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The Prospective Association of Socioeconomic Status with C-Reactive Protein Levels in the CARDIA Study

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Abstract

Better health is a well-documented benefit of having a higher socioeconomic status (SES). Inflammation may be one pathway through which SES influences health. Using 2658 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, we examine whether two measures of SES assessed at baseline (mean age, 32 ± 4 years)—years of education and household income—predict change in C-reactive protein (CRP) concentrations over the course of 13 years. We also examine whether four health-related behaviors—smoking, fruit and vegetable consumption, physical activity, and alcohol consumption—mediate the prospective association of SES with CRP. Both higher education and household income predicted smaller increases in CRP over the 13 years of follow-up independent of age, sex, race, CARDIA center, body mass, medical diagnoses, medications, and hormone use (among women). Associations did not differ by race or sex. When examined in separate analyses, smoking and fruit and vegetable intake each accounted for a significant proportion of the respective effects of education and household income on CRP change, and physical activity a significant proportion of the effect of household income. These findings suggest that poor health behaviors among persons of lower socioeconomic status can have long-term effects on inflammation.

Keywords

C-reactive protein; CARDIA Study; health behaviors; inflammatory markers; mediation; socioeconomic status

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1. Introduction

Better health is a well-documented benefit of having a higher socioeconomic status (SES), with those at each successive level of SES enjoying comparatively better health than those at the preceding level (Adler et al., 1994; Avendano et al., 2004). In addition to the literature linking SES with clinical disease and mortality, a growing body of evidence supports an association between SES and biomarkers of future disease risk in initially healthy adults. Several studies, for example, have investigated the relation of SES with inflammation (Nazmi and Victoria, 2007). Inflammation is thought to underlie the pathogenesis of several chronic diseases including coronary artery disease (Ross, 1999), type II diabetes mellitus (Pickup and Crook, 1998), and some forms of dementia (McGreer and McGreer, 1998). Further, circulating concentrations of inflammatory biomarkers, such as C-reactive protein (CRP), have proven to be valuable prognostic indicators both of incident disease in healthy adults (Pradhan et al., 2002; Ridker et al., 2000) and poor outcomes in clinical populations (He et al., 2010).

Much of the evidence linking SES and CRP has been cross-sectional (Friedman and Herd, 2010; Gruenewald et al., 2009; Kershaw et al., 2010; Nazmi and Victoria, 2007), with only one study to date investigating a prospective association (Gimeno et al., 2007). Results of this study showed that among members of the Whitehall II cohort, higher employment grade at an average age of 50 years was associated longitudinally with lower CRP measured after approximately 10 years of follow-up, and prospectively with a smaller absolute increases in CRP over that period (Gimeno et al., 2007).

These data suggest that the increasing risk of morbidity and mortality with decreasing SES might be explained to some extent by an increased propensity toward inflammation. A remaining question, however, is through what mechanism might socioeconomic factors “get under the skin” to influence inflammatory marker concentrations? One factor that has been suggested to explain the SES disparity in health and disease involves socioeconomic differences in the prevalence of health-related behaviors. Persons of lower SES are both more likely to engage in risky behaviors, and less likely to engage in health-promoting behaviors. For example smoking rates decrease (United States Department of Health and Human Services, 2009) and the likelihood of maintaining a balanced diet that includes fruits and vegetables and engaging in physical activity both increase with increasing SES (Irala-Estevez et al., 2000; Schoenborn and Barnes, 2002). Patterns of alcohol consumption, as well, vary by SES, with higher SES individuals drinking more frequently, but in smaller quantities than their lower SES counterparts (Knupfer, 1989). Importantly, not being a smoker, engaging in regular physical activity, eating fruits and vegetables, and consuming moderate amounts of alcohol each have been associated with lower circulating CRP concentrations (Gao et al., 2004; Kasapis and Thompson, 2005; O'Connor and Irwin, 2010; Volpato et al., 2004).

Several studies have included health behaviors as covariates when examining the association of SES with CRP (e.g., (Friedman and Herd, 2010)). Only three, however, have actually tested whether health behaviors account for any of variance in CRP attributable to SES (Gimeno et al., 2007; Gruenewald et al., 2009; Kershaw et al., 2010). In all three studies, being a smoker and not engaging in regular vigorous exercise each played a role in the association of lower SES with higher CRP. Gimeno et al. (2007) and Kershaw et al. (2010) also found poor diet to explain some of the increased CRP among those with lower SES. Though compelling, a limitation of these findings is that (Gruenewald et al., 2009) and (Kershaw et al., 2010) examined the mediation of a cross-sectional association and (Gimeno et al., 2007) a longitudinal, but not prospective, association. Thus, although all three studies

demonstrated statistical mediation by health behaviors, the direction of causation of the SES-CRP association cannot be inferred.

