Serum Albumin and Cerebro-cardiovascular Mortality During a 15-year Study in a Community-based Cohort in Tanushimaru, a Cohort of the Seven Countries Study

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Abstract

Objective  There is little long-term data on the association between the serum albumin levels and mortality in community-based populations. We aimed to determine whether the serum albumin level is an independent risk factor for all-cause and cause-specific death in a community-based cohort study in Japan.

Methods  In 1999, we performed a periodic epidemiological survey over a 15-year period in a population of 1,905 healthy subjects (783 males, 1,122 females) who were older than 40 years of age and who resided in Tanushimaru, a rural community, in Japan. Over the course of the study, we periodically examined the blood chemistry of the study subjects, including their serum albumin levels. Their baseline serum albumin levels were categorized into quartiles.

Results  The baseline albumin levels were significantly associated with age ( inversely), body mass index (BMI), diastolic blood pressure, lipid profiles [ high density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c) and triglycerides] and estimated glomerular filtration rate ( eGFR). After adjusting for confounders, a Cox proportional hazards regression analysis demonstrated that a low serum albumin level was an independent predictor of all-cause death [ hazard ratio (HR): 0.39, 95% confidence interval (CI): 0.24-0.65], cancer death ( HR: 0.43, 95% CI: 0.18-0.99), death from infection ( HR: 0.21, 95% CI: 0.06-0.73) and cerebro-cardiovascular death ( HR: 0.19, 95% CI: 0.06-0.63). The HRs for all-cause and cerebro-cardiovascular death in the highest quartile vs. the lowest quartile of albumin after adjusting for confounders were 0.59 (95%CI:0.39-0.88) and 0.15 (95%CI: 0.03-0.66), respectively.

Conclusion  The serum albumin level was thus found to be a predictor of all-cause and cerebro-cardiovascular death in a general population.

Key words: albumin, mortality, epidemiology

(Intern Med 55: 2917-2925, 2016)  
(DOI: 10.2169/internalmedicine.55.6931)

Introduction

Although it has been reported that low levels of serum albumin are associated with greater all-cause mortality in the general population (1, 2), the impact of serum albumin and nutrient intake on long-term mortality remains scant. The normal serum concentration of albumin in healthy adults is ≥4.0 g/dL, while hypoalbuminemia is defined as a serum albumin level of ≤3.4 g/L (3). A meta-analysis by Vincent et al. (4) suggested that hypoalbuminemia is a powerful, reproducible and independent risk factor that predicts a poor outcome in patients with acute illness. This finding has been consistently and pervasively observed. In older veteran pa-

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Received for publication December 3, 2015; Accepted for publication February 17, 2016

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Previously reported, the demographic background of the study population (13). As a cohort of the Seven Countries Study (12), this study was performed in Tanushimaru, a small rural community in southwestern Japan.

Subjects

In 1999, we performed an epidemiological survey in Tanushimaru, a small rural community in southwestern Japan. This was a cohort of the Seven Countries Study (12). As previously reported, the demographic background of the subjects in this area is similar to that of the general Japanese population (13). Subjects with a known history of myocardial infarction (n=2), stroke (n=3), cancer (n=5) or abnormal Q waves (n=5) (Minnesota codes I-1,2) (14) were excluded from the study. Finally, serum albumin data were obtained from 1,905 subjects (783 males, 1,122 females) of 40 to 95 years of age [40-49 years, n=282 (male, n=102; female, n=180); 50-59 years, n=450 (male, n=178; female, n=272); 60-69 years, n=623 (male, n=259; female, n=364); 70-79 years, n=464 (male, n=206; female, n=258); ≥80 years, n=86 (male, n=48; female, n=38)], over a 15-year period (Fig. 1). The respondents accounted for 48.2% of the men and 62.0% of the women in Tanushimaru who were older than 40 years of age (total target population: 3,463). The follow-up rate was 95.1%.

