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published in
American Journal of Epidemiology
2006

DOI (link to publisher)
10.1093/aje/kwj312

document version
Publisher's PDF, also known as Version of record

American Journal of Epidemiology

Vol. 164, No. 10
DOI: 10.1093/aje/kwj312
Advance Access publication September 15, 2006

Original Contribution

Change of Serum Albumin and Risk of Cardiovascular Disease and All-Cause Mortality

Longitudinal Aging Study Amsterdam

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Received for publication December 11, 2003; accepted for publication April 14, 2006.

The aim of this longitudinal study was to investigate 3-year change in serum albumin concentration as a determinant of incident cardiovascular disease (CVD) and all-cause mortality. Data were from 713 respondents of the Longitudinal Aging Study Amsterdam initially aged 55–85 years. Serum albumin was measured at baseline (1992/1993) and after 3 years. At the 6-year follow-up, incident CVD (among 456 respondents with no prevalent CVD at the 3-year follow-up) and all-cause mortality were ascertained. Overall, 18.9% developed CVD and 10.9% died. After adjustment for potential confounders, a higher level of serum albumin at the 3-year follow-up was associated with a lower risk for incident CVD (relative risk = 0.88, 95% confidence interval (CI): 0.79, 0.98). The risk of incident CVD was 0.88 (95% CI: 0.78, 0.99) per unit (g/liter) increase in change in albumin between 3-year follow-up and baseline. Chronic low serum albumin ($\leq$43 g/liter at baseline and 3-year follow-up) was not associated with incident CVD ($p = 0.22$). A clinically relevant decrease in serum albumin ($\geq$1 standard deviation (2.5 g/liter) between baseline and 3-year follow-up) tended to be associated with a twofold risk (relative risk = 2.00, 95% CI: 0.91, 4.39). For all-cause mortality, no associations were observed. These findings suggest that older persons with a decrease in serum albumin concentration, even within the normal range, might be at increased risk of incident CVD. Change in serum albumin may be used as an early marker for CVD risk.

aging; cardiovascular diseases; longitudinal studies; mortality; serum albumin

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ICD, *International Classification of Diseases*; LASA, Longitudinal Aging Study Amsterdam; RR, relative risk; SKZL, Dutch Foundation for Quality Assessment in Clinical Laboratories.

Low serum albumin concentrations, even within the normal range ($\geq$38 g/liter), are associated with morbidity and mortality. Low serum albumin concentrations have been shown to be associated with a higher risk of myocardial infarction (1), coronary heart disease morbidity and mortality (2–8), and stroke morbidity and mortality (9). In addition, low serum albumin has been shown to be associated with a higher risk of total cardiovascular mortality (10, 11), all-cause mortality (1, 4, 8, 10–15), and cancer mortality (10, 11, 13, 16).

Several biologic mechanisms might explain these associations. First, albumin is a negative acute-phase protein, and

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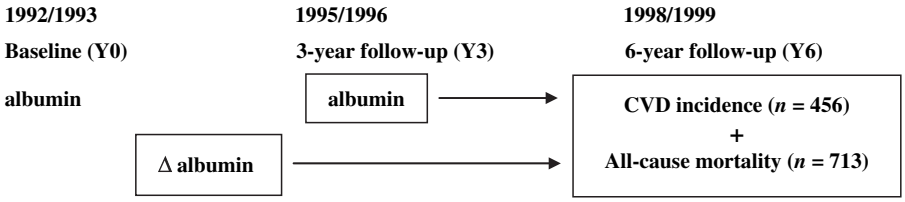

FIGURE 1. Study design: determinants and outcomes, Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999. Δ albumin, albumin concentration at 3-year follow-up (Y3) – albumin concentration at baseline (Y0); CVD, cardiovascular disease.

the albumin concentration falls approximately 20 percent during the inflammatory process (17–20). During this process, cytokines including interleukin-1, interleukin-6, and tumor necrosis factor, which induce the acute-phase response, are produced. Inflammation is associated with cardiovascular disease (CVD) incidence and mortality (20–22). In the inflammatory state, the activity of macrophages and other cells of the immune system is enhanced, and macrophages show an increased free radical production. Free radicals are implicated in the development of cancer and CVD (23, 24). In addition, cytokines have a proliferative effect on fibroblasts that play an important role in the atherosclerotic process. Another important part of this process is the abnormal platelet aggregation. Albumin binds to several ligands (variety of substances), interacts with free fatty acids, and inhibits their promoting effects on platelet aggregation and thrombosis (25–27).

