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C - Reactive Protein, Inflammatory Conditions and Cardiovascular Disease Risk

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Abstract

Background—It is uncertain to what extent high C-reactive protein (CRP) concentrations reflect the presence of inflammatory conditions in the community.

Methods—We evaluated 3782 Framingham participants (mean age 55 years; 52% women) free of baseline cardiovascular disease. Logistic regression models examined the prevalence of common inflammatory conditions by CRP categories whereas a separate matched case-referent analysis evaluated the prevalence of uncommon inflammatory conditions. Cox models were used to assess the influence of common inflammatory conditions on relations between CRP and incident cardiovascular disease.

Results—Common inflammatory conditions were reported by nearly half of the participants; these individuals were more likely to have markedly-high CRP concentrations (>10mg/L, *P* for trend=0.001). In multivariable models, there were increased odds of having at least one common inflammatory condition with CRP concentrations of 1–3.0, 3.01–10, and >10mg/L, compared to the referent category (<1mg/L); the respective odds ratios with 95% confidence intervals were 1.41 (1.07–1.86), 1.45 (1.07–2.98) and 1.64 (1.09–2.47) in men, and 1.08 (0.82–1.43), 1.07 (0.80–1.44) and 1.38 (0.97–1.96) in women. In case-referent analyses, uncommon inflammatory conditions were more common in individuals with CRP >10mg/L compared to those with CRP <1mg/L (12.1% versus 6.6%; *P*=0.0001). In multivariable models, higher CRP categories were not associated with incident

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cardiovascular disease, and with additional adjustment for inflammatory conditions, results remained unchanged.

Conclusion— There is high prevalence of common and uncommon inflammatory conditions in individuals with high CRP concentrations. Higher CRP concentrations should be interpreted with caution in cardiovascular disease risk assessment.

Keywords

C-reactive protein; Inflammation; Arthritis; Cardiovascular Disease; Cohort Study

INTRODUCTION

C-reactive protein (CRP) is a non-specific marker of inflammation and a predictor of incident coronary heart disease,[1] cardiovascular disease,[2] and subclinical vascular disease.[3,4] Available evidence suggests that moderately-high CRP concentrations (3–10mg/L) predict increased risk of myocardial infarction[5] and stroke,[6] even though it remains controversial if CRP provides significant prognostic insights over and above other traditional risk factors.[7,8] Nevertheless, in some studies, markedly-high CRP concentrations (>10mg/L) have also been shown to predict cardiovascular risk.[9]

Several factors are known to influence the CRP concentrations including body mass index (BMI),[10] diabetes,[10] hypertension,[11] cigarette smoking,[12] estrogen replacement therapy,[13] cholesterol concentrations,[2] and genetic polymorphisms in the *CRP* gene.[14,15] There are large intra-individual variations in circulating CRP concentrations,[16] as well as differences by ethnicity and gender.[17] Prior studies have documented associations of high CRP concentrations with numerous inflammatory conditions, such as rheumatoid arthritis,[18,19] or chronic lung conditions[20] as recently reviewed.[21] CRP, an acute phase reactant, is also known to increase in acute inflammatory states,[22–24] such as acute viral infections.[22] However, data are sparse regarding the extent to which inflammatory conditions are associated with circulating concentrations of CRP in the community.

High-sensitivity CRP has been proposed for use in cardiac risk stratification and preventive decision making.[5,25] Therefore, to address the influence of inflammatory conditions on CRP concentrations in the community, we examined the relations between higher concentrations of CRP with common and uncommon inflammatory diseases in the Framingham Offspring Study participants. Additionally, we examined the impact of common inflammatory conditions on the relation between CRP concentrations and incident cardiovascular disease.

METHODS

Study Sample

The design and selection criteria for Framingham Offspring Study have been described previously.[26] For primary analyses, we selected all participants who attended the fifth examination cycle (1991–1995) and had CRP concentrations measured (n=3782; 1973 women). We excluded participants with prevalent cardiovascular disease at baseline (n=365), resulting in an available sample of 3417 (1842 women) participants. This sample was used to assess the prevalence of common inflammatory conditions (as described below) cross-sectionally and to analyze the incidence of cardiovascular disease prospectively. For assessing the prevalence of uncommon inflammatory conditions (from the same examination cycle), we conducted a case-referent analysis matching 463 participants with CRP concentrations >10mg/L by age and smoking status to a referent group of 463 participants with CRP concentrations <1mg/L.

