Albumin, haemoglobin, BMI and cognitive performance in older adults

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Abstract

Objectives: to examine the relationships between serum albumin, haemoglobin and body mass index (BMI) with cognitive performance among community-living older adults.

Method: design—population-based cross-sectional study; setting—local community in Southeast Region of Singapore; subjects—Chinese older adults aged 55 and above (N = 2,550); measurements—serum albumin, haemoglobin, BMI and Mini-Mental State Examination (MMSE).

Results: in multivariable analyses controlling for gender, age, education and vascular risk factors, low albumin in the bottom quintile (OR 2.04; 95% CI 1.22–3.41) and low haemoglobin in the bottom quintile (OR 1.56; 95% CI 1.00–2.47) and low BMI with chronic comorbidity (OR 1.73; 95% CI 1.02–2.95) were independently associated with poor cognitive performance (MMSE ≤ 23). Among cognitively intact respondents (MMSE ≥ 24), albumin concentration showed a significant inverse linear relationship with MMSE scores (P for trend = 0.002).

Conclusion: low albumin, low haemoglobin and low BMI (in the presence of chronic comorbidity) are independently associated with poor cognitive performance in community-living older adults.

Keywords: albumin, haemoglobin, anaemia, body mass index, cognition, elderly

Introduction

There is much interest in studies elucidating the role of nutritional factors for impaired cognition and dementia risk. Many studies have investigated specific nutrients such as folic acid, cyanocobalnine, dietary antioxidants, n-3 polyunsaturated fatty acids and fish intake [1], but to date the evidence remains inconclusive. It is possible that the individual effects of single nutritional factor(s) are less discernible or pronounced than their collective effect. Researchers pursuing this line of inquiry have assessed general dietary and nutritional status using conventional clinical markers, such as body mass index (BMI), albumin and haemoglobin.

A few population-based studies have reported that a healthy and well-balanced diet was associated with better cognitive function [2, 3]. In hospital-based studies, cognitive impairment was shown to be inversely associated with increasing BMI and serum albumin [4]. A few population-based studies have suggested that low albumin may be an independent risk factor for poor cognitive status and dementia [5–8]. However, population studies that investigated the link between anaemia and cognitive status and dementia risk have produced inconsistent results [9–14]. Results of the relationship between high BMI or obesity and cognitive status are also inconsistent [15–20], but most studies suggested that low BMI was related to dementia risk [17–20]. Most studies did not investigate albumin, haemoglobin and low BMI concurrently in the same individual, hence their independent relationship with cognitive function are unclear.

Large numbers of community-living elderly are known to be at risk of malnutrition, due to chronic diseases, multiple drug use, reduced mobility and age-related physiological and social changes [21]. Thus, establishing the relationship between nutritional markers such as BMI, albumin and haemoglobin with cognitive status has potential practical significance for preventing cognitive impairment and improving cognitive functioning in the elderly.

In this population-based study, we examined the independent associations of low albumin, low haemoglobin and low BMI with cognitive performance in community-living older adults.
Obesity Prevention and Control in Singapore [24]. Consultation and Recommendations of the Taskforce as below 18.5 kg/m², according to recent WHO Expert trained research nurses, in the preferred language or dialect interviews, assessments and tests, which were performed by of Singapore Institutional Review Board, and all participants excluded. The study was approved by the National University of Singapore Institutional Review Board, and all participants gave signed informed consent. Participants completed an extensive series of face-to-face interviews, assessments and tests, which were performed by trained research nurses, in the preferred language or dialect (English or Chinese).

Cognitive performance
This was assessed by the Mini-Mental State Examination (MMSE) [22], which measures global cognitive functioning on domains that included memory, attention, language, praxis and visuo-spatial ability, with summed scores ranging from 0 to 30, higher values denoting better cognitive functioning. We used the Chinese version of the MMSE, which was externally validated for local use in another study population of Singaporean older adults [23]. Poor cognitive performance was defined by MMSE total score of 23 or less, which was externally validated to have high sensitivity (95.5%) and specificity (83.5%) for detecting cases of dementia in older Chinese adults [23].

Laboratory measurements
Overnight fasting venous blood samples were analysed for serum level of albumin (g/l) on Advia 2400 auto-analyser (Bayer HealthCare Diagnostics) using Bromcresol Green (BCG) dye binding method (CV ranging from 1% to 3%). The measurements of haemoglobin level (g/dl) and creatinine (μmol/l, Jaffe’s method) were performed on the same automated system. The APOE genotyping was identified by PCR amplification followed by restriction endonuclease digestion of the PCR product (PCR-RFLP).

