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White Blood Cell Count, C-Reactive Protein and Incident Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

PURPOSE—To test the hypothesis that inflammation measured by white blood cell count (WBC) and C-reactive protein (CRP) is associated positively with incident heart failure (HF).

METHODS—Using the Atherosclerosis Risk in Communities (ARIC) Study, we conducted separate Cox proportional hazards regression analyses for WBC (measured 1987 to 1989) and CRP (measured 1996 to 1998) in relation to subsequent heart failure occurrence. A total of 14,485 and 9,978 individuals were included in the WBC and CRP analyses, respectively.

RESULTS—There were 1647 participants that developed HF during follow up after WBC assessment and 613 developed HF after CRP assessment. After adjustment for demographic variables and traditional HF risk factors, the hazard ratio (95% CI) for incident HF across quintiles of WBC was 1.0, 1.10 (0.9-1.34), 1.27 (1.05-1.53), 1.44 (1.19-1.74), and 1.62 (1.34-1.96) (p trend <0.001); hazard ratio across quintiles of CRP was 1.0, 1.03 (0.68-1.55), 0.99 (0.66-1.51), 1.40 (0.94-2.09) and 1.70 (1.14-2.53) (p trend 0.002). Granulocytes appeared to drive the relation between WBCs and heart failure [hazard ratios across quintiles: 1.0, 0.93 (0.76-1.15), 1.26 (1.04-1.53), 1.67 (1.39-2.01) and 2.19 (1.83-2.61) (p trend <0.0001)], while lymphocytes or monocytes were not related.

CONCLUSIONS—Greater levels of WBC (especially granulocytes) and CRP are associated with increased risk of heart failure in middle-aged adults, independent of traditional risk factors.

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DISCLOSURES

None.

Keywords

Prospective Study; Risk Factors; Heart Failure; Inflammation; C-Reactive Protein; Leukocytes; Granulocytes

INTRODUCTION

Inflammation, as reflected by an elevated C-reactive protein (CRP) or white blood cell count (WBC), is considered to be important in the development of coronary heart disease (CHD) (1). A few population studies have suggested that higher CRP may also be associated with increased risk of heart failure (4-9). In several studies this association was independent of prevalent or incident CHD. CRP is associated positively with hypertension, obesity, diabetes, smoking and inactivity and inflammation accompanying these conditions could contribute to heart failure. While evidence for a link between CRP and heart failure is growing, to our knowledge, no population study has examined the association of WBC in men and women with incident heart failure. WBC and CRP may be implicated in the development of heart failure by the immune system acting as a modulator of myocyte injury (9) and inflammatory reactions contributing to the structural and functional deteriorations observed in failing human hearts (10). Higher levels of inflammatory markers also have been associated with increased severity, mortality and morbidity in patients with heart failure (11-14).

We used data from the Atherosclerosis Risk in Communities (ARIC) Study, a cohort of middle-aged adults, to test the hypotheses that CRP and WBC are associated positively with incidence of heart failure.

METHODS

Study Population and Design

The Atherosclerosis Risk in Communities (ARIC) Study (15) is a prospective cohort study of 15,792 men and women aged 45 to 64 years in 1987 to 1989 in four US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. The baseline visit (visit 1) included interviews, laboratory measurements, and clinic examinations. Additional visits were conducted in 1990 to 1992 (visit 2), 1993 to 1995 (visit 3) and 1996 to 1998 (visit 4). This study was approved by the institutional review board (IRB) of the University of Minnesota.

Baseline Variables and Data Collection

Family history of CHD was defined by a history of CHD (myocardial infarction, coronary reperfusion procedure) or sudden death due to CHD in a sibling or parent. Technicians measured resting, seated blood pressure 3 times with a random-zero sphygmomanometer and the average of the second and third readings was used for analysis. Body mass index was calculated as measured weight (kg)/height (m²). Technicians measured circumferences of the waist (umbilical level) and hip (maximum buttocks) to the nearest centimeter, and calculated the waist/hip ratio (WHR). Medication use was self-reported and verified by the inspection of medication bottles. Physical activity was self-reported and quantified as a sports activity index ranging from 1 (low) to 5 (high) (16).