All participants signed the informed consent and the protocol for the study was approved by the Institutional Review Board of the Boston Medical Center.

Measurements of CRP

Blood samples for CRP were drawn from antecubital vein of individuals after an overnight fast. For examination cycle 5, CRP concentrations were measured by an enzymatic immunoassay (Hemagen Diagnostics, Inc.) as described previously.[6] The coefficient of variation (CV) for replicate CRP measurements on 36 subjects was 0.86. CRP was used as a categorical predictor in our analyses, and the kappa statistic was 0.75 for CRP values in the fourth compared with first through third quartiles, as previously described.[6] For examination 7 cycle participants, CRP was measured by Dade Behring BN100 nephelometer (Deerfield, Illinois), and the mean CV on 139 phantom replicates was 3.2%.

Ascertainment of Cardiovascular Disease and Risk Factors

At each examination visit, participants underwent a medical history, physical examination, anthropometry, and laboratory assessment of risk factors, as previously described.[26] Individuals who reported smoking one or more cigarettes/day in the year of examination were considered current smokers.

Surveillance for cardiovascular events occurred during each examination cycle and adjudication occurred by an endpoint committee consisting of three investigators, as previously described.[27] A cardiovascular event was defined as coronary heart disease (stable angina, coronary insufficiency and myocardial infarction), cerebrovascular disease (stroke and transient ischemic attack), intermittent claudication, or congestive heart failure. A family history of premature cardiovascular disease was present if a validated event occurred in father before the age of 55 or in mother before age 65, as previously described.[28]

Ascertainment of Common and Uncommon Inflammatory Conditions

Information on common inflammatory conditions was obtained from the database collected during the clinic visit on a structured questionnaire administered at each examination cycle by physician-examiners blinded to CRP concentrations. Participants were classified as having a common inflammatory condition if they answered ‘yes’ during the interview by a physician-examiner regarding any one of the following conditions: chronic urinary tract diseases (urinary diseases); chronic gastro-duodenal ulcer (i.e. gastro-duodenal diseases); chronic cough, chronic bronchitis, asthma (i.e. pulmonary diseases); rheumatoid arthritis, gout, degenerative joint disease (i.e. musculoskeletal diseases); or any cancer (excluding non-melanoma skin cancers). These conditions were further categorized according to body system/type— urinary, gastro-duodenal, pulmonary, musculoskeletal, and cancers as displayed in Table 3.

Information about uncommon inflammatory conditions was elicited during the participants’ interview and physical examination by the physician-examiner and noted in text form on the questionnaire. Information about these uncommon inflammatory conditions was not recorded in the computerized database and could only be obtained by retrospective review of the participants’ medical charts (heart study charts). Therefore, to assess the prevalence of uncommon inflammatory conditions, we selected a total of 926 participants by matching all participants in the markedly-high CRP category (>10mg/L; n=463) for age and smoking status to equal number of referent participants with low concentrations of CRP (<1mg/L). Before conducting the chart review, a separate pre-specified list of uncommon inflammatory conditions was made after reviewing the literature for conditions associated with high concentrations of CRP[29] and by consensus of 2 cardiologists and a rheumatologist (Appendix Table 1). All charts were reviewed by a single physician blinded to CRP concentration and case-referent status. Charts were then screened for the pre-specified inflammatory conditions

(e.g., connective tissue disorders, inflammatory bowel disease, as listed in Table 5) for the fifth, sixth or the seventh examination cycle visits. For intra-observer reproducibility of chart review, we re-reviewed 20 randomly selected charts and found high concordance (>95%) of results.

Statistical Analyses

Sex-specific baseline characteristics of participants were assessed according to presence or absence of common inflammatory conditions.

