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Growth Horm IGF Res. Author manuscript; available in PMC 2010 October 1.

Published in final edited form as:
Growth Horm IGF Res. 2009 October ; 19(5): 420–425. doi:10.1016/j.ghir.2008.12.002.

Serum IGF-I and C-reactive protein in healthy black and white young men: The CARDIA Male Hormone Study

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Abstract

Objective—Animal and human studies suggest that C-reactive protein (CRP) may be inversely associated with serum insulin-like growth factor-I (IGF-I) concentrations. However, most human studies have not controlled adequately for confounding factors, particularly nutritional intake. This population-based study examined whether CRP is inversely associated with IGF-I and IGFBP-3 concentrations.

Methods—In cross-sectional analysis, multivariable linear regression with adjustment for age, BMI, smoking status, alcohol intake, and nutritional factors was used to relate log CRP, the independent variable, to IGF-I and IGFBP-3 in a sample of black (n = 364) and white men (n = 486) separately by race.

Results—Only black men had positive findings: log CRP was significantly associated with IGF-I ($\beta = -13.1$ ng/ml, $p = 0.02$) and the difference in mean IGF-I concentrations between the highest and lowest quartiles of CRP was 26 ng/ml. There was a statistically significant interaction between log CRP and smoking status ($p = 0.02$); the regression coefficient for IGF-I predicted from log CRP was significant in smokers ($\beta = -39.8$ ng/ml, $p = 0.0001$), but not in non-smokers. The difference in mean IGF-I concentrations between highest and lowest quartiles of CRP was 100 ng/ml for black smokers. There were no associations for IGFBP-3.

Conclusions—In our study, CRP levels are inversely associated with IGF-I concentrations in black male smokers; however, the causal nature of the association is unclear and should be studied further.

Keywords

Insulin-like growth factor-I; Insulin-like growth factor binding protein-3; C-reactive protein; Men

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INTRODUCTION

Insulin-like growth factor-I (IGF-I) is a peptide hormone produced primarily by the liver and is regulated, in part, by growth hormone (GH). The predominate binding protein (BP), IGFBP-3, regulates IGF-I's bioavailability and mediates its actions through the IGFBP-3 receptor [1,2]. Early in life, the GH-IGF axis has a critical role in normal postnatal growth. Disruption of this axis with reductions in IGF-I concentrations results in growth impairment. Stunted growth is a complication of childhood diseases characterized by inflammation such as inflammatory bowel disease (IBD) and systemic juvenile idiopathic arthritis [3]. It is hypothesized that one mechanism by which inflammatory diseases in children might lead to stunted growth is through the IGF axis. That is, inflammatory cytokines, which stimulate C-reactive protein (CRP) production [4], reduce IGF-I concentrations, contributing to stunted growth. This hypothesis is also supported by several animal models [5,6].

In addition to their significance to postnatal growth, the IGF-axis and inflammatory processes are both important in a number of disease contexts. In adults, serum IGF-I concentrations and markers of inflammation have been associated with risk of cardiovascular disease and the metabolic syndrome [7–11], type 2 diabetes [12,13], and site-specific cancers [14–19]. Most of these studies [7,10,12–19] focused separately either on the IGF axis or on inflammatory markers but did not consider their inter-relationships. On the other hand, in adult patients with cancer or IBD, inflammatory markers have been inversely correlated, albeit not causally related, with IGF-I levels [20–22]. However, these studies were limited in that nutritional deficiency concomitant with these diseases may have contributed to reduced IGF-I levels. It is well established that energy and protein restriction reduces IGF-I concentrations [23,24]. Two population-based studies reported inverse correlations between CRP and IGF-I, but in neither study was it clear that potential confounding factors, such as body mass index (BMI) or smoking, were adjusted for in computing these correlations [9,25].

