Department of Medicine

Hypoalbuminaemia and Incident Heart Failure in Older Adults

Gerasimos S. Filippatos MD, PhD

Ravi V. Desai MD
Lehigh Valley Health Network, ravi_v.desai@lvhn.org

Mustafa I. Ahmed MD

Gregg C. Fonarow MD

Thomas E. Love PhD

See next page for additional authors

Authors

Gerasimos S. Filippatos MD, PhD; Ravi V. Desai MD; Mustafa I. Ahmed MD; Gregg C. Fonarow MD; Thomas E. Love PhD; Inmaculada B. Aban PhD; Ami E. Iskandrian MD; Marvin A. Konstam; and Ali Ahmed MD, MPH

Hypoalbuminaemia and incident heart failure in older adults

Gerasimos S. Filippatos[1]*, Ravi V. Desai[2], Mustafa I. Ahmed[3], Gregg C. Fonarow[4], Thomas E. Love[5], Inmaculada B. Aban[3], Ami E. Iskandrian[3], Marvin A. Konstam[6], and Ali Ahmed[3,7]

[1]University of Athens, 28 Doukissis Plakentias Street, 11523 Athens, Greece; [2]Lehigh Valley Hospital, Allentown, PA, USA; [3]University of Alabama at Birmingham, Birmingham, AL, USA; [4]University of California, Los Angeles, CA, USA; [5]Case Western Reserve University, Cleveland, OH, USA; [6]Tufts Medical Center and Tufts University, Boston, MA, USA; and [7]VA Medical Center, Birmingham, AL, USA

Aims	To test the hypothesis that baseline hypoalbuminaemia is associated with incident heart failure (HF) in community-dwelling older adults.
Methods and results	Of the 5795 community-dwelling adults aged ≥65 years in the Cardiovascular Health Study, 5450 were free of centrally adjudicated prevalent HF at baseline, and also had data on baseline serum albumin. Of these, 599 (11%) had hypoalbuminaemia, defined as baseline serum albumin levels ≤3.5 mg/dL. Propensity scores for hypoalbuminaemia were calculated for each patient and used to assemble a matched cohort of 582 pairs of participants with and without hypoalbuminaemia, who were well balanced on 58 baseline characteristics. Using Cox regression models, we estimated the association of hypoalbuminaemia with centrally adjudicated incident HF during 9.6 years of median follow-up. Matched participants had a mean ($\pm$ SD) age of 74 ($\pm$ 6) years, 62% were women, and 16% were African Americans. Incident HF occurred in 25 and 20% of matched participants with and without hypoalbuminaemia, respectively [hazard ratio when hypoalbuminaemia was compared with normoalbuminaemia, 1.40; 95% confidence interval, 1.05–1.85; $P = 0.020$]. Pre-match unadjusted, multivariable-adjusted, and propensity-adjusted hazard ratios (95% confidence intervals) for incident HF associated with hypoalbuminaemia were 1.33 (1.12–1.58; $P = 0.001$), 1.33 (1.11–1.60; $P = 0.002$), and 1.25 (1.04–1.50; $P = 0.016$), respectively. The combined endpoint of incident HF or all-cause mortality occurred in 59 and 50% of matched participants with and without hypoalbuminaemia, respectively (hazard ratio, 1.33; 95% confidence interval, 1.11–1.61; $P = 0.002$).
Conclusions	Among community-dwelling older adults without HF, baseline hypoalbuminaemia was associated with increased risk of incident HF during 10 years of follow-up.
Keywords	Heart failure • Hypoalbuminaemia • Mortality • Propensity score

Introduction

Serum albumin is a major determinant of plasma oncotic pressure and the presence of hypoalbuminaemia may reduce the threshold for development of pulmonary oedema in response to elevated left atrial pressure.[1,2] Hypoalbuminaemia is frequently observed in patients with established heart failure (HF) and is independently associated with increased mortality risk.[3] Although hypoalbuminaemia has been implicated in the development of pulmonary oedema and increased mortality risk in patients with established HF,[2,4,5] it is unknown whether hypoalbuminaemia is associated with incident HF. We used public-use copies of Cardiovascular Health Study (CHS) datasets to determine whether baseline hypoalbuminaemia is associated with incident HF in community-dwelling older adults without baseline HF.

Methods

Study design and participants

The CHS is a National Heart, Lung, and Blood Institute (NHLBI)-funded ongoing longitudinal study of cardiovascular risk factors in community-dwelling older adults.[6] A cohort of 8555 Medicare-eligible adults aged $\geq$65 years were recruited from Forsyth County, NC, Sacramento County, CA, Washington County, MD, and Pittsburgh, PA. An initial cohort (n = 5201) recruited between 1989 and 1990 was supplemented by a second cohort of African-Americans (n = 687) recruited between 1992 and 1993. For the purpose of the current study, we used a public-use copy of the CHS data obtained from the NHLBI that included 5795 participants (93 participants did not consent to be included in the de-identified public-use copy of the data).

