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Serum Albumin and Muscle Strength: A Longitudinal Study in Older Men and Women

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OBJECTIVES: To examine whether low serum albumin is associated with low muscle strength and future decline in muscle strength in community-dwelling older men and women.

DESIGN: Population-based cohort study.

SETTING: The Longitudinal Aging Study Amsterdam.

PARTICIPANTS: Six hundred seventy-six women and 644 men aged 65 to 88.

MEASUREMENTS: Serum albumin was determined at baseline. Muscle strength was assessed using grip strength at baseline, after 3 (n = 1,009), and 6 (n = 741) years. The outcomes were continuous baseline muscle strength, 3- and 6-year change in muscle strength, and a dichotomous indicator for substantial decline (a decrease if $\geq$1 standard deviations for women = 11 kg, for men = 12 kg) in muscle strength.

RESULTS: Mean serum albumin concentration ± standard deviation was 45.0 ± 3.3 g/L for women and 45.2 ± 3.2 g/L for men. At baseline, adjusting for age, lifestyle factors, and chronic conditions, lower serum albumin was cross-sectionally associated with weaker muscle strength ($P<.001$) in women and men. After 3 years of follow-up, mean decline in muscle strength was − 5.6 ± 10.9 kg in women and − 9.6 ± 11.9 kg in men. After adjustment for potential confounders, lower serum albumin was associated with muscle strength decline over 3 years ($P<.01$) in women and men (β = 0.57, standard error (SE) = 0.18; β = 0.37, SE = 0.16, respectively). Lower serum albumin was also associated with substantial decline in muscle strength in women (per unit albumin (g/L) adjusted odds ratio (OR) = 1.14, one-sided 95% confidence limit (CL) = 1.07) and men (per unit albumin (g/L) adjusted OR = 1.14, 95% CL = 1.08). Similar but slightly weaker associations were found between serum albumin and 6-year change in muscle strength ($P<.05$).

CONCLUSION: These results suggest that low serum albumin, even within the normal range, is independently associated with weaker muscle strength and future decline in muscle strength in older women and men. **J Am Geriatr Soc 53:1331–1338, 2005.**

Key words: albumin; grip strength; population-based study; aging

The release of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), which induce the acute-phase response, accompany inflammation.[1] Proinflammatory cytokines reduced serum albumin, a negative acute-phase protein.[1] It has also been suggested that proinflammatory cytokines reduce the synthesis of muscle proteins and the stimulation of protein breakdown in experimental studies in rats[2–5] and in humans.[6] This may cause sarcopenia, characterized by a reduction in muscle strength and muscle mass.[7]

Studies in which higher IL-6 and TNF-alpha levels were associated with lower muscle mass and strength[8] and decline of muscle strength[9] support this theory. Furthermore, low muscle strength is associated with disability, poor mobility, morbidity, and mortality.[10–12] A reduction of muscle strength and mass may ultimately lead to poorer physical function,[13] disability,[14] and mortality.[12]

Low serum albumin concentration is a known marker for poor health outcomes such as mortality, cardiovascular disease, future functional limitations, and disability.[15–18] One cross-sectional study has found an association between lower serum albumin concentration and lower muscle mass,[19] but no (prospective) studies have yet examined the relationship between serum albumin and muscle strength and its change with age.

The objectives of the present study were to examine whether low serum albumin is associated with low muscle strength and whether low serum albumin is independently associated with subsequent decline in muscle strength in a population-based sample of older women and men. In addition, the role of inflammation as potential mediator of the association was investigated.

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METHODS

Study Sample

The data presented were collected in the context of the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study that focuses on changes in physical, cognitive, emotional, and social functioning in older persons. The sampling and data collection have been described in detail elsewhere.[20] Briefly, a sample of older women and men (aged 55–85), stratified by age, sex, urbanization, and expected 5-year mortality, was drawn from the population registers of 11 municipalities in areas situated in the west (Amsterdam region), northeast (Zwolle region), and south (Oss region) of the Netherlands.

