Alcohol Consumption and Mild Cognitive Impairment: A Mendelian Randomization Study from Rural China

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Abstract

Background: Alcohol consumption has been associated with risk of Mild Cognitive Impairment (MCI) in observational studies. The result is inconsistent and whether the association is causal remains unknown.

Objective: To examine the causal effect of alcohol consumption on MCI in rural China.

Methods: This study used a cross-sectional dataset included 1,966 observations collected in rural China, of which 235 observations' genotyping were collected. All participants accepted mild cognitive impairment evaluation used Mini-Cog. We collected the frequency and intensity of participants' alcohol consumption behaviour. The causal effect of alcohol consumption on MCI was investigated by Mendelian randomization (MR) of genetic variation in aldehyde dehydrogenase 2 (*ALDH2* rs671) gene.

Results: The risk of MCI in Chinese rural area was 50.36%. Moreover, the risk of MCI was the higher in central China, followed by northeast China, northwest China and eastern China. Alcohol consumption was causally associated with a higher risk of MCI under MR design. Parameter estimates of drinking or not (b = 0.271, p = 0.007, 95% CI = 0.073 to 0.469), the number of drinking times during the past 30 days (b = 0.016, p = 0.003, 95% CI = 0.005 to 0.027), and the weekly ethanol consumption (b = 0.132, p = 0.004, 95% CI = 0.042 to 0.223) were all positive and statistically significant at the 5% level. Further investigations are needed to clarify the potential underlying mechanisms.

Conclusion: There was a high risk of MCI in rural China. Alcohol consumption was causally associated with a higher risk of MCI.

Keywords: alcohol consumption, Mild Cognitive Impairment, Mendelian Randomization, rural China

INTRODUCTION

Dementia has been a major public health problem (Fred Plum, 1979). There are currently 50 million people living with dementia worldwide, and this number will more than triple to 152 million by 2050 (Christina Patterson, 2018). The combined cost of healthcare and loss of earnings caused by dementia has reached $1trillion (USD) per year and is expected to rise to $2 trillion by 2030 (Christina Patterson, 2018). Considering Alzheimer's disease (AD) in particular, there is no curative treatment for AD, and clinical drug trials in the past decade have had a 99.6% failure rate (Jeffrey L Cummings et al., 2014, Lon S Schneider et al., 2014). One contributor to this high failure rate is the fact that brain pathology begins years before onset of objective cognitive symptoms and may be irreversible by the time of diagnosis (Reisa A Sperling et al., 2013). These depressing statistics have led many researchers to switch their focus toward delaying dementia in persons who are in preclinical phases of the disease.

Mild cognitive impairment (MCI) represents the preclinical, transitional stage between healthy aging and dementia and represents what researchers and clinicians view as a "window" in which it may be possible to intervene and delay progression to dementia (Nicole D Anderson, 2019). MCI means various disorders of mind or intellectual activity, such as sensation, perception, memory, language, etc. It is a sign of brain dysfunction and is also one manifestation of normal brain ageing (American Psychiatric Association, 2013, Serge Gauthier et al., 2006,

Perminder S Sachdev et al., 2014). However, population with MCI will progress to dementia faster than age-matched healthy controls (Katie Palmer et al., 2003). Moreover, MCI is believed to precede dementia as an earlier state (Hongwei Nie et al., 2011). Therefore, it is very important to prevent and treat chronic aging diseases such as MCI.