Height and weight was measured with a portable Seca stadiometer (Model 708, Vogel & Hake Hamburg, Germany), with BMI calculated as kg/m². Low BMI was defined as below 18.5 kg/m², according to recent WHO Expert Consultation and Recommendations of the Taskforce for Obesity Prevention and Control in Singapore [24].

Confounding risk factors
Socio-demographic data included age, gender and education. Respondents were asked to report whether in the 12 months prior to the interview they were diagnosed and treated by a doctor for any one or more specific medical conditions, which included asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, heart failure, hypertension, diabetes, stroke, hip fracture, arthritis, cataract and other conditions specified by them. The presence of hypertension was defined by a self-report of high blood pressure, and/or treatment with anti-hypertensive drugs and/or sitting systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg. The presence of diabetes was defined as self-report of diabetes and/or treatment with oral hypoglycemic agents or insulin, and/or fasting blood glucose > 7.0 mmol/l. Dyslipidemia was defined as self-reported lipid abnormality, and/or total cholesterol ≥ 6.5 mmol/l and/or LDL-cholesterol ≥ 4.1 mmol/l and/or TG ≥ 2.3 mmol/l and/or HDL-Cholesterol < 1.0 mmol/l and/or total cholesterol: HDL-cholesterol ratio > 4.5.

Participants were categorised by their alcohol and smoking history as drinkers who consumed at least one alcoholic drink daily, and current smokers, past-smokers or non-smokers.

A single question on self-rated health status (‘In general, would you say your health is excellent, very good, good, fair, poor?’) was used to categorise subjects as having ‘poor and fair’ versus ‘good, very good and excellent’ health.

Physical functional status was assessed by the subject’s dependence in performing basic activities of daily living (BADL) using items from the Barthel’s scale [25], and instrumental activities of daily living (IADL) from the Lawton scale [26]. Functional disability was defined as needing help in one or more BADL or IADL tasks, and respondents were categorised as independent, IADL disability only or BADL disability.

The presence of depression was determined by the short 15-item version of the Geriatric Depression Scale (GDS) [27]. The use of the GDS avoids the measurement artefact due to overlapping symptoms of the somatic illness and symptoms indicative of depression.

Participation in leisure time activities were measured by the frequency (0 = never, 1 = sometimes, 3 = often) with which the respondents engaged in fitness activities (such as walking, exercise routines and sports), social activities (such as attending religious services, cinemas and sports events; playing cards, games, karaoke, dancing) and productive activities (such as hobbies, preparing meals, shopping, community work, employment or business). Each respondent’s level of leisure time activities was measured by categorising the summed scores in tertile groups.

Statistical analysis
Data were analysed for 2,550 Chinese respondents after excluding a small number (N = 195) of Malays and Indians, 49 respondents without haemoglobin data and 11 respondents who did not complete MMSE. Respondents were categorised into quintile groups of albumin and haemoglobin concentrations, so as to explore variations in risks of cognitive impairment across the full range of biological values.

Group comparisons of categorical and continuous variables were performed using chi-squared test or analysis of
Chronic comorbidity (Wald statistic, 4.097, 1 df, there was a significant interaction between low BMI and associated with poor cognitive performance, but low BMI and haemoglobin quintiles were independently and in the presence of other nutritional variables (Table 2), multivariable analyses that controlled for gender, age and education, dyslipidaemia, hypertension, cardiovascular disease, stroke, diabetes, creatinine, smoking, alcohol, depression, self-rated health, physical functional status and APOE ε4 status (Model 2); and finally with haemoglobin, albumin and low BMI together (Model 3).

In further analyses, which excluded respondents with MMSE ≤ 23, we used generalised linear regression modelling techniques to compare adjusted mean MMSE scores among the albumin and haemoglobin quintile groups and BMI categories, controlling for confounding variables.

Collinearity checks were performed by preliminary inspection of correlation matrices, tolerance values <0.25 and variance inflation factor >4; in hierarchical logistic regression models, specific independent variables were added and omitted one at a time to assess if any effect was seen on the coefficients and fit of the final model. Adequacy of the fit was assessed by estimation of the deviance and the Hosmer-Lemeshow statistic. Statistical analyses were performed using SPSS statistical software version 14.0 (SPSS Inc, Chicago Il). All reported statistical tests were two-sided. A P value of <0.05 was accepted as statistically significant.

Results

The mean age of the respondents was 65.8 years (SD 7.6, range: 55–98); 51.8% had less than 6 years of schooling. Poor cognitive performance (MMSE ≤ 23) was present in 298 respondents (11.7%); low albumin (<40 g/l) in 497 respondents (19.5%), low haemoglobin (<12.2 g/dl in females, and 13.3 g/dl in males) in 472 respondents (18.5%); low BMI (<18.5 kg/m²) was found in 155 respondents (6.1%), and 137 (5.4%) had low BMI together with one or more chronic medical condition(s).

