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Intraindividual variability of C-reactive protein: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—The intraindividual variability of C-reactive protein (CRP) remains uncertain. Although guidelines suggest stability of serial CRP values comparable to that of cholesterol measures, several studies indicate greater fluctuations of CRP. We sought to compare the intraindividual variability of CRP with that of cholesterol measures using the Multi-Ethnic Study of Atherosclerosis (MESA).

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Methods—CRP measurements were available in 760 MESA participants after exclusion of those with comorbidities or medications known to affect CRP or CRP ≥ 10 mg/L. Serial values were available for 255 participants. The intraclass correlation coefficient (ICC) was quantified for CRP, total cholesterol (TC), and non-HDL-cholesterol (non-HDL-C) as the ratio of between-subject variance to the sum of between-subject and within-subject variance. Fluctuation between baseline and follow-up categories was calculated by cross-classifying participants according to baseline tertiles.

Results—The multivariable-adjusted ICC of CRP was 0.62 (95% CI, 0.55–0.68), significantly lower than that of TC (0.75; 95% CI, 0.70–0.81; $p=0.001$ vs CRP) and non-HDL-C (0.76; 95% CI, 0.71–0.81; $p=0.001$ vs CRP). 51% of participants in the highest baseline CRP tertile had discordant values on follow-up, while 54% and 27% were discordant in the middle and lowest baseline CRP tertiles. Among participants with baseline CRP levels exceeding 3 mg/L, a clinical threshold for higher risk, 69% had subsequent measurements falling within a lower risk category.

Conclusions—In the MESA cohort, intraindividual variation of CRP was significantly greater than that for cholesterol measures. Our results suggest that further evaluation of CRP variability is needed in large prospective studies using shorter intervals between measurements.

1. Introduction

The past decade has witnessed a proliferation of adjunctive risk prediction measures aiming to improve cardiovascular risk assessment. One of the more popular potential methods to address the so-called “detection gap” [1] in cardiovascular disease prognosis is C-reactive protein (CRP), a 110 kDa acute phase protein synthesized by hepatocytes, arterial smooth muscle cells, and adipocytes in response to inflammatory cytokines [2–5]. Circulating levels of CRP have demonstrated incremental prognostic value above and beyond traditional risk factors, resulting in incorporation of CRP into current guidelines for risk assessment [6].

Despite the use of CRP to refine cardiovascular risk assessment [7], the intraindividual variability of CRP remains uncertain. On the one hand, the 2010 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults described CRP concentrations as “fairly constant and repeatable over time [7]” citing three studies [8–10] including the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study. In a substudy of JUPITER, CRP was tracked in 8901 individuals randomized to placebo [8]. Inclusion criteria included LDL-cholesterol (LDL-C) <130 mg/dL, CRP ≥ 2 mg/L on two separate occasions performed four weeks apart, and absence of CHD (coronary heart disease) or CHD risk equivalents [11]. The study concluded that concentrations of CRP “show strong tracking,” although the intraclass correlation coefficient (ICC) of repeated CRP measurements was 0.50 (95% CI 0.49–0.51), lower than that of total cholesterol (TC) (0.60, 95% CI 0.59–0.61) [8].

Arguing against favorable stability over time, the other two publications cited as supporting evidence of acceptable variability in the 2010 ACCF/AHA Guideline [7] in fact suggest the contrary [9, 10]. A substudy of the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) cohort examined the variability of CRP and TC in 936

healthy men [9]. Comparing measurements obtained three years apart, the ICC of CRP was 0.54 (95% CI 0.48–0.59) and that of TC was 0.75 (95% CI 0.70–0.78). Observing “considerable within-subject variation over time,” the authors concluded that “three serial determinations (with a single assay measurement in each) should be done to achieve a reliability of 0.75, the reliability found for total cholesterol [9].” The analysis of the Seasonal Variation of Blood Cholesterol Study (SEASON), an observational study of healthy adults, examined serial CRP measurements in 113 participants [10]. TC and CRP levels were obtained every three months for one year. The ICC of CRP was 0.66; in comparison, that of TC was 0.82 [10].

The Multi-Ethnic Study of Atherosclerosis (MESA) provides an opportunity to further examine the intraindividual variability of CRP in a primary prevention population across a wide range of baseline CRP values. Importantly, the present study is novel compared to other large prospective studies [12] in that: 1) the time intervals between serial CRP measurements were shorter and 2) the cohort was better characterized, allowing for control of a greater number of covariates that may exaggerate CRP variability.

