Alcohol and Cognitive Function in Chinese Elderly: Heterogeneity in Different Domains

Jiaxi Han, Ziyang Lu*

School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, China

Abstract: Background: Cognitive decline has become an increasingly severe health issue in China. While alcohol's neurotoxicity is documented, the interaction between drinking patterns, dietary-mediated metabolic pathways, and domain-specific cognitive health remains biologically complex. Our study leverages bioinformatics modeling to elucidate these associations. Methods: 13130 subjects from Chinese Longitudinal Healthy Longevity Survey (CLHLS, 2008 - 2018) older than 65 and without dementia were introduced in this study. A linear mixed effects model (LMM), was deployed to investigate the interaction between alcohol consumption, lifestyle-related metabolic factors and cognitive decline across five neurological domains. Results: Continuous alcohol consumption was also negatively associated with the performance in cognitive domain orientation, attention & calculation, and recall. Short-term alcohol users had a better performance in registration and language domain compared to the non-drinkers. A novel biomedical interaction was identified: subjects with high vegetable intake were more susceptible to alcohol-induced decline, potentially linked to the inhibition of Vitamin B12 absorption and metabolic homeostasis. Conclusion: This study provides computational evidence for domain-specific neurotoxicity of chronic alcohol use. The findings highlight the importance of considering biochemical synergies between diet and alcohol in clinical neuro-management, offering new insights for personalized nutrition and preventive biomedicine in elderly populations.

1. Introduction

Cognitive decline has become an increasingly public health issue around the world, especially in China [1]-[3]. As of 2019, there are 13.14 million people in China suffer from dementia, accounting for 25.5% of the total number in the world, and the number has been rising continuously in recent years [2],[3].

Multiple factors have been linked to cognitive decline, including alcohol use. Alcohol intake is closely related to brain function [4],[5]. Chronic heavy alcohol consumption has been extensively studied for its detrimental effects on cognitive function, with several physiological mechanisms identified. Reductions in the cortical and hippocampal regions of the brain, neuronal damage, neuroinflammation, alterations in neurotransmitter systems, oxidative stress, and nutritional deficiencies are among the key mechanisms involved [6]-[12]. As a result, chronic heavy alcohol consumption impair the function of prefrontal lobe, temporal lobe, and cerebellar function [13]. However, studies have shown that moderate alcohol consumption can improve cognitive function primarily through its effects on neurotransmission and cerebral blood flow, despite it can cause damage to multiple organs such as liver and intestines [14]-[18]. This suggests that alcohol use may affect different cognitive domains differently, however the research is still insufficient.

Although alcohol consumption has been widely recognized as a risk factor for cognitive decline [19], the results of previous studies on the effects of alcohol on cognitive function among the elderly have been inconsistent. Some studies suggest that mild to moderate alcohol consumption has a protective effect on cognitive function, leading to better cognitive performance than non-drinkers and heavy drinkers [20]-[24]. Another study on Chinese elderly consistently suggest that alcohol has a persistent negative impact on cognitive function [25]. Three studies involving older adults in Japan, Sweden, and the United States found no significant association between alcohol consumption and cognitive performance [26]-[28].

Different effects in different cognitive domains might cause these controversial results. Two studies who analyzed the data of Women's Health Initiative and Johns Hopkins Precursors show a U-shaped curve relationship between alcohol intake and language competence. Another study of elderly Japanese men shows the impairment of abstraction and judgment domain in abstainers [28].

These conflicting results indicated that there is a more complex relationship between drinking and cognition. Therefore, further research into the relationship between alcohol and cognitive function is warranted. In addition to

*Corresponding author: ziyanglu@unc.edu

the different cognitive domains differ in their sensitivity to alcohol, dietary may be another important factor. Diet can affect cognition, and there is also a two-way interaction between alcohol and diet. This suggests that an interaction effect may occur between certain dietary habits and alcohol consumption in their effects on cognition.

Longitudinal data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) was used to evaluate the association between alcohol drinking behavior and cognitive function (different cognitive domains) in elders through linear mixed effects model (LMM), while adjusting for a range of lifestyle-related and disease factors.

2. Methods

2.1 Study design and population

This study employed a longitudinal cohort design with data derived from the Chinese Longitudinal Healthy Longevity Survey (CLHLS). The CLHLS, jointly conducted by the Center for Healthy Aging and Development Studies at Peking University and Duke University. The survey covered 23 provinces in China (Liaoning, Jilin, Heilongjiang, Hebei, Beijing, Tianjin, Shanxi, Shaanxi, Shanghai, Jiangsu, Zhejiang, Anhui, Fujian, Jiangxi, Shandong, Henan, Hubei, Hunan, Guangdong, Guangxi, Sichuan, Chongqing, Hainan), with respondents aged 65 and above and adult children aged 35-64. The baseline survey was conducted in 1998, followed by 7 waves of follow up in 2000, 2002, 2005, 2008-2009, 2011-2012, 2014, and 2017-2018.

