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# Early-life and adult socioeconomic status and inflammatory risk markers in adulthood

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**Abstract.** *Background*: Associations between childhood and adult socioeconomic status (SES) and adult levels of inflammatory markers (C-reactive protein [CRP], fibrinogen, white blood cell count [WBC], and von Willebrand factor [vWF]) were examined in the Atherosclerosis Risk in Communities (ARIC) Study cohort. *Methods*: A total of 12,681 white and African-American participants provided information on SES (via education and social class) and place of residence in childhood and adulthood. Residences were linked to census data for neighborhood SES information. Multiple imputation was used to impute missing data. Hierarchical and linear regression were used to estimate the effects of SES and possible mediation by adult cardiovascular disease (CVD) risk factors. *Findings*: Low childhood social class and education were associated with elevated levels of CRP, fibrinogen, WBC, and vWF (increments of 17%, 2%, 4% and 3% for lowest versus highest education in childhood, respectively) among whites. Findings were less consistent among African-Americans. Adult SES was more strongly associated with inflammation than childhood SES. Individual-level SES measures were more consistently associated with inflammation than neighborhood-level measures. Fibrinogen and WBC showed the most consistent associations with SES; the largest changes in inflammation by SES were observed for CRP. Covariate adjustment strongly attenuated these associations. Mediation of the SES-inflammation associations by BMI, smoking and HDL cholesterol (HDL-C) are suggested by these data. *Conclusion:* Low individual- and neighborhood-level SES in childhood and adulthood are associated with modest increments in adult inflammatory burden. These associations may operate through the influence of low SES on traditional CVD risk factors, especially BMI, smoking and HDL-C.

**Key words:** Childhood, CRP, Inflammation, Life-course, SES, Socioeconomic status

## Introduction

Low individual and contextual (neighborhood-level) socioeconomic status (SES) has been repeatedly associated with worse cardiovascular disease (CVD) risk factor profiles, health behaviors and CVD outcomes [1–5]. Inquiries into the possible mechanisms that underlie such associations have recently reported that elevated levels of inflammatory markers are associated with lower levels of adult SES, suggesting that inflammation may be one of the mediators of social differences in cardiovascular risk [6–9].

In recent years, studies have more closely examined the influence of socioeconomic conditions in early life on the development of CVD [10–17]. Interest in early-life SES research was stimulated by the development of the fetal origins of adult disease hypothesis by David Barker [18]. Later theories and studies expanded the scope of inquiry beyond the neonatal period to include the putative effects of adverse socioeconomic conditions and events during sensitive early-life periods on adult chronic disease risk, operating through various physiological and/or psychosocial mechanisms [19–21]. This literature provides support for an association between low early-life SES and elevated CVD risk, likely mediated by adult behavioral or biologic CVD risk factors [22, 23].

One potential link between low early-life SES and CVD risk is a sustained, elevated systemic inflammatory burden. Laboratory and epidemiologic evidence indicate that a chronic and systemic inflammatory up-regulation plays a central role in atherosclerosis and its sequelae [24–26]. Associations between inflammatory markers such as fibrinogen and white blood cell (WBC) count and CVD have

been demonstrated [27–29]. Prospective epidemiologic studies report associations between cytokines, acute-phase proteins including C-reactive protein (CRP), and other markers of inflammation including von Willebrand factor (vWF) and cardiovascular events in middle-aged men and women [14, 30–34]. A systemic inflammatory response has been associated with the prevalence and clustered occurrence of the component elements of the metabolic syndrome [35, 36].

Few studies have examined the impact of childhood SES on markers of inflammation in adulthood; some [37] but not all [38] have reported similar inverse associations, and none have examined a range of markers. To more thoroughly investigate this impact, we analyzed data from adult male and female participants from the Atherosclerosis Risk in Communities (ARIC) study and two ancillary studies. The impact of early-life and adult SES, measured at both the individual and community level, on adult levels of CRP, fibrinogen, WBC, vWF and a summary inflammatory score was evaluated. In addition, adult behavioral and physiologic CVD risk factors were examined as potential mediators of the hypothesized associations between SES and these inflammatory markers.

## Methods

ARIC is a prospective study of the etiology of atherosclerosis in 15,792 men and women 45–64 years of age at baseline (1987–1989), sampled from four U.S. communities [39, 40]. The overall recruitment response rate at baseline was 60%. African-Americans were exclusively recruited at one study site and oversampled at another, to provide sufficient power to investigate findings by ethnicity. Cohort members are contacted annually by telephone; approximately 95% of the cohort survivors were successfully contacted at the time the data for this study were collected.

The Life Course Socioeconomic Status, Social Context, and Cardiovascular Disease (LC-SES) Study, ancillary to ARIC, collected socioeconomic and place-of-residence information from childhood and early adulthood on the 12,681 African-American and white ARIC participants after Visit 4 (35 participants of other ethnicities were excluded due to small numbers) [41]. Individual-level SES data were collected at examinations and from telephone interviews.

SES was evaluated in childhood (approximately 10 years of age) and adulthood (45+). Individual-level SES was evaluated via social class and education; area-level SES was evaluated using an SES index.

In order to obtain area-level (neighborhood) SES data, participants' places of residence during childhood and in adulthood (at ARIC baseline) were linked to U.S. census data (county data for childhood and census tract data for adulthood) [41, 42]. Three hundred and four participants raised outside the U.S. were excluded. Of the remaining 12,377, 4% did not provide adequate city or county-level information. A total of 12,187 participants were thus linked with area-level data. The few African-Americans residing outside the Mississippi ARIC Center were excluded, giving 11,842 participants.

For the measures of individual-level SES, social class was evaluated utilizing a modification of E.O. Wright's schema for categorizing social class [43, 44]. This measure utilized education and three yes/no questions evaluating facets of participants' occupations to assign social class (Table 1). Father's occupation was used for childhood class; participant's current/last occupation was used for adulthood. Homemakers (17% of women) were excluded.

