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Three-Year Change in Inflammatory Markers in Elderly People and Mortality: The Invecchiare in Chianti Study

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Abstract

Objectives—To describe changes in interleukin-6 (IL-6) and C-reactive protein (CRP) and to determine how changes are related to mortality in elderly people.

Design—Prospective cohort study.

Setting—Two communities in the Tuscany region of Italy.

Participants—Randomly selected residents aged 65 and older who participated in the first two waves of data collection (N = 736).

Measurements—Two serum measurements of IL-6 and CRP taken 3 years apart. Mortality was observed for the 3 years after the second measurement; 79 deaths were observed in 2,079 person-years.

Results—Correlations indicated marginal to moderate stability in IL-6 and CRP, with clinical categories remaining relatively stable over time. Baseline levels were not related to mortality between follow-up Years 3 and 6, but increases in IL-6 and CRP predicted 3- to 6-year mortality. Controlling for follow-up IL-6 and CRP attenuated the relationship between inflammatory changes and mortality, but increases in CRP continued to increase odds of mortality. After controlling for sociodemographic characteristics, biological risk factors, health behaviors, and disease at both times, increases in CRP, but not IL-6, were related to mortality. Odds of death were more than three times as great in subjects

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in whom any CRP increase was observed (odds ratio = 3.10, 95% confidence interval = 1.25–7.68) as in subjects with stable or declining CRP.

Conclusion—CRP and IL-6 levels within individuals vary over time, and increases in CRP are associated with greater mortality risk. Three-year changes in inflammatory markers are better predictors of mortality than baseline measures.

Keywords

aging; epidemiology; interleukins

Inflammation contributes to the development of atherosclerosis¹ and is an important risk factor for cardiovascular disease^{2–4} and mortality,^{5–7} but research has typically relied on a single measurement of inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), to predict mortality.^{5–7}

Several studies have estimated variability in inflammatory markers,^{8–15} but little is known about how long-term variability is related to mortality. If changes in levels of inflammatory markers reflect underlying disease processes, such as instability of atherosclerotic lesions, accelerating disease severity, or progressive immune dysregulation, patterns of change in inflammatory levels might better reflect mortality risk than values assessed at one time point. The purpose of this study was to examine changes in IL-6 and CRP in older persons over 3 years and to determine whether changes in inflammatory markers predict subsequent all-cause mortality.

Methods

Study Population

Subjects include participants aged 65 and older in the Invecchiare in Chianti (InCHIANTI; Aging in the Chianti Area) Study, conducted in the Tuscany region of Italy.¹⁶ The Italian National Research Council on Aging (INRCA) ethical committee approved the protocol, and participants provided informed consent. In 1998, 1,299 persons aged 65 and older were randomly selected. Of these, 1,154 (92%) agreed to participate, 1,057 (84%) provided a blood sample, and 1,034 (80%) provided sufficient serum for analysis. From 2001 to 2003, follow-up data were collected, with complete blood samples available for 736 participants. One hundred four participants were lost because of death, 120 participants did not provide a blood sample or did not provide sufficient serum, and an additional 74 were lost to follow-up. Missing subjects were more likely to be aged 85 and older and female, to have diabetes mellitus, and to die before follow-up, although missing subjects at follow-up did not differ in baseline IL-6 or CRP levels.

Mortality data were obtained from death registries through 2005. An additional 79 subjects died during this interval. Descriptive analysis of changes in IL-6 and CRP was based on all subjects with serum measurements available at both time points ($n = 736$). Regression analysis predicting mortality was based on data from 683 participants with complete data on IL-6, CRP, and covariates at baseline, including 59 participants who died in follow-up Years 3 to 6. Additional regressions including covariates at follow-up were based on 545 participants, including 33 participants who died.