To take a longitudinal view, we use the CLHLS data from 2008-2018. In the 2008 wave, the study initially included 16,954 subjects. The situation after exclusion criteria have been implemented is shown in Figure 1. Exclusion criteria were as follows. Subjects with more than 10 missing data were considered as low-quality data and were excluded. Other missing data are filled by multiple imputation methods. Only subjects older than 65 years old were included into the analysis. Subjects with a MMSE score below 3.0 were considered to have not completed the test and were excluded.

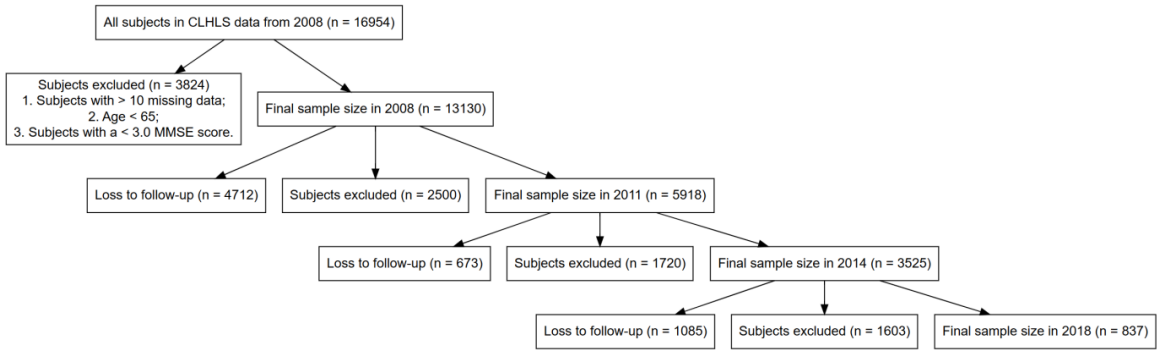

Figure 1: The situation after exclusion criteria

After applying the inclusion and exclusion criteria, the final sample size was 13,130. In the 2011 wave, 8,418 subjects were initially followed up, and the final sample size was 5,918. For the 2014 wave, 5,245 subjects were initially followed up, with the final sample size reduced to 3,525. In the 2018 wave, starting with 2,440 subjects, the final sample size was 837.

2.2 Measurement of cognitive functions

Cognitive function was evaluated annually in 2008, 2011, 2014 and 2018, using the Chinese version of standardized test Mini-Mental State Examination (MMSE, Table 1). It is important to note that this version of the MMSE has been modified from the standardized international version. These assessments provided total cognitive function scores as well as sub-scores across five cognitive domains, includes orientation, registration, attention and calculation, recall and language.

2.3 Measurement of alcohol consumption

Data on alcohol consumption were collected through structured questionnaires. Two alcohol-related questions were selected: “Do you drink alcohol at the present time?”, and “Did you drink alcohol in the past?”. Based on the responses, alcohol intake was categorized into four groups: non-drinker (drinking neither in the past nor at present), new drinker (drink at present but not in the past), former drinking (drink in the past but not at present), and persistent drinker (drink both in the past and at present).

Table 1 The Chinese version of standardized test mini-mental state examination

Cognitive domain	Question	Score
Orientation	**1.** What time of day is it right now (morning, afternoon, evening)?	1
	2. What is the month (Western or Chinese calendar) right now?	1
	3. What is the date (Chinese calendar day and month) of the mid-autumn festival?	1
	4. What is the season right now, spring, summer, fall, winter?	1
	5. What is the name of this district or town?	1

Registration	**6.** Please name as many kinds of food as possible in 1 minute. (1 point for each answer, 7 points max)	7
	7. I am now going to test your memory. I will mention three objects (***table, apple, clothes***). Please repeat these three objects.	3
Attention and calculation	**8.** I will ask you to spend 3 dollars from 20 dollars, then you must spend 3 dollars from the number you arrived at and continue to spend 3 dollars until you are asked to stop. (1 point for each correct answer, 5 points max)	5
	9. Ask the interviewee to draw the figure on B Card.	1
Recall	**10.** Please repeat the three words (in any order) that I asked you to repeat a little while ago.	3
Language	**11.** Give the interviewee a ***pen*** and then a ***watch*** and ask what these objects are called (1 point for each correct answer).	2
	12. I will now ask you to repeat the following sentence: "What you plant, what you will get."	1
	13. I will give you a piece of paper. You must take the paper using your ***right hand***, ***fold*** it in the middle using both hands, and place the paper ***on the floor***. (1 score for each correct action)	3

2.4 Covariates (socio-demographic and health related characteristics?)

Additionally, data on potential confounding variables were collected, covering a range of demographic, lifestyle, and health-related factors. Demographic variables included gender, age, education level, marital status (married and living with spouse, married but not living with spouse, divorced, widowed, never married), and residence (urban or rural). Health-related variables included self-reported conditions such as hypertension, diabetes, heart disease, stroke, and cancer. Lifestyle factors comprised smoking status, fish intake, meat intake, vegetable intake, and fruit intake. Dietary variables (fish, meat, vegetable, fruit) are divided into five categories based on how often the food is consumed at present, includes almost every day, not every day but at least once per week, not every week but at least once per month, not every month but occasionally, and rarely or never. Other variables included ability to perform daily activities which assessed the need for assistance with tasks including bathing, dressing, toileting, continence, feeding, and washing clothes.

