

Associations of Elevated Interleukin-6 and C-Reactive Protein Levels with Mortality in the Elderly*

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PURPOSE: To investigate whether interleukin-6 and C-reactive protein levels predict all-cause and cause-specific mortality in a population-based sample of nondisabled older people.

SUBJECTS AND METHODS: A sample of 1,293 healthy, nondisabled participants in the Iowa 65+ Rural Health Study was followed prospectively for a mean of 4.6 years. Plasma interleukin-6 and C-reactive protein levels were measured in specimens obtained from 1987 to 1989.

RESULTS: Higher interleukin-6 levels were associated with a twofold greater risk of death [relative risk (RR) for the highest quartile (≥ 3.19 pg/mL) compared with the lowest quartile of 1.9 [95% confidence interval, CI, 1.2 to 3.1]]. Higher C-reactive protein levels (≥ 2.78 mg/L) were also associated with increased risk (RR = 1.6; CI, 1.0 to 2.6). Subjects with elevation of both interleukin-6 and C-reactive protein levels were 2.6 times more

likely (CI, 1.6 to 4.3) to die during follow-up than those with low levels of both measurements. Similar results were found for cardiovascular and noncardiovascular causes of death, as well as when subjects were stratified by sex, smoking status, and prior cardiovascular disease, and for both early (<2.3 years) and later follow-up. Results were independent of age, sex, body mass index, and history of smoking, diabetes, and cardiovascular disease, as well as known indicators of inflammation including fibrinogen and albumin levels and white blood cell count.

CONCLUSIONS: Higher circulating levels of interleukin-6 and C-reactive protein were associated with mortality in this population-based sample of healthy older persons. These measures may be useful for identification of high-risk subgroups for anti-inflammatory interventions. *Am J Med.* 1999;106:506-512. ©1999 by Excerpta Medica, Inc.

Systemic inflammation, as measured by C-reactive protein, has been associated with acute myocardial ischemia (1,2) and long-term risk of coronary artery disease and stroke (3-5). The role of inflammation in the pathogenesis of atherothrombosis (6,7) and other acute and chronic conditions has been well described (8-11), but whether markers of inflammation, such as C-reactive protein, have broader applicability as indicators of mortality in the general population is unknown.

Inflammation is characterized by a local reaction that may be followed by activation of a systemic acute phase

reaction (12). Previous studies have estimated the severity of inflammation by use of circulating C-reactive protein levels (1-5). However, because C-reactive protein is a product of the acute phase reaction (13) and because the concentration of C-reactive protein may be subject to posttranscriptional regulation (14), C-reactive protein may not measure all of the relevant effectors of inflammation.

Interleukin-6 is the major initiator of the acute phase response by hepatocytes and induces the synthesis of C-reactive protein, as well as other acute phase reactants (13,15-17). A sensitive, reliable assay for circulating interleukin-6 is now available, but assays for the other major inflammatory cytokines, such as tumor necrosis factor and interleukin-1 β , are more problematic. Given the role of interleukin-6 in C-reactive protein regulation, the combined use of interleukin-6 and C-reactive protein levels as indicators of inflammation may provide a better prediction of risk associated with inflammation than would use of either indicator alone.

We investigated the predictive value of interleukin-6 and C-reactive protein levels as markers of persistent inflammation for all-cause and cause-specific mortality in a case-cohort study nested in the Iowa 65+ Rural Health Study. We hypothesized that both interleukin-6 and C-reactive protein levels would be associated with mortality and that the combined elevation of both markers would

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Supported in part by National Institute on Aging Contract AG-0-2106. This paper was finalized when Drs. Ferrucci and Corti were Visiting Scientists in the Epidemiology, Demography and Biometry Program at the National Institute on Aging.

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Manuscript submitted May 8, 1998, and accepted December 8, 1998.

be associated with the greatest and most consistent increases in risk.