Importantly, no large, population-based study in healthy adults has examined the association of IGF-I with inflammatory factors while controlling for diet [26–28] or other potential confounding factors. Given the independent importance of the IGF axis and inflammatory processes in health and disease states, it is essential to determine whether the causal relation between inflammation and IGF-I suggested by animal studies [5,6] can be observed at the population level. The Coronary Artery Risk Development in Young Adults (CARDIA) Male Hormone Study (CMHS) provides a unique opportunity to test the hypothesis that CRP is inversely associated with IGF-I in healthy, well-nourished men. Because of racial differences in cytokine genotype distributions [29], mean serum IGF-I levels [30] and nicotine metabolism [31], and differential impact of cigarette smoking on hepatic drug metabolism [32], it is also necessary to examine the interactions of race and smoking with CRP on IGF-I. Indeed, a study reported inverse CRP–IGF-I correlations that were significant in only one of three ethnic groups [9].

MATERIALS AND METHODS

Study sample

The CMHS was designed to compare 8-year longitudinal changes in serum hormone concentrations and growth factors between 624 black and 796 white male CARDIA subjects who had serum samples available at both year 2 (1987–88) and year 10 (1995–96) exams. Year 7 (1992–93) serum samples were not required to be available as part of the inclusion criteria, but were used in the CMHS, if available. A detailed description of the CMHS has been published elsewhere [33]. The present study examines associations of CRP with IGF-I and IGFBP-3 using data collected at the year 7 exam, as this is the only examination at which CRP data, growth factor, and diet data were obtained contemporaneously. Of the 1 420 men, 1 211

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had hormone data at year 7, and of these, 1 197 had CRP measured. Further exclusions from the analyses, with some men meeting multiple exclusions, included: History of heart problems (n = 92); cancer (n = 12); digestive disease (n = 53); liver disease (n = 14); peripheral vascular disease (n = 8); stroke or TIA (n = 1); gout in the past year (n = 3); current diabetes (n = 17); current use of aspirin (n = 48); current use of cholesterol-lowering medication (n = 1); current observation of a weight-reducing diet (n = 29); and current use of an anti-inflammatory drug (n = 23). This left 935 men. Additionally, we excluded data from men with missing (n = 21) or extreme energy intake at year 7 (<800 kcal/day or >8 000 kcal/day, n = 30) because these data are potentially unreliable, missing covariate data (n = 7) and men with CRP > 10 mg/L (n = 27), because these men potentially have an undiagnosed inflammatory condition. The final sample consisted of 364 and 486 black and white men, respectively.

Data collection

Data were collected by centrally trained and certified technicians according to the CARDIA manual of operations. The quality of the data collection was monitored by the Coordinating Center and the CARDIA Quality Control Committee throughout the study. Informed consent was obtained from each participant at each examination. Participants were asked to fast for 12 hours before each examination. Venous blood was drawn between 7:30 a.m. and noon from over 95% of the CMHS participants. There were no meaningful differences in average time of blood drawing between black men and white men.

Serum measures

C-reactive protein was measured using a BNII nephelometer (Dade Behring, Deerfield, IL) at the University of Vermont. Intra-assay coefficients of variation ranged from 2.3% to 4.4%, and interassay coefficients of variation ranged from 2.1% to 5.7%.

IGF-I and IGFBP-3 were measured using immunoradiometric assay kits (Diagnostic Systems Laboratory, Webster, TX) in the laboratory of the late Dr. Christopher Longcope. Assay variability was monitored by including 10% blind quality control samples in each batch of samples. The quality control serum was obtained from a large pool that was aliquoted into storage vials, labeled identically to those for the CARDIA participant samples. The within- and between-batch coefficients of variation were 4.4% and 10.4%, respectively, for IGF-I, and 4.8% and 8.0%, respectively, for IGFBP-3.

Potential confounders

Potential confounders of the relationship between CRP and IGF-I include lifestyle factors such as BMI, smoking [34,35], alcohol intake [36], exercise and dietary factors such as protein, low caloric intake, [26], fiber [27], magnesium [37,38], and omega-3 fatty acids [28]. Because the metabolic syndrome has been associated with both serum IGF-I concentrations and markers of inflammation [7–11], individual components of the metabolic syndrome are potential confounders as well.