2. Methods

2.1 Study population

The MESA cohort comprises 6814 community-based men and women, aged 45–84 years and free of self-reported cardiovascular disease, recruited from four ethnic groups (White, African American, Chinese American, and Hispanic) at 6 centers in the United States. The Institutional Review Board at the University of Pennsylvania approved the analysis herein, and all participants previously provided written informed consent prior to enrollment at the MESA study centers. CRP was measured in 6762 participants at baseline, that is, MESA Exam 1 (July 2000–August 2002). A second CRP was measured for an ancillary study on body composition in 780 participants at MESA Exam 2 (September 2002–February 2004) and 1187 participants at MESA Exam 3 (March 2004–September 2005). Exam 2 and Exam 3 are herein referred to as follow-up. Patients at any visit reporting the following comorbidities or medications that may augment the intraindividual variability of CRP were excluded: history of asthma, arthritis, cancer, or liver disease; within the past two weeks, history of fever, cold or flu, urinary infection, bronchitis, sinus infection, pneumonia, tooth infection, gout flare, or arthritis flare; oral steroids, statin and non-statin lipid-lowering medications, or non-steroidal anti-inflammatory drugs. Consistent with current clinical practice, patients with any CRP value ≥ 10 mg/L were also excluded.

2.2 CRP, cholesterol and study covariates

CRP was determined by immunonephelometry (N High Sensitivity CRP; Dade Behring Inc, Deerfield, IL, USA). Details regarding assay performance and specimen handling are presented in Supplementary Table 1. Intra-assay and inter-assay coefficients of variation (CV) for CRP were 2.3–4.4% and 2.1–5.7%, respectively. Fasting triglycerides were measured in plasma using a glycerol blanked enzymatic method (Trig/GB, Roche Diagnostics, Indianapolis, Indiana). Fasting total cholesterol (TC) was measured in plasma on the Hitachi 911 using a cholesterol esterase, cholesterol oxidase reaction (Chol R1,

Roche Diagnostics). The same reaction was also used to measure HDL-cholesterol (HDL-C) after precipitation of non-HDL-cholesterol (non-HDL-C) with magnesium/dextran. Non-HDL-C was calculated as TC minus HDL-C. TC was selected as a comparator for historical reasons, as this was the referent cholesterol measure used in prior studies of CRP variability. Non-HDL-C was also evaluated to provide insight into the intraindividual variability of a more clinically meaningful cholesterol parameter. Intra-assay and inter-assay CVs for TC were 1.6% and 2.0%, respectively. Intra-assay and inter-assay CVs for HDL-C were 3.6% and 4.1%. Systolic blood pressure was measured as previously described [13]. Diabetes status was defined according to the American Diabetes Association fasting criteria algorithm incorporating fasting glucose and use of diabetes medication. Highest level of education completed, amount of moderate and vigorous physical activity, smoking status, and current antihypertensive use were determined by patient report.

2.3 Statistical analyses

Standard descriptive statistics were calculated for participants at baseline and at follow-up. A $\ln$ (natural log) transformation was applied to normalize the distribution of CRP. We quantified the ICC of CRP, TC, and non-HDL-C as the ratio of between-subject variance to the sum of between-subject and within-subject variance. Variance components were estimated from a linear-mixed effects model with subject-specific random intercepts for each outcome [14], such that the variance of the random intercepts quantified the between-subject variance. All participants were included in the model regardless of the number of observations available (at least one and at most two). Because CRP, TC, and non-HDL-C levels were expected to vary according to covariate values, we obtained estimates from a model that adjusted for design variables, i.e. study site and time (in days) between measurements; a model that additionally adjusted for baseline age, gender, and ethnicity; and a model that additionally adjusted for education, current body mass index, current smoking, current physical activity, current diabetes status, current triglyceride level, and the interaction between current systolic blood pressure level and current antihypertensive medication use. A parametric bootstrap of 1000 iterations was used to calculate confidence intervals for the ICC and P values to determine whether the difference in ICC between TC (or non-HDL-C) and CRP was statistically significant [15]. A sensitivity analysis was performed restricting the calculation of ICC of CRP, TC, and non-HDL-C to the 255 subjects with serial CRP measurements.

For the subset of participants with two CRP measurements, the linear association between CRP and non-HDL-C at baseline and follow-up were explored using graphical representations and Pearson correlation coefficients. The discordance rate between baseline and follow-up categories was calculated by cross-classifying participants according to baseline tertiles to facilitate direct comparisons between CRP and non-HDL-C. Confidence intervals for the discordance rates were based on 1000 bootstrap samples.

