  
153 faster inhibition. SSRT data were available for  $n=3,201$  ( $M=258.60$ ,  $SD=53.19$ ).

154 *Emotion recognition*

155           Emotion recognition was assessed using a six alternative forced choice (6AFC) emotion  
156 recognition task (37) comprising of 96 trials (16 for each emotion) which measures the ability  
157 to identify emotions in facial expressions. In each trial, participants were presented with a  
158 face displaying one of six emotions: anger, disgust, fear, happiness, sadness, or surprise. An  
159 overall measure of ER (the number of facial emotions accurately identified) was used as the  
160 primary outcome. ER data were available for  $n=3,368$  ( $M=0.69$ ,  $SD=0.08$ ).

161 *Potential confounders*

162           We identified confounders from established risk factors for cognitive functioning that  
163 could plausibly have a causal relationship with earlier binge drinking including income,  
164 maternal education, socioeconomic position, housing tenure, sex, and maternal smoking  
165 during first trimester in pregnancy. Two measures were included to control for cognitive  
166 function prior to alcohol initiation. Working memory at approximately 11 years and  
167 experience of a head injury/unconsciousness up to 11 years. Finally, measures of cigarette  
168 and cannabis use were collected at 4 timepoints between ages ~14 and ~16.5 years (up to the  
169 first assessment of binge drinking). Further information on all measures are presented in  
170 Supplementary material.

171 *Statistical methods*

172 *Observational analyses*

173           The observational analyses were conducted in two stages. First, longitudinal latent  
174 class analysis was used to derive trajectories of binge drinking for individuals having at least  
175 one measure of binge drinking ( $n=6,353$ ). Starting with a single latent class, additional classes  
176 were added until model fit was optimised. See supplementary material for a description of  
177 model fit. Analyses were carried out using Mplus 8.1 (38).

178           Class membership was then related to covariates using the three-step method using  
179 the Bolck-Croon-Hagenaars (BCH) (39) method. The first stage estimated the latent class  
180 measurement model and saves the BCH weights. While, the second stage involved using these  
181 weights which reflect the measurement error of the latent class variable. Linear regression  
182 was used to examine the association between the continuous distal outcomes and latent class  
183 membership controlling for the confounding variables. Results are reported as  
184 unstandardised beta coefficients and 95% confidence intervals.

#### 185 *Missing data*

186           Missing data was dealt with in three steps. Of those invited to the age 24-year clinic  
187 ( $n=9,299$ ), 6,353 (68%) participants provided self-report information on binge drinking on at  
188 least one timepoint between 16 and 23 years. Of these,  $n=3,755$  (59%) had available  
189 information on all covariates. Next, multiple imputation was based on 3,155 (46%)  
190 participants who had information on at least one of the cognitive outcomes. The imputation  
191 model (based on 100 datasets) contained performance on all of the cognitive tasks, all  
192 measures of binge drinking, and potential confounding variables, as well as a number of  
193 auxiliary variables known to be related to missingness (e.g., substance use in early  
194 adolescence, parental financial difficulties, and other SES variables). Finally, inverse  
195 probability weighting was used where estimates of prevalence and associations were  
196 weighted to account for probabilities of non-response to attending the clinic. See Table S1 for  
197 a detailed description of attrition.

#### 198 *Genetic analyses*

199           Two-sample MR was used to test the hypothesised causal effect of alcohol use on  
200 cognitive functioning. The two-sample MR approach requires summary level data from two  
201 GWAS, enabling SNP-exposure and SNP-outcome effects to be derived from different data

