Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2012 September;67(9):970–976
doi:10.1093/gerona/glr261

Advance Access published on February 24, 2012

Long-term Assessment of Inflammation and Healthy Aging in Late Life: The Cardiovascular Health Study All Stars

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Background. Associations of inflammation with age-related pathologies are documented; however, it is not understood how changes in inflammation over time impact healthy aging.

Methods. We examined associations of long-term change in C-reactive protein (CRP) and interleukin-6 (IL-6) with concurrent onset of physical and cognitive impairment, subsequent cardiovascular disease (CVD), and mortality in 1,051 participants in the Cardiovascular Health Study All Stars Study. Biomarkers were measured in 1996–1997 and 2005–2006.

Results. In 2005–2006, median age was 84.9 years, 63% were women and 17% non-white; 21% had at least a doubling in CRP over time and 23% had at least a doubling in IL-6. Adjusting for demographics, CVD risk factors, and 1996–1997 CRP level, each doubling in CRP change over 9 years was associated with higher risk of physical or cognitive impairment (odds ratio 1.29; 95% confidence interval 1.15, 1.45). Results were similar for IL-6 (1.45; 1.20, 1.76). A doubling in IL-6 change over time, but not CRP, was associated with incident CVD events; hazard ratio (95% confidence interval) 1.34 (1.03, 1.75). Doubling in change in each biomarker was individually associated with mortality (CRP: 1.12 [1.03, 1.22]; IL-6 1.39 [1.16, 1.65]). In models containing both change and 2005–2006 level, only level was associated with CVD events and mortality.

Conclusions. Although increases in inflammation markers over 9 years were associated with higher concurrent risk of functional impairment and subsequent CVD events and mortality, final levels of each biomarker appeared to be more important in determining risk of subsequent events than change over time.

Key Words: Inflammation—Aging—Physical function—Cognitive function.

Received August 11, 2011; Accepted December 27, 2011

Decision Editor: Luigi Ferrucci, MD, PhD

CHRONIC inflammation is a key component of aging-related pathologies (1). For example, higher levels of the inflammatory biomarker C-reactive protein (CRP) are associated with increased risk of cardiovascular and non-cardiovascular morbidity and mortality (2,3) as well as dementia, sarcopenia, and osteoporosis (4). Many studies have likewise shown associations of interleukin-6 (IL-6) with aging-related declines in physical and cognitive function, frailty, and increased risk of death in older adults (5–10). Other inflammatory markers have also been associated with the components of the frail phenotype (11) as well as frailty itself (12).

Little is known about how inflammation evolves over time. Aging is a dynamic and complex process. There is remarkable heterogeneity in rates of declines in physical and cognitive functioning (13). Inflammation status likely also changes over time. We hypothesized that change in inflammation status over time would be more strongly associated

with functional changes, incident cardiovascular disease (CVD), and mortality than a measure at a single point in time; that is, that the rate of increase in the trajectory to higher levels of inflammation determines subsequent risk. Using data from the Cardiovascular Health Study (CHS) All Stars cohort, a follow-up study to CHS, and paired inflammatory marker assessments from 9 years prior, we examined cross-sectional associations of biomarker level and change with indices of physical and cognitive function and prospective associations with these measures as well as incident CVD events and all cause mortality in very old adults.

Methods

CHS and CHS All Stars

CHS is comprised of 5,888 men and women greater than or equal to 65 years of age at baseline (14). The original cohort (n = 5,201) was enrolled in 1989–1990. An additional African American cohort (n = 687) was enrolled in 1992–1993. Examinations were performed yearly through 1999 and phone follow-up continues through the present. In 2005–2006, surviving participants (CHS All Stars) were offered an in-person visit to reevaluate physical and cognitive functioning (15). In all, 1,677 members participated in the exam, which, similar to CHS, included updated medical history, medication inventory, social history, self-reported health, physical function, physical activity, Modified Mini-Mental Status Examination (3MSE) (16), digit symbol substitution test (DSST) (17), isometric grip strength, gait speed, and fasting blood sample (15). All subjects gave informed consent, and all procedures were conducted under institutionally approved protocols.

