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Incidence and risk factors associated with progression to mild cognitive impairment among middle-aged and older adults

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Abstract. – OBJECTIVE: We performed this longitudinal 2-year follow-up study to determine the incidence and risk factors associated with MCI in middle-aged and older adults.

SUBJECTS AND METHODS: This community-based longitudinal study was conducted in adults aged ≥ 50 years with normal cognitive function in Shanghai community, China, over a period of two years. Information about the socio-demographic, behavioral, anthropometric, and biochemical parameters was obtained at the baseline and cognitive function was assessed at the end of the follow-up period using the Montreal cognitive assessment tool.

RESULTS: A total of 985 participants aged ≥ 50 years were included in the analysis. Incidence of MCI during the 2-year follow-up period among the study participants was 26.7% (95% CI: 24.0%-29.6%). Participants with lower level of education [primary - adjusted RR=2.79 (95% CI: 1.38-5.64 and secondary - adjusted RR=1.62 (95% CI: 1.17-2.24)], with history of cerebral infarction (adjusted RR=1.49; 95% CI: 1.05-2.12), history of cerebral hemorrhage (adjusted RR=3.20; 95% CI: 1.22-8.40) were found to have significantly higher risk of MCI. Regular tea consumption was associated with significantly reduced risk of MCI development (adjusted RR=0.69; 95% CI: 0.49-0.96).

CONCLUSIONS: Our study found that one in four participants developed MCI during the 2-year follow-up period. Lower educational level, history of cerebral infarction, cerebral hemorrhage and tea consumption were significant determinants of MCI incidence. The target groups identified in this study should be closely monitored with regular follow-up investigations for early diagnosis and appropriate management of the condition.

Key Words:
Cognition, Mental Health, Noncommunicable diseases.

Introduction

According to the World Health Organization (WHO), dementia may soon become a worldwide epidemic, due to the constantly growing elderly population[1]. Mild cognitive impairment (MCI) is a stage between the process of cognitive decline due to the normal aging, and dementia[2]. MCI has the ability to cause significant physical, social, emotional, psychological and financial burden to the patients and their caregivers[3], increases the level of physical dependency and is associated with a higher risk of developing Alzheimer's disease in the future[2]. MCI also has significant impact on the mental health of caregivers, causing social and emotional isolation, and financial constraints[4]. The rise in the life expectancy of the elderly can further increase the burden of MCI in the near future in the developing, as well as developed countries[5].

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Currently, there are no pharmacological interventions or drugs to cure or alter the clinical course of the dementia, and symptomatic management using medication have only moderate effects on the patients[6-8]. Dementia treatment strategies put an emphasis on early detection and treatment, highlighting the significance of the prodromal stage of dementia, or MCI. Screening for risk factors of MCI may therefore help in early diagnosis of the unidentified dementia cases and guide patients and their caregivers to seek the healthcare services in timely manner to avert further complications. Identifying the baseline risk factors for application at the point of MCI diagnosis might help in prioritizing resources in healthcare setting and continuous monitoring of identified high-risk patients for signs of dementia.

Several research studies and reviews[9-15] have reported the risk factors of MCI across different settings. Sociodemographic factors like age, gender, education, and comorbidities, such as hypertension, dyslipidemia and biochemical parameters, were reported to be significant risk factors for MCI across these studies[9-15]. However, most studies have followed cross-sectional or retrospective design, which limits the causal interpretation of the risk factors. There are very limited studies[9,14] establishing the causality of the risk factors using longitudinal study design. The goal of this longitudinal 2-year follow-up study was to determine the incidence and risk factors associated with MCI amongst middle-aged and older adults in Shanghai community, China.

Subjects and Methods

Study Design and Subjects

We conducted this community-based longitudinal study in middle-aged and older adults in the Shanghai community, China. The current cross-section study was derived from Shanghai brain health foundation (SHBHF2016001). Data of 1,032 participants aged ≥ 50 years with normal cognitive function (without MCI or dementia) at the time of recruitment into the study were collected. In total, 986 participants were followed-up for a period of 2 years (loss to follow up = 46 participants) and included in the analysis.

