 doi:10.20944/preprints202104.0460.v1

Original article

Reaction time and visual memory in connection to alcohol use in schizophrenia and schizoaffective disorder

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**Years 2016-2018.

Abstract: Purpose of the study was to explore the association of cognition with hazardous drinking, binge drinking and alcohol use disorder in schizophrenia and schizoaffective disorder. Cognitive deficits are common in schizophrenia. Alcohol might be associated with additional cognitive impairment in schizophrenia patients. The study population included 3362 schizophrenia and schizoaffective disorder patients in Finland. Hazardous drinking was screened with the AUDIT-C (Alcohol Use Disorders Identification Test for Consumption) screening tool. Binge drinking was obtained from the AUDIT-C. Alcohol use disorder (AUD) 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 (5-CSRTT), or, reaction time (RT) test and the Paired Associative Learning (PAL) test. Association of alcohol use with RT test and PAL test was analyzed with log-linear regression and logistic regression, respectively. After adjustment for age, education and age at first psychotic episode, hazardous drinking in females was associated with lower median RT. Compared to never binge drinkers, male and female participants drinking 6 or more doses of alcohol monthly or less had lower

 doi:10.20944/preprints202104.0460.v1

median RT. In the PAL test both first trial memory score (FTMS) and total errors adjusted score (TEAS) were associated with better performance in males drinking 6 or more doses of alcohol weekly or more and in females drinking 6 or more doses monthly or less. Higher PAL TEAS was associated with AUD in females Some positive associations between alcohol and cognition were found in male and female schizophrenia and schizoaffective disorder patients with hazardous drinking and binge drinking.

Keywords: Cognition; Visual memory; Reaction time; Alcohol; schizophrenia and schizoaffective disorder.

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1. Introduction

Cognitive dysfunction is a persistent, disabling hallmark of schizophrenia found to be present in about 75% of schizophrenia patients [1]. It is associated with the severity of illness in schizophrenia [2]. Schizophrenia patients with comorbid AUD demonstrate marked impairment in multiple cognitive domains [3,4,5,6,7]. Most affected cognitive domains are sustained attention, concept formation and non-verbal cognitive flexibility [8].

Individuals with schizophrenia have three times more risk of heavy alcohol use than general population [10]. AUD is the second most common comorbidity in patients with schizophrenia, after nicotine dependence [11]. Systematic review and meta-analysis of 123 research papers published during 1990-2017 revealed 24.3% lifetime prevalence of AUD among subjects with schizophrenia [12].

About 90% of people who drink excessively would not be expected to meet the clinical diagnostic criteria for having AUD [13], rather could be screening-positive for hazardous drinking or binge (heavy episodic) drinking.

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 [14,15,16,17].

Binge drinking, or, heavy episodic drinking (HED) is the most common pattern of excessive alcohol use [13,18,19,20].

In general population males drink more alcohol than females [21]. However, in recent years male to female ratios for alcohol use, problematic alcohol use and alcohol-related harm have declined considerably [22,23].

Studies in general populations suggest that mild to moderate alcohol drinking might not decline cognition [24,25,26,27]. In schizophrenia patients, association of cognition with different drinking patterns has not been fully studied yet.

The main aim of the present study was to explore the association of reaction time and visual memory with different drinking patterns in persons with schizophrenia and schizoaffective disorder diagnoses.

The specific research aims are to study:

1. The association of hazardous drinking with reaction time and visual memory in persons with schizophrenia and schizoaffective disorder.
2. The association of binge drinking with reaction time and visual memory in persons with schizophrenia and schizoaffective disorder.

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3. The association of alcohol use disorder with reaction time and visual memory in persons with schizophrenia and schizoaffective disorder.

2. Materials and Methods

2.1. Approval of the full study

The Finnish Super study approval number from the Finnish Institute for Health and Welfare (THL) was THL/1007/5.05.00/2017.

2.2. Participants

The participants of this study were part of the study population of the SUPER (Suomalainen psykoosisairauksien perinnöllisyysmekanismien tutkimus/ Finnish study for the hereditary mechanisms behind psychotic illnesses)- study, which is part of the international Stanley Global Neuropsychiatric Genomics Initiative, USA. The SUPER-study 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 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 health care centers and supported housings. Participants were identified through local healthcare centers throughout the country from all levels of healthcare to ensure inclusive sampling. Subjects had also been recruited via advertisements on local newspapers.

Out of the original sample of 10555 participants, 6769 had clinical diagnosis of schizophrenia and schizoaffective disorder. Among those, 228 had missing information on alcohol use or education. Of the remaining 6541 participants, 1435 did not complete the cognitive tests or had duplicate test results. Finally, we had 3362 participants after excluding 1744 who did not live independently (living in supported housing, hospital or unknown residence) as alcohol use is restricted in those places. (Figure 1).

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

2.3. Schizophrenia and schizoaffective disorder diagnoses

The diagnoses of schizophrenia and schizoaffective disorder were obtained from the Care Register for Health Care (CRHC) of the Finnish Institute for Health and Welfare. In Finland the International Classification of Disease (ICD) system has been used in psychiatric diagnoses. In this study schizophrenia diagnoses included the code 295 according to ICD-8; and ICD-9 and F20 according to ICD-10 and schizoaffective disorder diagnoses included the code 295.7 according to ICD-8; and ICD-9 and F25 according to ICD-10. ICD-8 was used during 1968-1986, ICD-9 during 1987-1995 and ICD-10 since 1996 in Finland.

