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# Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood

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## ABSTRACT

**Objective:** To examine the association between cumulative life course and adult socioeconomic status (SES) and adult levels of inflammatory risk markers (fibrinogen, white blood cell count (WBC), C-reactive protein (CRP), von Willebrand factor (vWF) and an overall inflammatory score).

**Design:** Retrospective cohort study.

**Setting:** 12 681 white and African-American participants in the Atherosclerosis Risk in Communities (ARIC) study and two ancillary studies.

**Methods:** Participants provided information on SES and place of residence in childhood and young (30–40 years) and mature (45+) adulthood. Residences were linked to census data for neighbourhood SES information. Multiple imputation (MI) was used for missing data. Linear regression and adjusted geometric means were used to estimate the effects of SES on inflammatory risk marker levels.

**Results:** Graded, statistically significant associations were observed between greater cumulative life-course exposure to low education and social class and elevated levels of fibrinogen and WBC among white participants. Stronger graded, statistically significant associations were observed between low adult education, social class and neighbourhood SES and elevated inflammatory levels. Associations were weaker and less consistent in African-Americans. Covariate adjustment attenuated results but many associations remained strong.

**Conclusions:** Our results suggest that cumulative exposure to adverse SES conditions across the life course and low adult SES are associated with an elevated systemic inflammatory burden in adulthood. Chronic systemic inflammation may be one pathway linking low life-course SES and elevated cardiovascular disease risk.

An inverse association of individual<sup>1–3</sup> and contextual/neighbourhood<sup>4,5</sup> socioeconomic status (SES) in adulthood with cardiovascular disease (CVD) has been demonstrated. Low adult SES is associated with poor health behaviours and unfavourable CVD risk factor profiles.<sup>3,5–7</sup> Recent research has focused on the influence of life-course SES on CVD<sup>8,9</sup>: various study designs have been utilised to examine the impact of SES throughout the life course on adult cardiovascular health and several interrelated theories have been posited.<sup>10–15</sup> Results support a cumulative model of life-course risk, wherein the accumulation of adverse psychosocial and physiological exposures across the life course is associated with increased CVD.<sup>9,14–18</sup>

Inquiries into possible mechanisms underlying such associations suggest a sustained, elevated systemic inflammatory burden may mediate social differences in CVD. Chronic and systemic inflammatory

upregulation plays a central role in atherosclerosis and its sequelae.<sup>19–23</sup> Lower adult SES is associated with elevated levels of inflammatory markers such as fibrinogen, white blood cell count (WBC), C-reactive protein (CRP) and von Willebrand factor (vWF).<sup>24–26</sup> These and other inflammatory markers and cytokines have in turn been linked with CVD.<sup>27–34</sup> Atherosclerosis begins earlier in life than previously suspected.<sup>35</sup> SES plausibly affects health behaviours, nutrition, access to health care, exposure to infection and stress throughout life, thereby influencing an individual's systemic inflammatory burden and CVD risk.<sup>3,7</sup>

Early-life SES has been linked with elevated inflammatory marker levels in other studies<sup>36–38</sup> and in this cohort.<sup>39</sup> However, no studies have examined the cumulative influence of exposure to adverse SES across life on adult inflammatory levels. In order to explore cumulative adverse SES exposure and systemic inflammation as a potential pathway by which SES and CVD may be linked, we examined the impact of cumulative life-course and adult SES (measured at both the individual and community levels) on adult levels of fibrinogen, WBC, CRP and vWF and overall inflammatory burden in the Atherosclerosis Risk in Communities (ARIC) study.

## METHODS

### Data

ARIC is a prospective study of atherosclerosis in 15 792 men and women aged 45–64 at baseline (1987–9), sampled from four US communities with an overall 60% participation rate.<sup>40</sup> The Life Course Socioeconomic Status, Social Context and Cardiovascular Disease (LC-SES) Study is an ancillary study that retrospectively collected socioeconomic information from childhood (1930–50) and early adulthood (1960–80) on 12 681 African-American and white ARIC participants in 2001–2.<sup>41</sup> Individual-level SES and places of residence during childhood and at ages 30, 40 and 50 were collected in ARIC and from annual follow-up telephone interviews.

### SES measures

SES was evaluated in childhood (10 years of age), early adulthood (30–40 years of age) and mature adulthood (45+ years). Individual-level SES was evaluated via social class and education; contextual/neighbourhood-level SES was evaluated using SES indices, described below.