The primary aim of the present study is twofold: First we examine the prospective association of SES with CRP concentrations over a 13-year follow-up among a large sample of black and white men and women (mean age 32 years at baseline); second, we test the extent to which four health-related behaviors (smoking, physical activity, alcohol consumption, fruit and vegetable intake) each mediate that association. Because we use two different indicators of SES—one indicating the individual's own social rank (years of education), and the other the social rank of his or her family (household income) we further address the question of whether these four behaviors differ in relative importance depending on which SES marker is being examined; third, because adiposity—particularly central adiposity, has been associated with higher levels of circulating markers of inflammation, including CRP (Panagiotakos et al., 2005), we examine whether central weight gain during follow-up might provide a mechanism through which the examined health behaviors influence CRP; finally, because our sample is nearly equally distributed in terms of sex and race, we examine whether the associations of SES with CRP differ between men and women and blacks and whites. Race specificity in these associations was suggested in a previous report from CARDIA wherein lower education among 37–55 year-olds was related *cross-sectionally* to higher CRP among white men and both white and black women but not among black men (Gruenewald et al., 2009). Here, we determine whether these cross-sectional differences extend to prospective associations.

2. Methods

2.1. Sample

—In 1985–1986, 5115 adults aged 18–30 years were recruited into CARDIA at four sites: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The sampling strategy resulted in a population-based cohort that was balanced by race (52% black), sex (55% female), and education (40% with 12 years of education) both overall and within each clinical center (see (Friedman et al., 1988) for additional detail). The 20-year follow-up examination was conducted in 2005–2006. The present analyses are based on data from the Year 7 exam—when the first CRP measure was taken (“baseline”) and the Year 20 follow-up exam.

Exclusions: Of the 5115 participants who originally enrolled in CARDIA, 3549 (69%; 72% of the surviving sample) returned for the Year 20 exam. Participants were excluded from analysis if missing data on any of the following variables: CRP at Year 7 or 20 ($n = 483$); Year 7 household income or education ($n = 9$); any of the proposed mediators ($n = 154$); or any of the standard controls (see below; $n = 5$). An additional 240 participants were excluded for having CRP concentrations $>10\mu\text{g/ml}$, the standard cut-point for identifying CRP levels attributable to probable acute infection (Pearson et al., 2003). Thus, data from 2658 participants were included in the present report. In terms of the three demographic variables on which recruitment of the original CARDIA sample was based, the sample reported on here included smaller proportions of blacks (41% vs. 52%) and persons with 12 years of education at enrollment (32% vs. 40%) than the original sample, but did not differ in the proportion of women (53% vs. 55%).

2.2. Measures

Unless otherwise indicated, all baseline variables, including SES, health behaviors, baseline CRP, and covariates for this report were drawn from the Year 7 CARDIA exam, when

participants were on average 32 years of age. Follow-up CRP data were obtained at the Year 20 CARDIA exam, when participants were on average 45 years of age.

2.2.1. Socioeconomic Status

Education: As part of the demographic interview, participants were asked to report their total years of educational attainment (range, 0 to 20+ years). Education data were treated as continuous in all of the main analyses.

Household income: Participants reported their combined pre-tax family income for the past year by choosing one of nine provided income ranges (<\$5K, \$5K–\$11,999, \$12K–\$15,999, \$16K–\$24,999, \$25K–\$34,999, \$35K–\$49,999, \$50K–\$74,999, \$75K–\$99,999, \$100K). For analysis, the 9-level categorical variable was re-coded into a continuous variable by substituting the average dollar value for each range (Nickerson et al., 2003); values of \$2500 and \$150K were substituted for the lowest and highest categories, respectively. Values also were adjusted for concurrent household size by dividing by the square-root of the number of people living in the home (Buhmann et al., 1988). As the distribution of adjusted incomes was skewed toward higher values, the data were square-root transformed prior to analysis.