Fasting blood samples were drawn, and plasma and serum were frozen at -70° until analyzed. At baseline, following standard ARIC protocols, measurements of serum glucose, serum creatinine, plasma total cholesterol, triglycerides and high density lipoprotein (HDL)

cholesterol were performed, and low density lipoproteins (LDL) cholesterol levels were computed (17). WBC count was determined by automated particle counters within 24 hours after venipuncture in local hospital hematology laboratories. The reliability coefficient for the WBC count measurement was greater than 0.96 (18). Hemoglobin was determined in the same laboratories. Estimated GFR (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation (19). Apart from WBC and hemoglobin, all laboratory measurements were repeated at visit 4, when CRP was measured using an immunonephelometric assay (Dade Behring, Newark, Delaware). The reliability coefficient was 0.95 (20).

Hypertension was defined as DBP ≥ 90 mm Hg, SBP ≥ 140 mm Hg or use of antihypertensive medication. Diabetes was defined as a fasting serum glucose level ≥ 126 mg/dl, non-fasting glucose level ≥ 200 mg/dl, report of a physician diagnosis of diabetes or current use of diabetes medication. Prevalent CHD was defined by electrocardiographic evidence of previous myocardial infarction, history of physician diagnosed myocardial infarction, or previous coronary revascularization procedure (bypass, angioplasty). Prevalent heart failure was defined by the reported current intake of heart failure medication at visit 1 or evidence of manifest heart failure with presence of specific cardiac and pulmonary symptoms (21-23).

Assessment of Incident Heart Failure and CHD

Incident cardiovascular events through December 31, 2005 were identified through annual telephone calls to ARIC cohort participants to identify all hospitalizations, through a review of local hospital discharge indexes, and through retrieval of death certificates. Because the response to telephone calls is still over 93 percent and supplemented by hospital surveillance, event ascertainment is quite complete. Incident heart failure was defined by the first hospitalization or a death certificate with a heart failure discharge code (ICD9 428 or ICD10 I50). Incident CHD was defined by a definite or probable myocardial infarction, coronary angioplasty or coronary artery bypass surgery.

Statistical Analysis

From the 15,792 ARIC participants, we made exclusions as shown in Figures 1 and 2. Analyses were conducted using SAS version 9.2 (24), separately for visit 1 WBC and visit 4 CRP. The primary analyses had WBC and CRP modeled as quintiles. We determined the relation of WBC and CRP quintiles with other demographic and health characteristics, some of which may be confounders in the analysis, using χ^2 tests or ANOVA. Heart failure hazard ratios across quintiles of WBC and CRP and 95% confidence intervals were calculated using Cox-proportional hazards models. The proportionality assumption of all Cox models was assessed by inspecting the log (-log [survival function]) curves. Trends in the hazards across WBC and CRP quintiles were assessed by assigning equally spaced scores to the quintiles and treating this as a continuous variable in the regression models (25). Analyses were also conducted treating biomarkers as continuous variables or dichotomous variables above or below the 90th percentiles for WBC and <1 , 1-3 and ≥ 3 mg/L for CRP. We also evaluated the relation of WBC subtypes (i.e. granulocytes, lymphocytes, and monocytes) to heart failure risk. Follow up time began at entry into the study (visit 1 for WBC, visit 4 for CRP) and went to the first heart failure hospitalization, death, leaving the study, or else December 31, 2005.

Regression models first adjusted for demographics, including age (continuous), race (black, white), gender, educational level (less than high school, high school or vocational training, college or advanced degree) and ARIC field center. The second multivariate model adjusted additionally for continuous BMI and WHR, smoking status (current, former, never), and

sports activity index (scale 1 to 5). In the third model we evaluated whether the observed WBC and CRP associations were independent of established heart failure risk factors by further adjusting for hypertension, diabetes, prevalent CHD, family history of CHD, medication use (antihyperlipidemic, digitalis, beta-blocker), and continuous LDL cholesterol, HDL cholesterol, triglycerides, hemoglobin and eGFR. For all models, level of significance was taken as $p < 0.05$. Interactions were evaluated by including cross-product terms in the models.

Using life test procedures, we also created survival curves for the proportion of individuals who remained free of incident heart failure, stratified by WBC and CRP quintiles.

RESULTS

Baseline Characteristics

14,485 participants were included in the WBC (visit 1) analyses, and 9,978 were included in the CRP (visit 4) analyses. At baseline, the mean WBC (SD) was $6.09 (1.86) \times 10^9/L$. The mean age of the cohort was 54 years; 74% were white, 54% were female and 36% had more than a high school education. As Table 1 shows, participants with higher WBC levels were more often male, had higher levels of most heart failure risk factors, and as expected, were more often white than black (18).

