Article

Reaction Time and Visual Memory in Connection to Alcohol Use in Persons with Bipolar Disorder

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Abstract: The purpose of this study was to explore the association of cognition with hazardous drinking and alcohol related disorder in persons with bipolar disorder (BD). The study population included 1,268 persons from Finland with bipolar disorder. Alcohol use was assessed through hazardous drinking and alcohol related disorder including alcohol use disorder (AUD). Hazardous drinking was screened with the AUDIT-C (Alcohol Use Disorders Identification Test for Consumption) screening tool. Alcohol related disorder diagnoses were obtained from the national registrar data. Participants performed two computerized tasks from the Cambridge automated neuropsychological test battery (CANTAB) on tablet computer: the 5-choice serial reaction time task, or, reaction time (RT) test and the Paired Associative Learning (PAL) test. Association between RT-test and alcohol use was analyzed with log-linear regression, and eβ with 95% confidence intervals (CI) are reported. PAL first trial memory score was analyzed with linear regression, and β with 95% CI are reported. PAL total errors adjusted was analyzed with logistic regression and odds ratios (OR) with 95% CI are reported. After adjustment for age, education and housing status, hazardous drinking was associated with lower median and less variable RT in females while AUD was associated with a poorer PAL test performance in terms of the total errors adjusted scores in females. Our findings of positive associations between alcohol use and cognition in persons with bipolar disorder are unique.

Keywords: cognition; visual memory; reaction time; alcohol; Bipolar disorder

1. Introduction

Cognitive impairment is a prominent [1] and generally stable [2] core symptom [3] in persons with bipolar disorder (BD). BD patients show marked impairment on verbal and non-verbal learning and memory, attention, and executive functioning [4,5,6,7]. BD II patients with hypomanic episode show similar [8,9] or, slightly less severe [10] cognitive deficits compared to BD I patients with manic episode. In population based, representative, longitudinal samples, better cognitive functioning had been associated with increased risk of BD I [11,12]. However, a more recent study found no association between premorbid intelligence quotient (IQ) and risk of bipolar disorder [13].

About half of BD patients have lifetime diagnoses of alcohol use disorder (AUD) [14,15]. Alcohol use is the highest prevalent (42%) substance use disorder (SUD) among BD patients [16]. Alcohol misuse in BD is associated with worse outcome [17]. Even lower

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volume of alcohol consumption is associated with illness severity in both male and female BD patients [18]. Mood symptoms in BD are primarily outcomes of AUD [19]. Also, more severe BD may be a risk factor for alcohol and other substance related disorders, a point that might have an impact on cognition [20].

BD patients with AUD show impaired verbal learning and memory [21,22], higher delay discounting [23], significant memory deficits more specifically the recognition of previously presented information [24] and, more deficits in executive functioning [25,26]. One study found significant impairments in executive control, working memory, attention and cognitive flexibility in comorbid AUD and BD patients, compared to healthy individuals, and patients with only AUD or BD patients [27]. On the other hand, BD patients without AUD also show impaired verbal learning and memory [21,22]. However, one study found no association between cognitive dysfunction and lifetime comorbid alcohol use disorder in BD patients [28]. Systemic literature review of 8 studies (1998-2013) found association between current or past history of comorbid AUD and more severe cognitive impairment in BD patients [29].

Findings from normal population studies mostly suggest mild to moderate alcohol use not to be associated with cognitive impairment [30,31,32,33]. In persons with bipolar disorder, association of cognition with different drinking patterns other than alcohol use disorder, is yet to be studied.

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The main aim of the present study was to explore the association between reaction time and visual memory with two drinking patterns in the same population diagnosed with bipolar disorder.

The specific research aims were to study the following:

1. The association between hazardous drinking and reaction time and visual memory in persons with bipolar disorder.
2. The association between alcohol use disorder and reaction time and visual memory in persons with bipolar disorder.

2. Materials and Methods

2.1. Participants

The participants of this study were part of the study population of SUPER (*Suomalainen psykoosisairauksien perinnöllisyysmekanismien tutkimus* ("Finnish Study of the Hereditary Mechanisms behind Psychotic Illnesses")), which is part of the international Stanley Global Neuropsychiatric Genomics Initiative, USA. SUPER collected data during the period 2016–2019 from people with a lifetime diagnosis of psychosis in Finland to identify gene loci and gene variations predisposing patients to psychotic illnesses and comorbid diseases. Voluntary subjects with a diagnosis of schizophrenia spectrum psychotic disorder, bipolar I disorder, or major depressive disorder with psychotic features were recruited from psychiatric inpatient and outpatient departments, general healthcare centers, and supported housings. Participants were identified through local healthcare centers throughout the country from all levels of healthcare to ensure inclusive sampling. Subjects were also recruited via advertisements in local newspapers.

Out of the original 10,555 study population, we included 1,597 with a lifetime diagnosis of bipolar disorder and excluded those with a lifetime diagnosis of schizophrenia and schizoaffective disorder. Among the included participants, 47 had missing information on alcohol use or education. Of the remaining 1,550 participants, 1,367 were living independently. After excluding those aged 70 years or more 1,268 participants remained among which 1,170 participants (426 males, 744 females) completed reaction time (RT) test and 1,053 participants (374 males, 679 females) completed paired association learning (PAL) test (Figure 1).

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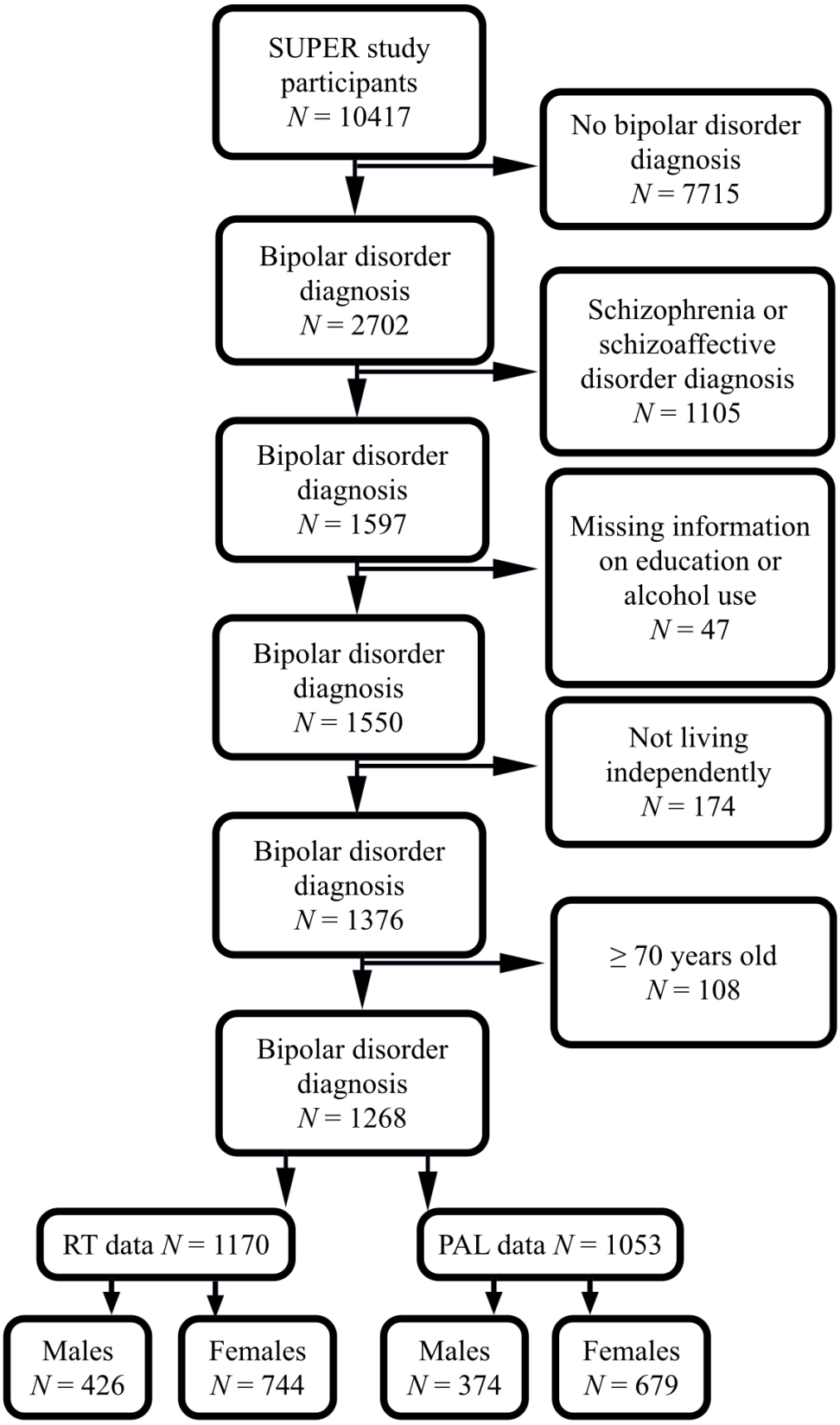

Figure 1. Flowchart showing the selected study population.

2.2. Bipolar Disorder Diagnoses

The diagnosis of bipolar disorder was obtained from the Care Register for Health Care (CRHC) of the National Institute for Health and Welfare of Finland. In Finland ICD-

system has been used in psychiatric diagnoses. In this study bipolar disorder diagnoses included both mania and bipolar disorder corresponding to the codes 296.1-296.8, 298.10 according to ICD-8; 296.2-296.4, 296.7A according to ICD-9 and F30, F31 according to ICD-10. In Finland ICD-8 was used during 1968-1986, ICD-9 during 1987-1995 and ICD-10 since 1996. During the use of ICD-9 in Finland, DSM-3 R criteria for bipolar disorder and other psychiatric disorders were used.

2.3. Hazardous Drinking Screening

About 90% people drinking excessive alcohol could positively be screened as hazardous drinker or binge (heavy episodic) drinkers instead of fulfilling the diagnostic criteria for AUD [34]. Hazardous drinking is a pattern of alcohol consumption that increases the risk of harmful consequences for the user or others. Hazardous drinking patterns are of public health significance despite the absence of any current disorder in the individual alcohol user [35,36,37,38].

