Inflammatory markers and cardiovascular health in older adults

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Abstract

In the past decade inflammatory markers have emerged as strong independent risk indicators for cardiovascular disease. Even though adults over the age of 65 experience a high proportion of such events, most epidemiologic data are from middle-aged populations. In this review we examine the role that inflammatory markers play in the prediction of incident cardiovascular disease specifically in older adults. In studies of adults > 65 years, IL-6, TNFα and IL-10 levels have been shown to predict cardiovascular outcomes. The data on C-reactive protein are inconsistent, but CRP levels appear to be less useful in old-age than in middle-age. Fibrinogen levels predict mortality but in a non-specific manner. In the elderly inflammatory markers are non-specific measures of health and predict both disability and mortality even in the absence of clinical cardiovascular disease. Thus it is possible that, in older age-groups, interventions designed to prevent cardiovascular disease through the modulation of inflammation would also be helpful in reducing disability and mortality.

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1. Introduction

Over the past two decades there has been a growing appreciation that the immune system plays a critical role at every stage of the atherosclerotic process from lesion initiation to the rupture of atherosclerotic plaque [1]. The involvement of the immune system is so central that atherosclerosis is now considered to be an essentially inflammatory phenomenon [2]. The inflammatory paradigm has be useful for interpreting a body of epidemiologic data and explains why serum levels of proteins such as ceruloplasmin, fibrinogen and albumin levels are related to cardiovascular disease risk [3,4]. These proteins are all “acute-phase” reactants meaning that they change in characteristic ways during the “acute” phase of injury and infection [5]. During acute inflammation some acute-phase reactants (C-reactive protein (CRP) and serum amyloid A) can increase many hundred-fold, others, like albumin, change less dramatically. Epidemiologic research in middle-aged populations has advanced understanding in this area by showing that even differences in CRP and other acute-phase proteins within the “normal” range discriminate those at high and low risk of atherosclerotic disease [6–9]. The purpose of this review is to examine the role of inflammatory markers for the prediction of cardiovascular events in older persons for whom data are considerably sparser.

In 2002, the American Heart Association and the Centers for Disease Control convened a workshop to make recommendations on how inflammatory markers should be used in conjunction with other assessments of cardiovascular risk [10]. The report focused on CRP because of the availability of standardized measurements and the large body of findings available. The workshop’s report said that the measurement of CRP could add value in predicting coronary events, and though it recommended against general population screening thought that CRP might be useful in those with a 10-year absolute risk of coronary heart disease (CHD) from 10% to 20% [10]. This recommendation has important implications for older adults. By virtue of age the Framingham risk...
equations indicate that virtually all American men and a large proportion of women over the age of 65 have a 10-year CHD risk of at least 10%, so the workshop recommendation would appear to apply to most older adults [11]. It should be noted, however, that almost none of the evidence on which this recommendation is based comes from elderly populations.

Extrapolating from middle- to old-age is problematic for a number of reasons. (1) The predictable ability standard risk factors to predict events changes in elderly populations. For example, total serum cholesterol and LDL-cholesterol are weaker predictors of future events in old age [12,13]. Indeed in some elderly populations, low cholesterol levels are associated with elevated risk [14,15]. Because of this, there is a great need for better cardiovascular risk markers in old age. (2) Older adults have a significant burden of subclinical vascular disease. In fact, the prevalence of subclinical disease in the Cardiovascular Health Study (CHS) among participants (all aged 65 years and older) with no evidence of clinical cardiovascular disease was 54% [16]. It is not clear that the strength of risk factors associations is the same in the context of significant subclinical disease. (3) Older adults are also much more likely to have comorbidities that are themselves associated with inflammation [17,18]. (4) Finally, the spectrum of cardiovascular pathology may change with age. In a review of sudden cardiac death cases, Burke et al. found evidence of acute thrombosis in a much higher proportion of younger sudden cardiac death cases than in older sudden cardiac death cases [19]. Because it is potentially misleading to directly apply results from middle-aged populations to older populations, it is important to specifically examine the evidence relating markers of inflammation to cardiovascular disease risk in adults over the age of 65.