For visit 4, the mean CRP (SD) was 4.04 (4.86) mg/L. The mean age of participants at visit 4 was 63 years. Associations of covariates with CRP were similar to those for WBC except that participants with higher CRP levels were more likely to be African American and female (Table 2).

Outcomes

For the WBC analyses, participants were followed for a mean (SD) of 15.5 (4.0) years, and 1647 participants developed heart failure (74/10,000 person-years). Mean (SD) follow up time for CRP analyses was 7.9 (1.7) years and 613 participants developed heart failure (77/10,000 person-years). Life test survival analysis (figures 3 and 4) demonstrated that higher levels of WBC and CRP were each risk factors for heart failure (log-rank $\chi^2=241$, $p < 0.0001$ and $\chi^2=104$, $p < 0.0001$ respectively).

As shown in Table 3, crude hazard ratios (95% CIs) across quintiles of WBC were 1.0, 1.19 (0.98-1.44), 1.59 (1.33-1.91), 2.28 (1.91-2.71), and 2.81 (2.37-3.31) (p trend < 0.0001). There was some attenuation of this association after adjustment for potential confounders (Models 2 and 3, Table 3), but a moderate positive association between WBC and heart failure remained. When WBC was modeled as a continuous variable, the hazard ratio (95% CI) for a 1 standard deviation ($1.86 \times 10^9/L$) increase in WBC was 1.17 (1.12-1.24), in Model 3. A significant positive association between WBC and incident heart failure still remained when WBC was modeled as high ($>9.0 \times 10^9/L$) vs. low ($\leq 9.0 \times 10^9/L$); the hazard ratio (95% CI) was 1.28 (1.08-1.51). When CHD was included as a time-dependent covariate, the results obtained were not substantially different from when only prevalent CHD at baseline was used (HR (95% CIs) for WBC quintiles adjusted for Model 3 covariates and CHD as a time-dependent covariate: 1.00, 1.10 (0.90-1.34), 1.24 (1.03-1.50), 1.41 (1.17-1.70), 1.54 (1.27-1.86); p -trend < 0.0001).

Differentiating WBC count showed a strong positive association between granulocytes (neutrophils, eosinophils and basophils) both individually and when assessed collectively, and heart failure incidence. There was no association between lymphocytes or monocytes and incident heart failure. After adjustment for potential confounders (Model 3), the hazard ratios (95% CIs) across quintiles of granulocytes were 1.0, 0.93 (0.76-1.15), 1.26

(1.04-1.53), 1.67 (1.39-2.01) and 2.19 (1.83-2.61) (p trend <0.0001). Hazard ratios across quintiles of lymphocytes and monocytes were 1.0, 0.93, 0.93, 0.95, 0.86 (p trend=0.20) and 1.0, 0.94, 0.94, 0.95, 0.89 (p trend=0.19) respectively.

CRP quintiles were strongly associated with heart failure incidence. Crude hazard ratios (95% CIs) were 1.0, 1.15(0.85-1.56), 1.34 (0.99-1.80), 1.79 (1.36-2.37) and 2.86 (2.20-3.72) (p trend <0.0001). After adjustment for potential confounders (Model 3, Table 4), there still was a moderate positive association between CRP and incident heart failure. Hazard ratios(95% CIs)across the quintiles were 1.0, 1.03 (0.68-1.55), 0.99 (0.66-1.51), 1.40 (0.94-2.09) and 1.70 (1.14-2.53) (p trend 0.002), suggesting CRP was associated with heart failure mostly above 3.2 mg/L. When we modeled CRP as a continuous variable, the hazard ratio (95% CIs) for a 1 standard deviation (4.86 mg/L) increase in CRP was 1.16(1.05, 1.28) in Model 3 covariates. The hazard ratios (95% CIs) were 1.00, 0.97 (0.74-1.27), 1.41 (1.09-1.82) for CRP levels <1, 1-3 and ≥ 3 mg/L respectively. P=0.0009.. Modeling CHD as a time-dependent variable did not change the results(HR (95% CIs) for CRP quintiles adjusted for Model 3 and CHD as a time-dependent covariate: 1.00, 0.91 (0.67-1.25), 0.87 (0.64-1.19), 1.19 (0.88-1.62), 1.54 (1.15-2.07); p-trend <0.0001).For the WBC analyses, there were 1620 incident CHD events that preceded HF and for the CRP analyses, 252 incident CHD events preceded HF.