Second, serum albumin may act as an indirect and sacrificial antioxidant (25, 26, 28–30) and inhibits peroxidase, free radical generation (29, 31), and hemolysis (26). Finally, serum albumin is an inhibitor of human endothelial apoptosis (32) that may also be reduced as a result of a general increased vascular permeability during disease as a result of tissue damage (33). These mechanisms might be implicated in the pathogenesis of many diseases such as atherosclerosis, cancer, and ischemia (34, 35), as well as in related mortality.

The mechanisms to explain the association between serum albumin and CVD and mortality are based on a decrease of the serum albumin concentration. Yet, all studies relating serum albumin concentration to morbidity and mortality are based on a single baseline measurement of serum albumin. It is unknown whether a decrease in serum albumin within the normal range might reflect a preclinical disease stage and might be an early marker for risk of CVD incidence or mortality. To our knowledge, no other studies have investigated change in serum albumin in relation to CVD and mortality in older women and men.

To confirm earlier studies, we first investigated the association between the serum albumin concentration measured at one time point and the incidence of CVD and all-cause mortality in the subsequent 3 years. To investigate whether the history of serum albumin concentration would influence the risk of CVD and mortality, the main aim of this study was to investigate the association between 3-year change in the serum albumin concentration and incidence of CVD and all-cause mortality in the subsequent 3 years. The design of this study is explained in figure 1.

MATERIALS AND METHODS

Study sample

The Longitudinal Aging Study Amsterdam (LASA) is an ongoing interdisciplinary longitudinal study that focuses on changes in physical, cognitive, emotional, and social functioning in the aging population of the Netherlands. The sampling and data collection have been described in detail elsewhere (36, 37). Briefly, a sample of older men and women (aged 55–85 years at baseline), stratified by age, sex, urbanization, and expected 5-year mortality, was drawn from the population registers of 11 municipalities in areas in the West (Amsterdam region), Northeast (Zwolle region), and South (Oss region) of the Netherlands. At baseline (in 1992/1993) and every 3 years, a new cycle of measurements was carried out. Each cycle consisted of a general and medical interview. Both interviews were carried out at the subject's home by specially trained interviewers. After each medical interview, a nurse interviewer collected blood samples. Informed consent was obtained from all respondents. The study was approved by the Medical Ethics Committee of the University Medical Center, Vrije Universiteit, in Amsterdam.

Of the 3,107 respondents who participated in the general baseline interview, 2,671 respondents participated in the medical interview. For practical and financial reasons, no blood was collected in the Oss region ($n = 661$) and part of the Amsterdam region ($n = 498$). Thus, at baseline, blood samples were available for 1,507 subjects. Blood was collected at baseline and at the 3-year follow-up for 780 respondents. Of the 727 respondents who had no blood sample taken at the 3-year follow-up, 325 respondents were born after 1930 (exclusion criterion for medical interview), 171 had died, 83 refused, 23 were ineligible to be interviewed, 11 could not be contacted, and 114 respondents were interviewed through proxy or telephone follow-up. Of the 780 respondents who had a medical interview at the 3-year follow-up, 65 did not give blood and, in two respondents, no serum albumin was determined, leaving 713 respondents with complete albumin assessments and medical interviews at both baseline and the 3-year follow-up. For the incident CVD analyses, 242 respondents were excluded who had

TABLE 1. Characteristics of respondents according to incident cardiovascular disease and all-cause mortality during follow-up, Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999