2.2.2. C-Reactive Protein—Blood samples for the measurement of CRP concentrations in EDTA-treated plasma were collected in the morning (before 10:30 am) at both baseline and follow-up. CRP was measured using high-sensitivity nephelometry- based methods (BNII nephelometer, Dade Behring, Eschborn, Germany). The assay range for CRP was 0.175 µg/mL to 1100 µg/mL (intra-assay CVs, 2.3% to 4.4%; interassay CVs, 2.1% to 5.7%) (Harris et al., 1999). CRP values were log₁₀-transformed prior to analysis.

2.2.3. Potential mediators—Data on *smoking status*, *typical alcohol consumption* (drinks per week), and *physical activity* were obtained by interview (see CARDIA website, <http://www.cardia.dopm.uab.edu/>). Here, smoking status was represented by a dichotomous variable (smokers = 1, former and never smokers = 0). Alcohol consumption was re-coded into a 5-level categorical variable that identified participants as being non-drinkers, former drinkers, or light (men, <7 drinks/week; women, <4 drinks/week), moderate (men, 7 to 14 drinks/week; women, 4 to 7 drinks /week) or heavy (men, >14 drinks/week; women, >7 drinks/week) drinkers (United States Department of Agriculture and United States Department of Health and Human Services, 2005). In the main analyses, this categorical indicator is represented by a set of four dummy variables with non-drinkers as the referent. Physical activity was assessed by asking participants to rate themselves relative to others of the same sex and age on how physically active they were during the past year. Response options were presented in a Likert-like format, with values ranging from 1 (*physically inactive*) to 5 (*very active*). Previous research has shown retrospective estimations of past year physical activity to correlate with 7-day recall measures (Aaron et al., 1995) and ratings of activity levels relative to comparable others to correlate with objective fitness indices (Buchman et al., 1991). Physical activity was represented by a continuous variable in all analyses.

Dietary data were collected using a detailed diet-history questionnaire that was developed specifically for CARDIA (McDonald et al., 1991). Participants were asked to recall the frequency, amount, and method of preparation of foods consumed during the past month. These data were converted to servings per day using the Nutrition Data Systems for Research (NDSR) software program (Nutrition Coordinating Center (NCC), University of Minnesota). *Fruit and vegetable (FV) intake* was computed by summing participants' total servings of citrus and non-citrus fruits, dark green vegetables, deep yellow vegetables, and tomatoes. FV intake values were log₁₀-transformed prior to analysis.

Waist circumference was measured at Years 7 and 20 by trained observers between the lower rib margin and the iliac crest. *Central weight gain* was operationalized as the simple difference in waist circumference between Year 7 and Year 20.

2.2.4. Covariates

Sociodemographics: Data on age, sex (male, female), and race (white, African American) were collected upon study entry. Marital status was assessed by asking participants to identify themselves as being married, widowed, divorced, separated, never married, or living with someone in a marriage-like relationship. For the present analyses, participant baseline marital status was re-coded into a dichotomous variable (married/living in a marriage-like relationship = 1, all others = 0).

Body mass index: Body mass index (BMI; kg/m^2) was computed from participants' height and weight measurements. Procedures for collection and measurement of these variables previously have been reported (Friedman et al., 1988).

Medical diagnoses and Medications: At all exams, participants reported whether they had ever been diagnosed by a health professional with any of several medical conditions and whether they currently were taking any over-the-counter or prescription medications, including oral contraceptives and hormone therapy (OC/HRT; women). Additional details are available at the CARDIA website (<http://www.cardia.dopm.uab.edu/>). From these data, we created three dichotomous variables. The first indicated whether participants had been diagnosed with one or more medical conditions; the second indicated whether participants reported taking any medications with the potential to influence inflammatory markers (i.e., antihypertensives, cholesterol-reducing drugs, asthma medications, daily aspirin, and "other"); and the third variable indicated whether female participants reported taking oral contraceptives or hormone replacement therapy (OC/HRT; men assigned a zero score).

2.3. Statistical Analyses

—All statistical analyses were conducted using SAS v9.1 (SAS Institute, Cary, NC). Multivariable linear regression was used to examine the prospective associations of baseline education and income, respectively, with follow-up CRP. Unless otherwise specified, all models included the following set of standard covariates in addition to baseline CRP: age, race, sex, CARDIA center, marital status, BMI, medical diagnoses, medications, and OC/HRT use. To examine the prospective association of baseline SES with follow-up CRP, as well as determine the independent contributions of each of the four health behaviors to the association, we conducted seven separate analyses. The first (Model 1) controlled only for baseline CRP, and the second (Model 2) baseline CRP and the standard covariates. Each of the four subsequent models built onto Model 2 by adding one of the four health behaviors. Prior to conducting the final model (Model 7), we used the (Sobel, 1982) test to identify which behaviors significantly reduced the variance in CRP attributable to SES. We then examined the independent mediation effects of all identified health behaviors by entering them simultaneously into a single model (Model 7).