All analyses were completed using R 2.12.0 (R Development Core Team, Vienna, Austria), including the nlme extension package.

3. Results

3.1 Study cohort

6773 participants underwent CRP measurement in the MESA cohort at Exam 1, 2, and/or 3. After excluding participants with comorbidities or medications that may increase CRP variability or any CRP ≥ 10 mg/L, a total of 760 participants (11%) were eligible for analysis (Supplementary Figure 1). Of these participants, 255 (34%) were evaluated with two serial CRP measurements at Exams 1 and 2 or Exams 1 and 3. A median of 1.4 years and 3.3 years elapsed between Exams 1 and 2 and Exams 1 and 3, respectively.

Table 1 provides the demographic information and cardiovascular risk factors of participants evaluated at baseline and/or follow-up. At baseline, the mean age of participants was 59 years, and 40% of participants were women. Whites, African Americans, Chinese Americans, and Hispanics comprised 35%, 23%, 22%, and 21% of the cohort, respectively. The median CRP level at baseline was 1.23 mg/L. Mean TC and non-HDL-C levels at baseline were 193 mg/dL and 142 mg/dL, respectively. Supplementary Table 2 summarizes the characteristics of the 255 patients for whom two CRP levels were available.

3.2 Intraclass correlation coefficients

A comparison of follow-up and baseline CRP and TC levels for the subset of participants with two CRP measurements is shown in Figure 1. The linear correlation coefficient for serial levels of CRP was 0.49 (95% CI, 0.40–0.58) and that of repeated TC measures was 0.77 (95% CI, 0.72–0.82) (Figure 1). The unadjusted ICC of CRP was 0.68 (95% CI, 0.62–0.72), significantly lower than that of TC (0.77; 95% CI, 0.73–0.82; $p=0.005$ vs CRP) and non-HDL-C (0.77; 95% CI, 0.73–0.82; $p=0.007$ vs CRP) (Table 2). After adjusting for site, time, age, gender, ethnicity, education, body mass index, current smoker, physical activity, diabetes status, systolic blood pressure level, antihypertensive medication, and triglyceride level, the ICC of CRP was 0.62 (95% CI, 0.55–0.68). This value was significantly lower than the multivariable-adjusted ICC of TC (0.75; 95% CI, 0.70–0.81; $p=0.001$ vs CRP) and non-HDL-C (0.76; 95% CI, 0.71–0.81; $p=0.001$ vs CRP). A sensitivity analysis restricted to the 255 participants with serial CRP measurement demonstrated similar ICC results.

3.3 Fluctuation between tertiles

Fluctuation between tertiles occurred more frequently with serial assessment of CRP than of non-HDL-C (Figure 2, Supplementary Table 3). Overall, the rate of discordance for CRP, that is, change in CRP tertile from baseline to follow-up measurement, was 44% (95% CI, 34%–49%). 51% of participants in the highest baseline tertile had values within the lowest or middle tertile on follow-up. For participants in the middle and lowest baseline CRP tertiles, discordant follow-up values were observed in 54% and 27%, respectively. Reclassification from the highest to the lowest CRP tertile occurred in 8 of 86 (9%) participants; conversely, reclassification from the lowest to the highest CRP tertile occurred in 5 of 85 (6%) participants. In contrast, the rate of discordance for non-HDL-C was 33% (95% CI, 27%–40%; $p=0.044$ vs CRP). Non-HDL-C levels were discordant on serial evaluation among 31%, 47%, and 22% of participants in the highest, middle, and lowest baseline non-HDL-C tertiles. Reclassification from the highest to the lowest non-HDL-C

tertile occurred in 3 in 89 (3%) participants; conversely, reclassification from the lowest to the highest non-HDL-C tertile occurred in 2 in 83 (2%). Results were similar for TC (Supplementary Table 3).

Similar findings were observed using clinical risk categories for CRP defined by the 2003 AHA/Centers for Disease Control (CDC) consensus document (<1 mg/L, 1–3 mg/L, >3 mg/L) (Supplementary Table 4) [2]. Among individuals with CRP values within the average risk category (1–3 mg/L), 13% had follow-up CRP levels classified as high relative risk (>3 mg/L). Among participants with CRP levels in the high relative risk category at baseline, 69% had subsequent measurements falling within the low or average relative risk category.