2. C-reactive protein

The inflammatory process is complex and incompletely understood. The inflammatory response is initiated when inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)α are released from distressed tissue [20]. These in turn lead to the release of IL-6, the cytokine that is primarily responsible for the induction of acute phase protein production by the liver [5]. The panel of changes in protein synthesis involves dozens of proteins, including a large increase in the production and release of CRP, less dramatic increases in the synthesis of other proteins such as fibrinogen, and the inhibition of synthesis of others, such as albumin.

CRP has been the most frequently studied inflammatory marker in epidemiologic studies. CRP is involved both in innate immunity and in the removal of necrotic and apoptotic cells [21]. CRP has pro- and anti-inflammatory properties. In cell culture CRP stimulates IL-18 production, a recently discovered cytokine that appears to be a very strong independent predictor of CHD risk in middle-aged men [22,23]. In addition to inducing inflammatory cytokines in monocytes, CRP also appears to buffer against inflammatory damage [5,24]. Because of its central role in the acute-phase there has been a question whether CRP is a true risk factor for CHD or an indicator of on-going inflammatory activation associated with developing atherosclerotic disease. The distinction is important for developing novel therapeutic strategies, but is less important in the identification of individuals at high risk in the population. The AHA working group has suggested that persons with CRP levels greater than 3 mg/L be considered at high risk [10]. Values over 10 mg/L are considered to be consistent with an active inflammatory process [5]. Elevated risk of cardiovascular disease is typically observed among those with CRP values above 2 mg/L, but in some studies elevated risk is seen above 1 mg/L [6]. In a recent meta-analysis of 22 studies, Danesh et al. reported the relative risk for coronary heart disease to be 50% higher for those with CRP levels in the highest third of the respective study populations compared to those with levels in the lowest third [25]. CRP levels appear to increase modestly with age through middle age in men, but not in women [26–28]. There is little evidence for a continuing increase above the age of 70 [29]. Several cardiovascular disease risk factors are associated with higher CRP levels including, smoking, blood pressure, diabetes, body mass index, and abdominal adiposity [26–32]. CRP is associated with lower HDL cholesterol and higher triglyceride levels, but is, at best, only weakly associated with total and LDL cholesterol levels [26,28,30,33,34]. Levels are higher in women taking oral hormonal replacement therapy [35,36]. It is noteworthy that large scale randomized trials used oral conjugated equine estrogens in women initiating therapy relatively late in life [35,37]. No large trials have evaluated 17β-estradiol. However, the few small comparative trials show oral conjugated equine estrogens increase CRP levels but oral low dose oral and transdermal 17β-estradiol do not [38,39]. Route of administration may also be important as transdermal administration has less of an effect on inflammation than oral administration [40,41]. CRP levels are lower in physically active older adults [42]. The pattern of association between CRP and alcohol consumption mirrors the relationship between alcohol consumption and vascular risk in that non-drinkers and heavy drinkers have higher CRP levels than light-to-moderate drinkers [43].

3. CRP and incident CHD in older adults

There are relatively few studies focusing specifically on the relationship between CRP and cardiovascular disease in older adults (see Table 1). Tracy et al. examined the relationship between CRP and incident CHD in a nested case-control study conducted in participants aged 65 years and older enrolled in the Cardiovascular Health Study (CHS) [44]. While there was no overall statistically significant finding in either men or women, CRP did predict the onset of
future events in women with evidence of subclinical cardiovascular disease at baseline (highest CRP quartile \[N \geq 2.79 \text{ mg/L}\] vs. lowest quartile \[b 0.97 \text{ mg/L}\]—all events OR 2.33; 95% CI 0.90–6.07; incident myocardial infarction OR 4.5; 95% CI: 0.97–20.83). CRP levels were especially elevated in women whose events occurred within the first 12 months of follow-up. Tracy et al. [44] confirmed these findings showing that women who developed CHD over the three years of follow-up had significantly higher levels of CRP at baseline compared to controls, but no adjustment for other CHD risk factors was applied.