Study Procedure

This study was approved by the Ethics Committee of the Shanghai Mental Health Centre (No. 2018-11R, Date: 2018-07-27). Data collection was initiated after getting ethical approval and informed written consent from the study participants. Anonymized dataset was obtained and semi-structured questionnaire was applied to obtain the demographic information such as age, gender, education, occupation, body mass index (BMI), and behavioral characteristics, such as self-reported smoking, alcohol use, tea consumption, physical activity, sleep problem, decline in daily activities; self-reported comorbidities, such as diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HTN), cerebral hemorrhage, cerebral infarction, history of traumatic brain injury (TBI), depression, dyslipidemia.

Baseline measurements were collected for the biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total cholesterol, low density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides. To retrieve information about the progression to MCI, the follow-up data until the date of discharge were collected using Montreal Cognitive Assessment (MoCA), a validated and highly sensitive instrument for early identification of MCI[16].

Operational Definitions

- MCI: participants having MoCA score between 18 and 25 were considered to have MCI[16].

- BMI category: BMI was categorized into "underweight (≤ 18.50 kg/m^2)", "normal (18.50-22.99 kg/m^2)", "overweight (23.00-24.99 kg/m^2)" and "obesity (≥ 25.00 kg/m^2)", based on the Asia-Pacific guidelines[17].

- Liver function abnormalities: participants having more than 40 IU/L in ALT or AST were considered to have liver function abnormalies[18].
- Hyperbilirubinemia: participants having more than 17 mmol/L in total bilirubin were considered to have hyperbilirubinemia[18].
- Hypercholesterolemia: participants having more than 5.17 mmol/L in total cholesterol were considered to have hypercholesterolemia[19].
- Hypertriglyceridemia: participants having more than 1.7 mmol/L in triglycerides were considered to have hypertriglyceridemia[19].
- High LDL cholesterol: participants having more than 3.4 mmol/L in LDL cholesterol were considered to have high cholesterol values[19].
- Low HDL cholesterol: participants having less than 1 mmol/L amongst males or less than 1.3 mmol/L amongst females in HDL cholesterol were considered to have low cholesterol values[19].

Independent and Dependent Variables

Development of MCI was considered as a dependent variable, while the following sociodemographic, behavioral, anthropometric and biochemical parameters were considered as independent variables: age category (50-59 years/60-79 years/≥ 80 years), sex (male/female/third gender), education (no formal education/primary/secondary/higher), marital status (married/unmarried/separated/divorced/widowed), family history of dementia (yes/no), self-reported history of smoking (yes/no), alcohol (yes/no), physical activity (active/inactive), tea consumption (yes/no), BMI category (underweight/normal/overweight/obese), self-reported decline in daily living activities (yes/no), self-reported sleep problems (yes/no), history of DM (yes/no), HTN (yes/no), CAD (yes/no), cerebral hemorrhage (yes/no), cerebral infarction (yes/no), depression (yes/no), TBI (yes/no).

Statistical Analysis

Data entry was done in Microsoft Excel and the analysis was done using STATA 14.2 (CollegeStation, TX, USA). Descriptive statistics were employed to summarize the continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR) depending on the normality of the variables; categorical variables were summarized as proportions. Incidence of MCI was summarized with 95% confidence interval (CI). Generalized linear model with binomial family and logit link was performed for each independent variable separately and the variables with the *p*-value up to 0.20 were considered for the multivariable model. Multivariable analysis results were reported as adjusted risk ratio (RR) with 95% CI. *p*-values lower than 0.05 were considered to be statistically significant risk factors for MCI.

Results

Amongst the 1,032 participants aged ≥ 50 years, recruited into the study, follow-up of two years was completed for 986 participants (loss to follow-up rate = 4.4%). Socio-demographic and comorbid details of the participants are reported in Table I. More than three fourth of the participants belonged to the 60-79 years age group; almost two third (65.1%) were females; more than

Table I. Sociodemographic characteristics of study participants (N = 985).

