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Tracking of High-Sensitivity C-Reactive Protein after an Initially Elevated Concentration: The JUPITER Study

Robert J. Glynn,[1,2*] Jean G. MacFadyen,[1,2] and Paul M Ridker[1,2,3]

BACKGROUND: The JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial suggests that increased high-sensitivity C-reactive protein (hsCRP) concentrations may be useful in decisions about the initiation of statin therapy for primary prevention of vascular disease. Although studies of specific populations have suggested that hsCRP is a reliable longitudinal marker, it is unclear how strongly hsCRP tracks in individuals after a single increased concentration.

METHODS: We evaluated tracking of hsCRP in 8901 individuals randomized to placebo in the JUPITER trial. These individuals had screening LDL cholesterol concentrations <130 mg/dL (<3.37 mmol/L) and hsCRP concentrations ≥2 mg/L, with subsequent hsCRP measurements made before randomization; at 13 weeks; 1, 2, 3, and 4 years later; and at trial termination. Longitudinal trends and associations were evaluated nonparametrically with box plots and Spearman correlations. After data transformation to achieve normality, repeated-measures regression models estimated the intraclass correlation of hsCRP, with and without controlling for known demographic, lifestyle, and medical determinants of hsCRP concentration. For comparison, we evaluated tracking of systolic and diastolic blood pressure; total, LDL, and HDL cholesterol; and fasting triglycerides.

RESULTS: The median hsCRP concentration in these untreated individuals showed modest regression to the mean over time, declining from 3.8 mg/L at randomization to 3.4 mg/L at 4 years. Tracking correlations for hsCRP over time were comparable to those for blood pressure and LDL cholesterol, but lower than those for HDL, fasting triglycerides, and total cholesterol. The intraclass correlation for repeated hsCRP measurements was 0.54 (95% CI, 0.53–0.55) without covariate adjustment and 0.50 (95% CI, 0.49–0.51) after adjustment for demographic, lifestyle, and comorbidity determinants.

CONCLUSIONS: Concentrations of hsCRP show strong tracking, even after selection of individuals with initially high values. Without statin therapy, increased concentrations of hsCRP generally remain high over time.

Measurement of high-sensitivity C-reactive protein (hsCRP)[4] provides independent information on the risk of future vascular events that can substantially improve risk classification *(1–6)*. Achieved hsCRP concentrations in both primary and secondary prevention trials of statin therapy correlate with the magnitudes of observed risk reductions in these trials *(7–9)*. The JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed that statin therapy directed to individuals with raised hsCRP concentrations could substantially reduce the rates of important vascular events *(10)*. An important question raised by these findings concerns the stability of increased hsCRP concentrations over time.

Several studies have examined the variation in hsCRP measurements within individuals over time, although most have followed small numbers of individuals or had only 2 repeated measurements. Among 214 patients in the placebo arm of the Cholesterol and Recurrent Events (CARE) trial who had 2 hsCRP measurements separated by 5 years, Ridker et al. found an age-adjusted partial correlation of 0.60 between the 2 log-normalized concentrations *(11)*. From 5 scheduled measurements made at 3-month intervals in 113 individuals, Ockene et al. found an estimated intraclass

[1] Center for Cardiovascular Disease Prevention, [2] Division of Preventive Medicine, and [3] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
* Address correspondence to this author at: Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue, Boston, MA 02215. E-mail rglynn@rics.bwh.harvard.edu.

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[4] Nonstandard abbreviations: hsCRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; CARE, Cholesterol and Recurrent Events.

correlation for hsCRP of 0.66 *(12)*, and from paired measurements 1 year apart in 1679 Japanese civil servants, Nasermoaddeli et al. estimated an intraclass correlation for log-normalized hsCRP of 0.61 *(13)*. Two studies evaluated the repeatability of log-normalized hsCRP based on paired measurements taken at wider intervals. Koenig et al. made 2 hsCRP measurements at a 3-year interval in 936 men participating in the MONICA Augsburg study and estimated an intraclass correlation of 0.54 *(14)*, and Danesh et al. found an intraclass correlation coefficient of 0.59 for measurements separated by a 12-year interval in 379 participants in the Reykjavik study *(15)*. Several of these studies have reported an hsCRP measurement reliability similar to that observed for blood pressure and total cholesterol.