Cesari et al. evaluated CRP in a cohort of 2225 participants, aged 70–79 years free of clinical cardiovascular disease and followed for up to 4 years [45]. Participants with CRP levels in the highest tertile \(>2.50 \text{ mg/L}\) were not at significantly elevated risk of incident CHD after adjusting for smoking, diabetes, hypertension, body mass index, HDL cholesterol, triglyceride levels and albumin levels. There was no statistical evidence for a gender interaction.

Harris and colleagues, Strandberg and Tilvis, and Tice et al., all examined the relationship between CRP and cardiovascular (CVD) mortality which included both stroke and coronary death [29,46,47]. Harris found a non-significant risk elevation in participants with CRP levels \(z 2.78 \text{ mg/L}\) (RR=1.8; 95% CI 0.9–3.6). In the Helsinki Heart Study, Strandberg and Tilvis found an increased risk of 10-year cardiovascular mortality in participants with CRP levels \(z 5 \text{ mg/L}\) \((p=0.023). In a case-control study nested within the Study of Osteoporotic Fractures cohort (including only older Caucasian women), Tice et al. reported an eight-fold increased relative risk in women with CRP levels over 3 mg/L compared to women with levels at or below 1 mg/L. However, there were very few deaths studied \((n=50)\) and the precision of the estimate was low (95% CI 2.2–29).

3.1. C-reactive protein and stroke

Several studies have examined the relationship between CRP and ischemic stroke. In the Framingham cohort [48], after multivariate adjustment, a significant trend was reported between risk of stroke or TIA and CRP concentrations in both genders, but the categorical analysis showed

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Age-range (%) Male</th>
<th>Follow-up (years)</th>
<th>Outcome (no. of events)</th>
<th>Statistical adjustment factors</th>
<th>CRP levels (mg/L) and associated relative risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracy, 1997 [44]</td>
<td>65+ (43%)</td>
<td>3</td>
<td>Incident CHD* (146)</td>
<td>Sex, subclinical disease</td>
<td>(&gt;2.78 \text{ vs. } \leq 2.79) men: 1.07</td>
</tr>
<tr>
<td>Tracy, 1997 [44]</td>
<td>65–79 (43%)</td>
<td>3</td>
<td>Incident CHD (145)</td>
<td>Sex, age</td>
<td>(Q_1 \text{ vs. } Q_{1–4}) men: 2.0</td>
</tr>
<tr>
<td>Harris, 1999 [29]</td>
<td>65+ (41%)</td>
<td>4.6</td>
<td>CVD death (74)</td>
<td>Age, sex, prevalent CVD, smoking diabetes, BMI</td>
<td>(&lt;0.91\text{–1.57} 1.0)</td>
</tr>
<tr>
<td>Gussekloo, 2000 [50]</td>
<td>85+ (33%)</td>
<td>5.0</td>
<td>Fatal stroke (80)</td>
<td>Age, sex, smoking status, total cholesterol, Diabetes, hypertension, NSAIDS, CVD</td>
<td>(&lt;5\text{–10 2.1} 1.2)</td>
</tr>
<tr>
<td>Strandberg, 2000 [46]</td>
<td>75–85 (28%)</td>
<td>10</td>
<td>CVD death (139)</td>
<td>Age, sex</td>
<td>Per 10 mg/L (1.2)</td>
</tr>
<tr>
<td>Rost, 2001 [48]</td>
<td>60–90 (40%)</td>
<td>14</td>
<td>Incident ischemic stroke or TIA (196)</td>
<td>Age, sex, systolic blood pressure, cigarette smoking, total HDL-C, diabetes</td>
<td>(&lt;1.1\text{–1.3} 0.9)</td>
</tr>
<tr>
<td>Cao, 2003 [49]</td>
<td>65+ (41%)</td>
<td>10.2</td>
<td>Incident ischemic stroke (469)</td>
<td>Age, gender, race, diabetes, hypertension, systolic bp, total cholesterol, smoking status</td>
<td>(&lt;1.12\text{–2.05 1.6} 2.1)</td>
</tr>
<tr>
<td>Cesari, 2003 [45]</td>
<td>70–79 (45%)</td>
<td>3.6</td>
<td>Incident CHD (188)</td>
<td>Age, gender, race smoking, diabetes, hypertension, BMI, HDL-C, triglyceride, albumin</td>
<td>(&lt;1.15\text{–2.50 1.1} 1.0)</td>
</tr>
<tr>
<td>Tice, 2003 [47]</td>
<td>65+ (0%)</td>
<td>6</td>
<td>CVD death (50)</td>
<td>Age, hypertension, LDL- and HDL-C, diabetes, smoking, BMI, estrogen use, education site.</td>
<td>(&lt;1.1\text{–1.3} 5.3)</td>
</tr>
</tbody>
</table>

