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Lower Socioeconomic Status Associates with Greater Systemic and Arterial Inflammation in HIV

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Abstract

Objectives: In the general population, lower socioeconomic status (SES) associates with greater systemic and arterial inflammation and a greater risk of cardiovascular disease. Because arterial inflammation is heightened in individuals living with HIV, we tested the hypothesis that SES associates with arterial inflammation in this population.

Settings: Prospective cohort study.

Methods: Men living with HIV were recruited. Arterial inflammation and leukopoietic activity (i.e., bone marrow activity) were measured using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. Zip code-level SES measures were derived from the U.S. Census Bureau. Linear regression and mediation analyses were utilized to assess associations between SES, arterial inflammation, leukopoietic activity, C-reactive protein (CRP) and interleukin-6.

Results: Thirty-nine virologically-suppressed men living with HIV were studied (mean±SD age 50.5±11.1 years). Median CD4 count was 663 cells/mm^3 (IQR: 399–922); 82% were receiving antiretroviral therapies. Local median income inversely associated with arterial inflammation (standardized β [95% CI]: −0.42 [−0.76, −0.08]) after adjusting for age, Framingham risk score, statin use, antiretroviral use, and nadir CD4 count. High school graduation rate independently associated with arterial inflammation (−0.45 [−0.78, −0.12]) and CRP (−0.49 [−0.86, −0.012]). Mediation analysis demonstrated the impact of SES on arterial inflammation was partially mediated by heightened circulating inflammatory levels: ↓SES (as high school graduation rate) →↑CRP →↑arterial inflammation accounting for 44% of the total effect (P<0.05).

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Authors' contributions: L.Z. and A.T. conceived the article, collated the data, analyzed the data, drafted and reviewed the article. S.A performed the imaging analysis and reviewed the article. N.N., A.N., S.R., and T.P. worked on clinical visits of participants, collected clinical data and reviewed the article. M.O., S.D., and P.H. provided clinical data and reviewed the article.

Parts of the data was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) on 3/6/2019 at Seattle.

Conclusion: In individuals living with HIV, lower SES independently associated with higher leukopoietic activity, circulating markers of inflammation, and arterial inflammation. Further, the link between SES and arterial inflammation was mediated by increased systemic inflammation.

Keywords

Arterial inflammation; atherosclerosis; C-reactive protein; HIV; inflammation; socioeconomic status

Introduction

In the era of highly effective antiretroviral therapies (ART), cardiovascular disease (CVD) remains the leading cause of death among people living with human immunodeficiency virus (PLWH).[1–4] Notably, among PLWH, lower socioeconomic status (SES) has been shown to associate with higher mortality and worse clinical outcomes,[5–8] especially CVD.[9–11] Greater insight into mechanisms driving this relationship is needed.

Chronic inflammation and immune activation play key roles in HIV-associated CVD.[12,13] Notably, atherosclerotic inflammation, which can be reproducibly measured using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT), is heightened in PLWH in proportion to circulating inflammatory biomarkers.[12,14] Such amplification of atherosclerotic inflammation may represent a key link to the elevated risk of CVD in PLWH, since inflammation is a critical driver of atherosclerotic CVD events.[13,15,16] Recent data, from uninfected individuals, demonstrates that lower SES may potentiate CVD via a biological pathway that involves greater leukopoietic activity (a precursor of systemic inflammation and predictor of CVD events) as well as heightened atherosclerotic inflammation.[17] Accordingly, we tested the hypotheses that lower SES independently associates with higher greater systemic inflammation, leukpopoietic activity, as well as atherosclerotic inflammation in PLWH. Additionally, we tested whether the link between lower SES and arterial inflammation is significantly mediated by increased systemic inflammation.