The sample for this study comprised respondents who participated in the first follow-up of LASA (1995/1996) and were born in or before 1930 (aged $\geq$65 at January 1, 1996).[21] In this study, the first follow-up of LASA will be referred to as baseline measurement. During a medical interview (n = 1,509), a nurse interviewer collected blood samples from 1,328 respondents, for two of whom no serum albumin levels were determined. Five respondents had no data on muscle strength at baseline, and one respondent was excluded because of extremely high muscle strength levels (>3 standard deviations above the mean), leaving a study sample of 1,320 respondents. During follow-up, muscle strength was measured in 1,009 respondents after 3 years and in 741 respondents after 6 years.

Of the 311 respondents with missing muscle strength information after 3 years, 298 did not participate in the follow-up examination (171 had died, 25 were ineligible due to frailty, 51 refused, 46 had a telephone interview, and 5 could not be contacted), and 13 participated but had no muscle strength measured. Of the 579 respondents with missing muscle strength information after 6 years, 561 did not participate in the follow-up examination (352 had died, 36 were ineligible due to frailty, 70 refused, 96 had a telephone interview, and 7 could not be contacted), and 18 participated but had no muscle strength measured.

Informed consent was obtained from all the respondents. The medical ethics committee of the VU University Medical Center in Amsterdam approved the study.

Serum Albumin

Nonfasting serum samples were obtained and analyzed directly. Serum samples obtained in Zwolle were analyzed in the laboratory of the ISALA Clinic (Location Weezelanden), and serum samples obtained in Amsterdam and Oss were analyzed in the laboratory of the VU University Medical Center in Amsterdam.

Information from the Dutch Foundation for Quality Assessment in Clinical Laboratories (SKZL) was used to control for between-laboratory differences. Every 2 months, eight standard serum samples were sent to the laboratories to be analyzed, and the serum albumin concentration was reported to the SKZL. Using linear regression, a regression line was fitted using the individual laboratory assessment of serum albumin for each sample and the overall national mean of the same sample. Separate lines were fitted for each laboratory to adjust the serum albumin levels in the LASA sample.

Serum albumin concentrations (g/L) were determined using a bromcresol green photometric assay with a Hitachi analyzer in the laboratory in Zwolle. The laboratory of the VU University Medical Center used a bromcresol purple method. To make the serum albumin levels comparable, the serum albumin levels that were determined using the bromcresol purple method were converted using a validated formula.[22]

Serum albumin was used as a continuous variable and was categorized into sex-specific quartiles (women: first quartile $\leq$43 g/L, second quartile 43.1–44.6 g/L, third quartile 44.7–47.1 g/L, and fourth quartile >47.1 g/L (reference group); in men: first quartile $\leq$43 g/L, second quartile 43.1–45 g/L, third quartile 45.1–47 g/L, and fourth quartile >47 g/L (reference group)) to examine potential nonlinear associations.

Muscle Strength

Muscle strength (kg) was assessed using grip strength and measured using a strain-gauged dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd, Tokyo, Japan). Subjects stood with arms and wrists stretched out at the sides of the body. They were asked to perform two maximum force trials with each hand. For the final scores, the maximum values of the right and the left hand were summed.[23,24] When only one hand could be used in any examination, the maximum value of that hand was doubled for all examinations (n = 38).

Muscle strength at baseline and 3- and 6-year decline in muscle strength were used as outcome variables. Change in muscle strength was calculated as the follow-up muscle strength minus baseline muscle strength. Change in muscle strength was also used as a dichotomous variable by defining substantial decline in muscle strength as a decline of one standard deviation (for 3-year decline in women 11 kg and in men 12 kg, for 6-year decline in women 10 kg and in men 13 kg) or more.

Covariates

Baseline covariates included age, smoking status (never (reference group), former, and current), alcohol consumption (none (reference group), 1–2 drinks/d, >2 drinks/d), body mass index (BMI; weight/height^2), physical activity (min/wk), serum total cholesterol (mMol/L), vitamin D and parathyroid hormone (PTH) status, and chronic conditions. The covariates were selected as potential confounders because they were associated at $P < .20$ with serum albumin and muscle strength or change in muscle strength or because they had been used as a confounder in previous studies.[19] Physical activity in the previous 2 weeks was based on the following activities: walking outdoors, cycling, light and heavy household activities, and a maximum of two sports activities.[25] Serum total cholesterol was measured using an enzymatic colorimetry assay with a Hitachi 747 analyzer. Serum concentration of PTH was measured using immunoradiometric assay, and vitamin D was assessed using serum 25-hydroxyvitamin D and was determined using a competitive binding protein assay summed.[24] Chronic conditions were self-reported and included the presence of diabetes mellitus, arthritis, stroke, cardiac disease, depressive symptoms, and cognitive status. For depressive symptoms, the