Education was categorized Low/Middle/High. In childhood, father's education was used: Low: 0–8th grade; Middle: 9th–12th grade; High: Some college/vocational training or more. In adulthood, participant's education was categorized: Low: < high school degree; Middle: high school degree; High: Some college or more.

Unmatched earlier-life addresses, recall difficulties and incomplete census information led to considerable missing early-life data: childhood class, education and area-level SES measures were missing at 4.5%, 16.5%, and 15.5%, respectively. Multiple imputation (MI) was therefore considered to reduce bias [45]. MI is a process in which different sets of plausible values for missing observations are created, reflecting the uncertainty about the non-response model. Each of these different datasets is analyzed and the results are combined, with the uncertainty regarding the imputation taken into account. Based on exploratory analyses, our data were considered to be missing at random (MAR) as required by MI [46]. Recent work suggests that in self-reported questionnaire data, the MAR assumption usually holds, while even an erroneous assumption of MAR often has

**Table 1.** Method of assignment of a participant's occupational class in childhood and young and mature adulthood, utilizing an adaptation of E.O. Wright class categorization schema

| Social class | Higher education[a] | Owns business/ self-employed | Supervisory or managerial job role |
|---|---|---|---|
| Worker class | No | No | No |
| Middle class | Yes | No | No |
| | No | No | Yes |
| | – | Yes | No |
| Capitalist/ | Yes | No | Yes |
| Expert | – | Yes | Yes |
| Manager class | | | |

[a]Higher education is some college education or more.

only a minor impact on estimates and standard errors [47, 48]. Multivariate imputation by chained equations (MICE) based on a Gibbs sampling method was carried out in STATA 8.2 SE using the MVIS ado-file [49], utilizing 5 imputations of 10 iterations. Twenty-nine demographic covariates were included; outcome measures were excluded.

Based on previous work, area-level SES was evaluated using five census measures in childhood and adulthood: (1) median/mean family income, (2) median/mean value of owner occupied house, (3) % of residents with high school education, (4) % of residents with college education, and (5) % of residents in professional, managerial, or executive occupations [3]. At each time point, race-specific *z*-scores of each measure were summed to create area-level SES indices, trichotomized at the 40th and 75th percentiles based on naturally occurring divisions.

Fibrinogen, vWF and WBC were measured at ARIC Visit 1. Hemostasis variables were analyzed in citrated samples [50, 51], fibrinogen by thrombin time titration [52], and vWF by enzyme-linked immunosorbent assay. Reliability coefficients were 0.72 for fibrinogen and 0.68 for vWF [53]. WBC counts were determined using automated cell counters; reliability coefficients from blind replicate controls ranged from 0.96 to 1.00 [54].

CRP measures were obtained from fasting blood from 5,552 ARIC participants in the Dental ARIC study during ARIC Visit 4 (1996–1998) [55]. Subjects lacking natural teeth or with medical contra-indications to periodontal probing were excluded. CRP was quantified using CRP-specific ELISA assay (detection range 0.5–50 mg/l) [56]. ELISA intra-plate coefficients of variation (CVs) ranged from 0% to 37.3% (interplate CVs: 0%–10.6%).

Inflammatory outcomes were log-transformed. To assess overall inflammatory burden, an inflammatory score was created (range 0–4), wherein one point was assigned for each inflammatory marker with a level above its race-specific median [57].

Separate models were run for each individual-level childhood and adulthood SES measure on each inflammatory outcome. Childhood models included terms for childhood county-level SES; adult models included terms for adulthood census tract-level SES. Due to large SES differences by race, models were race-stratified.

Hierarchical models were used to allow individual-level parameters to vary across neighborhoods as a function of neighborhood-level measures [58, 59]. At the individual level, childhood models estimated the impact of childhood SES on adult inflammation within each childhood county of residence; adult models estimated the impact of adult SES on inflammation within adult census tract of residence.

For each childhood SES exposure, three sets of models were run: Model A adjusted for age, gender and ARIC Center. Model B adjusted for Model A covariates, adult social class and area-level SES. Model C adjusted for Model B covariates and a series of adult CVD risk factors (see Table 3 for complete list of covariates) obtained at ARIC baseline [40, 60]. For the adult SES exposures, Model A and Model C were run.

Log-likelihood tests indicated random slope terms did not add to model predictivity. Furthermore, random intercept terms for neighborhood added no information in models for African-Americans. Therefore, hierarchical linear models with random intercepts were utilized for whites. Linear models (no random effects) were used for African-Americans.

Additional models examined the degree to which CVD risk factors mediated the associations between childhood or adult SES and inflammation. To assess the mediating role of CVD risk factors, risk factors were added individually to Model A for each SES measure – inflammatory marker combination. Percentage changes in the size of SES measure parameter coefficients when the potential mediator was added to the model were calculated [61, 62], permitting the relative strength of each CVD risk factor as a mediator to be considered.

## Results

African-American participants had lower scores for adult and childhood education, neighborhood SES and social class, and significantly higher mean HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), body mass index (BMI), fibrinogen, CRP, and vWF levels (all $p < 0.001$) at baseline than whites (Table 2). African-Americans also had significantly higher prevalence of diabetes and hypertension ($p < 0.001$) than whites. Whites had higher mean WBC and cigarette-years of smoking ($p < 0.001$). Patterns were similar across gender groups, although men smoked significantly more. Percents and percentage standard errors are presented for SES measures in Table 2 as these are composite averages from the five multiply-imputed datasets.

In hierarchical models (white participants), intraclass correlations (ICC's) were low for both childhood and adult data (the highest ICC's were 0.019 and 0.011, respectively). Inflammation levels were therefore not strongly correlated within childhood or adult neighborhood of residence [59].