There was no interaction of race, gender, or prevalent CHD with WBC or CRP in incident heart failure. There was a weak interaction of hypertension status with WBC (p = 0.04) but not with CRP. The hazard ratios(95% CIs) for WBC quintiles 1 to 5 were 1.0, 1.20 (0.90-1.56), 1.27 (0.99-1.63), 1.41 (1.09-1.82) and 1.49 (1.16-1.93) in participants with prevalent hypertension and 1.0, 0.96(0.71-1.30), 1.24 (0.93-1.65), 1.48 (1.12-1.97) and 1.77(1.34-2.35) in normotensive participants. There was no evidence of an interaction between WBC and CRP levels on risk of incident HF (p_{Interaction} = 0.97).When we evaluated the relation of baseline WBC to incident HF after adjusting for visit 4 CRP, the results were only slightly attenuated, and a significant association persisted between WBC and incident HF after CRP adjustment (p = 0.002).

CONCLUSIONS

In this analysis of a prospective, community-based, biracial sample of middle-aged adults, higher blood levels of WBC and CRP were strongly associated with increased incidence of heart failure. After adjustment for traditional risk factors, the associations were weakened but moderate positive associations still remained. These findings are consistent with previously published studies of the relationship between CRP and heart failure (4-8, 26). The present study extends previous findings to show that elevated WBC (particularly granulocytes) and CRP are associated with heart failure independent of CHD, race or gender in the general middle-age population.

WBC

Although elevated WBC has consistently been an independent risk factor for future cardiovascular outcomes (3), to our knowledge, our study is the first population based study to demonstrate that elevated WBC is an independent risk factor for incident heart failure in both men and women. Also, to our knowledge, this is the first study to show that the association exists and is similar when adjusted for CHD as a time-varying covariate. One population based study (27) investigating the association between WBC and incidence of hospitalizations due to heart failure in men without prior history of MI, observed HR of 1.0, 1.26, 1.24 and 1.73 across quartiles of WBC. Two other studies conducted in acute myocardial infarction patients with reduced ejection fraction reached similar conclusions. In the Studies of Left Ventricular Dysfunction (SOLVD) among CHD patients with reduced

ejection fraction (28), a WBC count of $> 7000/\text{mm}^3$ (compared with $\text{WBC} \leq 7000/\text{mm}^3$) was associated with a greater likelihood and increased severity of heart failure. In a prospective analysis of the Thrombolysis In Myocardial Infarction (TIMI) trials (29), even after controlling for numerous confounders, the WBC count remained independently associated with the development of new heart failure in patients with acute myocardial infarction. Although some studies have suggested that WBC may increase as a result of the low cardiac output situation in heart failure (10, 30), our results show that elevated WBC, probably reflecting greater systemic inflammation, may be etiologically relevant for heart failure. The strength of the association after adjustment for heart failure risk factors (about 67% increased risk in the highest quintile vs. the lowest quintile), the presence of a stepwise rise in heart failure risk across increasing quintiles of WBC, the demonstration of a temporal sequence, and the consistency of results in multiple analyses all support this notion (reviewed in Table 5). In the ARICdata, the increased risk for heart failure associated with increased WBC count was driven by granulocytes (neutrophils, basophils, eosinophils). Consistent with our findings, previous studies (31, 32) have suggested that higher neutrophil or granulocyte counts may be stronger predictors of CHD than other WBC components. A recent Mayo Clinic study (33) also found a positive association between neutrophil count and incident HF in patients with MI; however, mechanisms explaining this occurrence remain unclear. The hazard ratios of HF by WBC quintiles in non-hypertensives were higher and more pronounced than the hazard ratios in hypertensives. This was not hypothesized a priori, could be due to chance, and would require replication before it should be considered biologically real. However, we find it logical that in the absence of hypertension, a major risk factor for HF, inflammation would be a more potent HF risk factor.

CRP

Compared with patients in the lowest quintile of CRP, the adjusted hazard for heart failure was increased 1.7 fold in the highest CRP quintile (Table 4). Individuals in the second and third CRP quintiles did not seem to have a significantly increased risk for heart failure implying that only relatively high levels of CRP are associated with increased heart failure risk. Various studies have found a positive association between CRP and heart failure (4-8) (reviewed in Table 6). For example, investigators of the Cardiovascular Health Study (34) observed a RR of 1.93 for incident heart failure in elderly individuals with $\text{CRP} > 7.0\text{mg/L}$ (vs. $\leq 7.0\text{mg/L}$).

