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Inverse Relationship between Baseline Serum Albumin Levels and Risk of Mild Cognitive Impairment in Elderly: A Seven-Year Retrospective Cohort Study

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Mild cognitive impairment (MCI) is the prophase of dementia. MCI patients have a high risk of developing dementia. Relatively low serum albumin levels are associated with the development of several geriatric diseases, including stroke and poor cognitive performance. However, the potential relationship between serum albumin levels and MCI risk has not been fully elucidated. In the present study, we explored this relationship to increase our understanding of the pathogenesis of MCI, the finding of which may provide new ideas for the controlling of dementia. A total of 1,800 subjects who had normal cognitive function at their first health examinations (seven years ago) were retrospectively analyzed from a health database in Tianjin Medical University General Hospital. They were over 60 years old at baseline, and the follow-up period was 7 years. At the time of data collection (seven years after), 196 subjects suffered from MCI, diagnosed by symptoms and Mini-Mental State Examination. The remaining 1,604 subjects were still cognitively normal. Multivariate COX regression analysis showed that relatively low serum albumin levels at baseline (< 40.5 g/L) were associated with the increased risk of MCI (HR: 2.18, 95% CI: 1.67-2.82). Moreover, the effect of low serum albumin on the risk of MCI was further enhanced among the subjects with hypertension, diabetes, hyperlipemia, cardiovascular disease, cerebrovascular disease, high serum levels of C-reactive protein, or relatively low levels of uric acid or total bilirubin. In conclusion, relatively low serum concentrations of albumin may be an independent risk factor for MCI in elderly.

Keywords: albumin; dementia; elderly; mild cognitive impairment; risk factor
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Introduction

Dementia is a chronic and progressive clinical syndrome in elderly, which is characterized by several higher cortical dysfunctions, such as memory, thinking, orientation, understanding, calculation, language and learning (Burns and Zaudig 2002). The most common types of dementia are Alzheimer's disease, vascular dementia and Lewy body dementia. Alzheimer's disease contributes to more than 50% of the total cases. Around the world, about 46 million people had some kind of dementia in 2015 (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016), and 15 to 20% of them were in China (Yuan et al. 2016a). Dementia can not be cured in most cases, which causes long-term harm to individuals, families and society.

Mild cognitive impairment (MCI) is known as the prophase of dementia (Albert and Blacker 2006). MCI patients have cognitive impairment in some domains, but his or her daily life is not affected. Annually, more than 10% of these patients convert to typical dementia (Janoutová et al. 2015). Therefore, it is meaningful to conduct in-depth research on MCI, which is likely to provide new opportunities for controlling the development of dementia.

Serum albumin is a soluble protein in peripheral circulation, which constitutes nearly 50% of serum protein. It exerts a variety of biological functions, such as maintenance of blood pressure, nutritional support, anti-oxidation, transport and detoxification (Farrugia 2010). In recent years, many studies demonstrated an unexpected role of serum albumin in the development of common geriatric diseases. Relatively low serum level of albumin was associated with the increased risk of coronary heart disease (Vázquez-Oliva et al. 2018), heart failure (Gopal et al. 2010), venous thromboembolism (Kunutsor et al. 2018),

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type 2 diabetes (Hwang et al. 2018), diabetic ketosis (Cheng et al. 2016), metabolic syndrome (Jin et al. 2016), and breast cancer (Kühn et al. 2017). Furthermore, relatively low serum level of albumin contributed to the development of stroke (Alvarez-Perez et al. 2011), predicted the prognosis of stroke patients (Dziedzic et al. 2004) and was also implicated in the post-stroke depressive symptoms (Pascoe et al. 2015). An increasing number of studies explored the potential relationship between serum albumin and cognitive function, and reported that relatively low serum level of albumin was independently associated with poor cognitive performance in elderly (Ng et al. 2008; Llewellyn et al. 2010; Murayama et al. 2017). Taken together, we have reasons to believe that serum albumin participates in or affects the development of MCI, but related research is lacking.

Therefore, we performed a seven-year retrospective cohort study involving 1,800 subjects to explore the relationship between the serum level of albumin and the risk of MCI in elderly. Through this study, we hoped to increase our understanding of the pathogenesis of MCI and provided some new ideas for the prevention and control of MCI and dementia.