The prevalence rate of MCI reported varies greatly. Studies from America, Australia, Bulgaria, Japan, and Mexico reported that the prevalence rate of MCI ranges from 6.5% to 39.1% (Ivan Dimitrov et al., 2012, Teresa Juarez-Cedillo et al., 2012, Mindy J Katz et al., 2012, Ronald C Petersen et al., 2010, Perminder S Sachdev et al., 2012, Kristine Yaffe et al., 2011). In case of China, the study of MCI has been taken in some large cities such as Shanghai and Beijing, which found the prevalence rate of MCI ranges from 2.4% and 35.9% (Hongwei Nie, Yong Xu, Bin Liu, Yaodong Zhang, Ting Lei, Xiaoping Hui, Ling Zhang and Yan Wu, 2011). Age-related diseases are becoming more common as the number of elderly people in rural China grows rapidly (Shulin Chen et al., 2014). However, there are few studies in Chinese rural areas. The rural population accounts for one third of China's population and their health is worse than urban people. It should be the concerned the prevalence of MCI in Chinese rural areas.

There are many studies that have analyzed the risk factors associated with MCI, such as age, gender, educational level and cardiovascular risk factors (Sylvaine Artero et al., 2008, Deborah E Barnes and Kristine Yaffe, 2011, Antonio Di Carlo et al., 2000, Sujuan Gao et al., 1998, Brenda L Plassman et al., 2010). Alcohol consumption is considered a possible risk factor for MCI (Huadong Zhou et al., 2003). China is a country with a large production and consumption of alcohol. From World Health Organization (WHO) report, per capita alcohol

consumption in China has been increasing year by year, with an increase of 76%: 4.1 litres in 2005, 7.1 litres in 2010 and 7.2 litres in 2016 (World Health Organization, 2019). The alcohol consumption in rural was nearly 1.4 times higher than in urban areas (Iona Y Millwood et al., 2013). Moreover, alcohol abuse and dependence are common disorders among Chinese rural area (Liang Zhou et al., 2009). Existing research on the relationship between alcohol consumption and MCI remains controversial. A cohort study revealed participants who drank alcohol frequently at midlife were twice as likely to have MCI more than those who drank alcohol infrequently (Tiia Anttila et al., 2004). However, another study indicated light–moderate alcohol drinking decreased risks for dementia in elderly patients with MCI (Gelin Xu et al., 2009). Other studies found no significant association between alcohol consumption and the incidence rate of MCI (Tobias Luck et al., 2010, V Solfrizzi et al., 2007). As far as we know, there are few studies on the impact of alcohol consumption on MCI in China, especially in rural China.

It is difficult to estimate the causal impact of alcohol consumption and MCI using observational data. The observed MCI effects may have reverse causality, meaning that individuals with MCI may deliberately control alcohol intake considering their health condition (Gelin Xu, Xinfeng Liu, Qin Yin, Wusheng Zhu, Renliang Zhang and Xiaobing Fan, 2009). Furthermore, the observed effects may be caused by some confounding factors, such as socio-economic status, dietary habit or other health-related behaviors (Iona Y Millwood, Liming Li, Margaret Smith, Yu Guo, Ling Yang, Zheng Bian, Sarah Lewington, Gary Whitlock, Paul Sherliker and Rory Collins, 2013). Therefore, studying the causal relationship between alcohol

consumption and MCI is of great significance to evaluate the benefits or hazards of drinking alcohol.

Our study aims to to describe the risk of MCI among rural residents in rural China and analyze the causal impact of alcohol consumption on the risk of MCI among rural residents in China. We find instrumental variable (IV) for alcohol consumption, that is, the exogenous variable that affect MCI only through their impacts on alcohol consumption. We investigate the causal effect of alcohol consumption on MCI by using Mendelian Randomization (MR) on the genetic variation of aldehyde dehydrogenase 2 gene (*ALDH2* rs671) . MR is an ingenious causal research design, which uses genes as instrumental variables (Thomas A DiPrete et al., 2018, Amy E Taylor et al., 2015). The MR approach relies on random assignment of genes during meiosis in humans, resembling the random assignment into treatment groups in randomized controlled trials (RCT) (SL Au Yeung et al., 2012, Michael V Holmes et al., 2014, Debbie A Lawlor et al., 2013, Stephanie von Hinke et al., 2016, Liang Zhou, Kenneth R Conner, Michael R Phillips, Eric D Caine, Shuiyuan Xiao, Ruiling Zhang and Yu Gong, 2009). *ALDH2* rs671, our genetic instrument, is shown to have the strongest association with alcohol consumption but don't have association with MCI. Besides, this paper is the first to estimate the causal effects of alcohol drinking on the resulting MCI, at least in the context of rural China.