Missing data: Missing data on predictors (baseline household income and education) and standard covariates (including household size for income adjustment) were handled by substituting analogous values from the preceding CARDIA exam (Year 5), conducted two years prior to baseline (Year 7). Prior to substitution, Year 5 (1990–91) income values were adjusted using the consumer purchasing index to ensure equivalency to Year 7 values (1992–93). To ensure temporal precedence of the predictor variables, missing data on three of the four potential mediators (baseline smoker status, drinking, and physical activity) were handled by substituting analogous values from the following CARDIA exam which was

conducted three years after baseline (Year 10). As only one participant was missing data on smoker status following substitution, and only three were missing data on OC/HRT use, we conservatively assigned each to be either a non-smoker or a non-user of OC/HRT, respectively. Exclusion criteria were based on remaining missing values *after* these substitutions were made.

3. Results

3.1. Sample characteristics

On average, CRP values, adjusted for age, sex, race, and CARDIA center were within normal range both at baseline (mean = $1.71\mu\text{g/ml}$, interquartile range [IQR] = .43, 2.31) and follow-up (mean = $1.79\mu\text{g/ml}$, [IQR] = .45, 2.30). The average change in CRP (adjusted for age, sex, race, CARDIA center, and baseline CRP) over the 13-years between baseline and follow-up was $.11\mu\text{g/ml}$ (IQR = $-.90$, .53). Other characteristics of the sample including demographics, SES, and health behaviors are presented in Table 1.

3.2. Association of Year 7 SES with Year 20 CRP

3.2.1. Educational attainment—Table 2 presents results of the models examining the prospective association of baseline educational attainment with follow-up CRP. As shown in the first column of the table, having more education was associated with a smaller increase in CRP between baseline and follow-up (Model 1). Education remained an independent predictor of CRP when the standard controls were added, but the size of the association was reduced (Model 2). In regard to the potential mediating role of health behaviors, smoking status (Model 3), FV intake (Model 5), and physical activity (Model 6)—when examined in separate models, emerged as independent predictors of follow-up CRP, and accounted for some of the variance in CRP attributable to education. Specifically, not being a current smoker, eating more fruits and vegetables, and being more physically active accounted for 56%, 29%, and 10%, respectively, of the apparent protective effect of having more education on CRP. However, whereas smoking status and FV intake significantly reduced the proportion of variance in CRP attributable to education, physical activity did not (see Table 4). Thus, in Model 7, we simultaneously entered smoking status and FV intake. Results showed that both health behaviors remained independent correlates of CRP, and their cumulative effect accounted for 70% of the size of the effect of baseline education on CRP. This proportion of variance explained jointly by smoking and FV intake is smaller in magnitude than the sum of their individual contributions when examined separately (85%), thus indicating substantial overlap in the variance explained by these two health behaviors.

3.2.2. Household income—Table 3 presents results of the models examining the association of baseline household income with follow-up CRP. Findings for household income were largely similar to those for education, with higher income being associated with smaller 13-year increases in CRP independent of the standard covariates (Models 1 and 2). In regard to mediation, smoking status, FV intake, and physical activity again emerged as independent correlates of CRP. Compared to the education findings, however, smoking status and FV intake each explained smaller proportions of the variance in CRP attributable to household income (38% and 21%, respectively) and physical activity a larger proportion (17%). Further, all three health behaviors were associated with significant reductions in the variance attributable to income when added to their respective models (Table 4). In the final model, smoking status, FV intake, and physical activity remained independent predictors of CRP and their combined effect accounted for 57% of the association between income and CRP. Again, the joint contribution of these three behaviors was less than the sum of their individual contributions when examined separately (76%), thus indicating redundancy in the

proportion of variance in CRP attributable to income that is accounted for by smoking, FV intake, and physical activity.