Total triglyceride levels were determined enzymatically [39]. High density lipoprotein (HDL) cholesterol level was determined by the dextran sulfate method of Warnick et al. [40] and LDL cholesterol was calculated using the Friedewald equation [41]. Insulin resistance was assessed using homeostasis model assessment of insulin resistance (HOMA-IR [glucose(mmol/liter) *insulin(mIU/liter)/22.5]) [42].

Blood pressure was measured three times at 1-minute intervals using a random-zero cuff sphygmomanometer, and the average of the second and third readings was used. Height and weight were measured with the participant wearing light clothing and no shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest half-pound (0.2 kg). Body mass index

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was computed as weight (kg) divided by height squared (m^2). Waist circumference was measured in duplicate at the narrowest part of the waist. Age, race, and number of cigarettes smoked per day were self-reported. Alcohol intake (ml/day) was computed from self-reported weekly consumption of beer, wine, and liquor [43]. A physical activity score was obtained from the CARDIA Physical Activity History, a modified version of the Minnesota Leisure Time Physical Activity Questionnaire [44].

A dietary history using an interviewer-administered quantitative food-frequency questionnaire was obtained at year 0 and year 7 [45]. A certified nutritionist interviewed participants on frequency of food consumption in the past month from a list of approximately 100 foods. Subjects reported on frequency, amount, and method of food preparation for each food item reported during the previous month. The University of Minnesota Nutrition Coordinating Center Nutrient Database was used to estimate nutrient intake (NCC Nutrient Database, Version 20, October 1991, Nutrition Coordinating Center, University of Minnesota, Minneapolis). Details regarding the development and implementation of this instrument are provided elsewhere [45].

Statistical analysis

Year 7 descriptive statistics of potential confounders were calculated across quartiles of CRP for black men and white men separately. CRP was log transformed for regression analysis. Nutrient variables were adjusted for in analyses as absolute intakes and as nutrient densities. Because some studies suggest there are ethnic differences in the relationships of some potential cofounders with either IGF-I or CRP, crude associations and multivariable associations of log CRP with IGF-I were assessed with linear regression analysis separately for each race. To formulate a multivariable model, first age-adjusted associations of each potential confounder with IGF-I were assessed using linear regression. All potential confounders which were significant at the $p = 0.20$ level were then assessed in a multivariable regression model and those which were not significant at the $p = 0.10$ level were removed one at a time [46]. After a collection of significant variables was found, all variables that were originally excluded from the first multivariable model were added back one at a time to see if they became significant. Finally, log CRP was added to the model. We conducted tests for interaction between log CRP and selected variables such as cigarette smoking, which affects hepatic drug metabolism [32], intake of alcohol, which is metabolized by the liver and might affect liver enzyme activity [47,48], and BMI, which also might affect liver enzyme activity [48]. Finally, data from black and white men were combined and three way tests for interactions of race with log CRP and the selected variables were done. A similar analysis was done for IGFBP-3.

To assess the magnitude of the differences in IGF-I as a function of CRP, mean IGF-I was computed for quartiles of CRP adjusting for all covariates included in the regression model.

RESULTS

Mean IGF-I (168 ng/ml in black and 186 ng/ml in white men) and IGFBP-3 (3 076 ng/ml in black and 3 445 ng/ml in white men) levels were significantly lower ($p = 0.009$ and $p < 0.0001$, respectively), and mean log CRP levels (−0.01 in black and −0.24 in white men) were significantly higher ($p = 0.001$) in black men compared to white men. Mean BMI, alcohol consumption, cigarettes smoked per day, and animal protein consumed generally increased across quartiles of CRP in both black and white men (Table 1). Mean HDL cholesterol decreased and LDL cholesterol, triglycerides, glucose, waist circumference, systolic blood pressure, and HOMA-IR tended to increase across quartiles of CRP.