Center for Epidemiologic Studies Depression scale was used;[26] a score of 16 or greater was used to indicate depression.[27] Cognitive status was measured using the Mini-Mental State Examination; a score of 23 or less was used to indicate cognitive impairment.[28] Covariates were missing for some respondents: physical activity, n = 49; BMI, n = 10; alcohol consumption, n = 1; serum total cholesterol, n = 18; serum vitamin D, n = 10; serum PTH, n = 10; diabetes mellitus, n = 1; arthritis, n = 1; depressive symptoms, n = 38; and cognitive impairment, n = 3.

Inflammatory Markers

Other confounding factors, such as markers of inflammation, may contribute to the association between serum albumin levels and low muscle strength or future decline in muscle strength. As markers of inflammation, serum IL-6 concentration (pg/mL) and serum C-reactive protein (CRP) concentration (μg/mL) were used. IL-6 and CRP were determined using sensitive regular immunoassays at Sanquin Research in Amsterdam. CRP was categorized in tertiles (first tertile <1.9 μg/mL (reference), second tertile 1.9–5.1 μg/mL, and third tertile >5.1 μg/mL). Because of the high detection limit of 5 pg/mL, IL-6 was categorized in three categories, with levels above the 5 pg/mL in the highest category. Persons with lower levels were divided in two groups, based on the median level of IL-6 in this group (first group ≤ 1.7 pg/mL (reference), second group 1.8–5.0 pg/mL, third group >5.0 pg/mL). Intermediating factors were missing for some respondents (IL-6, n = 45; CRP, n = 44).

Statistical Analyses

In view of sex-related muscle strength differences[29] and because preliminary analyses showed a sex interaction for the cross-sectional associations ($P = .04$), all analyses were performed stratified by sex. Data were analyzed using the statistical package SPSS 10.1 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the respondents in the study sample. Differences between included and excluded respondents were tested using descriptive statistics, and statistical significance was considered present at the two-sided *P*-value of .05. When examining the associations between serum albumin and (change in) muscle strength, one-sided statistical tests were performed at $P < .05$. The use of the one-sided test corresponds to the one-sided hypothesis that the lower the serum albumin concentration, the weaker the muscle strength or the greater the decline in muscle strength.[30]

Linear regression models were used to examine the relationship between serum albumin and (change in) muscle strength. Results are presented as regression coefficients (β) with standard errors (SEs) with *P*-values. The *P*-value of the two-sided statistical test in the output from the statistical package was divided by two to make it a one-sided *P*-value. A regression coefficient of -0.2 can be interpreted as a decline in muscle strength of 0.2 kg during follow-up per unit (g/L) of lower baseline serum albumin concentration. Analyses of covariance were performed to examine the association between quartiles of albumin and (change in) muscle strength. Logistic regression models were used to examine the relationship between (quartiles of) serum albumin and the dichotomous variable substantial decline in muscle strength. Results are presented as odds ratios (ORs) with one-sided 95% confidence limits (CLs). The one-sided 95% CL was recalculated by hand to make it one-sided using a *z* score of 1.65 instead of the 1.96 that is used for two-sided tests. The analyses were adjusted for age, and—when change in muscle strength (or substantial decline) was the dependent variable—for baseline muscle strength in the first model. The second model additionally included lifestyle factors such as smoking, alcohol consumption, BMI, and physical activity. In the third model, diabetes mellitus, cardiac disease, stroke, arthritis, cognitive impairment, depression, serum total cholesterol, serum vitamin D, and serum PTH were additionally adjusted for. In the final model, results were additionally adjusted for the inflammatory markers IL-6 and CRP.

