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\textbf{ABSTRACT}

\textbf{Objective:} Although C-reactive protein (CRP) and albuminuria are well-documented cardiovascular risk markers, the functional implications of these biomarkers and their combination on functional disability and metabolic risks in patients with cardiovascular disease (CVD) are unknown.

\textbf{Methods:} Data were from 1403 adults (≥60 years, mean 73.2 years) with CVD, ascertained by self-reported diagnosis of angina, coronary heart disease, congestive heart failure, myocardial infarction or stroke, in the National Health and Nutrition Examination Survey 1999–2008. Disability in activities of daily living (ADL), instrumental activities of daily living (IADL), leisure and social activities (LSA), general physical activities (GPA), and lower-extremity mobility (LEM) were obtained from self-reports. The urinary albumin-to-creatinine ratio (UACR) was calculated by dividing the urinary albumin value by the urinary creatinine concentration. CRP levels were quantified by latex-enhanced nephelometry.

\textbf{Results:} Inflammation and albuminuria were associated with disability. In the full-adjusted models, odds ratios (ORs) (95\% confidence intervals [Cl]) of disability in ADL, LSA, and LEM were 1.60 (1.13–2.28), 1.76 (1.22–2.55) and 2.31 (1.62–3.11), respectively, comparing participants in the highest CRP quartile to the lowest (p values for trend across CRP quartiles < 0.01). The corresponding ORs (95\% CI) for disability in ADL, IADL, LSA, and LEM were 1.71 (1.20–2.45), 1.72 (1.21–2.45), 1.46 (1.01–2.12) and 2.50 (1.73–3.62), respectively, comparing participants in the highest UACR quartile to the lowest. We found combined association of inflammation and albuminuria with disability and with metabolic risks. Based on medians of both UACR and CRP, subjects with both higher levels of both markers had higher odds of disability and a more unfavorable metabolic profile than those with lower levels.

\textbf{Conclusions:} Elevated levels of CRP and UACR independently correlate with disability among older adults with CVD. There is a combined association of inflammation and albuminuria on multiple domains of disability and metabolic risks, suggesting the presence of elevated UACR may amplify the association of inflammation with disability and with metabolic risk in older adults living with CVD.

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1. Introduction

Cardiovascular disease (CVD) has become a major cause of disability. In the United States, the percentage of older adults with limitation of activity ranged from 25\% of adults 65–74 years to 60\% of adults 85 years and over in 2005–2006 [1]. Cardiovascular conditions were the second leading cause of functional limitation among adults 65 years and older [1]. The estimated cost of CVD for 2009 was $475.3 billion [2], including the cost of health care services and lost productivity from CVD-related disability. A better understanding of the relationship between CVD and disability may provide invaluable information to ameliorate the disablament process resulting from CVD. Preventing disability and relieving burden of disability among older adult population with CVD are public health issues. A key step in disability prevention is knowing potential biological pathways associated with the disablament process in older adults living with CVD.

C-reactive protein (CRP), a biological marker of low-grade inflammation, has important prognostic value in patients with pre-existing CVD [3–7] and in apparently healthy subjects [8,9]. CRP and other biological markers of inflammation such as interleukin-6 have also been shown to be an important predictor for late-life disability in several large-scale population-based studies [10,11]. On the other hand, albuminuria, a marker of
endothelial dysfunction, has been implicated as a cardiovascular risk marker in the general population as well as in individuals with hypertension or diabetes [12–14]. Albuminuria is thought to have a pivotal role in both the initiation and the progression of CVD [15]. Recent studies have shown that subclinical inflammation accompanied by evidence of albuminuria may have an interactive effect on metabolic disarray [16], atherosclerotic process [17] and even mortality [18]. Although CRP and albuminuria have been repeatedly documented as cardiovascular risk biomarkers, functional implications of these biomarkers along with their combined association with disability and with metabolic risks in patients already afflicted with CVD are largely unknown.