3.3. Mediating role of central weight gain

The apparent protective effects of FV intake and physical activity might be explained by each of these health behaviors having an attenuating effect on central weight gain over the 13 years of follow-up. We examined this possibility first by assessing the respective associations of FV intake and physical activity with 13-year change in waist circumference. Results of analyses that included the standard covariates plus Year 7 waist circumference revealed a marginal association between FV intake and central weight gain ($\beta = -.04$, $p = .06$) and no association between physical activity and central weight gain ($\beta = -.02$, $p = .18$). By comparison, greater central weight gain predicted greater CRP ($\beta = .38$, $p = .001$) independent of the standard covariates and Year 7 waist circumference. When central weight gain entered into the model simultaneously with FV intake, both remained independent predictors of CRP. Similar results were obtained when physical activity was substituted for FV intake (data available from first author by request). In both cases, however, central weight gain substantially reduced the variance in CRP explained by the relevant health behavior (for FV intake, 49%; for physical activity, 54%).

3.4. Moderating effects of sex and race

It is possible that the prospective associations of educational attainment and household income may differ between men and women or between blacks and whites. Accordingly, we conducted four sets of moderation analysis wherein the appropriate sex-by-SES or race-by-SES cross-product term was added to Model 2, which controlled for baseline CRP and the standard covariates (including sex and race). Save for a marginal moderating effect of race on the prospective association of education with CRP ($p = .09$ for interaction), associations of SES with CRP change appeared not to differ by sex or race ($ps > .34$ for remaining interactions).

3.5. Graded vs. threshold effects of SES

The seemingly protective effect of SES on future CRP levels may take the form of a continuous gradient, with each additional year of education or each thousand dollar increase in household income being associated with an incremental decrease in CRP change over time. Alternatively, there may be a threshold effect with only those individuals with the most education and the highest income showing an SES-related benefit in terms of CRP. To address this question, we examined change in CRP by quartiles of Year 7 education and household income, respectively. Table 5 displays CRP means (adjusted for the standard covariates) at Years 7 and 20 for each quartile of education and income. Results of separate general linear model analyses that included a categorical variable representing either Year 7 education or income quartiles, the standard covariates, and Year 7 CRP were consistent with the results of the multiple regression analyses examining the association of continuous SES variables with CRP in that the overall effects of education ($F = 4.49$, $p = .004$) and income ($F = 4.56$, $p = .003$) were significant. Results of planned contrasts supported threshold effects for both SES indicators. Specifically, persons in the top quartile of household income showed less change in CRP than those in any of the three lower quartiles ($ps < .03$), and persons in the top quartile of education showed less change in CRP than those in either of the bottom two quartiles ($ps < .008$), but not relative to those in the second highest quartile ($p = .14$).

4. Discussion

The present findings suggest that SES during early/middle adulthood may be an important correlate of change in circulating CRP over the course of the following thirteen years. Specifically, among the individuals studied here, more education and higher household income each were associated with a smaller 13-year increase in CRP independent of demographics, medical diagnoses, medication use, OC/HRT use (women), and baseline CRP. These findings replicate and extend those of the only known study to date to report a prospective association between SES and circulating CRP (Gimeno et al., 2007). Importantly, our data show that the apparent protective effects of higher SES on future CRP levels are reliable across SES indicators. Our results also show that the prospective association between SES and CRP observed in Whitehall II (Gimeno et al., 2007) extends to a North American sample that is substantially younger (mean age 32 years vs. 50 years at baseline) and more equally distributed in terms of sex (54% vs. 28% female) and race (42% vs. 11% non-white). That we detected a prospective association between SES and CRP in a relatively young sample is striking, as much of what is known about SES and inflammation has been derived from samples of middle-aged and older adults (Friedman and Herd, 2010; Gimeno et al., 2007; Kershaw et al., 2010; Nazmi and Victoria, 2007).

Our examination of sex and race differences suggested that, in general, the associations of higher education and household income with less CRP did not differ between men and women or between blacks and whites. We did, however, detect a marginal effect of race on the association of education with CRP, such that education was protective for whites but not blacks, especially black men (data not shown). This finding is consistent with a report from an earlier cross-sectional analysis of CARDIA data (Gruenewald et al., 2009), wherein Year 20 education was inversely associated with Year 20 CRP among white men and both black and white women but not among black men.

In addition to determining whether education and household income are related to future circulating CRP levels, our second aim was to investigate the relative importance of four health-related behaviors in explaining that association. Of the behaviors we examined, smoking status explained the largest proportion of variance in CRP attributable to either education or income. However, FV intake and in the case of household income, self-reported physical activity accounted for sizable proportions of variance in CRP attributable to SES as well. That smoking and FV intake made the largest contributions to the association of SES with CRP is consistent with the longitudinal findings of (Gimeno et al., 2007), wherein smoking and poor diet contributed more to the association of employment grade with CRP than either exercise or alcohol consumption. (Kershaw et al., 2010), as well, found smoking to account for the largest proportion of the variance in CRP attributable to education and poverty, respectively. However, exercise appeared to play a larger role than diet.