Data collection

The subjects’ medical history, alcohol intake, smoking habit, and current medications for hypertension, dyslipidemia, and diabetes were ascertained by questionnaire. The alcohol intake and smoking habit were classified according to whether or not the respondent was a current habitual user. The height and weight were measured, and the body mass index (BMI) was calculated as weight (kg) divided by the square of height (m²), as an index of obesity. Blood pressure (BP) was measured twice with the subject in the supine position. The second BP measurement was taken after 5 deep breaths and the 5th-phase diastolic pressure was used for the analysis. Blood was drawn from the antecubital vein for the determination of the fasting plasma glucose (FPG) and hemoglobin A1c level [HbA1c (NGSP)], the lipid profiles [total cholesterol, high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c) and triglycerides] and uric acid levels. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation modified with a Japanese coefficient: eGFR (ml·min⁻¹·1.73 m²⁻¹) = 194 × age⁻²·⁰³⁷ × serum creatinine¹·⁰⁶⁴ (if female × 0.739) (15).

The serum albumin level was measured according to standard methods in a commercial laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan).

Nutritional data

Dietary habits were evaluated by a food frequency questionnaire (13, 16). This questionnaire was modified for Japanese individuals by using an adaptation of atherosclerosis risk in communities (ARIC) study’s food frequency questionnaire (17). It consisted of 105 items. Habitual nutrient intake was estimated based on reports of the average portion size of foods and the frequency at which they were consumed over the previous year. Due to the difference between Caucasian and Japanese diets, we added items and changed the portion size of the foods consumed. The following items were added according to the Japanese standard food composition tables (18); thick wheat flour noodles (udon), buckwheat noodles (soba), soybean paste (miso), soybean curd (tofu), fermented soybeans (natto), mushrooms, seaweed, and Japanese sweet. The following items were deleted due to the low frequency at which they were consumed, hamburger, hot dog, French fries, brown bread, peanut but-
The present study was approved by the Ukiha and Tanushimaru Branches of the Japan Medical Association, the local citizens’ committee of Tanushimaru, and by the Regional Ethics Committee of the Kurume University School of Medicine (Process No. 9908/1999). The study conformed to the principles of the declaration of Helsinki. All of the participants provided written informed consent.

Statistical analysis

Natural logarithmic transformations were performed for the triglyceride values because of their skewed distribution. The triglyceride values after the analysis using log (natural)-transformed values are presented in the original scale (Table 1, 2). In Tables 1 and 2, the triglyceride values are presented as the geometric mean and range. Sex (men=0, women=1), smoking habits (non-smoker and former smoker =0, current smoker=1), alcohol intake (non-drinker and former drinker=0, current drinker=1), and medications for hypertension, dyslipidemia, and diabetes (no=0, yes=1) were used as dummy variables. The mean serum albumin levels were classified into the following quartiles: <4.2 g/dL, 4.2-4.4 g/dL, 4.4-4.6 g/dL, and ≥4.6 g/dL. The mean parameters, stratified by the albumin levels quartiles were compared using an analysis of variance. The survival curves for all-cause death for each albumin quartile were estimated and compared using the Kaplan-Meier method and the log-rank test was used to test differences among groups. Uni- and multivariate regression analyses were performed using Cox’s proportional hazards model to determine the factors associated with mortality from all causes, cancer, infection and cerebro-cardiovascular disease. In order to obtain hazard ratios (HRs) for all-cause, cancer, infection and cerebro-cardiovascular disease death, stratified by the serum albumin level quartiles, we performed a Cox proportional hazards regression analysis after adjusting for confounding factors. p values of <0.05 were considered to indicate statistical sig-

Table 1. Baseline Characteristics of the 1,905 Subjects Stratified by Serum Albumin Quartiles.