2.4. Hazardous drinking screening

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

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one occasion?'). AUDIT-C is derived from the hazardous alcohol use domain of the Alcohol Use Disorders Identification Test (AUDIT) questionnaire [28]. It has three questions and is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices valued from 0 points to 4 points.

Cutoff scores for hazardous drinking vary considerably [19,29]. In the present study we used cutoff scores recommended by Finnish National Guidelines; a score of 6 or more in males, and 5 or more in females [30].

2.5. Binge drinking screening

There exist several definitions of binge drinking [31,32]. In the present study binge drinking was screened using the bingeing question ('how often do you have six or more drinks on one occasion?') of the AUDIT C screening questionnaire.

2.6. Alcohol use disorder diagnoses

The diagnoses of alcohol use disorder were obtained from the CRHC data following ICD-8 291, 303, ICD-9 291, 3030, 3050A, ICD-10 F10 during 1969-2018.

2.7. Cognitive measures

Participants performed two computerized tasks from The Cambridge neuropsychological test automated battery (CANTAB) on tablet computer; the 5-choice serial reaction time task (5-CRTT) and the paired associative learning (PAL) task for the assessment of reaction time (RT) and visual memory respectively.

The PAL test is sensitive to the integrity of the frontal and medial temporal lobes, in particular the hippocampal and para-hippocampal regions, which corresponds to the changes seen in Alzheimer's Disease (AD). The PAL test provides markers for impaired visual memory in first-episode psychosis [33], normal variation in midlife cognitive function as well as earliest signs of Alzheimer's related decline [34,35].

These tasks were chosen to produce relevant information of cognition in psychotic disorders in the very restricted assessment schedule. The instructions to 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, the participant must select and hold a button at the bottom of the screen. Circles are presented above; five for the five-choice mode. A yellow dot will appear in one of the circles, and the participant must react as soon as possible, releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared (Cambridge Cognition, Reaction time). In the RT-test we used two continuous measurements: median of the five-choice reaction time and standard deviation (SD) of the five-choice reaction time. Median of the five-choice reaction time is the median duration between the onset of the stimulus and the release of the button. 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 five locations.

In the PAL-test we assessed visual memory using the primary outcome variable of 'total errors adjusted'. Here we assessed two different dichotomized variables, using data from Northern Finland Birth Cohort 1966 (NFBC 1966) as a reference data [36]. 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). For the first trial memory score, the 15th percentile (score of 17

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or more) was used as a cut-off for good performance in PAL test in the recent study, meaning the SUPER study population did better performance than 15% of NFBC 1966 study population. 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 . First Trial Memory Score is how many patterns the participant correctly places on the first attempt at each problem, while Total Errors Adjusted Score reflects how quickly the participant learns when the participant has multiple attempts at each problem.

2.8. Confounding factors

Age, education [37] and age of first psychotic episode [4] have effects on cognitive functioning, hence we considered them be the confounding variables in this study.

2.7.1. Age

Cognition is negatively associated with increased age in healthy populations [38] and debatably in alcohol users [39]. Age of the participants was calculated using participation date and year of birth of the participant. Age was used as continues variable.

2.8.2. Education

Education is strongly associated with cognitive performance [40]. The questions and possible answers addressing education of the participants were: 'What is your basic education?' (1= less than the primary school, 2= matriculation examination, 3= middle school, 4= part of general upper secondary school or general upper secondary education certificate, 5= part of a middle school or primary school less than 9 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').

2.8.3. Age of first psychotic episode

We used age at first psychotic episode as a marker of severity of the illness. Research shows that the earlier is the schizophrenia and schizoaffective disorder development, the mores severe is the illness in terms of the disease pattern and cognitive decline [41,42]. The data of age at first psychotic episode were obtained form the CRHC and were used in this research as continuous variable.

2.9. Statistical methods

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 total errors adjusted. Alcohol use was measured by different variables; dichotomous hazard drinking variable derived from AUDIT score; classified variable of binge drinking obtained from AUDIT questionnaire; and dichotomous variable indicating, if the study subject had had alcohol disorder diagnosis. We assessed crude models and also adjusted models with age, age of first psychosis episode 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-test and alcohol use was analyzed with logistic regression and odds ratios (OR) with 95% CI are reported.

All analyses were conducted separately in males and females. Males and females have differences in performing selected cognitive tests [43,44,45]. Also, males and females have differences in alcohol use patterns [18,46,47,48].

3. Results

 doi:10.20944/preprints202104.0460.v1

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3.1. Background factors and alcohol use patterns

Of the participants 51% were males and 49 % were females. Mean age was 45 years for males and 46 years for females. One third of the males and two fifth of the females had highest basic educational of 12 years (matriculation). Mean age at first psychotic episode was 27 years for male and 28 for female. Four fifth of the males and three fifth of the females were living alone. Most of the participants were on psychotropic medication (Table 1).