2.5 Statistical analysis

The data were analyzed by using R (R version 4.4.1 "race for your life" for X86_64, RStudio version 2024.09.0 + 375). The basic characteristics of the sample were summarized by descriptive statistics, including age, gender, and education level, such as means and standard error of the mean (SEM) of cognitive function scores across different alcohol consumption groups were estimated. To investigate the impact of alcohol consumption on changes in cognitive function, a Linear Mixed Model (LMM) was employed. This model incorporated random effects to account for individual variability and fixed effects include alcohol consumption, time (year of follow-up), and other covariates such as age, gender, and education level. All data were entered into the LMM model, regardless of loss to follow-up. Backward selection was deployed to select from all possible covariates pool to get the final model. Additionally, model diagnostics were performed to assess the goodness-of-fit, including examining the distribution of residuals and the validity of random effects. Multiple imputation was performed to address missing data.

3. Results

3.1 Characteristics of participants

The baseline characteristics of the participants varied significantly across the four groups: non-drinkers (n = 9,152), new drinkers (n = 447), former drinkers (n = 1,849), and persistent drinkers (n = 2,074) (**Table 2**). Persistent drinkers had the highest proportion of males (80.9%), were younger (average age 81.9 years), had higher MMSE scores (median 28), and more years of education (average 3.37 years) compared to non-drinkers, who had 32.6% males, a mean age of 85.7 years, a median MMSE score of 27, and a mean education of 1.98 years ($p < 0.001$ for all comparisons). Differences in dietary habits are also shown in Table 1; persistent drinkers reported higher daily intakes of fish (9.0%), and tea (45.1%) compared to non-drinkers (7.6% and 28.9%, respectively). The ability to stand up without assistance was most common among persistent drinkers (81.0%) and least common among non-drinkers (71.6%). The prevalence of stroke or cardiovascular disease (CVD) was highest among former drinkers (8.7%) and lowest among persistent drinkers (3.5%) ($p < 0.001$ for all comparisons).

Table 2 Basic Information

	Non-drinker N = 9,152	**New drinker N = 447**	**Former Drinker N = 1,849**	**Persistent Drinker N = 2,074**	**p-value**
Sex					< 0.001
Male	2984 (32.6%)	270 (60.4%)	1402 (75.8%)	1678 (80.9%)	
Female	6168 (67.4%)	177 (39.6%)	447 (24.2%)	396 (19.1%)	
Age[1]	85.7 (11.7)	82.8 (10.3)	84.4 (10.5)	81.9 (12.3)	< 0.001
MMSE score[2]	27.0 (22.0, 29.0)	28.0 (25.0, 30.0)	27.0 (23.0, 29.0)	28.0 (25.0, 30.0)	< 0.001
Fruit intake					0.035