Ascertainment of Cardiovascular Disease and Mortality

Potential CVD events were identified through semiannual contact with participants or proxies and were adjudicated as previously described (18). Incident CVD was defined as angina, myocardial infarction, congestive heart failure, claudication, stroke, or transient ischemic attack and was complete through June 30, 2008. Mortality data were available through June 30, 2009.

Laboratory Methods

All CRP and IL-6 measurements for this study were conducted from May 2008 to June 2008 at the Laboratory for Biochemical Research, University of Vermont. Assays were paired for participants with samples available in both 1996–1997 and 2005–2006 exams. CRP was measured by BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL). Ranges (minimum–maximum values) for the intra- and interassay coefficient of variations throughout the time period the assay was run were 0.68%–3.10% and 3.45%–5.97%, respectively. IL-6 was measured by ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). Intra- and interassay coefficient of variations ranged from 2.91% to 8.68% and 7.34% to 8.99%, respectively.

Clinical Definitions

Functional survival at the time of the All Stars examination was defined as being free of physical disability and cognitive impairment. Physical disability was defined as reporting any difficulty with at least one of five activities of daily living: transferring, bathing, dressing, eating, and toileting. Cognitive impairment was defined as a score of <80/100 on the 3MSE. For individuals without an in-person examination, a Telephone Interview for Cognitive Status (19) was obtained and for those with a proxy interview, the Informant Questionnaire for Cognitive Decline in the Elderly was administered (20). Based on a prior validation study (21), estimated 3MSE scores were calculated based on these tests to classify current level of cognitive function. For those participants with an in-person examination, function was also characterized by measuring gait speed, grip strength, and DSST (15).

Functional status was known for 1,662 individuals participating in the All Stars visit (2005–2006). Of these, 1,040 had CRP measurements and 986 had IL-6 measurements. Five extreme outliers in CRP (≥99th percentile) were excluded from analyses. Diabetes was classified by American Diabetes Association guidelines (22). Smoking was defined as never, former (more than 30 days since last cigarette), or current. Hypertension was defined as seated systolic blood pressure greater than or equal to 140 mmHg, diastolic blood pressure ≥90 mmHg, or history of hypertension and use of antihypertensive medication. Dyslipidemia was defined as total/high-density lipoprotein cholesterol ratio > 5 or use of lipid-lowering medication.

Statistical Methods

We calculated mean (*SD*), median (interquartile range) or prevalence of demographic characteristics, CVD risk factors, and biomarkers by functional impairment status at the 2005–2006 All Stars exam. Comparisons were based on t tests, Wilcoxon rank-sum tests, and χ^2 tests as appropriate. To accommodate skewness of CRP and IL-6, biomarkers were modeled as continuous variables using a log (base 2) transformation to quantify the impact of a doubling in the level of or change in each biomarker.

Cross-sectional associations of biomarker levels with physical and cognitive function at All Stars (2005–2006) were determined by multivariable logistic regression for physical or cognitive impairment and linear regression for individual measures of physical and cognitive function: gait speed, grip strength, 3MSE, and DSST.

Multivariable logistic regression was used to evaluate associations of 9-year change in biomarkers with concurrent onset of new physical or cognitive impairment, excluding