All types of alcohol use patterns were more common in males than in females. Every fifth male and every tenth female schizophrenia and schizoaffective disorder patients had positive screening for hazardous drinking. About half of the male and one third of the female were screened as binge drinkers, mostly binge drinking monthly or less frequently. About one third of male and one sixth of female schizophrenia and schizoaffective disorder patients had a lifetime diagnosis of AUD (Table 1).

Lower age associated with hazardous drinking both in males and females. In females lower age of onset and types of household associated with hazardous drinking (Supplementary table 1).

Median RT was 435 milliseconds (SD 50 milliseconds), PAL median FTMS was 8 and median total errors adjusted was 33 (Supplementary table 2).

Association between background factors and AUD with RT P-values are reported in supplementary table 3. Association between background factors and alcohol use patterns with PAL scores are reported in supplementary table 4 and supplementary table 5.

3.2. Association of reaction time and visual memory with hazardous drinking in schizophrenia and schizoaffective disorder patients

Crude median reaction time was shorter and less divers in male and female schizophrenia and schizoaffective disorder patients with hazardous drinking compared to those without hazardous drinking. After adjustment for age, education and age at first psychotic episode hazardous drinking in females associated with lower median RT (OR 0.97, 95% CI 0.95-0.99). After adjustment, reaction time was less diverse in male schizophrenia and schizoaffective disorder patients with hazardous drinking compared to male schizophrenia patients without hazardous drinking (Table 2). Association between hazardous drinking and RT scores are reported in supplementary table 6.

Crude PAL first trial memory score was higher in male and crude PAL total errors adjusted score were higher in both female schizophrenia and schizoaffective disorder patients with hazardous drinking compared to those without hazardous drinking (Table 2).

3.3. Association of reaction time and visual memory with binge drinking in schizophrenia and schizoaffective disorder patients

Crude median reaction time was shorter and less diverse in male schizophrenia and schizoaffective disorder patients binge drinking weekly compared to those binge-drinking monthly or less and in male schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those never binge drinking. Adjusted median reaction time was shorter in male schizophrenia patients binge drinking monthly or less compared to those binge-drinking never (OR 0.98, CI 0.96-0.99). After adjustment, reaction time was less diverse in male schizophrenia and schizoaffective disorder patients binge drinking weekly compared to those binge-drinking monthly or less. Crude median reaction time was shorter in female schizophrenia and schizoaffective disorder patients binge

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drinking weekly compared to those binge-drinking monthly or less and in female schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those never binge drinking (OR 0.98, CI 0.96-1.00). Both crude and adjusted median reaction time were less diverse in female schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those binge-drinking drinking never (Table 3).

Crude PAL FTMS and crude PAL total errors adjusted score were higher in male schizophrenia and schizoaffective disorder patients binge drinking weekly (for FTMS OR 2.09, CI 1.17-3.62; for total errors adjusted OR 0.63, CI 0.43-0,95) compared to those binge drinking monthly or less and in male schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those never binge drinking. Crude PAL first trial memory score and crude PAL total errors adjusted score were higher in female schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those never binge drinking (for FTMS OR 1.64, CI 1.08-2.49; for total errors adjusted OR 0.74, CI 0.56-0.97) and crude PAL total errors adjusted score was higher in female schizophrenia and schizoaffective disorder patients binge drinking weekly compared to those binge drinking monthly or less (Table 3).

3.4. Association of reaction time and visual memory with alcohol use disorder in schizophrenia and schizoaffective disorder patients

There was no significant difference in crude or adjusted reaction time in male and female schizophrenia and schizoaffective disorder patients with or without a lifetime history of alcohol use disorder (Table 4).

Crude PAL total errors adjusted score was higher in female schizophrenia and schizoaffective disorder patients with a lifetime history of alcohol use disorder compared to those without alcohol use disorder (OR 1.51, CI 1.06-2.17) (Table 4).

3.5. Figures, Tables and Schemes

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Figure 1. flowchart showing selection of study population