Sociodemographic characteristics	Frequency, N (%)
Age category (in years)	
45-59	96 (9.7)
60-79 years	772 (78.4)
≥ 80 years	117 (11.9)
Gender	
Male	344 (34.9)
Female	641 (65.1)
Education (based on years of schooling)	
No formal education	20 (2.0)
Primary (1-5)	37 (3.8)
Secondary (6-10)	357 (36.2)
Higher (11 and above)	571 (58.0)
Marital status	
Married and living together	747 (84.6)
Unmarried/widowed/separated/divorced	136 (15.4)
Family History of dementia	
Present	102 (10.4)
Absent	883 (89.6)
Non-communicable disease	
Hypertension	277 (28.1)
Diabetes Mellitus	235 (23.9)
Coronary Artery Disease	163 (16.5)
Dyslipidaemia	382 (38.8)
Cerebral infarction	204 (20.7)
Traumatic brain injury	73 (7.4)
Depression	24 (2.4)
Cerebral haemorrhage	21 (2.1)

Table II. Behavioural and anthropometric characteristics of the study participants (N = 985).

Characteristics	Frequency, N (%)
Current tobacco user (in past one month)	
Yes	185 (18.8)
No	800 (81.2)
Current alcohol user (in past one month)	
Yes	154 (15.6)
No	831 (84.4)
History of regular tea consumption	
Yes	484 (49.1)
No	501 (50.9)
Physical activity	
Adequate	668 (67.8)
Inadequate	317 (32.2)
BMI category	
Underweight	37 (3.9)
Normal	594 (62.2)
Overweight	283 (29.6)
Obese	41 (4.3)
Self-reported decline in daily living activities	
Present	28 (2.8)
Absent	954 (97.2)
Self-reported Sleep problem	
Present	269 (27.4)
Absent	713 (72.6)

half of the participants had higher educational level; majority (84.6%) was married and living together. The most common comorbidity amongst the study participants was dyslipidemia (38.8%) followed by hypertension (28.1%), DM (23.9%), cerebral infarction (20.7%) and CAD (16.5%).

Behavioral, anthropometric, and biochemical parameters of the participants are summarized in Table II and Table III. About 18.8% and 15.6% of the participants were current tobacco and alcohol users, respectively; almost half of the participants were regular tea consumers; almost one-third of the participants was physically active. Hypercholesterolemia (39%) was the most common biochemical abnormality, followed by high LDL (31.6%), hypertriglyceridemia (28.3%), low HDL (27.8%), hyperbilirubinemia (15.8%).

Incidence of MCI during the 2-year follow-up period among the study participants was 26.7% (95% CI: 24.0%-29.6%). Table IV shows the determinants of MCI in the study participants. Variables such as age group, gender, marital status, education, DM, CAD, alcohol use, cerebral infarction, cerebral hemorrhage, and regular tea consumption had *p*-values lower than 0.20 in the univariable analysis and were included in the multivariable model. Participants with lower level of education [primary - adjusted RR=2.79 (95% CI: 1.38-5.64) and secondary - adjusted RR=1.62 (95% CI: 1.17-2.24)] had higher risk of MCI when compared to participants with higher level of education and this association was statistically significant (p=0.004). Participants who had had a history of cerebral infarction had 1.49

Table III. Biochemical parameters of the study participants (N = 985).

Parameters	Frequency, N (%)
High ALT	
Present	60 (6.1)
Absent	925 (93.9)
High AST	
Present	33 (3.3)
Absent	952 (96.7)
Hyperbilirubinemia	
Present	156 (15.8)
Absent	829 (84.2)
Hypercholesterolemia	
Present	384 (39.0)
Absent	601 (61.0)
Hypertriglyceridemia	
Present	279 (28.3)
Absent	706 (71.7)
High LDL	
Present	311 (31.6)
Absent	674 (68.4)
Low HDL	
Present	274 (27.8)
Absent	711 (72.2)

Table IV. Determinants of mild cognitive impairment amongst adults aged ≥ 50 years in Shanghai community, China N = 985.