participants with the impairment in 1996–1997. Linear regression was used to examine associations of change in biomarkers with concurrent changes in individual measures of physical and cognitive function. Cox proportional hazards models were used to estimate the relative risk of incident CVD events and mortality after the 2005–2006 All Stars visit associated with both final level and antecedent change in biomarkers. Adjustment variables were age, sex, ethnicity, body mass index, smoking status, hypertension, dyslipidemia, and prevalent CVD (except when CVD was the outcome). Mortality analyses also adjusted for self-reported health and function status. When outcomes were assessed at or after the 2005–2006 All Stars visit, covariates were drawn from that visit, and the research focus was to assess whether knowledge of antecedent changes in biomarkers provides additional information beyond current biomarker level. When outcomes were changes in function from 1996 to 1997 to 2005 to 2006, the covariates were drawn from the 1996–1997 visit, and the focus was to assess whether changes in biomarkers were associated with concurrent change in function. We compared models with and without inclusion of initial biomarker level; results were similar so models are presented including initial level. We also tested for multiplicative interactions between level and change. Analyses were performed using R (R Development Core Team, Vienna, Austria) and STATA, version 11.

Results

Characteristics of the CHS All Stars Cohort

All Stars participant characteristics at the 2005–2006 exam are described in Table 1; 616 (59%) had a biomarker measure and had no impairment. Among the 434 who were functionally impaired and had a biomarker measure, 268 (62%) had physical impairment only, 105 (24%) had cognitive impairment only, and 61 (14%) had both. Compared with those with no impairment, those with any impairment were older, more likely to be female, less educated, and have diabetes and higher body mass index, CRP, and IL-6. Other factors were similar between groups. Participants missing biomarker measures were more likely to be female and were, on average, 1 year older than participants with measurements; there were no differences by ethnicity, body mass index, or CVD status; 21% had at least a doubling in CRP over time, but 27% had decreasing CRP (halving or greater) over time. Remaining participants had smaller or no changes in levels; 23% had at least a doubling in IL-6 over time, but 5% had decreasing IL-6; remaining participants had smaller or no changes in levels (Supplementary Table; Supplementary Figure).

Cross-sectional Associations of CRP and IL-6 With Functional Impairment

Each doubling in CRP or IL-6 level was associated with significantly higher risk for the presence of any impairment.

Table 1. CHS All Stars Demographic and Clinical Characteristics by Functional Status Among Those With CRP or IL-6 Measures at the 2005–2006 Exam

Characteristic	Functional Status		*p* Value
	No Impairment	Any Impairment	
N	616	434	
Age, years	85.3 (3.3)	86.4 (4.0)	<.01
Male, *n* (%)	251 (41%)	129 (30%)	<.01
Non-white, *n* (%)	97 (16%)	79 (18%)	.34
High school graduate, *n* (%)	530 (87%)	325 (75%)	<.01
Ever smoker, *n* (%)	301 (49%)	213 (49%)	.94
Hypertensive, *n* (%)	391 (64%)	289 (68%)	.26
Body mass index, kg/m^2	26.3 (4.1)	27.1 (5.4)	.02
Total cholesterol, mg/dL	180 (38)	183 (41)	.22
HDL cholesterol, mg/dL	55 (16)	54 (14)	.07
LDL cholesterol, mg/dL	100 (30)	103 (33)	.15
Dyslipidemia, *n* (%)	43 (7%)	42 (10%)	.15
Any clinical CVD, *n* (%)	193 (31%)	148 (34%)	.39
Diabetic, *n* (%)	81 (14%)	81 (21%)	.01
CRP, mg/dL, median (IQR)	1.73 (0.86, 3.81)	2.48 (1.13, 5.80)	<.01
IL-6, pg/mL, median (IQR)	3.25 (2.28, 4.94)	3.81 (2.60, 6.36)	<.01

Notes: Unless otherwise specified, values are mean (*SD*). Two-sample *t* tests used to compare symmetric continuous variables, Wilcoxon rank-sum tests for non-symmetric continuous variables, and χ^2 tests for binary variables. CRP = C-reactive protein; CVD = cardiovascular disease; HDL = high-density lipoprotein; IL-6 = interleukin-6; IQR = interquartile range; LDL = low-density lipoprotein.

This association appeared to be driven by the association of CRP levels with physical impairment (Table 2A). However, when cognitive scores were evaluated, higher levels of both biomarkers were associated with lower DSST scores, and IL-6 was associated with lower 3MSE scores (Table 2B). Consistent with results in Table 2A, higher levels of either biomarker were associated with slower gait speed and lower grip strength.