In unadjusted analysis (Table 2), mean IGF-I concentrations were lower across quartiles of higher CRP. This association was stronger in black men. The regression coefficient for log

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CRP was highly significant in blacks ($p = 0.0004$), but not in whites ($p = 0.11$). The full multivariable model adjusted for age, BMI, smoking status, alcohol intake, animal protein intake, calcium intake, total calories/day, triglycerides, HDL cholesterol, and HOMA-IR. Because 42 white men and 62 black men were missing data on some metabolic syndrome variables, we examined the effect of excluding triglycerides, HDL cholesterol, and HOMA-IR from the full model. These three variables did not appreciably confound the association of log CRP with IGF-I, and therefore we present the model excluding them (Table 2). In this model, the reduction in mean IGF-I remained significant ($p = 0.02$), albeit somewhat attenuated for black men. The difference in mean IGF-I concentrations between the highest and lowest quartiles of CRP was 26 ng/ml. After adjusting for confounders, there was no association for white men. Associations of log CRP with IGF-I were similar regardless of whether absolute nutrient intakes or nutrient densities were used.

In the unadjusted regression model for IGFBP-3 (Table 2), log CRP was not significant for either black ($p = 0.14$) or white men ($p = 0.64$). Similarly, in multivariable analysis, log CRP was not associated with IGFBP-3 for either black or white men.

We tested for interactions between log CRP and smoking status, alcohol intake, and BMI for black and white men separately. For IGF-I, only the two-way interaction with smoking status was statistically significant for black men ($p = 0.02$) (Table 3). For black non-smokers, there was no association between CRP and IGF-I levels. However, for smokers, there was a strong inverse association. The difference in mean IGF-I concentrations between highest and lowest quartiles of CRP was 100 ng/ml and the coefficient for log CRP was highly significant ($p = 0.0001$). When the model was additionally adjusted for number of cigarettes smoked per day, the association between CRP and IGF-I remained strong ($\beta = -38.6$, $p = 0.0003$). There were no associations for white men. There were no significant interactions for IGFBP-3.

After pooling the data for black and white men, only the three-way interaction of log CRP, smoking status and race was significant ($p = 0.03$).

DISCUSSION

Although the IGF-axis and inflammatory processes are important in several disease contexts, they generally have not been linked except in the setting of stunted growth in pediatric inflammatory and adult inflammatory conditions. In this study, we found an inverse association between CRP and IGF-I in black men but not white men. In black men, there was a 26 ng/ml difference in mean IGF-I levels between the highest and lowest quartiles of CRP. Smoking was a strong modifier of the effect of CRP on IGF-I in black men; the quartile 4 vs. quartile 1 difference was 100 ng/ml.

Many studies of CRP and inflammatory cytokines are limited in that they included only subjects with chronic inflammatory conditions. At least three studies documented low IGF-I levels in children with IBD [49–51], but attributed them to undernutrition or reduced energy intake. On the other hand, Katsanos et al. [52] examined differences in IGF-I concentrations in adults with IBD from a control group and, based on measures of BMI and skinfold thicknesses, serum albumin, prealbumin, and dietary protein and energy intake, determined the nutritional status of the patients to be adequate. Therefore, they concluded that undernutrition did not account for the lowered IGF-I concentrations, but suggested inflammatory cytokines, as evidenced by the raised IL-6 levels, had a role. In men with prostate cancer, Latif et al. [21] reported an age-adjusted partial correlation between CRP and IGF-I and IGFBP-3 of −0.412 ($p = 0.008$) and −0.277 ($p = 0.05$), but cautioned that the correlations might reflect the patients' nutritional decline associated with prostate cancer. The CRP–IGF-I association also was reported in subjects with the metabolic syndrome after adjusting for age, gender, smoking status, and waist

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circumference ($r = -0.18$, $p = 0.05$) [53], and in three ethnic groups without adjusting for confounders [9]. Based on a healthy and generally well-nourished sample of men, our results were similar even after adjustment for total caloric intake and other nutritional factors. Because most human studies, including the present study, are cross-sectional, the causal nature of the association between CRP and IGF-I is unclear.