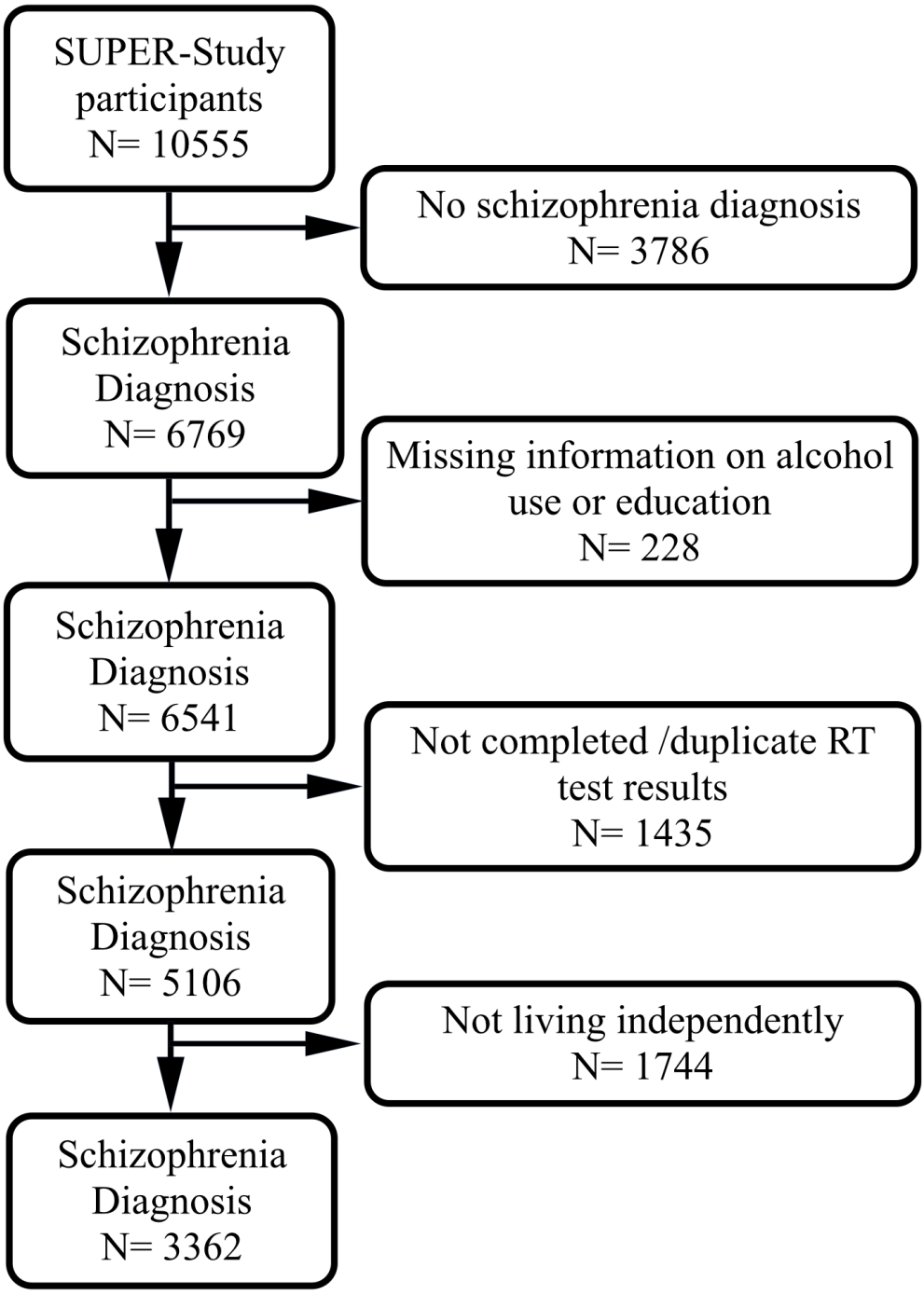

Table 1. Background factors and alcohol use patterns in schizophrenia and schizoaffective disorder.

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	Male	*Female*
	N = 1711	N = 1651
Age (mean (SD))	44.5 (12.8)	46.3 (13.2
Education		
No matriculation examination (%)	1191 (69.6)	981 (59.4)
Matriculation examination (%)	520 (30.4)	670 (40.6)
Age at first psychotic episode (Mean (SD))	26.84 (8.25)	28.01 (9.51)
Household pattern		
Alone (%)	1338 (78.2)	1065 (64.5)
With children without spouse (%)	7 (0.4)	63 (3.8)
With parents or siblings (%)	166 (9.7)	82 (5.0)
With spouse (%)	140 (8.2)	339 (20.5)
With spouse and children (%)	60 (3.5)	102 (6.2)
Current Psychotrophic medications		
No (%)	42 (2.45)	33 (2.00)
Yes (%)	1668 (97.49)	1614 (97.76)
Missing (%)	1 (0.06)	4 (0.24)
*Hazardous drinking**		
No (%)	1276 (74.6)	1390 (84.2)
Yes (%)	435 (25.4)	261 (15.8)
*Binge drinking***		
Never (%)	903 (52.8)	1134 (68.7)
Monthly or less frequently (%)	596 (34.8)	434 (26.3)
Weekly or more frequently (%)	212 (12.4)	83 (5.0)
Alcohol use disorder		
No (%)	1212 (70.8)	1395 (84.5)
Yes (%)	499 (29.2)	256 (15.5)

*AUDIT-C cutoff scores for hazardous drinking were ≥6 for males and ≥5 for females

**≥6 doses in single occasion

Table 2. Association of RT test and PAL test with hazardous drinking in schizophrenia and schizoaffective disorder.