Materials and Methods

The study was approved by the ethics committee of Tianjin Medical University General Hospital and was performed according to the Helsinki Declaration of the World Medical Association.

Subjects

Elderly in this area regularly came to the Department of Geriatrics, Tianjin Medical University General Hospital for health examination. Their medical records were properly organized and used to build a health database. Furthermore, the elderly had authorized us to use these data for scientific research including this study in the form of anonymity. Written informed consents had been signed.

Subjects in the study were collected from the database according to the following criteria. First, they were local residents. Second, they were ethnically Han Chinese. Third, they were over 60 years old at their first health examinations. Fourth, the first examinations were performed between January 1, 2008 and December 31, 2009, and the last examinations were conducted between January 1, 2015 and December 31, 2016. Fifth, they routinely received a basic cognitive assessment, and all of them were cognitively normal at the first health examinations. During the whole research period, MCI cases were diagnosed according to a standard procedure. Sixth, the subjects who had diabetic nephropathy, virus hepatitis, cirrhosis, any type of cancer, dementia or mental disease were not included in the study.

Data collection

In the study, the first health examination (January 1, 2008 and December 31, 2009) served as baseline or starting point, and the last health examination (January 1, 2015 and December 31, 2016) served as end point. Follow-up period of the study was 7 years. All research data were collected from their medical records. The date included demographic information, educational background, medical history, medication history, serum levels of albumin, uric acid (UA), total bilirubin (TBIL) and C reactive protein (CRP).

Cognitive function evaluation

In the health examination, cognitive function was preliminarily assessed by mini-mental state examination (MMSE). If a subject had any type of cognitive impairment, he or she would be introduced to a team of psychologists for comprehensive neuropsychological assessment.

MCI was diagnosed according to recognized diagnostic criteria. First, there was memory deterioration or other type of cognitive impairment, which was confirmed by MMSE. Second, basic cognitive functions still existed. Third, subjects were not affected by any type of dementia.

MMSE was a common neuropsychological assessment method including 30 items. Score of each item was one point, and total score was 30 points. The score < 20 points was considered to be cognitive impairment in subjects with primary school education. The score < 24 points indicated cognitive impairment in subjects with more than primary school education (Molloy and Standish 1997). A subject who did not confirmed any type of cognitive impairment was regarded to be a cognitively normal subject.

Definition

"High level of CRP" was defined as "serum CRP level ≥ 10 mg/L." Because the number of subjects with low level of UA or TBIL was very small, "relatively low level of UA and TBIL" were adopted in this study. "Relatively low level of UA" was defined as "serum UA level < 358.1 μmol/L (arithmetic mean of all subjects)". "Relatively low level of TBIL" was defined as "serum TBIL level < 16.0 μmol/L (arithmetic mean of all subjects)."

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Medication history was defined as taking one kind of drug regularly for six months or more in one's life.

Statistical analysis

Continuous variable was showed in the form of mean ± standard deviation, and two continuous variables were compared using independent sample t test. Categorical variable was expressed in the form of frequency and constituent ratio, and two categorical variables were compared by Chi-square test. P values were reported. If a P value was less than 0.05, difference between two variables was statistically significant. A receiver operating characteristic curve (ROC) analysis was conducted to detect the predictive significance of serum albumin levels on the risk of MCI. A cutoff value of serum albumin level with its sensitivity and specificity was reported. According to the cutoff value, the subjects were divided into two groups. Then, a multivariate COX regression analysis was performed to explore the relationship between the relatively low serum level of albumin and the increased risk of MCI. Hazard ratio (HR) and 95% confidence interval (CI) were reported. If the value one was not within the range of 95% CI, the relationship between serum albumin and the risk of MCI had statistical significance. Statistical analysis was performed using a commercial software SPSS version 19.0 (Chicago, IL, USA).

Results

In Table 1, there were 196 MCI patients and 1,604 cognitively normal controls in the study. At baseline,

Table 1. Characteristics of mild cognitive impairment patients and cognitively normal controls.