Because it is known that persons with hand arthritis perform poorly on muscle strength measures, analyses were repeated excluding persons with pain or recent surgery to the hands or who were observed to have hand rheumatoid arthritis by the medical interviewer at baseline (n = 309).

RESULTS

Study Sample

Baseline characteristics of the study sample are shown in Table 1. Those included in the baseline sample (n = 1,320) more often drank two or more glasses of alcohol daily, were less cognitively impaired and less depressed, and reported less often the presence of stroke than those excluded from the baseline sample (n = 189).

Participants with muscle strength measured after 3 years (n = 1,009), at baseline, were significantly younger; were more often female; had higher muscle strength; a higher serum albumin concentration, and higher BMI; more often drank 2 or more glasses of alcohol daily; were more physically active; had more education; were less cognitively impaired and less depressed; and reported less often the presence of diabetes mellitus, cardiac disease, and stroke than those without muscle strength information (n = 311).

Participants with muscle strength measured after 6 years (n = 741), at baseline, were significantly younger; were more often female; had higher muscle strength and a higher serum albumin concentration; were more physically active; had more education; were more often former or nonsmokers; more often drank 2 or more glasses of alcohol daily; had higher total cholesterol; were less cognitively impaired; and reported less often the presence of diabetes mellitus, cardiac disease, and stroke than those with no muscle strength assessment (n = 579).

Serum Albumin and Muscle Strength

Mean baseline serum albumin concentration was 45.0 ± 3.3 g/L for women and 45.2 ± 3.2 g/L for men. Mean baseline muscle strength was 41.9 ± 9.9 kg for women and 70.8 ± 16.5 kg for men (Table 1).

Lower serum albumin was associated with weaker muscle strength in women and men ($\beta = 0.41$, SE = 0.10 and $\beta = 0.65$, SE = 0.17, respectively; $P < .001$), after adjustment for age (Table 2). After additional adjustment for lifestyle factors, chronic conditions, serum total cholesterol, serum PTH, and serum vitamin D, the results remained

Table 1. Characteristics of Participants of the Longitudinal Aging Study Amsterdam

Characteristic	Women (n = 676)	Men (n = 644)
Age, mean ± SD	75.4 ± 6.6	75.6 ± 6.6
Cigarette smoking, %		
Never	60.1	10.1
Former	27.8	64.8
Current	12.1	25.2
Alcohol consumption, drinks/day, %		
0	34.2	14.0
<2	34.1	28.4
≥2	31.7	57.6
Body mass index, kg/m^2, mean ± SD	27.6 ± 4.8	26.1 ± 3.4
Physical activity, min/wk, mean ± SD	174.2 ± 102.7	124.8 ± 98.0
Diabetes mellitus, %	8.9	6.4
Cardiac disease, %	20.6	32.1
Stroke, %	6.4	8.9
Arthritis, %	58.1	33.7
Cognitive impairment, %	11.8	11.1
Depression, %	20.7	8.5
Serum total cholesterol concentration, mmol/L, mean ± SD	6.2 ± 1.7	5.7 ± 1.1
Serum vitamin D, nmol/L, mean ± SD	48.9 ± 22.9	57.9 ± 24.5
Parathyroid hormone, pmol/L, mean ± SD	3.6 ± 2.5	3.7 ± 2.5
Interleukin-6, mean ± SD	3.0 ± 5.3	2.9 ± 4.1
C-reactive protein, mean ± SD	6.7 ± 14.4	6.9 ± 12.8
Serum albumin concentration, g/L, mean ± SD	45.0 ± 3.3	45.2 ± 3.2
Muscle strength at baseline, kg, mean ± SD	41.9 ± 9.9	70.8 ± 16.5
3-year change in muscle strength, kg, mean ± SD	− 5.6 ± 10.9	− 9.6 ± 11.9
6-year change in muscle strength, kg, mean ± SD	− 5.6 ± 9.9	− 10.6 ± 13.2

SD = standard deviation.

statistically significant and were only slightly attenuated (women $\beta = 0.31$, SE = 0.11; men $\beta = 0.62$, SE = 0.17, $P < .01$). When CRP and IL-6 were added to the model, the beta for baseline muscle strength was reduced but still significantly associated with serum albumin.