Characteristics	Total	Mild cognitive impairment (%)*	Unadjusted risk ratio (95% CI)	*p*-value	Adjusted risk ratio (95% CI)	*p*-value
Age category (in years)						
45-59	96	25.0	Ref	-	Ref	-
60-79 years	772	25.8	1.01 (0.92-1.11)	0.87	0.85 (0.49-1.45)	0.54
≥ 80 years	117	34.2	1.10 (0.97-1.23)	0.13	1.06 (0.53-2.11)	0.87
Gender						
Male	344	22.1	Ref	-	Ref	-
Female	641	29.2	1.07 (1.01-1.14)	0.02	1.02 (0.70-1.49)	0.92
Education status						
No formal education	20	45.0	1.25 (1.03-1.53)	0.02	1.70 (0.61-4.74)	0.31
Primary	37	43.2	1.23 (1.07-1.43)	0.005	2.79 (1.38-5.64)	0.004
Secondary	357	31.1	1.09 (1.03-1.16)	0.003	1.62 (1.17-2.24)	0.004
Higher	571	22.2	Ref	-	Ref	-
Marital status						
Married	747	24.9	Ref	-	Ref	-
Unmarried/Widowed/Separated/Divorced	136	39.0	1.15 (1.06-1.25)	0.001	1.37 (0.92-2.05)	0.12
Diabetes Mellitus						
Present	235	31.1	1.06 (0.99-1.13)	0.08	1.40 (1.00-1.98)	0.05
Absent	750	25.3	Ref	-	Ref	-
Coronary artery disease						
Present	163	33.7	1.09 (1.01-1.17)	0.03	1.34 (0.92-1.97)	0.13
Absent	822	25.3	Ref	-	Ref	-
Cerebral infarction						
Present	204	35.3	1.11 (1.04-1.19)	0.002	1.49 (1.05-2.12)	0.03
Absent	781	24.5	Ref	-	Ref	-
Cerebral haemorrhage						
Present	21	47.6	1.24 (1.02-1.50)	0.03	3.20 (1.22-8.40)	0.02
Absent	964	26.2	Ref	-	Ref	-
Alcohol intake						
Present	154	20.8	0.93 (0.86-1.00)	0.07	0.68 (0.40-1.14)	0.14
Absent	831	27.8	Ref	-	Ref	-
History of regular tea consumption						
Present	484	21.3	0.90 (0.85-0.95)	< 0.001	0.69 (0.49-0.96)	0.03
Absent	501	31.9	Ref	-	Ref	-

Ref - Reference category; Variables such as BMI category, physical activity, sleep problem, decline in activities of daily living, hypertension, history of traumatic brain injury, depression, smoking, high ALT, high AST, hyperbilirubinemia, hypercholesterolemia, hypertriglyceridemia, high LDL and low HDL had a p-value higher than 0.20 in the univariable model and were not included in the multivariable model.

times higher risk of developing MCI (adjusted RR=1.49; 95% CI: 1.05-2.12) when compared to those who did not have history of cerebral infarction. Participants with history of cerebral hemorrhage had significantly higher risk of developing MCI (adjusted RR=3.20; 95% CI: 1.22-8.40) when compared to those without cerebral hemorrhage. Regular tea consumption was found to have significant protective role against the development of MCI (adjusted RR=0.69; 95% CI: 0.49-0.96).

Discussion

This study aimed at determining the incidence and risk factors of MCI in adults aged ≥ 50 years with normal cognitive function in Shanghai community, China. All the participants underwent comprehensive examination of sociodemographic, behavioral, anthropometric and biochemical parameters at the time of recruitment into the study. They were followed up for a period of two years and the presence/absence of MCI was checked during this period.