One common pathway through which smoking, FV intake, and physical activity are thought to influence circulating CRP concentrations involves their respective influences on more upstream mediators of inflammation. Smoking, for example, has been shown to promote inflammation in the lung by inducing fibroblast production of cyclooxygenase-2 and prostaglandin E₂ synthase, two important early mediators of the inflammatory response (Martey et al., 2004).

Whereas the *pro*-inflammatory effects of smoking are thought to result from direct cellular insult, the *anti*-inflammatory effects of regular FV intake and physical activity are thought to influence inflammation via an effect on intervening processes. Given the contribution of excess adipose tissue in creating a pro-inflammatory state (Mohamed-Ali et al., 1998),

weight control likely is an important pathway through which physical activity and healthy eating exert their anti-inflammatory effects (Hamer, 2007). We found support for this explanation by showing that central weight gain—operationalized by increasing waist circumference over the follow-up, reduced the variance in CRP attributable to each of these health behaviors by approximately 50%. Yet, despite this reduction in explained variance, FV intake and physical activity continued to predict CRP independent of Year 7 weight status (BMI and waist circumference) and central weight gain, thus suggesting that these two health behaviors also may influence inflammation via mechanisms other than reduced body weight. For example, antioxidant nutrients present in fruits and vegetables are thought to have an attenuating effect on inflammation by scavenging reactive oxygen species and suppressing the NF- κ B signaling pathway (Rahman et al., 2006). One mechanism that has been suggested to explain the apparent anti-inflammatory effects of physical activity involves toll-like receptors (TLRs), which play an important role in modulating systemic inflammation. Specifically, individuals who engage in regular moderate exercise have been found to show decreased monocyte cell-surface expression of TLR4 (Gleeson et al., 2006).

Alcohol consumption was unrelated to CRP when examined in multivariable analyses. However, ours is not the first study to report a lack of a mediating effect of alcohol consumption in the association of SES with CRP (Gimeno et al., 2007; Kershaw et al., 2010). Although the anti-inflammatory benefits of moderate drinking is a reliable finding (Imof et al., 2004; Volpato et al., 2004), the threshold at which alcohol consumption becomes detrimental in regard to levels of circulating inflammatory markers has yet to be determined (O'Connor and Irwin, 2010). Thus, the apparent lack of a role for alcohol consumption in explaining the association of SES with CRP may be due to inaccurate modeling of an elusive effect rather than there being no effect at all.

Though statistically significant, the effect sizes we report are small. One likely explanation for this is the relatively young age range over which CRP change was examined (i.e., from an average age of 32 years to an average age of 55). In an older sample with more variable CRP concentrations, larger effects might have been observed. Another potential explanation for the small size of our effects involves the nature of the study design. Complex assessments in large-scale epidemiologic studies with heterogeneous samples are subject to greater error relative to smaller, more tightly controlled studies. This increased risk for error is compensated for, in part, by large sample sizes which provide power to detect very small effects, such as those reported here. Still, though significant, these effects likely underestimate true associations. Accordingly, SES may in fact explain a greater—though not necessarily large in an absolute sense—proportion of variance in future CRP levels than observed here. That said, SES likely is only one of several factors that influence CRP in healthy individuals. Chronic psychological stress, for example, has been associated with comparatively elevated CRP concentrations (Ranjit et al., 2007), as have depression and hostility (Suarez, 2004). Moreover, given that persons of lower SES report more stress and tend to be more depressed than their higher SES counterparts (Adler et al., 1994), it is possible that that psychological factors—either directly or via health behaviors, may mediate the association of SES with CRP. Finally, even small differences in CRP concentrations that are comparable in size to the change in CRP associated with SES that we report here, have been found to predict clinical disease risk. For example, among adults aged 45 and over and free of cardiovascular disease, a difference in one log-transformed CRP unit was associated with a nearly 40% increased risk for experiencing a future cardiovascular event (Park et al., 2002).