Therefore, the objective of this study was to examine the association of chronic inflammation, urinary albumin excretion, and their combination, with late-life disability among older adults with CVD. We hypothesized that chronic inflammation and albuminuria are associated with disability and that these biomarkers have a joint association on late-life disability and metabolic risks.

2. Methods

2.1. Data source and study sample

The data come from the National Health and Nutrition Examination Survey (NHANES), a population-based cross-sectional survey designed to collect information on the health and nutrition of the US civilian noninstitutionalized population. In 1999, the NHANES became a continuous, annual survey rather than the periodic survey it had been in the past. The survey data are released every two years. Detailed Survey Operations Manuals, Consent Documents, and Brochures of the NHANES 1999–2008 are available on the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

A total of 1799 older adults (≥60 years) with CVD completed questionnaires for functional disability, health associated behaviors and chronic co-morbidities. Among them, 1403 participants had complete data for laboratory examinations, physical measurements and prescription medications. Compared with excluded participants (n = 396), the analytic sample (n = 1403) was younger (73.2 vs. 74.7 years, p < 0.001), had more male participants (59.9% vs. 52.8%, p = 0.011), had more non-Hispanic Whites (68.2% vs. 54.0%, p < 0.001) and was less disabled in all disability domains (p < 0.001).

2.2. Assessment of disability

The 19 questions in the Physical Functioning Questionnaire are designed to assess the functional status of participants. These questions are phrased to assess the individual’s level of difficulty in performing the task without using any special equipment. The 19 questions of functional dependence are categorized into five major domains according to published definitions [11]: (1) activities of daily living (ADL: eating, walking, dressing, getting out of bed), (2) instrumental activities of daily living (IADL: managing money, housekeeping, food preparation), (3) leisure and social activities (LSA: attending social events, going out to movies, in-home leisure activities), (4) lower extremity mobility (LEM: walking for a quarter mile, walking up ten steps), and (5) general physical activities (GPA: stooping, bending, standing, sitting, lifting, reaching, grasping). A subject’s answer to a given question was coded as “no difficulty,” “some difficulty,” “much difficulty” or “unable to do”. Functional disability was defined as any difficulty in performing one or more activities within a given domain.

2.3. C-reactive protein

Standard phlebotomy techniques were used to obtain specimens, which were frozen to −20 °C until used for laboratory analysis. CRP was analyzed using a highly sensitive assay technique. CRP was quantified by using latex-enhanced nephelometry with a Behring Nephelometer Analyzer System (Behring, Deerfield, IL). Detailed specimen collection and processing instructions are available in the NHANES Laboratory Procedure Manual (http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/crp_e_met.pdf).

2.4. Urinary albumin-to-creatinine ratio (UACR)

A casual urine specimen was collected and stored under frozen condition (−20 °C). A solid-phase fluorescent immunoassay, specifically useful to measure low levels of urinary albumin not detectable by dipstick methods, was used to measure urinary albumin. Urine creatinine was analyzed with the Jaffé reaction, in which creatinine reacts with picate in an alkaline solution to form a red creatinine–picate complex. The UACR, in the unit of mg/g, was calculated by dividing the urinary albumin volume by the urinary creatinine concentration.