Characteristics	Incident CVD*		*p* value†	All-cause mortality		*p* value†
	Yes ($n = 86$)	No ($n = 370$)		Dead ($n = 78$)	Alive ($n = 635$)	
Age, years (mean (SD*))	75.9 (5.9)	73.2 (6.1)	<0.01	78.0 (6.8)	74.3 (6.3)	<0.01
Male (%)	55.8	44.3	0.054	74.4	47.6	<0.01
Education (%)						
Low	62.8	57.0	0.45	64.1	59.1	0.014
Middle	24.4	31.4		16.7	29.9	
High	12.8	11.6		19.2	11.0	
Smoking (%)						
Never	32.6	39.2	0.49	19.2	36.9	<0.01
Former	48.8	42.7		52.6	46.5	
Current	18.6	18.1		28.2	16.7	
Alcohol consumption, drinks/day (%)						
None	21.2	21.1	0.92	21.8	23.0	0.57
<2 drinks	35.3	33.2		39.7	33.8	
≥2 drinks	43.5	45.7		38.5	43.2	
Body mass index, kg/m^2 (mean (SD))	26.6 (4.2)	26.6 (4.0)	0.98	26.1 (4.4)	26.8 (4.1)	0.14
Physical activity, minutes/week (mean (SD))	151.8 (105.8)	164.5 (100.5)	0.30	113.2 (117.8)	155.2 (102.0)	<0.01
Diabetes mellitus (%)	11.6	4.6	0.013	14.1	6.6	0.018
Diastolic blood pressure, mmHg (mean (SD))	86.1 (14.6)	84.8 (12.4)	0.42	83.2 (16.8)	84.4 (12.8)	0.46
Systolic blood pressure, mmHg (mean (SD))	157.8 (24.2)	153.5 (24.1)	0.15	160.0 (28.8)	154.2 (24.8)	0.057
Cognitive impairment (%)	11.6	5.7	0.048	29.5	7.9	<0.01
Serum total cholesterol, mmol/liter (mean (SD))	6.1 (1.2)	5.9 (1.1)	0.032	5.7 (1.2)	5.9 (1.1)	0.21

* CVD, cardiovascular disease; SD, standard deviation.
† Chi-square test for categorical variables; one-way analysis of variance for continuous variables.

prevalent CVD at the 3-year follow-up, and 15 respondents were excluded because information on CVD at the 6-year follow-up was missing. Thus, the final study sample consisted of 713 respondents for all-cause mortality and 456 respondents for CVD.

Serum albumin

Blood was collected when subjects were in a nonfasting state and in a sitting position. Serum samples were obtained and analyzed directly. The analyses were carried out in three laboratories in the Netherlands. To control for between-laboratory differences, we used information from the Dutch Foundation for Quality Assessment in Clinical Laboratories (SKZL). The quality assessment routine involves sending eight serum samples every 2 months to the laboratories for analysis, and the serum albumin concentration is reported to the SKZL. Using linear regression, we fit regression lines by use of the individual laboratory assessment of serum albumin for the LASA sample in each year (at baseline and 3-year follow-up) and each laboratory and the overall mean of the SKZL sample of that year and laboratory. Using the regression equations, we adjusted the serum albumin levels in the LASA data. Serum albumin concentrations were determined with a Hitachi model 747 analyzer (Hitachi High-Technologies Co., Minato-ku, Tokyo, Japan) by use of a bromcresol green dye-binding method and, in one laboratory, a bromcresol purple method. For the serum albumin concentrations to be comparable, those that were determined with the bromcresol purple method were converted by use of a validated formula (38). The coefficient of variation of serum albumin was less than 2 percent.

The serum albumin concentration at the 3-year follow-up and the change in serum albumin were used as continuous and dichotomous determinants. Serum albumin was categorized as one of the following: low serum albumin (≤43 g/liter) versus the normal serum albumin concentration. For serum albumin, the level of 43 g/liter (4, 39) was used as the cutpoint for low albumin, which represents approximately one-third percentile of the study sample at baseline. Change in serum albumin was categorized in two ways: 1) chronic low serum albumin (≤43 g/liter at both measurements) versus not low (reference value) and 2) a clinically relevant decrease in serum albumin (≥1 standard deviation) versus no decrease (reference value). The standard deviation was based on a 3-year change in serum albumin in the study sample = 2.5 g/liter.