	MCI[a] (n = 196)	Normal (n = 1,604)	P value
At baseline			
Male (n, %)	146 (74.5)	1,212 (75.6)	0.742
Age (yrs, mean±SD)[a]	71.5 ± 8.9	72.2 ± 7.6	0.255
Body mass index (kg/m^2, mean±SD)	24.6 ± 3.0	24.8 ± 3.5	0.587
Hypertension (n, %)	148 (75.5)	882 (55.0)	< 0.001
Diabetes (n, %)	56 (28.6)	312 (19.5)	0.003
Hyperlipemia (n, %)	62 (31.6)	270 (16.8)	< 0.001
Cardiovascular disease (n, %)	94 (48.0)	486 (30.3)	< 0.001
Cerebrovascular disease (n, %)	76 (38.8)	300 (18.7)	< 0.001
C reactive protein (mg/L, mean±SD)[b]	6.9 ± 1.1	6.2 ± 1.1	< 0.001
Uric acid (μmol/L, mean±SD) [b]	330.9 ± 103.2	361.4 ± 76.6	< 0.001
Total bilirubin (μmol/L, mean±SD)[b]	13.3 ± 4.0	16.3 ± 5.5	< 0.001
Albumin (g/L, mean±SD) [b]	40.0 ± 3.7	44.6 ± 3.0	< 0.001
At the end			
Body mass index (kg/m^2, mean±SD)	23.1 ± 3.1**	23.3 ± 3.6**	0.448
Hypertension (n, %)	161 (82.1)$^{\#}$	899 (56.0)$^{\#}$	< 0.001
Diabetes (n, %)	58 (30.0)$^{\#}$	330 (20.6)$^{\#}$	0.004
Hyperlipemia (n, %)	63 (32.1)$^{\#}$	281 (17.5)$^{\#}$	< 0.001
Cardiovascular disease (n, %)	116 (59.2)*	532 (33.2)$^{\#}$	< 0.001
Cerebrovascular disease (n, %)	96 (49.0)*	349 (21.8)*	< 0.001
C reactive protein (mg/L, mean±SD)	8.0 ± 1.1**	7.2 ± 1.1**	< 0.001
Uric acid (μmol/L, mean±SD)	325.8 ± 103.0$^{\#}$	356.5 ± 76.8$^{\#}$	< 0.001
Total bilirubin (μmol/L, mean±SD)	12.8 ± 4.1$^{\#}$	15.8 ± 5.5*	< 0.001
Albumin (g/L, mean±SD)	39.0 ± 3.8*	43.6 ± 3.0**	< 0.001
During the whole research			
Use of calcium blockers (n, %)	114 (58.2)	512 (31.9)	< 0 .001
Use of ARBs/ACEIs (n, %)[a]	92 (46.9)	471 (29.4)	< 0.001
Use of oral antidiabetic drugs (n, %)	47 (24.0)	289 (18.0)	0.043
Use of statins (n, %)	76 (38.8)	310 (19.3)	< 0.001
Use of NSAIDs (n, %)[a]	128 (65.3)	490 (30.5)	< 0.001
Use of β-blockers (n, %)	85 (43.4)	387 (24.1)	< 0.001
Use of nitrates (n, %)	79 (40.3)	312 (19.5)	< 0.001

[a]MCI, mild cognition impairment; ARB, angiotensin II receptor antagonist; ACEI, angiotensin converting enzyme inhibitor; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

[b]Normal ranges of serum C reactive protein, total bilirubin and albumin were < 10 mg/L, 3.4-17.1 μmol/L and 35-50 g/L, respectively. Normal ranges of uric acid were 149-416 μmol/L in male and 178.4-297.4 μmol/L in female.

[#]Compared to the corresponding value at baseline, P ≥ 0.05.

[*]Compared to the corresponding value at baseline, P < 0.05.

[**]Compared to the corresponding value at baseline, P < 0.001.

hypertension, diabetes, hyperlipemia, cardiovascular disease and cerebrovascular disease were more common in the MCI patients compared with the controls (P < 0.001 for each, except for diabetes, P = 0.003). Serum level of CRP was higher in the MCI patients than in the controls (P < 0.001). By contrast, serum levels of UA, TBIL and albumin were higher in the controls than in the patients (P < 0.001 for each). Importantly, there was no noticeable effect of sex, age, or BMI on the MCI risk.