Studies from mouse models provide evidence of a causal relation, though indirect, between high IL-6 levels and low IGF-I concentrations. DeBenedetti et al. [5], showed that NSE/hIL-6 transgenic mice expressing high levels of IL-6 since birth had a reduced growth rate resulting in the mice being 50–70% the size of nontransgenic littermates. These transgenic mice had normal production of GH, but markedly reduced levels of circulating IGF-I. Importantly, food intake was controlled and ensured to be comparable between small transgenic mice and nontransgenic littermates. They concluded that the decrease in IGF-I production that was mediated by IL-6 was a mechanism by which chronic inflammation impairs growth. In a later study [3], they reported that NSE/hIL-6 mice have normal liver IGF-I production, though they have accelerated IGF-I clearance, resulting in low serum IGF-I levels. Thissen and Verniers [6] showed that in primary culture of rat hepatocytes, IL-1β and TNF-α, but not IL-6, inhibit IGF-I mRNA response to GH, suggesting these two cytokines may directly decrease circulating IGF-I at the hepatocyte level. Thus, whereas IL-1β and TNF-α might diminish hepatic production of IGF-I, overexpression of IL-6 does not, but rather increases clearance of IGF-I, and so reduces IGF-I concentrations [3].

The interrelationships of cigarette smoking and the IGF and inflammatory systems may be complex. Cigarette smoking has been associated with lower IGF-I and IGFBP-3 levels in men [54] and with higher CRP levels in some [34,55] studies. These observations are consistent with the hypothesis that CRP is inversely associated with IGF-I concentrations. However, cigarette smoking is also an effect modifier in studies in which CRP has been either an exposure or an outcome. For example, one study found smoking is a powerful modifier of the associations of gender, obesity, and diabetes status with CRP [56]. In the case of gender, mean levels of CRP are higher in women than in men among never smokers, but among ever smokers mean CRP levels are higher in men [56]. More recently, cigarette smoking has been reported to modify the relation of hormone replacement therapy with CRP in women [57]. Smoking is also an effect modifier for the association between CRP and common carotid artery intima-media thickness [58], a measure of subclinical atherosclerosis, and risk of coronary heart disease [59]. The mechanism underlying the interaction of smoking and CRP is unknown. It is also unclear why this interaction was not present in white men.

The possibility that our finding for black men was spurious can not be ruled out. However, given that the test for a three-way interaction of race with smoking and CRP was statistically significant, and that there are racial differences in nicotine metabolism [31] and in cytokine genotype distributions [29], the interaction might be plausible. Moreover, there is precedent for studying associations of factors with IGF-I levels separately by race. McGreevy et al. [60] identified variables that influence IGF-I levels differently in black and white men: they found age is inversely associated with IGF-I levels in white men, but not in black men. On the other hand, height was positively associated with IGF-I levels in black men, but inversely associated in white men [60]. Another study provides some evidence, although not very strong, that racial differences in the association of CRP with IGF-I exist [9]. Heald et al. [9] reported Spearman correlations of −0.10, −0.13, and −0.31, in Europeans, African Caribbeans, and Pakistanis, respectively. Only the correlation for Pakistanis was statistically significant, however these correlations were not adjusted for confounders.

There are some limitations to this study. In addition to being cross-sectional with associations observed at only one point in time, no data on IL-6 or other cytokines that stimulate CRP

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production were available. Such data would have provided more direct evidence of an inverse association between inflammation and IGF-I concentrations. However, this study was sufficiently large to permit examination of the IGF- CRP associations separately by race. This is of value since there are ethnic differences in the distributions of CRP and IGF-I [61,62] and some studies suggest that there are ethnic differences in the relationships of BMI and fitness with either IGF-I or CRP [63,64].

In summary, results of this study show an inverse association of CRP with IGF-I in black men and the inverse association was modified by smoking status. These findings were observed only in black men and not white men. Given the importance of the IGF system to major health matters that include development, aging, cancer, diabetes, and cardiovascular disease, future studies could also focus on the causal nature of the association between CRP and IGF-I.