Everyday or almost everyday	1,217 (13.3%)	64 (14.3%)	254 (13.7%)	243 (11.7%)	
Quite often	2,437 (26.6%)	102 (22.8%)	490 (26.5%)	606 (29.2%)	
Occasionally	3,448 (37.7%)	184 (41.2%)	663 (35.9%)	743 (35.8%)	
Rarely or never	2,050 (22.4%)	97 (21,7%)	442 (23.9%)	482 (23.2%)	
Vegetables intake at present					< 0.001
Everyday or almost everyday	5,766 (63.0%)	328 (73.4%)	1,171 (63.3%)	1,359 (65.5%)	
Quite often	2,359 (25.8%)	90 (20.1%)	464 (25.1%)	541 (26.1%)	
Occasionally	853 (9.3%)	25 (5.6%)	178 (9.6%)	143 (6.9%)	
Rarely or never	174 (1.9%)	4 (0.9%)	36 (1.9%)	31 (1.5%)	
Meat intake at present					< 0.001
Almost everyday	2,490 (27.2%)	135 (30.2%)	524 (28.3%)	664 (32.0%)	
At least once per week	3,524 (38.5%)	172 (38.5%)	746 (40.3%)	851 (41.0%)	
At least once per month	1,111 (12.1%)	54 (12.1%)	197 (10.7%)	222 (10.7%)	
Occasionally	1,030 (11.3%)	51 (11.4%)	200 (10.8%)	193 (9.3%)	
Rarely or never	997 (10.9%)	35 (7.8%)	182 (9.8%)	144 (6.9%)	
Fish intake at present					< 0.001
Almost everyday	698 (7.6%)	42 (9.4%)	120 (6.5%)	187 (9.0%)	
At least once per week	2,984 (32.6%)	152 (34.0%)	567 (30.7%)	777 (37.5%)	
At least once per month	1,777 (19.4%)	92 (20.6%)	392 (21.2%)	413 (19.9%)	
Occasionally	1,580 (17.3%)	79 (17.7%)	344 (18.6%)	368 (17.7%)	
Rarely or never	2,113 (23.1%)	82 (18.3%)	426 (23.0%)	329 (15.9%)	
Tea intake at present					< 0.001
Almost everyday	2,643 (28.9%)	201 (45.0%)	753 (40.7%)	936 (45.1%)	
At least once per week	533 (5.8%)	25 (5.6%)	113 (6.1%)	133 (6.4%)	
At least once per month	256 (2.8%)	17 (3.8%)	54 (2.9%)	51 (2.5%)	
Occasionally	726 (7.9%)	28 (6.3%)	156 (8.4%)	149 (7.2%)	
Rarely or never	4,994 (54.6%)	176 (39.4%)	773 (41.8%)	805 (38.8%)	
Years of education[1]	1.98 (3.42)	2.88 (3.98)	2.95 (3.75)	3.37 (3.80)	< 0.001
Current marital status					
Married and living with spouse	2,893 (32%)	207 (46%)	767 (41%)	1,001 (48%)	
Divorced	30 (0.3%)	2 (0.4%)	6 (0.3%)	7 (0.3%)	
Widowed	6,023 (66%)	231 (52%)	1,006 (54%)	969 (47%)	
Never married	68 (0.7%)	1 (0.2%)	26 (1.4%)	31 (1.5%)	
Able to use chopsticks					< 0.001
Yes	8,754 (95.7%)	442 (98.9%)	1,774 (95.9%)	2,033 (98.0%)	
No	398 (4.3%)	5 (1.1%)	75 (4.1%)	41 (2.0%)	
Stand up from a chair					< 0.001
Yes	6,557 (71.6%)	364 (81.4%)	1,342 (72.6%)	1,679 (81.0%)	
Hand assistance	2,103 (23%)	70 (15.7%)	399 (21.6%)	329 (15.9%)	
No	492 (5.4%)	13 (2.9%)	108 (5.8%)	66 (3.2%)	
Stroke or CVD					< 0.001
Yes	479 (5.2%)	19 (4.3%)	160 (8.7%)	72 (3.5%)	
No	8,673 (94.8%)	428 (95.7%)	1,689 (91.3%)	2,002 (96.5%)	

[1] Standard error of the mean (SEM); [2] Median (IQR)

3.2 Associations between alcohol drinking patterns and MMSE scores

The cognitive function was evaluated through MMSE scores. After adjusting for age and sex, significant differences in total MMSE scores were observed among the different alcohol consumption groups. Persistent drinkers had notably lower MMSE scores compared to non-drinkers, with an estimate difference of -3.02 (95% CI: -4.45 to -1.59, $p < 0.001$). No significant difference was found in MMSE scores between former and new drinkers compared to non-drinkers (**Table 3**). After

further adjusting sex, age, dietary intake (including fruit, vegetables, fish, and tea), education, stand up from a chair and stroke or CVD, the rate of cognitive decline in persistent drinkers remained high, with an estimate of -3.02 (95% CI: -4.45 to -1.59, $p < 0.001$). The interaction between time and alcohol consumption indicated that persistent drinkers experienced a higher rate of cognitive decline compared to non-drinkers, with an interaction term estimate of 0.04 (95% CI: 0.00 to 0.08, $p = 0.054$). Former drinkers and new drinkers did not show difference significantly interactions with time, suggesting that their rates of cognitive decline were comparable to those of non-drinkers (**Table 4**).

Table 3 Associations between alcohol drinking patterns and MMSE scores

Predictors	**MMSE Score Total**		
	Estimates	***CI***	***p***
Alcohol			
New drinker	-0.32	-2.98 – 2.34	0.812
Former drinker	-1.25	-2.77 – 0.28	0.110
Persistent drinker	-3.02	-4.45 – -1.59	**< 0.001**
Year	0.00	-0.03 – 0.02	0.847
Sex = Female	-1.42	-1.59 – -1.26	**< 0.001**
Age	-0.19	-0.20 – -0.19	**< 0.001**
Interactions			
Persistent drinker × Female	-0.65	-1.06 – -0.18	**0.006**
Persistent drinker × Age	0.04	0.02 – 0.06	**< 0.001**

Several significant factors were identified in the examination of cognitive function in relation to alcohol drinking patterns (**Table 4**). Male participants showed higher cognitive scores than females ($p < 0.001$), and younger age was associated with better cognitive function ($p < 0.001$). Persistent drinkers had lower MMSE scores compared to other drinkers ($p < 0.001$). Regular intake of fruit and vegetables, higher education levels, the ability to stand up from a chair independently, frequent consumption of fish and tea, and the absence of stroke or cardiovascular disease were all associated with better cognitive scores ($p < 0.001$). It is worth mentioning that, comparing to those whose vegetable intake is low, the subjects with high vegetable intake are actually more susceptible to alcohol induced cognitive decline (95% CI: -0.49 to -0.17, $p < 0.001$). These findings underscore the complex interplay between alcohol consumption patterns and cognitive function, moderated by various demographic, lifestyle, and health-related factors.