Prevalence of Common Inflammatory Conditions—In sex-specific analyses prevalence of common inflammatory conditions was calculated according to the clinically recommended CRP categories {low (<1mg/L), borderline (1–3mg/L) moderately-high (3.01–10mg/L) and markedly-high concentrations (>10mg/L)}.[5,9]

Cross-sectional Analyses of CRP to Common Inflammatory Conditions—Sex-specific multiple logistic regression models[30] were constructed to examine the relations of CRP concentrations in categories, to the presence or absence of common inflammatory conditions (dichotomous variable). The following sex-specific models were constructed hierarchically: (a) age-adjusted models; (b) adjusting for age, BMI, systolic blood pressure, antihypertensive medications, diabetes mellitus, total/HDL cholesterol, smoking status and estrogen replacement therapy (in women). Additionally, we repeated these analyses using CRP concentrations in quartiles. We also investigated for interactions of the relations of CRP categories with common inflammatory conditions by age or by smoking status.

Prospective Analyses of CRP to Cardiovascular Disease Risk—Sex-specific Cox proportional hazard regression models were constructed to analyze the risk of incident cardiovascular disease on follow up, according to CRP concentrations in continuous models (log transformed to normalize the distribution) and by CRP categories (as above). All models were adjusted for covariates as described above (models a and b) with and without adjustment for presence of common inflammatory condition.

Case-referent Analyses of CRP to Uncommon Inflammatory Conditions—In the case-referent analysis, Cochran Mantel-Haenszel[31] test and Chi-square test accounting for the matched design (age and smoking status) compared the odds of uncommon inflammatory conditions in cases (CRP >10mg/L) to referents (CRP <1mg/L). Further, sex-pooled multivariable conditional-logistic regression adjusting for all the covariates (model b, as above) was used to assess the odds of having an uncommon inflammatory condition in cases compared to referents.

RESULTS

Mean age of the participants was 55±10years (52% women; Table 1). Participants with prevalent inflammatory conditions were more likely to report current cigarette smoking. Blood pressure, total/HDL cholesterol ratio and prevalence of diabetes were slightly higher among men compared to women.

Prevalence of Common Inflammatory Conditions

The prevalence of inflammatory conditions in participants according to CRP concentrations is presented in Table 2. Common inflammatory conditions were reported by 30.9% of men and 30.8% of women. Markedly-high CRP concentrations (>10mg/L) were present in 9.4% of men and 14.0% of women overall. Chronic inflammatory conditions were significantly less likely to be present in men and women with CRP concentrations <1 mg/L (P=0.001; Table 2). A test

for linear trend showed increasing prevalence of inflammatory conditions from the lowest CRP concentration to the highest CRP concentration (*P* for both gender <0.001). The prevalence of common inflammatory conditions according to body system/type is displayed in Table 3. Pulmonary conditions and cancer were most common, followed by gastro-duodenal, urinary and musculoskeletal conditions.

Cross-sectional Relations of CRP to Common Inflammatory Conditions

In sex-specific age-adjusted models, the probability of a reported inflammatory condition in individuals with markedly-high CRP concentrations was significantly higher in both men and women, compared to those in the lowest CRP concentration category (Table 4). After further adjustment for traditional cardiovascular disease risk factors, the association remained statistically significant in men and marginally significant in women (Table 4).

Similar results were noted when these analyses were conducted by CRP quartiles rather than CRP categories (see footnote Table 4). There was no evidence of effect modification by age or smoking status for the relations of CRP to inflammatory conditions in our primary cross-sectional analyses.

Prospective Relations of CRP to Cardiovascular Disease Risk

During follow-up (mean 8 years, range 4.6–10.1 years), 347 participants developed cardiovascular events. In sex-pooled Cox models with CRP modeled as a continuous variable, increase in log CRP concentration (each log CRP= 0.27mg/L) was associated with a higher incidence of cardiovascular disease on follow up (hazard ratio [HR] 1.15, 95% CI, 1.04–1.28); however, with additional adjustment for inflammatory conditions these relations became non-significant (HR 1.20, 95% CI, 0.96–1.50). In sex-specific multivariable Cox models, adjusted for traditional risk factors, the hazard ratios for incident cardiovascular disease associated with a CRP level >10 mg/L compared with the referent (<1 mg/L) were 1.31 (95% CI, 0.81–2.10) for men and 1.74 (95% CI, 0.97–3.13) for women, respectively, as previously reported.[8] With additional adjustment for inflammatory conditions, there was no significant increased risk for cardiovascular disease associated with CRP (Appendix Table 2). Further, in a subset analysis of individuals with available information on family history of premature myocardial infarction (used as a covariate), these relations were not significantly altered (data not shown). We did not find evidence of effect modification by presence or absence of inflammatory condition in the prospective models relating CRP with cardiovascular disease.