Measures

Venipuncture was performed in the morning after a 12-hour fast. Baseline IL-6 assays were performed at the INRCA central laboratory with immunoassay kits (BioSource International Inc., Camarillo, CA). The interassay variation coefficient was 7%. Follow-up IL-6 assays were

performed at the University of Vermont Laboratory for Clinical Biochemistry Research (R & D Systems, Inc., Minneapolis, MN). A subset of baseline samples ($n = 75$) was reanalyzed using the follow-up assay. The two assays were correlated (correlation coefficient = 0.88), and values obtained from the follow-up assay were regressed on values from the baseline assay to develop a transformation equation. Remaining baseline values were then transformed to maximize comparability between the two assays. For analysis purposes, IL-6 was coded into clinical risk categories based on research demonstrating greater risk of disability for individuals with IL-6 levels greater than 2.5 pg/mL.¹⁷

CRP was measured in duplicate using an enzyme-linked immunosorbent assay and colorimetric competitive immunoassay (Roche Diagnostics, Mannheim, Germany). The minimum detectable threshold was 0.03 mg/L, with an interassay variation coefficient of 5%. CRP was categorized using clinical cutpoints as low (≤ 1.0 mg/L), moderate (1.1–3.0 mg/L), high (3.1–10.0 mg/L), and very high (> 10.0 mg/L).¹⁸

Potential confounding variables in the relationship between IL-6, CRP, and mortality, including sociodemographic characteristics, biological risk factors, behavioral characteristics, and chronic disease presence, were assessed in a detailed interview and medical examination. Sociodemographic predictors associated with inflammation included age, sex, and education.^{19,20}

Biological confounders included indicators of body composition, cardiovascular health, and metabolic function associated with inflammation and mortality.^{19,21} Table 1 provides cutpoints used to determine clinical risk values. Several health behaviors were also considered as potential confounders. Smoking is associated with inflammation.²² Pack-years, a measure of smoking exposure combining intensity and duration, was calculated based on self-report of packs smoked per day multiplied by years of smoking. Moderate alcohol consumption has been related to lower levels of inflammatory markers.²³ Alcohol consumption (g/wk) was determined as part of a comprehensive food frequency questionnaire.²⁴ Physical activity was coded as low (participant reported hardly any activity or mostly sitting and walking) or high (participant reported at least 2 h/wk of light activity). Higher levels of physical activity are associated with lower serum levels of inflammation.^{25,26}

Several chronic diseases have been associated with inflammation, including liver disease,²⁷ coronary heart disease,³ diabetes mellitus,²⁸ and depression.²⁹ Chronic disease status was ascertained according to preestablished algorithms combining information from physician diagnosis, medical records, clinical examination, and blood tests for liver disease, coronary heart diseases (angina pectoris, myocardial infarction, and congestive heart failure), diabetes mellitus, and cancer.^{17,19} Depressive symptomatology was measured using the Italian version of the Center for Epidemiological Studies Depression Scale, with depression defined as a score greater than 16.³⁰

Analysis

Change in different clinical levels of IL-6 and CRP was first examined using frequencies and descriptive statistics, then Pearson correlation coefficients were used to describe continuous variability. The association between changes in inflammatory markers and mortality in the following 3 years was next examined (3–6 years after baseline). Descriptive statistics were used to compare changes in IL-6 and CRP according to survivorship status and to determine the incidence of mortality according to decile of change in inflammatory markers.

Logistic regression analysis was used to examine the effect of inflammation and change in inflammatory markers on mortality. The first model, termed the level model, examined the effect of IL-6 and CRP levels at baseline and follow-up on 3- to 6-year mortality, controlling

for covariates. Subsequent models investigated whether adding change in IL-6 and CRP provided additional predictive power beyond a single measurement, at baseline or at follow-up. These models compared participants whose CRP or IL-6 increased with those with stable or decreasing scores, regardless of the amount of the change. That is, all participants with a positive change score were compared with those with change scores of 0 or below. Models also investigated whether controlling for confounders at baseline or follow-up accounted for associations between inflammatory markers and mortality. The baseline change model includes baseline IL-6 and CRP and increases in either marker, controlling for covariates first at baseline (Model 1) and then at follow-up (Model 2), so that chronic conditions prevalent at baseline and incident conditions at Time 2 were controlled for. The follow-up change model similarly includes follow-up levels of IL-6 and CRP and changes in either marker, controlling for covariates at baseline (Model 1) and follow-up (Model 2). All analysis was conducted using SAS Version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Table 1 provides sample characteristics at baseline. Age ranged from 65 to 94, with a mean of 73.3. The sample was 54.8% female and had relatively low education levels, with a mean of 5.7 years, reflecting education levels in this regional cohort of older persons. High blood pressure was the most common health problem in the sample, affecting 77.6% of participants, and 11.9% of participants had been hospitalized in the year before the baseline examination. Among chronic conditions, depression was the most common (27.4%), followed by diabetes mellitus (10.3%) and coronary heart disease (9.1%). The average participant had some history of smoking and reported regular alcohol intake, but most were also physically active.