TABLE 2. Cardiovascular disease incidence according to serum albumin and 3-year change in serum albumin, Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999

	Incident CVD*		*p* value†
	Yes ($n = 86$)	No ($n = 370$)	
Albumin at 3-year follow-up, g/liter (mean (SD*))	43.6 (2.7)	44.2 (2.4)	0.03
Low albumin, ≤43 g/liter (%)			
Yes	37.2	26.8	0.05
No	62.8	73.2	
Absolute change in serum albumin, g/liter (mean (SD))	−0.03 (2.5)	0.43 (2.4)	0.12
Chronic low albumin, ≤43 g/liter at both measurements (%)			
Yes	23.3	17.8	0.25
No	76.7	82.2	
Clinically relevant decrease in albumin‡ (%)			
Yes	17.4	11.1	0.11
No	82.6	88.9	

* CVD, cardiovascular disease; SD, standard deviation.

† Chi-square test for categorical variables; one-way analysis of variance for continuous variables; *p* values for two-sided tests.

‡ Decline of ≥1 SD (2.5 g/liter).

Cardiovascular incidence and all-cause mortality

At the 6-year follow-up, the incidences of CVD and all-cause mortality between 3-year follow-up and 6-year follow-up were ascertained. CVD was defined as angina pectoris, myocardial infarction, congestive heart failure, cardiac arrhythmia, peripheral arterial disease, or stroke. For each CVD, an algorithm was made, combining three data sources: self-reported (symptoms of) CVD, medication use during the past 2 weeks based on inspection of containers by the medical interviewers, and medical records of general practitioners. Angina pectoris was considered present when at least two of three criteria were met: 1) self-reported angina pectoris or symptoms, such as pain or a heavy or unpleasant feeling in the chest during exertion that disappeared within 10 minutes when standing still or after taking a tablet under the tongue, or chest pain without exertion; 2) use of nitroglycerin; and 3) a confirmed diagnosis by the general practitioner. Myocardial infarction was considered present when at least one of two criteria was met: 1) self-reported myocardial infarction and/or 2) a confirmed diagnosis by the general practitioner. Congestive heart failure was considered present when at least two of three criteria were met: 1) self-reported symptoms of congestive heart failure, such as sleeping with one or more than one pillow at night because of shortness of breath and often having edema in the ankles, feet, or legs when getting up in the morning; 2) use of diuretics and either digitalis or an antihypertensive; and 3) a confirmed diagnosis by the general practitioner. Cardiac arrhythmia was considered present when one of two criteria was met: 1) use of antiarrhythmic medications and/or 2) a confirmed diagnosis by the general practitioner. Peripheral arterial disease was considered present when one of two criteria was met: 1) self-reported symptoms of peripheral arterial disease, such as pain in one or both calves when walking that disappears when standing still, and/or 2) a confirmed diagnosis by the general practitioner. Stroke was considered present when one of two criteria was met: 1) self-reported stroke or attack (including transient ischemic attack) and/or 2) a confirmed diagnosis by the general practitioner.

For respondents who died, the date of death was traced through death certificates of the municipal registries. Between baseline and January 1, 2000, the mortality follow-up was 100 percent complete. For CVD mortality, the causes of death were obtained through Statistics Netherlands according to the *International Classification of Diseases* (ICD), Ninth Revision (40) and Tenth Revision (41). ICD, Ninth Revision, codes 390–459 and ICD, Tenth Revision, codes i00–i99 identify CVD deaths. CVD incidence was defined as new CVD or CVD mortality.