In bi-variate analyses, albumin, haemoglobin and BMI status were all significantly associated with poor cognitive performance. Demographic, vascular and other risk factors and correlates of poor cognitive performance varied across quintile groups of the nutritional variables (Table 1). In multivariable analyses that controlled for gender, age, education, as well as vascular risk factors and other correlates, and in the presence of other nutritional variables (Table 2), low albumin and haemoglobin quintiles were independently associated with poor cognitive performance, but low BMI was not (Wald statistic 2.053, 1 df, P = 0.15). However, there was a significant interaction between low BMI and chronic comorbidity (Wald statistic, 4.097, 1 df, P = 0.043).

Albumin

The prevalence of poor cognitive performance increased from 7.0 to 21.9% with descending quintiles of albumin. In multivariable analyses (Model 3, Table 2), the linear trend in ORs across the albumin quintiles was statistically significant (P < 0.001); the lowest albumin quintile was associated with a 2-fold increased risk of poor cognitive performance (OR 2.04; 95% CI 1.22–3.41) independently of other risk and nutritional factors.

Haemoglobin

The prevalence of poor cognitive performance increased from 7.4 to 20.1% with descending quintiles of haemoglobin. In multivariable analysis (Model 3, Table 2), the lowest haemoglobin quintile was associated with an increased risk of poor cognitive performance (OR 1.56; 95% CI 1.00–2.47) independently of albumin and other factors. However, there was no significant linear trend of relationship of poor cognitive performance across descending quintiles of haemoglobin.

Low BMI and chronic comorbidity

We found that low BMI by itself was not significantly associated with poor cognitive performance, but in the presence of chronic comorbidity it was. We therefore estimated OR for low BMI and chronic comorbidity as a predictor variable. The prevalence of poor cognitive performance in respondents with low BMI and chronic comorbidity was 22.6%, significantly more than in those without (11.1%). In multivariable analyses (Model 3, Table 2), low BMI and chronic comorbidity was associated with an increased risk of poor cognitive performance (OR 1.73; 95% CI 1.02–2.95), independently of low albumin, low haemoglobin and other risk factors.

We also repeated the analysis in a subset of 2,252 (Table 3) respondents after excluding those with poor cognitive performance (MMSE score ≤ 23). In these respondents, increasing albumin quintiles showed a significant inverse linear relationship with MMSE scores (P for linear contrast = 0.022) in generalised linear regression models, which fully adjusted for confounding variables (Table 3). Neither haemoglobin quintiles nor low BMI and chronic comorbidity were significantly associated with MMSE scores in this analysis.

Discussion

The results of our study suggested that low albumin levels, low haemoglobin and being underweight while having a chronic disease(s) were independent risk factors of poor cognitive performance in older persons.

In case-control studies [5, 7], serum albumin has been reported to be decreased in patients with Alzheimer’s disease (AD) compared to controls, but it is possible that it might be lowered because of poor feeding associated with the underlying cognitive impairment. The association of low albumin and cognitive impairment observed in our cross-sectional study is also subject to the same limitation in causal inference. However, we were able to show that in cognitively better functioning individuals it was inversely associated with
has also reported an association of low albumin with MMSE performance. A previous cross-sectional study [8] has also reported an association of low albumin with MMSE scores in the whole sample, but not when respondents with MMSE scores <21 were excluded. Our result however was based on a larger sample size and stricter exclusion criteria for MMSE at ≤ 23, and hence was more robust. Our results also agree with a previous longitudinal study that showed an association of serum albumin with cognitive decline [6].
Studies investigating the association of anaemia with cognitive decline and dementia risk have given mixed results [9–14]. Case-control [9–11] and longitudinal studies have reported increased odds of association of anaemia with dementia or Alzheimer’s disease [13] or cognitive decline [14] or failed to show an association [9]. Cross-sectional studies of community-living elderly have variously reported a linear relationship [12] or a U-shaped relationship [11]. Our results did not support a U-shaped relationship. Our study of community-living older adults also agrees with a study of chronic heart failure (CHF) patients that reported independent associations

### Table 2. Odds ratios (95% CI) of association of quintiles of haemoglobin and albumin and low BMI-and-chronic illness with cognitive impairment