4. Discussion

Most [6] but not all [16] studies have demonstrated a statistically significant improvement in cardiovascular risk prediction with the addition of CRP to traditional risk factors. Compared to lower risk CRP levels (<1 mg/L), higher risk values (>3 mg/L) confer an average 1.6-fold increase in the risk of cardiovascular events in multivariate-adjusted analyses [6]. Incorporation of CRP improves the area under the receiver operating curve (AUROC) by up to 0.009 in men and 0.002 in women [17, 18]. CRP appropriately reclassifies patients between risk categories, with a clinical net reclassification index of 15% [17, 18]. Based on these data, the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults provided CRP the following class IIa recommendation:

In men 50 years of age or older or women 60 years of age or older with LDL cholesterol less than 130 mg/dL; not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy [7].

Despite growing acceptance by national professional societies and continuing uptake by clinicians, concerns remain regarding available biologic variability data for CRP, a “fundamental prerequisite” for the appropriate application of CRP in the clinical setting [19, 20]. In the MESA cohort, our analysis demonstrated greater intraindividual variability for CRP than for TC or non-HDL-C. While TC and non-HDL-C demonstrated good reproducibility via ICC analysis [21], CRP did not. Fluctuation between tertiles was significantly higher for CRP than for the cholesterol comparators. Using clinically defined categories, one in eight participants deemed at average relative risk based on a single CRP measurement were reclassified as high relative risk based on subsequent evaluation, and the majority of participants with a high relative risk CRP level spontaneously developed values in the low or intermediate relative risk range on follow-up.

The 2003 AHA/CDC consensus statement [2] and the 2009 Canadian Cardiovascular Society guidelines [22] recommended analysis of CRP at more than one occasion, optimally several weeks apart. The stipulation for serial assessment was absent in the recent 2010 ACCF/AHA Guidelines for the Assessment of Cardiovascular Risk in Asymptomatic Adults. No specific justification for this omission was provided in the guidelines. Our results

suggest that CRP levels may not be constant and repeatable over time and support the limitation of single CRP measurement to accurately refine cardiovascular risk.

In addition, our data suggest that, contrary to several prior reports, within-individual variability of CRP is not comparable to that of cholesterol [2]. In a systematic review of the literature, we observed that the weight of the evidence accumulated from multiple studies suggests that intraindividual variability of CRP in serial measurements exceeds that observed with cholesterol (Figure 3, Supplementary Figure 2) [8–10, 12, 23–28]. It should be noted that eligibility criteria for the JUPITER trial required two serial measurements of CRP above the threshold of 2 mg/L [11]. Because individuals with any CRP below 2 mg/L were excluded – in particular, those with an initial CRP level above 2 mg/L and a subsequent follow-up CRP value below 2 mg/L – the JUPITER substudy of CRP tracking may underestimate the true intraindividual variability of CRP in the general population.

Our study has several advantages over the recently published Emerging Risk Factors Collaboration (ERFC) analysis of 22,124 individuals, which reported comparable intraindividual variability for CRP and TC (age- and sex-adjusted regression-dilution ratios 0.58 versus 0.59) [12]. In the ERFC study, the mean interval between serial measurements was 5.1 years, with a standard deviation of 2.4 years and a range of 1 to 15 years. These intervals are greater than the intervals observed in our analysis (mean 2.6 years, standard deviation 0.9 years, and range 1.1 to 4.3 years). In the ERFC study, such a prolonged time frame attenuates the stability of TC relative to other parameters. Moreover, limited covariate data were available for adjustment in ERFC. Unmeasured secular trends, particularly over a prolonged timeframe, weaken the ability of the ERFC analysis to study intraindividual variability of CRP and TC. On the other hand, MESA's well-characterized cohort provided the opportunity to adjust for numerous covariates.

Strengths of this study include comprehensive adjustment for covariates and incorporation of non-HDL-C as a comparator in addition to TC, given the clinically relevant role of the former as a secondary goal of lipid-lowering therapy [29]. In addition, we expressed intraindividual variability of CRP in both statistically rigorous and clinically meaningful terms.

Rigorous eligibility criteria resulted in a sample size of 760 participants for the present analysis. While the study cohort represented only a minority (11%) of the MESA population, we believe that multiple exclusion criteria were necessary to minimize the variability of CRP. Infection, inflammation, and malignancy are a few of the disease states associated with higher circulating levels of the acute phase reactant [30]. For this reason, one might hypothesize that in a “real-world” setting, CRP variability may be greater than our findings suggest. In addition, the fact that only one-ninth of study participants were free of acute or chronic conditions that may exaggerate CRP levels suggests that appropriate measurement of CRP may not be straightforward in the clinical setting.