METHODS

Subjects

Study subjects were participants in the Iowa 65+ Rural Health Study, one of four sites of the Established Populations for Epidemiologic Studies of the Elderly (18). In 1982, 3,673 persons (80% of those eligible) living in two Iowa counties participated in a comprehensive interview. Interviews were repeated annually for 7 years, and follow-up for mortality was continued until December 31, 1992. Blood was obtained from 1,940 participants who were reinterviewed between 1987 and 1989 at the seventh follow-up interview (76% of those reinterviewed). Specimens were drawn in the morning and early afternoon from participants and frozen at -70°C until thawed for assay.

We conducted a prospective case-cohort study of the association of interleukin-6 and C-reactive protein levels with death and disability. Because the study focused on those in good health (defined as participants without reported disability), we excluded 647 persons who needed help walking a half mile, climbing a flight of steps, moving from bed to chair, using a toilet, bathing, or walking across a small room. We measured interleukin-6 and C-reactive protein levels on a random sample of the 1,293 remaining eligible high-functioning participants. This sample was augmented by all others in the high-functioning group who died during follow-up. The analytic sample for this case-cohort study included 499 survivors and 176 subjects who died.

Measurement of Interleukin-6 and C-Reactive Protein Levels

Plasma interleukin-6 levels were measured by enzyme-linked immunosorbent assay (ELISA; High Sensitivity Quantikine kit, R&D Systems, Minneapolis, MN). The detectable limit for interleukin-6 was 0.10 pg/mL, and the interassay coefficient of variation was 7%. C-reactive protein was measured by an ELISA with a sensitivity of .08 mg/L and an interassay coefficient of variation of 9% (3,19). Values were measured in duplicate, and the average value was reported for both assays.

Mortality follow-up

Mortality was ascertained by collection of local obituaries, contact with proxies for those who died, and linkage with the National Death Index. Death certificates were obtained for 99% of all subjects who died. Cause-specific mortality was based on underlying cause of death, coded by the International Classification of Diseases (ICD-9) as any cardiovascular mortality (ICD-9 codes 410-414, 430-438, 440-442; 74 deaths) or all other mortality (102 deaths).

Study Variables

Potential confounders of the associations between interleukin-6 and C-reactive protein with mortality included reported cardiovascular disease (heart attack or stroke), diabetes, and cancer (based on report of an overnight hospitalization for cancer during the baseline interview, or any subsequent annual interview before the plasma samples were obtained from 1987 to 1989). Cigarette smoking was categorized as never smokers and ever smokers, as there were only 35 current smokers. Alcohol intake was characterized as any alcohol use in the past year versus none. Body mass index (weight in kilograms divided by height in meters squared) was calculated on the basis of measured height and weight from the seventh follow-up (99% of participants) or reported weight if the measured weight was unavailable.

We created a variable indicating the use of antioxidant supplements, including vitamin A, C, or E, and a variable indicating use of anti-inflammatory drugs, including aspirin, salicylates, glucocorticoid preparations, or nonsteroidal anti-inflammatory drugs, based on drug use reported for the 2 weeks before the 1987 to 1989 interview. Of the 286 people taking anti-inflammatory drugs, 229 reported aspirin or salicylate use.

The associations of interleukin-6 and C-reactive protein levels with three other indicators of inflammation were examined to test whether the associations of interleukin-6 and C-reactive protein levels with mortality were independent of these indicators. These included serum albumin level, measured using dye-binding bromocresol green in a sequential autoanalyzer (SMAC; Technicon, Tarrytown, NY), white blood cell count, measured using a Coulter counter, and plasma fibrinogen level, measured by a modification of the Clauss clot-rate method (20). The laboratory coefficient of variation for fibrinogen was approximately 3%.

Statistical Analysis

Characteristics of the 499 survivors and the 176 subjects who died were compared using *t* tests for continuous variables (age, body mass index) and chi-square statistics for categorical variables (gender, alcohol intake, smoking status, medical conditions, and antioxidant and anti-inflammatory use). When interleukin-6 and C-reactive protein levels were used as continuous variables, values were log transformed to normalize the distributions. Quartile categories of interleukin-6 and C-reactive protein levels, derived from the distribution of the cohort random sample, were used to model the mortality associations.