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
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<tr>
<td><strong>Albmin</strong></td>
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<tr>
<td>1 (&lt;40 g/l)</td>
<td>3.72  2.39, 5.81</td>
<td>2.20  1.32, 3.65</td>
<td>2.04  1.22, 3.41</td>
</tr>
<tr>
<td>2 (40–41 g/l)</td>
<td>1.72  1.07, 2.76</td>
<td>1.54  0.91, 2.62</td>
<td>1.51  0.89, 2.56</td>
</tr>
<tr>
<td>3 (42–43 g/l)</td>
<td>1.63  1.02, 2.59</td>
<td>1.59  0.94, 2.67</td>
<td>1.53  0.91, 2.58</td>
</tr>
<tr>
<td>4 (44–45 g/l)</td>
<td>0.92  0.54, 1.55</td>
<td>1.02  0.58, 1.81</td>
<td>1.03  0.58, 1.84</td>
</tr>
<tr>
<td>5 (≥46 g/l)</td>
<td>1.00  1.00</td>
<td>1.00  1.00</td>
<td>1.00  1.00</td>
</tr>
<tr>
<td><strong>P (linear trend)</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;12.2 g/dl)</td>
<td>3.14  2.13, 4.62</td>
<td>1.66  1.05, 2.61</td>
<td>1.56  1.00, 2.47</td>
</tr>
<tr>
<td>2 (12.2–13.1 g/dl)</td>
<td>1.85  1.23, 2.78</td>
<td>1.36  0.86, 2.16</td>
<td>1.33  0.84, 2.12</td>
</tr>
<tr>
<td>3 (13.1–14.1 g/dl)</td>
<td>1.28  0.83, 1.98</td>
<td>1.27  0.78, 2.07</td>
<td>1.26  0.88, 2.05</td>
</tr>
<tr>
<td>4 (14.1–15.3 g/dl)</td>
<td>1.33  0.86, 2.05</td>
<td>1.48  0.91, 2.42</td>
<td>1.48  0.91, 2.42</td>
</tr>
<tr>
<td>5 (≥15.4 g/dl)</td>
<td>1.00  1.00</td>
<td>1.00  1.00</td>
<td>1.00  1.00</td>
</tr>
<tr>
<td><strong>P (linear trend)</strong></td>
<td>&lt;0.001</td>
<td>0.017</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Low BMI-and-chronic comorbidity</strong></td>
<td>2.35  1.54, 2.58</td>
<td>1.93  1.15, 3.24</td>
<td>1.73  1.02, 2.95</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted. Model 2: Adjusted for gender, age, education, dyslipidaemia, hypertension, cardiovascular disease, stroke, diabetes, creatinine, smoking, alcohol, depression, self-rated health, physical functional status, leisure time activity level, APOE e4 status. (variables categorised as in Table 2). Model 3: Adjusted for variables in Model 2 and albumin, haemoglobin, low BMI-and-chronic comorbidity. In these models, creatinine and GDS scores were entered as continuous variables.

### Table 3. MMSE scores by albumin, haemoglobin, BMI categories in subset of respondents with MMSE ≥ 24 (N = 2,252)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>MMSE scores adjusted*</th>
<th>Analysis of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SE</td>
<td>Overall F = 2.862, 4 df, P = 0.022</td>
</tr>
<tr>
<td><strong>Albumin quintiles</strong></td>
<td></td>
<td></td>
<td>Linear contrast, P = 0.002</td>
</tr>
<tr>
<td>1 (&lt;40 g/l)</td>
<td>388</td>
<td>27.67 ± 0.22</td>
<td>Quadratic contrast: P = 0.56</td>
</tr>
<tr>
<td>2 (40–41 g/l)</td>
<td>470</td>
<td>27.87 ± 0.22</td>
<td>Quadratic contrast: P = 0.56</td>
</tr>
<tr>
<td>3 (42–43 g/l)</td>
<td>546</td>
<td>27.86 ± 0.22</td>
<td>Quadratic contrast: P = 0.56</td>
</tr>
<tr>
<td>4 (44–45 g/l)</td>
<td>490</td>
<td>27.99 ± 0.22</td>
<td>Quadratic contrast: P = 0.56</td>
</tr>
<tr>
<td>5 (≥46 g/l)</td>
<td>358</td>
<td>28.02 ± 0.23</td>
<td>Quadratic contrast: P = 0.56</td>
</tr>
<tr>
<td><strong>Haemoglobin quintiles</strong></td>
<td></td>
<td></td>
<td>Overall F = 2.37, 4 df, P = 0.05</td>
</tr>
<tr>
<td>1 (Men: &lt;13.3 g/dl; women: &lt;12.2 g/dl)</td>
<td>377</td>
<td>27.90 ± 0.22</td>
<td>Linear contrast: P = 0.56</td>
</tr>
<tr>
<td>2 (Men: 13.3–14.1 g/dl; women 12.2–12.7 g/dl)</td>
<td>445</td>
<td>27.97 ± 0.21</td>
<td>Quadratic contrast: P = 0.99</td>
</tr>
<tr>
<td>3 (Men: 14.2–14.7 g/dl; women 12.8–13.2 g/dl)</td>
<td>466</td>
<td>27.73 ± 0.22</td>
<td>Quadratic contrast: P = 0.99</td>
</tr>
<tr>
<td>4 (Men: 14.8–15.3 g/dl; Women: 13.3–13.7 g/dl)</td>
<td>441</td>
<td>27.99 ± 0.22</td>
<td>Quadratic contrast: P = 0.99</td>
</tr>
<tr>
<td>5 (Men: ≥15.4 g/dl; women: ≥13.8 g/dl)</td>
<td>523</td>
<td>27.82 ± 0.22</td>
<td>Quadratic contrast: P = 0.99</td>
</tr>
<tr>
<td><strong>Low BMI-and-chronic comorbidity</strong></td>
<td></td>
<td></td>
<td>Overall F = 0.047, 1 df, P = 0.83</td>
</tr>
<tr>
<td>Yes</td>
<td>124</td>
<td>27.90 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2128</td>
<td>27.86 ± 0.20</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for gender, age, education, dyslipidaemia, hypertension, cardiovascular disease, stroke, diabetes, creatinine, smoking, alcohol, depression, self-rated health, physical functional status, leisure time activity level and APOE e4 status, albumin, haemoglobin, low BMI-and-chronic comorbidity (variables categorised as in Table 2). Creatinine and GDS scores were entered as continuous variables.
of anaemia and low serum albumin with cognitive impairment [7].