High versus Low CRP Concentrations to Uncommon Inflammatory Conditions

The presence of at least one uncommon inflammatory condition was recorded by the physician examiner in the participants' chart for 11% (52/463) of individuals with markedly-high CRP (>10mg/L) compared with 6% (29/463) of referents with CRP <1mg/L (p =0.008; Table 5). In logistic regression analyses after excluding participants with prevalent cardiovascular disease (65 individuals with a markedly-high CRP and 39 subjects with low CRP concentrations), there was a higher odds of having at least one uncommon inflammatory condition in individuals with markedly-high versus low concentrations of CRP (multivariable-adjusted OR 2.39, 95% CI, 1.26–4.54).

Secondary analyses—At a later examination using a high sensitivity CRP assay, the prevalence of common inflammatory conditions according to body system/type (Appendix Table 3) and in the markedly-high CRP category (>10.0 mg/L) (Appendix Table 4) was higher in both men and women. Overall, these results were very similar to the relations seen using the Hemagen assay in examination cycle 5, such that individuals with CRP>10 mg/L had a significantly higher prevalence of inflammatory conditions, and conversely, those with low CRP concentrations had a significantly lower prevalence.

DISCUSSION

In our sample of middle-aged to elderly men and women, markedly-high CRP concentrations (>10mg/L) were not uncommon (9.4% of men and 14.0% women). At least one chronic inflammatory condition was reported by nearly half of men and women who were free of prevalent cardiovascular disease. The prevalence of common inflammatory conditions increased with increasing concentrations of CRP. Conversely, participants with low CRP concentrations (<1 mg/L) were less likely to report a common chronic inflammatory condition. In prospective multivariable-adjusted analyses for incident cardiovascular disease, further adjustment for common inflammatory conditions did not alter the magnitude or direction of the relations between CRP concentrations and incident cardiovascular disease. Finally, in case-referent analyses, we documented that uncommon inflammatory conditions occur infrequently, as expected, but tend to occur more commonly in those with markedly-high CRP concentrations. To our knowledge, this is the first comprehensive study of inflammatory conditions related to high CRP concentrations in a community-based sample.

An AHA/CDC statement (2002)[5] and a more recent CDC/AHA workshop statement (2004) suggested clinically relevant CRP categories and emphasized the existence of considerable biological variability in circulating CRP concentrations.[25] Intermediate to high concentrations of CRP clearly confer increased risks for myocardial infarction, stroke and other cardiovascular disease,[2,6,9] though it is unclear whether and how to implement screening.[32,33] At present, it remains uncertain how clinicians should interpret an elevated CRP concentration when assessing cardiovascular risk especially in presence of a chronic inflammatory condition. Considering large intra-individual variability in the concentrations of CRP,[16,22] and apparently important differences by race,[17] our data supports repeat testing for CRP in persons with high CRP concentrations. In addition, caution should be exercised if a chronic inflammatory condition is present or suspected. Indeed, the AHA/CDC statement (2002) recommended that persons with active infection or systemic inflammatory conditions should not be tested.[5] A few studies have shown that CRP concentrations also predict the risk of death from cardiovascular disease in inflammatory arthritis patients.[34,35] In this respect, some investigators even believe that CRP can be pro-inflammatory,[36,37] whereas others disagree.[38,39] An important objective of further research is to assess whether there is any utility, and particularly what is the risk/benefit ratio, of initiation of drug therapy in the setting of markedly-high values of CRP in persons with documented inflammatory conditions.

Our study has some potential limitations. First, inflammatory conditions were collected retrospectively from the research charts and we were not able to validate each diagnosis of inflammatory conditions reported by the participants, and some common inflammatory conditions may not have been ascertained. Thus, our data may underestimate the prevalence and acuity of inflammatory conditions, which would likely lead to a bias towards the null. We hope our study findings will motivate accurate, validated prospective collection of information regarding common and uncommon inflammatory conditions and the inter-relations with CRP in cardiovascular cohort studies. Second, due to the cross-sectional design of our study we cannot infer a causal relation between inflammatory conditions and elevated CRP concentrations. Third, majority of our participants are middle-aged to elderly whites of European descent, which may limit the generalizability of our findings to other ethnic/racial and age groups.