| Characteristics | Q1 (Lowest) | Q2 | Q3 | Q4 (Highest) | p for trend |
|----------------|-------------|----|----|-------------|------------|
| Albumin (g/dL) | 4.1 ± 0.2   | 4.3 ± 0.1 | 4.5 ± 0.1 | 4.7 ± 0.1 | <0.0001 |
| Age (years)    | 66.4 ± 11.2 | 63.6 ± 10.6 | 61.6 ± 10.8 | 59.1 ± 10.1 | <0.0001 |
| Sex (%males)   | 213 (44.7) | 186 (39.1) | 180 (37.8) | 204 (42.8) | 0.107 |
| BMI (kg/m²)    | 23.0 ± 3.4 | 23.0 ± 3.0 | 23.3 ± 3.0 | 23.1 ± 3.1 | 0.495 |
| Systolic BP (mmHg) | 140.8 ± 21.7 | 139.0 ± 21.2 | 140.4 ± 22.7 | 140.2 ± 20.7 | 0.584 |
| Diastolic BP (mmHg) | 81.2 ± 11.8 | 81.6 ± 12.2 | 82.2 ± 12.5 | 82.9 ± 12.0 | 0.144 |
| Total cholesterol (mg/dL) | 187.9 ± 35.3 | 196.4 ± 32.7 | 203.0 ± 32.0 | 211.8 ± 34.0 | <0.0001 |
| HDL-cholesterol (mg/dL) | 53.7 ± 12.6 | 55.9 ± 14.0 | 55.4 ± 13.2 | 58.2 ± 15.9 | <0.0001 |
| LDL-cholesterol (mg/dL) | 114.4 ± 31.3 | 119.0 ± 30.8 | 123.9 ± 30.8 | 128.5 ± 34.1 | <0.0001 |
| TG (mg/dL)*[range] | 89 [28-392] | 95 [33-963] | 101 [29-843] | 109 [28-1284] | <0.0001 |
| eGFR (mL/min1.73m²) | 56.5 ± 13.4 | 57.1 ± 12.5 | 57.8 ± 12.7 | 58.9 ± 13.0 | 0.027 |
| Uric acid (mg/dL) | 5.0 ± 1.5 | 4.9 ± 1.3 | 4.9 ± 1.3 | 5.1 ± 1.5 | 0.351 |
| HbA1c (%) | 5.2 ± 0.8 | 5.2 ± 0.8 | 5.2 ± 0.6 | 5.2 ± 0.7 | 0.590 |
| Alcolch intake (%yes) | 107 (22.5) | 100 (21.0) | 92 (19.3) | 122 (25.6) | 0.116 |
| Current smoking (%yes) | 87 (18.3) | 78 (16.4) | 69 (14.5) | 92 (19.3) | 0.205 |
| Medications
| Hypertension (%yes) | 101 (21.2) | 95 (20.0) | 87 (18.3) | 92 (19.3) | 0.716 |
| Hyperlipidemia (%yes) | 24 (5.0) | 23 (4.8) | 18 (3.8) | 26 (5.5) | 0.661 |
| Diabetes (%yes) | 19 (4.0) | 11 (2.3) | 17 (3.6) | 12 (2.5) | 0.377 |

Data are means ±standard deviations, geometric mean, range, or percent. *Variables represented in the original scale after analysis using log (natural)-transformed values. BMI: body mass index, BP: blood pressure, eGFR: estimated glomerular filter, TG: triglycerides.
The novel findings of the present study were that the se-

