

# Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam

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## Abstract

**Background:** both serum albumin and total cholesterol are potential markers of frailty. A decline in functional status is one of the key components of frailty.

**Objective:** the aim of this study was to investigate the association of serum albumin and total cholesterol, separately and combined, with future decline in functional performance.

**Design:** the Longitudinal Aging Study Amsterdam, an ongoing population-based longitudinal study, started in 1992/1993 with a follow-up every 3 years.

**Participants:** 1,064 men and women aged 55–85 years with complete data on serum albumin and total cholesterol at baseline, and functional performance at baseline and 3-year follow-up.

**Measurements:** at baseline, serum albumin and total cholesterol were measured. At baseline and 3 years later, decline in functional status was measured with three performance tests (chair stand, 3-metre walk, putting on and taking off a cardigan). Associations were adjusted for age, life-style and health-related factors.

**Results:** albumin concentration was not associated with decline in functional performance in men and women. Women with lower serum total cholesterol concentration ( $\leq 5.2$  mmol/l) were more likely to decline in functional status compared to women with higher serum total cholesterol concentration (reference; OR = 2.50; 95% CI 1.07–5.84). Men with lower serum albumin ( $\leq 43$  g/l) and lower serum total cholesterol concentration were three times more likely to decline in functional performance compared to men with higher levels (OR = 3.00; 95% CI 1.00–8.97). In women, a similar trend was found (OR = 1.73; 95% CI 0.34–8.94), although not statistically significant.

**Conclusions:** a combination of low albumin and low cholesterol levels may increase the risk of future functional decline.

**Keywords:** serum albumin, serum cholesterol, functional status, performance test, frailty, elderly, longitudinal

## Introduction

For the ageing population, frailty is nowadays a commonly used concept, but no standardised definition has yet been established. It is clear that frailty is not solely a result of the deterioration of one single system, but multiple systems such as musculoskeletal, cardiovascular, metabolic or immunological systems [1–3]. Frail persons are considered to be at risk for morbidity and mortality [4]. One way in which frail persons can be identified is by screening several systems together, and another way is by using biochemical markers.

Both serum albumin and total cholesterol levels might be possible markers of frailty [5].

Serum albumin is the main protein synthesised by the liver. This protein maintains osmotic pressure and transports various substances through the bloodstream [6]. Total cholesterol is a lipid or fat, and is synthesised in many types of tissue, but particularly in the liver and intestinal wall. Approximately three-quarters of cholesterol is synthesised in the body, and one-quarter originates from dietary intake [7].

Previous studies have investigated serum albumin and total cholesterol in relation to functional status. Two cross-sectional

studies have reported an association between hypoalbuminaemia and self-reported functional status in community-dwelling older persons. Hypoalbuminaemia, serum albumin levels of  $<35$  g/l, was associated with two or more limitations in activities of daily living (ADL) [8] and with impaired functional status, defined as having at least one self-reported ADL limitation [9].

Four studies focused on the association of albumin or total cholesterol with longitudinal change in functional status. The first study showed that low serum albumin levels were associated with a decline in self-reported functioning during a 2-year follow-up in older disabled nursing home residents [10]. The second study found that low serum albumin ( $<38$  g/l) was associated with 3-year and not with 7-year functional decline in high-functioning older persons [11]. The third study found that persons in the lowest tertile of total cholesterol had an increased risk for decline in self-reported function during a 2-year follow-up compared to those in the highest tertile [12]. The fourth study found combined levels of lower serum albumin and lower serum total cholesterol concentration to be associated with an increased risk for 3-year change in self-reported functional decline [13]. Nevertheless this association was not adjusted for potential confounders.

These prospective studies were carried out in either low or high functioning groups, but not in a population-based cohort. Whether serum albumin and total cholesterol are early markers for functional decline, based on performance-based tests, has not yet been investigated. Furthermore, the study that combined serum albumin and total cholesterol levels reported unadjusted results. Tests of functional performance are a more objective measurement for decline in functional status than self-reports [10, 12–14].