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	*Five choice reaction time**				*Five choice reaction time**			
	Median				SD			
	Crude		Adjusted[a]		Crude		Adjusted[a]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Male								
Hazardous drinking	0.97 (0.95-0.99)	0.002	0.99 (0.97-1.01)	0.323	0.86 (0.81-0.91)	<.001	0.92 (0.87-0.98)	0.005
Female								
Hazardous drinking	0.94 (0.92-0.97)	<.001	0.97 (0.95-0.99)	0.010	0.89 (0.83-0.96)	0.002	0.98 (0.92-1.05)	0.606
	*PAL first trial memory score***				*PAL total errors adjusted score***			
	Better performance than 15% of NFBC 1966 members				Higher error scores than 50% of NFBC 1966 members			
	Crude		Adjusted[a]		Crude		Adjusted[a]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Male								
Hazardous drinking	1.76 (1.13-2.66)	0.001	1.21 (0.77-1.86)	0.397	0.56 (0.43-0.73)	<.001	0.79 (0.60-1.05)	0.106
Female								
Hazardous drinking	1.58 (0.95-2.52)	0.064	1.07 (0.63-1.74)	0.798	0.58 (0.43-0.80)	<.001	0.88 (0.64-1.22)	0.440

[a] Adjusted with age, education and age at first psychotic episode

* Analyzed with log-linear regression

** Analyzed with logistic regression

Table 3. Association of RT test and PAL test with binge drinking in schizophrenia and schizoaffective disorder.

	*Five choice reaction time**		*Five choice reaction time**	
	Median		SD	
	Crude	Adjusted[a]	Crude	Adjusted[a]

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	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Binge drinking								
Male								
Monthly or less frequently	0.95 (0.93-0.96)	<.001	0.98 (0.96-0.99)	0.009	0.85 (0.81-0.90)	<.001	0.94 (0.89-1.00)	0.040
Weekly or more frequently	0.96 (0.94-0.99)	0.002	0.98 (0.96-1.00)	0.102	0.83 (0.77-0.90)	<.001	0.89 (0.83.0.96)	0.003
Female								
Monthly or less frequently	0.94 (0.93-0.96)	<.001	0.98 (0.96-1.00)	0.015	0.81 (0.76-0.86)	<.001	0.91 (0.86-0.96)	0.001
Weekly or more frequently	0.95 (0.91-0.99)	0.007	0.97 (0.93-1.01)	0.114	0.87 (0.77-0.98)	0.027	0.94 (0.84-1.06)	0.307
	*PAL first trial memory score***				*PAL total errors adjusted score***			
	Better performance than 15% of NFBC 1966 members				Higher error scores than 50% of NFBC 1966 members			
	Crude		Adjusted[a]		Crude		Adjusted[a]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Binge drinking								
Male								
Monthly or less frequently	1.80 (1.17-2.77)	0.008	0.99 (0.63-1.55)	0.876	0.48 (0.37-0.62)	<.001	0.82 (0.63-1.09)	0.170
Weekly or more frequently	2.99 (1.70-5.07)	<.001	2.09 (1.17-3.62)	0.010	0.45 (0.31-0.65)	<.001	0.63 (0.43-0.95)	0.023
Female								
Monthly or less frequently	2.56 (1.71-3.81)	<.001	1.64 (1.08-2.49)	0.019	0.46 (0.35-0.59)	<.001	0.74 (0.56-0.97)	0.029
Weekly or more frequently	1.43 (0.49-3.33)	0.456	1.01 (0.34-2.41)	0.983	0.44 (0.27-0.74)	0.001	0.61 (0.36-1.06)	0.071

[a] Adjusted with age, education and age at first psychotic episode

* Analyzed with log-linear regression

** Analyzed with logistic regression

Table 4. Association of RT test and PAL test with alcohol use disorder in schizophrenia and schizoaffective disorder.

	*Five choice reaction time**				*Five choice reaction time**			
	Median				SD			
	Crude		Adjusted[a]		Crude		Adjusted[a]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value

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Male								
Alcohol use disorder	1.01 (0.99-1.02)	0.545	1.00 (0.99-1.02)	0.785	1.02 (0.96-1.08)	0.482	1.00 (0.95-1.06)	0.833
Female								
Alcohol use disorder	0.99 (0.96-1.01)	0.246	0.99 (0.96-1.00)	0.228	1.03 (0.96-1.11)	0.413	1.03 (0.96-1.11)	0.371
	*PAL first trial memory score***				*PAL total errors adjusted***			
	Better performance than 15% of NFBC 1966 members				Higher error scores than 50% of NFBC 1966 members			
	Crude		Adjusted		Crude		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Male								
Alcohol use disorder	0.71 (0.45-1.09)	0.131	0.88 (0.55-1.36)	0.567	1.36 (1.05-1.77)	0.021	1.14 (0.86-1.51)	0.364
Female								
Alcohol use disorder	0.53 (0.28-0.94)	0.043	0.57 (0.29-1.02)	0.076	1.57 (1.13-2.22)	0.009	1.51 (1.06-2.17)	0.024

[a] Adjusted with age, education and age at first psychotic episode

* Analyzed with log-linear regression

** Analyzed with logistic regression

Supplementary table 1 Association between background factors and hazardous drinking in schizophrenia and schizoaffective disorder.