*Abbreviations: CHD—coronary heart disease, CVD—cardiovascular disease; BMI—body mass index; HDL-C—High density lipoprotein cholesterol; LDL—low density lipoprotein; NSAIDS—non-steroidal anti-inflammatory drugs.

1 Highest quintile of the CRP distribution compared to the lower 4 quintiles.
a significant association only in women (RR=2.1; 95% CI: 1.2–3.8 for highest quartile [≥6.9 mg/L]). In men, the relative risk was 1.6 (95% CI: 0.87–3.1). In adjusted analyses from the CHS study, Cao et al. [49] showed that participants with CRP≥4.3 mg/L had a 1.6 fold increase in the rate of stroke incidence compare to those with CRP<1.12 mg/L. There was a statistically significant interaction (p<0.05) between CRP and IMT, and CRP was only associated with stroke in those with higher IMT levels. In the Health ABC cohort, there was a non-significant association with incident stroke [45]. Gussekloo et al. [50] found that very old persons with CRP levels above 5 mg/L had a significant increase in the risk of fatal stroke after adjustment for potential confounding factors. To some extent, this relationship was driven by deaths occurring close to baseline.

The Honolulu Heart Study explored the relationship of CRP levels with myocardial infarction and stroke from a case-control study nested within a cohort of Japanese-American men (follow-up 20 years) [27,51]. The median CRP level among controls (0.56 mg/L) was substantially lower than in most other population-based studies. Among men 48–55 years of age, those with CRP levels over >1.0 mg/L had 2 times (OR=2.0; 95% CI: 1.2–3.2) the risk of developing myocardial infarction, and 3 times the risk of developing thromboembolic stroke (OR=3.0; 95% CI: 1.4–6.4) compared to men with CRP levels ≤1.0 mg/dL after adjusting for multiple risk factors. Results were much weaker in the participants aged 56–70 years (myocardial infarction OR=1.4; 95% CI: 0.9–2.2; stroke OR=1.3; 95% CI: 0.8–2.0). The apparent reduction in the strength of the relationship with age was also found in the Quebec Cardiovascular study where a strong association was seen only in men aged 55 years or younger [52].

### 4. Interleukin-6

Gerontologic interest in IL-6 predates the interest in its role in cardiovascular disease [53]. Many problems common older adults—anorexia, lethargy, anemia and the catabolism of muscle—can be induced by IL-6. A wide variety of cells in the body can both make IL-6 and respond to IL-6 [20]. It has been recently shown that subcutaneous fat produces IL-6 and that adipose tissue may be responsible for a considerable proportion of circulating IL-6 levels [54]. In the cardiovascular context, IL-6 is an important activator of immune cells, and may be important in the destabilization of atherosclerotic plaque [20,55,56]. CRP and IL-6 levels are associated with correlation coefficients typically near 0.5 [34,57]. IL-6 levels also mirror cardiovascular risk factors in a fashion similar to CRP, though hormone replacement therapy is not associated with higher IL-6 levels [34,35,58]. As noted above, these studies used conjugated equine estrogens, and therefore, these results may not apply for other sex hormones. Higher IL-6 levels are found with advancing age [29,59,60].