In the Longitudinal Aging Study Amsterdam (LASA), a population-based study among 3,107 men and women aged 55–85 years, functional status was measured with three performance tests. These tests were repeated every 3 years to assess the longitudinal change in functional status. Furthermore, many potentially confounding variables were taken into account. The aim of this study was to investigate the association between serum albumin, total cholesterol, and combined serum albumin and total cholesterol levels, with future decline in functional performance in population-based older persons.

## Methods

### Study sample

The data presented were collected in the context of the LASA, which is an interdisciplinary longitudinal study that focuses on changes in physical, cognitive, emotional and social functioning in older persons. Details of LASA are described elsewhere [15, 16]. Briefly, a random sample stratified for age and sex was drawn from the population registers of 11 municipalities in three regions (West, North-east and South) of the Netherlands. Each area consists of one middle- to large-size city and two or more rural municipalities that border on the city. To ensure sufficiently large numbers in all cells 5 years into the study, the numbers of

males and females in each age category were weighted using survival rates. In 1992, at baseline, LASA started with 3,107 respondents, aged 55–85 years, 1,506 men and 1,601 women. Data were collected in a face-to-face main interview, which was carried out at the subject's home and by specially trained interviewers. Two to six weeks later the main interview was followed by a medical interview, during which a nurse-interviewer collected blood samples if informed consent was obtained. The same data-collection procedures were carried out after 3 years. The Medical Ethics Committee of the Academic Hospital of the VU University Medical Center approved this study.

Of the 3,107 respondents who participated in the LASA main baseline interview (response rate 81.7%), 2,671 participated in the medical interview. No blood samples were collected in the South region ( $n=661$ ) or in part of the West region ( $n=498$ ). Blood samples from 5 respondents were not analysed. As a consequence, complete data on albumin and total cholesterol concentration were available for 1,507 LASA respondents. Respondents were excluded when they had been taking cholesterol-lowering medication ( $n=23$ ) or when they had no complete data on functional performance at baseline ( $n=84$ ) or at 3-year follow-up ( $n=336$ ). Of the latter 336 respondents, 144 had died, 26 refused, 11 were ineligible to be interviewed, 8 could not be contacted and 147 had no complete data on the performance tests.

In total, the present study sample consisted of 1,064 (70.6%) older persons, 515 men and 549 women. Compared to those who were excluded (29.4% of the respondents with measures of serum total cholesterol and albumin), the respondents in the present study sample ( $n=1,064$ ) had fewer depressive symptoms, a better cognitive status, a higher level of education, a higher overall baseline performance score, a higher serum albumin concentration, were younger, were more often of female gender, drank more often 2 glasses or more per day, and reported less often the presence of diabetes, CVA (cerebrovascular accident), heart disease or cancer at baseline [Appendix 1 (available as supplementary data at <http://www.ageing.oupjournals.org>),  $P<0.05$ ].

### Blood markers

Blood was collected in a non-fasting state, in a sitting position. Serum samples were obtained and analysed directly. The analyses were carried out in two laboratories in the Netherlands. Serum albumin concentrations were determined by using a bromocresol green (BCG) dye-binding method. Total cholesterol was measured by enzymatic colorimetry assay with a Hitachi 747 analyser. The clinically accepted cut-off point for low albumin is 38 g/l. Since only one person had an albumin level below 38 g/l, 43 g/l was used as the cut-off point for lower albumin [17]. Only 20 persons (1.9%) of the sample had a total cholesterol level lower than 4.1 mmol/l, the commonly used cut-off point of serum total cholesterol. Therefore the cut-off point used for lower serum total cholesterol was 5.2 mmol/l [18]. Thus, subjects were classified into two serum albumin categories ( $\leq 43$  g/l and  $>43$  g/l) and into two serum total cholesterol categories ( $\leq 5.2$  mmol/l ( $\leq 200$  mg/dl) and  $>5.2$  mmol/l).

