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Serum Albumin Concentration and Cognitive Impairment

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Abstract

Results from clinical samples suggest low serum albumin may be associated with cognitive impairment, though evidence from population-based studies is inconclusive. Participants were 1,752 adults (699 men and 1,053 women) aged 65 years and over from the Health Survey for England 2000, a nationally representative population-based study. Cognitive impairment was assessed using the Abbreviated Mental Test Score. The cross-sectional relation of serum albumin quartiles to cognitive impairment was modelled using logistic regression. Two hundred and twelve participants were cognitively impaired (68 men and 144 women). Odds ratios (95% confidence intervals) for cognitive impairment in the first (2.2–3.8 g/dl), second (3.9–4.0 g/dl), and third (4.1–4.3 g/dl) quartiles of serum albumin compared with the fourth (4.4–5.3 g/dl) were 2.5 (1.3–5.1), 1.7 (0.9–3.5), and 1.5 (0.7–2.9), after adjustment for age, sex, education and additional risk factors for cognitive impairment (p for linear trend = 0.002). A highly similar pattern of associations was observed for men and women. Our data provide new evidence to suggest that low serum albumin is independently associated with increased odds of cognitive impairment in the elderly population.

Keywords

Cognition; cognitive disorders; dementia; risk factors; serum albumin

INTRODUCTION

The etiology of cognitive impairment remains unclear, though this debilitating condition has been estimated to affect around 8.7 million people aged 71 years or older in the United States. [1,2] Critical to translating new therapies into improved patient care is the development of cost-effective panels of biomeasures that complement cognitive testing, clinical examination, and neuroimaging. Serum albumin is of interest as it is the most abundant protein in human plasma, a marker of liver function, a negative acute-phase marker, and a key antioxidant [3–5]

Findings from highly selected clinical samples suggest serum albumin concentration may be associated with cognitive impairment and dementia. For example, low levels of serum albumin were found to be associated with an increased risk of cognitive impairment in 1,511 hospitalized patients with heart failure,[6] and 331 elderly rehabilitation patients with hip fractures.[7] Lower levels of serum albumin have also been observed in Alzheimer's disease (AD) patients in comparison with healthy volunteer controls in some,[5,8] but not all small clinical studies [9]. However, results from large representative population-based studies are limited and equivocal, and the external validity of previous clinical results is largely unknown. Low levels of serum albumin were independently associated with poor cognitive performance on the Mini-Mental State Examination (MMSE) in a study of 2,550 Chinese community-living older adults. [10] An association between low serum albumin and cognitive function and decline was also observed in 1,284 older adults from the Longitudinal Study Amsterdam, though this was limited to a borderline association with MMSE scores.[3] While serum albumin concentrations did not differ according to cognitive function in 540 older cognitively normal adults from the single-centre Conselice Study of Brain Aging.[11] We therefore examined the association between serum albumin and cognitive impairment in a large representative sample of elderly adults.

MATERIALS AND METHODS

Participants

Participants were from the Health Survey for England 2000 (HSE), a nationally representative population-based study of the adult and child population living in private households and adults aged 65 and over resident in nursing and residential homes (care homes).[12] For community residents, a stratified sample of 360 postcode sectors (geographic areas) were selected as primary sampling units, and 19 addresses were selected from each of these, giving a total selected sample of 6,840 addresses, of which 91% contained private households. All people within eligible households were invited to participate, and 7,988 interviews were conducted, of which 1,677 were aged 65 years or over (the response rate for this group was 71%). For the institutionalized sample, care homes were selected through multilevel stratified sampling using local authorities as the primary sampling unit. A random sample of six residents aged 65 and older were randomly selected from each care home. Interviews were conducted in person or using proxies where appropriate. Of the 607 care homes sampled, 544 (90%) took part. Of the 2,493 interviews, 1,220 (49%) were conducted in person and 1,273 (51%) by proxy. A blood sample was obtained from 1,818 participants who gave written informed consent, and a valid serum albumin sample was obtained from 1,752 participants (699 men and 1,053 women). The HSE was approved by the London Multicentre Research Ethics Committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Serum Albumin