		Male			*Female*		
		Hazardous drinking			Hazardous drinking		
		No	Yes	p	No	Yes	p
n		1276	435		1390	261	
Age		45.79	40.84	<0.001	47.45	40.19	<0.001
		(13.03)	(11.54)		(13.11)	(11.97)	

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Education	No matriculation examination	889 (69.7)	302 (69.4)		818 (58.8)	163 (62.5)	
	Matriculation examination	387 (30.3)	133 (30.6)	0.971	572 (41.2)	98 (37.5)	0.308
Age at first psychotic episode		26.77 (8.48)	27.04 (7.57)	0.561	28.36 (9.71)	26.14 (8.13)	0.001
Household pattern	Alone	986 (77.3)	352 (80.9)	0.307	895 (64.4)	170 (65.1)	0.045
	With children without spouse	6 (0.5)	1 (0.2)		60 (4.3)	3 (1.1)	
	With parents or siblings	132 (10.3)	34 (7.8)		73 (5.3)	9 (3.4)	
	With spouse	103 (8.1)	37 (8.5)		275 (19.8)	64 (24.5)	
	With spouse and children	49 (3.8)	11 (2.5)		87 (6.3)	15 (5.7)	
Psychotropic medication	No	35 (2.7)	7 (1.6)		30 (2.2)	3 (1.1)	
	Yes	1240 (97.2)	428 (98.4)		1356 (97.6)	258 (98.9)	
	Missing	1 (0.1)	0 (0.0)	0.352	4 (0.3)	0 (0.0)	0.385

Supplementary table 2 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	288	298	434.5	450.2	482	1610
RT SD	14.78	37.98	49.95	66.50	69.87	922.02
PAL FTMS	0.0	4.0	8.0	8.3	12	20
PAL Total errors adjusted	0.0	14	35	33.16	50	70

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Supplementary table 3. RT median and RT SD P-values for background factors and alcohol use disorder in schizophrenia and schizoaffective disorder.

P-values

	Male		Female		
	RT		RT		
	median	SD	median	SD	Test
Age	<.001	<.001	<.001	<.001	Spearman
Education	0.563	0.104	<.001	<.001	Spearman
Age at first psychotic episode	<.001	<.001	<.001	<.001	Spearman
Alcohol use disorder	0.445	0.245	0.178	0.211	Point biserial

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Supplementary table 4. PAL first trial memory scores (FTMS) for background factors and alcohol use patterns in schizophrenia and schizoaffective disorder.

		Male			*Female*		
		PAL FTMS			PAL FTMS		
		0	1	p	0	1	p
n		1462	79		1361	100	
Age		44.86	33.77	<0.001	46.28	37.44	<0.001
		(12.58)	(9.41)		(12.97)	(10.87)	
Education	Matriculation	452	35 (44.3)	0.018	564	58	0.002
	examination	(30.9)			(41.4)	(58.0)	
	No matriculation	1010	44 (55.7)		797	42	
	examination	(69.1)			(58.6)	(42.0)	
Age at first		26.90	24.38	0.008	28.11	25.93	0.028
psychotic episode		(8.26)	(5.93)		(9.69)	(7.69)	
Household pattern	Alone	1162	50 (63.3)	0.002	888	49	<0.001
		(79.5)			(65.2)	(49.0)	

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	With children without spouse	5 (0.3)	1 (1.3)		45 (3.3)	10 (10.0)	
	With parents or siblings	137 (9.4)	12 (15.2)		66 (4.8)	7 (7.0)	
	With spouse	109 (7.5)	8 (10.1)		277 (20.4)	20 (20.0)	
	With spouse and children	49 (3.4)	8 (10.1)		85 (6.2)	14 (14.0)	
Psychotropic medication	No	34 (2.3)	7 (8.9)		26 (1.9)	5 (5.0)	
	Yes	1427 (97.6)	72 (91.1)		1334 (98.0)	94 (94.0)	
	Missing	1 (0.1)	0 (0.0)	0.002	1 (0.1)	1 (1.0)	0.006
Hazardous drinking	No	1101 (75.3)	51 (64.6)	0.044	1146 (84.2)	80 (80.0)	0.335
	Yes	361 (24.7)	28 (35.4)		215 (15.8)	20 (20.0)	
Binge drinking	Never	784 (53.6)	30 (38.0)		937 (68.8)	53 (53.0)	
	Monthly or less frequently	505 (34.5)	31 (39.2)	0.004	352 (25.9)	44 (44.0)	<0.001
	Weekly or more frequently	173 (11.8)	18 (22.8)		72 (5.3)	3 (3.0)	
Alcohol use disorder	No	1037 (70.9)	62 (78.5)	0.188	1143 (84.0)	90 (90.0)	0.145
	Yes	425 (29.1)	17 (21.5)		218 (16.0)	10 (10.0)	

Supplementary table 5. PAL total errors adjusted sores for background factors and alcohol use patterns in schizophrenia and schizoaffective disorder.

		Male			*Female*		
		PAL total errors adjusted			PAL total errors adjusted		
		0	1		0	1	
n		241	1300		297	1164	
Age		35.46 (10.11)	45.93 (12.43)	<0.001	37.82 (10.90)	47.68 (12.76)	<0.001
Education	No matriculation examination	129 (53.5)	925 (71.2)		129 (43.4)	710 (61.0)	
	Matriculation examination	112 (46.5)	375 (28.8)	<0.001	168 (56.6)	454 (39.0)	<0.001
Age at first psychotic episode		24.34 (5.99)	27.23 (8.45)	<0.001	25.94 (7.70)	28.47 (9.94)	<0.001
Household pattern	Alone	174 (72.2)	1038 (79.8)	0.031	167 (56.2)	770 (66.2)	<0.001
	With children without spouse	1 (0.4)	5 (0.4)		23 (7.7)	32 (2.7)	