2.5. Assessment of demographics, co-morbidities, and laboratory examinations

Age, gender, race, and alcohol consumption (≥12 alcoholic drinks/year) were obtained by self-report. CVD was ascertained by several self-reported questions: “Has a doctor or other health professional ever told you that you had congestive heart failure, coronary heart disease, angina (also called angina pectoris), heart attack (also called myocardial infarction) or stroke?” Answering yes to any question was coded positive for CVD. Using serum cotinine concentrations (ng/ml), we classified smoking status of participants in four groups: nonsmoker (<14), light smoker (14–99), moderate smoker (100–199), and heavy smoker (>200) [19]. Co-morbidities including chronic lung disease (defined as emphysema or chronic bronchitis) or arthritis were ascertained by self-report. Diabetes mellitus (DM) was further defined by self-report of a physician’s diagnosis, the presence of a fasting (fasting ≥ 6 h) plasma glucose level > 126 mg/dl or a non-fasting (fasting < 6 h) glucose level > 200 mg/dl, hemoglobin A1C (A1C) > 6.5% [8], or the use of diabetic medications. Hypertension was defined as mean systolic blood pressure (BP) ≥ 140 mmHg, mean diastolic BP ≥ 90 mmHg, physician diagnosis, or use of anti-hypertensive medications. Mean BP was composed of up to four readings on two separate occasions. Waist circumference was measured at the top of the iliac crest to the nearest 0.1 cm. Use of statins, anti-hypertensive medications, aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, was ascertained from the drug information file containing data on prescription medications. Use of anti-hypertensive agents was categorized into use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), use of all other anti-hypertensives or use of none. Serum triglycerides, high-density lipoprotein (HDL) cholesterol, and serum creatinine were analyzed by laboratory methods reported elsewhere [6,20]. Estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease (MDRD) study equation [21].

2.6. Analysis

Demographic and clinical characteristics of the study population were presented according to CRP quartiles. Chi-squared test or analysis of variance (ANOVA) was used to determine differences between groups. The distributions of CRP levels in
the study population were right skewed. Therefore, we used natural-log-transformed values, which provided the best-fitting model for analysis, in which the plasma levels of CRP were treated as continuous variables. Standard-deviation scores of CRP were obtained from the formula

$$X_i = \frac{X_m}{SD}$$

where $X_i$ is the natural-log-transformed level of CRP in the individual participant, $X_m$ the mean natural-log-transformed level of CRP in the study cohort and $SD$ the standard deviation of the natural-log-transformed levels of CRP in the study cohort. This calculation allowed us to determine the changes in functional implications for each increment of 1SD in the natural-log-transformed CRP levels. In addition, we divided CRP levels into quartiles, using participants in the lowest quartile of CRP level as the reference group. The cut-off concentrations (mg/dL) for CRP quartiles were <0.14, 0.14–0.28, 0.29–0.60 and >0.60. Multiple logistic regressions were used to examine the relation of CRP levels to odds of functional disability in ADL, IADL, LSA, LEM or GPA. We used an extended-model approach for covariate adjustment: Model 1 = age, sex and race; Model 2 = Model 1 + health behaviors (smoking status and alcohol consumption) + medical co-morbidities (chronic lung disease and arthritis) and eGFR; Model 3 = Model 2 + cardiovascular risk factors and management (hypertension, DM, waist circumferences, levels of triglycerides and HDL cholesterol, use of statins and use of anti-hypertensive agents) + use of anti-inflammatory drugs (aspirin and NSAIDs); and Model 4 = Model 3 + log-transformed UACR level. The association of UACR and functional disability among participants with CVD was examined using the same modeling pattern and similar statistical approach of categorizing UACR. The cut-off concentrations (mg/g) for UACR quartiles were <6.54, 6.54–13.16, 13.17–43.10, and >43.10. To consider various metabolic risk factors as a whole, we also calculated the metabolic z-score. The score was derived by converting each component of the metabolic risk factor (namely blood pressure, waist circumference, levels of glucose, triglyceride level and HDL level) into a z-score based on means of the study population [22]. The metabolic z-score was calculated by summing the former 4 z-scores minus the HDL z-score.

To evaluate the joint association of chronic inflammation and albuminuria on disability as well as on various metabolic risks, study participants were re-classified in one of four groups based on whether their CRP and UACR were above or below the respective study medians (medians for CRP and UACR were 0.28 mg/dL and 13.16 mg/L, respectively): (1) low-CRP/low-UACR (n = 374), (2) low-CRP/high-UACR (n = 328), (3) high-CRP/low-UACR (n = 328) and (4) high-CRP/high-UACR (n = 369). The odds ratios (ORs) for disability were obtained using participants with low-CRP/low-UACR as the reference group. Adjusted means of various metabolic risks (blood pressure, waist circumference, and levels of blood glucose, triglycerides and HDL cholesterol) were obtained from multiple linear regressions.