Assembling a heart failure-free baseline cohort

The process of identifying baseline prevalent cardiovascular conditions has been described previously.[7–10] Briefly, all CHS participants responded to a standard questionnaire that included questions about medication history and underwent clinical examination including a 12-lead resting electrocardiogram and echocardiogram. Participants were asked whether a physician had ever told them that they had HF. Those responding 'yes' were then asked for the date of the event, the name and address of the treating physician, whether they were hospitalized, and if so, the name and address of the hospital and pertinent outpatient and hospitalization data including history, physical examination, chest x-ray, and medications were collected. Self-reports of physician-diagnosed HF were then centrally adjudicated by the CHS Events Committee based on pertinent data that included symptoms (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue), signs (oedema, pulmonary rales, third heart sound, and evidence of an enlarged heart by clinical examination or chest x-ray), and by the use of medications commonly used in HF [a diuretic and digitalis or a vasodilator such as nitroglycerin, hydralazine, or an angiotensin-converting enzyme (ACE) inhibitor]. Overall, 274 participants were diagnosed with prevalent HF at baseline and were excluded, resulting in a cohort of 5521 participants.

Hypoalbuminaemia and other baseline measurements

Baseline serum albumin was measured by a Kodak Ektachem 700 analyser with reagents (Eastman Kodak, Rochester, NY, USA).[11] Hypoalbuminaemia was defined as serum albumin $\leq$3.5 g/dL.[12] Data on socio-demographic, clinical, sub-clinical, and laboratory variables were collected at baseline and have been previously described in detail.[6,7] After excluding 71 participants without data on baseline serum albumin, the final sample consisted of 5450 participants. Missing values for continuous variables were imputed based on values predicted by age, sex, and race.

Incident heart failure

The primary outcome for this study was definite incident HF. The process of adjudication of incident HF in the CHS has been well documented in the literature.[13–19] The process of adjudication of incident HF began with data on self-reports of physician-diagnosed HF collected every 6 months. The central CHS Events Committee then adjudicated incident HF among those without baseline HF by examining inpatient and outpatient medical records for evidence of HF. Self-reports of physician-diagnosed HF were adjudicated as HF if the use of HF medications (the use of a diuretic and digoxin or a vasodilator, including an ACE inhibitor) could be documented in medical records. In addition, chart documentation of symptoms, signs, and chest x-ray evidence of HF were used to define HF. Autopsy and coroner reports and family interviews were used to adjudicate fatal HF events. Secondary outcomes were combined endpoints of incident HF or all-cause mortality and all-cause mortality. Deaths were identified during surveillance calls or during scheduling calls for annual clinic visits, or through local daily newspaper obituaries.

Assembly of a balanced study cohort

As a result of significant differences in key baseline characteristics between participants with and without hypoalbuminaemia (Table 1 and Figure 1), we used propensity scores to assemble a matched cohort in which participants with and without hypoalbuminaemia would be well balanced in all measured baseline characteristics. Propensity score is the conditional probability of having an exposure given a set of measured baseline characteristics.[20,21] Propensity scores for hypoalbuminaemia for each of the 5450 participants were estimated using a non-parsimonious multivariable logistic regression model.[22,23] In the model, hypoalbuminaemia was used as the dependent variable, and the 58 baseline characteristics displayed in Figure 1 were entered as covariates along with one significant interaction term (between age and baseline serum creatinine). We were able to match 582 (97% of the 599) participants with hypoalbuminaemia to 582 participants with normal albumin who had very similar propensity scores. Our algorithm first attempted to match each participant with hypoalbuminaemia with a participant with normal albumin who had a similar propensity score to five decimal places. Then we removed those matched pairs of patients and repeated the process matching to four, three, two, and one decimal place. Absolute standardized differences for all 58 covariates were estimated to assess pre-match imbalances and post-match balances achieved between participants with and without hypoalbuminaemia and are presented in Love plots.[22,23] An absolute standardized difference of 0% on a covariate indicates no residual bias for that covariate.

Statistical analysis

For descriptive analyses, Pearson χ^2, Wilcoxon rank-sum tests, McNemar's tests, and paired sample t-tests were used as appropriate for pre- and post-match between-group comparisons. To estimate the association between hypoalbuminaemia and outcomes, we used Kaplan−Meier and matched Cox proportional hazard analyses. Proportional hazards assumptions were checked using log-minus-log scale survival plots. We also repeated our analysis in the full pre-match cohort of 5450 participants using three different approaches: (i) unadjusted, (ii) multivariable-adjusted, using all covariates used in the propensity score model, and (iii) propensity score adjusted. To determine whether the association between hypoalbuminaemia and incident HF was homogeneous across various subgroups of patients, we conducted subgroup analyses and formally tested for interactions using Cox regression models. All statistical tests were two tailed with 95% confidence levels and P-values <0.05 were considered significant. SPSS for Windows (Version 15) was used for all data analyses.

Sensitivity analyses

Even though our matched cohort was well balanced in 58 measured baseline covariates between participants with and without hypoalbuminaemia, bias due to imbalances in unmeasured covariates is possible.

Table 1 Baseline characteristics by hypoalbuminaemia (albumin ≤3.5 g/dL), before and after propensity score matching