MATERIALS & METHODS

Sample Collection

This study uses a cross-sectional dataset which collected in rural areas of Xinjiang, Shandong, Henan, Anhui and Heilongjiang provinces in 2019. Using an income-stratified sampling method, 35 counties in total were randomly selected based on their per capita gross value of industrial output. In each selected county, we randomly selected 6 villages. In each village, we randomly enrolled 10 famers and there is a total of 2,355 observations. Before the survey begun, trained investigators explained the purpose and content of the survey to each participant in detail, and told them that their responses were completely voluntary and confidential. If they had any further questions about any aspect of this survey, they could contact the research team at any time. All participants signed an informed consent form. The Institutional Review Board of China Agricultural University approved the protocol.

The survey collected routine demographic and socio-economic status information of participants, such as age, gender, education level, annual family income, as well as personal drinking information of participants.

The survey collected regular demographic and socioeconomic status information of participants, such as age, gender, education level, annual family income, as well as personal alcohol consumption information of participants. In addition, 1 ml saliva samples were collected for genotyping in professional test tubes from part of respondents. A total of 1,966 observations were collected, 235 of which were genotyped, excluding individuals who did not complete the questionnaire and whose quality was not qualified Excluding individuals who failed pass the quality control yielded and didn’t complete the whole questionnaire, a total of

1,966 observations were successfully collected, of which 235 observations were genotyped. As showed in Table 1A, the average age of the respondent in total sample was 50.45 years old, with 7.75 years of educational experience. Table 1B reported the basic characteristic of genetic sample. The average age of respondent in genetic sample was 49.68 years old, with 8.63 years of educational experience. By comparing Table 1A and Table 1B, it is can be seen that there was no significant difference in mainly characteristics between the total sample and the genetic sample, which indicated that the genetic sample was representative of the total sample.

Table 1A
Basic characteristics of sample

Variable	Definition	Observation	Mean	S.D.
Socio-demographic characteristics:				
Male	dummy; 0=female; 1=male	1,966	0.77	0.42
Age	age measure by year	1,966	50.45	10.78
Ethnic minority	dummy; 0=no; 1=yes	1,966	0.19	0.39
Education	educational years	1,966	7.75	3.31
Income	income is taking log	1,966	0.63	2.39
Parents drinker	Number of parents that drink	1,966	0.51	0.61
Drinking behaviors:				
Drinking or not	dummy; 0=no; 1=yes	1,966	0.43	0.50
Drinking times during the past 30 days	drinking times	1,966	7.92	16.24
Weekly ethanol consumption	100g/week	1,966	1.07	2.42
Genetic variants:				
ALDH2 (rs671)	AA/AG	81	34.47%	-
	GG	154	65.53%	-

Table 1B
Basic characteristics of gene's sample

Variable	Definition	Observation	Mean	S.D.
Socio-demographic characteristics:				
Male	dummy; 0=female; 1=male	235	0.78	0.42
Age	age measure by year	235	49.68	11.25

Ethnic minority	dummy; 0=no; 1=yes	235	0.07	0.25
Education	Educational years	235	8.63	3.05
Income	income is taking log	235	0.96	2.15
Parents drinker	Number of parents that drink	235	0.42	0.63
Drinking behaviors:				
Drinking or not	dummy; 0=no; 1=yes	235	0.52	0.50
Drinking times during the past 30 days	drinking times	235	9.62	16.66
Weekly ethanol consumption	100g/week	235	1.24	2.41

Genotyping

DNA was extracted from saliva samples using the Illumina WeGene V2 Array. Imputation and quality control were performed using PLINK (1.90 Beta), SHAPEIT (v2.17), and IMPUTE2 (v2.3.1).