Changes in IL-6 and CRP clinical levels are shown in Figure 1. Categorical clinical values were relatively stable. Of subjects with low IL-6 values at Time 1, 61.0% still had low IL-6 at Time 2. In the high IL-6 group, 72.0% of those in the high category remained high across both waves. Of subjects with low, moderate, and high CRP values at Time 1, the majority of subjects remained in their initial category at Time 2, although variability increased as CRP value increased. Of subjects with low CRP values at Time 1, 63.8% still had low CRP values at Time 2, whereas of subjects with high CRP values at Time 1, only 50.0% still had high CRP values at Time 2. At the highest CRP values (> 10.0 mg/L), only 31.5% of subjects had very high CRP values at Time 2. Across all categories, 66.7% of participants remained in their baseline clinical category at follow-up in IL-6, and 52.4% of participations remained stable in CRP. The correlation coefficients for the two IL-6 and CRP measurements were 0.44 ($P<.001$) and 0.33 ($P<.001$), respectively. These correlations indicate marginal to moderate reproducibility in measurements over 3 years.

Table 2 provides descriptive statistics on IL-6 and CRP change according to survivorship status within 3 years after follow-up, adjusted for age and sex. Neither baseline IL-6 nor CRP was significantly different in subjects who died within 3 years after follow-up and those who survived, although follow-up IL-6 was significantly higher in subjects who died than in those who survived (5.3 vs 3.4 pg/mL, $P<.001$). Average IL-6 change was also higher in subjects who died; survivors experienced no change in IL-6, whereas those who died experienced an average increase of 1.4 pg/mL in IL-6 ($P<.001$). Baseline CRP did not differ in subjects who died within 3 years of follow-up, although follow-up CRP was more than twice as high in those who died (8.7 vs 3.9 mg/L, $P<.001$). The average CRP change in survivors was a small decline (-0.7 mg/L), whereas the average change in those who died was an increase of 4.4 mg/L ($P<.001$).

Figure 2 shows mortality after follow-up according to decile of IL-6 and CRP change. Mortality incidence begins to rise rapidly in those experiencing increases in either marker, roughly

corresponding to the top half of the distribution. Three-year mortality incidence rose from 2.6% in the fifth IL-6 decile to 27.8% in the top decile. Similarly, mortality incidence rose in the upper half of the CRP distribution, from 5.1% in the fifth decile to 31.1% in the top decile.

Table 3 provides odds ratios (ORs) for mortality in the 3 years after follow-up (3–6 years from baseline). The first model predicts mortality based on IL-6 and CRP level at baseline and at follow-up, controlling for covariates at baseline. Results indicate that baseline IL-6 and CRP are not related to mortality 3 to 6 years later but that follow-up CRP predicts mortality. High CRP at follow-up more than tripled the odds of subsequent mortality (OR = 3.48, 95% confidence interval (CI) = 1.64–7.54).

Subsequent models investigated whether adding change in IL-6 and CRP provided additional predictive power beyond a single measurement, at baseline or at follow-up. The baseline change model includes baseline IL-6 and CRP and change in either marker, controlling for covariates first at baseline (Model 1) and then for baseline demographic and behavioral covariates and health conditions at follow-up (Model 2). Results of baseline change Model 1 suggest that an increase in IL-6 more than doubled the odds of mortality (OR = 2.43, 95% CI = 1.15–5.13) and that subjects with an increase in CRP experienced mortality five times as high (OR = 5.49, 95% CI = 2.63–11.43) as those with stable or decreasing IL-6 and CRP. Controlling for health conditions at follow-up (baseline change Model 2) accounted for the increased risk of mortality associated with IL-6 increase (OR = 1.59, 95% CI = 0.65–3.87) but did not account for elevated mortality risk associated with increases in CRP (OR = 4.99, 95% CI = 1.93–12.88). The associations between follow-up levels of IL-6 and CRP and changes in either marker (follow-up change Model 1) indicate that change in IL-6 did not significantly predict mortality when follow-up level of IL-6 was included, but increases in CRP continued to predict mortality when follow-up values were controlled. Those who experienced an increase in CRP had more than three times the odds of mortality within 3 years of follow-up (OR = 3.10, 95% CI = 1.25–7.68), even after controlling for CRP and confounders at follow-up (follow-up change Model 2).