202 sources. As the genetic instrument for alcohol consumption we used the 99 conditionally  
203 independent genome-wide significant SNPs associated with ‘number of drinks per week’,  
204 identified by the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN  
205 <https://gscan.sph.umich.edu/>) based on a sample of  $n=941,280$ . The 99 SNPs explain 2.5% of  
206 the variance in number of drinks per week (27). 87 of these SNPs were available in ALSPAC.  
207 As outcomes, we used GWAS conducted in ALSPAC for each of our three primary cognitive  
208 measures: i) working memory assessed using  $d'$  ( $n=2,471$ ); ii) response inhibition assessed  
209 using SSRT ( $n=2,446$ ); and iii) emotion recognition assessed using total number of correctly  
210 recognised emotions ( $n=2,560$ ). Further information is provided in the Supplementary  
211 material (Figures S4-S9). The main strength of using summary data from large GWAS consortia  
212 in two-sample MR is the increased statistical power. Analyses were performed using the  
213 TwoSampleMR R package, part of MR-Base (40). Power calculations conducted for one-  
214 sample MR analyses using mRnd (41) indicated that we had 80% power to detect an effect  
215 size of 0.335 for number of drinks per week using a sample size of  $n\sim 2,500$  (participants with  
216 available genetic data).

217 It should be noted that neither the study nor the analysis plan were pre-registered on  
218 a publicly available platform, so the results should be considered exploratory.

219

## 220 **RESULTS**

### 221 *Observational analyses*

#### 222 *Patterns of binge drinking*

223 The prevalence of both monthly and weekly binge drinking increased across time  
224 apart from a slight decrease at age 23 years (Table S2). There was good agreement that a  
225 four-class solution was adequate in explaining the heterogeneity in binge drinking based on

226 increasing Bayesian Information Criterion (BIC) (42) and sample size adjusted Bayesian  
227 Information Criterion (SSABIC) (43) values in the five-class model and an LRT value of  $p=0.05$ .  
228 See Table S3 in the Supplementary Material for a comparison of model fit indices. The four-  
229 class solution (Figure 1) comprised patterns of binge drinking that were labelled as ‘low-risk’  
230 (47.1%), ‘early-onset monthly’ (19.0%), ‘adult frequent’ (18.7%), and ‘early-onset frequent’  
231 (19.0%). See Table S4 in the Supplementary Material for class validation. A detailed  
232 description of confounding factors associated with binge drinking class membership is  
233 provided in Table S5.

234 [Figure 1]

#### 235 *Working memory – 2-back task*

236 Table 1 presents unadjusted and adjusted associations between patterns of binge  
237 drinking from 16 to 23 years and working memory at age 24. There was little evidence to  
238 suggest an association between patterns of binge drinking and working memory performance  
239 in the fully adjusted models (‘early-onset monthly’:  $b=0.54$ , 95%CI=-1.92 to 0.82; ‘adult  
240 frequent’:  $b=0.03$ , 95%CI=-0.80 to 0.86; ‘early-onset frequent’:  $b=-0.42$ , 95%CI=-1.24 to 0.41).  
241 Furthermore, there was little evidence to suggest that patterns of binge drinking were  
242 associated with the secondary outcomes (i.e., number of hits and false alarms) (Table S6).

243 [Table 1]

#### 244 *Response inhibition - stop signal task*

245 Table 2 presents unadjusted and adjusted associations between patterns of binge  
246 drinking and an overall measure of response inhibition. There was little evidence to suggest  
247 an association between patterns of binge drinking and ability to inhibit responses in the fully  
248 adjusted models (‘early-onset monthly’:  $b=-3.9$ , 95%CI=-109.3 to 101.5; ‘adult frequent’:  
249  $b=15.9$ , 95%CI=-38.2 to 69.9; ‘early-onset frequent’:  $b=31.9$ , 95%CI=-25.3 to 89.2).

250 Furthermore, there was little evidence to suggest that patterns of binge drinking were  
251 associated with any of the secondary outcomes (i.e., Go reaction time, Go accuracy, and Stop  
252 accuracy) (Table S7).

253 [Table 2]

#### 254 *Emotion recognition – 6AFC task*

255 Table 3 presents unadjusted and adjusted associations between patterns of binge  
256 drinking and number of correctly identified emotions. There was little evidence to suggest an  
257 association between patterns of binge drinking and emotion recognition in the fully adjusted  
258 models ('early-onset monthly':  $b=0.01$ , 95%CI=-0.12 to 0.14; 'adult frequent':  $b=0.04$ , 95%CI=-  
259 0.04 to 0.13; 'early-onset frequent':  $b=0.02$ , 95%CI=-0.07 to 0.10). Furthermore, there was  
260 little evidence to suggest that patterns of binge drinking were associated with any of the  
261 secondary outcomes (i.e., anger, disgust, fear, happy, sad, and surprise) (Table S8).