One non-fasting blood sample was collected into a 6ml plain tube (no anticoagulant) by a nurse. [12] Specimens were then dispatched to The Royal Victoria Infirmary in Newcastle in England for analysis. Analyses were carried out using the DAX system (Bayer Diagnostic, Dublin, Ireland) according to standard operating procedures by State Registered Medical Laboratory Scientific Officers under the supervision of the senior officer. An anionic dye, bromocresol green (BCG) preferentially binds serum albumin at pH 4.2, this albumin-dye complex is determined spectrophotometrically. The increase of absorbance measured at 604nm after 30 seconds is directly proportional to the concentration of complexed albumin.[13] Assay parameters are pre-programmed into each DAX system. Monthly internal quality control results and external quality assessment results for serum albumin were acceptable [12]

Cognitive impairment

Cognitive function was measured using the Abbreviated Mental Test (AMT), a widely used neuropsychological test composed of items primarily covering attention, time and space orientation, and memory. [14] Cognitive impairment was defined on the basis of three or more incorrect responses out of 10. Such a cut-point has been used in previous studies and is a sensitive and specific marker of cognitive impairment [15–17]. The AMT is also highly correlated with the MMSE [18].

Data analysis

Two-sample t-tests (equal variances not assumed) and Fisher's exact tests were used as appropriate to compare unadjusted continuous and categorical characteristics of the study population by cognitive status. Multivariable logistic regression models were used to determine the relationship of serum albumin to cognitive impairment. We divided levels of serum albumin (g/dL) into quartiles to aid clinical interpretation. In basic adjusted models we adjusted for age in years, sex and education (those with any educational qualifications versus those with none) as these are established potential confounders in cognitive research. [19] In fully adjusted models we also adjusted for additional correlates of cognitive impairment: ethnic origin (collapsed into white and ethnic minorities), current smoking status, alcohol consumption (g/day), psychiatric morbidity (>3 symptoms on the 12-item General Health Questionnaire [20]), vitamin D deficiency (serum 25-hydroxyvitamin D <50 nmol/L), [21] and self-reported medical history (diagnosed diabetes, cardiovascular disease, stroke, and hypertension). Because concomitant illness, such as influenza, may lower levels of serum albumin we also adjusted for self-reported acute sickness occurring within the previous two weeks in the fully adjusted models³. Possible two-way interactions between serum albumin and age or sex were tested by including product terms into a fully adjusted logistic regression model. In a series of secondary analyses we examined whether the same pattern of associations was observed when men, women, community residents and the institutionalized were analyzed separately.

As an alternative cut-point of four or more incorrect responses (a score of <7) is sometimes used to define cognitive impairment using the AMT, [6,14] we examined the effect of changing the cut-point used to define cognitive impairment in a sensitivity analysis. Information on body mass index (BMI [kg/m²]) was available for a subsample of 1,268 participants, and we examined whether the same pattern of associations was observed with additional adjustment for BMI. Clusters (individual households or institutions), strata (residential status), and survey weights derived using inverse probability weighting were used to adjust for the survey design, sampling strategy and possible non-response bias. We used Stata SE version 9.2 for all analyses (StataCorp, College Station, TX).

RESULTS

The characteristics of the study population are described in Table 1. Unadjusted mean serum albumin levels were higher in the cognitively normal than the cognitively impaired, and very few people with cognitive impairment had levels of serum albumin in the fourth quartile of the distribution (4.4–5.3 g/dL). The cognitively impaired group was also generally older than the cognitively normal group, less likely to have any educational qualifications, report having an acute sickness in the preceding fortnight and consume moderate amounts of alcohol, and more likely to have lower BMI, vitamin D deficiency and a history of stroke.

In an unadjusted logistic regression model those in the lowest quartile of serum albumin concentration were more than six times more likely to be cognitively impaired, and there was clear evidence for a dose-response relationship (Table 2). This association was attenuated with adjustment for age, sex and education, though it remained significant. Adjustment for

additional correlates of cognitive impairment had little effect, and in the fully adjusted model those with the lowest levels of serum albumin were more than twice as likely to be cognitively impaired. No two-way interaction between serum albumin and age was observed ($p = 0.375$).