Acknowledgments

This research was supported by U.S. Public Health Service grant RO1-CA770403 from the National Cancer Institute and U.S. Public Health Service contracts NO1-HC-48047, NO1-HC-48048, NO1-HC-48049, NO1-HC-48050, and NO1-HC-95095 from the National Heart, Lung, and Blood Institute. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1

Year 7 characteristics of 364 black and 486 white male participants from the CARDIA Male Hormone Study (1992–93) by quartile of C-reactive protein (CRP)*

	Black men				White men			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
CRP range, mg/L	0.15–0.41	0.42–0.83	0.84–1.79	1.80–9.96	0.15–0.41	0.42–0.83	0.84–1.79	1.80–9.96
Age (yrs)	31.6 (3.7)	30.1 (3.6)	31.1 (3.5)	32.1 (4.0)‡	32.1 (3.7)	32.3 (3.3)	33.2 (3.0)	32.2 (3.2)‡
BMI (kg/m^2)	24.6 (3.5)	25.8 (3.4)	26.9 (4.7)	29.2 (5.9)‡	23.8 (2.6)	25.5 (2.8)	26.6 (3.3)	28.0 (5.4)‡
Alcohol intake (ml)	12.6 (19.5)	12.5 (21.7)	17.8 (29.4)	19.3 (33.5)	12.1 (17.1)	14.1 (18.9)	12.9 (18.6)	19.2 (27.8)‡
Heavy PA†	361 (251)	355 (259)	284 (228)	307 (282)	259 (189)	283 (211)	264 (204)	228 (207)
Smokers, N (%)	17 (21.0)	24 (28.9)	39 (41.9)	39 (36.4)	18 (13.6)	27 (20.6)	28 (23.9)	34 (32.1)
Cigarettes/d	2.1 (5.2)	2.6 (5.3)	4.7 (6.9)	4.0 (7.4)‡	1.6 (5.2)	2.9 (6.8)	4.3 (8.8)	7.7 (12.6)‡
Caloric intake (kcal)	3477 (1401)	3514 (1514)	3275 (1564)	3867 (1530)‡	3085 (1090)	3078 (1004)	2914 (1106)	3319 (1249)
Animal protein (gm)	83.6 (41.8)	87.9 (45.6)	78.8 (38.4)	98.1 (48.6)‡	70.7 (32.1)	71.5 (26.9)	72.1 (35.3)	78.4 (34.1)
Milk (servings)	0.84 (1.01)	0.82 (0.98)	0.81 (1.04)	0.87 (1.06)	1.38 (2.00)	1.19 (1.26)	1.31 (2.00)	1.49 (1.61)
Calcium (mg)	1159 (564)	1166 (526)	1072 (506)	1279 (641)	1399 (794)	1269 (476)	1242 (730)	1365 (666)
Magnesium (mg)	463 (258)	465 (227)	440 (211)	506 (251)	507 (226)	506 (213)	469 (210)	471 (182)
Fiber (gm)	23.4 (10.2)	25.5 (13.4)	23.1 (11.2)	26.4 (13.6)	28.3 (12.8)	27.4 (13.0)	24.4 (9.5)	29.6 (51.9)
Omega-3 fatty acids (gm)	0.22 (0.27)	0.22 (0.24)	0.21 (0.27)	0.23 (0.20)	0.14 (0.20)	0.16 (0.28)	0.16 (0.18)	0.12 (0.11)
Education (years)	13.8 (1.9)	14.1 (2.5)	13.5 (2.1)	13.7 (2.5)	15.5 (2.6)	15.4 (2.7)	15.6 (2.6)	14.7 (2.7)‡
HDL cholesterol	56.2 (13.3)	51.1 (14.4)	51.3 (14.1)	46.7 (11.9)‡	48.3 (10.7)	45.7 (10.4)	43.4 (11.1)	40.4 (9.3)‡
LDL cholesterol	105 (33)	104 (32)	113 (36)	119 (31)‡	108 (32)	116 (30)	115 (30)	117 (34)
Triglycerides	68 (32)	82 (59)	80 (44)	100 (81)‡	87 (82)	96 (60)	110 (79)	115 (68)‡
Glucose	90 (7)	90 (9)	90 (9)	93 (10)	89 (11)	91 (7)	93 (9)	93 (8)‡

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	Black men				White men			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Waist circumference	81.1 (8.0)	84.8 (8.4)	87.6 (10.5)	93.1 (14.0)‡	82.1 (7.2)	86.4 (7.3)	90.2 (8.8)	93.6 (12.4)‡
SBP	111 (10)	113 (11)	116 (12)	115 (12)‡	107 (9)	112 (10)	111 (10)	113 (11)‡
HOMA-IR	2.54 (1.16)	3.43 (3.32)	3.18 (2.91)	4.10 (2.86)‡	2.20 (0.72)	2.54 (1.18)	2.97 (1.53)	3.36 (1.84)‡

*Values expressed as mean (SD) unless noted otherwise.