Measure of Alcohol Consumption

We investigated the frequency and intensity of alcohol consumption behaviour from three aspects. First, we conducted a binary measurement of whether the respondents drank or not, where 0 represented *current non-drinkers* (56.7%) and 1 represented *current drinkers* (43.3%). Second, we asked participants the total times of three kinds of Chinese common alcoholic drinks (beer, wine and liquor) during the past 30 days (mean = 7.92 (drink about once every 4 days on average), SD = 16.24). Third, using the three information of the number of times of three Chinese common alcoholic drinks (beer, wine and liquor) during one month, the average amount of the three alcoholic drinks each time, and the alcohol content of each alcoholic drinks,

we calculated the weekly ethanol (100 grams of pure alcohol per week) consumption as a continuous measure of alcohol consumption (mean =1.07, SD = 2.42).

Genetic Instruments

In MR studies of alcohol use, the aldehyde dehydrogenase 2 gene (*ALDH2* rs671) is usually used. This gene encode enzymes involved in ethanol metabolism pathway, which can change the metabolic balance of acetaldehyde in human body (Giia-Sheun Peng and Shih-Jiun Yin, 2009). Ethanol is first converted to acetaldehyde by alcohol dehydrogenase (*ADH*), and then further converted to acetate by acetaldehyde dehydrogenase (*ALDH*).

The enzyme activity of *ALDH* are largely determined by the number of effect alleles in *ALDH2* rs671, specifically the number of the A allele. In East Asian populations, three genotypes for *ALDH2* rs671 allele are GG (the number of A allele is 0), AG (the number of A allele is 1), and AA (the number of A allele is 2). The presence of A allele can significantly decrease the detoxification of acetaldehyde generated during alcohol metabolism in humans (Howard J Edenberg and Jeanette N McClintick, 2018, Giia-Sheun Peng and Shih-Jiun Yin, 2009) making people feel uncomforted after drinking alcohol. As can be seen from Table 1A, 34.47% of respondents in genetic sample are A-allele carriers for *ALDH2* rs671 (genotypes of AA and AG). Specifically, the percentages of genotype AA and AG are 2.55% and 31.92%, respectively.

Measure of MCI

All participants accepted mild cognitive impairment evaluation used Mini-Cog (Soo Borson et al., 2007). Mini-Cog combined the clock drawing task (CDT) (normal versus abnormal) and three words memory (0-3 scores) into a tool to assess MCI. These tests did not require high education level of the respondents and were easily understood by the respondents. Whether the participant is MCI or not is determined based on the completion of CDT and three-word recall. The specific simple decision rules are shown in Figure 1 (Soo Borson, James Scanlan, Jeffrey Hummel, Kathy Gibbs, Mary Lessig and Elizabeth Zuhr, 2007). Specifically, there were three rules: subjects recalling none of the words were classed as MCI; those recalling all three words were classed as non-MCI; and those with intermediate word recall (1-2) were classed based on the CDT (abnormal = MCI, normal = non-MCI). According to Table 2A, the risk of MCI in rural China was 50.36% in total sample, and the risk of MCI varies among different provinces. According to Table 2B, the risk of MCI in the genetic samples was basically consistent with that in the total samples.