Mechanisms

The development and progression of heart failure is multi-factorial and there is growing evidence that systemic inflammation (indicated by elevated WBC and CRP) may be mechanistically involved by contributing to myocardial dysfunction and other aspects of advanced heart failure including weight loss, anemia and endothelial dysfunction (35, 36). Oxidative stress and proinflammatory cytokines released by white blood cells are associated with myocyte dysfunction and pulmonary edema (35, 37). In addition, elevated WBC can lead to abnormal leukocyte aggregation, vessel obstruction, endothelial injury and decreased perfusion in heart muscle, leading to CHD which can predispose to heart failure (3). Furthermore, just as in other chronic inflammatory conditions, granulocyte colony-stimulating factor (G-CSF) and other pro-inflammatory cytokines may cause granulocytes to live longer in individuals with clinical and subclinical HF, and thus enhance their function as effector cells of the inflammatory process in these individuals (38). Other studies in both animal and human models have however proposed that G-CSF may improve outcomes in heart failure of ischemic etiology (39). In addition, CRP may activate the complement system, stimulate cytokine production, cause myocyte loss and promote cardiac dysfunction which leads to heart failure (40). Adjusting for CHD as a time-varying covariate had little impact on our results. The motivation of this analysis was to gauge whether our findings that

inflammation was associated with a greater risk of HF were simply due to the fact that inflammation is associated with a greater risk of CHD, and CHD is associated with a greater risk of HF. The fact that our results were similar after more carefully accounting for CHD by using incident CHD as a time-varying covariate suggests that inflammation may be associated with risk of HF at least partly independently of CHD.

Study Limitations

One limitation, as in all observational studies, is potential residual confounding. Second, it is theoretically possible that subclinical heart failure may have caused an increase in WBC and CRP levels, rather than increased levels of WBC and CRP having predisposed to heart failure. However, there was a long follow-up between the baseline evaluation and incident events (mean follow-up time of 15.5 and 7.9 years respectively for eventual cases of incident HF). Third, we had single measures of WBC and CRP, which may theoretically lead to some misclassification of exposure, but short-term reliability of WBC and CRP was high and so there is probably little bias. It is unlikely that an acute inflammatory response would have impacted our results much, as we excluded individuals with extreme values from our analyses. One of our criteria for prevalent HF was reported use of HF medications. Some HF medications are also commonly used in treatment of hypertension and CHD, but we required the participant report medication was used for HF to meet this prevalent HF criterion. In any case, there should be little impact of misclassification bias on hazards ratios, because all these individuals with presumed baseline HF were excluded from the analysis. Furthermore, some studies have found other markers, like brain natriuretic peptide and urinary albumin:creatinine, ratio to be associated with incident HF. We did not have other biomarkers at similar time periods to compare with WBC and CRP. Finally, WBC and CRP were measured many years apart, thus assessment of independent or joint associations of these markers with heart failure incidence may yield biased results.

We found that elevated WBC (especially granulocytes) and CRP appear to be risk factors for incident heart failure, independent of traditional risk factors. Further studies designed to investigate the role of these inflammatory markers in heart failure are needed to determine whether this is indeed a causal relation and whether measuring these markers may be helpful in prediction and prevention of heart failure.

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
CHD	coronary heart disease
CRP	C-reactive protein
DBP	diastolic blood pressure

eGFR	estimated glomerular filtration rate
G-CSF	granulocyte colony-stimulating factor
HDL	high density lipoprotein
HF	heart failure
LDL	low density lipoprotein
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
RR	relative risk
SD	standard deviation
SOLVD	Studies of Left Ventricular Dysfunction
TIMI	Thrombolysis In Myocardial Infarction
WBC	white blood cell count
WHR	waist/hip ratio

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Figure 1.
Inclusion and exclusion criteria for WBC Visit 1 analysis

Figure 2.
Inclusion and exclusion criteria for CRP Visit 4 analysis

Figure 3. Life-test estimates of survival function. Proportion of participants free of heart failure by WBC quintiles, ARIC 1987-2005

Figure 4. Life-test estimates of survival function. Proportion of participants free of heart failure by CRP quintiles, ARIC 1996-2005

TABLE 1
Unadjusted baseline characteristics by quintiles of white blood cell count (WBC), ARIC, 1987-1989