Potential confounders

Age was used as a continuous variable. Self-reported lifestyle variables included education (low, middle (reference), and high); smoking (never (reference), former, and current); alcohol consumption (none (reference), <2 drinks daily, ≥2 drinks daily); body mass index (weight (kg)/height $(m)^2$); and physical activity (minutes/week). Physical activity in the past 2 weeks was based on the following activities: walking outdoors, bicycling, light and heavy household activities, and a maximum of two sports activities. Health status variables included self-reported diabetes, pulmonary disease (asthma or chronic obstructive pulmonary disease), arthritis, cancer, and measured diastolic blood pressure (mmHg) and systolic blood pressure (mmHg). Blood pressure was measured while subjects were in a sitting position. For depressive symptoms, the Center for Epidemiologic Studies Depression Scale (42) was used, and a score of 16 or higher was considered to indicate depression (43). Cognitive functioning was measured with the Mini-Mental State Examination, and a score of 23 or less was considered to indicate cognitive impairment (44). Serum total cholesterol (mmol/liter) was measured by use of the enzymatic colorimetry assay with a Hitachi model 747 analyzer. Serum creatinine (μmol/liter) was measured by means of the Jaffe alkaline picrate reaction with a Hitachi model 747 analyzer. Covariates were missing for some respondents: physically active, 16 missing; body mass index, two missing; total cholesterol, nine missing; alcohol consumption, one missing; diabetes mellitus, one missing; pulmonary disease, one missing; cancer, one missing; arthritis, one missing; diastolic and systolic blood pressure, eight missing; depressive symptoms, 10 missing; and cognitive impairment, 10 missing.

TABLE 3. Logistic regression analyses of change in serum albumin and cardiovascular disease incidence, Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999

	Incident CVD*					
	Adjusted†			Adjusted‡		
	Relative risk	95% confidence interval	*p* value§	Relative risk	95% confidence interval	*p* value§
Albumin at 3-year follow-up, g/liter	0.90	0.81, 0.99	0.03	0.88	0.79, 0.98	0.02
Low albumin, ≤43 g/liter						
Yes	1.62	0.99, 2.66	0.055	1.72	0.98, 3.01	0.059
No	1.00			1.00		
Absolute change in serum albumin, continuous, g/liter¶	0.88	0.79, 0.99	0.03	0.88	0.78, 0.998	0.05
Chronic low albumin, ≤43 g/liter at both measurements						
Yes	1.40	0.80, 2.46	0.25	1.49	0.79, 2.83	0.22
No	1.00			1.00		
Clinically relevant decrease in albumin#						
Yes	2.03	1.01, 4.09	0.05	2.00	0.91, 4.39	0.09
No	1.00			1.00		

* CVD, cardiovascular disease.

† Adjusted for serum albumin at baseline (except for chronic low albumin).

‡ Adjusted for serum albumin at baseline (except for chronic low albumin) and for age, sex, education, smoking, alcohol consumption, body mass index, physical activity, diabetes mellitus, diastolic blood pressure, systolic blood pressure, cognitive impairment, and serum total cholesterol at 3-year follow-up.

§ *p* values for two-sided tests.

¶ For an increase in change in serum albumin of 1 g/liter.

Decline of ≥1 standard deviation (2.5 g/liter).

Statistical analyses

Using the SPSS, version 9.0, statistical package (SPSS, Inc., Chicago, Illinois), we performed the analyses. Characteristics of the respondents according to incident CVD (yes or no) and all-cause mortality (dead or alive) were compared by use of Student's *t* test and chi-square statistics. Differences between the study sample and those excluded were tested with descriptive statistics. Statistical significance was considered present at the two-sided *p* value of 0.05.

The albumin concentration at 3-year follow-up and the change in serum albumin in relation to CVD incidence and all-cause mortality were tested with the chi-square test for categorical variables and one-way analysis of variance for continuous variables. Results are presented as percentages or mean values (standard deviation) with two-sided *p* values. Logistic regression models were used to examine the association of serum albumin at 3-year follow-up and change in serum albumin with CVD incidence, adjusting for the confounders that were selected according to one of two criteria: 1) when associated ($p < 0.20$) with absolute change in serum albumin and either CVD incidence or all-cause mortality or 2) when reported as confounders in the literature. Inclusion of education was based on the univariate criterion's being associated with absolute change in serum albumin and either CVD incidence or all-cause mortality. Age, sex, alcohol consumption, and systolic and diastolic blood pressures were based on the criterion's being reported as a confounder in the literature (1, 4). Smoking, body mass index, physical activity, diabetes mellitus, cognitive impairment, and serum total cholesterol were included when based on both criteria. Cox regression analyses were performed, examining the association between serum albumin at the 3-year follow-up and change in serum albumin with all-cause mortality, adjusting for the selected confounders. "Time" was defined as the number of days between the 3-year follow-up assessment of each respondent and the time of death or, in the event that the participant was still alive, the end of the follow-up period (January 1, 2000).