At the end of the study, there was no significant difference in BMI between the MCI patients and the controls (P = 0.448). Serum albumin levels in the MCI patients were decreased during the 7-year follow-up period (P < 0.001), and serum CRP levels were increased during the same period (P < 0.001). MCI patients were more commonly affected by cardiovascular disease or cerebrovascular disease at the end compared with the patients at baseline (P < 0.05 for each) (Table 1).

Moreover, calcium blockers, angiotensin II receptor antagonists (ARBs)/angiotensin converting enzyme inhibitors (ACEIs), oral antidiabetic drugs, statins, non-steroidal anti-inflammatory drugs (NSAIDs), β-blockers and nitrates were more commonly used in the MCI patients than in the controls (Table 1).

In Table 2, there was no difference in the score of MMSE between the MCI patients and the controls at baseline (P = 0.504). At the end, the score of MMSE was significantly decreased in the MCI patients than in the controls (P < 0.001).

In Fig. 1, a ROC analysis proved a predictive significance of serum albumin on the risk of MCI. The cutoff point of serum albumin was 40.5 g/L with a sensitivity of 82.1% and a specificity of 78.2% (Area under the curve = 0.860, P < 0.001).

According to the cutoff point of serum albumin level (40.5 g/L), the subjects were divided into high level group (≥ 40.5 g/L) and low level group (< 40.5 g/L) in the following analysis. In Table 3, the subjects in the low level group showed an increased risk of MCI compared with that in the high level group (HR: 2.18, 95% CI: 1.67-2.82).

In Table 4, the relationship between the serum level of albumin and the risk of MCI was explored in specific baseline metabolic, vascular, inflammatory or oxidative stress condition. The multivariate analysis showed that low serum levels of albumin (< 40.5 g/L) were associated with a higher risk of MCI among the subjects with hypertension (HR: 2.21, 95% CI: 1.63-2.99), diabetes (HR: 3.24, 95% CI: 2.12-5.28), hyperlipemia (HR: 2.90, 95% CI: 1.79-4.71), cardiovascular disease (HR: 2.67, 95% CI: 1.80-4.20), or cerebrovascular disease (HR: 2.63, 95% CI: 1.46-4.76). Moreover, among the subjects with high levels of CRP (≥ 10 mg/L), relatively low levels of UA (< 358.1 μmol/L) or relatively low levels of TBIL (< 16.0 μmol/L), the effect of the low serum albumin level on the risk of MCI was enhanced (HR: 10.11, 95% CI: 4.44-22.89; HR: 3.28, 95% CI: 2.42-4.46; and HR: 3.09, 95% CI: 2.31-3.44, respectively).

In Table 5, the relationship between the serum level of albumin and the risk of MCI was explored in multiple metabolic, vascular, inflammatory and oxidative stress conditions. In the subjects with 0-1 condition, there was no association between the serum level of albumin and the risk of MCI (HR: 1.10, 95% CI: 0.46-2.82). In the subjects with 2-3 conditions, 4-5 conditions or 5-6 conditions, the association was gradually strengthened (HR: 1.96, 95% CI: 1.32-2.89; HR: 2.34, 95% CI: 1.52-3.62; and HR: 4.52, 95% CI: 1.96-12.80, respectively).

Discussion

It was the first study around the world exploring the association of serum albumin levels with the risk of MCI. Based on the results from the study, the subjects with

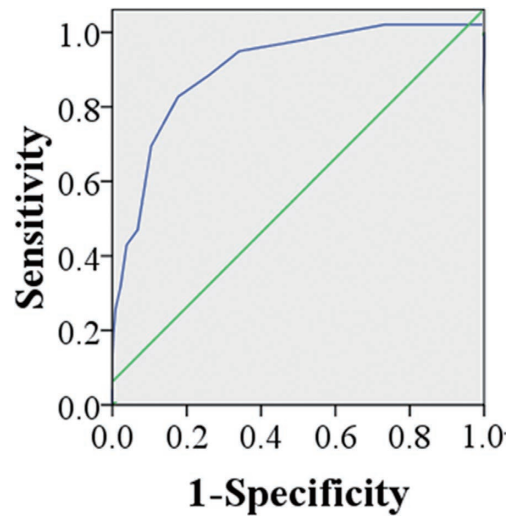

Fig. 1. Receiver operating characteristic curve analysis for mild cognitive impairment risk prediction.
A total of 1,800 subjects who had normal cognitive function seven years ago were enrolled. A cutoff point for baseline serum albumin level was 40.5g/L with a sensitivity of 82.1% and a specificity of 78.2% in predicting the risk of mild cognitive impairment (Area under the curve = 0.860, P < 0.001).