IL-6 in older adults has been examined in three studies (see Table 2). Cesari et al. found IL-6 to be a better predictor of incident coronary disease than CRP [45]. Its relationship to incident stroke was particularly strong (RR=3.7; 95% CI:1.67–8.21). Harris et al. also found IL-6 to be a stronger predictor than CRP for predicting cardiovascular mortality [29]. Jenny et al. looked at IL-6 levels in a study that compared several subgroups selected from the CHS cohort [61]. One group consisted of participants with incident cardiovascular events (MI, stroke, angina) drawn from participants free of clinical cardiovascular disease at baseline. One comparison group was a sample of those who at baseline had no evidence of either clinical or subclinical CVD. Another comparison group was a sample of those who at baseline had no clinical CVD but some evidence of subclinical disease. IL-6 levels strongly discriminated between those with subclinical CVD and those with no subclinical CVD. However, IL-6 did not clearly predict incident CVD cases when compared to controls with evidence of subclinical disease. These findings are difficult to interpret because the source population of the cases (participants free of clinical CVD at baseline) is dissimilar to the actual comparison group used (participants free of clinical CVD but with evidence of subclinical disease). Among the clinical outcomes examined in this study, IL-6 was significantly higher among those going on to have stroke compared to both comparison groups. The association between subclinical disease and IL-6 is consistent with data from Health ABC finding that both IL-6 and TNFα are higher in older adults with subclinical cardiovascular disease [57].

### 5. Other inflammatory markers

TNFα is an important initiator of the inflammatory response, but it has not been frequently measured in epidemiologic studies [5]. In Health ABC, it was moderately correlated with IL-6 (Spearman’s r=0.27) and weakly correlated with CRP (r=0.12) [57]. Cesari et al. found a stronger relationship between TNFα and CHD incidence than with either IL-6 or CRP but no relationship with stroke [45].

Elkind et al. evaluated the association between TNFα and TNF receptor 1 and receptor 2 levels and maximal carotid plaque thickness in those above and below 70 years of age [62]. In participants younger than 70 years of age, levels of both receptors were associated with increased maximal plaque thickness. In participants over the age of 70 there was no significant association between any marker and plaque thickness.

IL-10 is an anti-inflammatory cytokine that inhibits the production of a variety of inflammatory cytokines such as IL-2, TNFα and IFN-γ, and it is strongly associated with
Table 2
Studies of inflammatory markers other than C-reactive protein and cardiovascular risk in older adults

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Age-range (% Male)</th>
<th>Follow-up (years)</th>
<th>Outcomes (no. of events)</th>
<th>Statistical adjustment factors</th>
<th>Marker and relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenny, 2002 [61]</td>
<td>65+ (39%)</td>
<td>5</td>
<td>Incident CVD, new MRI* detectable infarcts (200)</td>
<td>Age, sex, race, study site</td>
<td>IL-6 (pg/ml)</td>
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<td>≤1.27 reference group</td>
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<td>1.27-1.84 1.34</td>
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<td>1.84-2.79 1.40</td>
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<td>≥2.79 1.09</td>
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<td></td>
<td>（comparison group had subclinical CVD）</td>
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<td>Harris, 1999 [29]</td>
<td>65+ (41%)</td>
<td>4.6</td>
<td>CVD death (74)</td>
<td>Age, sex, prevalent CVD, smoking, diabetes, BMI</td>
<td>IL-6 (pg/ml)</td>
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<td>&lt;1.46 reference group</td>
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<td>1.46-2.08 1.5</td>
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<td>2.08-3.19 1.0</td>
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<td>≥3.19 2.2²</td>
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<tr>
<td>Cesari, 2003 [45]</td>
<td>70–79 (45%)</td>
<td>3.6</td>
<td>Incident CHD (188) Stroke (60)</td>
<td>Age, gender, race smoking, diabetes, hypertension, BMI, HDL-C, triglyceride, albumin</td>
<td>IL-6 (pg/ml)</td>
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<td>&lt;1.35 reference group</td>
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<td>1.35-2.29 1.2</td>
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<td>≥2.29 2.0</td>
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<td>3.2³</td>
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<td>＜2.61 Stroke reference group</td>
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<td>2.61-3.61 1.4</td>
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<td>＞2.29 1.8³</td>
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<tr>
<td>Van Exel, 2002 [65]</td>
<td>85 (33%)</td>
<td>2.6</td>
<td>Stroke death (26)</td>
<td>Gender, diabetes, hypertension, use of NSAIDS, cardiovascular disease</td>
<td>IL-10 (stimulated production) per 500 pg/ml</td>
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<tr>
<td></td>
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<td>0.67³</td>
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<tr>
<td>Tracy, 1999 [70]</td>
<td>65+ (40%)</td>
<td>6.3</td>
<td>Incident angina (589), CHD (521), Stroke/TIA (473)</td>
<td>Age, race, clinic, smoking status, pack-years of smoking diabetes, hypertension, body mass index, HDL and LDL-C, subclinical CVD</td>
<td>Fibrinogen (mg/dL)</td>
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<td>Per 1 SD CHD Men</td>
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<td>1.16³ NS</td>
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<td></td>
<td></td>
<td></td>
<td>Stroke/TIA Women NS</td>
</tr>
<tr>
<td>Yano, 2001 [68]</td>
<td>71–93 (100%)</td>
<td>4.4</td>
<td>CVD, circulatory disease death (258)</td>
<td>BMI, total and HDL-C, triglyceride, hematocrit, white blood cell count, physical activity, smoking, hypertension, diabetes, preexisting CHD, stroke and cancer</td>
<td>Fibrinogen (mg/dL)</td>
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<tr>
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<td></td>
<td>Per 1 SD (64 mg/dL) CVD</td>
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<td>All-cause 2.7³</td>
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</tbody>
</table>