Associations of 9-Year Changes in CRP and IL-6 With Concurrent Onset of Functional Impairment

Among the 833 individuals with data who were at risk, there were 210 cases (25%) of incident physical impairment and105 cases (13%) of cognitive impairment between 1996 –1997 and 2005–2006; 183 participants (22%) had at least a twofold increase in CRP level and 193 (23%) had at least a twofold increase in IL-6 level over the 9-year interval. Each doubling in CRP change over time was associated with higher odds of any incident impairment and higher odds of physical or cognitive impairment (Table 3A). Results were similar for a doubling in IL-6 change over time. Initial 1996 –1997 CRP levels were associated with risk of any incident impairment and physical but not cognitive impairment. IL-6 levels were associated with physical impairment only. There was no evidence that the association between changes in CRP or IL-6 and incident physical impairment depended on initial levels of CRP or IL-6. However, the higher odds of incident cognitive impairment associated with elevations in both markers was reduced at higher initial levels of CRP (p for interaction between level and change = .02) and

Table 2. Associations of CRP and IL-6 Levels With Functional Status at the All Stars Visit (2005–2006)

A: Categories of impairment				
	CRP		IL-6	
Impairment	OR (95% CI)*	*p* value	OR (95% CI)*	*p* value
Any impairment	1.17 (1.07, 1.28)	<.10	1.31 (1.11, 1.56)	<.01
Physical only	1.17 (1.07, 1.29)	<.01	1.30 (1.09, 1.56)	<.01
Cognitive only	1.06 (0.94, 1.20)	.31	1.23 (0.98, 1.55)	.08
B: Individual measures of impairment				
	CRP		IL-6	
	Coefficient (95% CI)*	*p* value	Coefficient (95% CI)*	*p* value
Physical impairment				
Gait speed (0.22 m/s)	−0.054 (−0.095, −0.013)	.01	−0.177 (−0.254, −0.100)	<.01
Grip strength (8.8 kg)	−0.043 (−0.073, −0.014)	<.01	−0.116 (−0.173, −0.060)	<.01
Cognitive impairment				
3MSE score (12)	−0.029 (−0.064, 0.006)	.10	−0.078 (−0.143, −0.013)	.02
DSST score (14)	−0.042 (−0.079, −0.005)	.03	−0.115 (−0.184, −0.045)	<.01

Notes: Individual measures divided by their *SD*s shown in parentheses; 1,050 participants included in analyses. Adjustments: age, sex, ethnicity, body mass index, hypertension, smoking, dyslipidemia, any clinical CVD at 2005–2006 exam. 3MSE = Modified Mini-Mental Status Examination; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; DSST = digit symbol substitution test; IL-6 = interleukin-6; IQR = interquartile range; OR = odds ratio.

*ORs or coefficients and 95% CIs compare between two populations whose CRP or IL-6 level differs by a multiplicative factor of 2.

IL-6 ($p = .05$), indicating that if the initial biomarker level was already high, there was little additional risk associated with an increase in level.

We also examined associations of change in CRP and IL-6 over time with changes in measurements of physical and cognitive function over the same time frame. There was no association of CRP change with changes in measures of physical impairment (Table 3B); however, each doubling in CRP change over time was associated with significant declines in 3MSE and DSST scores (Table 3C). Each doubling

Table 3. Associations of Changes in CRP and IL-6 and Concurrent Onset of New Functional Impairment Between 1996–1997 and 2005–2006