### Table 2. Baseline Means of Nutrient Intake Stratified by Albumin Quartiles.

| Characteristics                        | Quartiles of albumin (g/dL) | p for trend |
|----------------------------------------|-------------------------------|-------------|
|                                        | Q1 (Lowest) | Q2 | Q3 | Q4 (Highest) | p for trend |
| Total, n                               | 476 | 476 | 476 | 477 | <0.0001 |
| Albumin (g/dL)                         | 4.1 ± 0.2 | 4.3 ± 0.1 | 4.5 ± 0.1 | 4.7 ± 0.1 |
| Energy (kcal/day)^[range]              | 1,858 [817-4,339] | 1,882 [869-4,962] | 1,850 [913-4,097] | 1,897 [849-4,443] | 0.486 |
| Total protein (g/day)                  | 91.3 ± 33.6 | 92.4 ± 32.6 | 92.0 ± 32.1 | 93.1 ± 35.3 | 0.870 |
| Animal protein (g/day)                 | 38.7 ± 18.1 | 40.2 ± 18.6 | 38.8 ± 18.7 | 39.2 ± 19.5 | 0.586 |
| Vegetable protein (g/day)              | 52.6 ± 23.4 | 52.2 ± 22.0 | 53.2 ± 22.6 | 53.9 ± 24.0 | 0.693 |
| Total fat (g/day)                      | 49.1 ± 19.3 | 51.2 ± 20.1 | 50.5 ± 19.9 | 50.5 ± 21.7 | 0.425 |
| Animal fat (g/day)                     | 22.9 ± 12.9 | 24.2 ± 13.3 | 23.2 ± 13.3 | 23.7 ± 13.9 | 0.394 |
| Vegetable fat (g/day)                  | 26.3 ± 10.1 | 27.0 ± 10.5 | 27.3 ± 10.7 | 26.8 ± 11.2 | 0.462 |
| Carbohydrate (g/day)                   | 333.9 ± 103.4 | 331.1 ± 106.9 | 331.0 ± 100.2 | 340.3 ± 110.0 | 0.484 |
| Saturate fat (g/day)                   | 11.1 ± 4.8 | 11.6 ± 5.0 | 11.5 ± 5.0 | 11.6 ± 5.4 | 0.449 |
| Monounsaturated fat (g/day)            | 14.5 ± 6.3 | 15.1 ± 6.6 | 14.9 ± 6.4 | 14.9 ± 6.9 | 0.557 |
| Polysaturated fat (g/day)              | 10.7 ± 4.0 | 11.0 ± 4.4 | 11.1 ± 4.0 | 10.8 ± 4.5 | 0.450 |
| N-6 fatty acid (mg/day)                | 8,144.0 ± 3,128.2 | 8,474.7 ± 3,509.5 | 8,461.6 ± 3,180.8 | 8,261.4 ± 3,445.7 | 0.345 |
| Linoleic acid (mg/day)                 | 126.5 ± 56.0 | 127.3 ± 58.0 | 122.8 ± 56.3 | 125.3 ± 58.1 | 0.650 |
| Arachidonic acid (mg/day)              | 126.5 ± 56.0 | 127.3 ± 58.0 | 122.8 ± 56.3 | 125.3 ± 58.1 | 0.650 |
| N-3 fatty acid (mg/day)                | 1,281.4 ± 615.1 | 1,336.0 ± 685.4 | 1,319.6 ± 624.5 | 1,278.9 ± 652.0 | 0.434 |
| Linolenic acid (mg/day)                | 311.7 ± 192.0 | 306.6 ± 182.2 | 322.3 ± 247.3 | 330.8 ± 223.0 | 0.299 |
| EPA (mg/day)                           | 311.7 ± 192.0 | 306.6 ± 182.2 | 322.3 ± 247.3 | 330.8 ± 223.0 | 0.299 |
| DHA (mg/day)                           | 493.6 ± 281.7 | 486.1 ± 266.8 | 507.5 ± 361.8 | 518.2 ± 318.7 | 0.387 |

Data are means ±standard deviations, geometric mean, range, or percent.

*Variables represented in the original scale after analysis using log (natural) transformed values.

**EPA**: Eicosapentaenoic acid, **DHA**: Docosahexaenoic acid
Table 3. Cox Proportional Hazards Model with All-cause and Cause-specific Deaths as the Outcome Variables.

| Parameter                  | β   | SE  | HR (95%CI) | p value |
|----------------------------|-----|-----|------------|---------|
| Albumin (g/dL)             | -0.931 | 0.256 | 0.39 (0.24 - 0.65) | <0.0001 |
| Age (years)                | 0.099 | 0.007 | 1.10 (1.09 - 1.12) | <0.0001 |
| Total cholesterol (mg/dL)  | -0.004 | 0.010 | 1.00 (0.98 - 1.02) | 0.718   |
| HDL-cholesterol (mg/dL)    | 0.007 | 0.012 | 1.01 (0.98 - 1.03) | 0.544   |
| LDL-cholesterol (mg/dL)    | -0.006 | 0.010 | 0.99 (0.98 - 1.01) | 0.557   |
| Triglycerides (mg/dL)      | 0.218 | 0.319 | 1.24 (0.67 - 2.32) | 0.493   |
| eGFR (mL/mL⁻¹/1.73m⁻²)    | -0.004 | 0.005 | 1.00 (0.99 - 1.01) | 0.463   |

Cancer deaths (n=99)

| Parameter                  | β   | SE  | HR (95%CI) | p value |
|----------------------------|-----|-----|------------|---------|
| Albumin (g/dL)             | -0.855 | 0.435 | 0.43 (0.18 - 0.99) | 0.049   |
| Age (years)                | 0.078 | 0.012 | 1.08 (1.06 - 1.11) | <0.0001 |
| Total cholesterol (mg/dL)  | -0.059 | 0.036 | 0.94 (0.88 - 1.01) | 0.105   |
| HDL-cholesterol (mg/dL)    | 0.049 | 0.038 | 1.05 (0.98 - 1.13) | 0.198   |
| LDL-cholesterol (mg/dL)    | 0.048 | 0.036 | 1.05 (0.98 - 1.13) | 0.184   |
| Triglycerides (mg/dL)*     | 1.512 | 0.891 | 4.54 (0.79 - 26.03) | 0.090   |
| eGFR (mL/mL⁻¹/1.73m⁻²)     | 0.015 | 0.009 | 1.02 (1.01 - 1.03) | 0.084   |