n (%) or mean (± SD)	Before matching			After matching		
	Normal albumin (n = 4851)	Hypoalbuminaemia (n = 599)	P-value	Normal albumin (n = 582)	Hypoalbuminaemia (n = 582)	P-value
Age, years	73 (± 5)	74 (± 6)	<0.001	74 (± 6)	74 (± 6)	0.536
Female	2763 (57%)	374 (62%)	0.010	357 (61%)	363 (62%)	0.760
Non-White	733 (15%)	101 (17%)	0.261	91 (16%)	98 (17%)	0.634
Married	3264 (67%)	373 (62%)	0.014	363 (62%)	364 (63%)	1.000
College or higher education	2097 (43%)	256 (43%)	0.819	248 (43%)	251 (43%)	0.908
Income ≥ $25 000/year	1774 (37%)	221 (37%)	0.876	207 (36%)	214 (37%)	0.710
Self-reported fair to poor general health	1117 (23%)	152 (25%)	0.199	132 (23%)	144 (25%)	0.458
Activities of daily living (ADL)	0.11 (± 0.46)	0.14 (± 0.46)	0.106	0.12 (± 0.46)	0.14 (± 0.45)	0.600
Instrumental ADL	0.32 (± 0.69)	0.40 (± 0.78)	0.006	0.37 (± 0.74)	0.39 (± 0.76)	0.536
Current smoker	592 (12%)	71 (12%)	0.804	78 (13%)	70 (12%)	0.523
Smoking, pack years	18 (± 27)	15 (± 24)	0.015	15 (± 23)	15 (± 24)	0.734
Alcohol, drinks per week	3 (± 7)	2 (± 5)	0.007	2 (± 6)	2 (± 5)	0.226
Past medical history						
Coronary artery disease	847 (18%)	101 (17%)	0.715	98 (17%)	100 (17%)	0.940
AMI	397 (8%)	41 (7%)	0.255	45 (8%)	41 (7%)	0.738
Hypertension	2834 (58%)	334 (56%)	0.213	322 (55%)	330 (57%)	0.678
Diabetes mellitus	769 (16%)	79 (13%)	0.090	71 (12%)	77 (13%)	0.648
Stroke	180 (4%)	28 (5%)	0.245	34 (6%)	28 (5%)	0.519
Ankle arm index <0.9	605 (13%)	70 (12%)	0.582	2 (0.3%)	3 (0.5%)	1.000
Chronic obstructive pulmonary disease	597 (12%)	77 (13%)	0.701	70 (12%)	76 (13%)	0.664
Arthritis	2435 (50%)	343 (57%)	0.001	331 (57%)	331 (57%)	1.000
Cancer	702 (15%)	77 (13%)	0.286	62 (11%)	76 (13%)	0.250
Clinical examination						
Body mass index, kg/m^2	27 (± 4)	27 (± 4)	0.978	26 (± 4)	27 (± 4)	0.366
Pulse, b.p.m.	68 (± 11)	67 (± 11)	0.157	66 (± 10)	67 (± 11)	0.212
Systolic blood pressure (BP), mmHg	137 (± 21)	135 (± 22)	0.097	135 (± 22)	136 (± 22)	0.973
Diastolic BP, mmHg	71 (± 11)	69 (± 11)	<0.001	69 (± 11)	69 (± 11)	0.818
Loss of balance	1073 (22%)	176 (29%)	<0.001	146 (25%)	168 (29%)	0.155
Medications						
ACE inhibitors	285 (6%)	37 (6%)	0.768	24 (4%)	36 (6%)	0.134
Beta-blockers	612 (13%)	81 (14%)	0.530	67 (12%)	80 (14%)	0.294
Calcium channel blockers	617 (13%)	61 (10%)	0.076	82 (14%)	61 (11%)	0.080
Aspirin	146 (3%)	22 (4%)	0.376	20 (3%)	21 (4%)	1.000
Diuretics	1319 (27%)	161 (27%)	0.871	169 (29%)	155 (27%)	0.381
NSAIDs	582 (12%)	108 (18%)	<0.001	85 (15%)	106 (18%)	0.115
Laboratory blood values						
Haemoglobin, g/dL	14.1 (± 1.3)	13.4 (± 1.3)	<0.001	13.5 (± 1.3)	13.5 (± 1.3)	0.849
White blood cells, 10^3/μL	6.3 (± 2.0)	6.4 (± 2.8)	0.224	6.4 (± 2.7)	6.4 (± 2.8)	0.778
Platelets, 10^3/μL	251 (± 73)	251 (± 89)	0.873	252 (± 81)	251 (± 89)	0.882
Albumin, g/dL	4.06 (± 0.24)	3.50 (± 0.13)	<0.001	3.99 (± 0.23)	3.50 (± 0.13)	<0.001
Creatinine, mg/dL	0.96 (± 0.39)	0.95 (± 0.34)	0.454	0.93 (± 0.31)	0.94 (± 0.32)	0.404
Potassium, mEq/L	4.17 (± 0.38)	4.11 (± 0.38)	<0.001	4.10 (± 0.37)	4.10 (± 0.39)	0.553
Glucose, mg/dL	111 (± 36)	108 (± 42)	0.024	106 (± 26)	108 (± 43)	0.346
Uric acid, mg/dL	5.7 (± 1.5)	5.4 (± 1.5)	<0.001	5.5 (± 1.5)	5.5 (± 1.5)	0.759