### Performance tests

Performance-based tests have been used in several recent studies and have been found to be a good objective indicator of physical function [19–21]. In LASA, at baseline and at 3-year follow-up performance-based tests were carried out. These tests included walking, repeated chair stands, and putting on and taking off a cardigan [20, 22]. Each test was timed, and scored according to quartiles based on the LASA cohort at baseline [23]. For the walking test, the participants were asked to walk 3 metres, to turn around and to walk back 3 metres as quickly as possible and were categorised: unable (0);  $\geq 10$  seconds (score 1); 8–9 seconds (score 2); 7 seconds (score 3); and  $\leq 6$  seconds (score 4). For the repeated chair stands, participants were asked to fold their arms across their chest and to stand up five times from a kitchen chair. This test was categorised: unable (0);  $\geq 15$  seconds (score 1); 12–14 seconds (score 2); 10–11 seconds (score 3); and  $\leq 9$  seconds (score 4). The time to put on and take off a cardigan was categorised: unable (0);  $\geq 15$  seconds (score 1); 12–14 seconds (score 2); 10–11 seconds (score 3); and  $\leq 9$  seconds (score 4). An advantage for the use of categorisation is the inclusion of persons who could not perform one of the tests (these persons were assigned a score 0). Each performance test resulted in a score ranging from 0 to 4. As was done in previous studies, summing the scores of the three tests for each respondent provided an overall performance score [20, 23]. A lower score indicates a poorer physical function. The predictive validity of the performance score has been established as it predicts nursing home admission, mortality, hospitalisation, and subsequent disability [20, 23]. For descriptive purposes absolute change in performance was computed by subtracting the follow-up overall performance score from the baseline overall performance score.

### Other potential determinants

Baseline variables were selected if they were potential confounders. Age was used as a continuous variable. Self-reported life-style variables included education (low, middle (reference) and high), smoking (never (reference), former and current), alcohol consumption (none (reference),  $>0$  to  $<2$  drinks daily,  $\geq 2$  drinks daily), body mass index (BMI; weight/height<sup>2</sup>;  $\leq 25$ , 25–30 (reference),  $\geq 30$  in kg/m<sup>2</sup>) and physical activity (tertiles). Physical activity (minutes per day) during the past 2 weeks was based on the following activities: walking outdoors, cycling, light and heavy household activities, and a maximum of two sport activities. Disease-related variables included self-reports of the presence of diabetes mellitus, heart disease, CVA, pulmonary disease (asthma or chronic obstructive pulmonary disease), arthritis (osteoarthritis or rheumatoid arthritis), cancer, peripheral artery disease (PAD), depressive symptoms and cognitive function. For depressive symptoms the Center for Epidemiologic Studies Depression (CES-D) Scale was used [24], and a score of  $\geq 16$  was used to indicate depression [25]. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE), and a score of  $\leq 23$  was used to indicate cognitive impairment [26]. Missing values for height and weight were replaced by self-reported measurements at baseline for height ( $n = 8$ ) and weight ( $n = 10$ ) or at the 3-year follow-up

( $n = 5$ ). Missing values for MMSE ( $n = 6$ ) and CES-D ( $n = 3$ ) were replaced by values obtained at the 3-year follow-up. When missing values were not imputed, the analyses produced highly similar results.