Infection deaths (n=43)

| Parameter                  | β   | SE  | HR (95%CI) | p value |
|----------------------------|-----|-----|------------|---------|
| Albumin (g/dL)             | -1.584 | 0.644 | 0.21 (0.06 - 0.73) | 0.014   |
| Age (years)                | 0.133 | 0.018 | 1.14 (1.1 - 1.19) | <0.0001 |
| Total cholesterol (mg/dL)  | 0.001 | 0.033 | 1.00 (0.94 - 1.07) | 0.973   |
| HDL-cholesterol (mg/dL)    | 0.017 | 0.035 | 1.02 (0.95 - 1.09) | 0.628   |
| LDL-cholesterol (mg/dL)    | -0.009 | 0.032 | 0.99 (0.93 - 1.05) | 0.771   |
| Triglycerides (mg/dL)*     | 0.077 | 0.888 | 1.08 (0.19 - 6.15) | 0.931   |
| eGFR (mL/mL⁻¹/1.73m⁻²)     | 0.009 | 0.013 | 1.01 (0.98 - 1.04) | 0.503   |

CVD deaths (n=47)

| Parameter                  | β   | SE  | HR (95%CI) | p value |
|----------------------------|-----|-----|------------|---------|
| Albumin (g/dL)             | -1.643 | 0.599 | 0.19 (0.06 - 0.63) | 0.006   |
| Age (years)                | 0.091 | 0.016 | 1.10 (1.06 - 1.13) | <0.0001 |
| Total cholesterol (mg/dL)  | 0.014 | 0.017 | 1.01 (0.98 - 1.05) | 0.412   |
| HDL-cholesterol (mg/dL)    | -0.002 | 0.021 | 1.00 (0.96 - 1.04) | 0.943   |
| LDL-cholesterol (mg/dL)    | -0.022 | 0.016 | 0.98 (0.95 - 1.01) | 0.162   |
| Triglycerides (mg/dL)*     | -0.330 | 0.623 | 0.72 (0.21 - 2.44) | 0.597   |
| eGFR (mL/mL⁻¹/1.73m⁻²)     | -0.016 | 0.012 | 0.98 (0.96 - 1.01) | 0.984   |

CVD: Cerebro-cardiovascular diseases, CI: confidence interval, HR: hazard ratio, eGFR: estimated glomerular filter

The serum albumin level was a predictor of all-cause and cerebro-cardiovascular disease death, even in healthy individuals, during a 15-year follow-up period, and that the serum albumin level was not correlated with nutrition intake. Although two previous reports (1, 2) from Japanese investigators demonstrated a strong association between the serum albumin level and all-cause death in a community-based population, the present study reported that the serum albumin level was associated with both all-cause and cerebro-cardiovascular disease death.

To determine the causes of death, we used a review of obituaries, medical records, death certificates, hospital charts, and interviews with primary care physicians, family members of the deceased and other witnesses. The information was carefully independently coded in accordance with the rules of the Seven Countries Study (12).

Among the participants of the present study (mean albumin level; 4.4 g/dL), only 89 subjects (4.7%) showed an albumin level of ≤4.0 g/dL. Based on the findings of this study, we hypothesize that nutritional deficiencies (low albumin and low cholesterol) may be important in the pathology of all-cause and cause-specific death. It is interesting to note that hypoalbuminemia has been associated with hemorrhagic stroke in previous studies (21, 22), and that hypoalbuminemia has been associated with cause-specific death and diseases in many studies including our own study (23-31). It has been demonstrated that low albumin levels are associated with long-term protein-energy deprivation, liver disease (30) and renal disease (6, 7, 25), acute illness (4, 9-11, 26, 29) and chronic illness (8, 25), inflammation (31) and poor physical function (24). There is increasing evidence to show that low albumin levels are associated with cancer (27). However, whether low levels of albumin are associated with the nutritional status and disease of healthy participants has not previously been elucidated. Four subjects died within 1 year of enrollment due to hepatocyte cell car-
Table 4. Cox Proportional Hazards Model with All-cause and Cause-specific Deaths as the Nutrient Intakes.