Continued

Table 1 *Continued*

n (%) or mean (± SD)	Before matching			After matching		
	Normal albumin (n = 4851)	Hypoalbuminaemia (n = 599)	P-value	Normal albumin (n = 582)	Hypoalbuminaemia (n = 582)	P-value
Total cholesterol, mg/dL	213 (± 40)	198 (± 37)	<0.001	199 (± 35)	199 (± 37)	0.730
Low density lipoprotein, mg/dL	132 (± 35)	118 (± 33)	<0.001	199 (± 32)	199 (± 39)	0.831
Triglyceride, mg/dL	141 (± 78)	129 (± 71)	<0.001	127 (± 64)	129 (± 72)	0.496
Fibrinogen, mg/dL	321 (± 64)	336 (± 81)	<0.001	333 (± 71)	334 (± 78)	0.844
Coagulation factor VII, units/mL	124 (± 29)	123 (± 35)	0.692	122 (± 27)	123 (± 34)	0.564
Interlukin-6, units/mL	2.12 (± 1.84)	2.60 (± 2.05)	<0.001	2.65 (± 3.13)	2.58 (± 1.99)	0.840
C-reactive protein, mg/dL	4.3 (± 7.2)	7.3 (± 13.1)	<0.001	6.4 (± 14.1)	6.7 (± 11.9)	0.630
Insulin, μIU/mL	16.8 (± 24)	15.6 (± 23)	0.234	15.4 (± 21)	15.7 (± 23)	0.837
Electrocardiographic findings						
Bundle branch block	398 (8%)	60 (10%)	0.131	43 (7%)	58 (10%)	0.137
LV hypertrophy	203 (4%)	29 (5%)	0.453	21 (4%)	29 (5%)	0.322
Atrial fibrillation	101 (2%)	14 (2%)	0.682	12 (2%)	13 (2%)	1.000
Echocardiographic findings						
LV systolic dysfunction	367 (8%)	43 (7%)	0.735	43 (7%)	41 (7%)	0.910

ACE, angiotensin-converting enzyme; LV, left ventricular; NSAID, non-steroidal anti-inflammatory drugs.

As such, we conducted a formal sensitivity analysis to quantify the degree of hidden bias that would need to be present to invalidate our main conclusions.[24]

Results

Participants' characteristics

Overall, matched participants had a mean age (± SD) of 74.1 (± 6.0) years, 62% were women, and 16% were African-Americans. Pre- and post-match comparisons between participants with and without hypoalbuminaemia are displayed in *Table 1* and *Figure 1*. In general, before matching, participants with hypoalbuminaemia were older, more likely to be women, have lower uric acid, total cholesterol, and higher C-reactive protein and interleukin levels. After matching, absolute standardized differences for all measured covariates were <10% (most <5%), suggesting close covariate balance across the two groups (*Figure 1*).
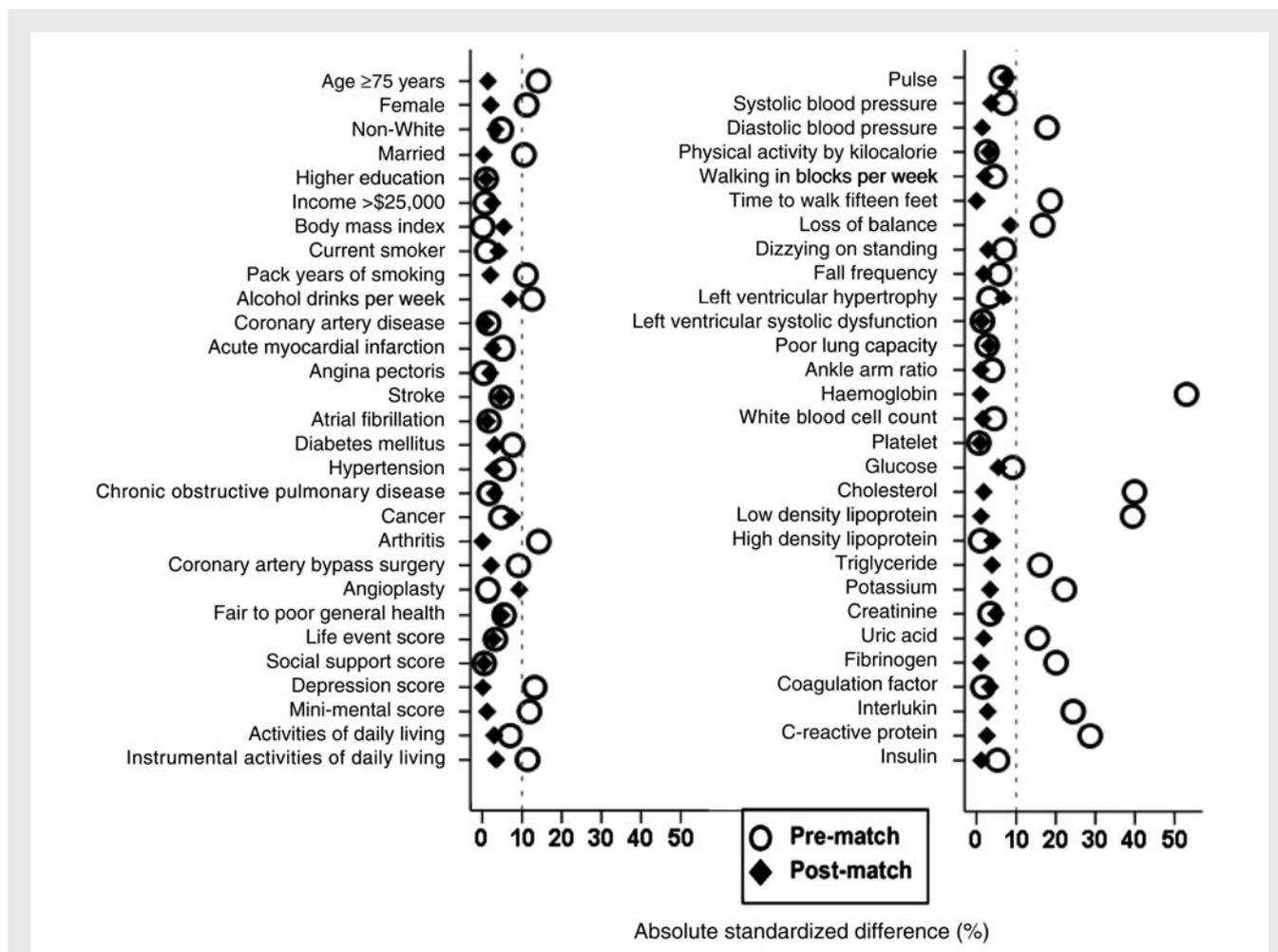
Association of hypoalbuminaemia with incident heart failure