When change in serum albumin (continuous variable) or a clinically relevant decrease in albumin was used as the central determinant, we adjusted additionally for serum albumin at baseline. Results are presented as relative risks with 95 percent confidence intervals.

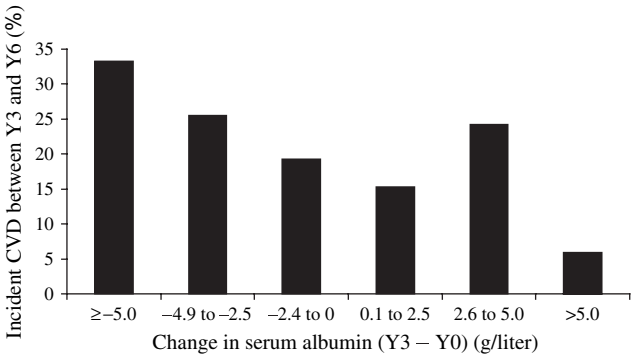

FIGURE 2. Incidence of cardiovascular disease (CVD) according to change in serum albumin (g/liter), Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999. Y0, baseline; Y3, 3-year follow-up; Y6, 6-year follow-up.

TABLE 4. All-cause mortality according to serum albumin and 3-year change in serum albumin, Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999

	All-cause mortality		*p* value*
	Deceased ($n = 78$)	Alive ($n = 635$)	
Albumin at 3-year follow-up, g/liter (mean (SD†))	43.8 (2.5)	44.1 (2.4)	0.24
Low albumin, ≤43 g/liter (%)			
Yes	29.5	28.7	0.88
No	70.5	71.3	
Absolute change in serum albumin, g/liter (mean (SD))	0.19 (2.7)	0.32 (2.5)	0.67
Chronic low albumin, ≤43 g/liter at both measurements (%)			
Yes	20.5	17.8	0.56
No	79.5	82.2	
Clinically relevant decrease in albumin‡ (%)			
Yes	14.1	12.4	0.68
No	85.9	87.6	

* Chi-square test for categorical variables; one-way analysis of variance for continuous variables; *p* values for two-sided tests.
† SD, standard deviation.
‡ Decline of ≥1 standard deviation (2.5 g/liter).

RESULTS

Study sample

Compared with those who did not give blood at the 3-year follow-up ($n = 65$), the respondents of the present study sample ($n = 713$) were younger, had a lower body mass index, were more active, and were less cognitively impaired at the 3-year follow-up ($p < 0.05$).

Cardiovascular incidence

Incident CVD was observed in 86 respondents (18.9 percent). Respondents with incident CVD were older, more likely to be male, and more cognitively impaired; reported more often the presence of diabetes; and had a higher serum total cholesterol concentration compared with respondents without CVD (table 1).

Respondents with incident CVD had a significantly lower mean serum albumin concentration at the 3-year follow-up compared with respondents without incident CVD (table 2) and were more likely to have a low (≤43 g/liter) serum albumin concentration at the 3-year follow-up (37.2 percent vs. 26.8 percent) ($p = 0.05$). The mean change in serum albumin tended to be different for respondents with and without incident CVD ($p = 0.11$). The percentage of respondents with chronic low albumin did not differ significantly between those with and without incident CVD (23.3 percent vs. 17.8 percent) ($p < 0.25$). The percentage with a relevant decrease in serum albumin concentration tended to be different between those with and without incident CVD (17.4 percent vs. 11.1 percent) ($p = 0.11$).

As reported in other studies, serum albumin concentration (measured at one point in time) was associated with the risk of incident CVD after adjustment for age, sex, education, smoking, alcohol consumption, body mass index, physical activity, diabetes mellitus, diastolic blood pressure, systolic blood pressure, serum total cholesterol, and cognitive impairment. Per unit (1 g/liter) increase in serum albumin concentration at 3-year follow-up, a lower risk (relative risk (RR) = 0.88, 95 percent confidence interval (CI): 0.79, 0.98) for incident CVD was observed (table 3). Respondents with low albumin (≤43 g/liter) tended to have a higher risk for incident CVD compared with respondents with a normal serum albumin concentration (>43 g/liter) after full adjustment (RR = 1.72, 95 percent CI: 0.98, 3.01).