As shown in Figure 1, women and men in the lower quartiles of serum albumin had lower mean muscle strength after adjustment for age, lifestyle factors, and chronic conditions (P for trend in women = .009 and in men = .003). Men in the first, second, and third quartile had significantly lower mean muscle strength than those in the highest quartile of serum albumin. Women in the first and second quartile of serum albumin had significantly weaker mean muscle strength than those in the highest quartile. When the inflammatory markers were added to the model, the first and second quartiles were not significantly different from the highest quartile of serum albumin in women. In men, the first and second quartile of serum albumin had significantly lower mean muscle strength than the highest quartile of serum albumin ($P \leq .05$).

Serum Albumin and Change in Muscle Strength

After 3 years of follow-up (women, n = 532; men, n = 477), mean decline in muscle strength was − 5.6 ± 10.9 kg in

Table 2. Cross-Sectional Association Between Baseline Serum Albumin (g/L) and Baseline Muscle (kg) Strength in Women and Men

	First model*		Second model†		Third model‡		Fourth model§	
Subjects	β (Standard Error)	*P*-value	β (Standard Error)	*P*-value	β (Standard Error)	*P*-value	β (Standard Error)	*P*-value
Women	0.41 (0.10)	<.001	0.36 (0.10)	<.001	0.31 (0.11)	.002	0.20 (0.11)	.04
Men	0.65 (0.17)	<.001	0.63 (0.17)	<.001	0.62 (0.17)	<.001	0.53 (0.18)	.002

* Adjusted for age.
† Additionally adjusted for smoking, alcohol consumption, body mass index, and physical activity.
‡ Additionally adjusted for diabetes mellitus, cardiac disease, stroke, arthritis, cognitive impairment, depression, total serum cholesterol, serum parathyroid hormone, and serum vitamin D.
§ Additionally adjusted for interleukin-6 and C-reactive protein.

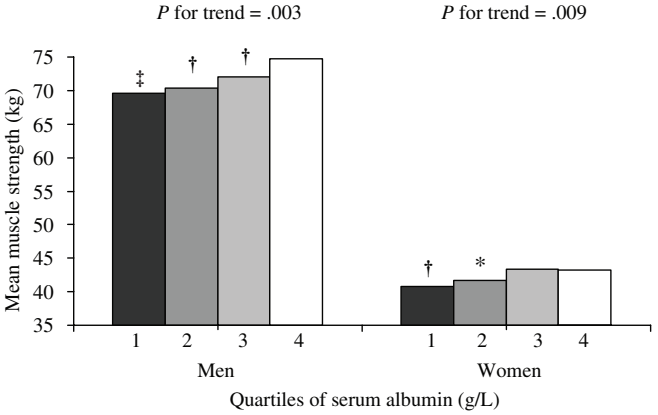

Figure 1. Mean muscle strength at baseline according to sex-specific quartiles of serum albumin concentration (g/L) after adjustment for age, lifestyle factors, and chronic conditions (including serum total cholesterol, parathyroid hormone, and vitamin D). Serum albumin quartiles in women: 1. ≤43.0 g/L; 2. 43.1–44.6 g/L; 3. 44.7–47.1 g/L; 4. >47.1 g/L. Serum albumin quartiles in men 1. ≤43.0 g/L; 2. 43.1–45.0 g/L; 3. 45.1–47.0 g/L; 4. >47.0 g/L. $P<$*.10, †.05, ‡.001; *P*-values indicate statistically significant differences in mean muscle strength when compared with the highest quartile of serum albumin.