The JUPITER trial raises the possibility that an increased hsCRP concentration should play a role in the decision to initiate statin therapy for primary prevention. Data are needed on the stability of hsCRP measurements, particularly at higher concentrations, to inform possible treatment algorithms. In this report, we describe the tracking of hsCRP concentrations among the 8901 participants randomized to placebo in the JUPITER trial, each of whom had a screening hsCRP concentration of at least 2 mg/L.

Materials and Methods

POPULATION

The JUPITER trial was a randomized, double-blind, placebo-controlled primary-prevention trial that tested whether 20 mg/day rosuvastatin compared with placebo would decrease the rate of a composite endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The main eligibility criteria were an age ≥50 years for men or ≥60 years for women, an LDL cholesterol concentration <130 mg/dL (<3.37 mmol/L), and an hsCRP concentration ≥2.0 mg/L. Exclusion criteria included previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, diabetes mellitus, and uncontrolled hypertension. Also excluded were patients with inflammatory conditions, such as severe arthritis, lupus, or inflammatory bowel disease, as were patients taking immunosuppressant agents such as cyclosporine, azathioprine, or long-term oral glucocorticoids. The JUPITER trial randomized 17 802 individuals from 26 countries and had followed them for a median of 1.9 years when it was stopped early because of convincing evidence of benefit for the primary endpoint. Further details about the study design and results are presented elsewhere *(10, 16)*.

MEASURES

Between February 2003 and December 2006, JUPITER investigators screened 89 890 people for enrollment. This visit included a blood sample that required participants to have fasted for at least 8 h and to be sitting for at least 5 min. Plasma samples were shipped to a central laboratory for lipid and hsCRP testing. hsCRP evaluation used a validated high-sensitivity assay with the Behring nephelometer and reagent. Assessment for total cholesterol used an enzymatic procedure (cholesterol esterase) with a colorimetric endpoint. The method was standardized by both the isotope-dilution mass spectrometry and the Abell–Kendall method. Triglycerides were measured with an enzymatic-hydrolysis procedure to obtain a colorimetric endpoint triglyceride value. This method was standardized against the NIST SRM 909b and triolein standard. Both of these lipid assays were performed with the Roche Modular/Hitachi system and reagent. HDL cholesterol was measured in the resulting supernatant after heparin–manganese precipitation of apolipoprotein B–containing proteins. LDL cholesterol concentrations were calculated by the Friedewald equation from concentrations of total cholesterol, triglycerides, and HDL cholesterol as long as the triglyceride concentration was <400 mg/dL (<4.52 mmol/L). Systolic and diastolic blood pressures were also measured at this visit.

The screening revealed 37 611 individuals to be ineligible because of an LDL cholesterol concentration of 130 mg/dL (3.37 mmol/L) or higher, and another 25 993 individuals had hsCRP concentrations of <2.0 mg/L. Individuals who met other eligibility criteria and remained willing to participate returned a median of 2 weeks later for a second assessment of hsCRP and entered a 4-week run-in period with placebo therapy. After randomization, the 17 802 randomized participants had scheduled follow-up hsCRP assessments at 3 months and at 1, 2, 3, and 4 years. A lipid panel was also performed on the blood drawn at the 1-, 2-, 3-, and 4-year visits. After the trial was stopped on March 30, 2008, all participants were scheduled for a final close-out evaluation, including both hsCRP and lipid assessment, before unblinding. Participants were required to be fasting at each of these visits, and blood sampling and processing followed the same protocol as for the screening visit. Blood pressure was remeasured only at this final visit.