Hazardous drinking was screened using the AUDIT-C questionnaire to assess an individual's alcohol consumption frequency ("How often do you have a drink containing alcohol?"), quantity ("How many drinks containing alcohol do you have on a typical day when you are drinking?"), and bingeing ("How often do you have six or more drinks on one occasion?"). AUDIT-C is derived from the hazardous alcohol use domain of the Alcohol Use Disorders Identification Test (AUDIT) questionnaire [39]. It has three questions and is scored on a scale of 0 to 12. Each AUDIT-C question has five answer choices valued from zero to four points.

Cutoff scores for hazardous drinking vary considerably [40,41]. In the present study, we used the cutoff scores recommended by Finnish National Guidelines: a score of 6 or more in males and 5 or more in females [42].

2.4. Alcohol Use Disorder Diagnoses

Alcohol use disorders include F10.1 (harmful alcohol use) and F10.2 (alcohol dependence), hence we have used the term "alcohol-related disorder" in our text elsewhere for better understanding. The diagnoses of alcohol use disorder were obtained from the CRHC data according to codes ICD-8 291 and 303; ICD-9 291, 3030, and 3050A; and ICD-10 F10 for the period from 1969 to 2018.

2.5. Cognitive Measures

Processing speed and visual learning are the two cognitive domains affected invariably in psychotic illnesses; hence, we selected the Five-Choice Serial Reaction Time Task (5-CRTT) and the Paired Associative Learning (PAL) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) for schizophrenia for the assessment of reaction time (RT) and visual memory, respectively.

These tasks were chosen to produce relevant information on cognition in psychotic disorders in the very restricted assessment schedule. The instructions for both tests were translated into Finnish. The CANTAB tests were performed before venipuncture in order to avoid malfunction of the arm due to pain or bandaging. The study nurses were given standardized instructions on how to guide the study subjects in performing the CANTAB test beforehand.

In the RT test, we used two continuous measurements: the median of the five-choice reaction time and the standard deviation (SD) of the five-choice reaction time. The median of the five-choice reaction time is the median duration between the onset of the stimulus and the release of the button. The standard deviation of the five-choice reaction time is the standard deviation of the time taken to touch the stimulus after the button has been released. Both variables were calculated for correct, assessed trials where the stimulus could appear in any of the five locations.

In the PAL-test we assessed visual memory using the primary outcome variables of 'total errors adjusted' and first trial memory score. First Trial Memory Score (FTMS) is how many patterns the participant correctly places on the first attempt at each problem,

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while Total Errors (Adjusted) (TEA) reflects how quickly the participant learns when the participant has multiple attempts at each problem. For PAL TEA we assessed a dichotomized variable because the distribution of the PAL TEA does not follow any known distribution with multiple peaks, using data from Northern Finland Birth Cohort 1966 (NFBC 1966) as a reference data [43]. The NFBC 1966 consists of all born with expected date in the year 1966. The data used in this study consist of a 46-year follow-up when cohort members took the PAL-test during clinical examination (N=5,608). Scores for total errors adjusted of NFBC66, the 50th percentile (10 error score or less) was used as a cut-off for good performance in PAL test in the recent study, meaning the SUPER study population made better error score than a 50% of NFBC 1966 study population . The PAL FTMS variable was used as a continuous variable.

2.6. Confounding Factors

Age, education [44] and housing status [45] have effects on cognition. However, we considered age and education to be the confounding variables in this study.

2.6.1. Age

Cognition is negatively associated with increased age in healthy populations [46] and debatably in alcohol users [47]. The age of the participants was calculated using the participation date and year of birth of the participant. Age was used as continuous variable.

Both illness duration of bipolar disorder [48] and late-onset bipolar disorder [49] is associated with more severe cognitive impairments hence we could also use age of first bipolar episode as a cofounder. However, we did not take age of onset as a confounder considering the complex effects of age. Younger age is associated with both better performance in cognitive tests and with more alcohol use. In addition, younger age is associated with younger age at onset. If we included age of onset in the analysis, we in a way would include the age twice. What it meant if age is correlated both with the outcome of interest and our main explanatory variable (alcohol use). The multicollinearity might exist in the adjusted analysis. However, multicollinearity affects only the specific independent variables that are correlated. Therefore, if multicollinearity was not present for the independent variables that we were particularly interested in, we might not need to resolve it. If we would desire to keep both (age and age of first bipolar episode) in the analysis, the multicollinearity would be hard to avoid.

2.6.2. Education

Education is strongly associated with cognitive performance [50]. The question and possible answers addressing the education of the participants were as follows: “What is your basic education?” (1 = less than primary school, 2 = matriculation examination, 3 = middle school, 4 = partial general upper secondary school or general upper secondary education certificate, 5 = partial middle school or primary school less than nine years, 6 = primary school, 7 = four-year elementary school). During the analysis, we combined classes 1, 3, 4, 5, 6, and 7 as “No matriculation examination” versus class 2 (“Matriculation examination”).

It would be more informative if we could categorize education into three groups. However, it might be difficult for a general reader to understand the diverse categories in the Finnish education system reflecting changes over the past seventy years plus additional categories reflecting the small proportion of immigrants who might have lower general education than that provided in the Finnish education system. We used the general education variable because the youngest participants could still be students.

2.6.3. Household Pattern

Household patterns, especially living without a spouse, might affect cognition [45,51], and thus we considered household patterns as a confounder.

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2.7. Statistical Methods

	Male	Female
	N = 470	N = 798
Age (mean (SD))	45.30 (13.03)	44.43 (12.75)
Education		
No matriculation examination (%)	312 (66.4)	439 (55.0)
Matriculation examination (%)	158 (33.6)	359 (45.0)
Household pattern		
With spouse	173 (36.8)	342 (42.9)
Without spouse	297 (63.2)	456 (57.1)
Current Psychotrophic medications		
No (%)	27 (5.7)	36 (4.5)
Yes (%)	443 (94.3)	760 (95.2)
Missing (%)	0 (0.0)	2 (0.3)
Hazardous drinking$^{\Psi}$		
No (%)	289 (61.5)	589 (73.8)
Yes (%)	181 (38.5)	209 (26.2)
Lifetime alcohol-related disorder		
No (%)	290 (61.7)	602 (75.4)
Yes (%)	180 (38.3)	196 (24.6)

SD= Standard deviation

$^{\Psi}$AUDIT-C cutoff scores for hazardous drinking were ≥6 for males and ≥5 for females

We evaluated the association between cognition and alcohol use by using four different cognition variables: median and standard deviation of RT, PAL FTMS and PAL TEA. Alcohol use was measured by different variables; dichotomous hazard drinking variable derived from AUDIT-C score; and dichotomous variable indicating if the study subject had had alcohol-related ICD- diagnosis. We assessed crude models and adjusted models with age, household pattern and education. Association between RT-test and alcohol use was analyzed with log-linear regression, and eβ with 95% confidence intervals (CI) are reported. Association between PAL FTMS-test was analyzed with linear regression, and β with 95% CI are reported. All continuous variables used in models were normalized using z-score. Association between PAL-TEA and alcohol use was analyzed with logistic regression and odds ratios (OR) with 95% CI are reported.

All the analyses were conducted separately for males and females. Males and females showed differences in performing the selected cognitive tests [52,53,54]; additionally, males and females showed differences in alcohol use patterns [55,56,57,58].

3. Results

3.1. Background Factors and Alcohol Use Patterns in Persons with Bipolar Disorder

Of the participants about two-fifth were males and three-fifth were females. Mean age was 45 years for males and 44 years for females. One-third of the males and about half of the females had the highest basic educational of 12 years (matriculation). One-third of the males and two-third of the females were living with their spouses. Most of the participants were on psychotropic medication (Table 1).

Table 1. Background factors and alcohol use patterns in persons with bipolar disorder.

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Hazardous drinking and AUD were more common in males than in females. About two-fifth of the males and one-fourth of the females were screened positive for hazardous drinking. Also, two-fifth of the males and one-fourth of the females had a lifetime diagnosis of alcohol-related disorder (Table 1).

Lower age was associated with hazardous drinking, both in males and females (see Supplementary Materials, Table S1).

The median RT was 416 ms (SD = 45 ms); the PAL median FTMS was 11 and the median total errors adjusted was 17 (see Supplementary Materials, Table S2).

The association between background factors and AUD with RT *p*-values is reported in the Supplementary Materials, Table S3. The association between background factors and alcohol use patterns with PAL scores is reported in the Supplementary Materials, Tables S4.

The Cohen's d measure of effect size is shown in the Supplementary Materials, Table S6.

3.2. Association of Reaction Time and Visual Memory with Hazardous Drinking in Bipolar Disorder

After adjustment for age, education and household patterns, hazardous drinking was associated—in females—with a lower median RT (OR = 0.97; 95% CI, 0.95–0.99) and in males with a less variable reaction time (Table 2). The association between hazardous drinking and RT scores is reported in the Supplementary Materials, Table S6.

Table 2. Association of reaction time and visual memory with hazardous drinking$^{\Psi}$ in bipolar disorder.

	Five choice reaction time*							
	Median				**SD**			
	Crude		**Adjusted[a]**		**Crude**		**Adjusted[a]**	
	e^{β} (95% CI)	**p-value**	**e^{β} (95% CI)**	**p-value**	**e^{β} (95% CI)**	**p-value**	**e^{β} (95% CI)**	**p-value**
Male								
Hazardous drinking	**0.76 (0.63, 0.92)**	**0.005**	0.83 (0.69, 1.00)	0.052	**0.80 (0.66-0.98)**	**0.027**	0.89 (0.74-1.07)	0.225
Female								
Hazardous drinking	**0.77 (0.67, 0.89)**	**<.001**	**0.82 (0.71, 0.95)**	**0.007**	**0.76 (0.65, 0.89)**	**<.001**	**0.84 (0.73, 0.97)**	**0.017**
	Good performance in PAL							
	FTMS**				**TEA*****			
	Crude		**Adjusted[a]**		**Crude**		**Adjusted[a]**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Male								
Hazardous drinking	0.06 (-0.16, 0.27)	0.595	-0.06 (-0.25, 0.13)	0.520	0.96 (0.61, 1.52)	0.875	0.71 (0.42, 1.19)	0.202
Female								
Hazardous drinking	0.12 (-0.04, 0.28)	0.147	0.02 (-0.13, 0.17)	0.830	1.16 (0.80, 1.65)	0.434	1.00 (0.68, 1.46)	0.989

RT= Reaction time PAL= Paired association learning SD= Standard deviation CI= Confidence interval

$^{\Psi}$AUDIT-C cutoff scores for hazardous drinking were ≥6 for males and ≥5 for females

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[a] Adjusted with age, household pattern and education

* Analyzed with log-linear regression

** Analyzed with linear regression

*** Analyzed with logistic regression

3.3. Association of Reaction Time and Visual Memory with Alcohol Related Disorder in Bipolar Disorder

There was no significant difference in reaction times between male and female schizophrenia and schizoaffective disorder patients with or without a lifetime history of alcohol use disorder (Table 3).