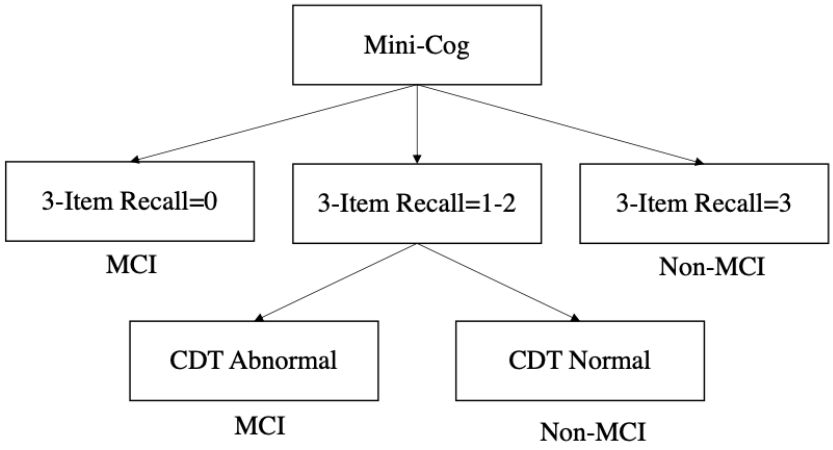

Fig.1 Mini-Cog scoring algorithm

Table.2A

The risk of MCI in each province

Nature of the samples	Number of sample (%)					
	Total	Sample from				
		Heilongjiang	Henan	Xinjiang	Shandong	Anhui
MCI	990 (50.36)	406 (43.47)	60 (66.67)	237 (39.43)	25 (36.23)	126 (46.32)
Non-MCI	976 (49.64)	528 (56.53)	30 (33.33)	364 (60.57)	44 (63.77)	146 (53.68)
All sample	1,966	934	90	601	69	272

Abbreviation: MCI= Mild Cognitive Impairment; Non-MCI= Non Mild Cognitive Impairment

Table.2B

The risk of MCI in genetic sample in each province

Nature of the samples	Number of genetic sample (%)					
	Total	Heilongjiang	Henan	Xinjiang	Shandong	Anhui
MCI	100 (42.37)	40 (42.96)	13 (68.42)	18 (36.73)	5 (38.46)	24 (38.10)
Non-MCI	135 (57.63)	51 (56.04)	6 (31.58)	31 (63.27)	8 (61.54)	39 (61.90)
All sample	235	91	19	49	13	63

Abbreviation: MCI= Mild Cognitive Impairment; Non-MCI= Non Mild Cognitive Impairment

Statistical analysis

We used multivariable linear regression to examine the correlation between alcohol consumption and MCI. Next, we used MR analysis to verify the effectiveness of genetic tool (ALDH2), and then used instrumental variables to evaluate the causal relationship between alcohol consumption and MCI using two-stage least squares (2SLS)we used MR analyses to verify the validity of genetic instrument (*ALDH2* rs671), and then used two-stage least squares (2SLS) to evaluate the causal relationship between alcohol consumption and MCI. The concept of MR is analogous to randomized controlled trials (RCT) which are difficult to implement but can help us make causal inferences about the effects of alcohol use/drinking behavior on MCI (Michael V Holmes, Caroline E Dale, Luisa Zuccolo, Richard J Silverwood, Yiran Guo, Zheng Ye, David Prieto-Merino, Abbas Dehghan, Stella Trompet and Andrew Wong, 2014, Stephanie von Hinke, George Davey Smith, Debbie A Lawlor, Carol Propper and Frank Windmeijer,

2016) Figure 2 illustrates the design of MR in our study. Considering that demographic characteristics and socioeconomic status factors might be highly correlated with both alcohol consumption and MCI, we adjusted age, gender, ethnic minorities, income, years of education and province fixed effects in all regressions. In MR analysis, we additionally adjusted for the number of drinking parents.

