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Interpretation of Serum C-Reactive Protein (CRP) Levels for Cardiovascular Disease Risk is Complicated by Race, Pulmonary Disease, Body Mass Index, Gender, and Osteoarthritis

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Abstract

Objective—High sensitivity serum C-reactive protein (hsCRP) is used as a marker of risk for cardiovascular disease (CVD); however CRP is a non-specific acute phase reactant. We evaluated the association between hsCRP concentrations and the most common form of arthritis, osteoarthritis (OA), and assessed the applicability of hsCRP for CVD risk prediction.

Methods—Participants (n=662) were selected from the population-based Johnston County Osteoarthritis Project, using stratified simple random sampling to achieve balance according to radiographic knee OA status, ethnic group, gender, and age group. The presence and severity of knee and hip OA were determined radiographically. CVD risk was estimated by hsCRP concentration and independently with the Framingham risk algorithm.

Results—Serum ln hsCRP was higher in African-Americans ($p<0.0001$) and women ($p<0.0001$), was higher in participants who had chronic pulmonary disease ($p = 0.01$), hypertension ($p < 0.0001$), or used pain medications ($p = 0.004$), and correlated with BMI ($r=0.40$, $p<0.0001$) and waist circumference ($r=0.33$, $p<0.0001$), but not with age, CVD, or current smoking. Ln hsCRP was strongly positively associated with all definitions of radiographic OA ($p<0.0001$), but this association was not independent of BMI. Although 183 participants reported no CVD and were classified as low risk by the Framingham CVD score, 61% of them were classified as moderate or high risk for CVD using hsCRP; this proportion designated high risk for CVD on the basis of hsCRP consisted primarily of women ($p<0.05$) and individuals with OA ($p<0.01$).

Conclusions—The pathogenic significance of hsCRP elevations in this subgroup is unclear. Serum hsCRP for predicting risk of CVD is confounded by obesity, ethnicity, gender and comorbidities.

Keywords

C-reactive protein; osteoarthritis; cardiovascular disease risk

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BACKGROUND

The development of robust assays of superior sensitivity compared to those for basic CRP measurement, has allowed for the distinction of patients who have low levels of inflammation. These high-sensitivity CRP (hsCRP) assays have led to increasing use of this protein in the study of the inflammatory nature of many chronic diseases including atherosclerosis [1, 2] and OA [3]. Although CRP has been evaluated in the setting of OA for almost two decades, it was not until the advent of the high sensitivity assays that associations with the disease were recognized. Serum hsCRP concentrations are higher in individuals with OA [4, 5], and are associated with OA severity [6] and joint pain [7], as well as incident and progressive disease [8–11]. None of these studies has looked extensively at the impact of comorbidities on hsCRP in a population-based study, nor have any of these studies evaluated the impact of OA on the use of hsCRP for cardiovascular disease (CVD) risk assessment. This prompted us to evaluate the current published American Heart Association and Centers for Disease Control and Prevention (AHA/CDC) guidelines for estimating CVD risk based upon hsCRP concentrations, and the possible confounding of these guidelines by the presence of OA and other comorbidities, in an ethnically diverse, population derived sample.