Methods

Study cohort

Men living with HIV were recruited from the SCOPE (Observational Study of the Consequences of the Protease Inhibitor Era) cohort, a cohort of individuals receiving care at San Francisco General Hospital and San Francisco Veteran's Affairs Medical Center.[14] HIV infection status was confirmed using HIV antibody testing prior to recruitment. Study participants included in the current analysis had undetectable viral loads using conventional assays (typically < 40 copies/ml) regardless of their ART treatment status and had ^{18}F-FDG/PET-CT imaging. The study was approved by the institutional review board of University of California, San Francisco, and all participants provided written informed consent.

Estimation of Socioeconomic Status

The U.S. Census Bureau's 2015 American Community Survey 5-Year Estimates were used to derive zip code-level SES measures.[18] Participants' residential addresses were utilized to derive residence-specific metrics, including local income and high school graduation rate. Although zip code-level SES measures may be a less precise proxy for individual-level SES, neighborhood-level SES measures can reflect the impact on individual health outcome by the community of residence and has been previously validated.[19,20]

^{18}F-FDG PET/CT Imaging Protocol

^{18}F-FDG-PET/CT imaging was performed with a Biograph 64 (or similar) scanner (Siemens Healthcare 64, Siemens, Forshiem, Germany). Following an overnight fast, subjects received ~370 MBq of intravenous ^{18}F-FDG. Individuals sat quietly after radiotracer administration before imaging was performed after approximately two hours. A non-gated, non-contrast-enhanced CT (140 kVp, ~35 mAs) was acquired for attenuation correction. The reconstruction of attenuation-corrected images was performed using OSEM algorithm.

Atherosclerotic inflammation and bone marrow metabolic activity were measured according to previously validated methods.[13,21] ^{18}F-FDG uptake within the arterial wall provides a validated index of atherosclerotic inflammation (Figure 1A), as the standardized uptake value (SUV) in the wall of the ascending aorta adjusted for background venous blood activity (as a target-to-background ratio (TBR)).[22] Similarly, bone marrow leukopoietic activity (Figure 1B) was assessed by deriving the SUV from regions of interest placed within vertebrae (T1 to L5).[21] Image analyses was conducted by an investigator blinded to clinical and SES data.

Laboratory Measurements

Blood was drawn in the fasting state from the time point closest to imaging for measurement of circulating inflammatory markers (i.e., IL-6 and CRP). These were assessed in cryopreserved plasma samples using a multiplex electrochemiluminescence assay (MesoScale Discovery, Rockville, Maryland, and Dade Behring, Deerfield, Illinois).

Statistical analysis

Continuous variables are presented as mean (standard deviation (SD)) or as median (interquartile range (IQR)) when not normally distributed. Multivariable linear regression was utilized to assess the association between SES indices and inflammatory markers (i.e., arterial inflammation, bone marrow leukopoietic activity, CRP and IL-6) with adjustment of age, Framingham risk score, statin use, anti-retroviral therapy (ART), and nadir CD4 count. Statistical analyses were performed using SPSS Version 25 (IBM Corp, Armonk, New York) and Stata 15 (StataCorp, College Station, Texas). Mediation analysis was performed with the SPSS PROCESS macro (v2.16.3), which implements an ordinary least squares-based path framework to estimate direct and indirect effects from bias-corrected bootstrap samples.[23] We examined the pre-specified hypothesized mediator path (using PROCESS Model 6): ↓SES (as high school graduation rate)→↑systemic inflammation (as CRP)→↑arterial inflammation. Statistical significance was determined as $P<0.05$ for all analyses.

Results

Baseline characteristics

Thirty-nine virologically-suppressed men living with HIV in the SCOPE cohort were included in the analysis. The mean ± SD age was 50.6 ±11.0 years and 71.8% were Caucasian. The median Framingham risk score was 6 (IQR: 3–8) and 12.8% were on statin therapy. The median nadir CD4 count was 227 cells/mm^3 (IQR: 100–400 cells/mm^3); 82.1% were receiving ART. Median income was $71,043 (IQR: $46,140–97,563) and median high school graduation rate was 86.1% (IQR: 83.9–93.3%). The demographics and CVD risk factors were similar between participants with high versus low income and high versus low high school graduation rate (Supplemental Table 1).