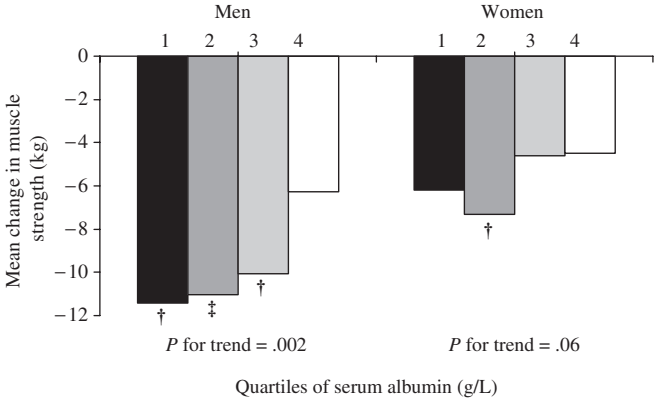

Figure 2. Mean change in muscle strength over 3 years according to sex-specific quartiles of serum albumin concentration (g/L) after adjustment for baseline muscle strength, age, lifestyle factors, and chronic conditions (including serum total cholesterol, parathyroid hormone, and vitamin D). Serum albumin quartiles in women: 1. ≤43.0 g/L; 2. 43.1–44.6 g/L; 3. 44.7–47.1 g/L; 4. >47.1 g/L. Serum albumin quartiles in men 1. ≤43.0 g/L; 2. 43.1–45.0 g/L; 3. 45.1–47.0 g/L; 4. >47.0 g/L. $P<$*.10, †.05, ‡.001; *P*-values indicate statistically significant differences in mean muscle strength when compared with the highest quartile of serum albumin.

women and -9.6 ± 11.9 kg in men. Of the women, 20.1% experienced a substantial decline in 3-year muscle strength (≥13 kg) and, of the men, 34.6% experienced a substantial decline in muscle strength.

After adjustment for age, baseline muscle strength, lifestyle factors, and chronic conditions, lower serum albumin concentration was associated with greater decline in muscle strength over 3 years; women declined 0.37 kg and men 0.57 kg during follow-up per unit (g/L) of lower albumin ($P<.01$, Table 3). After adjustment for IL-6 and CRP, the results remained significant and were slightly attenuated (women $\beta = 0.30$ and men $\beta = 0.53$; $P<.05$). Figure 2 shows the adjusted mean 3-year change in muscle strength for each serum albumin quartile. After full adjustment, a linear trend was observed between quartiles of serum albumin and 3-year change in muscle strength in men (*P* for trend = .002). In women, those in the second serum albumin quartile differed significantly in muscle strength decline from those in the highest quartile. After adjustment for markers of inflammation, the results did not change. During follow-up, men showed a greater decline in muscle strength than women, but when the analyses were repeated, replacing absolute change (kg) in muscle strength with relative change (%) in muscle strength, the decline in muscle strength was similar for men and women (data not shown).

Regarding substantial muscle strength decline, lower serum albumin concentration was associated with substantial 3-year decline in muscle strength in women (per unit (g/L) albumin OR = 1.14, 95% CL = 1.07) and men (per unit (g/L) albumin OR = 1.14, 95% CL = 1.08) (Table 4). After adjustment for potential confounders and markers of inflammation, these results did not change markedly. As shown in Figure 3, women and men in the lowest three quartiles of serum albumin showed a greater risk of substantial decline in muscle strength than those in the highest quartile after adjusting for age, baseline muscle strength, lifestyle factors, and chronic conditions. These results did not markedly change after additional adjusting for IL-6 and CRP.

With regard to measured muscle strength at 6 years of follow-up (women, n = 400; men, n = 341), the mean

Table 3. Longitudinal Association Between Baseline Serum Albumin (g/L) and Subsequent 3-Year Decline in Muscle Strength (kg) in Women and Men

	First model*		Second model†		Third model‡		Fourth model§	
Subjects	β (Standard Error)	*P*-value	β (Standard Error)	*P*-value	β (Standard Error)	*P*-value	β (Standard Error)	*P*-value
Women	0.42 (0.15)	.002	0.42 (0.15)	.003	0.37 (0.16)	.009	0.30 (0.17)	.04
Men	0.61 (0.17)	<.001	0.63 (0.17)	<.001	0.57 (0.18)	.001	0.53 (0.19)	.003

* Adjusted for baseline muscle strength and age.
† Additionally adjusted for smoking, alcohol consumption, body mass index, and physical activity.
‡ Additionally adjusted for diabetes mellitus, cardiac disease, stroke, arthritis, cognitive impairment, depression, total serum cholesterol, serum parathyroid hormone, and serum vitamin D.
§ Additionally adjusted for interleukin-6 and C-reactive protein.