### Statistical analyses

Analyses were performed using SPSS 9.0 as a statistical package. The outcome variable of interest was 3-year change in functional performance, and was calculated according to the Edwards-Nunnally index method (EN-index) [27, 28]. This method was used in previous studies [29] in the context of LASA. It takes regression to the mean into account. This was necessary because regression to the mean was present in the study sample (data not shown). Using this method we compare each measurement on baseline and 3-year follow-up per individual. The EN-index was computed from the reliability of the overall performance score at baseline ( $\alpha = 0.64$ ) and the 90% CI ( $90\% \text{ CI} \pm 1.645 \times \text{standard error (se)}$ ) of the mean score at baseline ( $M = 7.86$ ,  $se = 1.60$ ). [If  $T2 < (\alpha \times (T1 - M) + M - 1.645 \times se)$  EN-index = decline; if  $T2 \geq (\alpha \times (T1 - M) + M - 1.645 \times se)$  and  $T2 \leq (\alpha \times (T1 - M) + M + 1.645 \times se)$  or if  $T2 > (\alpha \times (T1 - M) + M + 1.645 \times se)$  EN-index = no decline;  $se = SD^*$  (extract the root of  $(1 - \alpha)$ ), where  $T1$  = score at baseline,  $T2$  = score at 3-year follow-up,  $\alpha$  = reliability on  $T1$ ,  $M$  = mean score at  $T1$ ,  $SD$  = standard deviation on  $T1$  and  $SE$  = standard error.] A significant change requires that the 3-year follow-up score is not included in the 10% CI. The 3-year change in functional performance, based on the EN-index, was categorised into two categories: decline *versus* no decline.

Preliminary analyses showed different results for men and women, which was confirmed by a  $P$ -value of  $<0.10$  for the interaction of albumin and gender, and combined albumin and total cholesterol with gender with respect to the outcome of decline in functional performance. Therefore, all analyses were performed separately for men and women.

Preliminary analyses also showed that for persons with high cholesterol levels the risk was similar to that of persons with intermediate cholesterol levels. This justified the decision to dichotomise the cholesterol variable, using cut-off points that had previously been reported in the literature.

We first compared the baseline characteristics between men and women using Student's  $t$ -test and Chi-square statistics. We used the Chi-square test to analyse the relationship of serum albumin concentrations and total cholesterol concentration with 3-year decline in functional performance. To investigate the relationship of serum albumin concentration and total cholesterol concentration, separately and combined, with 3-year decline in functional performance, multiple logistic regression analysis was used ( $P$ -values were based on the Wald-test). Results are presented as odds ratios (OR) with 95% CI. Baseline variables were included in three successive models to provide insight into potential confounders. In model 1, baseline performance score and age were included. In model 2, mainly life-style factors were included, i.e. education, smoking, physical activity, alcohol consumption and BMI. In the final model, disease-related factors, including prevalent heart disease, CVA, pulmonary disease, diabetes,

arthritis, cancer, PAD, CES-D and MMSE score were additionally included.

**Results**

The characteristics of the study sample are presented in Table 1. Compared with women, men were more likely to smoke, more often consumed two or more drinks of alcohol daily, were less obese, were less depressed, had a higher level of education, a lower level of physical activity, and a higher prevalence of CVA and heart disease. The mean values of the baseline performance score, the follow-up performance score and the absolute 3-year change in performance score did not differ between men and women. More men (18.1%) than women (7.8%) had a lower serum total cholesterol concentration ( $\leq 5.2$  mmol/l). Albumin levels were similar in men and women.

Appendix 2 (available as supplementary data) presents the percentages and absolute numbers of men and women with 3-year decline in functional performance according to baseline serum albumin (g/l) and total cholesterol (mmol/l) concentration. A decline in functional performance was observed more often in men with lower serum albumin concentration (22.1%) than in men with higher serum albumin concentration (13.2%,  $P=0.01$ ). In women these percentages

did not differ (16.9% and 17.9%, respectively,  $P=0.75$ ). In women a slight difference ( $P=0.08$ ) was found between lower and higher serum total cholesterol concentrations and functional decline. More women with lower total cholesterol (27.9%) showed a decline compared to women with higher serum total cholesterol (16.8%), while in men no difference was found ( $P=0.46$ ).

Only 12 women (2.2%) and 22 men (4.3%) had lower levels of both albumin and total cholesterol. Men with lower serum albumin and lower serum total cholesterol showed decline more often (31.8%) compared to men with high levels of both markers (13.3%) ( $P<0.10$ ). Although in women a trend similar to men was noted, no significance was found ( $P>0.10$ ).