262 [Table 3]

#### 263 *Sensitivity analyses*

264 Models using complete cases were included to assess the impact of missing data (Table S9).  
265 A latent growth model of the five repeated measures of binge drinking was conducted to  
266 examine the association with working memory, response inhibition, and emotion recognition  
267 while controlling for potential confounding variables ( $n=3,155$ ) (Figure S3 and Table S10).

#### 268 *Genetic analyses*

##### 269 *Mendelian randomisation*

270 The two-sample MR method provides little evidence to suggest that alcohol use (SNPs  
271 associated with number of drinks per week) is a causal risk factor for deficits in cognitive  
272 functioning (Table 4). Focusing on the IVW estimate as the primary measure, SNPs associated  
273 with the number of alcoholic drinks per week were not associated with  $d'$  on the working

274 memory task ( $b=0.285$  95% CI=-0.42 to 0.99;  $p=0.43$ ); SSRT on the response inhibition task  
275 ( $b=-0.321$  95%CI=-1.04 to 0.39;  $p=0.38$ ); or total hits in the emotion recognition task ( $b=0.028$   
276 95% CI=-0.55 to 0.61;  $p=0.93$ ). Sensitivity analyses did not alter the main findings.

277 [Table 4]

## 278 **DISCUSSION**

279 We found insufficient evidence to suggest an association between binge drinking  
280 between the ages of 16 and 23 and working memory, inhibition, and emotion recognition at  
281 age 24 using a combination of observational and genetic approaches. In the observational  
282 analyses, there was no evidence to suggest that binge drinking patterns identified in  
283 adolescence and early adulthood were associated with later measures of working memory,  
284 inhibition, and emotion recognition. While, the genetic analyses provided no clear causal  
285 evidence.

### 286 *Comparison with previous studies*

287 Unlike the studies that have demonstrated a prospective association between binge  
288 drinking and cognitive functioning in adolescence e.g. (17–20), we found little evidence in  
289 support of this association. The contrast in findings could be due to a number of possibilities.  
290 First, our study used a large population sample incorporating data from over 3,000 individuals  
291 spanning maternal pregnancy to 24 years of age. Previous studies (19,20) used functional  
292 magnetic resonance imaging based on youths at high-risk for substance use disorders ( $n=40$   
293 for both studies), while the study by Peeters and colleagues (18) used a sample at high-risk  
294 for externalising problems ( $n=374$  at baseline). Second, this study assessed cognitive  
295 functioning in early adulthood, a time when cognitions are thought to reach maturity (2–5),  
296 in comparison to all four studies who assessed cognitive functioning up to 19 years of age.  
297 Examining peak levels of cognitive functioning helps to reduce the possibility that cognitive

298 functioning is influencing earlier alcohol use (i.e., reverse causation). Third, as alcohol use  
299 behaviours typically change over time (44), repeated measures of binge drinking were used  
300 in this study to capture heterogenous patterns across this sensitive period in comparison to  
301 our previous study which assessed alcohol use on one occasion (17). Finally, most of the  
302 previous studies (18–20) assessed cognitive functioning using different measures to the more  
303 widely used measures in this study (i.e., *N*-back task, Stop signal task, and 6AFC task).

304 Our findings support and extend those of Boelema and colleagues (45) who found  
305 insufficient evidence to suggest that alcohol use prospectively affected maturation of  
306 cognitive functions in a large prospective study of Dutch adolescents (46). First, Boelema and  
307 colleagues examined cognitive functioning across adolescence, while we were able to  
308 examine peak levels of cognitive functioning. Second, assessing binge drinking in young  
309 adulthood allowed us to capture heterogenous patterns during the sensitive period (i.e.,  
310 going to University or in full-time paid employment). Finally, WM performance was measured  
311 in reaction times only, as opposed to the more comprehensive approach used in our study  
312 (i.e., number of hits, false alarms, and  $d'$ ).