†PA: physical activity.

‡$p < 0.05$ across quartiles.

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Table 2

Unadjusted and multivariable-adjusted associations of CRP with IGF-I and IGFBP-3 (1992–1993) in the CARDIA Male Hormone Study

		Black men		White men	
	Quartile of CRP	**Mean (se) (ng/ml)**	***p* value**	**Mean (se) (ng/ml)**	***p* value**
IGF-I					
Unadjusted	Q1	184.7 (11.09)		195.8 (8.09)	
	Q2	182.8 (10.96)		191.6 (8.12)	
	Q3	166.8 (10.35)		174.1 (8.60)	
	Q4	145.4 (9.65)		178.4 (9.03)	
	B[†] for log CRP	−17.9 (4.96)	0.0004	−6.7 (4.19)	0.11
Multivariable	Q1	181.0 (11.26)		187.8 (8.44)	
adjusted[*]	Q2	176.2 (10.88)		190.8 (8.02)	
	Q3	164.7 (10.22)		178.3 (8.60)	
	Q4	155.1 (9.94)		184.7 (9.43)	
	β[†] for log CRP	−13.1 (5.36)	0.02	−0.7 (4.66)	0.89
IGFBP-3					
Unadjusted	Q1	3170 (100.8)		3465 (80.4)	
	Q2	3131 (99.6)		3548 (80.7)	
	Q3	2997 (94.1)		3364 (85.4)	
	Q4	3030 (87.7)		3381 (89.7)	
	β[†] for log CRP	−67.6 (45.3)	0.14	−19.6 (41.6)	0.64
Multivariable	Q1	3181 (101.2)		3429 (80.6)	
adjusted[‡]	Q2	3102 (100.7)		3533 (80.1)	
	Q3	2991 (94.4)		3396 (85.1)	
	Q4	3049 (88.2)		3408 (90.7)	
	β[†] for log CRP	−59.7 (45.8)	0.19	9.7 (42.6)	0.82

[*] Adjusted for age, BMI, smoking status, alcohol intake, animal protein intake, calcium intake, and total caloric intake.

[†] β represents change in IGF-I or IGFBP-3 level associated with 1 unit change of log CRP.

[‡] Adjusted for age and cigarettes/day.

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Table 3

Multivariable-adjusted* associations of CRP with IGF-I at year 7 (1992–1993) stratified by smoking status in the CARDIA Male Hormone Study

		Black		White	
	Quartile of CRP	**Mean (se) (ng/ml)**	***p* value**	**Mean (se) (ng/ml)**	***p* value**
Non-smokers	Q1	169.1 (12.53)		195.1 (9.22)	
	Q2	175.0 (12.8)		198.1 (9.14)	
	Q3	176.2 (13.29)		175.9 (10.00)	
	Q4	173.5 (12.31)		187.6 (11.6)	
	β† for log CRP	−2.0 (6.27)	0.75	−2.9 (5.48)	0.59
Current	Q1	221.3 (24.44)		159.9 (21.69)	
smokers	Q2	182.4 (20.34)		162.9 (16.90)	
	Q3	151.2 (15.92)		182.8 (17.34)	
	Q4	120.8 (16.69)		171.4 (15.46)	
	β† for log CRP	−39.8 (10.13)	0.0001	5.6 (8.92)	0.53

*Adjusted for age, BMI, alcohol intake, animal protein intake, calcium intake, and total caloric intake.

†β represents change in IGF-I level associated with 1 unit change of log CRP.