Table 2 shows the results of multiple logistic regression analysis of the association of 3-year decline in functional performance with baseline serum albumin and total cholesterol concentration in men and women in three models. After adjustment, decline in functional performance was not associated with albumin concentration in men and women. Similarly, no significant association was found between serum total cholesterol concentration and decline in functional performance in men. However, women with lower serum total cholesterol concentrations were more likely to decline in functional status compared to women with higher serum

**Table 1.** Characteristics of participants in the Longitudinal Aging Study Amsterdam

	Women ( <i>n</i> = 549)	Men ( <i>n</i> = 515)	Total ( <i>n</i> = 1064)
Age, years, mean (interquartile range)	68.0 (61.2–74.7)	68.9 (62.1–76.1)	68.5 (61.5–75.4)
Education*, <i>N</i> (%) Low	363 (66.2)	266 (51.7)	629 (59.2)
BMI (kg/m <sup>2</sup> )*, <i>N</i> (%)			
$\leq 25$	167 (30.6)	192 (37.4)	359 (33.9)
25–30	230 (42.1)	265 (51.7)	495 (46.7)
$\geq 30$	149 (27.3)	56 (10.9)	205 (19.4)
Physical activity (min/day)*, <i>N</i> (%)			
Low (<108.5)	105 (19.3)	236 (46.0)	341 (32.3)
Smoking *, <i>N</i> (%)			
Never	294 (53.6)	40 (7.8)	334 (31.5)
Former	166 (30.3)	311 (60.5)	477 (44.9)
Current	88 (16.1)	163 (31.7)	251 (23.6)
Alcohol consumption (per day)*, <i>N</i> (%)			
None	76 (13.8)	24 (4.7)	100 (9.4)
>0–<2 drinks	257 (46.8)	133 (25.8)	390 (36.7)
$\geq 2$ drinks	216 (39.3)	358 (69.5)	574 (53.9)
Number of chronic diseases, <i>N</i> (%)	52 (9.5)	55 (10.7)	107 (10.1)
CES-D, depressed ( $\geq 16$ )*, <i>N</i> (%)	89 (16.2)	38 (7.4)	127 (11.9)
MMSE, cognitive impaired ( $\leq 23$ ), <i>N</i> (%)	32 (5.9)	30 (5.8)	62 (5.8)
Baseline performance score, mean (sd)	7.89 (2.81)	7.82 (2.54)	7.85 (2.68)
3-year performance score, mean (sd)	7.35 (2.93)	7.47 (2.67)	7.41 (2.80)
Change in performance score, mean (sd)	–0.54 (2.36)	–0.35 (2.35)	–0.45 (2.36)
Albumin, g/l, <i>N</i> (%)			
$\leq 43$	130 (23.7)	113 (21.9)	243 (22.8)
>43	419 (76.3)	402 (78.1)	821 (77.2)
Cholesterol, mmol/l, <i>N</i> (%)			
$\leq 5.2$	43 (7.8)	93 (18.1)	136 (12.8)
>5.2	506 (92.2)	422 (81.9)	928 (87.2)

Differences between men and women were tested with the Student *t*-test or the Chi-square test.

BMI = body mass index; CVA = cerebrovascular accident; PAD = peripheral artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination.

\*Missing data for education 1, BMI 5, physical activity 8, smoking 2, no of chronic diseases (CVA, diabetes, heart disease, arthritis, PAD, cancer and pulmonary disease) 2, CES-D 1, MMSE 2.