A final, important potential limitation is that various high-sensitivity CRP assays may differ in their reproducibility characteristics even if they may not differ in their predictive value.[40] The coefficient of variation for the Hemagen assay is somewhat higher at low concentrations (CRP<1.00 mg/L), but it is within an acceptable range at higher (CRP>1.00 mg/L) concentrations.[6] Moreover, the between-assay agreement as assessed by the kappa statistic

was excellent for CRP categories used in our analyses.[6] Reductions in reproducibility at low CRP concentrations would be expected to bias associations toward the null. To address potential limitations of the Hemagen CRP assay, we conducted a similar cross-sectional analysis of the association of CRP categories with inflammatory conditions during a later Offspring examination cycle 7 (1999–2002) using a widely used high-sensitivity CRP assay (Dade-Behring, nephelometric assay) and found very similar results (Appendix table 3 & 4). While our prospective analyses using the Hemagen assay do not suggest any significant impact of inflammatory conditions on associations between CRP and incident cardiovascular disease, these findings warrant confirmation in other prospective cohorts using the more widely used high-sensitivity CRP assay.

CONCLUSION

In our community-based sample, elevated and in particular markedly-high concentrations of CRP (>10mg/L) are associated with a significantly higher prevalence of common, as well as uncommon inflammatory conditions. Further research is warranted using comprehensive, validated ascertainment of inflammatory conditions and high sensitivity CRP assays to assess the impact of common inflammatory conditions on cardiovascular disease risk prediction. Our findings reinforce previous statements that the presence of active inflammatory conditions should be excluded before assessing an individuals' risk of cardiovascular disease by using CRP concentrations.

Clinical Significance

- We evaluated 3782 middle aged men and women free of cardiovascular disease for inflammatory conditions according to CRP categories: <1 (referent), 1–3.0, 3.01–10, and >10 mg/L.
- There was a higher prevalence of common and uncommon inflammatory conditions in those with a high CRP concentration (>10mg/L) versus low CRP (<1mg/L).
- High CRP levels warrant evaluation for evidence of an underlying inflammatory condition and consideration of repeat testing.

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Table 1

Baseline Characteristics of Study Participants

Characteristic	Men (n=1575)		Women (n=1842)	
	Common Inflammatory Conditions			
	Present n = 486	Absent n =1089	Present n = 568	Absent n = 1274
Age, years	57.1 ± 9.6	52.9 ± 9.6	56.6 ± 9.8	53.3 ± 9.6
Body mass index, kg/m^2	28.2 ± 4.4	28.1 ± 4.1	27.3 ± 5.6	26.4 ± 5.4
Cigarette smoking, %	29.0*	15.5	26.9*	15.5
Diabetes mellitus, %	12.3	8.2	7.7	5.3
Systolic blood pressure, mmHg	131±18	128±17	126±21	122±19
Diastolic blood pressure, mmHg	77 ± 10	77 ± 9	73 ± 11	73 ± 10
Hypertension drug therapy, %	21.2	16.1	18.9	14.1
Total cholesterol, mg/dL	202.6±37.2	201.0±33.9	209.7±38.0	206.1±37.6
Total/HDL cholesterol ratio	5.1 ± 1.6	4.9 ± 1.5	4.1 ± 1.4	3.9 ±1.3
Cholesterol drug therapy, %	5.8	6.2	8.6	3.7
Family history of premature cardiovascular disease†, %	16.6	14.9	17.6	15.4
Estrogen replacement therapy, %	NA	NA	16.4	17.3

*Chi-squared test p-value < 0.001 comparing presence versus absence of inflammatory conditions across CRP categories.

†Total number of participants with available information = 1717 [men with (259) and without (582) and women with (278) and without (661) inflammatory conditions]

NA denotes not applicable

Values are mean ± 1 standard deviation.