Social class was evaluated utilising a derivation of Wright's schema for categorising social class, an established sociological schema previously examined in epidemiology.<sup>42–44</sup> Participants were

**Table 1** Assignment of a participant's social class in childhood (via father's education/occupation) and young and mature adulthood (based on Wright's class categorisation) for ARIC participants

Social class	Higher education*	Owens business/self-employed	Supervisory or managerial job role
Worker class	No	No	No
Middle class	Yes	No	No
	No	No	Yes
	–	Yes	No
Capitalist/expert manager class	Yes	No	Yes
	–	Yes	Yes

\*Higher education is some college education or more.

assigned a class at each time point based on education and items evaluating ownership, authority and control facets of their job (table 1). Father's data were used for childhood; principal occupation at 30–40 years of age and current/last occupation were used for young and mature adulthood, respectively. Homemakers were excluded from social class analyses.

Education was evaluated in childhood and adulthood and categorised low/middle/high (table 2). In childhood, father's education was used; in adulthood, participant's education was used.

To evaluate neighbourhood SES, participants' places of residence during childhood and adulthood were linked to US census data (county data for childhood and census tract data for adulthood).<sup>45</sup> Of 12 681 participants, 12 373 had US residences in childhood. Of these 12 373, 98.5% (12 187) had their childhood residences successfully linked with US county data. Linkage rates in young adulthood were lower: 66% for 1960 census data, 76% for 1970 data and 85% for 1980 data. A neighbourhood SES index was created for each period (table 3) to evaluate contextual/neighbourhood SES.<sup>46</sup>

Cumulative social class, education and contextual/neighbourhood SES measures were created by summing the number of times across the life course one was exposed to the lowest category of SES (table 4).<sup>14 47</sup>

### Physiological covariates and outcomes

CVD risk factors, fibrinogen, vWF and WBC were measured at baseline.<sup>40</sup> Diabetic status was determined by fasting plasma glucose  $\geq 126$  mg/dl, non-fasting plasma glucose  $\geq 200$  mg/dl, self-reported history of physician-diagnosed diabetes or current medication for diabetes.<sup>5 40</sup>

Haemostasis variables were analysed in citrated samples,<sup>48</sup> fibrinogen by the thrombin time titration method and vWF antigen by enzyme-linked immunosorbent assay.<sup>49</sup> Reliability coefficients were 0.72 for fibrinogen and 0.68 for vWF.<sup>50</sup> White cell counts were determined using automated cell counters (reliability coefficients 0.96–1.00).

CRP measures were obtained from fasting blood taken from the 5552 participants in the Dental ARIC study during the 1996–8 ARIC Visit (eligibility required having teeth, no medical contraindications to periodontal probing and consent).<sup>51</sup> CRP was quantified using ELISA assay (range of detection 0.5–50 mg/l).<sup>52</sup> Intra-plate and inter-plate coefficients of variation ranged from 0–37.3% and 0–10.6%, respectively.

### Statistical methods

Incomplete earlier-life address, education and census data resulted in high missing data rates for cumulative education (16.4%), class (28.1%) and neighbourhood SES (36.6%) measures for the overall cohort. Multiple imputation (MI) was used to reduce bias.<sup>53</sup> Data were considered to be missing at random (MAR), an assumption that usually holds in self-reported questionnaire data and when erroneous data tend to have only a minor impact on estimates.<sup>54 55</sup> Multivariate imputation by chained equations (MICE) was carried out in Stata 8.2 SE utilising 29 demographic covariates and five imputations of 10 iterations.<sup>56</sup>

Inflammatory outcomes were log-transformed. Overall inflammatory burden was assessed using an inflammation score ranging from 0 to 4 (one point was assigned for each of the four inflammatory markers with a level above its race/ethnicity-specific median). This score has been previously utilised and demonstrated a graded, statistically significant association with risk of incident diabetes.<sup>57</sup> Analyses using CRP or the inflammatory score as outcomes were limited to the 5022 dental ARIC study participants with early-life SES data.

We initially fitted multi-level models with random intercepts for each tract or county to account for residual within-area correlation. However, as they did not significantly improve model fit, we subsequently used linear regression to examine the impact of each SES measure on each inflammatory outcome.

One set of race/ethnicity-specific models (model A) adjusted for age, gender and ARIC centre. A second set (model B) additionally adjusted for high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), hypertension (HTN) and HTN medication, family history of CVD, diabetes status, alcohol intake, smoking status and cigarette-years smoked. For cumulative SES measures, the referent was zero exposures to adverse life-course SES conditions; for adult SES measures, the referent was highest SES.

Geometric mean levels of inflammatory markers were computed for each level of SES by exponentiating parameter estimates. Statistical interaction between SES and potential confounders was assessed using partial *F* tests.<sup>58</sup> Tests for linear trend were run using interval SES variables.