Overall, 260 (22%) participants developed incident HF during 9.6 median years of follow-up. Incident HF occurred in 25 and 20% of matched participants with and without hypoalbuminaemia, respectively [hazard ratio when hypoalbuminaemia was compared with normal albumin, 1.40; 95% confidence interval (CI), 1.05–

1.85; *P* = 0.020; *Table 2* and *Figure 2*]. The Kaplan–Meier curves seem to separate after ∼5 years of follow-up (*Figure 2*). While a sign-score test for matched data with censoring provides significant evidence (*P* = 0.0193) that participants without hypoalbuminaemia outlived those with it, this result is sensitive to even a small amount of unmeasured confounding. Specifically, an unmeasured covariate (unrelated to the propensity score) that increased the odds of incident HF by as little as 5.5% could potentially explain this association. Unadjusted, multivariable-adjusted, and propensity-adjusted associations between hypoalbuminaemia and incident HF among the 5450 pre-match participants are displayed in *Table 2*.

Findings from the subgroup analyses

Except for the age and coronary artery disease subgroups, the association between hypoalbuminaemia and incident HF was homogeneous across various subgroups of participants (*Figure 3*). Among the older adults who were aged <73 years (median age), hypoalbuminaemia was associated with increased risk of incident HF (hazard ratio, 2.09; 95% CI, 1.41–3.10; *P*<0.001) but not among those aged ≥73 years (hazard ratio, 0.96; 95% CI, 0.69–1.30; *P* = 729; *P* for interaction, 0.002; *Figure 3*). When we examined the association between hypoalbuminaemia and incident HF among older adults by tertiles of age, we observed a progressive decrease in association with increase in age. Hazard ratio (95% CI) for those <70 years (n = 274), 70–75 years (n = 432), and ≥76 years (n = 458) were 3.37 (1.70–6.69; *P* = 0.001), 1.44 (0.95–2.99; *P* = 0.089), and 0.93 (0.66–1.31; *P* = 0.671), respectively.

Figure 1 Absolute standardized differences before and after propensity score matching comparing covariates for patients with and without hypoalbuminaemia.

Table 2 Association of hypoalbuminaemia (albumin ≤3.5 g/dL) with incident heart failure in the Cardiovascular Health Study

| Incident heart failure	Events (%)		Absolute risk increase[a] (%)	Hazard ratio (95% CI)	*P*-value
	Normal albumin	Hypoalbuminaemia			
Before matching (*n* = 5450)	*n* = 4851	*n* = 599			
Unadjusted	982 (20%)	147 (25%)	+5	1.33 (1.12–1.58)	0.001
Multivariable adjusted				1.33 (1.11–1.60)	0.002
Propensity adjusted				1.25 (1.04–1.50)	0.016
After matching (*n* = 1164)	*n* = 582	*n* = 582			
Propensity match	115 (20%)	145 (25%)	+5	1.40 (1.05–1.85)	0.020

[a]Absolute risk increase was calculated by subtracting the percentage of events in the normal albumin group from that of the hypoalbuminaemia group (before values were rounded).

Association of hypoalbuminaemia with other outcomes

The combined endpoint of incident HF or all-cause mortality occurred in 59 and 50% of matched participants with and without hypoalbuminaemia, respectively (hazard ratio, 1.33; 95% CI, 1.11–1.61; *P* = 0.002). All-cause mortality occurred in 50 and 43% of matched participants with and without hypoalbuminaemia, respectively (hazard ratio, 1.23; 95% CI, 1.02–1.49; *P* = 0.035; *Table 3*).
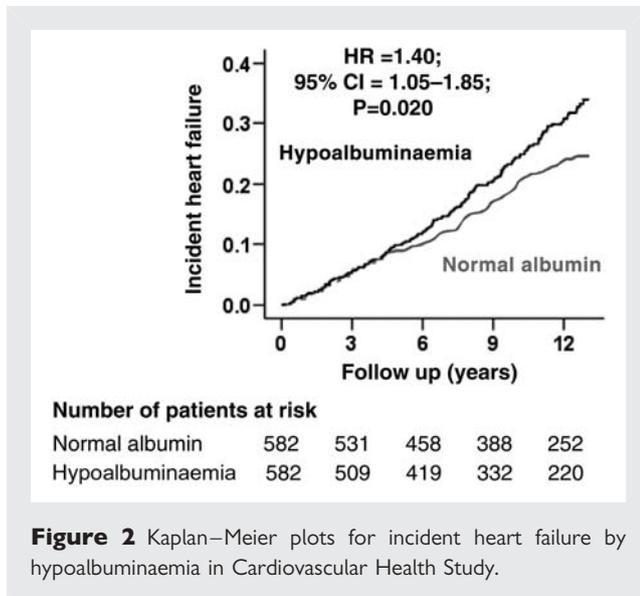
Figure 2 Kaplan–Meier plots for incident heart failure by hypoalbuminaemia in Cardiovascular Health Study.