STATISTICAL ANALYSIS

Initial descriptive analyses compared baseline characteristics of the 8901 participants randomized to placebo in the JUPITER trial across categories defined by screening concentrations of hsCRP. Cutpoints to form categories of hsCRP concentrations were chosen both

Table 1. Baseline characteristics of participants in the placebo arm of the JUPITER trial according to the screening concentrations of hsCRP.

Characteristic	hsCRP 2.0–2.9 mg/L	hsCRP 3.0–4.4 mg/L	hsCRP 4.5–6.9 mg/L	hsCRP ≥7.0 mg/L
Participants, n[a]	2389	2217	1895	2398
Age, years[b]	65 (60–71)	66 (60–71)	66 (61–71)	66 (61–71)
Female sex, %	33.0	38.9	39.7	40.5
Race or ethnicity, %				
White	77.3	73.8	69.7	63.3
Black	8.2	9.3	13.7	19.1
Hispanic	12.0	13.4	13.0	12.9
Other or unknown	2.4	3.5	3.5	4.6
High school education or less, %	56.0	58.6	59.2	63.5
Body mass index, kg/m^2[b]	27.8 (25.0–30.8)	28.6 (25.6–31.9)	28.9 (25.8–32.4)	28.4 (25.1–33.0)
Cigarette smoker, %	14.4	14.3	16.2	18.8
Exercise >3 times/week, %	23.4	20.2	19.7	17.5
Daily alcohol consumption, %	21.9	19.9	17.8	16.1
Hypertension, %	54.8	58.4	57.9	59.7
Family history of CHD[c]	11.9	12.9	11.5	11.0
Region,				
US or Canada, %	36.4	34.5	33.5	31.9
Central or South America, %	13.5	14.8	14.9	15.3
Europe, %	40.5	38.9	36.3	30.8
South Africa, %	8.7	11.0	14.7	21.3
Israel, %	0.9	0.8	0.6	0.8

[a] Two of the 8901 individuals randomized to placebo had a missing screening value for hsCRP.
[b] Data are presented as the median (interquartile range).
[c] CHD, coronary heart disease.

for clinical relevance and to yield approximately equal numbers of individuals in each category. Graphical comparison of the distributions of hsCRP across time used box plots with whiskers extending from the ends of the box (marking the interquartile range) to the extremes of the data or to one and a half times the interquartile range, whichever was closer *(17)*. In addition to hsCRP, we display box plots of distributions of total, LDL, and HDL cholesterol, as well as triglycerides, at the same time points. For these analyses only, we also show for comparison the distributions by time among the 8901 participants randomized to active rosuvastatin.

We obtained Spearman correlation coefficients as nonparametric measures of association between pairs of measures of hsCRP at different times. For comparison, we also show Spearman correlations between pairs of measures of total cholesterol, LDL cholesterol, HDL cholesterol, fasting triglycerides, and systolic and diastolic blood pressure at different times.

Parametric analyses began with an exploration of optimal transformations to normalize the distribution of hsCRP concentrations, as well as the distributions of cholesterol and triglyceride concentrations. We used the TRANSREG procedure in version 9 of the SAS statistical package (SAS Institute) to identify an appropriate transformation from the Box–Cox family *(18)*. Specifically, we considered transformations of the form $T(y) = (y^{\lambda} - 1)/\lambda$, for $\lambda \neq 0$, and $T(y) = \ln(y)$, for $\lambda = 0$, where ln is the natural logarithm. After transformation, we used the unbalanced repeated-measures models of Jennrich and Schluchter to estimate the between- and within-individual components of variance for hsCRP and separately for the lipid variables *(19)*. The model specifies:

$$Y_{it} = \beta_0 + \sum_j \beta_j X_{ijt} + \varepsilon_i + \delta_{it},$$

where Y_{it} is the normalized value of hsCRP in the ith individual at time t, X_{ijt} is the jth covariate in the ith