One limitation of this study is the lack of serial CRP data at shorter time intervals, precluding analysis of shorter-term intraindividual variability. However, our intent was to shed light on the clinical utility of a single CRP measure, not to assess short-term variability.

For this objective, our findings using intervals greater than one year remain clinically significant. A testing interval of one to three years is not prolonged from the perspective of primary prevention care and the critical clinical decision to initiate lifetime statin use. Serial global risk assessment is recommended every five years for patients at low or intermediate risk according to the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults and the 2002 National Cholesterol Education Program Adult Treatment Panel III [7, 29]. As a result, significant spontaneous fluctuations in a risk metric are undesirable even when observed over a span of a few years. For this reason, there is ample precedent for drawing clinical conclusions based on serial CRP levels obtained at intervals exceeding one year. One of the three key studies cited in the discussion of CRP variability in the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults compared CRP measurements obtained three years apart [7, 9].

In addition, the magnitude of the variability of CRP observed in our study makes it difficult to dismiss the results simply because CRP levels were obtained at intervals exceeding one year. The analysis of fluctuation was unadjusted and therefore could be confounded. Although physical activity, BMI, and treated diabetes were not significantly different between baseline and follow-up ($p=0.87$, 0.34 , and 0.22 , respectively), there was significantly greater use of antihypertensive medications at follow-up ($p=0.009$) (Supplementary Table 2). 70% of participants exhibiting high relative risk CRP values at baseline subsequently developed low relative risk or average relative risk CRP levels on follow-up. It seems unlikely that these changes in CRP levels reflect true changes in risk. This reduction in atherothrombotic risk would have had to occur spontaneously, as participants initiating any lipid-lowering therapy were excluded from the analysis. Even if the assumption is made that substantial fluctuations in CRP levels accurately capture a rapidly changing, dynamic element of atherosclerotic risk, the variability of CRP may limit the utility of a single measurement for clinical decision-making. The clinical question prompting CRP measurement for cardiovascular risk refinement is whether or not long-term statin therapy should be initiated. It seems incongruous with chronic preventive management to deem 10 patients high relative risk and warranting statin therapy one year, but only 3 of these 10 patients remain high relative risk patients the next absent intervention. For example, glucose levels accurately depict the metabolic milieu at one particular moment. However, this reliable association does not overcome limitations of glucose in guiding clinical care. A single glucose measurement, regardless of how well it may describe the underlying metabolic state, does not provide sufficient information to guide the titration of hypoglycemic therapy. Accuracy alone does not render variability irrelevant.

Finally, though our study lacks very short-term variability data, our findings are consistent with available studies evaluating short-term CRP variability using intervals of less than one month. Macy evaluated CRP in 26 participants at baseline and 3, 6, 9, 12, 15, 18, 21, and 24 weeks thereafter [23]. Based on frequent short-term repeated assessment, within-subject variability was calculated at 42% for CRP, substantially higher than that of TC, which was 9%. Bogaty analyzed 70 stable CHD patients for whom two serial CRP levels separated by less than one month were available [25]. Although the interval was short, 38%, 46%, and 50% of the patients in the high-, average-, and low-risk groups, respectively, changed AHA/CDC risk categories at the second CRP measurement. Short-term variability remains a

data gap for CRP, an important one to address given the incorporation of CRP into national guidelines.

Clarifying the clinical value of CRP in the context of highly varied levels will be challenging. The ideal summary metric of multiple CRP measures to guide management decisions remains uncertain, as evidenced by conflicting recommendations. The 2003 AHA/CDC guidelines suggest averaging two measurements. The 2003 AHA/CDC guidelines suggest averaging two values [2], while the 2009 Canadian guidelines recommend using the lower of two values [22]. Efforts to identify a reliable approach to CRP interpretation may be important. Intraindividual variability suggests the possibility of underestimating the true association between CRP and cardiovascular outcomes due to regression-dilution bias.