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	With parents or siblings	30 (12.4)	119 (9.2)		19 (6.4)	54 (4.6)	
	With spouse	20 (8.3)	97 (7.5)		56 (18.9)	241 (20.7)	
	With spouse and children	16 (6.6)	41 (3.2)		32 (10.8)	67 (5.8)	
Psychotropic medication	No	11 (4.6)	30 (2.3)		10 (3.4)	21 (1.8)	
	Yes	230 (95.4)	1269 (97.6)		286 (96.3)	1142 (98.1)	
	Missing	0 (0.0)	1 (0.1)	0.124	1 (0.3)	1 (0.1)	0.143
Hazardous drinking	No	166 (68.9)	986 (75.8)	0.027	239 (80.5)	987 (84.8)	0.085
	Yes	75 (31.1)	314 (24.2)		58 (19.5)	177 (15.2)	
Binge drinking	Never	100 (41.5)	714 (54.9)		170 (57.2)	820 (70.4)	
	Monthly or less frequently	106 (44.0)	430 (33.1)	0.001	111 (37.4)	285 (24.5)	<0.001
	Weekly or more frequently	35 (14.5)	156 (12.0)		16 (5.4)	59 (5.1)	
Alcohol use disorder	No	186 (77.2)	913 (70.2)	0.035	259 (87.2)	974 (83.7)	0.160
	Yes	55 (22.8)	387 (29.8)		38 (12.8)	190 (16.3)	

Supplementary table 6. RT median and RT SD for hazardous drinking in schizophrenia and schizoaffective disorder.

		Male			*Female*		
		Hazardous drinking			Hazardous drinking		
		0	1	p	0	1	p
n		1276	435		1390	261	
RT	Median	453	438.30	0.004	455.75	426.66	<.001
		(96.06)	(79.04)		(98.50)	(64.39)	
	SD	67.93	53.65	<.001	70.60	59.26	0.021
		(71.75)	(32.57)		(75.62)	(54.18)	

4. Discussion

4.1. Main findings

Our findings did not support our hypothesis that alcohol use is associated with additional cognitive impairment in schizophrenia and schizoaffective disorder patients. In contrast, crude median reaction time was significantly shorter in female schizophrenia and schizoaffective disorder patients with hazardous drinking. Crude PAL total errors adjusted score were significantly higher in male and female schizophrenia and

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schizoaffective disorder patients with hazardous drinking. Crude PAL first trial memory score and crude PAL total errors adjusted score were significantly higher in male and female schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those never binge drinking.

4.2. Comparison with other studies

There hardly exist any studies investigating association of different alcohol use patterns in schizophrenia and schizoaffective disorder patients hence it is difficult to compare our findings with other studies.

Most studies investigating cognitive impact of alcohol in schizophrenia patients with comorbid AUD revealed negative association between alcohol use and cognitive function [6,7,49,50,51,52]. On the other hand, some studies suggested that AUD had no additive effects on cognitive impairment in schizophrenia patients [53,54,55], or had positive associations with social cognition [56,57,58,59], task making and the speed processing domains [60].

Meta-analysis of 6 research findings published during 1996-2009 revealed that younger (<30 years) schizophrenia patients with comorbid alcohol use disorders had better cognition than schizophrenia patients without AUD. In contrast, older (> 40 years) schizophrenia patients with comorbid alcohol use disorders had worse cognition than their non-comorbid counterparts [5]. A systematic review of research papers published during 1990-2012 revealed that cognition was more preserved in schizophrenia patients with comorbid substance/ alcohol use disorders compared schizophrenia patients without comorbidity [61]. It is likely that unmeasured confounding contributes to the discrepant findings in previous studies.

General population cross-sectional studies investigating effects of alcohol on cognitive function revealed that moderate to heavy drinking was associated with cognitive decline [62,63,64,65] and mild to moderate drinking was associated with either no effects on cognition [66,67] or cognitive enhancement [65,68,69,70,71].

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 [26,27,72,73,74] whereas other cohort study found no association between light to moderate alcohol consumption and better or worse cognitive functions [75,76,77]. One study reported a positive association between moderate to heavy drinking and cognitive function [78]. In contrast, another cohort study revealed negative association between heavy alcohol use and cognitive function in normal population [79]. One cohort study found dose-response positive association of alcohol use and cognitive function compared to abstainers and former drinkers [80]. Another cohort study revealed significant cognitive impairment in low functioning non-drinkers and light to moderate drinkers and high functioning non-drinkers [81].

A brief review of 29 studies (2003-2013) revealed that acute alcohol mostly impaired executive function in normal population [82]. 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 [83]. 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 [25]. Meta-analysis of 27 cohort studies (2007-2018) revealed that moderate alcohol use improved cognition insignificantly among male and slightly among female compared to current non-drinkers [24]. Moderate alcohol has been found to be associated with reduced amyloid-beta deposition in human brain [84].