Current study found that about 26.7% of the study participants aged ≥ 50 years with normal cognitive function in Shanghai community has developed MCI during the follow-up period. The rate observed in our study was substantially higher than the pooled prevalence of MCI reported by a systematic review and meta-analysis conducted in Chinese adults aged ≥ 55 years[20]. This may be explained by the substantially higher average age of our study participants, comparing to a previous study[20]. Additionally, most of the studies[10-12] included in the systematic review were cross-sectional in design. However, the estimate found in our study was almost in line with the previous longitudinal studies[8,14,21] reporting the incidence of MCI among older adults in China and neighboring regions.

We demonstrated that education, cerebral hemorrhage, cerebral infarction, and tea consumption were significant determinants of MCI. Our findings are in agreement with previous studies[9-15,22-25] reporting possible risk factors of MCI. Identifying these factors will potentially allow to develop targeted intervention practices for high-risk population groups, especially post-stroke patients (either infarction or hemorrhage induced stroke).

In agreement with previous studies[22,26], we showed that lower educational levels are associated with the higher incidence of MCI, probably due to the possibility of lower cognitive reserve, difficulty in cognitive evaluation, poor adaptations of the cognitive test and poorer control of the cerebrovascular risk factors. Therefore, older adults with lower educational qualifications can be considered as an important target group requiring regular follow-up for cognitive disorders.

The mechanism behind higher rate of MCI progression in post-stroke patients (either cerebral infarction or hemorrhage induced stroke) is still unclear. However, some studies[23,25] proposed that the underlying causes of this phenomenon may include stroke-induced neuroanatomical lesions in certain strategic areas (i.e., hippocampus and lesions in white matter), presence of cerebral microbleeds because of the smaller cerebrovascular diseases (CVDs) and accompanying Alzheimer's disease (AD). These mechanisms, either alone or combined, may contribute to the development of MCI.

Lastly, the protective role of tea consumption on the cognitive function has been widely studied. Though the exact mechanism behind the protective role of tea is still elusive, various bioactive components of the tea such as tea polyphenols (especially epigallocatechin gallate), theanine, theaflavins were shown to modulate the neuronal function through their neuroprotective, anti-inflammatory, anti-apoptosis and antioxidant functions[27]. Based on these mechanisms, we may speculate that the tea consumption can protect cognitive processes later in life[24]. BMI, physical activity did not show significant association with MCI, which was in contrast with the previous study reporting the association[28,29].

Strengths and Limitations

Our study has certain strengths and limitations. Longitudinal nature of the study is its major strength, as it helps in establishing the causality between the risk factors and the MCI. We have also performed comprehensive baseline assessment of the study participants and explored the association between various sociodemographic, behavioral, anthropometric, and biochemical risk factors and outcomes. Additional strengths of our study include higher sample size, lower loss-to-follow-up rate, and the use of validated instruments. However, our study also has some limitations, such as self-reported nature of certain variables (smoking, alcohol, sleep problem, limitation in activity of daily living, and comorbidities). These factors were not confirmed, which may have affected the validity of their association

with MCI. Future studies with comprehensive assessment of these parameters based on validated or standard criteria are needed.

The current study has certain important implications for the clinicians, public health professionals, geriatric health researchers and policymakers. First, this study provides a reliable estimate for the development of MCI in Chinese older adults as it was conducted by following up the participants with normal cognitive function. In addition, we have also identified certain risk factors which will help the policymakers to develop targeted interventions for these high-risk populations. However, further research with comprehensive assessment of risk factors using validated instruments is needed to accurately establish the causative risk factors for MCI.

Conclusions

Our study found that one in four participants developed MCI during the 2-year follow-up period. Lower educational qualification, history of cerebral infarction, cerebral hemorrhage and tea consumption were found to be significant determinants of MCI incidence. The target groups identified in this study should be closely monitored with regular follow-up investigations for early diagnosis and appropriate management of the condition.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Informed written consent was obtained from the study participants.

Ethics Approval

The study was approved by the Ethics Committee of the Shanghai Mental Health Centre (No. 2018-11R, Date: 2018-07-27).

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Authors' Contribution

NZ and WL contributed to the study concept and design. NZ and ZQ analyzed the data and drafted the manuscript. WL and YJ directed the analysis and statistics of data. All the authors have read and approved the final version of the manuscript.

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