313 There are a number of differences with the findings from Kumari and colleagues (26).  
314 First, the observational study examines weekly alcohol consumption (and was dichotomised  
315 into 'any versus none' per week), compared to the repeated measures approach used in this  
316 study. Second, different cognitive outcome measures were used. Third, alcohol and cognition  
317 were assessed in mid-late adulthood (mean age across six studies ranged from 55 to 66 years)  
318 compared to adolescence/ young adulthood in this study. The MR analyses was based on a  
319 single SNP (rs1229984) as opposed to 87 SNPs in this study. The main disadvantage to using  
320 single SNPs is that statistical power may be low and an inability to separate horizontal from  
321 vertical pleiotropy (47).



322 *Limitations*

323 First, the ALSPAC cohort suffers from attrition which reduces study power and is  
324 higher among the socially disadvantaged (48) (Table S1). We attempted to minimise the  
325 impact of attrition using sensitivity analyses. Missingness was related to having information  
326 on binge drinking, potential confounders and cognitive information. However, the pattern of  
327 results remained the same in the complete case (Table S9) and imputed analyses, suggesting  
328 that the pattern of missing data did not lead to biased effect estimates. Second, it is possible  
329 that both the observational and two-sample MR analyses are underpowered. For example,  
330 poor entropy (a measure of class separation) could indicate poor misclassification in the  
331 latent classes. Although binge drinking assessments spanned 7 years, it is possible that the  
332 use of a single item, with three possible response options, may diminish the ability to assess  
333 heterogeneous drinking patterns. Misclassification of this kind (non-differential) when the  
334 exposure variable has more than two categories can bias the association in either direction  
335 (49) suggesting that true underlying associations could be stronger or weaker than we  
336 observed. Although this is likely, we are unable to validate these classes with an alcohol  
337 biomarker as an adequate biomarker for binge drinking in adolescents/young adulthood is  
338 not available in ALSPAC. Patterns of binge drinking were however shown to have a dose-  
339 response association with a later AUDIT-consumption measure, assessed at 24 years of age  
340 (Table S4).

341 Third, including yearly binge drinking assessments would have helped class formation,  
342 however given the pattern of results, it is plausible that they would not change the pattern of  
343 results. Fourth, although it is possible to either under- or over-estimate drinking behaviour  
344 using self-reported data, participants completed questionnaires individually and were  
345 assured of their anonymity. Fifth, different measures of alcohol use for the observational and

346 MR analyses were used. Along with deriving latent classes of binge drinking, we used the  
347 largest GWAS consortia (GSCAN) which has identified 87 genetic instruments for 'number of  
348 alcohol drinks per week' which is a continuous measure. To our knowledge it is not currently  
349 possible to use a nominal exposure (as was used in the observational analyses) and  
350 consequently the effect sizes are not directly comparable.

351 Sixth, as we examined one potential causal pathway, it is possible that the association  
352 could work in the opposite direction, that is, impairments in cognitive functioning may  
353 precede (and increase the risk of developing) alcohol problems (18,23). We were however  
354 able to include a number of measures to maximise the robustness of our findings: (i)  
355 ascertaining the time order of exposures and outcomes; (ii) controlling for premorbid working  
356 memory function and brain insults prior to the onset of alcohol use; and (iii) a number of  
357 relevant confounders were included to help reduce the possibility of residual confounding. It  
358 is possible that a common risk factor is influencing both binge drinking and deficits in  
359 cognition, however the two-sample MR analyses helps to protect against this possibility by  
360 minimising bias from reverse causation and residual confounding. Seventh, genetic variants  
361 were based on number of drinks per week, whereas the observational analyses used  
362 frequency of binge drinking. Although not directly comparable, there was evidence of a dose  
363 response relationship between binge drinking patterns and the AUDIT-C measure, which taps  
364 into quantity and frequency (see Supplementary material).