Because the NHANES weights apply to prevalence estimates of the entire population and our study aimed to evaluate associations in certain subsets of participants with CVD, no NHANES weights were adjusted for in the analyses. Data analyses were performed using STATA 10.0 software (STATA Corp., College Station, TX).

3. Results

3.1. Characteristics of study participants

The mean age of the study population was 73.2 years and 40.1% was female. Characteristics of the study population by quartiles of CRP are summarized in Table 1. Of the 1403 study participants with self-reported history of CVD, 419 (29.9%) had angina, 611 (43.6%) had coronary heart disease, 391 (27.9%) had congestive heart failure, 594 (42.3%) had myocardial infarction, and 426 (30.4%) had stroke. Participants with higher CRP tended to be smokers, to have congestive heart failure, and were less likely to use statins. Participants in higher quartiles of CRP were inclined to have higher waist circumference, glucose levels and UACR, and were more likely to be disabled in all aspects of functional disability.

3.2. Chronic inflammation, urinary albumin excretion, and functional disability

After adjustment for age, sex, race, health behaviors, medical co-morbidities (chronic lung disease and arthritis) and eGFR, elevated levels of CRP were associated with increased odds of disability. ORs (95% confidence intervals [CIs]) of disability in ADL, IADL, LSA, LEM and GPA for each standard deviation (SD) of increase in the natural-log-transformed level of CRP were 1.24 (1.10–1.40), 1.17 (1.04–1.31), 1.29 (1.14–1.47), 1.30 (1.13–1.49) and 1.57 (1.39–1.78), respectively (table not shown). After additionally controlling for cardiovascular risk factors (hypertension, DM, waist circumference and levels of triglycerides and HDL cholesterol) as well as use of statins, anti-hypertensive agents and anti-inflammatory drugs (Model 3), the relation of CRP levels to disability in IADL was no longer significant. Although elevated CRP remained statistically related to disability outcomes in ADL, LSA and LEM, the OR sizes were reduced, suggesting that these variables, to some extent, may explain the association between CRP and disability. ORs (95% CI) of disability in ADL, LSA and LEM with each SD increase in the natural-log-transformed level of CRP were 1.18 (1.04–1.34), 1.24 (1.09–1.42) and 1.43 (1.25–1.62), respectively. Further adjustment of log-transformed UACR (Model 4) did not essentially change the associations.

We subsequently analyzed the CRP levels divided into quartiles; the results of quartile-based multiple logistic regressions are shown in Table 2. After controlling for covariates in Model 1 and Model 2, we observed positive associations between CRP levels and all disability outcomes. The trends of disability across increasing CRP quartiles were statistically significant. Likewise, when Model 3 covariates were additionally introduced into the quartile-based logistic regression models, the sizes of ORs were moderately reduced. Participants in the higher quartiles of CRP concentrations tended to have higher odds of disability in ADL, LSA and LEM. The associations were unchanged after additional consideration of albuminuria (Model 4, Table 2).

We also examined associations between albuminuria (UACR) and disability in participants with CVD. A higher UACR was associated with disability in ADL, IADL, LSA and LEM. The corresponding ORs (95% CI) comparing participants in the highest quartile of UACR to the lowest were 1.98 (1.41–2.79), 1.92 (1.37–2.69), 1.69 (1.19–2.42) and 2.80 (1.99–3.93), respectively, after controlling for variables in Model 2. The trend test across increasing UACR quartiles was significant in these disability outcomes. Although further covariate adjustment (Model 3 covariates + log-transformed CRP levels) moderately diminished the association between UACR and functional disability, elevated UACR remained a significant correlate for disability in ADL, IADL, LSA and LEM in the full-adjusted models. The corresponding ORs (95% CI) for disability in ADL, IADL, LSA and LEM were 1.71 (1.20–2.45), 1.72 (1.21–2.45), 1.46 (1.01–2.12) and 2.50 (1.73–3.62), respectively, comparing participants in the highest quartile of UACR to the lowest.