### RESULTS

African-American participants had lower scores for adult and cumulative SES measures, higher mean fibrinogen, CRP and

**Table 2** Assignment of participants' education group in childhood and adulthood for ARIC participants

Time point	Low education group	Middle education group	High education group
Childhood	0–8th grade	9th–12th grade	Some college or more
Adulthood	< High school degree	High school degree	Some college or more

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**Table 3** Contextual/neighbourhood SES index for a participant's place of residence at each of the three measured time points (childhood, young adulthood and mature adulthood) for ARIC participants

Step 1 Compute race-specific z-scores of five US census measures:
(1) Median/mean family income
(2) Median/mean value of owner occupied house
(3) Percentage of residents with high school education
(4) Percentage of residents with college education
(5) Percentage of residents in professional/managerial occupations
Step 2 Sum these five z-scores to create a neighbourhood SES index for that time
Step 3. Categorise each index low/middle/high at the 40th and 75th percentiles (based on naturally occurring divisions in the distributions)

vWF levels, and lower mean WBC levels (all  $p < 0.001$ ) than white participants (table 5). Patterns were similar across gender groups. Percentages and standard errors are presented for SES measures as these are composite estimates from five multiply imputed datasets. Neighbourhood SES categories were based on race/ethnicity-specific distributions and cannot be directly compared across race/ethnicity groups.

**Cumulative life-course SES, white participants**

Among white participants, increasing cumulative life-course exposure to lower SES conditions for all SES measures was associated with elevated levels of each adult inflammatory marker in minimally adjusted models (table 6; vWF results in supplementary table 1). Graded increments in fibrinogen and WBC levels were observed with greater adverse SES exposure ( $p$  for trend  $< 0.01$  for individual-level SES measures in minimally adjusted models).

Greater cumulative exposure to unfavourable SES was strongly associated with elevated fibrinogen and WBC (table 6). For example, white participants with three versus zero life-course exposures to the worker social class group had geometric mean fibrinogen of 296.3 mg/dl (95% CI: 292.4 to 300.2), versus 283.9 mg/dl (95% CI: 281.8 to 286.1) ( $p < 0.001$ ).

Lower categories of all measures were associated with graded elevations in the overall inflammatory score (supplementary table 2). Differences between lowest and highest individual-level SES categories all attained statistical significance in minimally adjusted models, suggestive of a greater overall inflammatory burden ( $p$  for trend  $< 0.01$ ).

While CVD risk factor adjustment attenuated all cumulative SES-inflammation associations, increasing adverse life-course exposures remained associated with higher CRP, fibrinogen and vWF (table 6). For fibrinogen, the associations for the most-exposed versus least-exposed groups remained statistically significant in all cumulative SES measures.

**Adult SES, white participants**

Lower adult SES was strongly associated with elevated inflammatory levels among white participants (table 6; vWF results in supplementary table 1). Graded elevations in inflammatory markers were observed with decreasing SES for all adult measures ( $p$  for trend  $< 0.001$  for fibrinogen and WBC in minimally adjusted models). For every adult SES measure, participants in lowest versus highest SES groups had statistically significantly higher levels of all markers; the sole exception was for Worker class adults and CRP. As with cumulative SES, fibrinogen and WBC were strongly associated with adult SES.

Lower categories of all measures were associated with graded elevations in the overall inflammatory score (supplementary

**Table 4** Cumulative life-course social class, education and contextual/neighbourhood SES measures based on a participant's SES in childhood and young and mature adulthood for ARIC participants

Cumulative life-course SES measure	Method of creation and range
Cumulative social class	Sum the number of times a participant was in the worker (lowest) social class category, out of childhood, young adulthood and mature adulthood. Range: 0–3
Cumulative education	Sum the number of times a participant was in the low education group, out of participant's and father's education. Range: 0–2
Cumulative neighbourhood SES*	Sum the number of times a participant lived in a low SES category neighbourhood, out of childhood, young adulthood and mature adulthood. Range: 0–3

\*Example: a participant who was in the low neighbourhood SES group in childhood, the middle group in young adulthood and the low group in mature adulthood would have a cumulative neighbourhood SES measure score of 2.

table 2); differences between lowest and highest SES categories were all significant in minimally adjusted models. Relative increments in inflammatory score by SES were similar in size to those observed within levels of cumulative SES.

CVD risk factor adjustment attenuated most associations (table 6). However, low education remained significantly associated with elevated fibrinogen and WBC. Elevated fibrinogen also remained significantly associated with lowest social class and neighbourhood SES. Associations with the inflammatory score were no longer statistically significant after covariate adjustment, but graded associations remained.