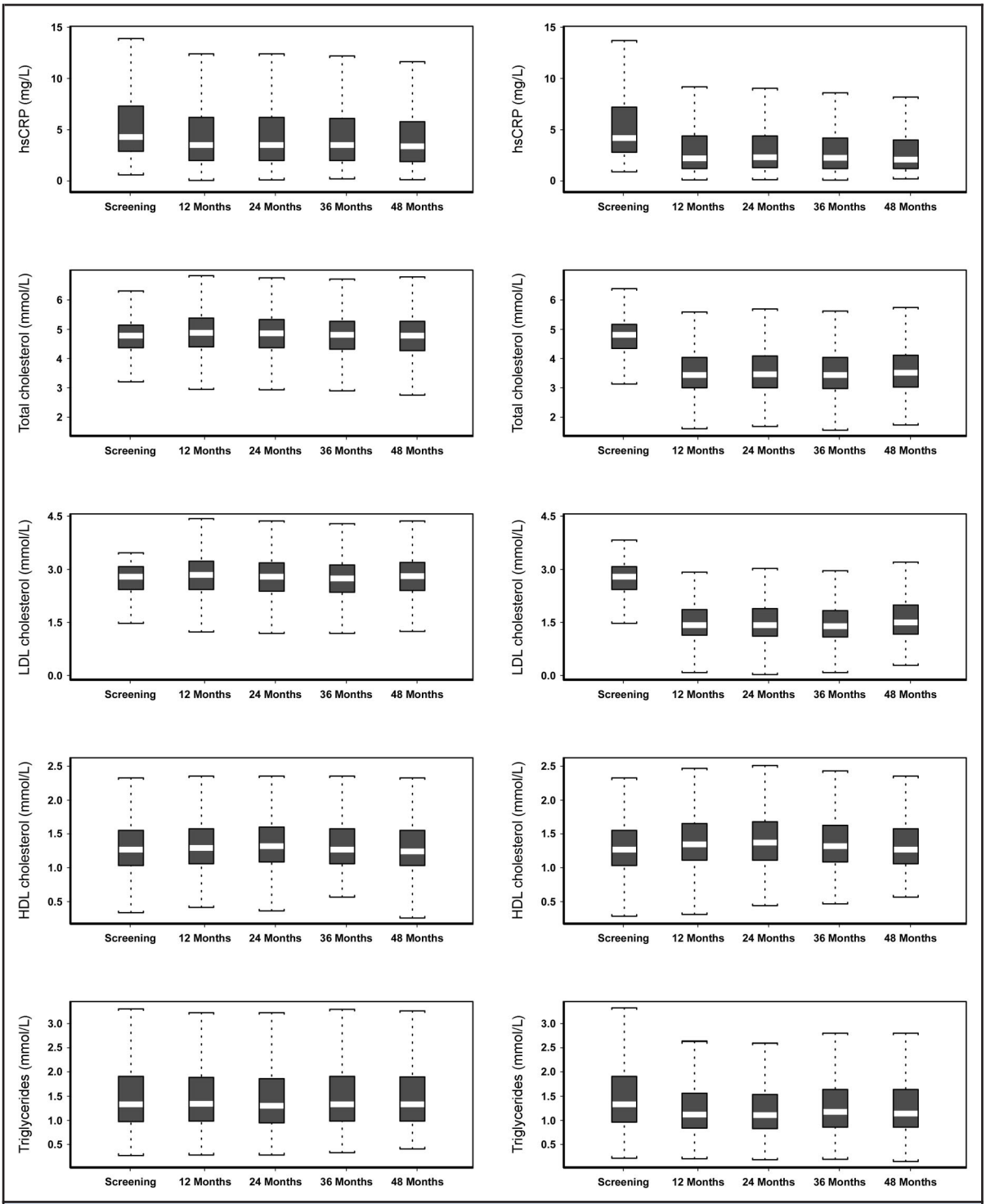

Fig. 1. Box plots of the distributions of hsCRP, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides at the screening visit and at 12, 24, 36, and 48 months after randomization.