Characteristics	Quintiles of WBC ($\times 10^9/L$)				
	1	2	3	4	5
Range	2.1 – 4.5	4.6 – 5.3	5.4 – 6.2	6.3 – 7.3	7.4 – 18.8
N	2793	2963	3194	2775	3032
Age (yrs) Mean (SD)	54(6)	54(6)	54(6)	54(6)	54(6)
Race (White) N (%)	1653 (59)	2159 (73)	2483 (78)	2208 (80)	2465 (81)
Gender (female) N (%)	1687(60)	1651(56)	1721(54)	1442(52)	1512 (50)
Educational Level N (%)					
Up to high school	1707(61)	1848(63)	2006(63)	1815(66)	2050(68)
More than high school	1080(39)	1111(38)	1182(37)	956(35)	978(32)
Sport Index Mean (SD)	2.46(0.81)	2.47(0.80)	2.48(0.81)	2.43(0.78)	2.36(0.77)
BMI (kg/m^2) Mean (SD)	26.7(4.9)	27.3(5.0)	27.7(5.1)	28.1(5.5)	27.8(5.5)
WHR Mean (SD)	0.90(0.08)	0.92(0.08)	0.93(0.08)	0.94(0.08)	0.94(0.07)
LDL Cholesterol (mg/dl) Mean (SD)	135 (39.3)	137 (39.8)	138 (38.7)	139 (38.9)	140 (39.6)
HDL Cholesterol (mg/dl) Mean (SD)	58 (18.4)	53 (16.9)	52 (16.4)	49 (16.0)	47 (15.4)
Triglycerides (mg/dl) Mean (SD)	103 (58.5)	121 (83.3)	133 (85.9)	142 (95.7)	151 (105.4)
Hemoglobin (g/dl) Mean (SD)	13.4(1.4)	13.7(1.4)	13.9(1.3)	14.1(1.4)	14.4(1.5)
eGFR ($ml/min/1.73m^2$) Mean (SD)	97 (15.3)	96 (14.9)	95 (14.6)	95 (14.8)	96 (15.2)
Diabetes N (%)	192(7)	249(8)	336(11)	366(13)	471(16)
Hypertension N (%)	850(31)	917(31)	1067(34)	941(34)	1020(34)
Medication Use N (%)					
Antihyperlipedemic	51(1.8)	55(1.9)	79(2.5)	48(1.7)	54(1.8)
Digoxin	12(0.4)	25(0.8)	28(0.9)	35(1.3)	37(1.2)
Beta-blockers	181(6.5)	241(8.1)	288(9.0)	296(10.7)	302(10.0)
Smoker N (%)					
Ever	1194(43)	1460(49)	1773(56)	1765(64)	2394(79)
Never	1595(57)	1502(51)	1415(44)	1007(36)	637(21)
History of CHD N (%)	75(3)	79(3)	138(4)	134(5)	174(6)
Family history of CHD N (%)	1005(36)	1167(39)	1262(40)	1164(42)	1291(43)

ARIC = Atherosclerosis Risk in Communities Study; BMI = body mass index; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; LDL = low density lipoprotein; HDL = high density lipoprotein; N = number of participants; SD = standard deviation; WBC = white blood cell count; WHR = waist-to-hip ratio.

TABLE 2
Visit 4 characteristics by quintiles of C-reactive protein (CRP), ARIC, 1996-1998

Characteristics	Quintiles of CRP (mg/L)				
	1	2	3	4	5
Range	0.15-0.89	0.89-1.69	1.69-3.22	3.22-6.17	6.17-36.29
N	1995	1996	1996	1996	1995
Age (yrs) Mean (SD)	63(6)	63(6)	63(6)	63(6)	62(6)
Race (White) N (%)	1648(83)	1652(83)	1598(80)	1522(76)	1336(67)
Gender (female) N (%)	904(45)	941(47)	1069(54)	1320(66)	1475(74)
Educational Level N (%)					
Up to high school	1077(54)	1144(57)	1219(61)	1263(63)	1309(66)
More than high school	912(46)	850(43)	775(39)	730(37)	684(34)
Sport Index Mean (SD)	2.75(0.86)	2.62(0.81)	2.55(0.79)	2.46(0.78)	2.36(0.76)
BMI (kg/m ²) Mean (SD)	25.7(3.9)	27.5(4.2)	28.6(4.7)	29.9(5.6)	31.5(6.7)
WHR Mean (SD)	0.92(0.07)	0.94(0.07)	0.95(0.07)	0.95(0.07)	0.95(0.07)
LDL Cholesterol (mg/dl) Mean (SD)	120 (32.2)	124 (32.8)	125 (34.4)	124 (34.1)	121 (34.5)
HDL Cholesterol (mg/dl) Mean (SD)	54 (17.2)	50 (16.3)	49 (16.0)	49 (16.0)	51 (17.0)
Triglycerides (mg/dl) Mean (SD)	117 (66.7)	137 (77.2)	147 (88.4)	155 (95.2)	154 (94.5)
Hemoglobin (g/dl) Mean (SD)	13.9(1.3)	14.0(1.3)	13.9(1.3)	13.8(1.3)	13.4(1.3)
eGFR (ml/min/1.73m ²) Mean (SD)	85 (13.5)	84 (14.0)	85 (14.4)	84 (15.5)	85 (16.8)
Diabetes N (%)	180(9)	233(12)	295(15)	350(18)	452(23)
Hypertension N (%)	677(34)	827(42)	867(44)	955(48)	1180(59)
Medication Use N (%)					
Antihyperlipemic	230(11.5)	245(12.3)	227(11.4)	212(10.6)	188(9.4)
Digoxin	26(1.3)	24(1.2)	24(1.2)	27(1.4)	48(2.4)
Beta-blockers	151(7.6)	196(9.8)	183(9.2)	200(10.0)	251(12.6)
Smoker N (%)					
Ever	1132(57)	1129(57)	1170(59)	1123(57)	1161(58)
Never	853(43)	858(43)	810(41)	862(43)	824(42)
History of CHD N (%)	54(3)	65(3)	62(3)	51(3)	62(3)
Family history of CHD N (%)	751(38)	771(39)	811(41)	837(42)	794(40)