To test the hypothesis that joint elevation of interleukin-6 and C-reactive protein levels would confer the greatest risk, we created five mutually exclusive groups based on combinations of interleukin-6 and C-reactive

Table 1. Levels of C-Reactive Protein and Interleukin-6 by Selected Characteristics of the Subjects

| Characteristics | Percent of Study Sample | C-Reactive Protein Level (mg/L), Mean \pm SD (log values)* | Interleukin-6 Level (pg/mL), Mean \pm SD (log values)* |
|--|-------------------------|--|--|
| Age (years) | | | |
| 71–72 (reference) | 15 | 0.67 \pm 1.01 | 0.73 \pm 0.66 |
| 73–74 | 19 | 0.56 \pm 0.99 | 0.79 \pm 0.65 |
| 75–76 | 17 | 0.43 \pm 1.04 | 0.84 \pm 0.66 |
| 77–80 | 24 | 0.36 \pm 0.91 [†] | 0.79 \pm 0.66 |
| \geq 80 | 25 | 0.46 \pm 1.24 | 0.96 \pm 0.65 [†] |
| Sex | | | |
| Women | 59 | 0.39 \pm 1.07 | 0.74 \pm 0.61 |
| Men | 41 | 0.61 \pm 1.02 [‡] | 0.96 \pm 0.71 [†] |
| Cigarette smoker | | | |
| Never | 71 | 0.43 \pm 1.06 | 0.78 \pm 0.61 |
| Ever | 29 | 0.62 \pm 1.04 [†] | 0.99 \pm 0.74 [†] |
| Sex-specific body mass index quintile | | | |
| Quintile 1 (reference) | | 0.12 \pm 1.00 | 0.77 \pm 0.77 |
| Quintile 2 | | 0.39 \pm 1.08 [†] | 0.78 \pm 0.63 |
| Quintile 3 | | 0.54 \pm 1.04 [‡] | 0.78 \pm 0.61 |
| Quintile 4 | | 0.69 \pm 0.94 [‡] | 0.82 \pm 0.58 |
| Quintile 5 | | 0.67 \pm 1.02 [‡] | 1.00 \pm 0.68 [†] |
| History of diabetes | | | |
| No | 86 | 0.43 \pm 1.04 | 0.81 \pm 0.65 |
| Yes | 14 | 0.82 \pm 1.07 [‡] | 0.98 \pm 0.71 [†] |
| History of cardiovascular disease | | | |
| No | 82 | 0.43 \pm 1.06 | 0.78 \pm 0.65 |
| Yes | 18 | 0.73 \pm 1.00 [‡] | 1.07 \pm 0.64 [†] |
| Use of anti-inflammatory drugs | | | |
| Yes | 43 | 0.42 \pm 1.11 | 0.80 \pm 0.62 |
| No | 57 | 0.53 \pm 1.01 | 0.86 \pm 0.69 |
| Use of specific anti-oxidant supplements | | | |
| Yes | 8 | 0.41 \pm 1.05 | 0.77 \pm 0.62 |
| No | 92 | 0.49 \pm 1.10 | 0.84 \pm 0.66 |

* A log mean value of 0.5 for C-reactive protein corresponds to a level of 1.7 mg/L, and a value of 1.0 for interleukin-6 corresponds to 2.8 pg/mL.

[†] .01 < *P* < 0.05 for category contrasted with reference.

[‡] *P* < 0.01 for category contrasted with reference.

protein levels. The high extreme group (high both) included those with interleukin-6 and C-reactive protein levels both in quartile 4 (interleukin-6 level \geq 3.19 pg/mL, C-reactive protein level \geq 2.78 mg/L; *n* = 90). The low extreme (low both), considered as the reference category in the analysis, included only participants with values below the median (interleukin-6 level < 2.08 pg/mL, C-reactive protein level < 1.57 mg/L; *n* = 227). The three intermediate categories were defined as interleukin-6 level in quartile 4 and C-reactive protein level less than quartile 4 (high interleukin-6), C-reactive protein level in quartile 4 and interleukin-6 level less than quartile 4 (high C-reactive protein), and either C-reactive protein or interleukin-6 level in quartile 3 but neither in the upper quartiles

(mid-both). All analyses of risk were performed using EPICURE PEANUTS (21), which calculates hazard ratio estimates and confidence intervals (CIs) for a case-cohort study (22) with the time variable calculated as person-years from the baseline. Relative risks (RR) and 95% CIs were estimated from models that included sex, age, smoking history, diabetic status, body mass index, and history of cardiovascular disease, unless otherwise indicated. Additional models tested whether other indicators of inflammation affected the results, and models stratified by specific characteristics examined the consistency of results among selected subgroups. Statistical significance was set at *P* < 0.05, two sided. Continuous values are reported as means \pm SD.