365 Finally, the main limitation of two-sample MR is that the quality of the pooled results  
366 in the GWAS consortia is dependent on the individual studies. Another limitation is that the  
367 same sample may contribute to both GWAS (i.e., GWAS for exposure and outcome) which  
368 was the case in the current study as ALSPAC was in both the exposure and outcome. This  
369 will bias the MR estimate towards the observed estimate. However, as the MR found no

370 clear evidence for an effect, this suggests it was not biased by overlapping samples. See  
371 Lawlor et al. (25) for a more comprehensive description of limitations associated with MR  
372 studies.

### 373 *Implications and Conclusions*

374 In order to rule out the possibility of deficient cognitive functioning preceding binge  
375 drinking in adolescence, future research should use an equally robust approach to examine  
376 the alternate hypothesis. We found insufficient evidence to suggest an association between  
377 binge drinking between the ages of 16 and 23 and cognitive deficits at age 24 using a  
378 combination of observational and genetic approaches, although both approaches are likely  
379 to be underpowered. Future studies should use larger observational samples and meta-  
380 analyses of related cognitive measures in GWAS to help to increase power.

381

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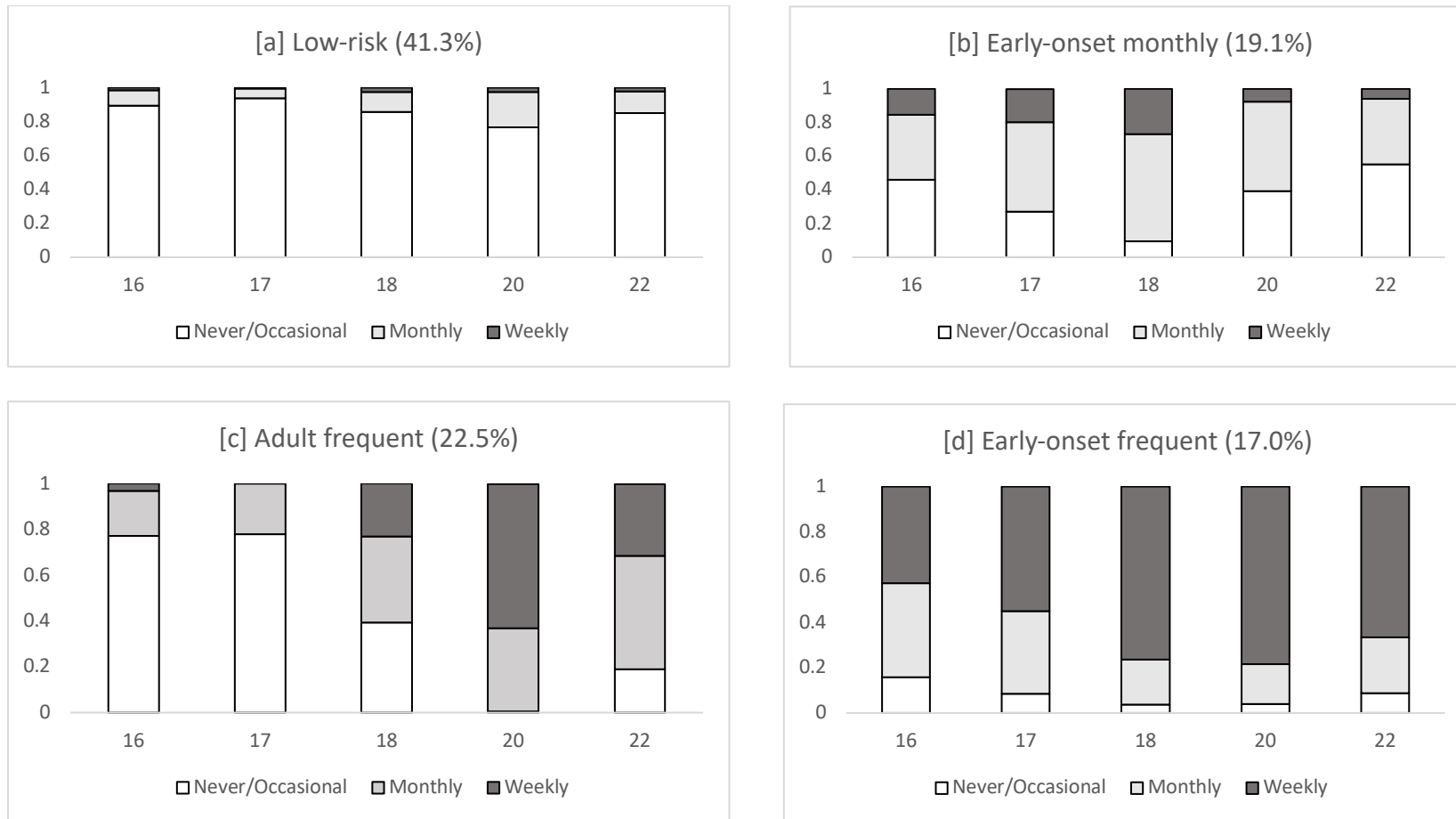
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**Figure 1.** Distribution of binge drinking response across latent classes at each timepoint ( $n=6,353$ ). Class proportions based on estimated posterior probability<sup>1</sup>