Table 4. Longitudinal Association Between Baseline Serum Albumin (g/L) and Subsequent 3-Year Substantial Decline in Muscle Strength (kg)* in Women and Men

	First model†		Second model‡		Third model§		Fourth model‖	
Subjects	Odds Ratio (95% Confidence Limit)	*P*-value	Odds Ratio (95% Confidence Limit)	*P*-value	Odds Ratio (95% Confidence Limit)	*P*-value	Odds Ratio (95% Confidence Limit)	*P*-value
Women	1.14 (1.07)	<.001	1.14 (1.07)	<.001	1.13 (1.06)	.001	1.11 (1.03)	.008
Men	1.14 (1.08)	<.001	1.14 (1.08)	<.001	1.13 (1.07)	<.001	1.13 (1.06)	<.001

* Decline of one standard deviation (women 11 kg, men 12 kg) or more during 3 years of follow-up.
† Adjusted for baseline muscle strength and age.
‡ Additionally adjusted for smoking, alcohol consumption, body mass index, and physical activity.
§ Additionally adjusted for diabetes mellitus, cardiac disease, stroke, arthritis, cognitive impairment, depression, total serum cholesterol, serum parathyroid hormone, and serum vitamin D.
‖ Additionally adjusted for interleukin-6 and C-reactive protein.

decline in muscle strength was -5.6 ± 9.9 kg in women and -10.6 ± 13.2 kg in men. In total, 20.3% of the women and 39.0% of the men experienced a substantial decline in muscle strength. The association between serum albumin—used continuously as well as in quartiles—and 6-year change in muscle strength was similar but slightly weaker than the association with 3-year change in muscle strength (for continuous: women $\beta = 0.28$, SE = 0.16 kg; men $\beta = 0.39$, SE = 0.23; for quartiles: 1st to 4th quartiles for women: −6.50, −5.95, −6.34, −4.25, *P* for trend = .16; for men: −13.20, −10.04, −11.48, −8.45, *P* for trend = .07). With respect to 6-year substantial muscle strength decline, similar results were observed as for 3-year substantial decline (per unit (g/L) lower serum albumin (women, OR = 1.08, 95% CL = 1.01; men, OR = 1.09, 95% CL = 1.01; first quartile vs highest quartile: women, OR = 1.97, 95% CL = 1. 10; men, OR = 2.42, 95% CL = 1.26).

Restricting the analyses to older persons without pain or recent surgery to the hands and without the medical interviewer having observed rheumatoid arthritis showed similar results (data not shown).

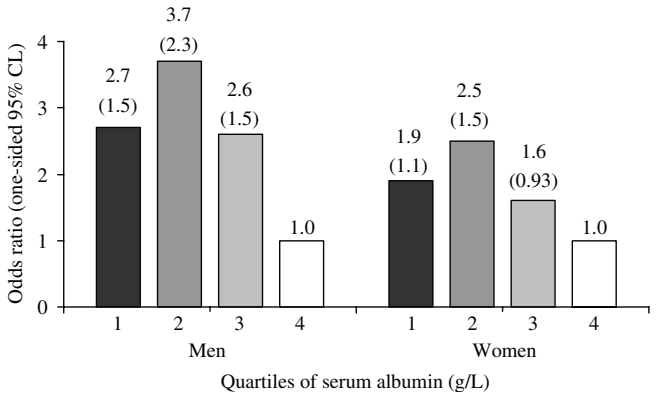

Figure 3. Risk of substantial decline in muscle strength over 3 years according to sex-specific quartiles of serum albumin concentration (g/L) after adjustment for baseline muscle strength, age, lifestyle factors and chronic conditions (including serum total cholesterol, parathyroid hormone, and vitamin D). Serum albumin quartiles in women: 1. ≤43.0 g/L; 2. 43.1–44.6 g/L; 3. 44.7–47.1 g/L; 4. >47.1 g/L. Serum albumin quartiles in men 1. ≤43.0 g/L; 2. 43.1–45.0 g/L; 3. 45.1–47.0 g/L; 4. >47.0 g/L. The highest quartile of serum albumin (>47.0 g/L) is the reference group. 95% CL = one-sided 95% confidence limit.