**Cumulative SES, African-American participants**

Among African-Americans, increasing cumulative exposure to adverse SES was inconsistently associated with elevated inflammatory levels (table 7; vWF results in supplementary table 1). Greater life-course exposure to lower education and social class was associated with elevated fibrinogen and vWF (and CRP for social class) in minimally adjusted models; greater exposure to low-SES neighbourhoods was associated with elevated CRP and fibrinogen. Associations were weaker and less consistent among African-American participants than among white participants. Stepwise, graded elevations in inflammatory marker levels were not consistently observed by cumulative SES category, as they were in white participants. Only slight increments in the overall inflammatory score by greater exposure to adverse SES conditions were observed (supplementary table 2).

CVD risk factor adjustment strongly attenuated the cumulative SES-inflammation marker associations. Moreover, certain associations were inverted after CVD risk factor adjustment, with greater exposure being associated with lower inflammatory levels.

**Adult SES, African-American participants**

Lower adult SES was associated with elevated inflammatory levels among African-Americans (table 7; vWF results in supplementary table 1). Patterns were more consistent than for cumulative SES. Levels of all markers were higher for lowest versus highest category of all SES measures; graded associations were observed for fibrinogen and WBC.

The influence of lower adult SES on inflammation was generally smaller among African-American participants than white participants. For example, the relative increments in CRP,

**Table 5** Means and percentage of socioeconomic measures, inflammatory markers and covariates for white and African-American participants

	White participants				African-American participants			
	Females (n = 4952)		Males (n = 4129)		Females (n = 1807)		Males (n = 954)	
<b>Non-imputed data (age-adjusted)</b>	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	53.7	5.6	54.3	5.6	52.6	5.6	52.8	5.7
HDL-C (mg/dl)	57.8	15.0	43.0	15.0	58.5	16.7	50.4	16.7
LDL-C (mg/dl)	134.5	37.2	139	37.2	137.8	42.4	139.1	42.4
BMI (kg/m <sup>2</sup> )	26.6	4.8	27.4	4.8	30.9	5.9	28.0	5.9
Diabetes (%)	7.0	26.1	8.4	25.9	17.1	4.2	13.8	37.4
Hypertension (%)	24.3	43.3	26.0	42.6	54.5	5.1	50.4	48.9
Hypertension medication (%)	18.2	38.4	18.0	38.1	43.3	48.0	31.1	48.0
Ethanol intake (g/week)	23.3	84.9	67.9	84.9	9.6	80.6	64.2	80.6
Cigarette-years of smoking	205.5	392.9	424.7	392.9	123.5	314	306.3	314.0
Fibrinogen (mg/l)	297.1	59.3	289.5	59.3	321.8	64.9	300.2	64.9
White blood cell count ( $\times 1000$ cells per $10^6/l$ )	6.1	1.8	6.3	1.8	5.5	1.9	5.5	1.9
C-reactive protein (mg/l)	7.6	10.9	4.3	10.9	9.6	14.0	6.3	14.0
von Willebrand factor (%)	109.8	40.8	110.4	40.8	131.2	53.4	126.9	53.4
Inflammatory score (0-4)	1.9	1.2	1.8	1.2	2.1	1.1	1.6	1.1
<b>Multiply imputed data: cumulative life-course SES measures</b>	%	SE	%	SE	%	SE	%	SE
Number of exposures to lowest education group (0-2)								
0	45.2	0.7	45.6	0.8	20.2	4.0	18.2	3.1
1	43.6	0.7	42.7	0.8	50.4	2.2	50.3	2.9
2	11.2	0.5	11.7	0.5	29.4	5.0	31.5	4.6
Number of exposures to worker class group (0-3)								
0	33.3	1.0	45.3	0.8	21.3	1.1	24.0	1.4
1	23.9	0.9	29.3	0.7	28.3	1.2	28.7	1.5
2	23.3	0.9	15.7	0.6	21.0	1.1	21.7	1.4
3	19.4	0.8	9.8	0.5	29.4	1.3	25.7	1.5
Number of exposures to lowest neighbourhood SES group (0-3)								
0	25.7	0.6	28.7	0.7	21.7	1.0	25.7	1.5
1	34.2	0.7	32.5	0.8	37.3	1.3	37.5	1.6
2	26.2	0.7	24.5	0.7	28.2	1.2	23.5	1.4
3	13.9	0.5	14.4	0.6	12.9	0.9	13.3	1.1
<b>Multiply imputed data: adult SES measures</b>	%	SE	%	SE	%	SE	%	SE
Educational level								
High	33.6	0.7	44.3	0.8	31.6	1.1	33.9	1.5
Middle	51.2	0.7	39.8	0.8	29.8	1.1	25.5	1.4
Low	15.2	0.5	15.9	0.6	38.6	1.2	40.7	1.6
Social class								
Capitalist/expert manager	23.5	0.7	44.4	0.8	19.1	1.0	31.8	1.5
Middle	38.2	0.8	33.7	0.7	35.8	1.2	32.8	1.5
Worker	38.3	0.8	21.9	0.6	45.1	0.0	36.0	1.6
Neighbourhood SES								
High	24.8	0.6	25.7	0.7	24.0	1.0	28.7	1.5
Middle	34.4	0.7	34.6	0.8	31.1	1.1	33.6	1.5
Low	40.8	0.7	39.7	0.8	44.9	1.2	37.7	1.6