Discussion

The purpose of this paper was to describe 3-year change in IL-6 and CRP and to determine whether changes are associated with subsequent mortality. Significant variability was found in IL-6 and CRP in this sample of community-dwelling older persons. Correlations for IL-6 and CRP indicated marginal to moderate stability over a 3-year period. Previous studies of IL-6 stability in elderly people have relied on small samples and shorter time frames,¹⁴ but the correlation estimate of 0.44 for IL-6 was similar to results in young women over 2 years.¹⁰ The estimate of a correlation of 0.33 for CRP was somewhat lower than previous estimates of intraindividual CRP stability, ranging from 41% to 65% over periods from 5 months to 12 years,^{8,9,11–13,15} although previous samples have been primarily drawn from special populations.^{8,9,12,13,15} The only population-based study found a within-subject reliability of 0.54 in middle-aged men over 3 years.¹¹ CRP variability may be higher in older people living in the community than in younger people and those participating in clinical trials.

Despite significant intraindividual variation, clinical categories of IL-6 and CRP were somewhat more stable over time than continuous measures. Except at the highest values of CRP (>10.0 mg/L), the majority of individuals remained in their baseline category at follow-up. This is consistent with the relatively small average change observed in both markers; the mean change was an increase of 0.1 pg/mL in IL-6 and a decline of 0.2 mg/L in CRP. This is also consistent with previous research on CRP, suggesting significant continuous variation¹² but a greater reliability in clinical categories.¹³

Descriptive results show that those who died within 3 years of the second measurement experienced greater average increases in IL-6 and CRP than those who survived, and regression results show that increases in CRP elevated mortality adds three to five times relative to those who experienced no change or a decrease in CRP, even after controlling for demographic, biological, health behavior, and disease characteristics. Descriptive results further suggest that mortality risk may be related to the size of the increase, with those who had the greatest increases (>3.3 pg/mL of IL-6 or >3.6 mg/L of CRP) having the greatest mortality incidence. Regression results were based on a dichotomous coding of inflammatory change, comparing subjects experiencing any increase with those with stable or decreasing values of IL-6 and CRP, although a variety of ways of operationalizing change for regression analysis were considered. Using continuous coding of IL-6 and CRP and controlling for baseline values, it was found that a 1U (pg/mL) increase in IL-6 was related to a 14% increase in mortality risk (OR = 1.14, 95% CI = 1.03–1.27), whereas a 1U (mg/L) increase in CRP was related to a 3% increase in mortality risk, although this difference was only marginally significant (OR = 1.03, 95% CI = 1.00–1.05). Nevertheless, continuous coding is problematic, because the relationship between change in inflammation and mortality is nonlinear (Figure 2). A simple piecewise model, or spline model, was tested with a knot at zero to allow for different probability slopes for subjects with positive and negative change. This model was significant for CRP, but the spline term was not significant for IL-6, although the small number of deaths in this sample ($n = 79$) limits the ability to detect nonlinear relationships. Additionally, results were tested excluding participants with CRP greater than 10 mg/L at baseline; excluding these participants did not significantly change results.

The results suggest that changes in IL-6 and CRP are important predictors of mortality. Whether baseline or follow-up CRP measurement was controlled for, changes in CRP were significant, and one-time measures were not, suggesting that change in CRP is a more important predictor of mortality than CRP levels at any given point in time. Change in IL-6 appeared to be significant when controlling for baseline IL-6 but not for follow-up IL-6, suggesting that changes in IL-6 may also be predictive of mortality but may act through their association with CRP or with follow-up IL-6 levels. Consistent with previous research,³¹ results also suggest that a single measurement of CRP may predict mortality in the short term (0–3 years) but may not predict mortality in the longer term (3–6 years in this study). High baseline CRP values were associated with mortality between baseline and follow-up (OR = 2.00, 95% CI = 1.17–3.43, results not shown) but were not associated with mortality after follow-up. Follow-up CRP was also associated with subsequent 3-year mortality, but change in CRP appeared to be a more-powerful predictor of mortality than either of these individual measures.