ARIC = Atherosclerosis Risk in Communities Study; BMI = body mass index; CHD = coronary heart disease; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; LDL = low density lipoprotein; HDL = high density lipoprotein; N = number of participants; SD = standard deviation; WBC = white blood cell count; WHR = waist-to-hip ratio.

TABLE 3

Hazard ratios for heart failure by quintiles of white blood cell count (WBC), ARIC, 1987-2005

	Quintiles of WBC ($\times 10^9/L$)					P for trend
	1	2	3	4	5	
Range	2.1 – 4.5	4.6 – 5.3	5.4 – 6.2	6.3 – 7.3	7.4 – 18.8	
N cases	189	234	333	389	502	
Person-years	44306	46360	49299	40892	43256	
Rate/10,000 person-yrs	43	51	68	95	116	
HR (95% Confidence Intervals)						
Crude *	1.0	1.19 (0.98-1.44)	1.59 (1.33-1.91)	2.28 (1.91-2.71)	2.81 (2.37-3.31)	<.0001
Adjusted 1 [†]	1.0	1.27 (1.05-1.54)	1.76 (1.47-2.11)	2.48 (2.08-2.96)	3.13 (2.64-3.72)	<.0001
Adjusted 2 [‡]	1.0	1.13 (0.93-1.37)	1.40 (1.17-1.68)	1.75 (1.46-2.10)	1.91 (1.60-2.30)	<.0001
Adjusted 3 [§]	1.0	1.10 (0.90-1.34)	1.27 (1.05-1.53)	1.44 (1.19-1.74)	1.62 (1.34-1.96)	<.0001

ARIC = Atherosclerosis Risk in Communities Study; HR = hazard ratio; N = number of participants; WBC = white blood cell count.

* Unadjusted

[†] Adjusted for age, race, gender, educational level, ARIC field center[‡] Adjusted 1 + BMI, WHR, smoking status, sports activity index[§] Adjusted 2 + hypertension, diabetes, prevalent CHD, family history of CHD, LDL-C, HDL-C, Medications (antihyperlipidemic, digitalis, beta-blocker), triglycerides, hemoglobin, eGFR

TABLE 4

Hazard ratios for heart failure by quintiles of C-reactive protein (CRP), ARIC, 1996-2005

	Quintiles of CRP (mg/L)					P for trend
	1	2	3	4	5	
Range	0.15-0.89	0.89-1.69	1.69-3.22	3.22-6.17	6.17-36.29	
N cases	77	89	102	135	210	
Person-years	16036	16108	15934	15740	15403	
Rate/10,000 person-yr	48	55	64	86	136	
HR (95% Confidence Intervals)						
Crude *	1.0	1.15 (0.85-1.56)	1.34 (0.99-1.80)	1.79 (1.36-2.37)	2.86 (2.20-3.72)	<.0001
Adjusted 1 [†]	1.0	1.13 (0.83-1.54)	1.32 (0.98-1.77)	1.87 (1.41-2.48)	3.05 (2.34-3.99)	<.0001
Adjusted 2 [‡]	1.0	0.99 (0.72-1.35)	0.99 (0.73-1.34)	1.29 (0.96-1.74)	1.86 (1.40-2.49)	<.0001
Adjusted 3 [§]	1.0	1.03 (0.68-1.55)	0.99 (0.66-1.51)	1.40 (0.94-2.09)	1.70 (1.14-2.53)	0.002

ARIC = Atherosclerosis Risk in Communities Study; HR = hazard ratio; N = number of participants; CRP = C-reactive protein.