SD, standard deviation; SE, standard error.

fibrinogen, WBC and vWF observed for lowest versus highest education among African-American participants were 18%, 4%, 0% and 7%, respectively, versus 37%, 6%, 10% and 5% for white participants, respectively. Low adult SES was most notably associated with adult fibrinogen, where graded associations were observed for all adult SES measures ( $p$  for trend  $<0.05$ ).

Lower adult SES was modestly associated with an elevated overall inflammatory score among African-Americans (supplementary table 2). Associations were smaller than for white participants for individual-level measures, but larger for neighbourhood-level SES ( $p$  for trend  $<0.05$ ).

As for cumulative SES, CVD risk factor adjustment substantially attenuated (and in some instances inverted) most associations (table 7).

## DISCUSSION

Cumulative life-course and adulthood SES were markedly, inversely associated with adult inflammatory marker levels among white people. Fibrinogen and WBC were most strongly associated with life-course and adult SES; statistically significant, linear, graded increments in these markers' levels were observed with decreasing SES. CRP and vWF were also inversely associated with SES, although associations did not consistently attain statistical significance. Results among African-Americans were less clear: patterns of association were inconsistent, particularly in covariate-adjusted models. Adult SES was generally more strongly associated with inflammatory levels than life-course SES. Graded, stepwise increments in the overall inflammatory score observed with worse SES (both cumulative

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**Table 6** Adjusted geometric means and 95% CI for levels of inflammatory biomarkers by cumulative and adult life-course SES measures and p value for linear trend among white participants