A: Categories of impairment						
	Any		Physical only		Cognitive only	
Impairment exposure	OR (95% CI)*	*p* value	OR (95% CI)*	*p* value	OR (95% CI)*	*p* value
Doubling of CRP 1996–1997 to 2005–2006	1.29 (1.15, 1.45)	<.01	1.18 (1.05, 1.33)	.01	1.18 (1.03, 1.35)	.02
$\log_2$(CRP) in 1996–1997	1.19 (1.05, 1.34)	.01	1.22 (1.06, 1.39)	<.01	1.02 (0.86, 1.20)	.85
Doubling of IL-6 1996–1997 to 2005–2006	1.45 (1.20, 1.76)	<.01	1.34 (1.09, 1.65)	.01	1.35 (1.06, 1.72)	.02
$\log_2$(IL-6) in 1996–1997	1.17 (0.93, 1.47)	.19	1.33 (1.04, 1.71)	.02	1.07 (0.79, 1.44)	.68
B: Individual measures of physical impairment						
	Gait speed (0.24), m/s		Grip strength (5.18), kg			
Impairment exposure	β (95% CI)*	*p* value	β (95% CI)*	*p* value		
Doubling of CRP 1996–1997 to 2005–2006	−0.041 (−0.089, 0.007)	.10	−0.036 (−0.080, 0.008)	.11		
$\log_2$(CRP) in 1996–1997	−0.025 (−0.079, 0.029)	.37	0.011 (−0.039, 0.062)	.66		
Doubling of IL-6 1996–1997 to 2005–2006	−0.086 (−0.173, 0.001)	.05	−0.201 (−0.281, −0.122)	<.01		
$\log_2$(IL-6) in 1996–1997	−0.006 (−0.108, 0.096)	.91	−0.087 (−0.181, 0.008)	.07		
C: Individual measures of cognitive impairment						
	3MSE score (10.2)		DSST score (10.3)			
Impairment exposure	β (95% CI)*	*p* value	β (95% CI)*	*p* value		
Doubling of CRP 1996–1997 to 2005–2006	−0.058 (−0.099, −0.018)	.01	−0.045 (−0.089, −0.001)	.05		
$\log_2$(CRP) in 1996–1997	−0.014 (−0.061, 0.032)	.55	−0.059 (−0.109, −0.009)	.02		
Doubling of IL-6 1996–1997 to 2005–2006	−0.072 (−0.146, 0.003)	.06	−0.097 (−0.177, −0.018)	.02		
$\log_2$(IL-6) in 1996–1997	−0.053 (−0.141, 0.035)	.24	−0.065 (−0.159, 0.028)	.17		

Notes: Individual change measures divided by *SD* of change, shown in parentheses; 833 participants included in analyses. β = β coefficients; 3MSE = Modified Mini-Mental Status Examination; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; DSST = digit symbol substitution test; IL-6 = interleukin-6; IQR = interquartile range; OR = odds ratio.

*ORs or β and 95% CIs compare mean standardized change between two populations whose CRP or IL-6 change or level differs by a multiplicative factor of 2. Adjustments: age, sex, ethnicity, body mass index, hypertension, smoking, lipid-lowering medication, total cholesterol, any clinical CVD, CRP, or IL-6 levels at 1996–1997 exam.

Table 4. Associations of Levels and Antecedent Changes With Incident CVD Events

Exposure	HR (95% CI)*	*p* Value
CRP level and change		
1. Doubling of CRP 1996–1997 to 2005–2006	1.08 (0.94, 1.24)	.26
2. $\log_2$(CRP) in 2005–2006	1.13 (0.98, 1.31)	.09
3. Both level and change		
Doubling of CRP 1996–1997 to 2005–2006	1.04 (0.88, 1.23)	.66
$\log_2$(CRP) in 2005–2006	1.07 (0.89, 1.30)	.45
IL-6 level and change		
1. Doubling of IL-6 1996–1997 to 2005–2006	1.34 (1.03, 1.75)	.029
2. $\log_2$(IL-6) in 2005–2006	1.54 (1.14, 2.07)	.005
3. Both level and change		
Doubling of IL-6 1996–1997 to 2005–2006	1.07 (0.77, 1.49)	.07
$\log_2$(IL-6) in 2005–2006	1.51 (1.03, 2.23)	.035

Notes: HR, 95% CI compare risk of CVD events between two populations whose CRP or IL-6 change differs by a multiplicative factor of 2; 597 participants included in analyses. CI = confidence interval; HR = hazard ratios; CRP = C-reactive protein; CVD = cardiovascular disease; IL-6 = interleukin-6.