Table 3. Association of reaction time and visual memory with alcohol related disorder in bipolar disorder.

	Five choice reaction time				**Five choice reaction time**			
	Median				**SD**			
	Crude		**Adjusted[a]**		**Crude**		**Adjusted[a]**	
	***e*$^{\beta}$ (95% CI)**	**p-value**	***e*$^{\beta}$ (95% CI)**	**p-value**	***e*$^{\beta}$ (95% CI)**	**p-value**	***e*$^{\beta}$ (95% CI)**	**p-value**
Male								
Alcohol related disorder	1.18 (0.97, 1.43)	0.100	1.01 (0.84, 1.23)	0.888	1.13 (0.92, 1.38)	0.236	0.92 (0.76, 1.12)	0.409
Female								
Alcohol related disorder	1.05 (0.90, 1.23)	0.518	1.03 (0.88, 1.19)	0.732	1.03 (0.88, 1.20)	0.728	1.00 (0.87, 1.16)	0.958
	Good performance in PAL							
	FTMS**				**TEA*****			
	Crude		**Adjusted[a]**		**Crude**		**Adjusted[a]**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Male								
Alcohol related disorder	**-0.27 (-0.49, -0.05)**	**0.015**	-0.05 (-0.25,0.15)	0.615	**0.60 (0.36, 0.97)**	**0.040**	0.87 (0.50, 1.51)	0.623
Female								
Alcohol related disorder	-0.11 (-0.31,0.02)	0.091	-0.09 (-0.24, 0.07)	0.262	**0.51 (0.33, 0.76)**	**0.001**	**0.54 (0.35, 0.83)**	**0.006**

RT = Reaction time

PAL = Paired association learning

SD = Standard deviation

CI = Confidence interval

[a] Adjusted with age, household pattern and education

* Analyzed with log-linear regression

** Analyzed with linear regression

*** Analyzed with logistic regression

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Females with AUD performed more poorly in the PAL test than females without AUD (OR = 0.54; 95% CI, 0.35, 0.83) (Table 3).

4. Discussion

4.1. Main Findings

Our findings did not support our assumption that problematic drinking was associated with impaired cognitive function in persons with bipolar disorder. On the contrary, some positive associations were found between hazardous drinking and reaction time scores in and females. As our study is the first of its kind, it is difficult to compare it to literature. However, our findings were in line with those in normal population studies [59,60].

Another finding in our study, association of AUD with poor visual memory in females but not in males, was not fully aligned with findings from most of the previous studies [61,62].

4.2. Comparison with Other Studies

As per our knowledge, there is no other studies investigating association between cognitive testing in terms of reaction time and visual memory, and different alcohol use patterns, namely hazardous drinking and alcohol related disorder, in persons with bipolar disorder hence it is difficult to compare our findings with other studies. Most of the studies investigating cognitive impact of alcohol in persons with bipolar disorder with comorbid AUD revealed correlation between alcohol use and cognitive impairment.

A recent study showed that verbal learning and memory, rather than selective attention and executive function, were impaired among BD patients with and without AUD [21]. Impairment of verbal learning and memory was also found in previous clinical studies of participants with comorbid BD and SUDs [22,26,63]. AUD patients without BD have also shown impaired verbal learning and memory [64].

BD patients with AUD show higher delay discounting [23] and significant memory deficits more specifically the recognition of previously presented information [24].

BD patients with a history of alcohol dependence showed decreased executive functioning [26]. BD patients with comorbid alcohol dependence also showed more severe impairment in executive functioning [25] and less recovery from cognitive deficits than only BD patients [63]. However, one recent research showed that BD patients with comorbid alcohol dependence had initial delay but subsequent recovery in executive domain [65].

One recent study revealed that patients with comorbid alcohol dependence and affective disorder manifested significant impairments in executive control, working memory, attention and cognitive flexibility compared to healthy individuals, and patients with only alcohol dependence or affective disorder [27].

BD patients with AUD exhibit less recovery from cognitive deficits than only BD patients [63]. However, one recent research showed that BD patients with comorbid AUD had initial delay but subsequent recovery in executive domain [65].

Marshall et al. (2012) found significantly worse performance on tasks of visual memory and reasoning in BD patients with comorbid AUD [66]. Chang et al. (2012) found widespread cognitive deficits, especially in terms attention/concentration and working memory, in BD patients with comorbid AUD [67]. Levy et al. (2012) found that BD patients with comorbid AUD had more deficits in verbal memory, visual memory, executive functioning, and a poorer neurocognitive recovery [63]. Shan et al. (2011) found more impaired visual memory, verbal memory, attention, psychomotor speed, working memory, and executive functioning in type-II BD patients with comorbid AUD [68]. Bonnín CM et al. (2009) found more deficits in verbal memory and executive functions in euthymic BD patients with and without past history of AUD, compared to healthy controls [69]. Levy et al. (2008) found an association of more severe mnemonic and executive dysfunction in BD patients with comorbid AUD [22]. van Gorp et al. (1998) found verbal memory deficits in

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BD patients with or without comorbid AUD, and, an additional executive deficit in comorbid group [26].

Based on a post-hoc analysis, one study suggested lifetime comorbid AUD not to be associated with cognition in BD patients [28]. Another study found no association between cognitive dysfunction and mood disorder in AUD patients [70]. A third study suggested association of creativity with comorbid alcohol dependence in BD patients [71].

General population cross-sectional studies investigating effects of alcohol on cognitive function revealed that moderate to heavy drinking was associated with cognitive decline [72,73,74,75] and light to moderate drinking was associated with either no effects on cognition [59,76] or cognitive enhancement [60,75,77,78,79]. Light, moderate, and heavy drinking can be defined operationally as 1.2, 2.2, 3.5 drinks/day respectively [80]. However, these definitions vary considerably worldwide.

Most cohort studies in the general population addressing the same issue revealed a positive correlation between light / light to moderate alcohol use and cognitive function [32,33,81,82,83] whereas other cohort study found no association between light to moderate alcohol consumption and better or worse cognitive functions [84,85,86]. One study reported a positive association between moderate to heavy drinking and cognitive function [87]. In contrast, another cohort study revealed negative association between heavy alcohol use and cognitive function in normal population [88]. One cohort study found dose-response positive association of alcohol use and cognitive function compared to abstainers and former drinkers [89]. Another cohort study revealed significant cognitive impairment in low functioning non-drinkers and light to moderate drinkers and high functioning non-drinkers [90].

A recent study with similar settings among schizophrenia patients found positive association between hazardous drinking and lower median RT in females and less variable RT in males diagnosed with schizophrenia and schizoaffective disorders. The same study also found a positive association between AUD and was poorer PAL test performance in females diagnosed with schizophrenia [91].

General population studies on adolescent binge drinking yielded mixed results. Most cross-sectional studies suggested a negative association between adolescent binge drinking and cognitive functioning [92,93]. Some prospective studies suggested that binge drinking preceded cognitive impairment in young adults [94,95,0′96,97], while other prospective studies suggested that cognitive impairment preceded binge drinking in young adults [98,99,100]. A recent prospective study using a combination of observational and genetic approaches, found no evidence of binge drinking in between the ages of 16 and 23 and cognitive deficits at age 24 [101]. Prospective study in population study also found no evidence of heavy drinking in adolescent and cognitive impairment in later life [102].

A brief review of 29 studies (2003-2013) revealed that acute alcohol mostly impaired executive function in normal population [103]. In contrast, A systematic review of 143 studies (1977-2011) revealed that light to moderate alcohol use did not impair cognition in young male and female individuals and reduced the risk of all forms of dementia and cognitive decline in older individuals [104]. Another systematic review of 28 reviews (2000-2017) revealed that light to moderate alcohol use in middle to late adulthood was associated with a decreased risk of cognitive impairment and dementia [31]. Meta-analysis of 27 cohort studies (2007-2018) revealed that moderate alcohol uses improved cognition insignificantly among male and slightly among female compared to current non-drinkers [30]. Moderate alcohol has been found to be associated with reduced amyloid-beta deposition in human brain [105].

Low data quality of self-reported alcohol use is associated with illness severity in BD patients [106,107] hence more severe BD patients might misreport or under-report about

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their alcohol consumption. 'Selection bias' can lead to compare healthy drinkers with unhealthy nondrinkers, 'sick quitter' hypothesis [108].

Study findings suggesting association between alcohol consumption and better performance in cognitive testing could be attributed by unmeasured or residual confounding factors [109,110] like: smoking [111], drink type [112], drink pattern [113], personality [111,114], intelligence [85,115,116], educational attainment [117,118], potential abstainer errors [119,120,121,122], reverse causality bias [123], recall error [124], within person temporal variation [125,126]. Study findings suggesting negative association between alcohol and cognition could be attributed by poor motivation [127,128,129].

4.3. Strengths

We used a large dataset comprising of persons with bipolar disorder to investigate cognitive impact of different alcohol use patterns. We studied multiple alcohol use patterns in the same study population and used age and education as potential confounding variables.

We exclude people of the of 70 years and above to minimize reverse causality bias. However, we performed analyses keeping those over 70 years of age and found almost no differences. Similarly, we also analyzed our data keeping both age and age of onset as confounders but got almost same results.

We have included all persons with bipolar disorder living independently and excluded those whose living circumstances (living in supported housing, hospitals, or unknown residence) might affect their alcohol use. We have also confounded household patterns (those living with spouses versus those without). However, current housing situation is not that relevant while using alcohol-related disorder information during lifetime.