Table 2. Mini-mental state examination in mild cognitive impairment patients and cognitively normal controls.

MMSE[a]	MCI[a] (n = 196)	Normal (n = 1,604)	P value
At baseline	28.6 ± 1.2	28.5 ± 1.3	0.504
At the end	24.5 ± 1.2	28.4 ± 1.3	< 0.001
P value	< 0.001	0.209	

[a]MCI, mild cognition impairment; MMSE, mini-mental state examination.

Table 3. Association of baseline serum albumin levels with mild cognition impairment risk.

Serum albumin level at baseline	MCI[a] (n)	Normal (n)	Univariate adjusted HR (95% CI) [a]	Multivariate adjusted HR (95% CI)[c]
High level group[b]	90	1,069	Reference	Reference
Low level group[b]	106	535	2.17 (1.66-2.80)	2.18 (1.67-2.82)

[a]MCI, mild cognition impairment; HR, hazard ratio; CI, confidence interval.
[b]According to the cutoff point of baseline serum albumin level (40.5 g/L), the subjects were divided into high level group (≥ 40.5 g/L) and low level group (< 40.5 g/L).
[c]Multivariate analysis was adjusted by sex, age, race, body mass index, medical history, medicine history, serum levels of C reactive protein, uric acid and total bilirubin.

Table 4. Association of baseline serum albumin levels with mild cognition impairment risk in subjects with some kind of baseline metabolic, vascular, inflammatory or oxidative stress condition.

Subjects with some kind of baseline condition	MCI[a] (n)	Normal (n)	Univariate adjusted HR (95% CI)[a]	Multivariate adjusted HR (95% CI)[d]
Hypertension				
High level group[b]	65	584	Reference	Reference
Low level group[b]	83	298	2.20 (1.63-2.98)	2.21 (1.63-2.99)
Diabetes				
High level group	28	252	Reference	Reference
Low level group	28	60	3.23 (2.10-5.27)	3.24 (2.12-5.28)
Hyperlipemia				
High level group	20	171	Reference	Reference
Low level group	42	99	2.89 (1.78-4.70)	2.90 (1.79-4.71)
Cardiovascular disease				
High level group	26	264	Reference	Reference
Low level group	68	222	2.66 (1.80-4.19)	2.67 (1.80-4.20)
Cerebrovascular disease				
High level group	11	103	Reference	Reference
Low level group	65	197	2.62 (1.45-4.75)	2.63 (1.46-4.76)
High level of CRP				
High level group	6	82	Reference	Reference
Low level group	15	7	10.10 (4.43-22.88)	10.11 (4.44-22.89)
Relatively low level of UA[c]				
High level group	63	654	Reference	Reference
Low level group	75	188	3.27 (2.42-4.45)	3.28 (2.42-4.46)
Relatively low level of TBIL[c]				
High level group	75	659	Reference	Reference
Low level group	81	189	3.08 (2.30-3.43)	3.09 (2.31-3.44)

[a]MCI, mild cognition impairment; HR, hazard ratio; CI, confidence interval; CRP, c reactive protein; UA: uric acid; TBIL: total bilirubin.

[b]According to the cutoff point of baseline serum albumin level (40.5 g/L), the subjects were divided into high level group (≥ 40.5 g/L) and low level group (< 40.5 g/L).

[c]Because the number of subjects with low level of UA or TBIL was very small, "relatively low level of UA and TBIL" were adopted in the study. "Relatively low level of UA" was defined as "serum UA level < 358.1 μmol/L (arithmetic mean of all subjects)". "Relatively low level of TBIL" was defined as "serum TBIL level < 16.0 μmol/L (arithmetic mean of all subjects)."

[d]Multivariate analysis was adjusted by sex, age, race, body mass index, medical history, medicine history, serum levels of C reactive protein, uric acid and total bilirubin.

relatively low serum levels of albumin showed a more than 100% increased risk of MCI than the subjects who had relatively high serum levels of albumin, which was partly consistent with the previous studies involving Alzheimer's disease patients (Kim et al. 2006; Cankurtaran et al. 2013).