Table 2. Associations between Interleukin-6 and C-Reactive Protein Levels and All-Cause and Cause-Specific Mortality

| Inflammatory Marker | N | Deaths/ Person-years | Mortality Rate/1,000 Person-years | All-Cause Mortality, Relative Risk (95% confidence interval) | | Cause-Specific Mortality, Relative Risk (95% confidence interval) | |
|---------------------------------|-----|-------------------------|--------------------------------------|--|----------------|---|-------------------------|
| | | | | Model 1* | Model 2† | Any cardiovascular disease (n = 74)† | All other (n = 102)† |
| Interleukin-6 level (pg/mL) | | | | | | | |
| <1.46 | 165 | 30/737 | 41 | 1.0 | 1.0 | 1.0 | 1.0 |
| 1.46–<2.08 | 167 | 34/735 | 46 | 1.0 (0.6, 1.7) | 1.0 (0.6, 1.7) | 1.5 (0.7, 3.4) | 0.7 (0.4, 1.5) |
| 2.08–<3.19 | 160 | 35/695 | 50 | 0.9 (0.6, 1.6) | 1.0 (0.6, 1.6) | 1.0 (0.4, 2.4) | 1.0 (0.5, 1.8) |
| ≥3.19 | 183 | 77/703 | 110 | 2.1 (1.3, 3.4) | 1.9 (1.2, 3.1) | 2.2 (1.0, 4.8) | 1.9 (1.1, 3.4) |
| C-reactive protein level (mg/L) | | | | | | | |
| <0.91 | 173 | 40/752 | 53 | 1.0 | 1.0 | 1.0 | 1.0 |
| 0.91–<1.57 | 157 | 32/695 | 46 | 0.9 (0.6, 1.5) | 0.9 (0.6, 1.6) | 1.0 (0.5, 2.2) | 0.9 (.4, 1.7) |
| 1.57–<2.78 | 166 | 44/699 | 63 | 1.3 (0.8, 2.0) | 1.4 (0.8, 2.2) | 0.9 (0.4, 2.1) | 1.7 (.9, 3.0) |
| ≥2.78 | 179 | 60/724 | 83 | 1.7 (1.1, 2.6) | 1.6 (1.0, 2.6) | 1.8 (0.9, 3.6) | 1.4 (0.8, 2.5) |

* Adjusted for age and sex.

† Adjusted for age, sex, prevalent cardiovascular disease, smoking status, diabetes, body mass index.

RESULTS

Diseases and Risk Factors Associated with Interleukin-6 and C-Reactive Protein

The sample consisted of 279 men and 396 women, with a mean age of 77.8 ± 3.2 years. Twenty-nine percent were former or current cigarette smokers, and 18% reported cardiovascular disease or diabetes (Table 1). Less than 4%

of the group had levels of C-reactive protein greater than the clinically relevant threshold of 10 mg/L. Male sex, cigarette smoking, greater body mass index, history of diabetes, and history of any cardiovascular disease were all associated with greater levels of interleukin-6 and C-reactive protein. Interleukin-6 and C-reactive protein levels were lower in those who reported use of anti-inflammatory drugs or antioxidant supplements, but these