Table 4 Associations between alcohol drinking patterns, covariates, and MMSE scores

Predictors	**MMSE Score Total**		
	Estimates	***Confidence Interval***	***p-value***
Alcohol			
New drinker	2.81	-0.16 – 5.77	0.063
Former drinker	-0.04	-1.53 – 1.46	0.963
Persistent drinker	-2.86	-4.37 – -1.35	**< 0.001**
Year	-0.02	-0.04 – 0.00	**0.036**
2008 score	0.74	0.73 – 0.75	**< 0.001**
2008 age	-0.04	-0.04 – -0.03	**< 0.001**
Edu year	0.01	0.00 – 0.03	**0.023**
Stroke or CVD = No	0.61	0.45 – 0.76	**< 0.001**
Current marital status	-0.02	-0.05 – 0.01	0.112
Stand up from a chair			
Hand assistance	-0.17	-0.28 – -0.05	**0.004**
No	-0.36	-0.57 – -0.15	**0.001**
Sex = Female	-0.32	-0.42 – -0.23	**< 0.001**
Able to use chopsticks = No	-0.89	-1.12 – -0.66	**< 0.001**
Dietary			
Vegetables intake at present	0.26	0.20 – 0.33	**< 0.001**
Fruit intake at present	0.14	0.10 – 0.19	**< 0.001**
Fish intake at present	0.08	0.04 – 0.11	**< 0.001**
Tea intake at present	0.03	0.01 – 0.06	**0.003**
Interactions			
New drinker × YEAR	-0.02	-0.12 – 0.08	0.653
Former drinker × YEAR	0.01	-0.03 – 0.06	0.622
Persistent drinker × YEAR	0.04	-0.00 – 0.08	0.054
New drinker × 2008 score	-0.06	-0.11 – -0.00	**0.046**
Persistent drinker × 2008 score	0.03	0.00 – 0.06	**0.031**
Persistent drinker × 2008 age	0.02	0.01 – 0.03	**0.004**
Persistent drinker × Vegetables intake at present	-0.33	-0.49 – -0.17	**< 0.001**

3.3 Associations between alcohol drinking patterns and scores of four cognitive domains

The associations between alcohol drinking patterns and cognitive domains, as measured by the MMSE, revealed several significant findings (**Table 5**). The results indicated that persistent drinkers showed significantly lower scores in orientation (-0.94, 95% CI: -1.73 to -0.15, $p = 0.019$), attention and calculation (-1.19, 95% CI: -1.88 to -0.49, $p = 0.001$), and recall (-0.81, 95% CI: -1.27 to -0.34, $p = 0.001$) compared to non-drinkers, and experienced a faster rate of cognitive decline in attention

and calculation (interaction term estimate of 0.03, 95% CI: 0.01 to 0.04, p = 0.008). New drinkers showed higher registration scores (0.77, 95% CI: 0.08 to 1.46, p = 0.029), while no significant differences were observed in other cognitive domains for former and new drinkers compared to non-drinkers.

Table 5 Associations between alcohol drinking patterns and different cognitive domains

Predictors	**Orientation**			**Registration**			**Attention and Calculation**		
	Estimates	***Confidence Interval***	***p-value***	***Estimates***	***Confidence Interval***	***p-value***	***Estimates***	***Confidence Interval***	***p-value***
ND[1]	0.15	-1.39 – 1.69	0.849	0.77	0.08 – 1.46	**0.029**	0.48	-0.87 – 1.83	0.488
FD[2]	-0.30	-1.08 – 0.49	0.458	-0.07	-0.42 – 0.27	0.680	0.26	-0.43 – 0.95	0.459
PD[3]	-0.94	-1.73 – -0.15	**0.019**	-0.13	-0.48 – 0.22	0.475	-1.19	-1.88 – -0.49	**0.001**
Year	-0.02	-0.03 – -0.01	**0.002**	0.00	-0.00 – 0.01	0.082	-0.02	-0.03 – -0.01	**< 0.001**
2008 score	0.23	0.22 – 0.23	**< 0.001**	0.08	0.08 – 0.08	**< 0.001**	0.22	0.21 – 0.22	**< 0.001**
2008 age	-0.02	-0.02 – -0.02	**< 0.001**	-0.00	-0.00 – -0.00	**< 0.001**	-0.01	-0.01 – -0.01	**< 0.001**
ND[1] × Year	0	-0.05 – 0.05	0.936	-0.01	-0.04 – 0.01	0.296	0.00	-0.04 – 0.05	0.940
FD[2] × Year	0.01	-0.02 – 0.03	0.578	-0.00	-0.01 – 0.01	0.487	0.01	-0.01 – 0.03	0.445
PD[3] × Year	0.01	-0.01 – 0.04	0.183	0.00	-0.01 – 0.01	0.789	0.03	0.01 – 0.04	**0.008**