*Abbreviations: MRI—magnetic resonance imaging; CHD—coronary heart disease, CVD—cardiovascular disease; BMI—body mass index; HDL-C—High density lipoprotein cholesterol; LDL—low density lipoprotein; NSAIDS—non-steroidal anti-inflammatory drugs; TIA—transient ischemic attack; NS—not statistically significant. Highest tertile of the IL-10 distribution compared to the lowest 2 tertiles.

³ P<0.05.
better prognosis in patients with acute coronary syndromes [63,64]. Van Exel et al. found IL-10 to be strongly inversely correlated with stroke mortality in the Leiden 85-Plus study [65]. IL-10 has not been evaluated in any other epidemiologic study in older persons.

6. Fibrinogen

Fibrinogen is a component of the coagulation cascade and a determinant of blood viscosity [66]. Elevated fibrinogen levels also increases platelet reactivity [66]. There is some inconsistency as to whether fibrinogen is considered an inflammatory marker. It is clear that it is responsive to inflammatory stimuli; during the acute-phase its levels can increase 100–200% over baseline [5]. However, there is a close interaction between the inflammatory system and the hemostatic system [67]. Inflammatory stimuli can prime the coagulation system, down regulate the proteins involved in the control of the coagulation response, and impair fibrinolysis. Similarly, proteins in the coagulation pathways can affect inflammatory pathways. In epidemiologic studies, fibrinogen and CRP levels are correlated to a similar extent as that seen between IL-6 and CRP [34,68]. Fibrinogen levels are also associated with cardiovascular risk. In a recent meta-analysis Danesh et al. estimate the relative risk for CHD for those in the upper third of the distribution (~350 mg/dL) to be 80% higher compared to those with levels in the lower third (~<250 mg/dL) [3]. This is a stronger association than they found for CRP [25]. In at least two studies, when both fibrinogen and CRP were entered into the same multivariate model fibrinogen diminished CRP’s association with cardiovascular events to non-significance, indicating that fibrinogen might be the better measure of the two [32,69].

Tracy et al. evaluated fibrinogen as a predictor in the CHS cohort [70]. After adjustment for established risk factors fibrinogen was not associated with cardiovascular events in women. In men, it was significantly associated with CHD, stroke/TIA. Fibrinogen was also associated with all-cause mortality in men, and particularly for men dying within 2.5 years of baseline were the relative risk for the highest quintile was 5.8 times higher (95% CI: 3.1–11.0) than the lowest quintile. (Quintile cut-points were not provided.) However, it was still associated with increased risk in men more than 2.5 year after baseline.

Yano et al. evaluated the relationship between fibrinogen and total and cause-specific mortality in older Japanese men (aged 71–93) followed for 4.4 years [68]. After adjusting for multiple cardiovascular disease risk factors, the relative risk associated with a 1-standard deviation difference in fibrinogen (64 mg/dL) was 1.18 (95% CI: 1.03–1.36). Interestingly, fibrinogen was even more strongly associated with all-cause, cancer and non-cancer, non-CVD mortality in this population.