Thus, increases in CRP independently predicted mortality when single measures (at baseline or follow-up) were controlled. There are a number of potential explanations for this association. First, increases in CRP may indicate elevated coagulability³² and plaque instability,³³ thereby marking greater risk for cardiovascular mortality. Second, increases in CRP may reflect accelerating severity of chronic disease. Although presence of disease at follow-up was controlled for, general increases in severity of disease cannot be accounted for. Finally, increases in CRP may reflect progressive immune dysregulation related to acute or recurrent infections, inflammatory diseases, or immune changes with age.

Nevertheless, it is important to note the limitations of this study. First, it is based on a sample drawn from two communities of older Italians. InCHIANTI participants differ from U.S. population-based samples in a number of meaningful ways that may limit the generalizability of the results. Second, the IL-6 assay changed between the two waves. Although every effort was made to ensure comparability of values, it remains possible that this change affected IL-6 findings. In particular, if the assay change introduced additional error in IL-6 measurement, it might bias results in favor of the null hypothesis. The finding that IL-6 was not related to

mortality after controlling for covariates should therefore be interpreted with caution. Third, this analysis was based on a small number of deaths ($n = 79$). Future analysis with a larger sample could examine more-nuanced patterns of changes in inflammatory markers and differences in mortality according to cause of death. Without cause-of-death information, whether the effects of changes in inflammatory markers are specific to cardiovascular mortality cannot be determined. Fourth, categorical controls were used for biological risk factors, reflecting clinical risk cutoffs for waist circumference, blood pressure, and lipids. These categories are likely to identify individuals at high risk for poor health outcomes but do not capture the full range of variation. Controlling for biological confounders measured continuously did not change results. Finally, a significant portion of the baseline sample (19%) lacked follow-up inflammation data, and those lost were more likely to be older and female and to die before the second wave of serum collection.

Logistic regression was used to examine differences in 3- to 6-year mortality according to inflammatory status. An alternative analytical approach would have been to use survival analysis. Because of the short time period (3 years) and the use of death registries to limit the potential for differential observation of the outcome (mortality), observation time was unlikely to bias the results. To confirm this, survival analysis was conducted using Cox proportional hazard models, and results were consistent with those reported here, although IL-6 violated the proportional hazards assumption, with the relationship between IL-6 and mortality increasing over time. Future analysis exploring the changing relationship between inflammatory markers and mortality over time is warranted.

Conclusion

This study finds significant variability in inflammatory markers over a 3-year period but relatively stable clinical risk categories across individuals. Results demonstrate that a recent increase in inflammatory markers is a more-robust risk factor for mortality than a single measure. This suggests the utility of multiple measurements of inflammatory markers, which may be useful in understanding inflammatory trajectories and their diagnostic implications. In particular, neither baseline nor follow-up inflammatory status was a significant predictor of 3- to 6-year mortality after accounting for changes in IL-6 and CRP levels, suggesting that changes in inflammation over time may be more important than levels of inflammation at a given time.

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Figure 1.

Three-year change in interleukin-6 (IL-6) and C-reactive protein (CRP) clinical levels (N = 736). (A) IL-6 Time 2 clinical status according to Time 1 status. (B) CRP Time 2 clinical status according to Time 1 status.

Figure 2.

Three-year mortality incidence according to change in interleukin-6 (IL-6) and C-reactive protein (CRP) (N = 736). (A) IL-6. (B) CRP.

Table 1

Baseline Characteristics of Invecchiare in Chianti Study Population (N = 683)

Characteristic	Value
Sociodemographic characteristics	
Age, mean $\pm$ SD	73.3 $\pm$ 6.1
Female, %	54.8
Education, years mean $\pm$ SD	5.7 $\pm$ 3.3
Health characteristics, %	
High waist circumference [†]	42.9
High blood pressure [‡]	77.6
Low HDL [§]	24.7
High LDL	25.6
High triglycerides [#]	11.0
Hospitalization in previous year	11.9
Behavioral characteristics	
Smoking, pack-years, mean $\pm$ SD	11.9 $\pm$ 19.7
Alcohol intake, g/d, mean $\pm$ SD	15.4 $\pm$ 21.3
Low physical activity, %	14.5
Chronic disease, %	
Liver disease	4.7
Diabetes mellitus	10.3
Depression	27.4
Coronary heart disease	9.1
Cancer	6.4

[†] ≥ 102 cm for men, ≥ 88 cm for women.