SES Indices versus Circulating Biomarkers of Inflammation

High school graduation rate inversely associated with CRP and IL-6. Each SD increase in graduation rate associated with a nearly 50% SD decrease in CRP (standardized β [95% confidence interval (CI)]: −0.49 [−0.86, −0.12], P=0.012) after adjusting for age, Framingham risk score, statin use, CD4 nadir and ART (Table 1). Income also inversely associated with IL-6 in a fully adjusted model (Table 1).

SES Indices versus Arterial Inflammation and Bone Marrow Activity

Median income inversely associated with arterial inflammation (standardized β [95% CI]: −0.42 [−0.76, −0.08], P=0.018, Table 1) after multivariable adjustment. Similarly, high school graduation rate inversely associated with arterial inflammation (−0.45 [−0.78, −0.12], P=0.010, Table 1). Additionally, graduation rate associated with bone marrow leukopoietic activity (−0.42 [−0.77, −0.07], P=0.019, Table 1). Sensitivity analyses among 32 treated-controlled individuals yielded similar results (Supplemental Table 2).

Mediation Analysis

Mediation analysis was performed to examine the pre-specified pathway of: ↓SES→↑systemic inflammation→↑arterial inflammation. SES was estimated using local high school graduation rate, and systemic inflammation was estimated as CRP. We observed that this stepwise path was significantly associated with arterial inflammation (standardized β [95% CI]: −0.23 [−0.42, −0.04], P<0.05, Supplemental Figure 1), accounting for 55% of the total effect (c=−0.41, P=0.028) after adjusting for Framingham risk score.

Discussion

In HIV-infected men, we observed that lower SES independently associates with higher levels of systemic inflammatory markers, heightened bone marrow leukopoietic activity, and greater arterial inflammation. Furthermore, mediation analysis suggested that lower SES links to arterial inflammation through heightened systemic inflammation. Accordingly, the current study highlights a key role of SES-associated systemic inflammation in the pathogenesis of atherosclerotic disease and illuminates a biological pathway linking SES to CVD among PLWH.

SES is a critical factor affecting HIV-related outcomes including CVD.[9–11] This relationship may in-part be attributed to lower healthcare access (resulting in greater viremia) and excessive exposure to CVD risk factors. However, additional mechanisms are suspected. In the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS), PLWH with lower incomes were more than twice as likely to have heightened CVD risk, independent of demographics, CVD risk factors, and ART, suggesting the existence of alternative biological mechanisms beyond risk factors and HIV control. However, this finding has been inconsistently observed,[24] prompting the need for further study of the association between SES and CVD among PLWH.

The current study leverages both circulating measures as well as multi-tissue imaging to bridge this knowledge gap. We found that lower SES associates with higher bone marrow leukopoietic activity, CRP and IL-6, and arterial inflammation after adjusting for CVD and virological factors. These observations are consistent with studies in uninfected individuals, showing that lower SES links to increased systemic and arterial inflammation, which in turn boost the risk of CVD.[25–27] These results were further strengthened by the mediation analysis linking ↓SES→↑CRP→↑arterial inflammation, suggesting a serial inflammatory cascade. Hence, the current findings support an immune-arterial mechanism underlying the inverse relationship between SES and risk of CVD beyond healthcare disparities in HIV.