The left and right columns of panels show data from the placebo group and the rosuvastatin group, respectively. Data are presented as the median and interquartile range; whiskers extend to the extremes of the data or to one and a half times the interquartile range, whichever was closer.

Table 2. Spearman correlation coefficients for agreement over time for hsCRP, lipid, and blood pressure measurements.

Measure	Time	12 Months	24 Months	36 Months	48 Months
hsCRP	Screening	0.38	0.35	0.38	0.37
	Randomization	0.55	0.53	0.49	0.53
	13 Weeks	0.58	0.55	0.51	0.51
	12 Months	1.0	0.60	0.57	0.53
Total cholesterol	Screening	0.62	0.60	0.56	0.51
	12 Months	1.0	0.70	0.66	0.59
LDL cholesterol	Screening	0.55	0.54	0.47	0.43
	12 Months	1.0	0.65	0.60	0.54
HDL cholesterol	Screening	0.85	0.84	0.86	0.83
	12 Months	1.0	0.87	0.86	0.86
Triglycerides	Screening	0.74	0.71	0.68	0.66
	12 Months	1.0	0.75	0.72	0.69
Systolic blood pressure	Screening	0.50 (Final visit)			
Diastolic blood pressure	Screening	0.45 (Final visit)			

individual at time t, ε_i is the individual-specific error (assumed to follow a normal distribution with mean 0 and variance σ_b^2), and δ_{it} is the within-individual error (assumed to follow a normal distribution with mean 0 and variance σ_w^2). The intraclass correlation is the ratio of the variance between individuals to the total variance of an observation, $\sigma_b^2 / (\sigma_b^2 + \sigma_w^2)$. Estimated parameters in the model were obtained by maximum likelihood with the MIXED procedure in SAS version 9. Confidence intervals for the estimated intraclass correlation used the δ method to estimate the variance of the ratio *(20)*. The estimated intraclass correlation is expected to vary according to the covariates included in the model. We obtained 3 estimates, one based on a model with only an intercept, a second model also including indicator variables for visit times, and a third model also including variables that potentially influence hsCRP concentrations *(21–24)*. The variables considered included age as a time-varying covariate, whereas all other covariates kept their values from baseline. Models for hsCRP included up to 6 measurements of hsCRP per individual: randomization, 13 weeks later, and then at the 1-, 2-, 3-, and 4-year visits. The screening visit was not included because the distribution was truncated by design. For all analyses, if an individual had a missing value for a postrandomization visit and if that individual's hsCRP concentration was available from a final visit within 6 months of that scheduled visit, the concentration at the final visit was substituted for the missing value. For comparison, the same unbalanced repeated-measures models with the same covariates were used to estimate the intraclass correlation coefficients for total, LDL, and HDL cholesterol and for fasting triglycerides. For these estimates, we used observations at screening and at 1, 2, 3, and 4 years after randomization. Observations from an individual's last visit were used to replace a missed observation from an annual visit, as for hsCRP.

Results

Between 21% and 27% of the 8901 participants randomized to placebo in JUPITER had screening concentrations of hsCRP in each of the following 4 categories: 2.0–2.9 mg/L, 3.0–4.4 mg/L, 4.5–6.9 mg/L, and ≥7.0 mg/L (Table 1). Women, blacks, those with a high school education or less, cigarette smokers, and participants from South Africa were more likely to have higher hsCRP concentrations. Conversely, participants who exercised regularly, drank alcohol daily, and resided in Europe were more likely to have lower hsCRP concentrations.