### *White participants, childhood SES*

Table 3 gives the exponentiated parameter coefficients for the lower categories in each SES measure, providing estimates of the percent increment/decrement in the level of each inflammatory marker for lower versus highest SES category (vWF data not presented due to space constraints, but is available in Additional Table 1 online). Lower versus

**Table 2.** Means and % of socioeconomic measures, inflammatory markers, and CVD covariates for white and African-American LC-SES study participants

| | Whites N = 9081 | | | African-Americans N = 2761 | | |
|---|---|---|---|---|---|---|
| | N | Mean | Std. Dev. | N | Mean | Std. Dev. |
| *Non-imputed data (age-adjusted)* | | | | | | |
| Age (years) | 9081 | 53.92 | 5.63 | 2761 | 52.67 | 5.60 |
| HDL-C (mg/dl) | 9058 | 51.08 | 16.74 | 2618 | 55.66 | 17.15 |
| LDL-C (mg/dl) | 8926 | 136.79 | 37.22 | 2599 | 138.22 | 42.39 |
| BMI ($kg/m^2$) | 9075 | 26.97 | 4.82 | 2753 | 29.89 | 6.06 |
| Diabetes (%) | 9061 | 0.07 | 0.26 | 2680 | 0.16 | 0.37 |
| Hypertension (%) | 9035 | 0.26 | 0.43 | 2750 | 0.53 | 0.49 |
| Hypertension medication (%) | 9031 | 0.18 | 0.38 | 2750 | 0.39 | 0.48 |
| Ethanol intake (gm/week) | 9059 | 43.38 | 87.63 | 2713 | 28.36 | 84.67 |
| Cigarette-years of smoking | 8970 | 306.73 | 407.40 | 2674 | 186.32 | 325.73 |
| Fibrinogen (mg/l) | 9043 | 294.00 | 59.36 | 2619 | 314.23 | 65.69 |
| WBC count ($\times$ 1000 cells/$mm^3$) | 9041 | 6.17 | 1.84 | 2639 | 5.50 | 1.91 |
| vWF (%) | 9044 | 110.43 | 40.80 | 2621 | 129.67 | 53.44 |
| hs-CRP (mg/l) | 4294 | 6.11 | 11.05 | 728 | 8.41 | 14.09 |
| Inflammatory score (0–4) | 4268 | 1.87 | 1.16 | 687 | 1.91 | 1.16 |
| | % | Std. Err. (%) | | % | Std. Err. (%) | |
| *Multiply-imputed data: Early-life SES Measures* | | | | | | |
| Educational level | | | | | | |
| High | 14.1 | 0.4 | | 4.9 | 1.4 | |
| Middle | 35.4 | 0.5 | | 23.8 | 7.8 | |
| Low | 50.5 | 0.6 | | 71.3 | 8.0 | |
| Class | | | | | | |
| Capitalist/Expert Manager | 35.1 | 0.5 | | 26.0 | 0.9 | |
| Middle | 26.8 | 0.5 | | 13.0 | 0.8 | |
| Worker | 38.2 | 0.5 | | 61.0 | 1.1 | |
| Area-level SES | | | | | | |
| High | 25.0 | 25.0 | | 16.6 | 16.6 | |
| Middle | 31.4 | 31.4 | | 43.5 | 43.5 | |
| Low | 43.6 | 43.6 | | 39.9 | 39.9 | |
| *Multiply-imputed data: Adult SES Measures* | | | | | | |
| Educational level | | | | | | |
| High | 38.5 | 0.5 | | 32.4 | 0.9 | |
| Middle | 46.0 | 0.5 | | 28.3 | 0.9 | |
| Low | 15.5 | 0.4 | | 39.3 | 0.9 | |
| Class | | | | | | |
| Capitalist/Expert Manager | 33.9 | 0.5 | | 23.4 | 0.8 | |
| Middle | 36.0 | 0.5 | | 34.7 | 0.9 | |
| Worker | 30.1 | 0.5 | | 41.9 | 1.0 | |
| Area-level SES | | | | | | |
| High | 25.2 | 25.2 | | 25.6 | 25.6 | |
| Middle | 34.5 | 34.5 | | 31.9 | 31.9 | |
| Low | 40.3 | 40.3 | | 42.4 | 42.4 | |

Capitalist/Expert Manager (i.e., highest) childhood social class and lower versus High childhood education were associated with elevated levels of all inflammatory markers in whites. Relative increments in fibrinogen, WBC and vWF for lowest versus highest SES categories were statistically significant ($p < 0.05$) but small (2%–4%). Relative increments associated with lowest SES were larger for CRP (Low versus High childhood education whites had 1.17 [95% CI: 0.97–1.42] times higher CRP).

The inflammatory score (range: 0–4; mean for whites: 1.87) for lowest versus highest childhood class and education were 0.13 (95% CI: 0.06–0.21) and 0.14 (0.05–0.23) points higher, respectively, suggesting a greater overall inflammatory burden in whites of lower childhood SES (Table 4).

Adjustment for adult social class moderately attenuated associations; parameter estimates changed from 9% to 35% and from 10% to 50% in predictive models for childhood class and education, respectively. Notably, all significant class – inflammation associations remained significant after adult class adjustment. Full CVD risk factor adjustment strongly attenuated associations.