Discussion

Summary and relevance of the key findings

The findings of the current study demonstrate that hypoalbuminaemia is an independent predictor of incident HF among community-dwelling older adults. Furthermore, hypoalbuminaemia was associated with increased risk of death but had no association with incident cardiovascular events including incident acute myocardial infarction (AMI). Serum albumin is the major contributor to the plasma oncotic pressure, which along with pulmonary capillary wedge pressure determines the pulmonary capillary filtration pressure. Hypoalbuminaemia may therefore lower the threshold for the development of pulmonary oedema in patients with HF. Findings from our study suggest that hypoalbuminaemia may also play a pathogenetic role in the development of new-onset HF among older adults.
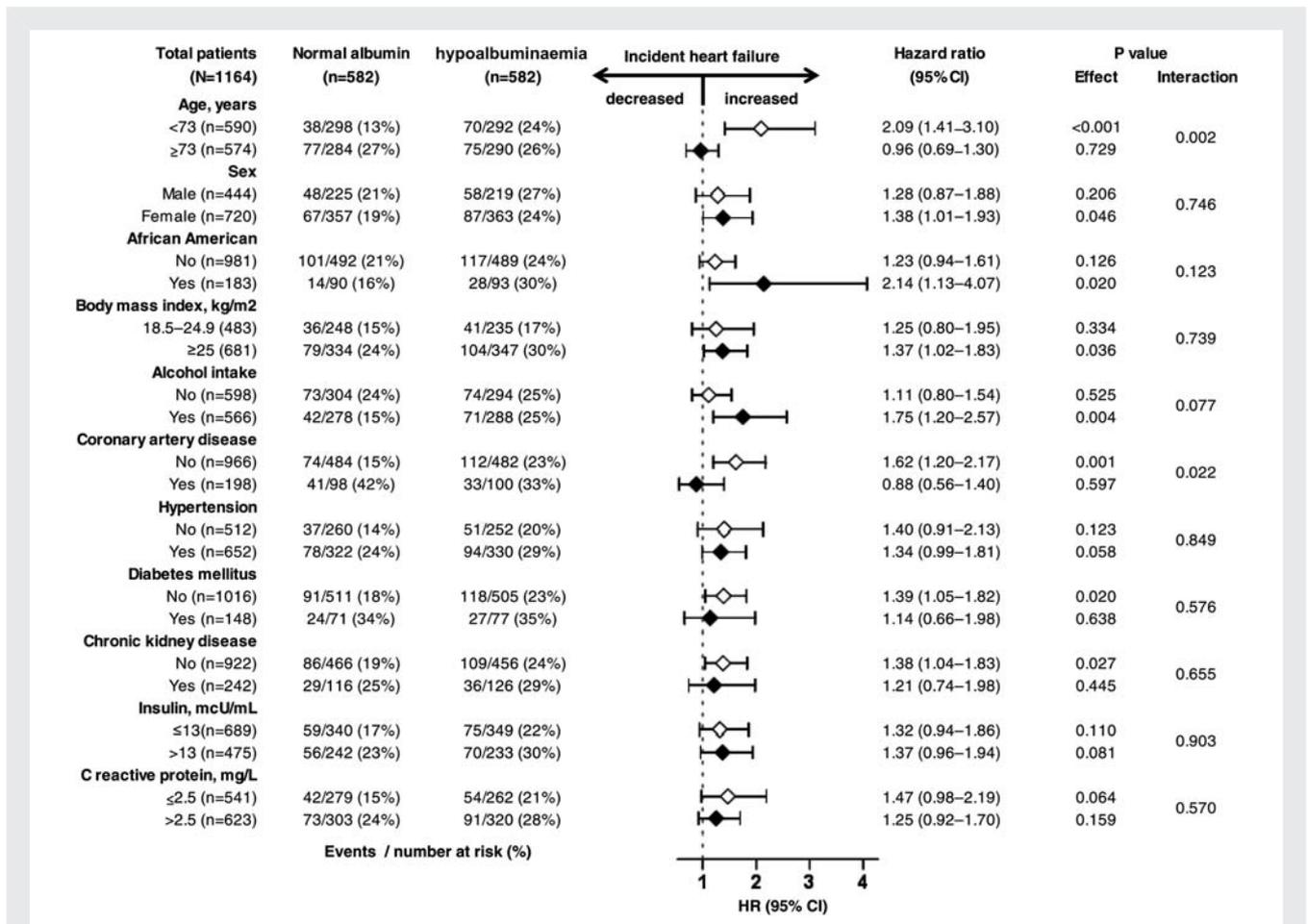
Figure 3 Association of baseline hypoalbuminaemia (albumin ≤3.6 g/dL) with new onset heart failure in subgroups of propensity score-matched participants in the Cardiovascular Health Study (CI, confidence interval; HR, hazard ratio).

Table 3 Association of hypoalbuminaemia (albumin <3.6 g/dL) with other outcomes in a propensity-matched cohort of the Cardiovascular Health Study participants

Outcomes	Events (%)		Absolute risk increase[a] (%)	Hazard ratio (95% CI)	P-value
	Normal albumin (*n* = 582)	Hypoalbuminaemia (*n* = 582)			
Combined incident HF or all-cause mortality	290 (50%)	343 (59%)	+9	1.34 (1.11–1.61)	0.002
All-cause mortality	252 (43%)	291 (50%)	+7	1.23 (1.02–1.49)	0.035

[a]Absolute risk increase was calculated by subtracting the percentage of events in the normal albumin group from that of the hypoalbuminaemia group (before values were rounded).