[‡] Average of three measurements, high if ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic.

[§] High-density lipoprotein ≤ 40 mg/L for men, ≤ 50 mg/L for women.

^{||} Low-density lipoprotein ≥ 160 mg/L.

[#] ≥ 200 mg/L.

SD = standard deviation.

Table 2

Change in Inflammatory Markers According to Survivorship Status: Means Adjusted for Age and Sex

	Survivors (N = 657)	Died (N = 79)	
Inflammatory Marker	Mean (95% Confidence Interval)		P-Value [†]
Interleukin-6, pg/mL			
Baseline	3.4 (3.2–3.6)	3.9 (3.3–4.4)	.12
Follow-up	3.4 (3.2–3.6)	5.3 (4.6–5.9)	<.001
Average change	0.0 (–0.2–0.2)	1.4 (0.7–2.0)	<.001
C-reactive protein, mg/L			
Baseline	4.6 (4.0–5.1)	4.3 (2.6–6.0)	.78
Follow-up	3.9 (3.2–4.6)	8.7 (6.6–10.9)	<.001
Average change	–0.7 (–1.4–0.0)	4.4 (2.2–6.7)	<.001

[†]P-value obtained from *t*-test of difference between means.

Table 3

Logistic Regression Results Predicting Mortality

Covariate	Level Model [*]	Baseline Change Model 1 [*]	Baseline Change Model 2 [†]	Follow-Up Change Model 1 [*]	Follow-Up Change Model 2 [‡]
N	683	683	545	683	545
Died, n	59	59	33	59	33
Baseline inflammation (relative to low) OR (95% CI)					
IL-6 >2.5 pg/mL	0.82 (0.39–1.71)	1.25 (0.55–2.82)	0.62 (0.23–1.70)		
CRP >3.0 mg/L	0.70 (0.33–1.49)	1.78 (0.87–3.63)	1.98 (0.80–4.86)		
Follow-up inflammation (relative to low) OR (95% CI)					
IL-6 >2.5 pg/mL	1.60 (0.68–3.77)			1.32 (0.54–3.22)	1.78 (0.63–5.07)
CRP >3.0 mg/L	3.48 (1.64–7.54)			1.78 (0.85–3.71)	2.06 (0.81–5.23)
Change in inflammation, OR (95% CI) [§]					
IL-6 increase		2.43 (1.15–5.13)	1.59 (0.65–3.87)	2.00 (0.97–4.13)	1.35 (0.57–3.24)
CRP increase		5.49 (2.63–11.43)	4.99 (1.93–12.88)	4.19 (1.99–8.83)	3.10 (1.25–7.68)

* Controls for inflammatory markers, age, sex, education, and covariates at baseline: health characteristics (high waist circumference, high blood pressure, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, high triglycerides, hospital stay in previous year), health behaviors (alcohol intake, smoking in pack-years, low physical activity), and disease (liver disease, coronary heart disease, diabetes mellitus, depression, cancer).

[†] Controls for inflammatory markers, age, sex, education, and health behaviors (alcohol intake, smoking in pack-years, low physical activity) at baseline, and covariates at follow-up: high waist circumference, high blood pressure, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, high triglycerides, hospital stay in previous year, liver disease, coronary heart disease, diabetes mellitus, depression, cancer.

[‡] Controls for inflammatory markers and all covariates at follow-up: age, sex, education, health behaviors (alcohol intake, smoking in pack-years, low physical activity), high waist circumference, high blood pressure, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, high triglycerides, hospital stay in last year, liver disease, coronary heart disease, diabetes mellitus, depression, cancer.

[§] Effect of any increase (based on change score) relative to no change or a decrease in interleukin-6 (IL-6) and C-reactive protein (CRP). OR = odds ratio; CI = confidence interval.