The relationship between fibrinogen and cardiovascular disease risk was evaluated over a wide age-span was evaluated in the Framingham study [71]. The 12-year risk of cardiovascular disease increased with increasing fibrinogen levels for women below the age of 70 but not for those above 70. In men, there was an association but no effect modification by age was seen. Age-stratified rates of incident CHD were not provided. However, age-adjusted relative risks comparing the upper tertile (≥312 mg/dL) to the lower tertile (<265 mg/dL) were provided for then entire population (ages 47–79) and the population excluding the older segment (ages 60–79). The relative risks for the entire population were 1.6 for men (p<0.05) and 1.8 (p<0.05) for women. For the younger segment the relative risks were 2.9 for men (p<0.01) and 2.3 for women (p<0.05) indicating a much weaker association among the older age-group. While multivariate modeling was done to adjust for multiple confounders, age-specific models were not presented.

7. Should inflammatory markers be evaluated in combination?

Because of the complexity and inter-relatedness of cytokine signaling and the proteins of the acute phase response, it is likely that no single biomarker can capture all of the important risk information. To address this issue Koukkunen et al. used factor analysis to extract an “inflammation factor” combining CRP, fibrinogen and IL-6 in a study of unstable angina [72]. TNFα did not load to this factor, but it was associated with Troponin T and Creatine kinase MB mass. The “inflammatory” factor was a strong predictor of the outcome, but whether the factor was stronger than any individual marker was not evaluated. Markers can also be combined to increase the specificity of the definition of inflammation. Cesari et al. combined IL-6, CRP and TNFα into a single measure by identifying participants with all three markers in the respective highest tertile [45]. In unadjusted models, this combination led to a stronger prediction of CHD events (relative risk=2.3; 95% CI: 1.5–3.5) compared to the single strongest individual predictor IL-6 (relative risk=1.7; 95% 1.3–2.3). Interactions between markers are also likely. In a cohort study of individuals with documented coronary artery disease only those with both high CRP and low IL-10 levels were at increased risk of acute myocardial infarction or death [64]. Yano et al. found a significant interaction between fibrinogen levels and white blood cell count [68]. Individuals with elevated levels of both were much more likely to die during follow-up. Harris et al. found a synergy between IL-6 and CRP in predicting mortality but only in men; those elevations in both were at increased mortality risk [29].

The markers evaluated in older adults represent only a proportion of potential markers that could be evaluated, and so it is understandable that the importance of combinations of markers has not been fully explored. In addition to
marker levels per se, future studies may find it useful to examine cytokine levels in relation to their soluble receptors which may be either inhibit or amplify the cytokine signaling [73].

8. Inflammatory markers predict more cardiovascular disease in the elderly

While there is great interest in the ability of inflammatory markers to predict cardiovascular outcomes, it should be noted that inflammatory processes have been implicated in a diverse set of chronic conditions affecting older adults ranging from depression, periodontal disease, pulmonary disease, osteoporosis, arthritis and cognitive impairment [16,59,74–76]. Indeed, in older adults inflammatory marker levels predict all-cause mortality as well as or better than they predict cardiovascular disease mortality [29,50,68]. Penninx et al. have shown that IL-6, CRP and TNFα levels predict the onset of mobility limitation even after excluding all participants with CVD at baseline or intercurrent CV events during follow-up [77].

9. Are inflammatory markers causally related to cardiovascular disease?

There is some debate as to whether inflammatory markers are signs of an active on-going disease process or causal determinants for the development of disease. The issue is important because of the implications for developing and targeting therapies. The importance of inflammatory processes in the progression of atherosclerotic disease and the development and rupture of plaque is strongly supported [1]. What is less clear is whether the cytokines measured in the blood derive primarily from the lesions themselves or whether the contributions from other tissues also accelerate the process. In mice, introducing physiologic levels of IL-6 can accelerate atherosclerosis [78]. In humans, autoimmune diseases associated with elevated cytokine activity are also associated with elevated risk of atherosclerotic disease [79–81]. Chronic infectious conditions such as periodontal disease are also associated with elevated disease risk [82–84]. On the other hand, data showing stronger associations with events occurring soon after baseline measurements than with later occurring events would suggest marker levels are elevated as a sign of an on-going pathologic process. Many studies in older adults have too short follow-up times to resolve this issue. Data in younger populations indicate a persistence of the prediction for many years [27]. In addition, while CRP is associated with clinical cardiovascular events, it is not associated with the extent of atherosclerosis suggesting that it is not involved in the early stages of atherosclerosis [10]. Tracy reviewing the data concluded that both interpretations are likely to be correct simultaneously [17]. Most data relates to CRP, and the situation may become clearer as other markers either alone or in combination are evaluated.