* Unadjusted

[†] Adjusted for age, race, gender, educational level, ARIC field center[‡] Adjusted 1 + BMI, WHR, smoking status, sports activity index[§] Adjusted 2 + hypertension, diabetes, prevalent CHD, family history of CHD, LDL-C, HDL-C, Medications (antihyperlipidemic, digitalis, beta-blocker), triglycerides, hemoglobin, eGFR

TABLE 5

Summary of existing studies on white blood cell count (WBC) and heart failure

Author	Design	Sample	Association
Barron (29)	Prospective analysis of clinical trial	TIMI: 975 MI patients; 64 incident HF events	OR of HF = NA, 0.11, 0.24, 1.00 per quartile of WBC (ref was highest quartile), multiply-adjusted
Engström (27)	Cohort	16,940 Swedish men; 436 hospitalizations for HF	HR of HF = 1.00, 1.26, 1.24, 1.73 ($p<0.0001$) per quartile of WBC, multiply-adjusted
Dragu (41)	Cohort	1037 MI patients; unknown number of rehospitalizations for HF	HR of HF 1.6 ($p=0.015$) in upper quartile of neutrophils compared to lower three quartiles, multiply-adjusted. No association for other WBC components
This study	Cohort	ARIC: 14,485 middle aged adults; 1,647 incident HF events	HR of HF = 1.00, 1.10, 1.29, 1.46, 1.67 ($p<0.0001$) per quintile of WBC, multiply-adjusted.

ARIC = Atherosclerosis Risk in Communities Study; HF = heart failure cases; HR = hazard ratio; MI = Myocardial infarction; NA = no one in the lowest quartile of WBC had heart failure, so these patients were dropped from the model; OR = odds ratio; TIMI =Thrombolysis In Myocardial Infarction 10 Study; WBC = white blood cell count.

TABLE 6

Summary of existing studies on C-reactive protein (CRP) and heart failure

Author	Design	Sample	Association
Gottdiener (5)	Cohort	CHS: 5,888 Elderly individuals >65years; 597 incident HF events	HR of HF = 1.0, 0.95, 1.01, 1.27, 1.91(p<0.0001) per quintile of CRP, multiply-adjusted
Vasan (6)	Cohort	Framingham: 732 Elderly men & women; 56 incident HF events	HR of HF = 2.81 (1.22-6.50) (p=0.02) for CRP ≥5 mg/dL vs. <5mg/dL, multiply-adjusted
Cesari (7)	Cohort	Health ABC: 2225 individuals 70-79 years; 92 incident HF events	HR of HF = 1.0, 1.43, 2.60 (p<0.001) per tertile of CRP, multiply-adjusted
Kardys (8)	Cohort	Rotterdam: 6,437 individuals ≥55years; 551 incident HF events	HR of HF = 1.0, 1.14, 1.17, 1.71 (p<0.001) per quartile of CRP, multiply-adjusted. Association stronger in men than women
Bahrami (9)	Cohort	MESA: 6,814 individuals 45-84 years; 79 incident HF events	HR of HF = 1.38 (1.01-1.86) per 1 SD CRP increment, multiply-adjusted
This study	Cohort	ARIC: 9,978 middle aged adults; 613 incident HF events	HR of HF = 1.27 (1.07-1.87) for CRP >11.5 mg/L vs. ≤11.5 mg/L, multiply-adjusted HR of HF = 1.16 (1.05-1.28) per 1 SD CRP increment, multiply-adjusted HR of HF = 1.00, 1.03, 0.99, 1.40, 1.70 (p=0.002) per quintile of CRP, multiply-adjusted

ARIC = Atherosclerosis Risk in Communities Study; CHS = Cardiovascular Health Study; CRP = C-reactive protein; Framingham = the Framingham Heart Study; Health ABC = the Health, Aging, and Body Composition Study; HF = heart failure cases; HR = hazard ratio; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NA = no one in the lowest quartile of WBC had heart failure, so these patients were dropped from the model; Rotterdam = the Rotterdam Study; SD = standard deviation; WBC = white blood cell count.