[1] New Drinker; [2] Former Drinker; [3] Persistent Drinker

Predictors	**Recall**			**Language**		
	Estimates	***Confidence Interval***	***p-value***	***Estimates***	***Confidence Interval***	***p-value***
ND[1]	0.56	-0.38 – 1.41	0.233	0.88	0.10 – 1.65	**0.026**
FD[2]	0.08	-0.35 – 0.55	0.742	0.04	-0.36 – 0.43	0.860
PD[3]	-0.81	-1.27 – -0.34	**0.001**	0.18	-0.21 – 0.58	0.365
Year	0	-0.00 – 0.01	0.114	0.01	0.00 – 0.01	**0.005**
2008 score	0.11	0.11 – 0.11	**< 0.001**	0.11	0.11 – 0.12	**< 0.001**
2008 age	-0.00	-0.01 – -0.00	**< 0.001**	-0.00	-0.00 – -0.00	**< 0.001**
ND[1] × Year	-0.02	-0.05 – 0.01	0.197	0.01	-0.02 – 0.03	0.622
FD[2] × YEAR	0.00	-0.01 – 0.01	0.973	0.00	-0.01 – 0.01	0.968
PD[3] × YEAR	0.00	-0.01 – 0.02	0.695	-0.00	-0.01 – 0.01	0.654

[1] New Drinker; [2] Former Drinker; [3] Persistent Drinker

3.4 Associations between alcohol and vegetable intake with current meat consumption

The association between drinking and current meat intake was examined by the LMM (**Table 6)**. Compared to non-drinkers, both former and persistent drinkers exhibited a statistically significant positive association with meat intake, with former drinkers showing an estimate of 0.09 (95% CI: 0.04–0.14, p < 0.001) and persistent drinkers a higher estimate of 0.17 (95% CI: 0.12–0.21, p < 0.001). However, no significant association was found between new drinkers and meat intake, with an estimate of 0.05 (95% CI: -0.03–0.14, p = 0.228). In contrast, vegetable intake was negatively associated with meat intake, with an estimate of -0.21 (95% CI: -0.23–-0.19, p < 0.001), suggesting that individuals who consume more vegetables tend to have lower meat intake.

Table 6 Alcohol and vegetable intake in relation to meat intake

Predictors	**Meat intake at present**		
	Estimates	***Confidence Interval***	***p-value***
Alcohol			
New drinker	0.05	-0.03 – 0.14	0.228
Former drinker	0.09	0.04 – 0.14	**< 0.001**
Persistent drinker	0.17	0.12 – 0.21	**< 0.001**
Vegetable intake at present	-0.21	-0.23 – -0.19	**< 0.001**

4. Discussion

Our study on longitudinal data on Chinese elderly found that alcohol drinking patterns were closely associated to cognitive function during the four-follow-up period of ten years between 2008-2018. Long-term negative impact was observed among persistent drinkers, with a steeper slope of decline in cognitive function in persistent drinkers than non-drinkers. Short-term positive impact on cognitive function among new drinkers was also observed.

The findings of this study regarding the relationship between continuous drinking and cognitive function align with those of previous research. In particular, Koch M. et al.'s research found association between at-risk drinking status (having over 14 drinks per week) and worse performance among American elderly. Previous research concluded that excessive alcohol intake was associated with hyaline arteriolosclerosis and neurofibrillary tangles, leading to increased risk of Alzheimer's disease and related dementia. Meanwhile, no significant difference was observed in cognitive decline between former drinkers and non-drinkers, this indicates that alcohol abstinence may restore cognitive function, which is consistent with the results of Drake AI et al. Bernardin F et al.'s research also acknowledges the restorative effect of alcohol abuse on cognitive function, but they believe that impaired cognitive function may persist partially.

Multiple studies indicated that higher vegetable intake is correlated to lower cognitive impairment risk. But our result had shown that subjects with high vegetable intake were more susceptible to alcohol induced cognitive decline. We assumed that the dietary habit is the main cause of this paradox. It is essential to highlight that Vitamin B12 plays a crucial role in cognitive functions, acting as a protective factor. Virtually all the vitamin B12 is obtained from eggs, meat and fermented foods. However, according to the dietary habit of the Chinese

elderly, more vegetable intake was usually correlated to less meat intake. Our result also supported this conclusion. Making matters worse, alcohol could affect the absorption of vitamin B12. This suggests to us that when alcohol intake is combined with a dominating vegetable diet, its negative impact on cognitive functions may deteriorate because of the lack of vitamin B12. Thus, the supplementation of vitamin B12 may be restorative. Furthermore, it raises the question of whether alcohol directly causes cognitive decline or if it does so indirectly by impairing vitamin B12 absorption. Research on this issue could contribute to the clinical management of alcohol-induced cognitive decline.