*Adjustments: age, sex, ethnicity, body mass index, hypertension, smoking, and dyslipidemia. All covariates measured at 2005–2006 exam.

Table 5. Associations of Levels and Antecedent Changes With Mortality

Exposure	HR (95% CI)*	*p* Value
CRP level and change		
1. Doubling of CRP from 1996–1997 to 2005–2006	1.12 (1.03, 1.22)	.012
2. $\log_2$(CRP) in 2005–2006	1.19 (1.09, 1.29)	<.001
3. Both level and change		
Doubling of CRP from 1996–1997 to 2005–2006	1.02 (0.91, 1.15)	.68
$\log_2$(CRP) in 2005–2006	1.15 (1.03, 1.30)	.016
IL-6 level and change		
1. Doubling of IL-6 from 1996–1997 to 2005–2006	1.39 (1.16, 1.65)	<.001
2. $\log_2$(IL-6) in 2005–2006	1.87 (1.55, 2.27)	<.001
3. Both level and change		
Doubling of IL-6 from 1996–1997 to 2005–2006	0.96 (0.78, 1.19)	.72
$\log_2$(IL-6) in 2005–2006	1.92 (1.50, 2.46)	<.001

Notes: HR, 95% CI compare risk of mortality between two populations whose CRP or IL-6 change differs by a multiplicative factor of 2; 985 participants included in analyses. CI = confidence interval; HR = hazard ratios; CRP = C-reactive protein; IL-6 = interleukin-6.

*Adjustments: age, sex, ethnicity, body mass index, hypertension, smoking, dyslipidemia, CVD, self-reported fair or poor health, functional status. All covariates measured at 2005-2006 exam.

in IL-6 change over time was associated with significant declines in grip strength, gait speed, and DSST score but not in3MSE score (Tables 3B and 3C). There was evidence to suggest that the decrease in gait speed associated with increased changes in IL-6 was reduced at higher initial levels of IL-6 (p for interaction between level and change = .01). Similarly, the decrease in 3MSE score associated with increased changes in CRP was reduced at higher initial levels of CRP (p for interaction = .01).

Longitudinal Associations of Changes in CRP and IL-6 With Incident CVD

Among the 597 participants at risk, there were 83 cases of incident CVD after the 2005–2006 All Stars exam. Median follow time for CVD was 2.6 years (maximum 3.2 years). Neither change nor level of CRP was associated with higher risk of CVD, but final IL-6 level was (Table 4). There was a marginally significant interaction between final level and change in IL-6 (p = .046), suggesting that at the same final level of IL-6, risk was higher for those who had a doubling or greater in level over 9 years (hazard ratios [95% CI] 2.52 [1.22, 5.21]) versus those whose levels remained stable or declined (1.25 [0.83, 1.89]). This pattern was not seen for CRP; p for interaction = .61.

Longitudinal Associations of Changes in CRP and IL-6 With Mortality

Nine-hundred and eighty-five All Stars participants (213 deaths, 22%) had data on change in CRP over 9 years and 925 (195 deaths, 21%) had data on change in IL-6. Median follow time for mortality was 3.6 years (maximum 4.2 years). Both change and final levels of CRP and IL-6 were associated with mortality in minimally and fully adjusted models (Table 5). However, when change and final level were both included in models, change was no longer significantly associated with mortality (Table 5). The risk of mortality associated with change did not differ by 2005–2006 level of CRP or IL-6 (p for interaction between level and change > .05 for all models tested).