Study findings suggesting positive association between alcohol and cognition could be attributed by unmeasured or residual confounding factors [85,86] like: smoking [87], drink type [88], drink pattern [89], personality [87,90], intelligence [76,91,92], educational attainment [93,94], potential abstainer errors [95,96,97,98], reverse causality bias [99], recall error [100] within person temporal variation [101,102], ascertainment of diseases [103]

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and sociability effect of alcohol [104]. Study findings suggesting positive association between alcohol and cognition could be attributed by poor motivation [105,106,107].

Animal-model studies suggested alcohol to be associated with cognition negatively through decreasing cell density in the cerebral cortex [108], altering accumbal cholinergic interneurons [109] and positively through enhancing brain metabolite clearance [110], activating vagus nerve [111], anti-oxidant system [112,113,114,115] and other biological processes [116,117,118]. However, none of these findings have so far been confirmed to be causally important.

Epidemiological studies suggested that apparent befitting effects of alcohol might largely be non-causal [27,119,120,121,122]. More research is needed for further clarification [123].

4.3. Strength

We were able to use a very large sample of schizophrenia and schizoaffective disorder patients to investigate cognitive impact of different alcohol use patterns. We studied multiple alcohol use patterns in the same study population, and used age, education and age of onset of schizophrenia and schizoaffective disorder as potential confounding variables.

Although long-term antipsychotic medication might be associated with additional loss of both gray and white matters in schizophrenia [124], in our study we did not confound antipsychotic medication because 98% of the study population was on antipsychotic medication hence it would not make any statistically significant differences.

We have included all schizophrenia and schizoaffective disorder patients living independently and excluded those whose living circumstances might affect their alcohol use.

4.4. Limitations

We used only two tests from CANTAB. Our study was cross-sectional, not longitudinal. Our study was cross-sectional, not longitudinal. 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.

We did not use information about poly-substance use and smoking. We did specify psychotropic medications. First generation antipsychotics have been found to be associated with increased volume of basal ganglia, namely globes pallidus, which might be reversed on switching into second-generation antipsychotics and clozapine [125,126]. However, antipsychotic induced brain volume loss has never been established to be associated with additional cognitive decline [12].

4.5. What is already known on this subject?

- Alcohol use disorder decline cognition in schizophrenia and schizoaffective disorder patients
- Mild alcohol use is not associated with impaired cognition in normal population.

4.6. What this study adds?

- Mild alcohol use is not associated with additional cognitive impairment in schizophrenia and schizoaffective disorder patients.

5. Conclusions

No additional cognitive impairment was associated with both male and female schizophrenia and schizoaffective disorder patients with hazardous drinking, binge drinking and alcohol use disorder. Some positive association between alcohol and cognition were found in terms of shorter crude median reaction time in female and higher crude PAL total errors adjusted score in male and female schizophrenia and schizoaffective disorder patients with hazardous drinking, higher crude PAL first trial memory score and crude PAL total errors adjusted score in male and female schizophrenia and schizoaffective disorder patients binge drinking monthly or less compared to those never binge drinking. Further genetic epidemiological studies could help resolving alcohol and cognition correlation-causality-reverse causality debate.

6. Patents

This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

Supplementary Materials: The following are available online at https://drive.google.com/drive/folders/1-9PUv7ZxZ9cSTE8RD_0sAPgV7NZfTsVq , Supplementary tables 1-6.

Author Contributions: All authors have contributed to the conception and design of the study as well as collection of data from various sources. SS performed the analyses. All authors were involved in text editing and discussion of findings. All authors have approved of the final version of the manuscript.

Funding: The work was supported by a grant from the Stanley Center for Psychiatric Research, Broad institute, 75 Ames Street, Cambridge, MA 02142, USA. (Grant no. IORG0000717, IRB00003181, FWA00004167).

The Principal author was supported by the Marie Skłodowskaja-Curie Action co-funding of regional, national, and international programmes (COFUND) (Grant Agreement no. 713606) for his doctoral programme (MSC-COFUND, I4FUTURE). The Principal author was also supported by the Iso-Mällisen Foundation (Iso-Mällisen Säätiö) through a medical grant of EUR 4,000 for the year 2019 (Grant no. 0400 584622).

Institutional Review Board Statement: Prior to seeking study permissions, a statement (202/13/03/00/2015) pertaining to the ethical considerations of the study was requested from the Coordinating Ethics Committee of the The Hospital District of Helsinki and Uusimaa, which is responsible for nationwide ethical statements. After receiving a favorable statement (HUS/1842/2016) the permissions to conduct the study was sought and obtained from all participating healthcare organizations individually. Permissions for use of national registries were obtained from relevant authorities.

The research was conducted also 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 the treatment of the study patients.

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 analysis, if not possible to remove from the completed analyses, would never be used in the future, unless a part of a large summary dataset. If the subject was in involuntary psychiatric care or the study nurse had any doubts on the subject's ability to give informed consent, permission would be asked to contact the attending physician of the subject to obtain a statement 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 study participants written informed consent for publication of the study results without disclosing their identities have been taken.

Data Availability Statement: Raw data and materials used for this study are available on request.

Acknowledgments: The authors are grateful to the participants and SUPER-Study staffs.

Conflicts of Interest: None of the authors has any conflicts of interest associated with this study. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: grant support for the submitted work is detailed above; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. However, Jennifer Barnett has been working in Cambridge Cognition since 2016.

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