DISCUSSION

The present study shows that low serum albumin, even within the normal range, is associated with weaker muscle strength, even after adjustment for age, lifestyle factors, chronic conditions, serum total cholesterol, PTH, and vitamin D. After additional adjustment for inflammatory markers, the association between low serum albumin and weaker muscle strength was somewhat less, indicating that inflammation could only partly explain the associations. To the authors' knowledge, this is the first study examining the cross-sectional association between serum albumin and muscle strength. Muscle strength was assessed using grip strength, which is a well-accepted indicator of overall muscle strength.[23,31] Furthermore, muscle strength is associated with disability, poor mobility, and mortality.[10–12] Previously, an association between low serum albumin and low muscle mass was observed.[19] Together with the present findings, these results suggest that low serum albumin within the normal range may be independently associated with sarcopenia.

Moreover, this study extends the previous findings by showing that low serum albumin concentration within the normal range is associated with subsequent decline in muscle strength after adjustment. When inflammation markers were included in the final model, the association between low albumin and subsequent decline in muscle strength was reduced. These results are even more remarkable when considering that 99% of the study sample had normal serum albumin levels (>38 g/L). Muscle strength decline is an independent predictor of poorer physical function[13] and mortality.[12]

Identifying early determinants of loss of muscle strength might be important in older persons to prevent the deterioration of health and physical functioning. The associations found in this study were obtained from an observational cohort study. Intervention studies using nutritional supplements in older hemodialysis patients, critically ill older inpatients, frail older persons, and persons in elderly homes have found conflicting results. This information has only been conducted in older frail populations. Therefore, future intervention studies, for example, nutritional

intervention studies, should determine whether increasing serum albumin concentrations will improve or stabilize muscle strength in older persons. It is well established that exercise can increase muscle strength in older persons.[32,33] Combining different interventions might be most favorable in preventing sarcopenia and its negative consequences for physical functioning in older persons.

Potential mechanisms might explain the observed association between serum albumin and muscle strength. The first mechanism, already referred to in the introduction, is the role of low-grade inflammation. Briefly, several cytokines downregulate serum albumin concentration (negative acute-phase response) and increase muscle protein breakdown.[1,6] In experimental studies, administration of IL-6 reduces the total skeletal muscle amino acid concentration and causes muscle wasting.[2–5] These effects of the inflammatory cytokines induces a catabolic state that may lead to a reduction in muscle strength and muscle mass, but the inflammation markers could only partly explain the associations between serum albumin and weaker muscle strength and future decline in muscle strength, suggesting that other mechanisms are active as well. A second mechanism might be nutritional status. Nutritional problems might be expected when older persons are living alone, have functional or cognitive impairments, use multiple medications or alcohol, or have limited income. The recommended nutrient intake is still based on younger populations, and this intake might not be sufficient for older persons. Low serum albumin is associated with low nutritional status. With malnutrition, degradation of protein synthesis is the main source of amino acids for protein synthesis. This may lead to muscle strength decline.[1,34–36]

Because this is the first study to examine the association between serum albumin and sarcopenia, further research is suggested on this topic. Future research should confirm the role of albumin in the development of sarcopenia. It may also be worthwhile to further explore the underlying mechanisms of the association between serum albumin and weaker muscle strength and future decline of muscle strength.

Some limitations of this study should be addressed. First, these results cannot be generalized to frail or institutionalized persons because this study was conducted in a relatively healthy, population-based study sample aged 65 and older. Second, participants excluded from the statistical analyses had lower serum albumin levels, weaker muscle strength, and poorer health status than those included. This might have resulted in an under- or overestimation of the relationship between serum albumin concentration and (change in) muscle strength.

Serum albumin and muscle strength are related to nutritional status. Because no data on dietary intake were available, BMI was used as an indirect marker for caloric intake and not as marker for nutrient intake. Nevertheless, serum albumin remained significantly associated with (change in) muscle strength after adjustment for BMI.

In conclusion, low serum albumin concentration, even within the normal range, was associated with lower muscle strength in older women and men. Moreover, low serum albumin was independently associated with 3- and 6-year loss of muscle strength. Serum albumin may be used as an early marker for future decline in muscle strength.

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