The mechanism by which lower SES prompts higher systemic inflammation in HIV deserves further study. One potential pathway involves stress-associated neurobiological mechanisms. In uninfected humans, lower SES associates with greater psychosocial stress and neurobiological activity,[28,29] resulting in a biological cascade that involves heightened bone marrow activity and arterial inflammation and culminates in CVD events.[30–32] Moreover, a recent study suggested that lower SES links to CVD through this same multi-organ, stress-associated mechanism.[17] Specifically, that study demonstrated that lower SES associated with heightened activity of the amygdala, a neural tissue that is critically involved in stress perception, and whose metabolic activity associates with increased bone marrow leukopoietic activity, arterial inflammation, and incident CVD risk.[17]

In light of these findings, a similar mechanism may be complicit in HIV. In PLWH, higher psychosocial stress associates with higher levels of inflammatory cytokines,[33,34] more HIV-related morbidity and mortality,[35–37] and greater CVD risk.[38] Further, higher indices of psychosocial stress associated with increased atherosclerosis and a greater risk of incident vascular events in PLWH.[38] Accordingly, we speculate that psychological stress may represent an important contributor to the link between SES, systemic inflammation, and CVD in PLWH.

The current study has potential clinical implications. The findings suggest that PLWH who live in neighborhoods with relatively lower SES are prone to develop higher levels of systemic and arterial inflammation. Accordingly, therapies targeting inflammation may exert disproportional benefits in this subgroup. Although SES is notoriously difficult to improve, it is conceivable that some of the biological consequences of lower SES may be ameliorated through effective anti-inflammatory strategies. To that end, inflammation has been a therapeutic target for the treatment of CVD for decades. Statins have been consistently

shown to reduce CVD events and mortality, in part via their anti-inflammatory effects,[39,40] and improve high-risk plaque morphology among PLWH.[41] Additionally, Canakinumab, a potent interleukin-1β antagonist, has been shown to reduce CVD events in uninfected individuals,[42] and was found to ameliorate atherosclerotic inflammation and leukopoietic activity in a pilot study of PLWH.[43]

The results of the present study should be interpreted with some limitations in mind. First, our study included a small sample of male participants from one geographic area with relatively high average income and graduation rates, which may limit the generalizability of our findings and may be confounded by sex-specific differences in markers of systemic inflammation among PLWH. Future studies should extend these analyses to regions with wider ranges of SES indices and should include women living with HIV. Second, we used zip code-level SES measures instead of individual-level SES. However, prior work has shown that community-level SES indices correlate well with individual-level SES and associate well with cardiovascular health.[44,45] Third, the current cross-sectional study cannot establish a causal relationship between SES and cardiovascular inflammation. Future prospective studies, especially ones containing anti-inflammatory interventions targeting the hypothesized pathway in PLWH, will be needed to confirm the relationship. Lastly, we were unable to measure stress-associated neurobiological activity or CVD events in our cohort. Future studies with neurological assessment and longitudinal follow-up are needed.

Conclusions

Among PLWH, community-level SES factors significantly associated with circulating and imaging cardiovascular inflammatory markers, independently of traditional risk factors, statin therapy, and level of HIV disease control. The link between lower SES and arterial inflammation was mediated by increased systemic inflammation. Strategies to improve recognition of SES's impact on CVD among PLWH and targeted interventions may be helpful in reducing HIV-associated arterial inflammation and improving cardiovascular outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest and Source of Funding:

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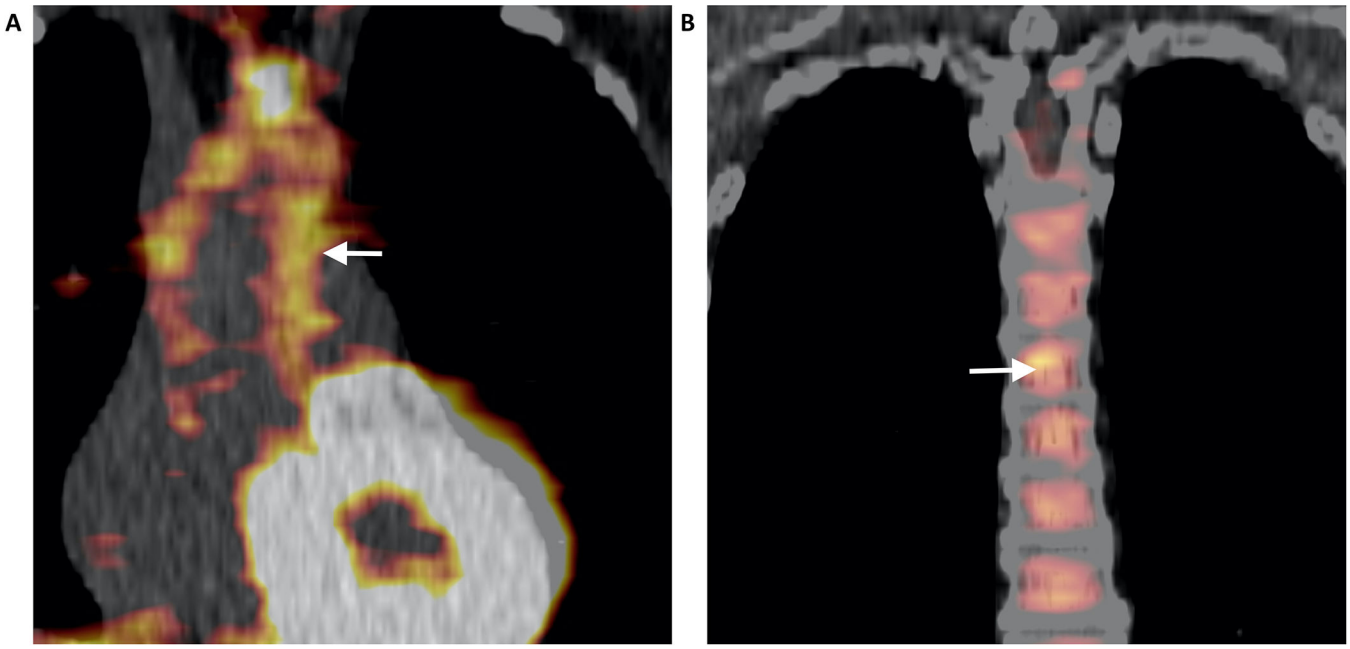

Figure 1.

Arterial Inflammation (A) and Bone Marrow Leukopoietic Activity (B) Measured with ^{18}F-FDG-PET/CT.

Arrows: ^{18}F-FDG uptake within the arterial wall (A) and vertebrae from T1 to L5 (B) indicating arterial inflammation and bone marrow activity, respectively.

Table 1.

Association Between Socioeconomic Status and Inflammatory Measures.

Outcomes		Covariable models	Median income		High school graduation rate	
			Standardized β (95% CI)	P*	Standardized β (95% CI)	P*
Circulating inflammatory markers	CRP	A	−0.30 (−0.67, 0.06)	0.102	−0.45 (−0.79, −0.11)	0.012
		B	−0.35 (−0.75, 0.04)	0.079	−0.49 (−0.86, −0.12)	0.012
	IL-6	A	−0.32 (−0.67, 0.03)	0.069	−0.31 (−0.66, 0.03)	0.074
		B	−0.39 (−0.72, −0.05)	0.026	−0.38 (−0.71, −0.04)	0.029
Imaging	Arterial Inflammation (Aortic TBR)	A	−0.37 (−0.69, −0.05)	0.025	−0.46 (−0.76, −0.15)	0.005
		B	−0.42 (−0.76, −0.08)	0.018	−0.45 (−0.78, −0.12)	0.010
	Leukopoietic Activity (Vertebral TBR)	A	−0.18 (−0.55, 0.18)	0.315	−0.39 (−0.73, −0.05)	0.027
		B	−0.27 (−0.65, 0.11)	0.151	−0.42 (−0.77, −0.07)	0.019

Model A: adjusting for age and Framingham risk score.

Model B: adjusting for age, Framingham risk score, statin use, CD4 nadir and antiretroviral therapy.

*Multivariable linear regression adjusting for model A or model B.

CRP= c-reactive protein; IL = interleukin; TBR = target-to-background ratio.