2. Materials and Methods

2.1 Subjects

Participants for this Johnston County OA Project Biomarker Sub-study were selected from individuals in the baseline examination of the Johnston County Osteoarthritis Project, a population-based study of OA in rural North Carolina [12] and included males and females aged 45 years and older. Ethnicity (African American and Caucasian) was ascertained by self-report. From the 3,187 participants, 388 African-Americans and 820 Caucasians had an available serum sample drawn at the time of radiography plus either Kellgren-Lawrence (K-L) grade 0 in both knees and both hips (radiographic OA unaffected) or K-L grade ≥2 in at least one knee (radiographic knee OA affected). Of these participants, we selected all 388 African-Americans and randomly selected 394 Caucasians, in approximately equal numbers from the 12 cells obtained from the cross-classification of sex, age group (ages 45–54 years, 55–64 years,≥ 65 years), and OA status (affected/unaffected). Selection was independent of knee symptoms. The presence of 14 self-reported, current, physician-, nurse-, or health professional-diagnosed co-morbid conditions was assessed with an interviewer-administered questionnaire in a format similar to that used by the National Health Interview Survey [13]. These current conditions included chronic pulmonary disease (asthma, chronic bronchitis, or emphysema), cardiovascular disease (heart attack, angina, congestive heart failure, coronary heart disease, other ‘heart condition’, stroke, or circulation problems), high blood pressure, chronic gallbladder or liver trouble, kidney, prostate or bladder trouble, diabetes or high blood sugar, insulin use, gout, rheumatoid arthritis, and cancer. We also ascertained information on the use of pain medications, current smoking status, and current hormone replacement therapy use (the last in women only). Participants with self-reported cancer, rheumatoid arthritis, and gout were excluded. After these exclusions, the sample numbered 662. Clinical measures included height (cm), weight (kg) measured with a balance beam scale to calculate body mass index (BMI in kg/m^2), and waist circumference (cm) measured at the level of the umbilicus. Blood pressure was measured three times in the right arm in the sitting position and the average of the 2nd and 3rd measurements used in the analyses. The Institutional Review Boards of the clinical site, the University of North Carolina at Chapel Hill, and the Centers for Disease Control and Prevention, approved all procedures.

2.2 Radiographic Measurements

Bilateral anteroposterior weight-bearing radiographs of the knees were performed on all participants. Anteroposterior supine pelvis radiographs were obtained on women 50 years of age or older and all men. A single musculoskeletal radiologist (JBR) scored all radiographs for Kellgren-Lawrence (K-L) radiographic grade [14] as described previously[12]. Non-OA controls were defined as K-L grade 0 in both knees and both hips; an OA case was defined as K-L grade ≥2 in at least one knee. Radiographic OA outcomes included knee OA (present or absent); knee OA laterality (none, unilateral or bilateral); knee OA severity (grades 0, 2, 3 or 4); concomitant knee and hip OA (none, knee only or present in knee and hip); and number of large joints with OA (0–4).

2.3 hsCRP Measurements

Serum samples were stored at −80°C prior to assay. Serum hsCRP concentrations were measured using the UBI Magiwel Enzyme Immunoassay (United Biotech Inc., Mountain View, CA) per the manufacturer's instructions and blinded to the clinical information. The assay is reported to have a minimum detectable concentration of 0.00035 mg/L. At a concentration of 0.003 mg/L, our inter-assay precision was 7.4% (n=20).

2.4 Cholesterol Measurements

Total serum cholesterol was measured enzymatically using cholesterol/HP reagent (Roche Diagnostics, Indianapolis, Indiana). High-density lipoprotein (HDL) was measured enzymatically using the "L-Type HDL-C" reagent kit (Wako, Richmond, VA) adapted to a microplate format per the manufacturer's instructions. The manufacturer's reported variability for this kit is 0.6–1.15% (intra-assay) and 0.59–2.8% (inter-assay). As with hsCRP, total cholesterol and HDL measurements were made blinded to the clinical information.

2.5 Framingham Risk Score for Cardiovascular Disease

The ten-year risk for CVD was computed for the participants without self-reported cardiovascular disease (n = 521) using the Framingham CVD risk prediction algorithm based upon the seven parameters of gender, age, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, smoking status and diabetes [15]. Participants were categorized as low (<10%), moderate (10–20%), or high risk (>20%) for future CVD based upon the Adult Treatment Panel III guidelines of the National Cholesterol Education Program [16].

2.6 Statistical Analysis

All statistical analyses were performed using SAS 8.2 software (SAS, Cary, NC). In order to satisfy the assumptions underlying the use of the statistical models, all analyses were done using natural log-transformed hsCRP (ln hsCRP) data. The Pearson correlation coefficients were determined for the relationship among ln hsCRP, age, BMI, and waist circumference. Analysis of covariance was used to assess differences in means of serum ln hsCRP concentrations between groups corresponding to ethnicity, gender, the presence and absence of self-reported chronic pulmonary disease, cardiovascular disease, hypertension, use of pain medications, smoking, diabetes, and insulin dependence. Analysis of covariance was also used to assess differences in means of serum ln hsCRP concentrations between groups corresponding to each definition of radiographic OA, while adjusting for age, ethnicity, gender, obesity (BMI or waist circumference), use of medications for arthritis pain, and selected self-reported co-morbid medical conditions associated with ln hsCRP in bivariate analyses.