The present study also explored the potential role of serum albumin levels on the risk of MCI in the subjects with specific conditions or their combination. In these conditions, hypertension, diabetes, hyperlipemia, cardiovascular disease, cerebrovascular disease and serum CRP were pathogenic factors for cognitive impairment, and serum UA and TBIL were regarded as protective factors. Synergistic effects of these factors and serum albumin on MCI risk were confirmed.

Many measures in the study ensured the reliability of the conclusion. First, the assessment of cognitive function and the diagnosis of MCI were conducted by a team of psychologists using recognized standards. Second, during the 7-year follow-up period, all the research data came from the medical records, which effectively avoided the recall bias. Third, it was a cohort study without a cross-section design, which avoided the possible reverse causality. Fourth, many potential confounding factors were not equally distributed between the MCI patients and the cognitively normal controls. A multivariate COX regression analysis was performed to eliminate the interference of the confounding factors.

In the study, the cutoff value for serum albumin level was 40.5 g/L, and it was much higher than the lower limit of normal range for serum albumin. This cutoff value should be verified by other studies in the future. If it was confirmed, the normal range for serum albumin in elderly might be adjusted. Because cognitive impairment is very common in this age group, updated normal range of serum albumin might be useful for the controlling of cognitive impairment.

Table 5. Association of baseline albumin levels with mild cognition impairment risk in subjects with a number of metabolic, vascular, inflammatory and oxidative stress conditions.

Number of condition in each subject	MCI[a] (n)	Normal (n)	Univariate adjusted HR (95% CI)[a]	Multivariate adjusted HR (95% CI)[c]
0-1				
High level group[b]	11	184	Reference	Reference
Low level group[b]	6	95	1.09 (0.45-2.81)	1.10 (0.46-2.82)
2-3				
High level group	43	426	Reference	Reference
Low level group	41	195	1.95 (1.31-2.88)	1.96 (1.32-2.89)
4-5				
High level group	31	339	Reference	Reference
Low level group	39	164	2.33 (1.51-3.61)	2.34 (1.52-3.62)
5-6				
High level group	5	120	Reference	Reference
Low level group	20	81	4.50 (1.95-12.79)	4.52 (1.96-12.80)

[a]MCI, mild cognition impairment; HR, hazard ratio; CI, confidence interval.
[b]According to the cutoff point of baseline serum albumin level (40.5 g/L), the subjects were divided into high level group (≥ 40.5 g/L) and low level group (< 40.5 g/L).
[c]Multivariate analysis was adjusted by sex, age, race, body mass index, medical history, medicine history, serum levels of C reactive protein, uric acid and total bilirubin.

Serum albumin is a common protein in human blood, and it exerts a variety of biological functions. Several possible mechanisms have been suggested to explain the effect of serum albumin on MCI risk. First, serum albumin is associated with nutritional status in elderly (Covinsky et al. 2002), and persistent malnutrition plays an important role in cognitive impairment (Yildiz et al. 2015; Karakis et al. 2016). Therefore, relatively low serum level of albumin partly reflects the malnutrition, which promotes the progression of MCI. Second, serum albumin is extremely important in maintaining colloid osmotic pressure and blood volume in human body (Ohlsson et al. 1981). Blood pressure and other vascular factors are implicated in cognitive impairment (Sabayan and Westendorp 2015; Yuan et al. 2016b). Lower albumin level interferes with the proper blood-supply to central nervous system and results in cognitive impairment. Third, oxidative stress injury is a non-negligible pathogenic factor for cognitive impairment (Owen et al. 1997; Mao 2013). Serum albumin has a strong anti-oxidative activity (Ishizaka et al. 2007; Guo et al. 2011), and the decrease of its level leads to oxidation/anti-oxidation imbalance and the development of cognitive impairment.

In conclusion, the study revealed that relatively low serum levels of albumin at baseline might be an independent risk factor for MCI in elderly. The study also obtained several lines of evidence that low albumin levels and other kinds of pathogenic factors (metabolic, vascular, inflammatory or oxidative stress) exert a significant synergistic effect on the risk of MCI.

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Conflict of Interest

The authors declare no conflict of interest.

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