Cumulative life-course SES measures	Fibrinogen (mg/dl)		WBC count ( $\times 1000$ cells per $10^6/l$ )		C-reactive protein (mg/l)	
	Model A† (n = 9043)‡	Model B (n = 8666)	Model A (n = 9041)	Model B (n = 8666)	Model A (n = 4294)	Model B (n = 4151)
	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)
Number of exposures to lowest education group (0–2)						
0	285 (283 to 287)	287 (285 to 288)	5.8 (5.8 to 5.9)	5.9 (5.8 to 5.9)	1.5 (1.4 to 1.7)	1.6 (1.4 to 1.7)
1	289 (288 to 291*)	289 (287 to 290)	6.0 (5.9 to 6.0*)	5.9 (5.9 to 6.0)	1.7 (1.6 to 1.9)	1.7 (1.5 to 1.9)
2	299 (295 to 303*)	292 (288 to 296*)	6.3 (6.2 to 6.5*)	6.0 (5.9 to 6.2*)	2.0 (1.6 to 2.6*)	1.8 (1.4 to 2.3)
p value for trend	<0.0001	0.0054	<0.0001	0.0014	0.03	0.29
Number of exposures to worker class group (0–3)						
0	284 (282 to 286)	286 (284 to 288)	5.8 (5.8 to 5.9)	5.9 (5.9 to 6.0)	1.4 (1.2 to 1.5)	1.4 (1.2 to 1.6)
1	289 (287 to 292*)	289 (286 to 291)	6.0 (5.9 to 6.1*)	6.0 (5.9 to 6.1)	1.5 (1.3 to 1.8)	1.5 (1.3 to 1.7)
2	290 (287 to 293*)	288 (285 to 291)	6.1 (6.0 to 6.1*)	6.0 (5.9 to 6.0)	1.5 (1.3 to 1.8)	1.4 (1.2 to 1.8)
3	296 (292 to 300*)	292 (288 to 296*)	6.2 (6.1 to 6.3*)	6.1 (6.0 to 6.2)	1.7 (1.3 to 2.1)	1.6 (1.2 to 2.0)
p value for trend	<0.0001	0.02	<0.0001	0.04	0.11	0.58
Number of exposures to lowest neighbourhood SES group (0–3)						
0	286 (283 to 288)	287 (285 to 289)	5.9 (5.8 to 5.9)	5.9 (5.8 to 6.0)	1.5 (1.3 to 1.7)	1.5 (1.3 to 1.7)
1	287 (285 to 289)	287 (285 to 289)	5.9 (5.8 to 6.0)	5.9 (5.9 to 6.0)	1.7 (1.6 to 1.9)	1.8 (1.6 to 2.0)
2	290 (287 to 293*)	288 (285 to 290)	6.0 (5.9 to 6.1*)	6.0 (5.9 to 6.0)	1.7 (1.5 to 2.0)	1.6 (1.4 to 1.8)
3	295 (291 to 298*)	293 (289 to 296*)	6.0 (5.9 to 6.1*)	5.9 (5.9 to 6.0)	1.9 (1.5 to 2.3)	1.8 (1.4 to 2.2)
p value for trend	<0.0001	0.11	0.0061	0.57	0.07	0.37
Adult SES measures						
Educational level						
High	283 (281 to 284)	286 (284 to 288)	5.8 (5.7 to 5.8)	5.9 (5.8 to 5.9)	1.5 (1.3 to 1.6)	1.6 (1.4 to 1.7)
Middle	290 (288 to 291*)	288 (287 to 290)	6.0 (5.9 to 6.0*)	5.9 (5.9 to 6.0)	1.8 (1.6 to 2.0*)	1.7 (1.5 to 1.9)
Low	300 (296 to 303*)	292 (290 to 295*)	6.3 (6.2 to 6.4*)	6.0 (6.0 to 6.1*)	2.0 (1.6 to 2.5*)	1.8 (1.4 to 2.2)
p value for trend	<0.0001	0.0004	<0.0001	0.0003	0.0011	0.23
Social class						
Capitalist/expert manager	283 (281 to 285)	285 (283 to 287)	5.8 (5.8 to 5.9)	5.9 (5.9 to 6.0)	1.5 (1.3 to 1.7)	1.5 (1.4 to 1.7)
Middle	289 (287 to 291*)	289 (287 to 291*)	6.0 (5.9 to 6.0*)	5.9 (5.9 to 6.0)	1.7 (1.6 to 2.0)	1.7 (1.6 to 1.9)
Worker	293 (291 to 295*)	290 (288 to 292*)	6.1 (6.0 to 6.1*)	6.0 (5.9 to 6.0)	1.6 (1.4 to 1.8)	1.5 (1.3 to 1.7)
p value for trend	<0.0001	0.0017	<0.0001	0.18	0.46	0.76
Neighbourhood SES						
High	283 (280 to 285)	286 (284 to 289)	5.8 (5.7 to 5.9)	5.9 (5.8 to 6.0)	1.4 (1.3 to 1.6)	1.6 (1.4 to 1.8)
Middle	287 (285 to 289*)	287 (285 to 289)	5.9 (5.9 to 6.0*)	5.9 (5.9 to 6.0)	1.6 (1.4 to 1.8)	1.6 (1.4 to 1.7)
Low	293 (291 to 295*)	290 (289 to 292*)	6.0 (6.0 to 6.1*)	5.9 (5.9 to 6.0)	1.9 (1.7 to 2.2*)	1.8 (1.6 to 2.0)
p value for trend	<0.0001	0.0096	<0.0001	0.27	0.0013	0.12

\*p&lt;0.05 for the SES measure parameter coefficient.

†Model A adjusts for ARIC Center, age and gender. Model B adjusts for model A covariates and HDL cholesterol, LDL cholesterol, body mass index, hypertension and hypertension medication, family history of cardiovascular disease, diabetes status, alcohol intake, smoking status and cigarette-years smoked.

‡n is number of participants available for analysis of a particular inflammatory response. Specific cell numbers vary by SES measure used.

life-course and adult measures) underline the consistency of the analytical results, particularly among white people.

Weaker, less consistent associations among African-Americans may be due to smaller sample size and power. Also, race/ethnicity-specific SES distributions differed significantly; the range of SES levels among African-American participants was (1) composed of lower SES scores and (2) narrower than the range among white participants. Potentially relevant aspects of SES (for example, healthcare access, experience with racism) were not available. Associations may be patterned differently by race/ethnicity, influenced by differential health selection by race/ethnicity or may point to limitations present in the evaluation of SES among African-Americans in ARIC.<sup>6 46 59</sup>

Studies have consistently reported associations between the number of adverse life-course SES exposures and levels of CVD risk factors and events.<sup>9</sup> Our results support these findings and

further suggest that earlier-life exposures to adverse conditions are linked to elevated adult inflammation.