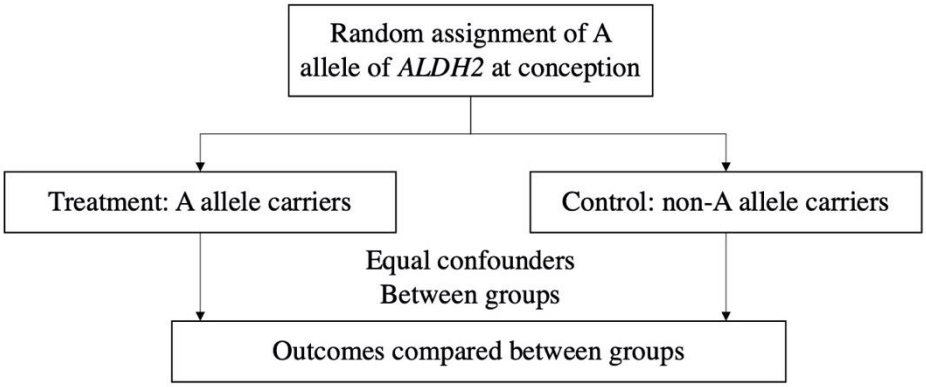

Figure 2. Design of Mendelian randomization in the current study

All statistical analyses were conducted using Stata version 14.0 (StataCorp LP, College Station, TX). Significance was set at $P < 0.05$.

RESULTS

In the total sample (1,966 participants), the risk of MCI was 50.36%. Moreover, from table 2A, we can see that the risk of MCI is the higher in central China (Henan and Anhui provinces), followed by northeast China (Heilongjiang province), northwest China (Xinjiang province) and eastern China (Shandong province). From Table 2B, we can see that, in the genetic sample (235

participants), the risk of MCI was 42.37%. Consistent with the results of the total sample and the risk of MCI varied among difference provinces.

Table 3 reported estimates of alcohol consumption on MCI from multivariable linear regressions on total sample (column 1), multivariable linear regressions on genetic sample (column 2), and MR analyses on genetic sample (column 3). As can be seen from the first column of Table 3, there was no significant correlation between three alcohol consumption variables and the risk of MCI in the multivariate linear regression estimation of the total sample. In order to prove the unbiased selection of genetic sample, we used multivariable linear regressions to analyze the genetic sample. From column 2, we also found none of the key explanatory variables were significantly associated with the risk of MCI, which was consistent with multivariable linear regressions estimates of the total sample. The current results showed that there was no significant correlation between the risk of MCI and alcohol consumption, which may be because alcohol consumption may still be confounded by various unobserved factors, such as socio-economic class, drinking attitude and so on.

Using *ALDH2* rs671 as a validity genetic instrument variable relied on the critical assumption of relevance and the exclusion restriction (Neil M Davies et al., 2018). Firstly, previous studies provided epidemiological evidence for the credibility of *ALDH2* rs671 as instrument variable for alcohol consumption (SL Au Yeung, CQ Jiang, KK Cheng, B Liu, WS Zhang, TH Lam, GM Leung and CM Schooling, 2012, Giia-Sheun Peng and Shih-Jiun Yin, 2009, Miaomiao Peng et al., 2019, Chen Zhu et al., 2020). In addition, We confirmed that the correlations between ALDH2 rs671 and alcohol consumption existed stably in the sample,

regardless of adjustments for additional controls. Further R-squared suggested that *ALDH2* rs671 could explain 3.6–16.8% of the total phenotypic variation in different alcohol consumption measurements, suggesting *ALDH2* rs671 was a validity genetic instrument variable. Secondly, We tested for weak instruments by using the First-stage F statistics from MR model. We found the First-stage F statistics in different models exceeded the conventional cut-off of 10 for weak instruments, indicating that genetic instrument variable was a strong instruments in our MR design. The potential pleiotropic effect was another crucial concern, which occurs when a genetic instrument variable can directly influence the outcome variable (Neil M Davies, Michael V Holmes and George Davey Smith, 2018). Through the query in phenoscanner (V2) (A database of human genotype-phenotype associations), there were no direct links of *ALDH2* rs671 with MCI-related phenotypes, further supporting the validity of this genetic instruments variable.