The 3-year change in serum albumin concentration was related to the risk of incident CVD after adjustment for the selected confounders (figure 2; table 3). Per unit increase (g/liter) in change in serum albumin concentration, a lower risk (RR = 0.88, 95 percent CI: 0.78, 0.99) for incident CVD was observed. After full adjustment, respondents with low serum albumin (≤43 g/liter) at both time points had no increased risk of incident CVD. However, respondents with a relevant decrease in serum albumin over time tended to have a twofold risk (RR = 2.00, 95 percent CI: 0.91, 4.39) for incident CVD after full adjustment. When missing values were imputed, similar results were found (data not shown).

All-cause mortality

During follow-up, 78 respondents (10.9 percent) died. Respondents who died during follow-up were older, more likely to be male, more likely to have a low educational level, more likely to be current or former smokers, and less physically active, and they had a higher systolic blood pressure. The prevalence of diabetes and cognitive impairment was higher in respondents who died (table 1).

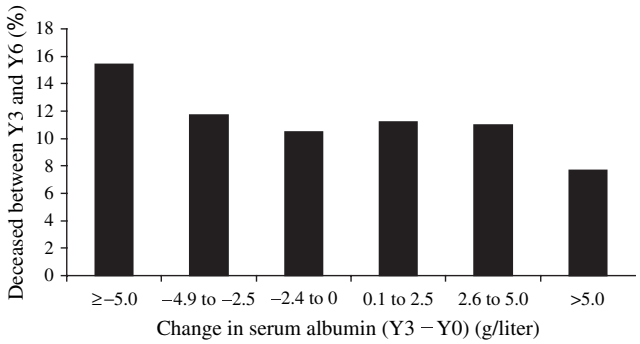

FIGURE 3. All-cause mortality according to change in serum albumin (g/liter), Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999. Y0, baseline; Y3, 3-year follow-up; Y6, 6-year follow-up.

Neither serum albumin at 3-year follow-up nor change in serum albumin concentration was significantly different between those who died and those who did not die during follow-up (table 4). No significant associations were found between serum albumin and all-cause mortality and between change in albumin and all-cause mortality (figure 3; table 5).

DISCUSSION

The results of this study confirm previous studies showing that low serum albumin is related to incident CVD. More importantly, the results suggest that a decrease in serum albumin concentration over time, even within the normal range, might be related to CVD incidence in older respondents. No association was observed between (change in) serum albumin and all-cause mortality.

Our findings extend the results of several studies showing the association between low serum albumin and CVD (1–8, 10–15) by demonstrating a possible association between a decrease in serum albumin concentration and incident CVD. It is striking that, even after adjustment for smoking, alcohol, age, body mass index, diastolic and systolic blood pressures, and other conventional CVD risk factors, a decrease in serum albumin within the normal range may be related to CVD. This information might be used to detect

TABLE 5. Cox regression analyses of serum albumin and change in serum albumin and all-cause mortality, Longitudinal Aging Study Amsterdam, the Netherlands, 1992/1993–1998/1999

	All-cause mortality					
	Adjusted*			Adjusted†		
	Relative risk	95% confidence interval	*p* value‡	Relative risk	95% confidence interval	*p* value‡
Albumin at 3-year follow-up, g/liter	0.94	0.86, 1.04	0.22	1.01	0.92, 1.12	0.83
Low albumin, ≤43 g/liter						
Yes	1.04	0.64, 1.69	0.89	0.86	0.50, 1.47	0.57
No	1.00			1.00		
Absolute change in serum albumin, continuous, g/liter§	0.95	0.85, 1.05	0.32	1.06	0.95, 1.19	0.32
Chronic low albumin, ≤43 g/liter at both measurements						
Yes	1.17	0.68, 2.03	0.57	1.25	0.69, 2.24	0.47
No	1.00			1.00		
Clinically relevant decrease in albumin¶						
Yes	1.29	0.66, 2.54	0.46	0.81	0.37, 1.75	0.59
No	1.00			1.00		

* Adjusted for serum albumin at baseline (except for chronic low albumin).