### All-cause deaths (n=337)

| Variables | β   | SE  | HR (95%CI)      | p value |
|-----------|-----|-----|-----------------|---------|
| Sex       | -0.837 | 0.140 | 0.433 (0.329 - 0.569) | <0.0001 |
| Age       | 0.116  | 0.007 | 1.123 (1.088 - 1.159) | <0.0001 |
| Energy    | 0.000  | 0.000 | 1.000 (0.999 - 1.000) | 0.402   |
| Animal protein | -0.009 | 0.011 | 0.991 (0.971 - 1.012) | 0.422   |
| Vegetable protein | 0.016 | 0.009 | 1.016 (0.999 - 1.034) | 0.066   |
| Animal protein/vegetable protein | 0.481 | 0.342 | 1.617 (0.828 - 3.159) | 0.159   |
| Animal fat | -0.005 | 0.013 | 0.995 (0.995 - 1.021) | 0.699   |
| Vegetable fat | 0.020 | 0.013 | 1.020 (0.994 - 1.047) | 0.135   |
| Animal fat/vegetable fat | 0.273 | 0.253 | 1.314 (0.800 - 2.158) | 0.282   |
| Carbohydrate | 0.023 | 0.023 | 1.023 (0.999 - 1.049) | 0.276   |
| EPA | 0.000 | 0.002 | 0.999 (0.995 - 1.004) | 0.451   |
| DHA | 0.001 | 0.001 | 1.001 (0.998 - 1.003) | 0.587   |

### Cancer deaths (n=99)

| Variables | β   | SE  | HR (95%CI)      | p value |
|-----------|-----|-----|-----------------|---------|
| Sex       | -0.571 | 0.234 | 0.565 (0.357 - 0.894) | 0.015   |
| Age       | 0.099  | 0.011 | 1.104 (1.080 - 1.128) | <0.0001 |
| Energy    | 0.000  | 0.001 | 1.000 (0.999 - 1.002) | 0.644   |
| Animal protein | -0.018 | 0.017 | 0.982 (0.949 - 1.016) | 0.295   |
| Vegetable protein | 0.028 | 0.014 | 1.028 (1.001 - 1.056) | 0.045   |
| Animal protein/vegetable protein | 0.324 | 0.605 | 1.382 (0.422 - 4.526) | 0.593   |
| Animal fat | -0.006 | 0.022 | 0.994 (0.953 - 1.037) | 0.778   |
| Vegetable fat | 0.009 | 0.021 | 1.009 (0.968 - 1.051) | 0.680   |
| Animal fat/vegetable fat | 0.374 | 0.415 | 1.453 (0.644 - 3.280) | 0.368   |
| Carbohydrate | -0.004 | 0.004 | 0.996 (0.996 - 1.004) | 0.743   |
| EPA | 0.000 | 0.002 | 0.999 (0.996 - 1.003) | 0.517   |
| DHA | 0.001 | 0.001 | 1.001 (0.998 - 1.003) | 0.587   |

### Infection deaths (n=43)

| Variables | β   | SE  | HR (95%CI)      | p value |
|-----------|-----|-----|-----------------|---------|
| Sex       | -1.591 | 0.396 | 0.204 (0.094 - 0.424) | 0.000   |
| Age       | 0.142  | 0.020 | 1.153 (1.109 - 1.198) | <0.0001 |
| Energy    | -0.001 | 0.001 | 0.999 (0.997 - 1.001) | 0.465   |
| Animal protein | -0.013 | 0.032 | 0.987 (0.926 - 1.052) | 0.692   |
| Vegetable protein | -0.006 | 0.027 | 0.994 (0.943 - 1.048) | 0.831   |
| Animal protein/vegetable protein | 0.193 | 0.160 | 1.121 (1.052 - 1.194) | 0.055   |
| Animal fat | 0.042  | 0.040 | 1.043 (0.964 - 1.128) | 0.299   |
| Vegetable fat | 0.013 | 0.040 | 1.014 (0.937 - 1.097) | 0.739   |
| Animal fat/vegetable fat | -0.608 | 0.842 | 0.495 (0.105 - 2.834) | 0.470   |
| Carbohydrate | 0.001 | 0.007 | 1.001 (0.998 - 1.015) | 0.820   |
| EPA | 0.009 | 0.005 | 1.009 (0.981 - 1.031) | 0.068   |
| DHA | 0.006 | 0.003 | 1.006 (0.999 - 1.013) | 0.080   |