Column 3 of Table 3 reported MR results by *ALDH2* rs671 as instrumental variable in genetic sample. In the MR design, three alcohol consumption variables was causally associated with a higher risk of MCI. Specifically, parameter estimates for current drinking or not (b = 0.271, p = 0.007, 95% CI = 0.073 to 0.469), drinking times during the past 30 days (b = 0.016, p = 0.003, 95% CI = 0.005 to 0.027), and the weekly ethanol consumption (b = 0.132, p = 0.004, 95% CI = 0.042 to 0.223) were positive and statistically significant at the 5% level.

Table 3

Effects of alcohol use on MCI – OLS and 2SLS estimation results

	Multivariable linear regressions (1)	Multivariable linear regressions (2)	Mendelian randomization (3)
Observation	N=1966	N=235	N=235
(1) Key explanatory variable: drinking or not			

b (95% CI)	-0.010 (-0.148, 0.128)	-0.045 (-0.333, 0.243)	0.271 (0.073, 0.469)
p	0.853	0.689	0.007
F (p)			34.88 (0.000)
(2) Key explanatory variable: drinking times during the past 30 days			
b (95% CI)	0.000 (-0.002, 0.003)	-0.000 (-0.012, 0.011)	0.016 (0.005, 0.027)
p	0.768	0.915	0.003
F (p)			37.23 (0.004)
(3) Key explanatory variable: weekly ethanol consumption (100g/week)			
b (95% CI)	-0.004 (-0.021, 0.013)	-0.006 (-0.054, 0.042)	0.132 (0.042, 0.223)
p	0.571	0.751	0.004
F (p)			31.89 (0.005)

MCI was defined as Mini-Cog (Soo Borson, James Scanlan, Jeffrey Hummel, Kathy Gibbs, Mary Lessig and Elizabeth Zuhr, 2007). Abbreviations: 95% CI represents 95% confidence interval. All models were adjusted for age, gender, ethnic minorities, education, income, and province fixed effects. MR results were additionally adjusted for the number of drinking parents. The First-stage Cragg-Donald F statistics (with values of p) is test statistics of the weak instrument and overidentification tests, respectively, which indicate that genetic instruments of *ALDH2* rs671 used in MR satisfied with the relevance assumption and exclusion restriction.

DISCUSSION

We found that the risk of MCI in rural China was 50.36% and the risk of MCI was higher in central China. However, this finding was difference from other review studies. Jiang Xue et al. (2018) found that prevalence of MCI in the Chinese elderly population was 14.71% and the prevalence of MCI was higher in western China. Hongwei Nie, Yong Xu, Bin Liu, Yaodong Zhang, Ting Lei, Xiaoping Hui, Ling Zhang and Yan Wu (2011) found prevalence of MCI for the elderly population was 12.7% and found prevalence from eastern China was lower than that from western China. The reported prevalence of MCI difference from our finding due to different assessment procedures and sample regions. The samples in this study were all from Chinese rural areas, while the samples in Jiang Xue, Jiarui Li, Jiaming Liang and Shulin Chen (2018) and Hongwei Nie, Yong Xu, Bin Liu, Yaodong Zhang, Ting Lei, Xiaoping Hui, Ling Zhang and Yan Wu (2011) were mostly from Chinese urban areas. The prevalence of MCI in rural areas is generally higher than that in urban areas, because of difference life environments,

medical conditions and education level between urban and rural areas . As more and more young and middle-aged rural residences worked in cities, there is a growing demand for health care, especially about cognitive impairment, for older people who stay in Chinese rural regions. Our findings provide new evidence for the need and urgency of monitoring the cognitive function in rural China.