The median hsCRP concentrations at screening were 4.3 mg/L in the placebo group and 4.2 mg/L in those subsequently assigned to rosuvastatin (Fig. 1). At the second screening visit before randomization, corresponding median concentrations were 3.8 mg/L and 3.7 mg/L in the placebo and active groups, reflecting the expected regression to the mean. After randomization, the placebo group displayed only slight additional regression to the mean, with median concentrations of 3.5, 3.6, 3.5, and 3.4 mg/L at the 1-, 2-, 3-, and 4-year

Table 3. Estimated variance components and intraclass correlation coefficients for hsCRP and lipid measures based on a repeated-measures regression model.

Measure	Estimate (95% CI)		
	Model with intercept only	Model adjusted for time	Model adjusted for time and covariates[a]
ln[hsCRP (mg/L)]			
Between-individual variance	0.47 (0.45–0.48)	0.47 (0.45–0.48)	0.40 (0.38–0.41)
Within-individual variance	0.39 (0.39–0.40)	0.39 (0.38–0.40)	0.39 (0.38–0.40)
Intraclass correlation	0.54 (0.53–0.55)	0.54 (0.53–0.55)	0.50 (0.49–0.51)
Total cholesterol (mg/dL)			
Between-individual variance	499.5 (481.3–517.7)	500.7 (482.5–518.9)	435.4 (419.1–451.6)
Within-individual variance	301.4 (295.0–307.8)	294.5 (288.3–300.7)	294.3 (288.1–300.6)
Intraclass correlation	0.62 (0.61–0.63)	0.63 (0.62–0.64)	0.60 (0.59–0.61)
LDL cholesterol (mg/dL)			
Between-individual variance	298.9 (287.4–310.4)	299.6 (288.2–311.0)	278.9 (268.1–289.7)
Within-individual variance	230.3 (225.4–235.2)	225.9 (221.1–230.7)	225.3 (220.5–230.1)
Intraclass correlation	0.56 (0.55–0.58)	0.57 (0.56–0.58)	0.55 (0.54–0.56)
ln[HDL cholesterol (mg/dL)]			
Between-individual variance	0.069 (0.067–0.072)	0.070 (0.067–0.071)	0.052 (0.051–0.054)
Within-individual variance	0.013 (0.012–0.013)	0.012 (0.0120–0.0125)	0.012 (0.0119–0.0125)
Intraclass correlation	0.85 (0.84–0.85)	0.85 (0.85–0.86)	0.81 (0.81–0.82)
ln[Triglycerides (mg/dL)]			
Between-individual variance	0.17 (0.17–0.18)	0.17 (0.17–0.18)	0.15 (0.15–0.16)
Within-individual variance	0.064 (0.063–0.065)	0.064 (0.062–0.065)	0.063 (0.062–0.065)
Intraclass correlation	0.73 (0.72–0.74)	0.73 (0.72–0.74)	0.71 (0.70–0.71)

[a] The model includes all variables shown in Table 1, with age allowed to vary according to the age at the time of the visit.

visits, respectively. In the rosuvastatin group, median hsCRP concentrations declined markedly after randomization to 2.2, 2.4, 2.25, and 2.1 mg/L at the 1-, 2-, 3-, and 4-year visits, respectively. As shown in Fig. 1, the median concentrations of total and LDL cholesterol also displayed some regression to the mean in the placebo group after randomization. In the rosuvastatin group, the median concentrations of total cholesterol, LDL cholesterol, and triglycerides declined markedly at year 1 and remained steady thereafter.

Spearman correlations between hsCRP measurements at pairs of visits were somewhat weaker in pairs involving the screening visit, reflecting the truncated distribution at that time (Table 2). For pairs of visits not involving the screening visit, these correlations ranged from 0.49–0.60. These correlations were somewhat stronger than the correlation observed for diastolic blood pressure over time, comparable to those observed for systolic blood pressure and LDL cholesterol, and somewhat weaker than those observed for total cholesterol, HDL cholesterol, and fasting triglycerides. As expected, correlations were generally weaker for pairs of measurements at greater time intervals, and hsCRP and lipid variables were similar in this attenuation over time.