We performed sensitivity analyses including also those aged 70 years and above and, those not living with their spouses. We also performed Cohen's d measure of effect size for our study findings.

4.4. Limitations

Our study was cross-sectional, not longitudinal. We used only two tests from CANTAB. We did not adopt more comprehensive approach to measure working memory performance.

We did not use information about the onset of alcohol use, any recent changes in drinking habits or any previous history of abstinence. We also did not differentiate previous alcohol users from never-alcohol users and did not exclude individuals who reduced drinking due to illness/doctor's advice which might attribute the results through reverse causality bias [110,130]. We did not correct self-report bias [131,132] and misreports and longitudinal changes (MLC) which could affect the study results [133,134].We did not confound household income, which, as indicative of socioeconomic status, could increase alcohol related mortality and morbidity despite lower reportedly alcohol consumption (alcohol harm paradox) [135]. We confounded education, which is another strong indicator of socioeconomic status, in a dichotomous fashion, not in a stratified one.

We did not confound antipsychotic medication because almost all of the persons with bipolar disorder were on antipsychotic medication. We did not confound benzodiazepines use as it could impair cognitive performance because of its acute sedative effect. We also did not confound smoking or other substance use during lifetime, and we did not confound other F1-diagnoses. We did not incorporate mendelian randomization to minimize possible reverse causality bias. We did not use continuous variables for PAL test.

We categorized education as completed general secondary education with matriculation examination versus lower. It would be more informative if we could categorize education into three groups. However, it might be difficult for a general reader to understand the diverse categories in the Finnish education system reflecting changes over the past seventy years plus additional categories reflecting the small proportion of immi-

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grants who might have lower general education than that provided in the Finnish education system. We used the general education variable because the youngest participants could still be students.

We did not correct for multiple comparisons (Bonferroni correction). Since most of the confidence intervals did not come close to 1.00 it was obvious that most results would remain significant also when these corrections were applied. It might be worth pre-emptying non-significant comparisons.

4.5. What Is Already Known on This Subject?

- Alcohol use disorder was associated with cognitive decline in persons with bipolar disorder.
- Mild alcohol use was not associated with impaired cognition in the normal population.

4.6. What Does This Study Add?

- Hazardous drinking was not associated with cognitive decline in persons with bipolar disorder.

5. Conclusions

Hazardous drinking was not associated with a cognitive decline in persons with bipolar disorder. Rather, some positive associations were found between hazardous drinking and cognition, which are unique to these psychiatric disorders but in line with the findings from general population studies.

Selection bias or severity of illness (other than duration) could have some undetected attributions on our results. Participants with more severe illness might drink less compared to those with risky drinking even though we have excluded those not living independently. Future studies should use larger observational samples, meta-analyses of related cognitive measures in GWAS, other proxy for severity of illness to increase power. Replication of this study by incorporating mendelian randomization with observational analysis might reduce possible bias from residual confounding and reverse causation [136]. Hence, our study might serve as a reference for future research.

Supplementary Materials: The following supplementary tables are available online at www.mdpi.com/xxx/s1, Table S1: Association between background factors and hazardous drinking$^{\psi}$ in male and female persons with bipolar disorder, Table S2: Distribution of RT median, RT SD, PAL first trial memory scores (FTMS), and PAL total error adjusted in the study population, Table S3: RT median and RT SD p-values for background factors and alcohol related disorder in male and female persons with bipolar disorder, Table S4: PAL total errors adjusted sores for background factors and alcohol use patterns in male and female persons with bipolar disorder, Table S5: RT median and RT SD for hazardous drinking in male and female persons with bipolar disorder, Table S6: Cohen's d measure of effect.

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Institutional Review Board Statement: Prior to seeking study permissions, a statement pertaining to the ethical considerations of the study was requested from the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa, which is responsible for nationwide ethical statements. After receiving a favorable statement, permission to conduct the study was individually

sought and obtained from all participating healthcare organizations. The Finnish Institute for Health and Welfare gave permission to access individual healthcare records in the registry data for which it is responsible (THL/1007/5.05.00/2017). The research was also conducted according to the guidelines of the following research ethics documents: The Responsible Conduct of Research and Procedures for Handling Allegations of Misconduct in Finland (http://www.tenk.fi/sites/tenk.fi/files/HTK_ohje_2012.pdf) and The European Code of Conduct for Research Integrity, revised edition 2017 (http://www.tenk.fi/sites/tenk.fi/files/ALLEA-European-Code-of-Conduct-for-Research-Integrity-2017.pdf).

Informed Consent Statement: Written informed consent was obtained from all participants. They were informed that participating in or abstaining from the study would not affect their treatment. The study subjects were also informed that they could withdraw their consent at any time, at which point any samples or data stored from them would be destroyed. Data already used in analyses, if not possible to remove from the completed analyses, would never be used in the future, unless part of a large summary dataset. If the subject was under involuntary psychiatric care or the study nurse had any doubts regarding the subject's ability to give informed consent, permission was sought to contact the attending physician of the subject to obtain a statement regarding whether the subject was able to give informed consent to participate in the study. Patients under guardianship were excluded from the study, as well as all minors. From all the study participants, written informed consent for the publication of the study results without disclosing their identities was sought.

Data Availability Statement: The raw data and materials used for this study are available upon request.

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References

1. Bosia, M.; Buonocore, M.; Bechi, M.; Santarelli, L.; Spangaro, M.; Cocchi, F.; Guglielmino, C.; Bianchi, L.; Bringheli, S.; Bosinelli, F.; et al. Improving Cognition to Increase Treatment Efficacy in Schizophrenia: Effects of Metabolic Syndrome on Cognitive Remediation's Outcome. Front. Psychiatry 2018, 9, 647. [Google Scholar] [CrossRef]
2. Szmulewicz, A.G., Samamé, C., Martino, D.J., & Strejilevich, S.A. (2015). An updated review on the neuropsychological profile of subjects with bipolar disorder. Archives of Clinical Psychiatry, 42, 139–146. https://doi.org/10.1590/0101-60830000000064
3. Balanzá-Martínez V., Dias V. V. (2013). Neurocognitive dysfunction in bipolar disorder, in Clinical Management of Bipolar Disorder, ed Mitchell P. B. (Future Medicine), 78–86. [Google Scholar]
4. Santos, J. L., Aparicio, A., Bagney, A., Sánchez-Morla, E. M., Rodríguez-Jiménez, R., Mateo, J., & Jiménez-Arriero, M. Á. (2014). A five-year follow-up study of neurocognitive functioning in bipolar disorder. Bipolar disorders, 16(7), 722–731. https://doi.org/10.1111/bdi.12215
5. Bourne, C., Aydemir, Ö., Balanzá-Martínez, V., Bora, E., Brissos, S., Cavanagh, J. T., Clark, L., Cubukcuoglu, Z., Dias, V. V., Dittmann, S., Ferrier, I. N., Fleck, D. E., Frangou, S., Gallagher, P., Jones, L., Kieseppä, T., Martínez-Aran, A., Melle, I., Moore, P. B., Mur, M., … Goodwin, G. M. (2013). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta psychiatrica Scandinavica, 128(3), 149–162. https://doi.org/10.1111/acps.12133
6. Kurtz, M. M., & Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology, 23(5), 551–562. https://doi.org/10.1037/a0016277
7. Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. Journal of affective disorders, 93(1-3), 105–115. https://doi.org/10.1016/j.jad.2006.02.016
8. McElroy, S. L., Altshuler, L. L., Suppes, T., Keck, P. E., Jr, Frye, M. A., Denicoff, K. D., Nolen, W. A., Kupka, R. W., Leverich, G. S., Rochussen, J. R., Rush, A. J., & Post, R. M. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. The American journal of psychiatry, 158(3), 420–426. https://doi.org/10.1176/appi.ajp.158.3.420
9. Solé, B., Bonnin, C. M., Torrent, C., Balanzá-Martínez, V., Tabarés-Seisdedos,R., Popovic, D., et al. (2012). Neurocognitive impairment and psychosocial functioning in bipolar II disorder. Acta Psychiatr. Scand. 125, 309–317. doi: 10.1111/j.1600-0447.2011.01759.x
10. Bora, E., Yücel, M., Pantelis, C., & Berk, M. (2011). Meta-analytic review of neurocognition in bipolar II disorder. Acta psychiatrica Scandinavica, 123(3), 165–174. https://doi.org/10.1111/j.1600-0447.2010.01638.x
11. MacCabe, J. H., Lambe, M. P., Cnattingius, S., Sham, P. C., David, A. S., Reichenberg, A., Murray, R. M., & Hultman, C. M. (2010). Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. The British journal of psychiatry : the journal of mental science, 196(2), 109–115. https://doi.org/10.1192/bjp.bp.108.060368