Childhood county-level SES was not strongly associated with fibrinogen, WBC or vWF; associations

**Table 3.** Relative differences in estimated levels of adult inflammatory risk markers for lower social class versus Capitalist/Expert Manager social class, lower versus High Education and lower versus High neighborhood SES in childhood and adulthood for white study participants

| Social Class Model | | | | | | | Education Model | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CRP N = 4190 | | Fibrinogen N = 8800 | | WBC N = 8797 | | | CRP N = 4294 | | Fibrinogen N = 9043 | | WBC N = 9041 | |
| Parameter | Relative Diff. | 95% CI | Relative Diff. | 95% CI | Relative Diff. | 95% CI | Parameter | Relative Diff. | 95% CI | Relative Diff. | 95% CI | Relative Diff. | 95% CI |
| *SES in Childhood* | | | | | | | *SES in Childhood* | | | | | | |
| Model A (Base Model) | | | | | | | Model A (Base Model) | | | | | | |
| Middle Class | 1.11 | (0.95, 1.29) | 1.01 | (1.00, 1.02) | 1.02 | (1.00, 1.04) | Middle Education | 1.06 | (0.85, 1.31) | 1.01 | (1.00, 1.02) | 1.03 | (1.01, 1.05) |
| Worker Class | 1.11 | (0.96, 1.29) | 1.02 | (1.01, 1.03) | 1.04 | (1.02, 1.05) | Low Education | 1.17 | (0.97, 1.42) | 1.02 | (1.01, 1.04) | 1.04 | (1.03, 1.06) |
| Middle County SES | 1.07 | (0.85, 1.35) | 1.01 | (1.00, 1.03) | 1.00 | (0.97, 1.03) | Middle County SES | 1.05 | (0.83, 1.33) | 1.01 | (0.99, 1.02) | 0.99 | (0.97, 1.02) |
| Low County SES | 1.12 | (0.91, 1.38) | 1.00 | (0.99, 1.02) | 1.01 | (0.99, 1.03) | Low County SES | 1.07 | (0.88, 1.30) | 1.00 | (0.99, 1.01) | 1.00 | (0.98, 1.02) |
| Model B (Adj. for Adult SES) | | | | | | | Model B (Adj. for Adult SES) | | | | | | |
| Middle Class | 1.06 | (0.90, 1.26) | 1.01 | (0.99, 1.02) | 1.02 | (1.00, 1.03) | Middle Education | 1.03 | (0.82, 1.29) | 1.00 | (0.99, 1.01) | 1.02 | (1.00, 1.04) |
| Worker Class | 1.10 | (0.94, 1.28) | 1.01 | (1.00, 1.03) | 1.03 | (1.02, 1.05) | Low Education | 1.15 | (0.93, 1.41) | 1.01 | (1.00, 1.03) | 1.04 | (1.02, 1.06) |
| Middle County SES | 1.04 | (0.82, 1.31) | 1.00 | (0.99, 1.02) | 1.00 | (0.97, 1.02) | Middle County SES | 1.03 | (0.81, 1.31) | 1.00 | (0.99, 1.02) | 0.99 | (0.97, 1.02) |
| Low County SES | 1.07 | (0.86, 1.34) | 1.00 | (0.98, 1.01) | 1.00 | (0.98, 1.02) | Low County SES | 1.04 | (0.84, 1.28) | 0.99 | (0.98, 1.01) | 1.00 | (0.98, 1.02) |
| Model C (Fully adjusted) | | | | | | | Model C (Fully adjusted) | | | | | | |
| Middle Class | 0.97 | (0.82, 1.15) | 1.00 | (0.99, 1.02) | 1.01 | (1.00, 1.02) | Middle Education | 0.93 | (0.75, 1.15) | 0.99 | (0.98, 1.00) | 1.01 | (0.98, 1.03) |
| Worker Class | 1.03 | (0.86, 1.24) | 1.01 | (0.99, 1.02) | 1.02 | (1.00, 1.03) | Low Education | 1.04 | (0.83, 1.30) | 1.00 | (0.98, 1.01) | 1.02 | (1.00, 1.03) |
| Middle County SES | 1.05 | (0.83, 1.32) | 1.00 | (0.99, 1.01) | 1.00 | (0.98, 1.02) | Middle County SES | 1.05 | (0.83, 1.33) | 1.00 | (0.99, 1.01) | 1.00 | (0.98, 1.02) |
| Low County SES | 1.09 | (0.88, 1.34) | 1.00 | (0.99, 1.01) | 1.01 | (0.99, 1.03) | Low County SES | 1.07 | (0.87, 1.31) | 1.00 | (0.99, 1.01) | 1.01 | (0.99, 1.03) |
| *SES in Adulthood* | | | | | | | *SES in Adulthood* | | | | | | |
| Model A (Base Model) | | | | | | | Model A (Base Model) | | | | | | |
| Middle Class | 1.13 | (0.95, 1.34) | 1.02 | (1.01, 1.03) | 1.02 | (1.00, 1.03) | Middle Education | 1.18 | (1.01, 1.37) | 1.02 | (1.01, 1.03) | 1.03 | (1.02, 1.04) |
| Worker Class | 0.99 | (0.81, 1.21) | 1.03 | (1.02, 1.04) | 1.04 | (1.02, 1.05) | Low Education | 1.28 | (1.01, 1.61) | 1.05 | (1.04, 1.07) | 1.09 | (1.07, 1.12) |
| Middle Tract SES | 1.05 | (0.86, 1.27) | 1.01 | (1.00, 1.02) | 1.02 | (1.00, 1.04) | Middle Tract SES | 1.01 | (0.84, 1.21) | 1.01 | (1.00, 1.02) | 1.01 | (0.99, 1.03) |
| Low Tract SES | 1.24 | (1.03, 1.50) | 1.03 | (1.02, 1.04) | 1.02 | (1.01, 1.04) | Low Tract SES | 1.16 | (0.97, 1.40) | 1.03 | (1.01, 1.04) | 1.01 | (0.99, 1.03) |
| Model C (Fully adjusted) | | | | | | | Model C (Fully adjusted) | | | | | | |
| Middle Class | 1.11 | (0.94, 1.32) | 1.01 | (1.00, 1.02) | 1.00 | (0.99, 1.02) | Middle Education | 1.07 | (0.92, 1.24) | 1.01 | (1.00, 1.01) | 1.00 | (0.99, 1.02) |
| Worker Class | 0.92 | (0.75, 1.13) | 1.02 | (1.00, 1.03) | 1.01 | (0.99, 1.02) | Low Education | 1.06 | (0.83, 1.35) | 1.02 | (1.00, 1.03) | 1.02 | (1.00, 1.04) |
| Middle Tract SES | 0.98 | (0.81, 1.19) | 1.00 | (0.99, 1.01) | 1.00 | (0.99, 1.02) | Middle Tract SES | 0.96 | (0.79, 1.16) | 1.00 | (0.99, 1.01) | 1.00 | (0.99, 1.02) |
| Low Tract SES | 1.08 | (0.89, 1.31) | 1.01 | (1.00, 1.02) | 1.00 | (0.98, 1.01) | Low Tract SES | 1.04 | (0.86, 1.26) | 1.01 | (1.00, 1.02) | 1.00 | (0.98, 1.01) |

Relative difference is the percent increment/decrement in the estimated inflammatory marker for lower versus highest SES category; thus a relative difference of 1.10 signifies a 10% increment in the estimated inflammatory marker level.