Highly similar patterns of associations was observed for women and men when examined separately using fully adjusted logistic regression models (Fig. 1), and there was no two-way interaction between serum albumin and sex ($p = 0.495$). There was evidence for a linear increase in the odds of cognitive impairment by serum albumin quartiles for both men ($p = 0.044$) and women ($p = 0.005$). When institutionalized and community living participants were examined separately the association was less clear. There was little evidence for an association amongst institutionalized participants (Table 3). There was evidence for a linear increase in the odds of cognitive impairment by albumin quartiles in community living participants in an unadjusted model, though this was not statistically significant in a fully adjusted model (Table 4). Neither using an alternative cut-point of four or more incorrect responses on the AMT to define cognitive impairment nor adding additional adjustment for BMI had a substantial impact on the pattern of results observed (data not shown).

DISCUSSION

The aim of the present study was to examine the association between serum albumin and cognitive impairment in a large population-based sample of elderly adults. Levels of serum albumin were generally lower in the cognitively impaired general population, and there was evidence of a dose-response relationship. Men and women showed the same pattern of results, and these results were not sensitive to adjustment for covariates or the cut-point chosen to define cognitive impairment.

The current findings are consistent with a number of case control studies linking low levels of serum albumin with cognitive impairment [6,7] and dementia [5,8]. However, results from previous population-based studies have been equivocal. Our results are similar to the linear association between serum albumin levels and MMSE performance in community-living older Chinese adults recently observed by Ng and colleagues. [10] Dik and colleagues observed a borderline association with the MMSE, but observed no significant associations with information-processing speed, immediate recall, delayed recall or fluid intelligence. [3] However, they do not appear to have adjusted for the complex survey sampling design of the Longitudinal Aging Study Amsterdam, nor did they incorporate any kind of correction for nonrandom response patterns, and these factors may have attenuated any associations with cognitive function given that non-response and attrition in population-based studies are known to vary on the basis of cognitive function. [22] Ravaglia and colleagues found no association between levels of cognitive function and serum albumin in cognitively normal subjects at a single-centre, [11] but the effects of the cognitive homogeneity or geographically limited nature of the population they studied are unclear.

When interpreting our results a number of limitations should be considered. Although information on cognitive impairment from a widely used standardized cognitive test was available, a neurological examination was not incorporated in the HSE. AMT items primarily relate to attention, orientation and memory, and it would be informative to examine the association between serum albumin and cognitive deficits in additional domains (for example verbal fluency and executive functions). Although we incorporated a large representative sample of the older English population whilst allowing for the complex sampling design, our results may not be generalizable to more ethnically diverse populations or those at different latitudes. In our secondary analyses where associations were examined in subsamples confidence intervals were inflated and statistical power was reduced. This may explain why relatively high odds ratios (>2.5) in the analysis of community living participants were not

statistically significant. Concomitant illness may lower levels of serum albumin, and the resulting noise may have led to an underestimation of the reported associations. [3] However, adjusting for acute sickness occurring within the preceding fortnight did not alter the pattern of results observed. As we analysed cross sectional data our study does not demonstrate a causal relationship. While we controlled for a wide range of potential confounders the possibility of residual confounding remains.