A number of mechanisms may plausibly underlie this link. The fetal origins hypothesis suggests that malnutrition and other physiological insults during critical developmental periods may lead to adult metabolic dysfunction associated with pro-inflammatory states.<sup>60</sup> Childhood exposure to adverse SES conditions during sensitive developmental periods may have similar effects. Low SES has been associated with adult health behaviours linked to inflammation,<sup>2 7</sup> and life-course SES may be a strong determinant of adult health behaviours given the early development of behaviour patterns. Stress, depression and/or hostility linked to low SES may lead to chronic activation of the hypothalamic-pituitary-adrenocortical axis, increased release of corticosteroids, abnormal platelet function and other conditions.<sup>5</sup> Finally, low SES conditions/environments plausibly increase exposure to potentially pro-inflammatory or

**Table 7** Adjusted geometric means and 95% CI of inflammatory markers by levels of cumulative life-course and adult SES measures and p values for linear trend for African-American participants

	Fibrinogen (mg/dl)		WBC count ( $\times 1000$ cells per $10^6/l$ )		C-Reactive protein (mg/l)	
	Model A† (n = 2619)‡	Model B (n = 2200)	Model A (n = 2639)	Model B (n = 2204)	Model A (n = 728)	Model B (n = 592)
Cumulative life-course SES measures	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)
Number of exposures to lowest education group (0–2)						
0	306 (300 to 311)	308 (302 to 314)	5.3 (5.2 to 5.5)	5.3 (5.1 to 5.5)	2.1 (1.5 to 3.1)	2.4 (1.7 to 3.5)
1	306 (303 to 310)	308 (304 to 311)	5.2 (5.1 to 5.3)	5.2 (5.1 to 5.3)	2.0 (1.6 to 2.6)	2.0 (1.6 to 2.5)
2	311 (306 to 316)	308 (303 to 314)	5.3 (5.1 to 5.4)	5.2 (5.1 to 5.3)	2.3 (1.6 to 3.4)	2.0 (1.4 to 3.1)
p for trend	0.14	0.94	0.63	0.29	0.76	0.52
Number of exposures to worker class group (0–3)						
0	300 (295 to 306)	305 (299 to 311)	5.2 (5.1 to 5.4)	5.3 (5.2 to 5.5)	1.9 (1.3 to 2.6)	1.8 (1.2 to 2.6)
1	303 (298 to 308)	305 (300 to 310)	5.2 (5.1 to 5.3)	5.2 (5.1 to 5.4)	1.8 (1.3 to 2.5)	1.8 (1.2 to 2.5)
2	306 (300 to 312)	303 (298 to 309)	5.2 (5.1 to 5.4)	5.2 (5.0 to 5.3)	2.2 (1.5 to 3.3)	2.3 (1.5 to 3.5)
3	314 (309 to 319*)	311 (306 to 317)	5.3 (5.2 to 5.5)	5.2 (5.1 to 5.4)	2.6 (1.8 to 3.9)	2.9 (1.9 to 4.6)
p for trend	0.0002	0.068	0.23	0.60	0.12	0.027
Number of exposures to lowest neighbourhood SES group (0–3)						
0	305 (300 to 310)	307 (302 to 312)	5.3 (5.1 to 5.4)	5.3 (5.2 to 5.4)	1.8 (1.3 to 2.6)	2.3 (1.6 to 3.4)
1	305 (301 to 310)	306 (302 to 311)	5.2 (5.1 to 5.3)	5.2 (5.1 to 5.3)	2.4 (1.7 to 3.3)	2.1 (1.5 to 2.8)
2	311 (306 to 317)	308 (302 to 314)	5.3 (5.1 to 5.4)	5.2 (5.0 to 5.3)	2.1 (1.4 to 3.3)	2.0 (1.3 to 3.0)
3	312 (305 to 320)	313 (305 to 321)	5.3 (5.1 to 5.5)	5.3 (5.1 to 5.5)	2.1 (1.3 to 3.5)	2.0 (1.1 to 3.3)
p for trend	0.029	0.39	0.79	0.66	0.65	0.57
Adult SES measures						
Educational level						
High	301 (297 to 305)	306 (301 to 310)	5.2 (5.1 to 5.3)	5.3 (5.2 to 5.4)	1.9 (1.5 to 2.5)	2.0 (1.9 to 2.0)
Middle	309 (304 to 313*)	309 (304 to 313)	5.2 (5.1 to 5.3)	5.2 (5.1 to 5.3)	2.3 (1.7 to 3.1)	2.4 (2.3 to 2.5)
Low	312 (308 to 316*)	309 (306 to 314)	5.3 (5.2 to 5.4)	5.2 (5.1 to 5.3)	2.3 (1.7 to 3.1)	2.0 (1.9 to 2.1)
p value for trend	0.0003	0.26	0.43	0.22	0.42	0.68
Social class						
Capitalist/expert manager	304 (299 to 309)	305 (300 to 311)	5.2 (5.1 to 5.3)	5.2 (5.1 to 5.3)	2.4 (1.7 to 3.4)	2.4 (2.3 to 2.6)
Middle	303 (299 to 307)	306 (302 to 310)	5.2 (5.1 to 5.3)	5.3 (5.2 to 5.4)	1.7 (1.3 to 2.2)	1.6 (1.5 to 1.6)
Worker	312 (308 to 316*)	310 (306 to 314)	5.3 (5.2 to 5.4)	5.2 (5.1 to 5.3)	2.5 (1.9 to 3.3)	2.6 (2.5 to 2.7)
p value for trend	0.0046	0.15	0.18	0.85	0.63	0.40
Neighbourhood SES						
High	305 (300 to 309)	308 (303 to 313)	5.2 (5.1 to 5.3)	5.3 (5.1 to 5.4)	1.7 (1.3 to 2.4)	1.6 (1.1 to 2.2)
Middle	305 (301 to 309)	307 (302 to 311)	5.2 (5.1 to 5.3)	5.2 (5.1 to 5.3)	2.2 (1.6 to 2.9)	2.4 (1.8 to 3.3)
Low	311 (308 to 315*)	309 (305 to 313)	5.3 (5.2 to 5.4)	5.2 (5.1 to 5.3)	2.4 (1.9 to 3.1)	2.3 (1.7 to 3.0)
p value for trend	0.021	0.91	0.28	0.76	0.13	0.089