The present findings should be considered within the context of a few limitations. Because our analyses were prospective and included several important explanatory variables, we both eliminated the possibility of reverse causation and reduced the likelihood of a third-factor

explanation. Still, it remains possible that some unknown factor may be influencing both SES and CRP change. Also, the mean baseline (Year 7) CRP concentration for those who did not provide data at Year 20 ($n = 743$)—and thus were excluded from the present analyses—was greater than the Year 7 mean reported here (data not shown). This difference in CRP levels likely results in part from the tendency of low educated and less healthy (i.e., higher BMI; smokers) individuals to become lost to follow-up. As these individuals also are more likely to show increases in CRP over time, their loss may have resulted in an underestimation of associations examined here. Third, all of our measures of health behaviors were self-reported. Thus, we cannot control for possible over-reporting of healthy behaviors by higher SES individuals. Finally, although CRP has been linked prospectively with risk for diseases of presumably inflammatory origin, whether mild elevations in CRP are themselves the result of underlying low-grade inflammation has been subject to debate (Kushner et al., 2006). Accordingly, we cannot infer from the present data alone that SES—via health behaviors, is influencing inflammatory processes, *per se*. Replication of the present findings using known pro-inflammatory agents that do not closely correlate with those of CRP, such as tumor necrosis factor- α and interleukin-1 β , would provide additional support for the SES-inflammation hypothesis.

In sum, the findings reported here suggest that SES is reliably associated with future circulating CRP concentrations, and that this association is accounted for to some extent by differences in smoking, FV intake, and physical activity among those at higher and lower ends of the socioeconomic hierarchy. These findings expand the existing literature on SES and CRP not only by underscoring the prospective nature of the association of SES with CRP via health behaviors, but also by demonstrating that this association exists when SES is operationalized either at the level of the person (education) or the family (household income). That the effects we report are small suggests that SES is not a primary determinant of future CRP concentrations in midlife. That is not to say, however, that the contribution of SES to CRP is unimportant. For example, individuals in the highest quartiles of education and income appeared to be relatively protected in terms of increasing CRP over time. Further investigation of the potential buffering effects of high SES on factors typically related to elevations in CRP may provide further insights into identifying why some individuals but not others appear to be at increased risk for future disease.

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Table 1Sample characteristics at CARDIA Year 7 ($n = 2658$)

Variable	Mean (SD)	Median (IQR)	Percent
Socioeconomic status			
Education (years)		15 (13 – 16)	
Pre-tax household income (\$1000 US)		42.5 (20.5 – 62.5)	
Adjusted household income (\$1000 US) ^a		24.5 (14.5 – 39.1)	
Demographics			
Age at baseline (years)	32.2 (3.5)		
Sex (% female)			53.4
Race (% black)			41.2
Marital status (% married)			47.7
Health status			
Body mass index (kg/m ²)	26.0 (5.3)		
Medical condition (% yes)			27.9
Medications (% yes)			18.6
OC/HRT (% yes; women only)			23.0
Health Behaviors			
Current smoker (% yes)			23.4
Non-drinker			21.0
Former drinker			20.7
Light drinker ^b			30.1
Moderate drinker			16.6
Heavy drinker			11.6
Physical activity ^c		3 (3 – 4)	
Fruit/vegetable intake (servings/day)	3.1 (2.6)		

SD = standard deviation; IQR = interquartile range; OC/HRT = oral contraceptive/hormone replacement therapy.

^aAdjusted income = pre-tax household income/(number of people in the home) ^{1/2}.^bLight: men, <7 drinks/wk; women <4 drinks/wk. Moderate: men, 7 to 14 drinks/wk; women, 4 to 7 drinks/wk. Heavy: men, >14 drinks/wk; women, >7 drinks/wk.^cSelf-reported physical activity in past year (5-pt scale: 1=physically inactive, 5=very active).

Standardized Regression Coefficients Describing the Prospective Association of Baseline Educational Attainment and Health Behaviors with C-Reactive Protein Measured 13 Years Later

Table 2

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Education (years)	-.09***	-.04*	-.03	-.04**	-.04*	-.04*	-.03
Smoker status (1=yes)			.05***				.05**
Non-drinker				ref			
Former drinker				-.02			
Light drinker ^a				-.01			
Moderate drinker				-.03			
Heavy drinker				.004			
Fruits/vegetables (servings/day)					-.06***		-.05**
Physical activity in past year ^b						-.05**	
Model adjusted R ²	.211	.272	.274	.272	.275	.274	.275

[†] $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

^a Light: men, <7 drinks/wk; women <4 drinks/wk. Moderate: men, 7 to 14 drinks/wk; women, 4 to 7 drinks/wk. Heavy: men, >14 drinks/wk; women, >7 drinks/wk.