**Table 2.** Associations between baseline serum albumin and total cholesterol concentration and 3-year decline in functional performance for men and women

	3-year decline in functional performance		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Albumin (g/l)			
Women			
≤43	0.73 (0.42–1.27)	0.71 (0.40–1.28)	0.68 (0.37–1.25)
>43	1.00	1.00	1.00
Men			
≤43	1.33 (0.75–2.34)	1.39 (0.76–2.53)	1.49 (0.80–2.77)
>43	1.00	1.00	1.00
Cholesterol (mmol/l)			
Women			
≤5.2	2.05 (0.97–4.36)*	2.38 (1.05–5.42)**	2.50 (1.07–5.84)**
>5.2	1.00	1.00	1.00
Men			
≤5.2	1.02 (0.55–1.91)	1.17 (0.61–2.25)	1.17 (0.60–2.29)
>5.2	1.00	1.00	1.00

Logistic regression using three models, model 1: adjusted for age and performance score at baseline; model 2: additionally adjusted for education, BMI, physical activity, smoking and alcohol consumption; model 3: additionally adjusted for presence of CVA, diabetes, heart disease, arthritis, PAD, cancer and pulmonary disease, MMSE and CES-D. BMI = body mass index; CVA = cerebrovascular accident; PAD = peripheral artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination; OR = odds ratio; CI = confidence interval.

\* $P < 0.10$ ; \*\* $P < 0.05$ .

total cholesterol (reference) after adjustment for life-style factors (OR = 2.38; 95% CI 1.05–5.42) and for disease-related factors (OR = 2.50; 95% CI 1.07–5.84).

Table 3 shows the association between combined concentrations of serum albumin and total cholesterol and decline in functional performance in three models. Men with lower serum albumin and lower serum total cholesterol concentrations were three times more likely to decline in functional performance compared to men with higher levels, after adjustment for all potential confounders (OR = 3.00; 95% CI 1.00–8.97). In women, the adjusted OR was 1.73 (95% CI 0.34–8.94), but not statistically significant.

## Discussion

This prospective study of older men and women provides insight into the relationship of two frailty markers, serum

albumin and total cholesterol concentration, with 3-year change in functional performance. The postulated relationship between lower serum albumin concentration and decline in functional performance was not found in men or women. Women with lower total cholesterol had a greater decline in functional status compared to women with higher serum total cholesterol. This association was not observed in men. Men, but not women, with combined lower serum albumin and lower serum total cholesterol concentration were three times more likely to decline in functional status compared to men with higher levels of both markers.

Previous studies which examined the association of serum albumin and total cholesterol levels with functional status were performed among older disabled residents living in nursing homes [10, 12] and among older high-functioning community-dwelling older persons [11, 13]. To our knowledge, our study is the first prospective study among population-based

**Table 3.** Associations between combined serum albumin and total cholesterol concentrations and 3-year decline in functional performance for men and women

	3-year decline in functional performance		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Women: albumin and cholesterol			
≤43 (g/l) and ≤5.2 (mmol/l)	2.06 (0.56–7.58)	2.14 (0.46–10.01)	1.73 (0.34–8.94)
>43 (g/l) and >5.2 (mmol/l)	1.00	1.00	1.00
Men: albumin and cholesterol			
≤43 (g/l) and ≤5.2 (mmol/l)	1.97 (0.72–5.41)	2.54 (0.87–7.43)*	3.00 (1.00–8.97)**
>43 (g/l) and >5.2 (mmol/l)	1.00	1.00	1.00

Logistic regression using three models, model 1: adjusted for age and performance score at baseline; model 2: additionally adjusted for education, BMI, physical activity, smoking and alcohol consumption; model 3: additionally adjusted for presence of CVA, diabetes, heart disease, arthritis, PAD, cancer and pulmonary disease, MMSE and CES-D. BMI = body mass index; CVA = cerebrovascular accident; PAD = peripheral artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination; OR = odds ratio; CI = confidence interval.

\* $P < 0.10$ ; \*\* $P < 0.05$ .

older men and women on the relation between combined serum albumin and total cholesterol concentration and 3-year decline in functional status that adjusts for several potential confounders. Furthermore, we measured functional status using performance tests instead of using (self-)reported functional status. Another strength of our study is the use of the EN-index to determine relevant change in functional status.