We observed that in the presence of low albumin and low haemoglobin, being underweight while having a chronic condition(s) appeared to be a significant risk marker. This variable may be a surrogate indicator for body mass loss associated with the presence of chronic diseases. Its association with poor cognitive performance is also consistent with reports of significant weight loss associated with a diagnosis of dementia and the high prevalence of cognitive impairment in association with cachexia in patients with congestive heart and renal failure [12].

There is increasing evidence that inflammatory mechanisms are involved in the pathogenesis of dementia and AD [28]. Chronic systemic low-grade inflammation may be the common factor mediating the relationships observed in our study. In older persons, inflammatory activity is increased by the contributions of genetic factors, smoking, infections, obesity and declining sex hormone activities, and exacerbated by the presence of age-associated diseases. Although low serum albumin and haemoglobin are conventionally regarded as biochemical and haematological markers of protein-calorie malnutrition, they are also involved in chronic inflammation. Albumin is a negative acute-phase protein whose plasma concentration in patients with chronic diseases typically decreases in response to chronic inflammation [29]. Anaemia in individuals with chronic diseases is the result of suppressed erythropoiesis by chronic inflammation. In the presence of chronic diseases, low BMI results when there is preferential loss of skeletal muscle mass (sarcopenia), as well as fat tissues and bone mass, and is a manifestation of inflammatory activities that characterise cachexia and chronic diseases. The combination of malnutrition and inflammation in older persons has been termed 'malnutrition–inflammation complex syndrome' (MICS) [30] and is well described in cachexic patients with CHF, renal failure, diabetes, COPD, cancers, severe infections, injury and geriatric conditions.

Our quintile cut-off values of low albumin (40 g/l) and low haemoglobin (12.2 g/dl in women and 13.3 g/dl in men) approximate the conventional cut-offs used clinically to define hypoalbuminemia (35 g/l) and anaemia (12 g/dl in women and 13 g/dl in men). Similar results were obtained in re-analysis using clinical cut-off of albumin <35 g/l. Our findings suggest that the identification of hypoalbuminemia, anaemia and loss of body mass in the elderly may be useful in the early detection and treatment of cognitive impairment and dementia. Limited evidence also suggests that in patients with CHF, cancer and stroke, restoration of haemoglobin levels and albumin [7] was associated with improved cognitive function. Further longitudinal and interventional studies in community-living elderly are needed.

Conclusion
In community-living older adults, low albumin, low haemoglobin and low BMI in the presence of chronic comorbidity are independently associated with cognitive impairment. These results suggest their practical use as nutritional risk markers of cognitive impairment in primary care programmes for the elderly.

Key points
• Albumin, haemoglobin and low BMI in the presence of chronic comorbidity were independently associated with poor cognitive performance in community-living older adults.
• Serum albumin, haemoglobin and BMI may be used as nutritional risk markers for screening and treating cognitive impairment in primary care.

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References


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