12. Tiihonen, J., Haukka, J., Henriksson, M., Cannon, M., Kieseppä, T., Laaksonen, I., Sinivuo, J., & Lönnqvist, J. (2005). Premorbid intellectual functioning in bipolar disorder and schizophrenia: results from a cohort study of male conscripts. The American journal of psychiatry, 162(10), 1904–1910. https://doi.org/10.1176/appi.ajp.162.10.1904
13. Kendler, K. S., Ohlsson, H., Mezuk, B., Sundquist, J. O., & Sundquist, K. (2016). Observed Cognitive Performance and Deviation From Familial Cognitive Aptitude at Age 16 Years and Ages 18 to 20 Years and Risk for Schizophrenia and Bipolar Illness in a Swedish National Sample. JAMA psychiatry, 73(5), 465–471. https://doi.org/10.1001/jamapsychiatry.2016.0053
14. Nery, F. G., Matsuo, K., Nicoletti, M. A., Monkul, E. S., Zunta-Soares, G. B., Hatch, J. P., Lafer, B., & Soares, J. C. (2011). Association between prior alcohol use disorders and decreased prefrontal gray matter volumes in bipolar I disorder patients. Neuroscience letters, 503(2), 136–140. https://doi.org/10.1016/j.neulet.2011.08.026
15. Cerullo, M. A., & Strakowski, S. M. (2007). The prevalence and significance of substance use disorders in bipolar type I and II disorder. Substance abuse treatment, prevention, and policy, 2, 29. https://doi.org/10.1186/1747-597X-2-29
16. Hunt, G. E., Malhi, G. S., Cleary, M., Lai, H. M., & Sitharthan, T. (2016). Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: Systematic review and meta-analysis. Journal of affective disorders, 206, 331–349. https://doi.org/10.1016/j.jad.2016.07.011
17. Berry, K., Barrowclough, C., Fitsimmons, M., Hartwell, R., Hilton, C., Riste, L., Wilson, I., & Jones, S. (2020). Overcoming challenges in delivering integrated motivational interviewing and cognitive behavioural therapy for bipolar disorder with co-morbid alcohol use: therapist perspectives. Behavioural and cognitive psychotherapy, 48(5), 615–620. https://doi.org/10.1017/S1352465820000272
18. Goldstein, B. I., Velyvis, V. P., & Parikh, S. V. (2006). The association between moderate alcohol use and illness severity in bipolar disorder: a preliminary report. The Journal of clinical psychiatry, 67(1), 102–106. https://doi.org/10.4088/jcp.v67n0114
19. Moriarity, D. P., Bart, C. P., Stumper, A., Jones, P., & Alloy, L. B. (2021). Mood symptoms and impairment due to substance use: A network perspective on comorbidity. Journal of affective disorders, 278, 423–432. https://doi.org/10.1016/j.jad.2020.09.086
20. Messer, T., Lammers, G., Müller-Siecheneder, F., Schmidt, R. F., & Latifi, S. (2017). Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry research, 253, 338–350. https://doi.org/10.1016/j.psychres.2017.02.067
21. Li, C., Palka, J. M., & Brown, E. S. (2020). Cognitive impairment in individuals with bipolar disorder with and without comorbid alcohol and/or cocaine use disorders. Journal of affective disorders, 272, 355–362. https://doi.org/10.1016/j.jad.2020.03.179
22. Levy, B., Monzani, B. A., Stephansky, M. R., & Weiss, R. D. (2008). Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care. Psychiatry research, 161(1), 28–35. https://doi.org/10.1016/j.psychres.2007.09.009
23. Mellick, W., Tolliver, B. K., Brenner, H., & Prisciandaro, J. J. (2019). Delay discounting and reward sensitivity in a 2 × 2 study of bipolar disorder and alcohol dependence. Addiction (Abingdon, England), 114(8), 1369–1378. https://doi.org/10.1111/add.14625
24. Cardoso, T. A., Bauer, I. E., Jansen, K., Suchting, R., Zunta-Soares, G., Quevedo, J., Glahn, D. C., & Soares, J. C. (2016). Effect of alcohol and illicit substance use on verbal memory among individuals with bipolar disorder. Psychiatry research, 243, 225–231. https://doi.org/10.1016/j.psychres.2016.06.044
25. Salazar-Guerra, Y.I., Broche-Pérez, Y., Muñoz, A.C., Caballero-Moreno, A., Hernández, J.P., & Mendoza-Quiñones, R. (2020). Neurocognitive Impairment and Personality Traits in Alcohol Addiction: Effect of Dual Pathology. International Journal of Mental Health and Addiction, 18, 432-442.
26. van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W. Cognitive Impairment in Euthymic Bipolar Patients With and Without Prior Alcohol Dependence: A Preliminary Study. Arch Gen Psychiatry. 1998;55(1):41–46. doi:10.1001/archpsyc.55.1.41
27. Galkin S.A., Peshkovskaya A.G., Kisel N.I., Vasilieva S.N., Ivanova S.A., Bokhan N.A. Cognitive Changes in Comorbidity Alcohol Dependence and Affective Disorders. Psikhiatriya. 2020;18(3):42-48. (In Russ.) https://doi.org/10.30629/2618-6667-2020-18-3-42-48
28. van der Werf-Eldering, M. J., Burger, H., Holthausen, E. A., Aleman, A., & Nolen, W. A. (2010). Cognitive functioning in patients with bipolar disorder: association with depressive symptoms and alcohol use. PloS one, 5(9), e13032. https://doi.org/10.1371/journal.pone.0013032
29. Balanzá-Martínez, V., Crespo-Facorro, B., González-Pinto, A., & Vieta, E. (2015). Bipolar disorder comorbid with alcohol use disorder: focus on neurocognitive correlates. Frontiers in physiology, 6, 108. https://doi.org/10.3389/fphys.2015.00108
30. Brennan SE, McDonald S, Page MJ, Reid J, Ward S, Forbes AB, McKenzie JE. Long-term effects of alcohol consumption on cognitive function: a systematic review and dose-response analysis of evidence published between 2007 and 2018. Syst Rev. 2020 Feb 13;9(1):33. doi: 10.1186/s13643-019-1220-4.
31. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. Alzheimers Res Ther. 2019; 11:1. [PMC free article] [PubMed] [Google Scholar]
32. Koch, M.; Fitzpatrick, A.L.; Rapp, S.R.; Nahin, R.L.; Williamson, J.D.; Lopez, O.L.; DeKosky, S.T.; Kuller, L.H.; Mackey, R.H.; Mukamal, K.J.; et al. Alcohol Consumption and Risk of Dementia and Cognitive Decline Among Older Adults with or Without Mild Cognitive Impairment. JAMA Netw. Open. 2019, 2, e1910319. [CrossRef]

33. Piumatti, G., Moore, S., Berridge, D., Sarkar, C. & Gallacher, J. The relationship between alcohol use and long-term cognitive decline in middle and late life: a longitudinal analysis using UK Biobank. J Public Health (Oxf) (2018). [PMC free article] [PubMed]
34. Esser MB, Hedden SL, Kanny D, Brewer RD, Gfroerer JC, Naimi TS. Prevalence of alcohol dependence among US adult drinkers, 2009–2011. Prev Chronic Dis. 2014; 11:140329. doi: http://dx.doi.org/10.5888/pcd11.140329.
35. Ng Fat L, Bell S, Britton A. A life-time of hazardous drinking and harm to health among older adults: findings from the Whitehall II prospective cohort study. Addiction. 2020 Mar 31. doi: 10.1111/add.15013. [Epub ahead of print]
36. Fujii H., Nishimoto N., Yamaguchi S., Kurai O., Miyano M., Ueda W., Oba H., Aoki T., Kawada N., Okawa K. The Alcohol Use Disorders Identification Test for Consumption (AUDIT-C) is more useful than pre-existing laboratory tests for predicting hazardous drinking: A cross-sectional study. BMC Public Health. 2016; 16:379. doi: 10.1186/s12889-016-3053-6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. Rehm, J.; Anderson, P.; Manthey, J.; Shield, K.D.; Struzzo, P.; Wojnar, M.; Gual, A. Alcohol Use Disorders in Primary Health Care: What Do We Know and Where Do We Go? Alcohol Alcohol. 2016, 51, 422–427. [Google Scholar] [CrossRef]
38. Babor TF, Longabaugh R, Zweben A, Fuller R K, Stout R L, Anton R F, Randall C L. Issues in the definition and measurement of drinking outcomes in alcoholism treatment research. Journal of Studies on Alcohol, Supplement 1994: s12, 101-111
39. Frank D, DeBenedetti AF, Volk RJ, Williams EC, Kivlahan DR, Bradley KA (2008) Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three race/ethnic groups. J Gen Intern Med 23(6):781-787. doi:10.1007/s11606-008-0594-0
40. Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 National and State Costs of Excessive Alcohol Consumption. American journal of preventive medicine, 49(5), e73–e79. https://doi.org/10.1016/j.amepre.2015.05.031
41. Public Health England. Alcohol use screening tests (2017) Available at: https://www.gov.uk/government/publications/alcohol-use-screening-tests
42. Lintonen T, Niemelä S, Mäkelä P. Alkoholinkäytön hälytysrajan ylittäviä käyttäjiä on Suomessa vähintään viisi prosenttia väestöstä. LÄÄKETIETEELLINEN AIKAKAUSKIRJA DUODECIM. 2019;135(16):1459-66. https://www.duodecimlehti.fi/lehti/2019/16/duo15071
43. Taivalantti M, Barnett JH, Halt AH, Koskela J, Auvinen J, Timonen M, Järvelin MR, Veijola J. Depressive symptoms as predictors of visual memory deficits in middle-age. J Affect Disord. 2020 Mar 1; 264:29-34. doi: 10.1016/j.jad.2019.11.125. Epub 2019 Nov 30.
44. Van Hooren, S. A. H., Valentijn, A. M., Bosma, H., Ponds, R. W. H. M., Van Boxtel, M. P. J., & Jolles, J. (2007). Cognitive functioning in healthy older adults aged 64-81: A cohort study into the effects of age, sex, and education. Aging, Neuropsychology, and Cognition, 14(1), 40–54. https://doi.org/10.1080/138255890969483 [Taylor & Francis Online], [Web of Science ®], [Google Scholar]
45. Biddle, K.D.; Jacobs, H.I.L.; Uquillas, F.D.; Zide, B.S.; Kirn, D.R.; Properzi, M.R.; Rentz, D.M.; Johnson, K.A.; Sperling, R.A.; Donovan, N.J. Associations of Widowhood and β-Amyloid With Cognitive Decline in Cognitively Unimpaired Older Adults. JAMA Netw. Open 2020, 3, e200121. [Google Scholar] [CrossRef]
46. Andersson C, Marklund K, Walles H, Hagman G, Miley-Akerstedt A. Lifestyle Factors and Subjective Cognitive Impairment in Patients Seeking Help at a Memory Disorder Clinic: The Role of Negative Life Events. Dement Geriatr Cogn Disord. 2020 Jan 24:1-11. doi: 10.1159/000505573. [Epub ahead of print]
47. Strandberg AY, Trygg T, Pitkälä KH, Strandberg TE. Alcohol consumption in midlife and old age and risk of frailty: Alcohol paradox in a 30-year follow-up study. Age Ageing. 2018;47(2):248–254. doi:10.1093/ageing/afx165
48. Cardoso, T., Bauer, I. E., Meyer, T. D., Kapczinski, F., & Soares, J. C. (2015). Neuroprogression and Cognitive Functioning in Bipolar Disorder: A Systematic Review. Current psychiatry reports, 17(9), 75. https://doi.org/10.1007/s11920-015-0605-x
49. Schouws, S. N., Comijs, H. C., Stek, M. L., Dekker, J., Oostervink, F., Naarding, P., van der Velde, I., & Beekman, A. T. (2009). Cognitive impairment in early and late bipolar disorder. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 17(6), 508–515. https://doi.org/10.1097/JGP.0b013e31819e2d50
50. Krahn D, Freese J, Hauser R et al. Alcohol use and cognition at mid-life: the importance of adjusting for baseline cognitive ability and educational attainment. Alcohol Clin Exp Res 2003;27(7): 1162–6.
51. Donovan, N.J.; Okereke, O.I.; Vannini, P.; Amariglio, R.E.; Rentz, D.M.; Marshall, G.A.; Johnson, K.A.; Sperling, R.A. Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults. JAMA Psychiatry 2016, 73, 1230–1237. [Google Scholar] [CrossRef]
52. Lee, J. K., & Son, Y. J. (2018). Gender Differences in the Impact of Cognitive Function on Health Literacy among Older Adults with Heart Failure. International journal of environmental research and public health, 15(12), 2711. https://doi.org/10.3390/ijerph15122711
53. Voyer, D., Voyer, S.D. & Saint-Aubin, J. Sex differences in visual-spatial working memory: A meta-analysis. Psychon Bull Rev 24, 307–334 (2017). https://doi.org/10.3758/s13423-016-1085-7
54. Herlitz A., Dekhtyar S., Asperholm M., Weber D. (2016) Gender Differences in Memory and Cognition. In: Pachana N. (eds) Encyclopedia of Geropsychology. Springer, Singapore
55. Berg, N. J., Kiviruusu, O. H., Lintonen, T. P., & Huurre, T. M. (2019). Longitudinal prospective associations between psychological symptoms and heavy episodic drinking from adolescence to midlife. Scandinavian Journal of Public Health, 47(4), 420–427. https://doi.org/10.1177/1403494818769174