For participants without self-reported CVD, we calculated the proportion within each of three CVD risk categories based upon hsCRP and established by a workshop sponsored by the AHA/CDC (< 1 mg/L low risk group, 1–3 mg/L average risk group, and > 3 mg/L high risk group)

[17]. Chi-square analysis was used to evaluate the proportions of participants who were low risk by Framingham scores but moderate or high risk by hsCRP concentrations, comparing OA and non-OA participants, and female and male participants. Female users of hormone replacement therapy were excluded for some analyses. A p value <0.05 was considered significant.

RESULTS

hsCRP, Osteoarthritis and Comorbidities

The sample consisted of 662 individuals, 48% African-Americans, 58% female, overall mean age (SD) of 61.4 (10.3) years, and mean BMI (SD) 30.0 (6.9) kg/m^2. Table 1 provides additional descriptive information for OA unaffected and affected subgroups. Strong associations were observed between ln hsCRP and all definitions of radiographic OA (Table 2). Additionally, the concentrations of ln hsCRP tended to increase on average with each successive joint involved with OA and with each successive increase in K-L grade of knee OA severity. An increase of one K-L grade of knee OA resulted in an average increase of 1.10 mg/L hsCRP (range 0.54–1.54 mg/L change in hs CRP per K-L grade over the range of K-L grades 0–4).

A moderate correlation was observed between ln hsCRP and BMI ($r = 0.40$, $p < 0.0001$), and waist circumference ($r = 0.33$, $p < 0.0001$), but not with age ($r = 0.01$, $p = 0.75$). Mean ln hsCRP was higher in African-Americans compared to Caucasians ($p < 0.0001$) and higher in women compared to men ($p < 0.0001$) (Table 3). The highest hsCRP concentrations were observed among African American women who had OA. In addition to OA, other conditions that might have affected hsCRP concentrations included chronic pulmonary disease, cardiovascular disease, hypertension, use of pain medication, current smoking, and diabetes, or insulin use. We found higher mean ln hsCRP concentrations in participants who had chronic pulmonary disease ($p = 0.01$), hypertension ($p < 0.0001$), or used pain medications ($p = 0.004$) however, concentrations were not significantly different on the basis of a self-report of CVD ($p = 0.36$) or current smoking ($p = 0.16$) (Table 3).

The associations of ln hsCRP with OA variables were greatly diminished after adjustment for age, ethnicity, gender, use of pain medications, chronic pulmonary disease, hypertension, diabetes, and waist circumference ($p=0.07$). When adjusted for the other covariates, ln hsCRP was independently associated only with BMI ($p<0.0001$), ethnicity ($p=0.009$), and chronic pulmonary disease ($p=0.007$).

hsCRP and CVD Risk Assessment

We calculated the Framingham risk score for the 521 participants without self-reported CVD (absence of heart attack, angina, congestive heart failure, coronary heart disease, other ‘heart condition’, stroke, or circulation problems) (Table 4). Of these 521 participants without self-reported CVD, 183 were classified as low risk by the Framingham CVD score; however, 61% of them were classified as moderate or high risk for CVD using hsCRP. Of those classified as low risk by Framingham score but moderate or high-risk by hsCRP concentration, 58% had OA ($p<0.01$ compared to the corresponding proportion among non-OA participants), and 86% were female ($p<0.05$ compared to the corresponding proportion among male participants).

DISCUSSION

High-sensitivity CRP was strongly associated with OA of the knees and hips. High-sensitivity CRP was also correlated with waist circumference and BMI, a strong risk factor for OA and OA progression. It remains unclear whether the association between hsCRP and OA is confounded by another factor present in those patients with obesity. CRP may be associated with obesity solely, or reflect the presence of underlying OA and the complex interaction of

OA and obesity. We believe that the CRP elevations associated with OA likely reflect a complex interaction of fat mass, joint inflammation, and systemic inflammation, as summarized in Figure 1. Obesity (fat mass) is both a mechanical risk factor for OA, capable of inducing localized joint degeneration and inflammation, and a contributor to a systemic proinflammatory state that could further exacerbate joint disease and promote CRP production by the liver [18, 19]. Moreover, the inflamed joint, in addition to fat mass, is potentially capable of increasing CRP synthesis by the liver by means of cytokines of joint tissue origin. Support for this hypothesis has been provided in a recent study of knee OA [20]. Serum hsCRP was positively associated with synovial inflammatory infiltrates, and synovial fluid IL-6 concentrations correlated with serum hsCRP concentrations. Taken together, these data suggest a direct link between the localized joint disease of OA and hsCRP production and support a complex interaction of factors acting in concert to promote CRP production.