Potential explanation and mechanism of the key findings

Age-related impairment of left ventricular (LV) relaxation and increased vascular stiffness have been shown to increase LV end-diastolic pressure in older adults, which, in turn may increase pulmonary capillary filtration pressure (the gradient between pulmonary capillary wedge pressure and serum oncotic pressure).[25–28] By decreasing the serum oncotic pressure, hypoalbuminaemia may increase the gradient above a critical threshold thus increasing the risk of clinical HF.[2] However, the exact aetiology of hypoalbuminaemia in this rather healthy representative sample of community-dwelling older Americans is not clear. The body mass index of participants with and without hypoalbuminaemia was similar (mean, 27; SD, ± 4 kg/m^2) before matching suggesting that malnutrition was unlikely to be a key aetiological component of hypoalbuminaemia. As albumin is a negative acute phase reactant, a pro-inflammatory state may have contributed to hypoalbuminaemia in older adults in our study.[29] This notion is supported by our observation that before matching, those with hypoalbuminaemia had higher mean values of C-reactive protein and other markers of inflammation (*Table 1*).

Although it might seem reasonable to infer that the underlying pro-inflammatory state may provide additional explanation into the association between hypoalbuminaemia and incident HF, a closer examination of our post-match data would suggest otherwise. After matching, participants with and without hypoalbuminaemia in our study had similar levels of C-reactive protein and other markers of inflammation (*Table 1*), suggesting that this association may be independent of inflammation, lending further support to the haemodynamic hypothesis. It is also possible that albumin may have a direct protective effect against developing HF via an anti-apoptotic and antioxidant activity, as has been observed in patients with established HF. Albumin has been shown to act as a 'sacrificial antioxidant' in scavenging free radicals such as free hydroxyl radicals.[30] Furthermore, the single free sulfhydryl of serum albumin is the most abundant thiol species in plasma that can react with oxides of nitrogen under physiological conditions and thereby stabilize endothelium-derived growth factor activity.[31]

Comparison with findings from relevant published literature

Our observation of a lack of an association between hypoalbuminaemia and incident AMI also lends support to our haemodynamic hypothesis. Several studies in the past have demonstrated an association between hypoalbuminaemia and incident AMI.[32,33] Although these studies adjusted for traditional risk factors, they did not adjust for markers of inflammation such as C-reactive protein, serum fibrinogen, and interleukin-6 levels, which were well balanced in our matched cohort. These findings suggest that hypoalbuminaemia may not have an intrinsic association with incident AMI and this association may largely be mediated by the underlying pro-inflammatory state. In contrast, the association between hypoalbuminaemia and incident HF seems to be independent of the effect of inflammation, rendering a haemodynamic explanation more likely. The late separation of the Kaplan–Meier plots is intriguing but may provide a long window of opportunity to reduce the risk of incident HF among community-dwelling older adults with hypoalbuminaemia by addressing other competing risk factors for HF.

Clinical and public health importance

Hypoalbuminaemia has previously been shown to be a marker of poor prognosis in patients with established HF.[3,34] However, to the best of our knowledge, this report is the first to demonstrate an association between baseline mild hypoalbuminaemia and incident HF in a prospective population-based study. These findings are important as they identify a less well-known but readily identifiable risk factor for new-onset HF in older adults. Since hypoalbuminaemia is also a marker of malnutrition, it provides further impetus for prospectively examining a potential preventative or therapeutic role of nutritional intervention in older adults.

Potential limitations and future direction

Several limitations need to be considered in our study. Despite our use of a propensity-matched design to assemble a balanced cohort,

bias due to an unmeasured covariate is possible. However, for an unmeasured covariate to become a confounder, it must be a near-perfect predictor of incident HF and be associated with hypoalbuminaemia, and not be strongly correlated with any of the 58 covariates used in our study, which is very unlikely. As noted, serial measures of albumin were not measured and thus could not be analysed. Hypoalbuminaemia has been shown to play a more important role in causing pulmonary oedema in patients with HF with preserved LV ejection fraction.[4] Although we had no data on LV ejection fraction of the patients with incident HF in our study, over half of the HF patients in this age group would be expected to have diastolic HF.[35]

Conclusions

Hypoalbuminaemia is a novel and easily identifiable risk factor predicting a late-onset incident HF among community-dwelling older adults. These findings provide epidemiological evidence into the role of Starling's hypothesis in the development of clinical HF and suggest a prolonged window of opportunity to develop risk intervention strategies.