Appendix Table 1

Coding Sheet Used During Chart Extraction of Uncommon Inflammatory Diagnosis

1 Conditions known to have probable association with high CRP concentrations

- **A.** Connective tissue disorders
- **B.** Lupus
- **C.** Polymyalgia rhuematica
- **D.** Ankylosing spondylitis
- **E.** Reiter disease*
- **F.** Psoriatic arthritis
- **G.** Vasculitides: Behcet's, Wegeners, Polyarteritis Nodosa*
- **H.** Inflammatory bowel disease
- **I.** Rheumatic fever*
- **J.** Familial Mediterranean Fever*
- **K.** Acute pancreatitis* †
- **L.** Acute bacterial infections including periodontal diseases†
- **M.** Acute deep vein thrombosis*†
- **N.** Others e.g. acute injuries or recent surgeries: Specify† _____

2 Conditions with unclear association with CRP concentrations

- **A.** Sarcoidosis
- **B.** End-stage renal disease*
- **C.** Others e.g. chronic pain, Specify _____

* For ascertainment of uncommon inflammatory conditions we reviewed charts for a wide range of potential diseases but some of the diagnoses were never reported in the chart review.

† Acute conditions, acute injuries or recent surgeries were considered if the same happened within one month of examination date.

Table 2

Prevalence of Common Inflammatory Conditions According to CRP Category in Participants Free of Cardiovascular Disease

CRP concentrations	Chronic Inflammatory Conditions			
	Men (n= 1575)		Women (n=1842)	
	Total (n)	Present (%) (n= 486)	Total (n)	Present (%) (n=568)
0–1mg/L	649	23.4*	719	26.2*
1–3 mg/L	417	33.6	422	30.1
3–10 mg/L	361	36.3	444	33.6
>10 mg/L	148	42.6†	257	40.5†
Trend P-value		0.001		0.001

* Chi-squared test p-value < 0.001 and

† p-value = 0.005 when comparing those with presence of inflammatory conditions to those without inflammatory conditions in each CRP category (e.g. men with CRP >10mg/L and having inflammatory conditions were compared to men with CRP >10mg/L but without inflammatory conditions)

Values are numbers or percentages of individuals with presence of inflammatory conditions.

Appendix Table 2

Cox Proportional Hazards Models (Sex-Specific) Examining the Relations of C - reactive protein to the Incidence of Cardiovascular Disease With and Without Adjustment for Common Inflammatory Conditions

CRP	Models							
	Without adjustment for inflammatory conditions				Additionally adjusted for inflammatory conditions			
	Age-adjusted		Multivariable†		Age-adjusted		Multivariable†	
CRP Categories, mg/L	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
				Men				
< 1	Referent		Referent		Referent		Referent	
1 – 3.0	1.28 (0.89–1.84)	0.19	1.12 (0.77–1.62)	0.56	1.25(0.87–1.80)	0.23	1.10 (0.76–1.60)	0.61
3.01 – 10	1.76 (1.25–2.48)	0.0013	1.37 (0.95–1.98)	0.09	1.72 (1.21–2.43)	0.002	1.35 (0.94–1.95)	0.11
> 10	1.86 (1.19–2.90)	0.0002	1.31 (0.81–2.10)	0.27	1.80 (1.15–2.82)	0.01	1.29 (0.80–2.07)	0.30
P for trend	<0.001		0.08		<0.001		0.09	
				Women				
< 1	Referent		Referent		Referent		Referent	
1 – 3.0	1.58 (0.94–2.67)	0.08	1.36 (0.80–2.31)	0.25	1.56 (0.93–2.63)	0.09	1.18 (0.87–1.60)	0.27
3.01 – 10	2.01 (1.24–3.25)	0.004	1.31 (0.78–2.20)	0.32	1.99 (1.23–3.21)	0.005	1.31 (0.78–2.21)	0.31
> 10	3.04 (1.84–5.02)	<0.0001	1.74 (0.97–3.13)	0.06	2.92 (1.77–4.84)	<0.0001	1.72 (0.96–3.10)	0.07
P for trend	<0.001		0.09		<0.001		0.10	

Multivariable models are adjusted for age, sex, BMI, diabetes mellitus, systolic blood pressure, treatment for hypertension, estrogen use (in women) and inflammatory conditions (as indicated).

Table 3

Prevalence of Common Inflammatory Conditions According to Body System/Type

Body System*	Men n=1575	Women n=1842
Urinary tract disease	83 (4.8)	90 (4.7)
Gastro-duodenal tract disease	166 (9.5)	117 (6.1)
Pulmonary disease	248 (14.2)	305 (15.8)
Musculoskeletal disease	25 (1.4)	23 (1.2)
Cancers	242 (13.2)	392 (19.8)

Values are numbers or percentages (in parentheses) of participants with inflammatory conditions.