<sup>1</sup> Overall, the low-risk group reported a low probability of binge drinking across all measurement occasions; 'early-onset monthly' binge drinkers was mostly characterised by binge drinking in the earlier measurement occasions (but not later ones), 'adult frequent' binge drinkers were mostly characterised by binge drinking in the later measurement occasions (but not earlier ones), while 'early-onset frequent' binge drinking was mostly characterised by binge drinking across all timepoints.

**Table 1.** Patterns of binge drinking from 16 to 23 years and working memory at age 24 (higher  $d'$  scores reflect better performance)

	Low risk	Early-onset monthly	Adult frequent	Early-onset frequent	
$n=3,155$ for all models	Reference group	$b$ (95% CI)	$b$ (95% CI)	$b$ (95% CI)	Wald (df) $p$ value
<b>Model 1</b>					
Working memory $d'$	-	-0.07 (-0.26, 0.12)	0.24 (0.12, 0.36)	0.15 (0.03, 0.28)	20.29 (3) $p<0.001$
<b>Model 2</b>					
Working memory $d'$	-	-0.54 (-1.55, 0.47)	-0.01 (-0.65, 0.37)	-0.28 (-0.93, 0.37)	1.93 (3) $p=0.59$
<b>Model 3</b>					
Working memory $d'$	-	-0.46 (-1.176, 0.85)	0.03 (-0.80, 0.86)	-0.43 (-1.25, 0.40)	1.68 (3) $p=0.64$
<b>Model 4: fully adjusted</b>					
Working memory $d'$	-	-0.54 (-1.92, 0.82)	0.03 (-0.80, 0.86)	-0.42 (-1.24, 0.41)	1.78 (3) $p=0.62$

Note. Model 1: unadjusted; Model 2 adjusted for sex, tenure, income, social status, housing tenure, maternal education, and maternal smoking in pregnancy; Model 3: further adjusted for working memory at age ~11 years and HI: head injury/ unconsciousness up to age 11 years; Model 4: further adjusted for tobacco and cannabis use up to age 16.5 years.

**Table 2.** Patterns of binge drinking from 16 to 23 years and response inhibition at age 24 (shorter scores reflect faster reaction times)

	Low risk	Early-onset monthly	Adult frequent	Early-onset frequent	
<i>n</i> =3,155 for all models	Reference group	<i>b</i> (95% CI)	<i>b</i> (95% CI)	<i>b</i> (95% CI)	Wald (df) <i>p</i> value
<b>Model 1</b>					
Stop signal reaction time	-	11.5 (-0.9, 23.8)	-8.7 (-16.8, -0.6)	-5.9 (14.0, 2.1)	10.74 (3) <i>p</i> =0.01
<b>Model 2</b>					
Stop signal reaction time	-	35.7 (-33.4, 104.8)	-12.3 (-54.9, 30.3)	12.0 (-31.3, 55.2)	2.13 (3) <i>p</i> =0.55
<b>Model 3</b>					
Stop signal reaction time	-	5.6 (95.3, 106.4)	15.7 (-38.3, 69.7)	32.6 (-24.6, 89.8)	1.39 (3) <i>p</i> =0.71
<b>Model 4: fully adjusted</b>					
Stop signal reaction time	-	-3.9 (-109.3, 101.5)	15.9 (-38.2, 69.9)	31.9 (-25.3, 89.2)	1.35 (3) <i>p</i> =0.72