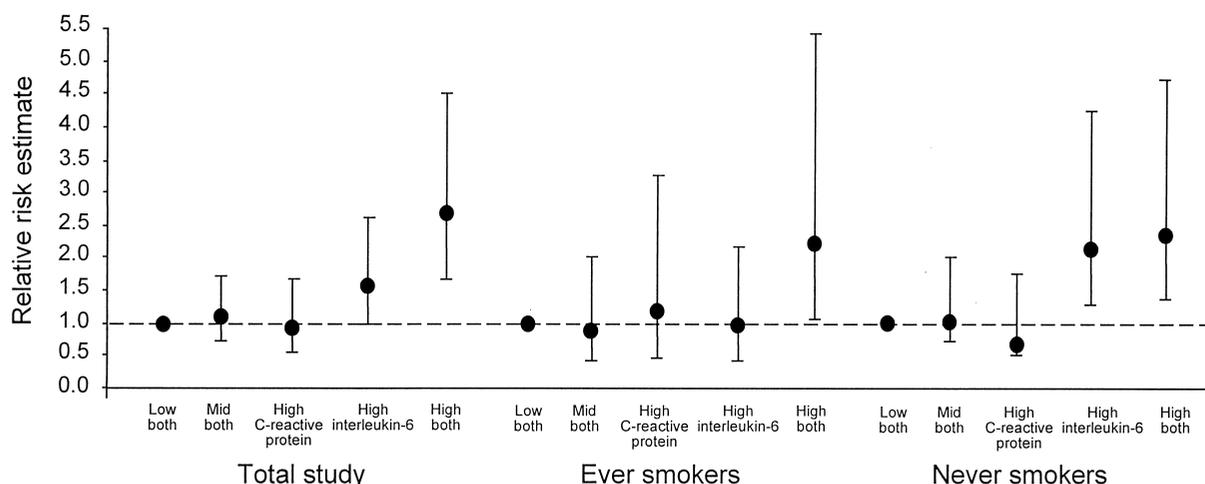


Figure 1. Combined levels of interleukin-6 and C-reactive protein and risk of mortality for the total study population (N = 675) and for subgroups defined by smoking history (ever smokers, n = 194, never smokers, n = 481). **Dots** represent relative risk estimates, and the **bars** represent 95% confidence intervals, adjusted for risk factors in Table 2. Low both is the reference category and includes values below the median for interleukin-6 levels (<2.08 pg/mL) and C-reactive protein levels (<1.57 mg/L); **Mid both** indicates C-reactive protein or interleukin-6 mid-range values but neither high; **High C-reactive protein** indicates high C-reactive protein levels only (C-reactive protein ≥2.78 mg/L and interleukin-6 <3.19 pg/mL); **High interleukin-6** indicates high interleukin-6 levels only (interleukin-6 ≥3.19 pg/mL and C-reactive protein <2.78 mg/L); and **High both** indicates both interleukin-6 and C-reactive protein levels in the highest quartile (interleukin-6 ≥3.19 pg/mL and C-reactive protein ≥2.78 mg/L).

Table 3. Joint Association between Interleukin-6 and C-Reactive Protein Levels and All-Cause Mortality, by Selected Characteristics

| Interleukin-6, C-Reactive Protein Categories [‡] | Stratified by Gender,* Relative Risk (95% confidence interval) | | Stratified by History of Cardiovascular Disease, [†] Relative Risk (95% confidence interval) | |
|---|--|------------------|---|--|
| | Men n = 279 | Women n = 396 | History of Cardiovascular Disease, n = 121 | No Cardiovascular Disease, n = 554 |
| Low both (n = 227) | 1.0 | 1.0 | 1.0 | 1.0 |
| Mid both (n = 176) | 1.0 (0.5, 1.9) | 1.1 (0.6, 2.1) | 0.8 (0.4, 2.0) | 1.1 (0.6, 2.0) |
| High C-reactive protein (n = 89) | 1.5 (0.7, 3.2) | 0.3 (0.1, 1.2) | 1.1 (0.4, 3.2) | 0.8 (0.4, 1.7) |
| High interleukin-6 (n = 93) | 1.1 (0.5, 2.4) | 2.5 (1.2, 5.0) | 0.9 (0.4, 2.3) | 2.3 (1.2, 4.2) |
| High both (n = 90) | 2.8 (1.4, 5.5) | 2.0 (0.9, 4.4) | 2.9 (1.1, 8.2) | 2.3 (1.3, 4.1) |

* Adjusted for age, smoking status, prevalent cardiovascular disease, diabetes, body mass index.