Model A: Model adjusted for ARIC Center, age and gender.

Model B: Model adjusted for ARIC Center, age, gender and adult social class.

Model C: Model adjusted for ARIC Center, age, gender, adult social class, HDL-C, LDL-C, BMI, hypertension (HTN) and HTN medication, family history of CVD, diabetes status, alcohol intake, smoking status and cigarette-years smoked.

**Table 4.** Absolute differences in the overall inflammatory score (range: 0–4) for lower social class versus Capitalist/Expert Manager social class, lower versus High Education and lower versus High neighborhood SES in childhood and adulthood for white and African-American study participants

| Social Class Model | | | | | Education Model | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Whites | | African-Americans | | | Whites | | African-Americans | |
| | Inflammatory score N = 4164 | | Inflammatory score N = 639 | | | Inflammatory score N = 4268 | | Inflammatory score N = 687 | |
| Parameter | Absolute Diff. | 95% CI | Absolute Diff. | 95% CI | Parameter | Absolute Diff. | 95% CI | Absolute Diff. | 95% CI |
| *SES in Childhood* | | | | | *SES in Childhood* | | | | |
| Model A (Base Model) | | | | | Model A (Base Model) | | | | |
| Middle Class | 0.07 | (−0.03, 0.17) | 0.19 | (−0.09, 0.47) | Middle Education | 0.06 | (−0.05, 0.16) | 0.04 | (−0.45, 0.54) |
| Worker Class | 0.13 | (0.06, 0.20) | 0.21 | (−0.01, 0.42) | Low Education | 0.14 | (0.05, 0.23) | 0.00 | (−0.46, 0.45) |
| Middle County SES | 0.07 | (−0.05, 0.20) | 0.15 | (−0.13, 0.43) | Middle County SES | 0.06 | (−0.07, 0.18) | 0.11 | (−0.16, 0.38) |
| Low County SES | 0.03 | (−0.07, 0.113) | 0.08 | (−0.20, 0.36) | Low County SES | 0.00 | (−0.10, 0.10) | 0.01 | (−0.26, 0.28) |
| Model B (Adj. for Adult SES) | | | | | Model B (Adj. for Adult SES) | | | | |
| Middle Class | 0.04 | (−0.06, 0.14) | 0.17 | (−0.12, 0.45) | Middle Education | 0.01 | (−0.09, 0.11) | 0.00 | (−0.49, 0.49) |
| Worker Class | 0.09 | (0.02, 0.17) | 0.21 | (−0.01, 0.44) | Low Education | 0.09 | (0.01, 0.18) | −0.04 | (−0.48, 0.41) |
| Middle County SES | 0.03 | (−0.10, 0.15) | 0.12 | (−0.17, 0.40) | Middle County SES | 0.02 | (−0.11, 0.15) | 0.08 | (−0.20, 0.35) |
| Low County SES | −0.02 | (−0.12, 0.09) | 0.08 | (−0.20, 0.36) | Low County SES | −0.03 | (−0.14, 0.07) | 0.02 | (−0.25,0.29) |
| Model C (Fully adjusted) | | | | | Model C (Fully adjusted) | | | | |
| Middle Class | 0.00 | (−0.08, 0.09) | 0.23 | (−0.07, 0.54) | Middle Education | −0.04 | (−0.14, 0.06) | 0.13 | (−0.47, 0.73) |
| Worker Class | 0.05 | (−0.02, 0.12) | 0.24 | (0.00, 0.49) | Low Education | 0.02 | (−0.07, 0.11) | 0.10 | (−0.49, 0.69) |
| Middle County SES | 0.01 | (−0.11, 0.13) | 0.07 | (−0.25, 0.38) | Middle County SES | 0.02 | (−0.11, 0.14) | 0.05 | (−0.25, 0.35) |
| Low County SES | 0.00 | (−0.11, 0.11) | 0.12 | (−0.19, 0.43) | Low County SES | −0.01 | (−0.11, 0.10) | 0.06 | (−0.24, 0.35) |
| *SES in Adulthood* | | | | | *SES in Adulthood* | | | | |
| Model A (Base Model) | | | | | Model A (Base Model) | | | | |
| Middle Class | 0.10 | (0.01, 0.19) | −0.12 | (−0.34, 0.11) | Middle Education | 0.08 | (0.00, 0.16) | −0.08 | (−0.29, 0.14) |
| Worker Class | 0.12 | (0.01, 0.233) | −0.05 | (−0.29, 0.18) | Low Education | 0.22 | (0.10, 0.34) | 0.01 | (−0.21, 0.223) |
| Middle Tract SES | 0.09 | (0.00, 0.19) | 0.14 | (−0.09, 0.36) | Middle Tract SES | 0.09 | (0.01, 0.18) | 0.16 | (−0.07, 0.38) |
| Low Tract SES | 0.17 | (0.08, 0.26) | 0.31 | (0.08, 0.53) | Low Tract SES | 0.16 | (0.08, 0.24) | 0.34 | (0.12, 0.57) |
| Model C (Fully adjusted) | | | | | Model C (Fully adjusted) | | | | |
| Middle Class | 0.07 | (−0.02, 0.16) | −0.13 | (−0.36, 0.11) | Middle Education | 0.01 | (−0.06, 0.09) | −0.07 | (−0.29, 0.15) |
| Worker Class | 0.05 | (−0.06, 0.16) | −0.12 | (−0.36, 0.13) | Low Education | 0.06 | (−0.05, 0.17) | −0.16 | (−0.40, 0.07) |
| Middle Tract SES | 0.06 | (−0.02, 0.15) | 0.10 | (−0.13, 0.34) | Middle Tract SES | 0.07 | (−0.01, 0.15) | 0.14 | (−0.10, 0.37) |
| Low Tract SES | 0.08 | (0.00, 0.16) | 0.16 | (−0.07, 0.40) | Low Tract SES | 0.09 | (0.01, 0.16) | 0.22 | (−0.02, 0.46) |