Note. Model 1: unadjusted; Model 2 adjusted for sex, tenure, income, social status, housing tenure, maternal education, and maternal smoking in pregnancy; Model 3: further adjusted for working memory at age ~11 years and HI: head injury/ unconsciousness up to age 11 years; Model 4: further adjusted for tobacco and cannabis use up to age 16.5years.

**Table 3.** Patterns of binge drinking from 16 to 23 and emotion recognition at age 24 (higher scores reflect better performance)

	Low risk	Early-onset monthly	Adult frequent	Early-onset frequent	
<i>n</i> =3,155 for all models	Reference group	<i>b</i> (95% CI)	<i>b</i> (95% CI)	<i>b</i> (95% CI)	Wald (df) <i>p</i> value
<b>Model 1</b>					
Total hits	-	-0.01 (-0.03, 0.01)	0.02 (0.01, 0.03)	0.01 (-0.00, 0.02)	14.85 (3) <i>p</i> =0.002
<b>Model 2</b>					
Total hits	-	-0.01 (-0.11, 0.09)	0.02 (-0.05, 0.08)	0.01 (-0.05, 0.07)	0.32 (3) <i>p</i> =0.96
<b>Model 3</b>					
Total hits	-	0.00 (-0.13, 0.13)	0.04 (-0.04, 0.13)	0.02 (-0.07, 0.10)	1.04 (3) <i>p</i> =0.79
<b>Model 4: fully adjusted</b>					
Total hits	-	0.01 (-0.12, 0.14)	0.04 (-0.04, 0.13)	0.02 (-0.07, 0.10)	1.07 (3) <i>p</i> =0.78

Note. Model 1: unadjusted; Model 2 adjusted for sex, tenure, income, social status, housing tenure, maternal education, and maternal smoking in pregnancy; Model 3: further adjusted for working memory at age ~11 years and HI: head injury/ unconsciousness up to age 11 years; Model 4: further adjusted for tobacco and cannabis use up to age 16.5years.

**Table 4.** Two-sample Mendelian randomization analyses of the effects of alcohol use on cognitive functioning

Exposure	Outcome	Method	N SNPs	Beta (95% CI)	P-value
<b>Drinks per week</b>	<b>Working memory</b>	Inverse-Variance Weighted	87	0.285 (-0.42, 0.99)	0.43
		MR Egger (SIMEX)	87	-0.473 (-1.70, 0.74)	0.45
		Weighted Median	87	0.408 (-0.50, 1.32)	0.38
		Weighted Mode	87	0.315 (-1.45, 2.08)	0.32
<b>Drinks per week</b>	<b>Response inhibition</b>	Inverse-Variance Weighted	87	-0.321 (-1.04, 0.39)	0.38
		MR Egger (SIMEX)	87	-1.213 (-2.23, 2.20)	0.29
		Weighted Median	87	-0.556 (-1.55, 0.43)	0.27
		Weighted Mode	87	-0.689 (-2.49, 1.13)	0.46
<b>Drinks per week</b>	<b>Emotion recognition</b>	Inverse-Variance Weighted	87	0.028 (-0.55, 0.61)	0.93
		MR Egger (SIMEX)	87	0.445 (-1.14, 2.03)	0.58
		Weighted Median	87	-0.157 (-1.01, 0.69)	0.72
		Weighted Mode	87	-0.180 (-1.78, 1.42)	0.82

Note: SIMEX = simulation extrapolation. SIMEX-corrected estimates were used based on regression dilution  $I^2_{GX}$  for number of drinks per week values between 0.3 and 0.9. SIMEX-corrected estimates are unweighted.