There is increasing evidence that inflammatory mechanisms are involved in the pathogenesis of cognitive impairment and dementia. [23] Case control studies of inflammatory proteins generally suggest that demented individuals have increased levels of interleukin-6, C-reactive protein and decreased serum albumin (a negative acute-phase marker).[7] Data from the population-based Honolulu-Asia Aging Study suggest that inflammatory processes may precede clinical symptoms by 25 years. [24] Oxidative injuries are also important in the pathogenesis of cognitive impairment and dementia. Free radicals induce cell death by damaging lipids, DNA, proteins, and carbohydrates while reactions between free radicals and neurotransmitters can lead to the formation of endogenous neurotoxins. [25] Serum albumin constitutes the plasma's primary oxygen radical trapping and antioxidant defense, both against oxidizing agents generated endogenously and exogenous substances. [26] Serum albumin plays a vital role in the binding of drugs, hormones, iron and free fatty acids, and reduced levels may contribute to cognitive impairment resulting from toxicity. [27] Albumin also inhibits the formation of amyloid beta-peptide fibrils, [28] and low levels of albumin in the brain and cerebrospinal fluid may therefore lead to increased Alzheimer's type pathology.[29] While serum albumin levels may lead to cognitive impairment, reverse causality is also possible, and cognitive impairment may result in lowered serum albumin. For example, cognitively impaired individuals unable to feed themselves adequately may become malnourished, [30] and malnutrition may in turn result in low levels of serum albumin.[31] Although adjustment for vitamin D deficiency and BMI had little effect, serum albumin levels may be modified by dietary factors that are not adequately captured by serum vitamin D concentration and BMI.

In conclusion, our results suggest that in a large representative sample of older adults low levels of serum albumin are associated with increased odds of cognitive impairment. Elucidating the causal mechanisms underlying this relationship could help to open new avenues for prevention and treatment, and further prospective research is warranted to investigate whether serum albumin is a useful diagnostic aid for screening and differential diagnosis.

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Fig. 1.

Odds of cognitive impairment by quartiles of serum albumin for men and women. Bars indicate 95% confidence intervals. Cognitive impairment was defined as a score <8 on the Abbreviated Mental Test.¹⁴ Population weights are used to adjust for the sampling design. Results are also adjusted for age, sex, education, ethnicity, current smoking status, alcohol consumption, psychiatric morbidity, vitamin D deficiency, acute sickness in the preceding 2 weeks, and medical history (stroke, heart disease, diabetes, and hypertension).

Table 1

Characteristics of the Study Population by Cognitive Status

Variables	All participants (n = 1,752)	Cognitively normal (n = 1,540)	Cognitively impaired (n = 212)	p value *
Serum albumin				
Mean serum albumin (SD), g/dL	4.0 (0.4)	4.1 (0.4)	3.9 (0.4)	<0.001
Quartiles of serum albumin, n (%)				<0.001
First (2.2–3.8 g/dL)	480 (27.4)	379 (24.6)	101 (47.6)	
Second (3.9–4.0 g/dL)	401 (22.9)	352 (22.9)	49 (23.1)	
Third (4.1–4.3 g/dL)	563 (32.1)	515 (33.4)	48 (22.6)	
Fourth (4.4–5.3 g/dL)	308 (17.6)	294 (19.1)	14 (6.6)	
Additional variables				
Mean age (SD), y	78.3 (8.6)	77.6 (8.5)	83.3 (7.9)	<0.001
Women, n (%)	1,053 (60.1)	909 (59.0)	144 (67.9)	0.014
No educational qualifications, n (%)	1,181 (67.4)	1,006 (65.3)	175 (82.6)	<0.001
White ethnic origin, n (%)	1,725 (98.6)	1,519 (98.8)	206 (97.2)	0.111
Current smokers, n (%)	204 (11.6)	180 (11.7)	24 (11.3)	1.000
Alcohol consumption, n (%)				<0.001
0 g/day	433 (24.7)	344 (22.3)	89 (42.0)	
0.1–29.9 g/day	1,227 (70.0)	1,112 (72.2)	115 (54.3)	
≥30 g/day	92 (5.3)	84 (5.5)	8 (3.8)	
Psychiatric morbidity [†] , n (%)	277 (15.8)	234 (15.2)	43 (20.3)	0.070
Vitamin D deficiency (<50 nmol/L), n (%)	1,033 (58.9)	866 (56.2)	167 (78.8)	<0.001
Acute sickness in preceding 2 weeks, n (%)	313 (17.9)	291 (18.9)	22 (10.4)	0.002
Stroke, n (%)	166 (9.5)	126 (8.2)	40 (18.9)	<0.001
Heart disease, n (%)	247 (14.1)	217 (14.1)	30 (14.2)	1.000
Diabetes, n (%)	155 (8.9)	130 (8.4)	25 (11.8)	0.121
Hypertension, n (%)	358 (20.4)	305 (19.8)	53 (25.0)	0.084
Mean BMI (SD) [‡] , kg/m ²	27.0(4.7)	27.2 (4.6)	25.3 (5.0)	<0.001

* p value for group difference between cognitively normal and cognitively impaired participants.