References

1. Parissis JT, Nikolaou M, Mebazaa A, Ikonomidis I, Delgado J, Vilas-Boas F, Paraskevaidis I, Mc Lean A, Kremastinos D, Follath F. Acute pulmonary oedema: clinical characteristics, prognostic factors, and in-hospital management. *Eur J Heart Fail* 2010;**12**:1193–1202.
2. Guyton AC, Lindsey AW. Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ Res* 1959;**7**:649–657.
3. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J* 2008;**155**:883–889.
4. Arquès S, Ambrosi P, Gélisse R, Luccioni R, Habib G. Hypoalbuminemia in elderly patients with acute diastolic heart failure. *J Am Coll Cardiol* 2003;**42**:712.
5. Konstam MA. Colloid osmotic pressure: an under-recognized factor in the clinical syndrome of heart failure. *J Am Coll Cardiol* 2003;**42**:717–718.
6. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Tracy RP, Weiler PG. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;**1**:263–276.
7. Psaty BM, Kuller LH, Bild D, Burke GL, Kittner SJ, Mittelmark M, Price TR, Rautaharju PM, Robbins J. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. *Ann Epidemiol* 1995;**5**:270–277.
8. Ekundayo OJ, Howard VJ, Safford MM, McClure LA, Arnett D, Allman RM, Howard G, Ahmed A. Value of orthopnea, paroxysmal nocturnal dyspnea, and medications in prospective population studies of incident heart failure. *Am J Cardiol* 2009;**104**:259–264.
9. Mittelmark MB, Psaty BM, Rautaharju PM, Fried LP, Borhani NO, Tracy RP, Gardin JM, O'Leary DH. Prevalence of cardiovascular diseases among older adults. The Cardiovascular Health Study. *Am J Epidemiol* 1993;**137**:311–317.
10. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;**137**:631–639.
11. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem* 1995;**41**:264–270.
12. Heymsfield SB, Williams PJ. *Nutritional Assessment by Clinical and Biochemical Methods*. Philadelphia: Lea & Febiger; 1988.
13. Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, Theroux S. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol* 1995;**5**:278–285.
14. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;**35**:1628–1637.
15. Mujib M, Desai RV, Ahmed MI, Guichard JL, Feller MA, Ekundayo OJ, Deedwania P, Ali M, Aban IB, Love TE, White M, Aronow WS, Rahimtoola SH, Bonow RO, Ahmed A. Rheumatic heart disease and risk of incident heart failure among community-dwelling older adults: a prospective cohort study. *Ann Med* 2011; doi:10.3109/07853890.2010.530685. Published online ahead of print 24 January 2011.
16. Iyer AS, Ahmed MI, Filippatos GS, Ekundayo OJ, Aban IB, Love TE, Nanda NC, Bakris GL, Fonarow GC, Aronow WS, Ahmed A. Uncontrolled hypertension and increased risk for incident heart failure in older adults with hypertension: findings from a propensity-matched prospective population study. *J Am Soc Hypertens* 2010;**4**:22–31.
17. Ekundayo OJ, Dell'Italia LJ, Sanders PW, Arnett D, Aban I, Love TE, Filippatos G, Anker SD, Lloyd-Jones DM, Bakris G, Mujib M, Ahmed A. Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study. *Int J Cardiol* 2010;**142**:279–287.
18. Ekundayo OJ, Allman RM, Sanders PW, Aban I, Love TE, Arnett D, Ahmed A. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. *Hypertension* 2009;**53**:458–465.
19. Carbone L, Buzkova P, Fink HA, Lee JS, Chen Z, Ahmed A, Parashar S, Robbins JR. Hip fractures and heart failure: findings from the Cardiovascular Health Study. *Eur Heart J* 2010;**31**:77–84.
20. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.
21. Rubin DB. Using propensity score to help design observational studies: Application to the tobacco litigation. *Health Serv Outcomes Res Methodol* 2001;**2**:169–188.
22. Ahmed A, Aban IB, Vaccarino V, Lloyd-Jones DM, Goff DC Jr, Zhao J, Love TE, Ritchie C, Ovalle F, Gambassi G, Dell'Italia LJ. A propensity-matched study of the effect of diabetes on the natural history of heart failure: variations by sex and age. *Heart* 2007;**93**:1584–1590.
23. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;**28**:1334–1343.
24. Rosenbaum PR. Sensitivity to hidden bias. In Rosenbaum PR, ed. *Observational Studies*. 2nd ed. New York: Springer-Verlag; 2002. p110–124.
25. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation* 2005;**112**:2254–2262.
26. Okura H, Takada Y, Yamabe A, Kubo T, Asawa K, Ozaki T, Yamagishi H, Toda I, Yoshikawa J, Yoshida K. Age- and gender-specific changes in the left ventricular relaxation: a Doppler echocardiographic study in healthy individuals. *Circ Cardiovasc Imaging* 2009;**2**:41–46.
27. Spirito P, Maron BJ. Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988;**59**:672–679.
28. Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 2007;**99**:1629–1636.
29. Heymans S, Hirsch E, Anker SD, Aukrust P, Balligand JL, Cohen-Tervaert JW, Drexler H, Filippatos G, Felix SB, Gullestad L, Hilfiker-Kleiner D, Janssens S, Latini R, Neubauer G, Paulus WJ, Pieske B, Ponikowski P, Schroen B, Schultheiss HP, Tschope C, Van Bilsen M, Zannad F, McMurray J, Shah AM. Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2009;**11**:119–129.
30. Halliwell B. Albumin—an important extracellular antioxidant? *Biochem Pharmacol* 1988;**37**:569.

31. Keaney JF, Simon DI, Stamler JS, Jaraki O, Scharfstein J, Vita JA, Loscalzo J. No forms an adduct with serum-albumin that has endothelium-derived relaxing factor like properties. *J Clin Invest* 1993;**91**:1582–1589.

32. Djousse L, Rothman KJ, Cupples LA, Levy D, Ellison RC. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. *Circulation* 2002;**106**:2919–2924.

33. Danesh J, Collins R, Appleby P, Peto R. Association of Fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of Prospective Studies. *JAMA* 1998;**279**:1477–1482.

34. Kinugasa Y, Kato M, Sugihara S, Hirai M, Kotani K, Ishida K, Yanagihara K, Kato Y, Ogino K, Igawa O, Hisatome I, Shigemasa C. A simple risk score to predict in-hospital death of elderly patients with acute decompensated heart failure—hypoalbuminemia as an additional prognostic factor. *Circ J* 2009;**73**: 2276–2281.

35. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;**87**:413–419.