56. Dir, A. L., Bell, R. L., Adams, Z. W., & Hulvershorn, L. A. (2017). Gender Differences in Risk Factors for Adolescent Binge Drinking and Implications for Intervention and Prevention. Frontiers in psychiatry, 8, 289. https://doi.org/10.3389/fpsyt.2017.00289
57. Hughes TL, Wilsnack SC, Kantor LW. The Influence of Gender and Sexual Orientation on Alcohol Use and Alcohol-Related Problems: Toward a Global Perspective. Alcohol Research: Current Reviews. 2016 ;38(1):121-132.
58. Kanny D, Naimi TS, Liu Y, Lu H, Brewer RD. Annual Total Binge Drinks Consumed by U.S. Adults, 2015external icon. Am J Prev Med 2018; 54:486–496.
59. Moussa, M. N., Simpson, S. L., Mayhugh, R. E., Grata, M. E., Burdette, J. H., Porrino, L. J., & Laurienti, P. J. (2015). Long-term moderate alcohol consumption does not exacerbate age-related cognitive decline in healthy, community-dwelling older adults. Frontiers in aging neuroscience, 6, 341. https://doi.org/10.3389/fnagi.2014.00341
60. Reas E. T., Laughlin G. A., Kritz-Silverstein D., Berrett-Connor E., McEvoy L. K. (2016). Moderate, regular alcohol consumption is associated with higher cognitive function in older, community-dwlling adults. J. Prev. Alzheimer's Dis. 3 105–113. [PMC free article] [PubMed] [Google Scholar]
61. Menkes, M. W., Armstrong, K., Blackford, J. U., Heckers, S., & Woodward, N. D. (2019). Neuropsychological functioning in early and chronic stages of schizophrenia and psychotic bipolar disorder. Schizophrenia research, 206, 413–419. https://doi.org/10.1016/j.schres.2018.10.009
62. Bora E. (2018). Neurocognitive features in clinical subgroups of bipolar disorder: A meta-analysis. Journal of affective disorders, 229, 125–134. https://doi.org/10.1016/j.jad.2017.12.057
63. Levy, B., Manove, E., & Weiss, R. D. (2012). Recovery of cognitive functioning in patients with co-occurring bipolar disorder and alcohol dependence during early remission from an acute mood episode. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists, 24(2), 143–154. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349462/
64. 64. Bell, M. D., Vissicchio, N. A., & Weinstein, A. J. (2016). Visual and verbal learning deficits in Veterans with alcohol and substance use disorders. Drug and alcohol dependence, 159, 61–65. https://doi.org/10.1016/j.drugalcdep.2015.11.007
65. Torres, I. J., Qian, H., Basivireddy, J., Chakrabarty, T., Wong, H., Lam, R. W., & Yatham, L. N. (2020). Three-year longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. Acta psychiatrica Scandinavica, 141(2), 98–109. https://doi.org/10.1111/acps.13141
66. Marshall, D. F., Walker, S. J., Ryan, K. A., Kamali, M., Saunders, E. F., Weldon, A. L., Adams, K. M., McInnis, M. G., & Langenecker, S. A. (2012). Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder. Psychiatry research, 200(2-3), 252–257. https://doi.org/10.1016/j.psychres.2012.06.013
67. Chang, Y. H., Chen, S. L., Lee, S. Y., Hsu, Y. W., Wu, J. Y., Chen, S. H., et al. (2012). Neuropsychological functions in bipolar disorders I and II with and without comorbid alcohol dependence. Prog. Neuropsychopharmacol. Biol. Psychiatry 37, 211–216. doi: 10.1016/j.pnpbp.2012.01.015
68. Shan, C., Lee, S. Y., Chang, Y. H., Wu, J. Y., Chen, S. L., Chen, S. H., et al. (2011). Neuropsychological functions in Han Chinese patients in Taiwan with bipolar II disorder comorbid and not comorbid with alcohol abuse/alcohol dependence disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 131–136. doi: 10.1016/j.pnpbp.2010.10.004
69. Bonnín, C. M., Martínez-Arán, A., Torrent, C., Pacchiarotti, I., Rosa, A. R., Franco, C., Murru, A., Sanchez-Moreno, J., & Vieta, E. (2010). Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. Journal of affective disorders, 121(1-2), 156–160. https://doi.org/10.1016/j.jad.2009.05.014
70. Lee, R. S., Dore, G., Juckes, L., De Regt, T., Naismith, S. L., Lagopoulos, J., Tickell, A., Hickie, I. B., & Hermens, D. F. (2015). Cognitive dysfunction and functional disability in alcohol-dependent adults with or without a comorbid affective disorder. Cognitive neuropsychiatry, 20(3), 222–231. https://doi.org/10.1080/13546805.2015.1014031
71. Demir, A., Sahin, S.K., , Elboga, G., Altindag, A., Dogan, I. Comparison of bipolarity features between art students and other university students. Annals of Medical Research. 2019;26(10):2214-8. DOI: 10.5455/annalsmedres.2019.07.413.
72. Bartholow, B. D., Fleming, K. A., Wood, P. K., Cowan, N., Saults, J. S., Altamirano, L., Miyake, A., Martins, J., & Sher, K. J. (2018). Alcohol effects on response inhibition: Variability across tasks and individuals. Experimental and clinical psychopharmacology, 26(3), 251–267. https://doi.org/10.1037/pha0000190
73. Mayhugh, R. E., Moussa, M. N., Simpson, S. L., Lyday, R. G., Burdette, J. H., Porrino, L. J., & Laurienti, P. J. (2016). Moderate-Heavy Alcohol Consumption Lifestyle in Older Adults Is Associated with Altered Central Executive Network Community Structure during Cognitive Task. PloS one, 11(8), e0160214. https://doi.org/10.1371/journal.pone.0160214
74. Carrilho P. E. M., Dos Santos M. B. M., Piasecki L., Jorge A. C. (2013). Marchiafava-Bignami disease: a rare entity with a poor outcome. Rev. Bras. Ter. Intensiva 25 68–72. 10.1590/S0103-507X2013000100013 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
75. Kim J. W., Lee D. Y., Lee B. C., Jung M. H., Kim H., Choi Y. S., et al. (2012). Alcohol and cognition in the elderly: a review. Psychiatry Invest. 9 8–16. 10.4306/pi.2012.9.1.8 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
76. Sabia S, Elbaz A, Britton A, Bell S, Dugravot A, Shipley M, Kivimaki M, Singh-Manoux A. Alcohol consumption and cognitive decline in early old age. Neurology Jan 2014, 82 (4) 332-339; DOI: 10.1212/WNL.0000000000000063
77. Panza F., Frisardi V., Seripa D., Logroscino G., Santamato A., Imbimbo B. P., et al. (2012). Alcohol consumption in mild cognitive impairment and dementia: harmful or neuroprotective? Int. J. Geriatr. Psychiatry 27 1218–1238. 10.1002/gps.3772 [PubMed] [CrossRef] [Google Scholar]