Deterioration in functional status (disability) has been found to be associated with serum albumin [10] and serum total cholesterol [12] separately. However, in our study no association with serum albumin was found. Therefore, either the specific population or the use of self-reports instead of performance tests for functional status might explain the observed relationship between low albumin and functional decline [10]. In another study an association was found between combined serum albumin and total cholesterol and decline in functional status [13]. However, these results were unadjusted for chronic diseases such as coronary heart disease (CHD), CVA or arthritis. Acute and chronic diseases are associated with inflammation [6, 30] and the release of inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor  $\alpha$  [31]. These cytokines induce an acute-phase response, which causes a decrease in serum albumin, and may result in hypoalbuminaemia [6, 31–33]. In addition, inflammatory cytokines may also cause hypocholesterolaemia [30, 32]. Furthermore, the presence of chronic diseases, such as CVA, CHD and arthritis, has been found to cause decline in functional status [34]. Thus, chronic diseases may lead to a decrease in serum albumin, total cholesterol and functional status. Nevertheless, in our study we adjusted for life-style and disease-related factors and found a three times increased risk for combined lower levels of serum albumin and total cholesterol with decline in functional status in men. Both albumin and total cholesterol are synthesised in the liver, and deterioration of the liver function might be attributable to changes in serum albumin concentration or total cholesterol concentration [6, 35, 36]. It has been suggested that an overall deterioration in the liver function might be associated with a poor health status, and might therefore contribute to a decline in functional status [36].

Different results were observed for men and women. Women have generally higher total cholesterol levels compared to men [37], which was also found in our study sample. Thus, there are relatively more women with high serum total cholesterol levels in the reference group, which may have led to the stronger associations in women. When the frailty markers were combined, a significant result occurred only in men. A similar trend was found for women, although not significant. Due to the low number of women, when serum albumin and total cholesterol levels were combined, the statistical power to detect significant differences may have been too low.

Possible limitations of the study should be addressed. The cut-off point for lower serum albumin was rather high. Generally, the cut-off point for hypoalbuminaemia is  $<35$  g/l and for low albumin  $<38$  g/l, but in our population-based study only one person had a serum albumin level lower than 38 g/l. The cut-off point for low serum total cholesterol is generally 4.1 mmol/l. Again, very few persons had levels below 4.1 mmol/l. The relatively high cut-off point for

lower albumin and lower serum total cholesterol may have resulted in an underestimation of the association between albumin and functional decline. Another potential limitation of the study is that both serum albumin and total cholesterol were measured in two different laboratories. Nevertheless the interaction terms laboratory\*serum albumin and laboratory\*serum total cholesterol were not statistically significant ( $P$ -value  $> 0.50$ ), suggesting that the associations under study were similar for both laboratories. A further limitation of the present study is that a substantial number of respondents had to be excluded from the initial sample. Those excluded from the present study had a poorer health status, lower albumin levels and poorer performance. Therefore it should be kept in mind that the present findings might not be extrapolated to frail older persons. The observed associations are likely to be underestimated. A final limitation of this study is that blood samples were taken in a non-fasting state, which might influence the concentration of serum albumin and cholesterol. This might have resulted in an underestimation of the observed associations.

In conclusion, no association was found between lower serum albumin and functional decline in men and women. Lower serum total cholesterol was associated with an increased risk in functional decline in women only. Combined lower serum albumin and lower total cholesterol levels were associated with an increased risk of deterioration in functional status, although this association was statistically significant only in men. Whether or not the cut-off points for serum albumin and total cholesterol used in this study could be used for diagnostics remains to be investigated with diagnostic research. Combining these frailty markers may be an important tool for detecting older persons who are at risk for future functional decline.

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## Key points

- Lower serum albumin was not associated with future decline in functional performance in older men and women.
  - Lower total cholesterol was associated with future decline in functional performance in women only.
  - A combination of lower serum albumin and lower total cholesterol was associated with a decline in functional performance in men. In women a similar trend was found, although not statistically significant.
  - Combining these blood markers might be an important tool for detecting older persons at risk for functional decline.
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