We found a strong independent association of hsCRP and ethnicity, in agreement with a recent report that median hsCRP concentration was 30% higher in blacks than in whites in Dallas County, characterized as a typical multiethnic U.S. urban population [21]. Occult infection, such as periodontal disease, has also been found to be associated with elevated hsCRP concentrations in otherwise healthy individuals [22]. Taken together with the strong independent association of hsCRP with chronic pulmonary disease, and association with BMI, serum CRP is unlikely to be useful as a single biomarker of OA or, as described below, of cardiovascular disease.

Surprisingly, we did not find an association of hs-CRP with smoking or with self-reported CVD. However, these results are also in agreement with the large population-based Dallas Heart study of 3373 individuals, aged 30–65 years that found no association of hs-CRP with smoking and also no independent association of hs-CRP with atherosclerotic burden defined by either coronary artery calcification on cardiac electron-beam computed tomography scans or by abdominal aortic plaque on magnetic resonance images [23]. In our study, CVD risk was estimated by hsCRP and independently, using the Framingham risk algorithm, for the subgroup without CVD by self-report. The Framingham risk algorithm was based upon the population of Framingham, MA, but has been validated subsequently in diverse populations in the US [15, 24]. These two methods of CVD risk assessment were incongruent, with greater CVD risk levels attributed, on the basis of hsCRP, to women (even after excluding hormone replacement users [data not shown]) and participants with OA. The CDC has estimated that one in three US adults has arthritis and joint symptoms [25], among them OA, which accounts for the majority of cases of arthritis. Although it is recommended that hsCRP testing should be performed in a “metabolically stable person without obvious inflammatory or infectious conditions” and without a systemic inflammatory process [17], traditionally, individuals with OA would not be considered to have a metabolic or systemic inflammatory disease, and therefore, would not be exempt from testing by these criteria. Individuals who are obese with arthritis may therefore contribute substantially to the recently reported phenomenon that half of U.S. adults have hsCRP levels greater than 2 mg/L [26]. Thus, the Framingham risk score would appear to be a preferred method of assessing CVD risk in an OA patient based on our data, and the report by Wilson et al [27] that hsCRP does not add prognostic information for predicting future major CVD beyond the traditional “office risk assessment” provided by the Framingham risk score.

Conclusions

Ethnicity, chronic pulmonary disease, and obesity exert strong influences on serum hsCRP concentration and confound the prediction of CVD risk based upon hsCRP. This is particularly problematic for individuals with OA in whom obesity is prevalent, and whose disease state may provide a pro-inflammatory stimulus, difficult or impossible to separate from obesity.