78. Bond G. E., Burr R., McCurry S. M., Graves A. B., Larson E. B. (2001). Alcohol, aging, and cognitive performance in a cohort of Japanese Americans aged 65 and older: The Kame project. Int. Psychogeriatr. 13 207–223. 10.1017/s1041610201007591 [PubMed] [CrossRef] [Google Scholar]
79. Spencer R. L., Hutchison K. E. (1999). Alcohol, aging, and the stress response. Alcohol Res. Health? 23 272–283. [PMC free article] [PubMed] [Google Scholar]
80. Abel, E. L., Kruger, M. L., & Friedl, J. (1998). How do physicians define "light," "moderate," and "heavy" drinking?. Alcoholism, clinical and experimental research, 22(5), 979–984. https://doi.org/10.1111/j.1530-0277.1998.tb03692.x
81. Zhang R, Shen L, Miles T, et al. Association of Low to Moderate Alcohol Drinking with Cognitive Functions from Middle to Older Age Among US Adults. JAMA Netw Open. 2020;3(6): e207922. doi:10.1001/jamanetworkopen.2020.7922
82. Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Alcohol consumption and cognitive function in late life A longitudinal community study. Neurology Oct 2005, 65 (8) 1210-1217; DOI: 10.1212/01.wnl.0000180520.35181.24
83. Britton A, Singh-Manoux A, Marmot M. Alcohol consumption and cognitive function in the Whitehall II Study. Am J Epidemiol. 2004;160(3):240-247. doi:10.1093/aje/kwh206
84. Sun L, Xu H, Zhang J, Li W, Nie J, Qiu Q, Liu Y, Fang Y, Yang Z, Li X and Xiao S (2018) Alcohol Consumption and Subclinical Findings on Cognitive Function, Biochemical Indexes, and Cortical Anatomy in Cognitively Normal Aging Han Chinese Population. Front. Aging Neurosci. 10:182. doi: 10.3389/fnagi.2018.00182.
85. Topiwala A., Allan C. L., Valkanova V., Zsoldos E., Filippini N., Sexton C., et al. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. BMJ 357: j2353. 10.1136/bmj. j2353 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
86. Lobo E, Dufouil C, Marcos G et al. Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline? Am J Epidemiol 2010; 172:708–16.
87. Richard EL, Kritz-Silverstein D, Laughlin GA et al. Alcohol intake and cognitively healthy longevity in community-dwelling adults: the Rancho Bernardo Study. J Alzheimers Dis 2017; 59:803–14. JAMA Netw Open. 2019 Sep 4;2(9): e1910319. doi: 10.1001/jamanetworkopen.2019.10319.
88. Parker ES, Parker DA, Harford TC: Specifying the relationship between alcohol use and cognitive loss: The effects of frequency of con- sumption and psychological distress. J Stud Alcohol 52:366-373, 1991
89. Davis B. J. K., Vidal J. S., Garcia M., Aspelund T., Van Buchem M. A., Jonsdottir M. K., et al. (2014). The alcohol paradox: light-to-moderate alcohol consumption, cognitive function, and brain volume. J. Gerontol. A Biol. Sci. Med. Sci. 69 1528–1535. 10.1093/gerona/glu092.
90. Vasiliadis HM, Payette MC, Berbiche D, Grenier S, Hudon C. Cognitive decline and alcohol consumption adjusting for functional status over a 3-year period in French speaking community living older adults. J Public Health (Oxf). 2019 Jun 1;41(2): e177-e184. doi: 10.1093/pubmed/fdy126.
91. Mazumder, A.H.; Barnett, J.; Lindberg, N.; Torniainen-Holm, M.; Lähteenvuo, M.; Lahdensuo, K.; Kerkelä, M.; Hietala, J.; Isometsä, E.T.; Kampman, O.; Kieseppä, T.; Jukuri, T.; Häkkinen, K.; Cederlöf, E.; Haaki, W.; Kajanne, R.; Wegelius, A.; Männynsalo, T.; Niemi-Pynttäri, J.; Suokas, K.; Lönnqvist, J.; Niemelä, S.; Tiihonen, J.; Paunio, T.; Palotie, A.; Suvisaari, J.; Veijola, J. Reaction Time and Visual Memory in Connection with Alcohol Use in Schizophrenia and Schizoaffective Disorder. Brain Sci. 2021, 11, 688. https://doi.org/10.3390/brainsci11060688
92. Gullo MJ, Loxton NJ, Price T, Voisey J, Young RM, Connor JP. A laboratory model of impulsivity and alcohol use in late adolescence. Behav Res Ther. 2017;97:52–63.
93. Parada M, Corral M, Mota N, Crego A, Rodriguez Holguin S, Cadaveira F. Executive functioning and alcohol binge drinking in university students. Addict Behav. 2012;37(2):167–72.
94. Mahedy L, Field M, Gage S, Hammerton G, Heron J, Hickman M, et al. Alcohol use in adolescence and later working memory: Findings from a large population-based birth cohort. Alcohol Alcohol. 2018;53:251–8.
95. Peeters M, Monshouwer K, Janssen T, Wiers RW, Vollebergh WAM. Working memory and alcohol use in at-risk adolescents: a 2-year follow-up. Alcohol Clin Exp Res. 2014;38(4):1176–83.
96. Wetherill RR, Squeglia LM, Yang TT, Tapert SF. A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. Psychopharmacology (Berl). 2013;230(4):663–71.
97. Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. J Stud Alcohol Drugs. 2012;73(5):749–60.
98. Peeters M, Janssen T, Monshouwer K, Boendermaker W, Pronk T, Wiers R, et al. Weaknesses in executive functioning predict the initiating of adolescents' alcohol use. Dev Cogn Neurosci. 2015;16:139–46.
99. Squeglia LM, Jacobus J, Nguyen-Louie TT, Tapert SF. Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. Neuropsychology. 2014;28(5):782–90.
100. Fernie G, Peeters M, Gullo MJ, Christiansen P, Cole JC, Sumnall H, et al. Multiple behavioural impulsivity tasks predict prospective alcohol involvement in adolescents. Addiction. 2013;108(11):1916–23.
101. Mahedy L., Suddell S., Skirrow C., Fernandes G. S., Field M.,Heron J. et al. Alcohol use and cognitive functioning in youngadults: improving causal inference. Addiction 2021; 116:292–302.2.
102. Boelema SR, Harakeh Z, Van Zandvoort MJE, Reijneveld SA, Verhulst FC, Ormel J, et al. Adolescent heavy drinking does not affect maturation of basic executive functioning: Longitudinal findings from the TRAILS study. PLoS One. 2015;10(10):1–15.

103. Day, A. M., Kahler, C. W., Ahern, D. C., & Clark, U. S. (2015). Executive Functioning in Alcohol Use Studies: A Brief Review of Findings and Challenges in Assessment. Current drug abuse reviews, 8(1), 26–40. https://doi.org/10.2174/1874473708666150416110515
104. Neafsey EJ, Collins MA: Moderate alcohol consumption and cognitive risk. Neuropsy-chiatr Dis Treat 2011; 7: 465–484.
105. Kim JW, Byun MS, Yi D, et al. Association of moderate alcohol intake with in vivo amyloid-beta deposition in human brain: A cross-sectional study. PLoS Med. 2020;17(2): e1003022. Published 2020 Feb 25. doi: 10.1371/journal.pmed.1003022
106. Draisma, S., van Zaane, J., & Smit, J. H. (2015). Data quality indicators for daily life chart methodology: prospective self-ratings of bipolar disorder and alcohol use. BMC research notes, 8, 473. https://doi.org/10.1186/s13104-015-1436-x
107. Mewton, L., Lees, B., & Rao, R. T. (2020). Lifetime perspective on alcohol and brain health. BMJ (Clinical research ed.), 371, m4691. https://doi.org/10.1136/bmj.m4691
108. Han, B. H., Moore, A. A., Ferris, R., & Palamar, J. J. (2019). Binge Drinking Among Older Adults in the United States, 2015 to 2017. Journal of the American Geriatrics Society, 67(10), 2139–2144. https://doi.org/10.1111/jgs.16071
109. Wallach JD, Serghiou S, Chu L, et al. Evaluation of confounding in epidemiologic studies assessing alcohol consumption on the risk of ischemic heart disease. BMC Med Res Methodol. 2020;20(1):64. Published 2020 Mar 14. doi:10.1186/s12874-020-0914-6
110. Emberson, J. R., & Bennett, D. A. (2006). Effect of alcohol on risk of coronary heart disease and stroke: causality, bias, or a bit of both?. Vascular health and risk management, 2(3), 239–249. https://doi.org/10.2147/vhrm.2006.2.3.239
111. Wootton RE, Greenstone HSR, Abdellaoui A, et al. Bidirectional effects between loneliness, smoking and alcohol use: evidence from a Mendelian randomization study [published online ahead of print, 2020 Jun 15]. Addiction. 2020;10.1111/add.15142. doi:10.1111/add.15142
112. Schutte R, Papageorgiou M, Najlah M, Huisman H.W, Ricci C, Zhang J, Milner N, Schutte A.E. Drink types unmask the health risks associated with alcohol intake – Prospective evidence from the general population. Clinical Nutrition; February 14, 2020 DOI: https://doi.org/10.1016/j.clnu.2020.02.009
113. Trevisan M, Schisterman E, Mennotti A, et al. Drinking pattern and mortality: the Italian risk factor and life expectancy pooling project. Ann Epidemiol. 2001; 11:312–19. [PubMed] [Google Scholar]
114. Hakulinen C, Elovainio M, Batty GD, Virtanen M, Kivimäki M, Jokela M. Personality and alcohol consumption: Pooled analysis of 72,949 adults from eight cohort studies. Drug Alcohol Depend. 2015; 151:110-114.
115. Stephenson M, Barr P, Ksinan A, et al. Which adolescent factors predict alcohol misuse in young adulthood? A co-twin comparisons study. Addiction. 2020;115(5):877-887. doi:10.1111/add.14888
116. Der, G., Batty, G. D., & Deary, I. J. (2009). The association between IQ in adolescence and a range of health outcomes at 40 in the 1979 US National Longitudinal Study of Youth. Intelligence, 37(6), 573–580. https://doi.org/10.1016/j.intell.2008.12.002
117. Cao M, Cui B. Association of Educational Attainment with Adiposity, Type 2 Diabetes, and Coronary Artery Diseases: A Mendelian Randomization Study. Front Public Health. 2020; 8:112. Published 2020 Apr 22. doi:10.3389/fpubh.2020.00112
118. Zhou T, Sun D, Li X, Ma H, Heianza Y, Qi L. Educational attainment and drinking behaviors: Mendelian randomization study in UK Biobank [published online ahead of print, 2019 Nov 25]. Mol Psychiatry. 2019;10.1038/s41380-019-0596-9. doi:10.1038/s41380-019-0596-9
119. Mugavin, J., MacLean, S., Room, R., & Callinan, S. (2020). Adult low-risk drinkers and abstainers are not the same. BMC public health, 20(1), 37. https://doi.org/10.1186/s12889-020-8147-5
120. Haber JR, Harris-Olenak B, Burroughs T, Jacob T. Residual Effects: Young Adult Diagnostic Drinking Predicts Late-Life Health Outcomes. J Stud Alcohol Drugs. 2016;77(6):859-867. doi:10.15288/jsad.2016.77.859
121. Saarni SI, Joutsenniemi K, Koskinen S, et al. Alcohol consumption, abstaining, health utility, and quality of life--a general population survey in Finland. Alcohol Alcohol. 2008;43(3):376-386.
122. Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W. Moderate Alcohol Use and Reduced Mortality Risk: Systematic Error in Prospective Studies and New Hypotheses. Annals of EpidemiologyVolume 17, Issue 5, SupplementMay 2007Pages s16-s2
123. Gémes K, Janszky I, Strand LB, et al. Light-moderate alcohol consumption and left ventricular function among healthy, middle-aged adults: the HUNT study. BMJ Open. 2018;8(5): e020777. Published 2018 May 3. doi:10.1136/bmjopen-2017-020777
124. Kilian C, Manthey J, Probst C, et al. Why Is Per Capita Consumption Underestimated in Alcohol Surveys? Results from 39 Surveys in 23 European Countries [published online ahead of print, 2020 Jun 3]. Alcohol Alcohol. 2020; agaa048. doi:10.1093/alcalc/agaa048
125. Mukamal KJ, Jensen MK, Gronbaek M, et al. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. Circulation. 2005; 112:1406–13. [PubMed] [Google Scholar]
126. Wellmann J, Heidrich J, Berger K, et al. Changes in alcohol intake and risk of coronary heart disease and all-cause mortality in the MONICA/KORA-Augsburg cohort 1987-97. Eur J Cardiovasc Prev Rehabil. 2004; 11:48–55. [PubMed] [Google Scholar]
127. Beck AT, Himelstein R, Bredemeier K, Silverstein SM, Grant P. (2018). What accounts for poor func-tioning in people with schizophrenia: a re-evaluation of the contributions of neurocognitive v. attitudinal and motivational factors. Psychol Med. 2018; 48(16): 2776–2785. https://doi.org/10.1017/ S0033291718000442 PMID: 29501072.
128. Moritz, S., Irshaid, S., Lüdtke, T., Schäfer, I., Hauschildt, M., and Lipp, M. (2018). Neurocognitive functioning in alcohol use disorder: cognitive test results do not tell the whole story. Eur. Addict. Res. 24, 217–225. doi: 10.1159/000492160.