[†] Adjusted for age, sex, prevalent cardiovascular disease, diabetes, body mass index.

[‡] Low both (reference): values below the median for interleukin-6 levels (< 2.08 pg/mL) and C-reactive protein levels (< 1.57 mg/L); mid both: C-reactive protein or interleukin-6 mid-range values but neither high; high C-reactive protein: high C-reactive protein levels only (C-reactive protein \geq 2.78 mg/L and interleukin-6 < 3.19 pg/mL); high interleukin-6: high interleukin-6 levels only (interleukin-6 \geq 3.19 pg/mL and C-reactive protein < 2.78 mg/L); high both: both interleukin-6 and C-reactive protein levels in highest quartiles (interleukin-6 \geq 3.19 pg/mL, C-reactive protein \geq 2.78 mg/L).

differences did not reach statistical significance. Cancer history and alcohol use were not related to interleukin-6 or C-reactive protein level (data not shown). Subjects with both elevated interleukin-6 and C-reactive protein levels had greater fibrinogen levels [age, sex-adjusted mean for group = 355 \pm 90 vs 286 \pm 53 mg/dL in those with low interleukin-6 and C-reactive protein levels ($P = .0001$)], higher white blood cell counts [7.6 \pm 3.2 vs 5.7 \pm 1.8 cells/ μ L ($P = 0.0001$)], and lower albumin levels [39.9 \pm 2.4 vs 41.6 \pm 2.6 g/L ($P = 0.0001$)].

Mortality Risk

Greater interleukin-6 levels were associated with a two-fold increase in the risk of death, comparing subjects in the highest quartile (\geq 3.19 pg/mL) with the lowest quartile (RR = 1.9; CI, 1.2 to 3.1, Table 2). Interleukin-6 levels were associated with both cardiovascular and other causes of mortality. C-reactive protein levels showed similar, but weaker, associations (Table 2). Inclusion of the use of anti-inflammatory drugs or antioxidants did not change these results.

The joint elevation of interleukin-6 and C-reactive protein levels was associated with 2.6 times greater mortality (Figure 1) when compared with lower values for both. The increased risk of mortality was present in both early (<2.3 years, RR = 3.5; CI, 1.7 to 7.1) and later follow-up (RR = 2.4; CI, 1.3 to 4.5). Risk was similar for cardiovascular mortality (RR = 2.7; CI, 1.4 to 5.4) and for all-other mortality (RR = 2.4; CI, 1.2 to 4.6). The increased mortality associated with joint elevation of interleukin-6 and C-reactive protein levels was independent of other indicators of systemic inflammation including albumin level (RR = 2.4; CI, 1.5 to 4.0), white blood cell count (RR = 2.5; CI, 1.5 to 4.1), fibrinogen level (RR = 2.2; CI, 1.3 to 3.7) or all three inflammatory indicators (RR = 1.9; CI, 1.1 to 3.4). Participants with high inter-

leukin-6 levels in the absence of high C-reactive protein levels also had an increased risk of death (data not shown). High C-reactive protein levels in the absence of high interleukin-6 levels were not associated with mortality.

In separate analyses among ever smokers and never smokers, the risk of death associated with elevated interleukin-6 and C-reactive protein levels was at least twofold higher than for the group with low interleukin-6 and low C-reactive protein levels (Figure 1). Similar results were found when the study sample was stratified by sex and by history of cardiovascular disease (Table 3). In these analyses, women, never smokers, and those with no history of cardiovascular disease who had high levels of interleukin-6 in the absence of high C-reactive protein levels also had increased mortality.