^b Self-reported physical activity in past year (5-pt scale: 1=physically inactive, 5=very active)

Model 1: education (years) + baseline CRP

Model 2: Model 1 + standard covariates (age, sex, race, marital status, CARDIA center, body mass index, medical diagnoses, medications, oral contraceptives/hormone therapy)

Models 3–6: Model 2 + indicated health behavior

Model 7: Model 2 + all health behaviors that significantly reduced the variance in CRP attributable to education.

Table 3

Standardized Regression Coefficients Describing the Association of Baseline Adjusted Household Income and Health Behaviors with C-Reactive Protein Measured 13 Years Later

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Household Income (\$1000 US)	-.10 ***	-.04 *	-.03 †	-.04 *	-.04 *	-.04 *	-.03
Smoker status (1=yes)			.05 **				.05 **
Non-drinker				ref			
Former drinker				-.02			
Light drinker ^a				-.01			
Moderate drinker				-.02			
Heavy drinker				.01			
Fruits/vegetables (servings/day)					-.06 ***		-.05 **
Physical activity in past year ^b						-.05 **	-.04 *
Model adjusted R ²	.212	.272	.274	.272	.275	.274	.276

† $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

^a Light: men, <7 drinks/wk; women <4 drinks/wk. Moderate: men, 7–14 drinks/wk; women, 4–7 drinks/wk. Heavy: men, >14 drinks/wk; women, >7 drinks/wk.

^b Self-reported physical activity in past year (5-pt scale: 1=physically inactive, 5=very active)

Model 1: household income (\$1000 US) + baseline CRP

Model 2: Model 1 + standard covariates (age, sex, race, marital status, CARDIA center, body mass index, medical diagnoses, medications, oral contraceptives/hormone therapy)

Models 3–6: Model 2 + indicated health behavior

Model 7: Model 2 + all health behaviors that significantly reduced the variance in CRP attributable to income.

Table 4

Mediated effects (computed with unstandardized betas) and Sobel test statistics (*z*) for mediation pathways linking baseline socioeconomic status (SES) with 13-year change in C-reactive protein (CRP).

Model	Mediation Pathway	Year 7 Education			Year 7 Household Income		
		Effect	<i>z</i>	P	Effect	<i>z</i>	P
3	SES → smoking → CRP	-.003	-3.24	.001	-.003	-3.37	.001
5	SES → FV intake → CRP	-.001	-2.99	.003	-.001	-2.65	.008
6	SES → physical activity → CRP	-.0005	-1.76	.08	-.001	-2.35	.02
7	SES → smoking → CRP	-.003	-2.92	.003	-.002	-2.73	.006
	SES → FV intake → CRP	-.001	-2.77	.006	-.001	-2.22	.03
	SES → physical activity → CRP				-.001	-1.89	.06

Effect = mediated effect (*ab*) computed from unstandardized betas.

Models 3–6 include the SES variable of interest, the indicated mediator, baseline CRP, and the standard covariates.

Model 7 includes the SES variable of interest, health behaviors that emerged as significant predictors of follow-up CRP, baseline CRP, and the standard covariates.

Table 5

Adjusted ^a mean C-reactive protein (CRP) concentrations at Years 7 and 20 by quartile of Year 7 education and household income.

	Year 7 CRP			Year 20 CRP		
	Mean	LCL	UCL	Mean	LCL	UCL
Year 7 education						
Quartile 1	1.07	1.00	1.15	1.10	1.02	1.19
Quartile 2	1.00	0.93	1.08	1.13	1.04	1.23
Quartile 3	0.94	0.87	1.01	0.99	0.92	1.07
Quartile 4	0.90	0.84	0.97	0.89	0.82	0.97
Year 7 household income						
Quartile 1	1.09	1.01	1.18	1.11	1.02	1.21
Quartile 2	1.03	0.96	1.11	1.07	1.00	1.16
Quartile 3	0.93	0.87	1.00	1.07	1.00	2.02
Quartile 4	0.89	0.83	0.96	0.87	0.81	0.95

^aCRP means at Years 7 and 20 adjusted for age, sex, race, marital status, CARDIA center, body mass index, medical diagnoses, medications, and oral contraceptives/hormone therapy; mean change in CRP adjusted for the aforementioned variables and Year 7 CRP.