129. Timothy R. Campellone, Amy H. Sanchez, Ann M. Kring, Defeatist Performance Beliefs, Negative Symptoms, and Functional Outcome in Schizophrenia: A Meta-analytic Review, Schizophrenia Bulletin, Volume 42, Issue 6, November 2016, Pages 1343–1352, https://doi.org/10.1093/schbul/sbw026.
130. Taylor, A., Lu, F., Carslake, D. et al. Exploring causal associations of alcohol with cardiovascular and metabolic risk factors in a Chinese population using Mendelian randomization analysis. Sci Rep 5, 14005 (2015). https://doi.org/10.1038/srep14005
131. Stockwell, T., Donath, S., Cooper-Stanbury, M., Chikritzhs, T., Catalano, P. and Mateo, .C. (2004), Under-reporting of alcohol consumption in household surveys: a comparison of quantity–frequency, graduated–frequency and recent recall. Addiction, 99: 1024-1033. https://doi.org/10.1111/j.1360-0443.2004.00815.x
132. Duffy, J. C., & Waterton, J. J. (1984). Under-reporting of alcohol consumption in sample surveys: the effect of computer interviewing in fieldwork. British journal of addiction, 79(3), 303–308. https://doi.org/10.1111/j.1360-0443.1984.tb00278.x
133. Xue, A., Jiang, L., Zhu, Z., Wray, N. R., Visscher, P. M., Zeng, J., & Yang, J. (2021). Genome-wide analyses of behavioural traits are subject to bias by misreports and longitudinal changes. Nature communications, 12(1), 20211. https://doi.org/10.1038/s41467-020-20237-6
134. Wood, A. M. et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 391, 1513–1523 (2018).
135. Peña S, Mäkelä P, Härkänen T, Heliövaara M, Gunnar T, Männistö S, Laatikainen T, Vartiainen E, Koskinen S. Measurement error as an explanation for the alcohol harm paradox: analysis of eight cohort studies. Int J Epidemiol 2020. Volume 49, Issue 6, December 2020, Pages 1836–1846 https://doi.org/10.1093/ije/dyaa113
136. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27(8):1133–63.

Supplementary documents

Supplementary Table S1. Association between background factors and hazardous drinking$^{\Psi}$ in male and female persons with bipolar disorder.

	Male			***Female***		
	Hazardous drinking			**Hazardous drinking**		
	No	**Yes**	**p-value**	**No**	**Yes**	**p-value**
n	289	181		589	209	
Age	47.06 (13.32)	42.50 (12.06)	<0.001	45.51 (12.82)	41.39 (12.09)	<0.001
Education						
No matriculation examination	191 (66.1)	121 (66.9)	0.945	313 (53.1)	126 (60.3)	0.089
Matriculation examination	98 (33.9)	60 (33.1)		276 (46.9)	83 (39.7)	
Household pattern						
with spouse	107 (37.0)	66 (36.5)	0.981	267 (45.3)	75 (35.9)	0.022
Other	182 (63.0)	115 (63.5)		322 (54.7)	134 (64.1)	
Psychotropic medication						
No	15 (5.2)	12 (6.6)	0.653	29 (4.9)	7 (3.3)	0.446
Yes	274 (94.8)	169 (93.4)		558 (94.7)	202 (96.7)	
Missing	0 (0.0)	0 (0.0)		2 (0.3)	0 (0.0)	

RT = Reaction time

PAL = Paired association learning

$^{\Psi}$AUDIT-C cutoff scores for hazardous drinking were ⩾6 for males and ⩾5 for females

SD = Standard deviation

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CI = Confidence interval

[a] Adjusted with age, household pattern and education

** Analyzed with log-linear regression*

*** Analyzed with linear regression*

**** Analyzed with logistic regression*

Supplementary Table S2. Distribution of RT median, RT SD, PAL first trial memory scores (FTMS) and PAL total errors adjusted in study population.

	Min	***1st Qu,***	***Median***	***Mean***	***3rd Qu.***	***Max***
RT Median	282.0	385.0	416.0	426.4	454.0	982.5
RT SD	17.44	35.03	45.09	55.12	58.39	1069.65
PAL FTMS	0.0	7.00	11.00	10.67	14.00	20
PAL TEA	0.0	8.00	17.00	23.76	41.00	69

RT = Reaction time

PAL= Paired association learning

FTMS = First trial memory score

TEA = Total error adjusted

SD = Standard deviation

Supplementary Table S3. RT median and RT SD *p*-values for background factors and alcohol related disorder in persons with bipolar disorder.

	Male			***Female***			
	RT		**PAL**	**RT**		**PAL**	
	median	SD	FTMS	median	SD	FTMS	Test
Age	<.001	<.001	<.001	<.001	<.001	<.001	Spearman
Education	0.242	0.028	<.001	0.031	0.030	<.001	Point biserial
Alcohol related disorder	0.234	0.472	0.015	0.910	0.657	0.090	Point biserial

RT = Reaction time

PAL = Paired association learning

SD = Standard deviation

Supplementary Table S4. PAL total error adjusted scores for background factors and alcohol use patterns in persons with bipolar disorder.

	Male			***Female***		
	PAL total errors adjusted		**p-value**	**PAL total errors adjusted**		**p-value**
	0	1		0	1	
n	269	105		456	223	
Age	47.67 (12.47)	35.92 (10.25)	<0.001	45.87 (12.51)	38.32 (10.17)	<0.001
Education						

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No matriculation examination	190 (70.6)	53 (50.5)	<0.001	266 (58.3)	97 (43.5)	<0.001
Matriculation examination	79 (29.4)	52 (49.5)		190 (41.7)	126 (56.5)	
Household pattern						
with spouse	108 (40.1)	34 (32.4)	0.203	199 (43.6)	101 (45.3)	0.745
Other	161 (59.9)	71 (67.6)		257 (56.4)	122 (54.7)	
Psychotropic medication						
No	17 (6.3)	7 (6.7)	1.000	19 (4.2)	15 (6.7)	0.309
Yes	252 (93.7)	98 (93.3)		436 (95.6)	207 (92.8)	
Missing				1 (0.2)	1 (0.4)	
Hazardous drinking						
No	159 (59.1)	63 (60.0)	0.968	342 (75.0)	161 (72.2)	0.491
Yes	110 (40.9)	42 (40.0)		114 (25.0)	62 (27.8)	
Alcohol related disorder						
No	164 (61.0)	76 (72.4)	0.051	331 (72.6)	187 (83.9)	0.002
Yes	105 (39.0)	29 (27.6)		125 (27.4)	36 (16.1)	

PAL = Paired association learning

Supplementary Table S5. RT median and RT SD for hazardous drinking in persons with bipolar disorder.

		Male			***Female***		
		Hazardous drinking			**Hazardous drinking**		
		0	**1**	**p-value**	**0**	**1**	**p-value**
RT	Median	440.50 (84.90)	418.85 (51.30)	0.003	428.10 (68.77)	409.81 (50.42)	0.001
	SD	60.75 (58.09)	49.15 (34.67)	0.019	57.06 (60.99)	47.47 (26.49)	0.034
PAL	FTMS	9.82 (5.26)	10.11 (4.93)	0.595	10.92 (4.75)	11.52 (4.52)	0.147

RT = Reaction time

PAL= Paired association learning

FTMS = First trial memory score

SD = Standard deviation

Supplementary Table S6. Cohen's d measure of effect.

	Male	Female
Hazardous drinking		
RT SD	0.23 (0.04, 0.43)	0.19 (0.02, 0.34)
RT Median	0.29 (0.10, 0.49)	0.28 (0.12, 0.45)
PAL FTMS	-0.05 (-0.26, 0.15)	-0.12 (-0.29, 0.04)
PAL TEA	0.02 (-0.19, 0.22)	-0.07 (-0.24, 0.10)
Alcohol related disorder		
RT SD	-0.10 (-0.29, 0.10)	0.18 (0.01, 0.34)

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RT median	0.29 (0.10, 0.49)	0.29 (0.12, 0.45)
PAL FTMS	0.26 (0.05, 0.48)	0.15 (-0.02, 0.33)
PAL TEA	0.22 (0.01, 0.44)	0.29 (0.12, 0.47)

RT = Reaction time

PAL= Paired association learning

FTMS = First trial memory score

TEA = Total error adjusted

SD = Standard deviation