Associations between CRP and UACR with functional disability across categories of various CVDs were provided in online supplementary material Tables 1 and 2. We found that there was some heterogeneity of associations across categories of CVDs and that both markers, in general, were significant correlates for several
disability outcomes (especially LEM disability) across CVD categories.

3.3. Combination of CRP and UACR on functional disability and metabolic risks

We computed the ORs for disability in analyses which stratified study participants into four groups: low-CRP/low-UACR (reference), low-CRP/high-UACR, high-CRP/low-UACR, and high-CRP/high-UACR. We found combined association of chronic inflammation and albuminuria on late-life disability. The odds of disability were lowest in participants with low CRP and low UACR and were highest in those with high UACR and high CRP (Fig. 1). The ORs (95% CIs) for disability in ADL, IADL, LSA, GPA and LEM were 1.74 (1.22–2.48), 1.75 (1.24–2.47), 1.66 (1.15–2.40), 1.58 (1.06–2.36) and 2.97 (2.08–4.24), respectively, comparing participants with high-UACR/high-CRP vs. low-CRP/low-UACR.

The adjusted means of various metabolic risks, namely blood pressure, waist circumference, and levels of blood glucose, triglycerides and HDL cholesterol, in the four interactive groups were calculated after controlling for multiple variables. There was a combined association of CRP and UACR on metabolic risks as well. Participants with high CRP and high UACR had a more unfavorable metabolic profile in systolic blood pressure, abdominal circumference, serum glucose, triglyceride, HDL cholesterol and overall metabolic z-score compared to those with low CRP and low UACR (online supplementary material Table 3).

4. Discussion

Using a community-dwelling sample of older men and women with history of myocardial infarction, congestive heart failure, coronary heart disease, angina or stroke, our study suggested that high CRP and high UACR are associated with different measures of disability in seniors with CVD, independent of health behaviors, chronic co-morbidities and traditional cardiovascular risk factors and their management. We also found a previously unreported combined association of elevated CRP and albuminuria with functional disability. Subjects with higher levels of both chronic inflammation and albuminuria have higher odds of disability and a more unfavorable metabolic profile compared with those with lower levels of both biomarkers. Likewise, the joint association of inflammation and albuminuria with disability is also independent of health behaviors and chronic co-morbidities, as well as traditional cardiovascular risk factors and their management. The presence of subclinical albuminuria may amplify the association of chronic inflammation with functional disability in older adults with CVD. On the other hand, our results indicate that low inflammation burden (low CRP) may moderate the relation of albuminuria to late-life functional disability in the setting of CVD.
Table 2
Association between C-reactive protein (CRP) with functional disability among participants with cardiovascular disease.