It is also interesting to notice that for new drinkers, higher baseline MMSE score was related to faster decline rate of cognitive functions. But for persistent drinkers, higher baseline score signifies a slower decline rate of cognitive functions. This might be related to different population backgrounds of alcohol tolerance between groups. For those who experience chronic alcohol use while have a high MMSE score, multiple protective factors have a great possibility to be possessed by the subjects such as high ALDH level. And the population with protective factors is less susceptible to alcohol use. Its overlap with the high-baseline-group population results in the slower decline rate of cognitive functions in persistent drinkers. However, more evidence is needed to support this inference.

Another important finding in our research is that the effects of alcohol in different domains were not consistent according to our analysis. For the persistent drinkers, significant negative correlation was only observed in orientation, attention and calculation, and recall. Meanwhile, significant positive correlation was observed in the rest of the domains, registration and language. We did not find such association in all five cognitive domains among abstainers. Multiple studies have shown that moderate drinking has a positive impact on cognitive function, which agrees with our results to some extent. At present, research on the relationship between alcohol consumption and various cognitive domains is insufficient. Due to the fact that the cognitive domains affected positively and negatively do not overlap, it was speculated that the positive effects of alcohol on registration and language are short-term, while long-term alcohol consumption can still cause damage to other cognitive domains.

With an investigation of 13,751 Chinese elderly aged over 65, our study has high representativeness in studying the association between alcohol intake and cognitive function. We conducted a more detailed study by employing domain-specific cognitive profiling and obtained significant results, which cast new light on the pathophysiological impact of alcohol on neural circuits involved in cognition. However, our study has several limitations. Firstly, it lacks data in the survey that can clearly standardize the amount and type of alcohol drinks consumed, therefore it poses difficulties for us to draw conclusions related to these factors. Secondly, although we controlled for the main factors that were strongly associated with cognitive level, there might be other underlying factors that were not taken into consideration. Finally, as we excluded a small amount of people who were thought to have dementia, it may have caused some deviation in the results we obtained. With the growing trend of Alzheimer's disease and related neurodegenerative diseases increasing every year, we urgently need comprehensive research on the effects of alcohol on brain function.

5. Conclusion

In summary, our study demonstrates that continuous alcohol intake is significantly associated with accelerated cognitive decline, specifically impacting the neural circuits of orientation and recall. From a biomedical perspective, the unexpected interaction between high vegetable intake and alcohol-induced impairment suggests a disruption in micronutrient bioavailability (specifically Vitamin B12). These results emphasize that cognitive health monitoring should integrate bioinformatics-driven risk assessment and metabolic profiling. Future research should focus on the molecular mechanisms of alcohol-diet interactions to develop targeted biomedical interventions for neurodegenerative disease prevention.

Acknowledgement

Jiaxi Han and Ziyang Lu contributed equally to this work and should be considered co-first authors.

References

1. Tay LX, Ong SC, Tay LJ, Ng T, Parumasivam T. Economic Burden of Alzheimer's Disease: A Systematic Review. Value Health Reg Issues. 2024 Mar; 40: 1-12. doi: 10.1016/j.vhri.2023.09.008. Epub 2023 Nov 14.
2. [Blue paper on Alzheimer's disease in China (simplified version)]. Zhonghua Yi Xue Za Zhi. Jul 30 2024;104(29):2701-2727. doi:10.3760/cma.j.cn12137-20240416-00883
3. Network GBoDC. Global Burden of Disease Study 2019 (GBD 2019) Disease and Injury Burden 1990-2019. 2020.
4. Bouajila N, Domenighetti C, Aubin HJ, Naassila M. Alcohol consumption and its association with cancer, cardiovascular, liver and brain diseases: a systematic review of Mendelian randomization studies. Front Epidemiol. 2024 Nov 7; 4: 1385064. doi: 10.3389/fepid.2024.1385064.
5. Egervari G, Siciliano CA, Whiteley EL, Ron D. Alcohol and the brain: from genes to circuits. Trends Neurosci. Dec 2021;44(12):1004-1015. doi:10.1016/j.tins.2021.09.006
6. Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. Alcohol Clin Exp Res. May 1997;21(3):521-9. doi:10.1111/j.1530-0277.1997.tb03798.x

7. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. Sep 2004;256(3):183-94. doi:10.1111/j.1365-2796.2004.01388.x
8. He J, Crews FT. Increased MCP-1 and microglia in various regions of the human alcoholic brain. Exp Neurol. Apr 2008;210(2):349-58. doi:10.1016/j.expneurol.2007.11.017
9. Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. Alcohol Alcohol. Mar-Apr 2009;44(2):115-27. doi:10.1093/alcalc/agn079
10. Harper C. The neuropathology of alcohol-related brain damage. Alcohol Alcohol. Mar-Apr 2009;44(2):136-40. doi:10.1093/alcalc/agn102
11. Thomson AD, Guerrini I, Marshall EJ. The evolution and treatment of Korsakoff's syndrome: out of sight, out of mind? Neuropsychol Rev. Jun 2012;22(2):81-92. doi:10.1007/s11065-012-9196-z
12. Zakhari S. Alcohol metabolism and epigenetics changes. Alcohol Res. 2013;35(1):6-16.
13. Florence L, Lassi DLS, Kortas GT, Lima DR, de Azevedo-Marques Périco C, Andrade AG, Torales J, Ventriglio A, De Berardis D, De Aquino JP, Castaldelli-Maia JM. Brain Correlates of the Alcohol Use Disorder Pharmacotherapy Response: A Systematic Review of Neuroimaging Studies. Brain Sci. 2022 Mar 14;12(3):386. doi: 10.3390/brainsci12030386. PMID: 35326342; PMCID: PMC8946664.
14. Baltariu IC, Enea V, Kaffenberger J, Duiverman LM, Aan Het Rot M. The acute effects of alcohol on social cognition: A systematic review of experimental studies. Drug Alcohol Depend. 2023 Apr 1;245:109830. doi: 10.1016/j.drugalcdep.2023.109830. Epub 2023 Mar 2. PMID: 36907121.
15. Tolentino NJ, Wierenga CE, Hall S, et al. Alcohol effects on cerebral blood flow in subjects with low and high responses to alcohol. Alcohol Clin Exp Res. Jun 2011;35(6):1034-40. doi:10.1111/j.1530-0277.2011.01435.x
16. Patel S, Behara R, Swanson GR, Forsyth CB, Voigt RM, Keshavarzian A. Alcohol and the Intestine. Biomolecules. Oct 15 2015;5(4):2573-88. doi:10.3390/biom5042573
17. Osna NA, Kharbanda KK. Multi-Organ Alcohol-Related Damage: Mechanisms and Treatment. Biomolecules. Apr 15 2016;6(2)doi:10.3390/biom6020020
18. Yan C, Hu W, Tu J, Li J, Liang Q, Han S. Pathogenic mechanisms and regulatory factors involved in alcoholic liver disease. J Transl Med. May 4 2023;21(1):300. doi:10.1186/s12967-023-04166-8
19. Wang G, Li DY, Vance DE, Li W. Alcohol Use Disorder as a Risk Factor for Cognitive Impairment. J Alzheimers Dis. 2023;94(3):899-907. doi: 10.3233/JAD-230181.
20. Listabarth S, Groemer M, Waldhoer T, Vyssoki B, Pruckner N, Vyssoki S, Glahn A, König-Castillo DM, König D. Cognitive decline and alcohol consumption in the aging population-A longitudinal analysis of the Survey of Health, Ageing and Retirement in Europe. Eur Psychiatry. 2022 Nov 18;65(1):e83. doi: 10.1192/j.eurpsy.2022.2344.
21. Zarezadeh M, Mahmoudinezhad M, Faghfouri AH, Mohammadzadeh Honarvar N, Regestein QR, Papatheodorou SI, Mekary RA, Willett WC. Alcohol consumption in relation to cognitive dysfunction and dementia: A systematic review and dose-response meta-analysis of comparative longitudinal studies. Ageing Res Rev. 2024 Sep;100:102419. doi: 10.1016/j.arr.2024.102419. Epub 2024 Jul 20.
22. Visontay R, Rao RT, Mewton L. Alcohol use and dementia: new research directions. Curr Opin Psychiatry. Mar 1 2021;34(2):165-170. doi:10.1097/yco.0000000000000679
23. Wang Z, Pang Y, Liu J, Wang J, Xie Z, Huang T. Association of healthy lifestyle with cognitive function among Chinese older adults. Eur J Clin Nutr. Feb 2021;75(2):325-334. doi:10.1038/s41430-020-00785-2
24. Zhang Y, Li Y, Zheng X, Zhu L, Xu B. Association between alcohol consumption in midlife and cognitive function in old age: Findings from the China health and Nutrition Survey. Nutr Metab Cardiovasc Dis. Oct 28 2021;31(11):3044-3053. doi:10.1016/j.numecd.2021.07.023
25. Woods AJ, Porges EC, Bryant VE, et al. Current Heavy Alcohol Consumption is Associated with Greater Cognitive Impairment in Older Adults. Alcohol Clin Exp Res. Nov 2016;40(11):2435-2444. doi:10.1111/acer.13211
26. Hogenkamp PS, Benedict C, Sjögren P, Kilander L, Lind L, Schiöth HB. Late-life alcohol consumption and cognitive function in elderly men. Age (Dordr). Feb 2014;36(1):243-9. doi:10.1007/s11357-013-9538-7
27. Kalapatapu RK, Ventura MI, Barnes DE. Lifetime alcohol use and cognitive performance in older adults. J Addict Dis. Jan-Mar 2017;36(1):38-47. doi:10.1080/10550887.2016.1245029
28. Siddiquee AT, Kadota A, Fujiyoshi A, et al. Alcohol consumption and cognitive function in elderly Japanese men. Alcohol. Jun 2020;85:145-152. doi:10.1016/j.alcohol.2020.01.001