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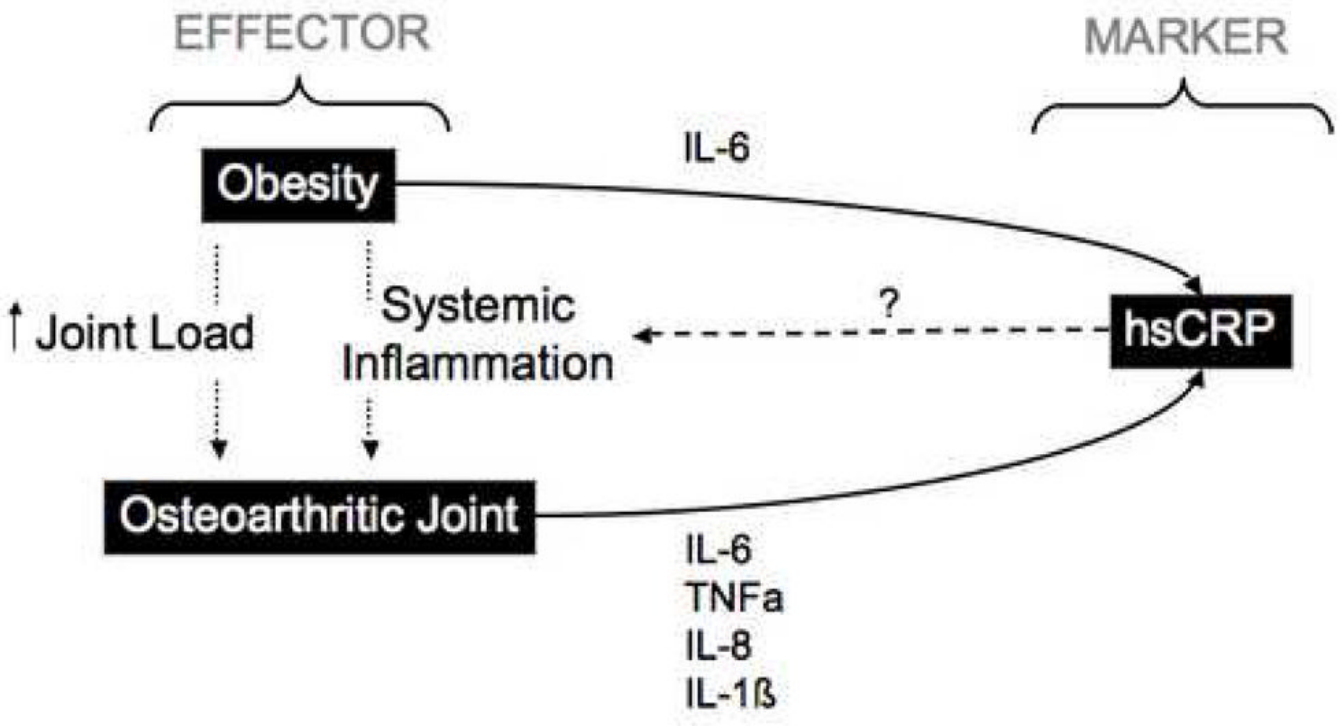

Figure 1. Osteoarthritis and obesity interact to promote C-reactive protein (CRP) production

In this model, both fat mass and the inflamed joint contribute to CRP induction by the liver. It is controversial whether CRP in turn, at high levels, may promote a proinflammatory state [see Pepys et. al. [28] and Bisoendial et. al. [29]].

Table 1

Demographics and clinical characteristics of the study participants.

	Osteoarthritis Unaffected* N=276	Osteoarthritis Affected** N=386
Age (years) (SD)	59.9 (9.2)	62.4 (10.9)
BMI (kg/m^2) (SD)	27.4 (4.60)	31.9 (7.59)
Female	50%	63.7%
African American	34.4%	61.1%
Chronic Pulmonary Disease	11.3%	8.9%
Cardiovascular Disease	22.1%	20.7%
Hypertension	33.1%	42.0%
Use of Pain Medication	28.5%	42.2%
Smoking	28.1%	12.8%
Diabetes	11.2%	14.8%
Insulin Use	5.4%	7.0%
hsCRP mean (SD) (mg/L)	3.38 (4.89)	5.88 (8.57)
hsCRP median (mg/L)	1.69	3.07

* Osteoarthritis unaffected = Kellgren-Lawrence radiographic grade 0 in both knees and both hips

** Osteoarthritis affected = Kellgren-Lawrence radiographic grade at least 2 in one or both knees BMI=body mass index, hsCRP=high sensitivity C-reactive protein in mg/L

Table 2

LnCRP by radiographic osteoarthritis affection status.

Group	N	Mean hsCRP (mg/L)	Mean Ln hsCRP	95% Confidence Intervals
Presence of knee rOA				
KL knee 0/KL hip 0	276	1.60	7.38	7.22 – 7.54
KL knee 2–4	386	2.56	7.85**	7.72 – 7.99
Knee rOA severity				
KL knee 0/KL hip 0	276	1.60	7.38	7.22 – 7.54
KL knee2	264	2.16	7.68*	7.52 – 7.84
KL knee 3	88	3.32	8.11**	7.82 – 8.39
KL knee 4	34	4.92	8.50**	8.05 – 8.96
Laterality of knee rOA				
KL knee 0/KL hip 0	276	1.60	7.38	7.22 – 7.54
Unilateral KL knee 2–4	192	2.07	7.64*	7.45 – 7.83
Bilateral KL knee 2–4	194	3.16	8.06**	7.87 – 8.25
Co-occurrence of knee & hip rOA				
KL knee 0/KL hip 0	276	1.60	7.38	7.22 – 7.54
KL knee 2–4/KL hip 0	218	2.27	7.73*	7.55 – 7.91
KL knee 2–4/hip 2–4	122	2.60	7.87*	7.62 – 8.11
Numbers of knees and hips with rOA				
0 joints affected	276	1.60	7.38	7.22 – 7.54
1 joint affected	115	1.75	7.47	7.22 – 7.72
2 joints affected	132	2.78	7.93**	7.70 – 8.16
3 joints affected	51	2.48	7.82*	7.45 – 8.19
4 joints affected	42	3.29	8.10*	7.69 – 8.51