† Adjusted for serum albumin at baseline (except for chronic low albumin) and for age, sex, education, smoking, alcohol consumption, body mass index, physical activity, diabetes mellitus, diastolic blood pressure, systolic blood pressure, cognitive impairment, and serum total cholesterol at 3-year follow-up.

‡ *p* values for two-sided tests.

§ For an increase in change in serum albumin of 1 g/liter.

¶ Decline of ≥1 standard deviation (2.5 g/liter).

respondents at an early stage and might therefore be helpful in preventing CVD.

It is interesting that chronic low serum albumin concentrations were not associated with incident CVD, while a low serum albumin concentration measured at one time point is. Our results suggest that not all respondents with low serum albumin are at risk for CVD but that those with a recently decreased serum albumin concentration might be at risk. Therefore, our results provide evidence that the history of serum albumin matters in the association with incident CVD.

Several putative mechanisms for the association between low serum albumin and CVD incidence have been proposed (20–22, 25–35, 45). These mechanisms may even better explain the association between decrease in serum albumin and CVD incidence. The most obvious mechanism is inflammation, which is associated with an albumin decrease and higher CVD risk (20–22). Therefore, antiinflammatory factors or parameters, such as antiinflammatory drugs, might be able to raise the serum albumin concentration and subsequently prevent CVD.

CVD is a leading cause of mortality in older respondents (46), and an early marker for CVD might be useful for detecting older respondents at risk for this disabling disease. The albumin determination in blood is done quickly and the costs are low.

Whether serum albumin is an important risk factor among the other well-known risk factors for CVD, such as blood lipids or other blood parameters, should be further examined. If so, it may be important to increase and stabilize the serum albumin concentration, for example, through nutritional interventions or by using antiinflammatory drugs. Although these issues remain to be investigated, CVD could be prevented by primordial prevention. ''Primordial prevention'' is a relatively new term involving attempts to prevent the deterioration of risk factors involving overall lifestyle (47). This kind of prevention advocates a healthy lifestyle, such as no smoking or stopping smoking, drinking one glass of alcohol a day, improving dietary habits, and promoting physical exercise (48, 49).

Our findings are not consistent with those of several other studies relating serum albumin (measured at one time point) with mortality. Our study suggests that there is no association between (change in) albumin and 3-year all-cause mortality in a community-based older population. Except for one study (50), most studies (4, 8, 13, 20) found that low serum albumin concentrations are associated with a twofold risk of all-cause mortality. It remains unclear why no associations were observed with all-cause mortality, but we cannot exclude that significant associations exist for cause-specific mortality, that is, CVD mortality.

Limitations of our study should be addressed. First, this study was restricted to a community-based older population. Therefore, these associations cannot be generalized to frail, institutionalized, or hospitalized older populations or to young populations. Second, the cutoff point of 43 g/liter for low serum albumin is relatively high compared with the generally clinically accepted cutoff point of 38 g/liter (51). However, in this community-dwelling population, only eight respondents (1 percent) had a serum albumin concentration of less than or equal to 38 g/liter at the 3-year follow-up, suggesting that in a community-based population the serum albumin concentrations are likely to be higher compared with those of hospitalized patients or nursing home residents. It is striking that, even in this high range, a decrease in albumin level may be related to an increased risk for future CVD. Third, because our definition of CVD was partly based on self-report, misclassification of CVD could potentially bias the study results. However, incident CVD was based on only self-report for only nine respondents. Moreover, when these nine respondents were excluded from the analyses, similar results were found (data not shown).

The results of this study confirm that a low albumin concentration is related to an increased risk of incident CVD in older respondents. More importantly, the present study extends the findings of previous studies by showing that respondents whose serum albumin concentration decreases, even within the normal range, may be at risk for incident CVD. A decrease in serum albumin concentration may be an early marker for CVD in an older population.

ACKNOWLEDGMENTS

LASA is funded by the Dutch Ministry of Health, Welfare, and Sports and by the Vrije Universiteit in Amsterdam.

Conflict of interest: none declared.

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