Consideration of a range of possible Box–Cox transformations identified the natural logarithm (Box–Cox $\lambda = 0$) as the optimal transformation to normalize the distribution of hsCRP. For the lipid variables, the identity ($\lambda = 1$) was optimal for total and LDL cholesterol, whereas a λ value of -0.25 was recommended for HDL cholesterol and triglycerides. We chose the natural log ($\lambda = 0$) to transform these variables, however, because it is more readily understood and because the estimated intraclass correlations obtained were virtually identical for either of these choices of λ. On the basis of regression models including >34 000 assessments of hsCRP over 4 years among individuals in the placebo group, the estimated intraclass correlation coefficient for ln(hsCRP) was 0.54 (95% CI, 0.53–0.55; Table 3). This estimate remained unchanged after controlling for time. With further controlling for all vari-

ables in Table 1, the estimated intraclass correlation was 0.50 (95% CI, 0.49–0.51). By comparison, estimated intraclass correlation coefficients were slightly higher for LDL cholesterol (0.55–0.57) and highest for HDL cholesterol (0.81–0.85).

Discussion

The results of the JUPITER trial will lead to a reassessment of guidelines for primary prevention of cardiovascular disease *(25)*. An evaluation of the tracking of hsCRP concentrations over time is an important consideration with respect to the role of hsCRP in these guidelines. Results of the JUPITER trial indicate that hsCRP concentrations track strongly over time, and after an initially elevated concentration, hsCRP is likely to remain increased in the absence of statin treatment.

Our estimated intraclass correlation of 0.54 is generally consistent with estimates from the prior smaller studies, in spite of the expected attenuation of the correlation due to the truncation of the baseline distribution by screening. Specifically, the truncation of the distribution of hsCRP at screening reduces the between-person variance, which forms the numerator of the intraclass correlation coefficient. Another factor influencing the magnitude of the intraclass correlation is the magnitude of the time interval between assessments. It is not surprising that the largest estimated intraclass correlation in the literature comes from the study of Ockene et al., which had a 3-month interval between hsCRP assessments *(12)*. We are unaware of other estimates of intraclass correlation for hsCRP that adjust for a wide range of determinants. Such adjustment accounted for only a small amount of the observed between-individual variation and only modestly attenuated the estimated intraclass correlation.

Comparisons of estimated intraclass correlations for other cardiovascular risk factors with hsCRP can provide a context for interpreting our observed estimates of tracking. Several longitudinal studies have examined tracking of systolic and diastolic blood pressure over various intervals *(26–28)*. These studies have generally found stronger tracking both in middle-aged individuals compared with older or younger individuals and for shorter intervals between assessments. For example, Tate et al. found Pearson correlations between pairs of systolic-pressure measurements separated by 5 years in men initially 40–65 years of age to range between 0.43 and 0.51, whereas the range of correlation coefficients for younger or older men was 0.30–0.37. For diastolic pressure, the correlations were slightly weaker *(28)*. Similarly, Glynn et al. estimated tracking correlations of 0.36–0.48 for systolic blood pressure over a 3-year interval in a population-based study of individuals initially older than 65 years *(27)*. In one of the few population-based studies to evaluate tracking of multiple risk factors, Wilsgaard et al. tracked coefficients over an 8-year interval for middle-aged men and women in Tromsø, Norway, and reported coefficients of 0.48 for diastolic blood pressure, 0.39–0.43 for triglycerides, 0.52–0.54 for systolic blood pressure, 0.55–0.64 for HDL cholesterol, and 0.65–0.77 for total cholesterol *(29)*. These observations suggest that the tracking observed for hsCRP in JUPITER is consonant with good overall tracking.

In conclusion, we found evidence of substantial tracking of hsCRP concentrations among the participants in the placebo arm of the JUPITER trial. In particular, it is likely that increased concentrations of hsCRP will remain high unless they are affected by treatment.

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