DISCUSSION

In this population-based study, moderately high levels of interleukin-6 and C-reactive protein were associated with increased mortality. Joint elevation of interleukin-6 and C-reactive protein levels was associated with mortality in the overall sample, as well as in ever and never smokers, and those with and without a history of cardiovascular disease. Our findings extend the results of previous studies of the associations between acute phase proteins and cardiovascular disease (1–6) by demonstrating a clear association between interleukin-6 levels and mortality. Furthermore, the risk associated with inflammation is a general phenomenon that is not limited to specific subgroups, such as those already affected by cardiovascular disease or who have cardiovascular risk factors. The increased risk is associated with levels of interleukin-6 and C-reactive protein that are not thought to be clinically

important, and it persists after adjustment for health factors associated with inflammation.

Interleukin-6 is a pleiotropic cytokine involved in the regulation of the immune response, including the acute phase response and hematopoiesis, as well as the regulation of bone metabolism (23). Interleukin-6 promotes coagulation in experimental animals (15,24), and C-reactive protein stimulates tissue factor production (25) and neutrophil aggregation. The propensity to coagulation could indicate a direct contribution of interleukin-6 and C-reactive protein to mortality. In our study, subjects with both high interleukin-6 and high C-reactive protein levels had significantly greater fibrinogen levels. Risk at these levels of interleukin-6 and C-reactive protein may also indicate chronic low-level inflammation that represents an immune "dysregulation" with aging (26). However, it is also possible that both interleukin-6 and C-reactive protein levels are indirect indicators of specific underlying conditions that increase risk. Inflammation may be due to infectious causes of atherosclerosis (7,27). Greater C-reactive protein levels identify persons at risk of progression of cardiovascular disease (1,2). Higher circulating interleukin-6 levels have been reported in severe congestive heart failure (11) and are prognostic indicators in multiple myeloma (8). Higher interleukin-6 levels may also reflect cellular damage, such as oxidative stress (28). Lastly, interleukin-6 may counterregulate levels of tumor necrosis factor- α and interleukin-1 β (29,30) so that higher interleukin-6 levels may reflect damage from other cytokines.

There is some evidence that the risk associated with inflammation can be modified. In a randomized trial, men with higher C-reactive protein levels who took aspirin had a lesser risk of myocardial infarction than those who did not take aspirin (3). Response to treatment in multiple myeloma may be associated with reductions in interleukin-6 levels (31). Treatment with antibodies to tumor necrosis factor- α has been reported to improve arthritis (9). In our study, use of anti-inflammatory drugs or antioxidants did not modify risk; however, we lacked information on dose and duration of use. Use of inflammatory markers, such as interleukin-6 or C-reactive protein, may identify patients at higher risk and improve the efficacy of anti-inflammatory interventions.

Our findings were based on single measurements of interleukin-6 and C-reactive protein levels from blood generally drawn in the morning or early afternoon. It is unclear whether interleukin-6 has a circadian pattern of circulation (32,33). However, in one study, the intraclass correlation coefficient was .87 for plasma interleukin-6 levels that were measured eight times during 36 days, suggesting stability for at least 1 month (34). A single measurement of C-reactive protein level correlates well with repeated measures for at least 6 months (19). Use of interleukin-6 and C-reactive protein levels in combination may increase the specificity for ongoing inflammation. C-reactive protein levels have been associated with

greater body mass index, history of cardiovascular disease, smoking, and diabetes (35,36). We found similar associations in our subjects, which, for the most part, were shared by interleukin-6. Age was the only exception, with high interleukin-6 levels associated with older age and C-reactive protein levels with younger age. The association between smoking and C-reactive protein levels has been demonstrated previously, but the association of past smoking with interleukin-6 levels deserves more attention. This association, previously reported in a cross-sectional study (26), raises the question of whether the physiologic effects of smoking on appetite, coagulation, and bone might be results of cytokine activation. Disability, a powerful risk factor for mortality, is associated with greater interleukin-6 levels (26). Therefore, finding an association between inflammation and mortality in the disabled elderly might be expected. Thus, we restricted our study to healthy, nondisabled older people, which simplifies the interpretation of these results and should allow generalizability to other populations.

In conclusion, we demonstrated an increased risk of death associated with elevated levels of interleukin-6 and C-reactive protein in nondisabled older persons. These findings may broaden our understanding of the health correlates and consequences of low-level inflammation, as well as providing a new way to identify high-risk subgroups for anti-inflammatory interventions.

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