Ln hsCRP = natural logarithm of high-sensitivity C-reactive protein in serum (for presentation purposes, hsCRP was expressed in μg/L prior to natural log transformation)

* $p < 0.05$ compared to control;

** $p < 0.0001$ compared to control Radiographic osteoarthritis (rOA) = Kellgren-Lawrence (K-L) grades 2–4

Table 3

Ln hsCRP and demographics and clinical characteristics.

		Mean hsCRP (mg/L)	Mean Ln hsCRP[§]	95% Confidence Intervals of Ln hsCRP
Race[**]	**Caucasian**	1.63	7.40	7.25 – 7.54
	African American	2.76	7.93	7.78 – 8.07
Gender[**]	**Male**	1.65	7.41	7.25 – 7.57
	Female	2.51	7.83	7.69 – 7.97
Chronic Pulmonary Disease[*]	**No**	2.01	7.61	7.50 – 7.72
	Yes	3.19	8.07	7.73 – 8.40
Cardiovascular Disease	**No**	2.03	7.62	7.50 – 7.74
	Yes	2.37	7.77	7.54 – 8.00
Hypertension[**]	**No**	1.77	7.48	7.35 – 7.61
	Yes	2.80	7.94	7.77 – 8.11
Use of Pain Medication[*]	**No**	1.86	7.53	7.40 – 7.66
	Yes	2.64	7.88	7.71 – 8.05
Smoking	**No**	2.18	7.69	7.57 – 7.81
	Yes	1.76	7.47	7.23 – 7.71
Diabetes[**]	**No**	1.94	7.57	7.46 – 7.68
	Yes	3.64	8.20	7.92 – 8.49
Insulin Use[*]	**No**	2.02	7.61	7.50 – 7.72
	Yes	3.86	8.26	7.84 – 8.68

Ln hsCRP = natural logarithm of high-sensitivity C-reactive protein in serum ([§]for presentation purposes, hsCRP was expressed in μg/L prior to natural log transformation)

[*] $p < 0.05$ compared to referent;

[**] $p < 0.0001$ compared to referent

Table 4

Cross-classification of participants for cardiovascular disease risk by both AHA/CDC (hsCRP) criteria and Framingham risk categories for the 521 participants without self-reported CVD.

		Framingham Risk Category					
		Osteoarthritis Unaffected (N, column %)			Osteoarthritis Affected (N, column %)		
		Low (N=90)	Moderate (N=86)	High (N= 57)	Low (N=93)	Moderate (N=119)	High (N=76)
AHA/CDC Risk Category	Low Risk	43 (48%)	36 (42%)	12 (21%)	29 (31%)	30 (25%)	20 (26%)
	Moderate Risk	20 (22%)	27 (31%)	17 (30%)	21 (23%)	24 (20%)	21 (28%)
	High Risk	27 (30%)	23 (27%)	28 (49%)	43 (46%)	65 (55%)	35 (46%)

Framingham Risk Category:10-year cardiovascular risk category defined as Low <10% Risk, Moderate 10–20% Risk, and High >20% Risk based upon Grundy et. al., 2004[16].

AHA/CDC Risk Category: American Heart Association and Centers for Disease Control and Prevention cardiovascular disease risk categories based upon hsCRP and defined as Low hsCRP < 1 mg/L, Moderate hsCRP 1–3 mg/L, and High hsCRP > 3 mg/L Risk based upon Pearson et. al., 2003[17].

hsCRP = high-sensitivity C-reactive protein in serum