The overall inflammatory score has a range of 0–4; one point is assigned for each inflammatory marker (out of CRP, fibrinogen, white blood cell count and vWF) with a level above its race-specific median. Absolute difference is calculated by subtracting the inflammatory score for lower versus highest SES category.

Model A: Model adjusted for ARIC Center, age and gender.

Model B: Model adjusted for ARIC Center, age, gender and adult social class.

Model C: Model adjusted for ARIC Center, age, gender, adult social class, HDL-C, LDL-C, BMI, hypertension (HTN) and HTN medication, family history of CVD, diabetes status, alcohol intake, smoking status and cigarette-years smoked.

were observed with CRP. Whites from Low- versus High-SES childhood counties had 12% (95% CI: 0.91–1.38) and 7% (0.88–1.30) higher CRP in the two minimally adjusted models.

*White participants, adult SES*

Worker class whites had significantly higher fibrinogen (3% increase), WBC (4% increase) and vWF (5% increase) versus Capitalist/Expert Manager class whites (Table 3). Increments in inflammation for Lower versus High education were all statistically significant, and generally larger than for class differences. WBC and CRP were notably elevated among those with Low versus High education (9% and 28% greater, respectively).

Mean inflammatory scores were significantly higher among whites of lower versus highest class and education, particularly for Low versus High education, where an increment of 0.22 (95% CI: 0.10–0.34) points was observed (Table 4).

CVD risk factor adjustment attenuated associations considerably. However, the impact of lowest versus highest class and education on fibrinogen and vWF (and WBC for education) remained significant.

Whites from Low- versus High-SES census tracts had significantly elevated levels of all inflammatory measures in minimally adjusted models. In particular, individuals from Low- versus High-SES census tracts had CRP levels 1.24 (95% CI: 1.03–1.50) or 1.16 (0.97–1.40) times higher, depending upon the model. The overall inflammatory score was also significantly associated with Low-SES neighborhood residence. Full covariate adjustment did not significantly attenuate these associations.

*African-American participants, childhood SES*

Results were weaker and less consistent among African-Americans. The impact of lower childhood social class or education on fibrinogen, WBC, and vWF was small among African-Americans (Table 5; vWF data in Additional Table 1 online). Associations between lower childhood SES and elevated CRP levels were observed, although they did not attain statistical significance. African-Americans of childhood Worker class had CRP levels 1.24 (95% CI: 0.81–1.89) times higher than those of Capitalist/Expert Manager class. Lower versus High childhood education was also associated with elevated CRP.

WBC and vWF levels were slightly higher among African-Americans from Lower versus High SES childhood counties. Low versus High childhood county-level SES was associated with considerable but not statistically significant increments in CRP in the childhood class and education models (41% and 24%, respectively). Adjustment for adult SES strengthened the association between childhood county and CRP in both models, but full covariate adjustment markedly decreased it.

*African-American participants, adult SES*

Lowest adult social class was associated with slightly higher levels of vWF ($p < 0.05$), fibrinogen and WBC in African-Americans. Lower education associated with modest but significant increments in fibrinogen and vWF. Adult individual-level SES had inconsistent effects on CRP: Middle class participants had only 0.69 (95% CI: 0.44–1.06) the mean CRP of Capitalist/Expert Manager African-Americans, while modest, non-significant increments were observed for Middle and Low versus High education (9% and 8%, respectively). Unlike in whites, there was no appreciable increment in the overall inflammatory score for African-Americans of lower social class or education.

Adjustment for CVD risk factors attenuated the effect of low SES on most inflammatory markers, but strengthened the association between Middle class and lower CRP (0.61, 95% CI: 0.38–0.97). Low versus High education remained significantly associated with vWF.

Adult neighborhood SES was not appreciably associated with fibrinogen, WBC or vWF among African-Americans. However, African-Americans from Low SES neighborhoods had markedly but not significantly higher CRP levels than those from High SES tracts in both models (31% and 35% increments, respectively). In addition, there were significant increments in the inflammatory score for Low versus High census tract SES in minimally adjusted models (Table 4).

*Mediation analysis results*

Covariate mediation analyses in whites indicated that the effects of childhood social class on inflammation were mediated most strongly by diabetes status (parameter estimate changes ranged from 8% to 82% in predictive models), HDL-C (9%–31%), smoking (7%–28%), and BMI (7%–18%). Results were similar for the adult social class measures, which were mediated most strongly by smoking (estimate changes from 4% to 47% in predictive models), HDL-C (8%–23%), and leisure sport activity (1%–16%). The influence of adult neighborhood SES was mediated most strongly by BMI (estimates changed from 25% to 55%) and HDL-C (16%–31%).

Results were comparable in education models for whites. The influence of childhood education was mediated most strongly by BMI (estimates changed from 13% to 49%), HDL-C (13%–40%) and smoking status (7%–21%). The covariates most strongly mediating the effect of adult education on inflammation were BMI (estimates changed from 9% to 44%), smoking (5%–44%), leisure sport activity (10%–34%), and HDL-C (9%–20%).