### CVD deaths (n=47)

| Variables | β   | SE  | HR (95%CI)      | p value |
|-----------|-----|-----|-----------------|---------|
| Sex       | -0.780 | 0.342 | 0.458 (0.234 - 0.896) | 0.023   |
| Age       | 0.118  | 0.017 | 1.126 (1.088 - 1.164) | <0.0001 |
| Energy    | -0.001 | 0.001 | 0.999 (0.997 - 1.001) | 0.314   |
| Animal protein | 0.032 | 0.024 | 1.032 (0.984 - 1.082) | 0.193   |
| Vegetable protein | 0.002 | 0.023 | 1.002 (0.958 - 1.048) | 0.933   |
| Animal protein/vegetable protein | 0.202 | 0.799 | 1.224 (0.256 - 5.855) | 0.801   |
| Animal fat | -0.013 | 0.032 | 0.987 (0.928 - 1.051) | 0.692   |
| Vegetable fat | 0.036 | 0.034 | 1.037 (0.970 - 1.108) | 0.288   |
| Animal protein/vegetable fat | 0.176 | 0.653 | 1.192 (0.331 - 4.269) | 0.788   |
| Carbohydrate | 0.003 | 0.006 | 1.003 (0.991 - 1.016) | 0.581   |
| EPA | -0.002 | 0.005 | 0.998 (0.995 - 1.003) | 0.751   |
| DHA | -0.001 | 0.003 | 0.999 (0.992 - 1.005) | 0.700   |

EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid

Cox proportional hazards model with all-cause and cause-specific deaths as the nutrient intakes. Hypoalbuminemia, which can be associated with various diseases, is frequently observed in hospitalized patients (24–31). Regardless of the cause, hypoalbuminemia has a strong impact on mortality and morbidity. However, in

cinoma (3.6 months), subarachnoid hemorrhage (4.8 months), lung cancer (6 months), and an accident (7.2 months). The low albumin levels in the 2 subjects who died of cancer might have affected the results; however, we were not able to exclude the cases, because their records did not describe any history of cancer treatment nor was there any information to suggest that they were undergoing cancer treatment at the start of the study period.
demonstrated that a low albumin level was an independent predictor of all-cause death and cerebro-cardiovascular disease death (Table 5). In contrast, the subjects with the highest albumin level had the lowest mortality rate, indicating that a small variation within the normal range of the albumin level could have an effect on future all-cause mortality, even in a general population. The precise mechanism underlying the relationship between serum albumin levels and mortality should be clarified in future studies.

Next, we focused on the association between nutrient intake and all-cause/cause-specific death, vegetable protein intake was the only nutrient-related factor that was found to be associated with mortality (Table 4). The previous reports did not consider the nutrient intake of their study populations (1, 2, 21-31). Our findings suggest that it is likely that the nutrient intake of the healthy subjects in the present study did not directly influence their serum albumin levels. Malabsorption or protein loss might be considered when an imbalance is detected between a subject’s albumin level and his or her nutrient intake. This issue should be clarified in future studies.

**Study limitations**

The present study is associated with several limitations. First, in order to exclude subjects with cardiovascular diseases, we carefully examined their medical history, and performed physical examinations. The subjects with Q waves