Many interventions are being evaluated for their ability to affect inflammatory marker levels. Several randomized trials show that HMG CoA reductase inhibitors (statins) lead to reductions in CRP [85–88]. The reduction in CRP associated with statins is not correlated with the degree of cholesterol reduction. This has been interpreted to mean that statins have an effect on inflammatory pathways independently of cholesterol lowering [85]. Direct immunomodulatory effects of statins have been demonstrated including the down-regulation of IFN-γ stimulated MHC-II expression, and on CD40 expression on atheroma-associated cells both in vitro and in vivo [89–91]. However, Jenkins et al. found a similar degree of CRP reduction associated with a diet that lead to similar cholesterol reductions as drug therapy [92]. Aspirin reduces IL-1 but not CRP [87,93,94]. Rofecoxib can lower IL-6 and CRP levels [95]. Emerging data linking rofecoxib use to increased cardiovascular mortality risk reduces the strength of arguments that the association between inflammatory markers and disease is causal [96,97]. It is certainly possible that the effect of rofecoxib on disease risk is through a non-inflammatory pathway, but the findings do suggest that inflammatory marker change per se may not be a reliable intermediate clinical trial endpoint. Angiotensin Converting Enzyme inhibitors and angiotensin II receptor blockers may have anti-inflammatory effects. Angiotensin II induces IL-6 synthesis and release in smooth muscle cells [56]. The administration of high dose enalapril (40 mg/day) was associated with reduced IL-6 levels in heart failure patients [98]. Angiotensin II type-1 receptor blockers have been shown to reduce CRP levels [99]. Thiazolidinediones have also been shown to reduce inflammatory markers though not IL-6 levels [100,101]. Randomized trials of exercise and weight loss show that both have the potential to reduce inflammatory marker levels [102,103]. However, in a study evaluating both interventions simultaneously, weight loss seemed to be the more important factor [104]. Oxidative stress can trigger inflammation, but supplemental vitamin C and α-tocopherol do not reduce CRP, IL-6 or TNFα [105]. However, in a post-hoc analysis of a randomized placebo-controlled trial, Church et al. found that a multivitamin/mineral supplement resulted in a statistically significant reduction in CRP levels [106]. Inflammatory markers have not been routinely evaluated in dietary intervention trials, but some data suggests that increasing omega-3 fatty acid intake may reduce inflammatory markers [107].

10. Conclusion

The role of the immune system and inflammatory pathways in the development of atherosclerotic disease is well established, and systemic markers of inflammation appear useful for indicating elevated cardiovascular disease
risk in middle-age. Although the incidence of cardiovascular events is extremely high in persons over 65 years of age relatively little epidemiologic data pertain specifically to this age-group. Studies including only elderly participants show that CRP and fibrinogen may not be as useful as other markers such as IL6 and TNFα. Several important issues require further investigation, however. The current evidence base is insufficient both because of the relatively few studies targeting older adults, and the limited number of markers that have been evaluated. Understanding which markers or sets of markers best predict risk in older adults is a high priority. Most studies that have looked at CHD risk in the elderly are of relatively short duration. Because inflammatory markers may indicate both the current inflammatory state and long-term risk, more work is needed to understand the ability of markers to predict over a longer periods of time in older populations. As markers are introduced into clinical practice, people will be observed with falling and rising marker levels. The implications of these changes are currently unknown. Finally, inflammatory markers predict functional decline in the elderly in addition to cardiovascular disease onset. Therefore, interventions that target inflammation for the prevention of vascular disease should also be evaluated for their ability to preserve function in older adults.

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References