**Table 5.** Relative differences in estimated levels of adult inflammatory risk markers for lower social class versus Capitalist/Expert Manager social class, lower versus High Education and lower versus High neighborhood SES in childhood and adulthood for African-American study participants.

| Social Class Model | | | | | | | Education Model | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CRP N = 676 | | Fibrinogen N = 2392 | | WBC N = 2412 | | | CRP N = 728 | | Fibrinogen N = 2619 | | WBC N = 2639 | |
| Parameter | Relative Diff. | 95% CI | Relative Diff. | 95% CI | Relative Diff. | 95% CI | Parameter | Relative Diff. | 95% CI | Relative Diff. | 95% CI | Relative Diff. | 95% CI |
| *SES in Childhood* | | | | | | | *SES in Childhood* | | | | | | |
| Model A (Base Model) | | | | | | | Model A (Base Model) | | | | | | |
| Middle Class | 0.94 | (0.52, 1.71) | 0.99 | (0.97, 1.02) | 1.00 | (0.96, 1.05) | Middle Education | 1.16 | (0.43, 3.14) | 1.00 | (0.96, 1.04) | 1.00 | (0.93, 1.07) |
| Worker Class | 1.24 | (0.81, 1.89) | 1.01 | (0.99, 1.03) | 1.00 | (0.97, 1.03) | Low Education | 1.12 | (0.46, 2.76) | 0.99 | (0.96, 1.03) | 0.98 | (0.92, 1.04) |
| Middle County SES | 1.46 | (0.84, 2.54) | 1.00 | (0.98, 1.03) | 1.02 | (0.98, 1.06) | Middle County SES | 1.33 | (0.78, 2.26) | 1.01 | (0.98, 1.03) | 1.02 | (0.98, 1.05) |
| Low County SES | 1.41 | (0.81, 2.45) | 1.00 | (0.98, 1.03) | 1.00 | (0.96, 1.04) | Low County SES | 1.24 | (0.73, 2.10) | 1.00 | (0.98, 1.02) | 0.99 | (0.96, 1.03) |
| Model B (Adj. for Adult SES) | | | | | | | Model B (Adj. for Adult SES) | | | | | | |
| Middle Class | 0.91 | (0.50, 1.68) | 0.99 | (0.96, 1.02) | 1.01 | (0.96, 1.05) | Middle Education | 1.07 | (0.38, 3.00) | 0.99 | (0.95, 1.03) | 0.98 | (0.91, 1.06) |
| Worker Class | 1.15 | (0.74, 1.78) | 1.01 | (0.99, 1.03) | 1.00 | (0.97, 1.03) | Low Education | 1.01 | (0.41, 2.50) | 0.98 | (0.95, 1.02) | 0.96 | (0.90, 1.03) |
| Middle County SES | 1.52 | (0.87, 2.66) | 1.00 | (0.98, 1.03) | 1.02 | (0.98, 1.06) | Middle County SES | 1.40 | (0.81, 2.39) | 1.01 | (0.98, 1.03) | 1.01 | (0.98, 1.05) |
| Low County SES | 1.49 | (0.84, 2.62) | 1.00 | (0.98, 1.03) | 1.00 | (0.96, 1.03) | Low County SES | 1.33 | (0.78, 2.27) | 1.00 | (0.98, 1.02) | 0.99 | (0.96, 1.03) |
| Model C (Fully adjusted) | | | | | | | Model C (Fully adjusted) | | | | | | |
| Middle Class | 0.77 | (0.40, 1.46) | 1.00 | (0.97, 1.03) | 1.00 | (0.96, 1.05) | Middle Education | 1.53 | (0.48, 4.82) | 0.99 | (0.94, 1.04) | 1.00 | (0.92, 1.08) |
| Worker Class | 1.18 | (0.74, 1.88) | 1.01 | (0.99, 1.03) | 0.99 | (0.96, 1.02) | Low Education | 1.12 | (0.38, 3.33) | 0.98 | (0.94, 1.03) | 0.98 | (0.91, 1.06) |
| Middle County SES | 1.11 | (0.61, 2.02) | 0.99 | (0.97, 1.02) | 1.03 | (0.96, 1.07) | Middle County SES | 1.07 | (0.60, 1.91) | 1.00 | (0.97, 1.02) | 1.02 | (0.98, 1.06) |
| Low County SES | 0.95 | (0.52, 1.75) | 1.00 | (0.97,1.03) | 1.00 | (0.96, 1.05) | Low County SES | 0.88 | (0.49, 1.57) | 1.00 | (0.97, 1.02) | 1.00 | (0.96, 1.03) |
| *SES in Adulthood* | | | | | | | *SES in Adulthood* | | | | | | |
| Model A (Base Model) | | | | | | | Model A (Base Model) | | | | | | |
| Middle Class | 0.69 | (0.44, 1.06) | 0.99 | (0.97, 1.02) | 1.00 | (0.97, 1.04) | Middle Education | 1.09 | (0.72, 1.65) | 1.02 | (1.00, 1.04) | 1.00 | (0.97, 1.03) |
| Worker Class | 0.99 | (0.62, 1.56) | 1.02 | (1.00, 1.04) | 1.02 | (0.99, 1.05) | Low Education | 1.08 | (0.70, 1.66) | 1.03 | (1.01, 1.05) | 1.01 | (0.98, 1.04) |
| Middle Tract SES | 1.28 | (0.82, 2.00) | 1.00 | (0.98, 1.02) | 1.00 | (0.97, 1.03) | Middle Tract SES | 1.23 | (0.79, 1.92) | 1.00 | (0.98, 1.02) | 1.00 | (0.97, 1.03) |
| Low Tract SES | 1.31 | (0.85, 2.03) | 1.02 | (1.00, 1.04) | 1.01 | (0.98, 1.04) | Low Tract SES | 1.35 | (0.87, 2.09) | 1.01 | (0.99, 1.03) | 1.01 | (0.98, 1.05) |
| Model C (Fully adjusted) | | | | | | | Model C (Fully adjusted) | | | | | | |
| Middle Class | 0.61 | (0.38, 0.97) | 1.00 | (0.98, 1.02) | 1.01 | (0.98, 1.05) | Middle Education | 1.14 | (0.73, 1.77) | 1.01 | (0.99, 1.03) | 0.98 | (0.95, 1.01) |
| Worker Class | 1.06 | (0.65, 1.73) | 1.01 | (0.99, 1.04) | 1.00 | (0.97, 1.04) | Low Education | 0.97 | (0.61, 1.56) | 1.01 | (0.99, 1.03) | 0.97 | (0.95, 1.01) |
| Middle Tract SES | 1.58 | (0.98, 2.53) | 0.99 | (0.97, 1.01) | 0.99 | (0.96, 1.02) | Middle Tract SES | 1.53 | (0.96, 2.45) | 0.99 | (0.97, 1.01) | 0.99 | (0.96, 1.02) |
| Low Tract SES | 1.45 | (0.91, 2.33) | 0.99 | (0.97, 1.02) | 0.99 | (0.95, 1.02) | Low Tract SES | 1.49 | (0.93, 2.40) | 0.99 | (0.97, 1.02) | 1.00 | (0.97, 1.03) |