In summary, intraindividual variation of CRP was observed in the MESA cohort, significantly greater than that for cholesterol measures. Further research is needed to evaluate the intraindividual variability of CRP across shorter time intervals; to re-assess the prognostic value of CRP using multiple assessments; and to determine the intraindividual variability of CRP within ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We examined the intraindividual variability of C-reactive protein (CRP) over time
- Intraclass correlation coefficients were calculated for CRP and non-HDL-cholesterol
- Fluctuation between tertiles and clinical categories was also assessed
- Our analysis controlled for covariates that can exaggerate CRP variability
- We report significantly greater variability for CRP than for non-HDL-cholesterol

Figure 1.

Follow-up versus baseline C-reactive protein level and total cholesterol level; shaded region indicates 95% confidence band based on the estimated linear association between follow-up and baseline.

Figure 2.

Change from baseline to follow-up C-reactive protein category and non-HDL cholesterol category; categories defined by tertiles of baseline levels.

Figure 3.

Overview of studies examining the intraindividual variability of C-reactive protein and total cholesterol. Time intervals from baseline CRP measures were as follows: JUPITER, 3 months, 1, 2, 3, 4 years, trial termination; MESA, 1.4 years, 3.3 years; MONICA, 3 years; Nasermoddelli, 1 year; SEASON, 3, 6, 9, 12 months; Wu, 2 years.

Table 1

Demographic information and cardiovascular risk factors for all participants.

Characteristic	Baseline N = 748	Follow-up N = 267
Age, mean (SD), y	59 (10)	60 (10)
Women, No. (%)	299 (40)	93 (35)
Ethnicity, No. (%)		
White	264 (35)	95 (36)
African American	169 (23)	44 (16)
Chinese American	161 (22)	61 (23)
Hispanic	154 (21)	67 (25)
Education beyond high school, No. (%)	634 (85)	227 (85)
Body mass index, mean (SD), kg/m ²	26.5 (4.3)	26.3 (4.1)
Current smoker, No. (%)	79 (11)	23 (9)
Physical activity, median (IQR), METmin/week	4364 (2190, 7663)	4868 (2265, 7928)
Diabetes status, No. (%)		
Normal	621 (83)	211 (79)
Impaired fasting glucose 82 (11)	34 (13)	
Untreated diabetes	13 (2)	8 (3)
Treated diabetes	32 (4)	14 (5)
Systolic blood pressure, mean (SD), mmHg	122 (20)	120 (20)
Antihypertensive medication, No. (%)	168 (22)	81 (30)
C-reactive protein, median (IQR), mg/L	1.23 (0.57, 2.61)	1.05 (0.53, 2.00)
Total cholesterol, mean (SD), mg/dL	193 (32)	195 (34)
Non-HDL-cholesterol, mean (SD), mg/dL	142 (33)	143 (34)
LDL-cholesterol, mean (SD), mg/dL	119 (30)	119 (29)
HDL-cholesterol, mean (SD), mg/dL	51 (14)	52 (16)
Triglycerides, mean (SD), mg/dL	119 (63)	119 (62)
Site, No. (%)		
University of California, Los Angeles, CA	169 (23)	45 (17)
Northwestern University, IL	183 (24)	75 (28)
Johns Hopkins University, MD	88 (12)	0
University of Minnesota, MN	99 (13)	50 (19)
Columbia University, NY	124 (17)	55 (21)
Wake Forest University, NC	85 (11)	42 (16)

SD = standard deviation; IQR = inter-quartile range

Table 2

Estimated intraclass correlation coefficients.

	C-reactive protein ICC (95% CI)	Total cholesterol ICC (95% CI); p value *	Non-HDL-cholesterol ICC (95% CI); p value *
Model 1	0.68 (0.62, 0.72)	0.77 (0.73, 0.82); 0.005	0.77 (0.73, 0.82); 0.007
Model 2	0.69 (0.64, 0.74)	0.77 (0.72, 0.82); 0.028	0.77 (0.72, 0.82); 0.038
Model 3	0.67 (0.62, 0.73)	0.76 (0.71, 0.81); 0.013	0.77 (0.72, 0.82); 0.011
Model 4	0.62 (0.55, 0.68)	0.75 (0.70, 0.81); 0.001	0.76 (0.71, 0.81); 0.001

ICC = intraclass correlation coefficient; CI = confidence interval

Model 1: Unadjusted

Model 2: Adjusted for site, time

Model 3: Adjusted for site, time, age, gender, ethnicity

Model 4: Adjusted for site, time, age, gender, ethnicity, education, body mass index, current smoker, physical activity, diabetes status, systolic blood pressure level, antihypertensive medication, triglyceride level

* Evaluating equality with ICC for C-reactive protein