<table>
<thead>
<tr>
<th>Model</th>
<th>CRP quartiles comparison</th>
<th>ADL disability</th>
<th>IADL disability</th>
<th>LSA disability</th>
<th>GPA disability</th>
<th>LEM disability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR* (95% CI) p for trend</td>
<td>OR* (95% CI) p for trend</td>
<td>OR* (95% CI) p for trend</td>
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<td>OR* (95% CI) p for trend</td>
<td>OR* (95% CI) p for trend</td>
</tr>
<tr>
<td>1</td>
<td>Q2 vs. Q1</td>
<td>1.11 (0.80–1.56) &lt;0.001</td>
<td>1.01 (0.73–1.41) &lt;0.001</td>
<td>1.24 (0.87–1.76) &lt;0.001</td>
<td>1.15 (0.82–1.61) &lt;0.001</td>
<td>1.49 (1.09–2.03) &lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Q2 vs. Q1</td>
<td>1.10 (0.78–1.56) &lt;0.001</td>
<td>1.00 (0.71–1.39) 0.002</td>
<td>1.26 (0.88–1.80) &lt;0.001</td>
<td>1.12 (0.78–1.58) &lt;0.001</td>
<td>1.49 (1.08–2.05) &lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>Q2 vs. Q1</td>
<td>1.03 (0.72–1.46) 0.004</td>
<td>0.94 (0.66–1.32) 0.047</td>
<td>1.15 (0.80–1.67) 0.001</td>
<td>0.97 (0.67–1.39) 0.066</td>
<td>1.29 (0.93–1.80) 0.001</td>
</tr>
<tr>
<td>4</td>
<td>Q2 vs. Q1</td>
<td>1.01 (0.71–1.44) 0.005</td>
<td>0.92 (0.65–1.30) 0.059</td>
<td>1.14 (0.79–1.65) 0.001</td>
<td>0.95 (0.66–1.37) 0.089</td>
<td>1.27 (0.90–1.77) 0.001</td>
</tr>
</tbody>
</table>

Adjusted covariates:
- Model 1 = age, sex, and race.
- Model 2 = Model 1 + health behaviors (smoking status and alcohol consumption) + medical co-morbidities (chronic lung disease and arthritis), and eGFR.
- Model 3 = Model 2 + cardiovascular risk factors and management (hypertension, DM, waist circumferences, levels of triglycerides and HDL cholesterol, use of statins, and use of anti-hypertensive agents), and use of anti-inflammatory drugs (aspirin, NSAIDs, and COX-2 inhibitors).
- Model 4 = Model 3 + log-transformed UACR level.

Abbreviations – ADL: activities of daily living; COPD: chronic obstructive lung disease; CRP: C-reactive protein; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; GPA: general physical activities; IADL: instrumental activities of daily living; LEM: lower extremity mobility; LSA: leisure and social activities; NSAIDs: nonsteroidal anti-inflammatory drugs; OR: odds ratio; and UACR: urinary albumin to creatinine ratio.

1 ORs are odds ratios of disability comparing participants in the 2nd, 3rd, or highest quartiles of C-reactive protein to those in the lowest quartile.

Our study supports and extends previous studies examining the interaction of inflammation and albuminuria on various outcomes. Jorgensen et al., by analyzing 5702 nondiabetic persons in a Norwegian population-based study, showed that albuminuria predicts all-cause and cardiovascular mortality. The mortality was especially high among individuals with elevated levels of both UACR and inflammatory markers (fibrinogen and white blood cell) [18]. Pedrinelli et al., by examining 220 sedentary white hypertensive men in Italy, found that subclinical inflammation accompanied by evidence of microalbuminuria is a strong correlate of metabolic abnormalities, including full-blown metabolic syndrome, low HDL, obesity, and concentric left ventricle hypertrophy. The combination of both biomarkers (namely, CRP and albuminuria) could identify a patient subset at very high cardiovascular risk [16]. Studies investigating the impact of inflammation, albuminuria, or their joint effect have typically focused on mortality, cardiovascular events or various metabolic outcomes. Little is known about how these measures are related to late-life disability in seniors with history of CVD. To the best of our knowledge, this is the first report to describe the relationship of inflammation and albuminuria both to late-life disability and to various metabolic risks by using a national sample of community-dwelling older adults with CVD. Our study advances knowledge in two ways. First, we found a combined association of inflammation and albuminuria with various metabolic risks including systolic blood pressure, abdominal circumference, serum glucose, triglyceride, HDL cholesterol, and overall metabolic burden. Second, we showed that inflammation and albuminuria, either alone or in combination, are associated with multiple domains of late-life disability. This joint association may reflect greater sensitivity for detecting CVD-related disability or various metabolic risks than either albuminuria or chronic inflammation alone. Major strengths of our study include comprehensive adjustments for potential confounders and use of multiple domains of disability measures, extending beyond traditional scope of ADL and IADL.