Relative difference is the percent increment/decrement in the estimated inflammatory marker for lower versus highest SES category; thus a relative difference of 1.10 signifies a 10% increment in the estimated inflammatory marker level.

Model A: Model adjusted for ARIC Center, age and gender.

Model B: Model adjusted for ARIC Center, age, gender and adult social class.

Model C: Model adjusted for ARIC Center, age, gender, adult social class, HDL-C, LDL-C, BMI, hypertension (HTN) and HTN medication, family history of CVD, diabetes status, alcohol intake, smoking status and cigarette-years smoked.

Mediation analyses were not carried out among African-Americans due to inconsistent parameter estimates in most models.

## Discussion

Lower adult and early-life SES measures were associated with levels of inflammatory outcomes between both race groups in almost all models. Associations were stronger and more consistent for education versus social class, for individual-level versus area-level SES, for adult versus childhood SES, and in whites versus African-Americans. Fibrinogen and WBC showed the most consistent associations with SES; the largest differences in inflammation by SES were seen for CRP. Adjustment for adult social class only moderately attenuated most childhood SES – inflammation associations and many remained significant after adjustment. This suggests that links between childhood and adult SES are likely not the primary pathway by which childhood SES – adult inflammation associations operate. Adjustment for adult CVD risk factors strongly attenuated most childhood SES – inflammation associations. This expected finding is consistent with an over-adjustment in the models, given that childhood SES may influence adult inflammation through learned behaviors (e.g., smoking) or physiologic characteristics (e.g., BMI). However, CVD risk factor adjustment did not completely attenuate most adult SES – inflammation associations, suggesting that mechanisms not considered in these analyses may be involved.

The link between early-life SES and CVD likely involves both behavioral and physiologic pathways, with systemic inflammation developing as part of such pathways. Behavior patterns established in early life probably play an important role: studies have repeatedly associated low early-life SES with elevated adult BMI/waist-hip-ratio, alcohol intake and smoking rates and little leisure physical activity [23, 63]. Our results agree with these findings, suggesting that low childhood SES may predispose to adverse health behaviors associated with elevated inflammation and CVD risk.

Area-level SES was particularly associated with CRP, generally having a stronger impact on CRP than individual-level SES. Previous studies report disparities in mortality by adult neighborhood SES [64, 65], but have not examined the impact of early-life area-level SES on measures of sub-clinical CVD. Our results suggest that contextual SES in early life and particularly in adulthood may contribute to the development of CVD risk.

Although many studies attempt to separate the influence of life-course SES on CVD into ''direct'' and ''indirect'' effects via mediation analyses, this approach has numerous limitations [66, 67]. As a mediation analysis for this paper, we estimated a total effect (i.e., unadjusted for measured causal intermediates) and a direct effect (i.e., adjusted for these intermediates), and expressed the relation between these estimates in percentage terms. BMI, smoking and HDL-C were identified as strong mediators across different SES measures and time points, suggesting biologically plausible pathways by which an association between SES and systemic inflammation may operate.

The weaker, less-consistent SES effects among African-Americans may be due to several reasons. Sample sizes were smaller, limiting power. SES distributions differed by race group; therefore the ranges of SES compared were different. Certain potentially important aspects of SES and the social environment (e.g., income, experience with racism) were not measured. As in previous ARIC studies, the associations of interest here might truly differ by race/ethnicity or may simply point to the limitations present in evaluating SES effects among African-Americans in ARIC [3, 64].

Other study limitations are that childhood contextual SES data was only available at the county level, CRP was available only in a healthier subset of participants, and use of the social class measure required excluding homemakers (17% of women). Among the strengths of this report are the use of different individual-level and area-level SES measures, the availability of different inflammatory outcomes, and the utilization of multi-level models. Additionally, the use of multiple imputation represents a careful, systematic effort to minimize possible biases.

The modest but consistent associations found between lower early-life SES and elevated adult inflammation are noteworthy, suggesting processes whose natural history parallels the development of atherosclerosis over many decades [68]. Consistent with this interpretation, the influence of SES on adult inflammation was most strongly mediated by smoking, BMI and HDL-C levels, attributes modulated early in life whose influence on CVD risk is documented throughout the life-course [69].

This study provides further support for the impact of low SES in early and later life on adult CVD risk. Our results highlight one pathway (i.e., chronic systemic inflammation) by which SES may act. Although the magnitude of the SES effects on inflammatory levels were modest, the population impact of such differences would be considerable, particularly if sustained over several decades as suggested by our early-life SES measures. This suggests an area of inquiry deserving further investigation.

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