Discussion

This is the first population-based study to evaluate associations of long-term change in inflammation status with aspects of healthy aging in older adults. We examined change in both CRP and IL-6 over a 9-year interval between 1996–1997 and 2005–2006 in the CHS All Stars cohort. Accounting for other factors and baseline biomarker levels, each doubling in CRP or IL-6 level over 9 years was significantly associated with increased odds of incident physical and cognitive impairment. Increases in CRP and IL-6 over time were also associated with declining cognitive performance and increases in IL-6 were associated with declining physical performance. Increases in IL-6, but not CRP, were associated with increased risk of cardiovascular events. Additionally, increases in both CRP and IL-6 were significantly associated with increased risk of mortality independent of other risk factors although these associations were no longer significant when final biomarker level was included in models.

Very few studies have examined long-term changes in biomarker levels. However, our results regarding associations of change in IL-6 level over time with incident CVD are similar to those published by Danesh et al. (23) who reported that long-term average IL-6 level was associated with coronary heart disease. In addition, Alley et al. (9)

reported that short-term increases (over 3 years) in CRP and IL-6 were associated with increased risk of mortality. This study also found that change in IL-6 did not add predictive value to final IL-6 level but that those with increasing CRP over 3 years and an elevated final CRP level were at greatest risk of mortality (9). Our results indicate that change in level over time is less predictive of mortality and cardiovascular events than final level of inflammation biomarkers. Differences in our results are likely to due to differences in follow-up time, 3 versus 9 years, and differences in study populations. Our study utilized a sample of older adults in the United States, but the study by Alley et al. utilized a sample of older adults in the Tuscany region of Italy (10). In addition, although we were underpowered to examine the interaction between change and final 2005–2006 levels, there was some evidence to suggest that at the same 2005–2006 level of IL-6, risk was higher for those who had an increase in level over 9 years versus those whose levels remained stable or declined. In other words, a new increase to a high level may confer greater risk than maintaining a constant high level over time. A recent study by Kizer et al. (24) also in the CHS All Stars cohort found that increases in CRP, IL-6, and adiponectin over 9 years independently predicted all-cause mortality. However, similar to our findings, changes in CRP and IL-6 were not significantly associated with risk of death when final levels of biomarkers were added to models.

Strengths of our study include a very well-characterized cohort of older white and black men and women with many measures pertaining to successful aging. Limitations should also be noted. Participants in CHS All Stars Study were a survival subset of the oldest old. Although this might bias toward the most functional survivors, the spectrum of function was very broad (15). However, it is likely that physical and cognitive impairment were underestimated because individuals with impairment are less likely to participate in follow-up visits (25). However, All Stars did offer a home visit to all participants, thereby minimizing the potential drop-out. CRP and IL-6 were measured from specimens taken in 1996–1997 only for the participants with valid measures in 2005–2006; no interim measures were available. This limited the number of participants with data on change in inflammatory markers.

In summary, our study and previous studies support the hypothesis that trajectories toward higher levels and/or sustained higher levels of inflammation underlie age-related declines in function and are associated with increased risk of CVD and all cause mortality. However, final levels of CRP and IL-6 appeared to be more important in determining risk of subsequent events than change over time. These findings may be useful clinically in formulating better strategies to prolong functionality through reducing inflammation. In the study by Kizer et al. (24), combining information from three biomarkers indicated that those with high adiponectin, CRP, and IL-6 had a significantly increased risk of death compared with those with low levels of all markers. Future research may identify a panel of biomarkers that could be used in risk assessment to provide for earlier interventions.

Funding

The research reported in this article was supported by the National Institute on Aging (R01-AG-023629). The CHS was supported by contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and grant HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through AG-15928, AG-20098, AG-027002, and AG-027058 from the National Institute on Aging. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/.

Conflict of Interest

The authors have no conflicts of interest and the funding agency did not participate in preparation of the manuscript.

Acknowledgments

Parts of the article were presented at the Gerontological Society of America meeting in November 2008 and November 2009. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi/htm.

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