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**Table 5. Hazard Ratios of All-cause, Cancer, Infection and CVD Mortality Using the Lowest Quartile as the Reference.**

| All-cause deaths | Quartiles of albumin (g/dL) | Q1 (Lowest) (≤4.2) | Q2 (4.2-4.4) | Q3 (4.4-4.6) | Q4 (Highest) (≥4.6) |
|------------------|-----------------------------|-------------------|-------------|-------------|-------------------|
| Total n          | 476                         | 476               | 476         | 477         |
| No.of deaths     | 145                         | 82                | 65          | 45          |
| Model 1          | 1.00 (0.53 (0.39 - 0.71)) ** 0.40 (0.29 - 0.55) ** 0.28 (0.20 - 0.40) ** 0.26 (0.19 - 0.36) ** 0.24 (0.17 - 0.33) ** 0.22 (0.15 - 0.30) ** 0.20 (0.13 - 0.27) ** 0.18 (0.11 - 0.25) ** 0.16 (0.09 - 0.23) ** 0.14 (0.07 - 0.21) ** 0.12 (0.05 - 0.19) ** 0.10 (0.03 - 0.16) ** 0.08 (0.01 - 0.14) ** 0.06 (0.00 - 0.12) ** 0.04 (0.00 - 0.10) ** 0.02 (0.00 - 0.08) ** 0.00 (0.00 - 0.06) ** 0.00 (0.00 - 0.04) ** |
| Model 2          | 1.00 (0.66 (0.49 - 0.89)) * 0.63 (0.46 - 0.87) * 0.56 (0.38 - 0.81) * 0.50 (0.32 - 0.77) * 0.44 (0.27 - 0.69) * 0.38 (0.20 - 0.66) * 0.32 (0.15 - 0.61) * 0.26 (0.10 - 0.56) * 0.20 (0.08 - 0.45) * 0.14 (0.05 - 0.35) * 0.08 (0.02 - 0.23) * 0.02 (0.00 - 0.10) * 0.00 (0.00 - 0.04) * 0.00 (0.00 - 0.02) * 0.00 (0.00 - 0.01) * 0.00 (0.00 - 0.00) * |
| Model 3          | 1.00 (0.68 (0.50 - 0.93)) * 0.65 (0.46 - 0.93) * 0.59 (0.39 - 0.88) * 0.53 (0.34 - 0.83) * 0.47 (0.28 - 0.78) * 0.41 (0.22 - 0.71) * 0.35 (0.16 - 0.64) * 0.29 (0.12 - 0.59) * 0.23 (0.08 - 0.54) * 0.17 (0.06 - 0.42) * 0.11 (0.03 - 0.31) * 0.05 (0.00 - 0.18) * 0.00 (0.00 - 0.06) * 0.00 (0.00 - 0.02) * 0.00 (0.00 - 0.01) * 0.00 (0.00 - 0.00) * |

CVD: Cerebro-cardiovascular diseases

Model 1: crude, Model 2: age and sex adjusted, Model 3: adjusted for age, sex, HDL-cholesterol, LDL-cholesterol, triglycerides and estimated glomerular filter.

*p<0.01 vs. Q1, **p<0.001 vs.Q1

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**Figure 2. Cumulative survival curves stratified by serum albumin quartiles in subjects estimated by the Kaplan-Meier method.** There was a significant trend across the quartiles (p<0.0001 by log-rank test). Q1: Albumin ≤4.2g/dL (n=476). Q2: Albumin 4.2-4.4g/dL (p=476). Q3: Albumin 4.4-4.6g/dL (p=476). Q4: Albumin ≥4.6g/dL (p=477)

In the present study, the enrolled subjects were free from apparent cerebro-cardiovascular disease at the start of the study period and their serum albumin levels were within the normal range. Furthermore, after adjusting for confounding factors, the Cox proportional hazards regression analysis demonstrated that a low albumin level was an independent
on an electrocardiogram were excluded. However, it is possible that some subjects with asymptomatic cardiovascular diseases might have been included. Second, we were not able to exclude subjects with undetected cancer. Third, the total number of deaths from cerebro-cardiovascular disease and cancers was small, which limited the statistical power of the outcome. Fourth, we used a single baseline measurement to predict the all-cause and cause-specific death. Fifth, we did not have data on chronic hepatitis in the present study. Thus, some subjects’ serum albumin levels might have been influenced by chronic hepatitis. Finally, the pathophysiological mechanism underlying the association between low albumin levels and all-cause death was not revealed from our observational study.

**Conclusion**

In conclusion, the present study demonstrated that the serum albumin level was an independent predictor of all-cause and cerebro-cardiovascular disease death in the Japanese general population.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

We are grateful to the members of the Japan Medical Association of Ukiha, the elected officials and residents of Tanushimaru, and the team of physicians who helped in performing the health examinations.

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