\* $p < 0.05$  for the SES measure parameter coefficient.

†Model A adjusts for ARIC Center, age and gender. Model B adjusts for model A covariates and HDL cholesterol, LDL cholesterol, body mass index, hypertension and hypertension medication, family history of cardiovascular disease, diabetes status, alcohol intake, smoking status and cigarette-years smoked.

‡n is number of participants available for analysis of a particular inflammatory response. Specific cell numbers vary by SES measure used.

infectious agents such as microbial pathogens, ambient air pollutants and adverse work conditions.<sup>61</sup>

Childhood contextual SES was evaluated at the county level while adult contextual SES was evaluated at the census tract level; the impact of early-life contextual SES is therefore probably underestimated. Additionally, the cumulative life-course model utilised assumes that adverse SES exposures have the same impact regardless of length or timing of exposure and does not address the potentially differential impact of upward or downward social mobility.<sup>9</sup> Selective survival of healthier participants, a 60% baseline participation rate and the availability of CRP only among healthier participants limited the socioeconomic and health diversity of participants and may have biased results towards the null. Errors in remembering early-life SES may also have biased results towards the null.<sup>62</sup>

Strengths of this study include use of SES measures from three life epochs, a separate analysis of adult SES, examination

of both individual-level and contextual-level SES and the availability of multiple inflammatory markers. Additionally, the use of MI represents a systematic effort to minimise biases due to missing data.

While the stronger association between adult SES and inflammation is unsurprising, inflammatory levels were closely tied to life-course SES. The graded relations between the number of life-course exposures to low SES and inflammatory levels suggest that the impact of these exposures is cumulative. These findings point to a sustained increase in inflammation as a response to adverse life-course SES, matching the development of chronic vascular disease in young adulthood and progressing throughout life.<sup>35</sup> Our results suggest a framework linking adverse life-course SES exposures to end-organ pathology in Western industrialised countries. These findings have implications for our understanding of the long-term development and progression of chronic vascular disease and speak to a need for

## Research report

## What is already known on this subject

- ▶ Low individual-level and neighbourhood-level SES in childhood and adulthood are associated with poor health behaviours and elevated risk of CVD.
- ▶ More recently, the accumulation of adverse SES conditions throughout life has been found to be strongly associated with CVD.
- ▶ While the pathways underlying these associations remain unclear, recent evidence suggests that one such pathway may be a chronic, systemic inflammatory burden.

## What this study adds

- ▶ These results suggest that the accumulation of adverse socioeconomic conditions (at both the individual and neighbourhood level) throughout life is associated with elevated systemic inflammation in adulthood.
- ▶ Thus, upregulated inflammatory pathways may be one link between adverse life-course SES exposures and end-organ pathology.
- ▶ Future research more thoroughly examining the cumulative health impacts of unfavourable socioeconomic conditions may further our understanding of the long-term development and progression of chronic vascular disease.

## Policy implications

Policies geared towards reducing cardiovascular health inequalities should consider the negative health effects of the accumulation of adverse socioeconomic conditions across the life course.

further examination of the earlier-life development of CVD risk factors and poor health behaviours.

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