[†] Four or more symptoms on the 12-item General Health Questionnaire.²⁰

[‡] Available for a subsample of 1,268 participants.

Table 2

Logistic Regression Models Illustrating the Odds of Cognitive Impairment (95% Confidence Intervals) by Quartiles of Serum Albumin in 1,752 Older Adults

	Unadjusted model	Basic adjusted model*	Fully adjusted model [†]
Serum albumin (g/dL)			
Fourth (4.4–5.3)	Ref.	Ref.	Ref.
Third (4.1–4.3)	2.16 (1.11–4.21)	1.73 (0.88–3.41)	1.47 (0.74–2.91)
Second (3.9–4.0)	3.10 (1.58–6.06)	2.02 (1.02–4.03)	1.74 (0.87–3.51)
First (2.2–3.8)	6.19 (3.31–11.56)	3.22 (1.65–6.31)	2.54 (1.27–5.07)
P for linear trend	<0.001	<0.001	0.002

Population weights are used to adjust for the sampling design. Cognitive impairment was defined as a score <8 on the Abbreviated Mental Test.¹⁴

* Adjusted for age, sex, and education.

[†] Adjusted for age, sex, education, ethnicity, current smoking status, alcohol consumption, psychiatric morbidity, vitamin D deficiency, acute sickness in the preceding 2 weeks, and medical history (stroke, heart disease, diabetes, and hypertension).

Table 3

Logistic Regression Models Illustrating the Odds of Cognitive Impairment (95% Confidence Intervals) by Quartiles of Serum Albumin for 714 Institutionalized Older Adults

	Unadjusted model	Fully adjusted model*
Serum albumin (g/dL)		
Fourth (4.3–5.1)	Ref.	Ref.
Third (4.1–4.2)	0.86 (0.44–1.65)	0.67 (0.34–1.31)
Second (3.9–4.0)	1.17 (0.67–2.04)	1.10 (0.61–1.99)
First (2.6–3.8)	1.22 (0.69–2.16)	1.05 (0.58–1.88)
p for linear trend	0.265	0.383

Population weights are used to adjust for the sampling design. Cognitive impairment was defined as a score <8 on the Abbreviated Mental Test.¹⁴

* Adjusted for age, sex, education, ethnicity, current smoking status, alcohol consumption, psychiatric morbidity, vitamin D deficiency, acute sickness in the preceding 2 weeks, and medical history (stroke, heart disease, diabetes, and hypertension).

Table 4

Logistic Regression Models Illustrating the Odds of Cognitive Impairment (95% Confidence Intervals) by Quartiles of Serum Albumin for 1,038 Community Living Older Adults

	Unadjusted model	Fully adjusted model*
Serum albumin (g/dL)		
Fourth (4.5–5.3)	Ref.	Ref.
Third (4.3–4.4)	2.15 (0.40–11.43)	1.84 (0.29–11.77)
Second (4.1–4.2)	5.03 (1.07–23.61)	4.09 (0.80–20.86)
First (3.2–4.0)	4.58 (1.01–20.67)	2.55 (0.50–13.00)
p for linear trend	0.009	0.203

Population weights are used to adjust for the sampling design. Cognitive impairment was defined as a score <8 on the Abbreviated Mental Test.¹⁴

* Adjusted for age, sex, education, ethnicity, current smoking status, alcohol consumption, psychiatric morbidity, vitamin D deficiency, acute sickness in the preceding 2 weeks, and medical history (stroke, heart disease, diabetes, and hypertension).