We observed attenuation in odds ratios after addition of cardiovascular risk factors, metabolic profile, and their management into Model 2. The moderate changes in point estimates for association of CRP and UACR with disability ranges from 10.4% to 21.3%, suggesting that these variables are important confounding factors which need to be considered in the multi-variable analyses. Moreover, cardio-metabolic risk factors and their management, to a moderate extent, might explain the association between elevations in biomarkers and late-life disability.

Several mechanisms may explain the associations between inflammation, albuminuria and increased odds of late-life disability in older adults with CVD. Chronic inflammation, negatively impacting on the endothelial integrity and blood flow control in the microcirculation, decreases the coordinated vasodilatory response to increase blood flow to meet the metabolic demands of the skeletal muscle [23]. Higher levels of inflammatory markers, linked to greater loss of muscle mass (sarcopenia) and strength [24], has been shown to be an important predictor for late-life disability [25]. On the other hand, proteinuria is associated with increased vascular permeability and is a proxy for generalized endothelial dysfunction [26]. Endothelial dysfunction, closely related to atherosclerotic change, could potentially lead to peripheral vascular disease which has been shown to be an essential risk factor of slow gait speed, decreased muscle strength, and physical disability [27,28]. Such findings from epidemiology and vascular pathophysiology studies provide plausible mechanistic explanations for the associations between albuminuria, inflammation and disability.

Our study has the following implication. Inflammation and proteinuria, independent of traditional cardiovascular risk factors and their management, is associated with increased odds of disability in several domains among older adults with CVD. In addition to being predictors of cardiovascular or survival outcomes, CRP and/or albuminuria appear to have functional implications. High levels of both inflammation and UACR in the setting of CVD may act as early warning signs of those elders at high risk of disability. If confirmed, high
CRP or UACR, especially in combination, may trigger close follow up to detect any ongoing early disability that may be amenable to physical therapy as well as management of any disabling condition or contributor to the disablement.

Our study has potential limitations deserving comments. First, because of the cross-sectional design, a causal relationship between albuminuria, inflammation and disability cannot be established. Such causal relationship requires longitudinal studies. Second,
determination of CVD is from self-reporting in the NHANES. Self-reporting may not fully reflect CVD presence and severity, and may suffer from recall bias or misclassification. Objective measures of cardiovascular outcomes, such as hospital record, echocardiogram, or coronary angiogram, are essential for future studies. Although the agreement between self-reported CVD (including myocardial infarction, stroke, pulmonary embolism, and venous thrombosis) and review by study physicians at clinical centers was substantial according to a recent study from the Women’s Health Initiatives Study [29], the association between biomarkers and CVD would be more consolidated if cardiovascular variables could be obtained more objectively in the future. Third, ascertainment of disability is from self-report and, likewise, may not reflect objective measures of functional performance. Although a high correlation between objective physical measures and self-report disability has been shown by recent studies [30,31], past research showed a high concordance between self-reported data and direct observations of ADL performance [32]. Likewise, investigators have demonstrated good agreement between self-report of diseases and objective documentation of medical events and co-morbid diseases [33].

In conclusion, albuminuria, inflammation and their combination were independently associated with functional disability among older people with CVD. Participants with higher levels of inflammation and albuminuria also had a more unfavorable metabolic profile compared with those with lower levels of both CRP and UACR. While it is important to optimally manage such cardiovascular risks as hypertension, diabetes or hypercholesterolemia, achieving target goals on these conditions may not necessarily reduce the risk of late-life disability. Measurements of CRP and UACR may have additional prognostic implication in patients already afflicted with a variety of cardiovascular problems. We provide new information and possible implication on the associations between UACR, CRP and disability among community dwelling elderly people with CVD where data currently are not complete.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2012.03.004.

References