* Diseases refer to common chronic inflammatory conditions and have been grouped according to body systems/type for simplicity and display. See methods for description of each body system.

Each participant can have inflammatory condition for more than one body system/type.

Appendix Table 3

Prevalence of Inflammatory Conditions According to Body System/Type Among Participants Free of Cardiovascular Disease who Attended a Later Examination Cycle 7

Body System	Men (n=1264)	Women (n=1617)
Urinary Tract Disease*	NA*	NA*
Gastro-Duodenal Tract Disease	140 (9.1)	122 (6.9)
Pulmonary Disease	410 (26.7)	483 (27.3)
Musculoskeletal Disease	311 (20.3)	359 (20.3)
Cancer	312 (20.3)	362 (20.5)

* Information about urinary tract diseases was not collected during this examination

Values are numbers or percentages (in parentheses) of participants with inflammatory conditions

Diseases refer to common chronic inflammatory conditions and have been grouped according to body systems for simplicity and display. See text for description of each body system

Table 4

Odds of Inflammatory Conditions According to CRP concentrations in Men and Women Free of Cardiovascular Diseases

CRP[†]	Models	
	Age-adjusted Odds ratio (95% CI)	Multivariable-adjusted[*] Odds ratio (95% CI)
CRP Category, mg/L	***Men***	
< 1	Referent	Referent
1 – 3.0	1.55 (1.17–2.04)	1.41 (1.07–1.86)
3.01 – 10	1.64 (1.23–2.18)	1.45 (1.07–1.98)
> 10	2.18 (1.49–3.19)	1.64 (1.09–2.47)
	Women	
< 1	Referent	Referent
1 – 3.0	1.12 (0.85–1.46)	1.08 (0.82–1.43)
3.01 – 10	1.23 (0.94–1.60)	1.07 (0.80–1.44)
> 10	1.69 (1.24–2.29)	1.38 (0.97–1.96)

[*] Multivariable models are adjusted for age, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, total cholesterol, smoking status, and estrogen replacement therapy (in women).

CI denotes confidence interval

[†] Compared with the lowest (first) quartile, the multivariable odds of having an inflammatory condition were 1.00 (95% CI, 0.72–1.40), 1.29 (95% CI, 0.93–1.80) and 1.60 (95% CI, 1.14–2.25) for the second (0.32 – 1.41mg/L), third (1.42 – 4.23mg/L) and fourth (≥4.24mg/L) quartiles, respectively in men. In women the odds ratios were 1.14 (95% CI, 0.85–1.55), 1.27 (95% 0.93–1.73) and 1.31 (95% CI, 0.93–1.83), for the second (0.28 – 1.70mg/L), third (1.71 – 5.70mg/L) and fourth (≥5.71mg/L) quartiles, respectively.

Appendix Table 4

Prevalence of Inflammatory Conditions According to CRP Concentrations in Participants Free of Cardiovascular Disease who Attended a Later Examination Cycle 7

CRP concentrations	Chronic Inflammatory Conditions			
	Men (n= 1264)		Women (n=1617)	
	Total (n)	Present (%) (n= 650)	Total (n)	Present (%) (n=741)
(0–1mg/L)	351	46.4	374	46.5
(1–3 mg/L)	511	48.5	515	51.7
(3–10 mg/L)	337	58.5	570	56.0
(>10 mg/L)	65	63.1	158	70.1
Trend P-value		<0.001		<0.001

Values are numbers or percentages of individuals with presence of inflammatory conditions.

Table 5

Number of Participants with Uncommon Inflammatory Conditions in Cases and Referents

Inflammatory Conditions	Cases (CRP>10 mg/L) N=398	Referents (CRP <1mg/L) N=424
Connective tissue disorders	9	2
Systemic Lupus Erythematosis	3	0
Polymyalgia Rheumatica	2	0
Psoriasis and psoriatic arthritis	7	5
Vasculities	1	0
Inflammatory bowel diseases	8	4
Sarcoidosis	1	0
Acute Infections*	12	13
Recent surgical procedures or injuries*	4	4
Total†	46	28

*Within previous month of the visit.

†Chi square p=0.012 comparing total cases (46/398) versus total referents (28/424).

Out of 463 cases and referents, 65 cases and 39 referents were excluded because of prevalent CVD.

Values in the table are the number of participants with inflammatory conditions