This study is one of the first studies using a MR design to investigate the causal relationship between alcohol consumption and MCI. This study also compensates for existing deficiencies by focusing on rural Chinese residents. Using a MR analyses in genetic sample of 235 participates from Chinese rural areas, we found that the effect of alcohol consumption on the higher risk of MCI was likely to be causal. This finding was consistent with a MR research which examined the causal relationship between alcohol consumption and Alzheimer's disease, which observed people who drank 1SD (1.90 drinks/week) of alcohol were twice as likely to develop Alzheimer's disease comparing with normal people at a given point of time (Shea J Andrews et al., 2019). There are other studies that are consistent with our finding. Tarja Järvenpää et al. (2005) in a longitudinal study on 554 twins persons above for 25 years, found drinking exceeding the amount of 5 bottles of beer or one bottle of wine on 1 occasion at least monthly was associated with a relative risk of 3.2 for dementia. Nicolas Cherbuin et al. (2009) found harmful alcohol consumption behavior (>42 units per week) increased risk of transitioning to MCI by analyzing 2,082 subjects aged 60 to 64. Huadong Zhou, Juan Deng, Jingcheng Li, Yanjiang Wang, Meng Zhang and Hongbo He (2003) suggested that alcohol consumption was closely associated with cognitive impairment (, p= 0.025). Although these studies are consistent with the conclusions of our finding, our research found that alcohol

consumption increase the risk of MCI regardless of heavy drinking or not. Comparing with previous studies, our research focuses on Chinese rural residents and provides empirical analysis results of a non-elderly sample (average age of the sample is 49.68 years).

However, our findings contradict several studies that suggest that mild to moderate alcohol consumption can prevent MCI or dementia (Tiia Anttila, Eeva-Liisa Helkala, Matti Viitanen, Ingemar Kåreholt, Laura Fratiglioni, Bengt Winblad, Hilkka Soininen, Jaakko Tuomilehto, Aulikki Nissinen and Miia Kivipelto, 2004, Jenni Ilomaki et al., 2015, Gelin Xu, Xinfeng Liu, Qin Yin, Wusheng Zhu, Renliang Zhang and Xiaobing Fan, 2009). These findings were in correlational studies that were limited by selection bias, and the heterogeneous nature of the non-drinker comparison group (Shea J Andrews, Alison Goate and Kaarin J Anstey, 2019). Because of the random assignment of genotypes from parents to children, MR analysis reduces the effect of confounding factors and reverse causality, which is the same as the principle of RCT. The advantages of MR analysis provide stronger support for causal effect analysis. Therefore, our study provides support for the cautious interpretation of casual effect of alcohol consumption on MCI, and further highlights the need for future studies to consider potential confounding factors.

The mechanism underlying the detected beneficial association of alcohol consumption and MCI is still under unclear. One mechanism for this result might be acute alcohol intoxication, which has been shown to interfere with memory and learning processes in animal studies (A Dahchour and Philippe De Witte, 2000, Andrey E Ryabinin, 1998). Another possible pathway

is that alcohol consumption has a high risk of head injury, which are a risk factor for dementia in adulthood (Brenda L Plassman et al., 2000).

There are several limitations in this study needed to be further addressed in later studies. The sample size of the genetic sample used in this study was relatively small, and there was a higher proportion of males in the sample. Chinese women rarely drink alcohol on a regular basis, and the large proportion of men in the sample may reduce the effectiveness of generalizing the results to women. In addition, there may be a time lag exists between alcohol consumption and subsequent cognitive changes. There may be limitations in using alcohol consumption over the past 30 days to assess the relationship between alcohol consumption and cognitive change.

CONCLUSIONS

In conclusion, we found risk of MCI in Chinese rural area was 50.36% and varied among different provinces. Specifically, the risk of MCI was the higher in central China (Henan and Anhui provinces), followed by northeast China (Heilongjiang province), northwest China (Xinjiang province) and eastern China (Shandong province). MR study found that alcohol consumption was causally associated with the higher risk of MCI in the genetic sample. Any amount of alcohol consumed increases the risk of MCI. we believed that our study provides empirical reference and evidence for the development of comprehensive and targeted programs, to reduce the incidence of cognitive impairment by reducing alcohol consumption among

Chinese rural residents. Nevertheless, further investigations are needed to clarify the potential underlying mechanisms.

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