ARIC Manuscript Proposal # 903r

PC Reviewed: _07/27/04	**Status: __A__**	**Priority: _2___**
SC Reviewed: __07/27/04__	**Status: _A__**	**Priority: _2____**

1.a. Full Title:

Lifecourse SES and systemic markers of inflammation

b. Abbreviated Title (Length 26 characters):

LCSES - Inflammation

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:
Data analyses are scheduled to begin immediately following approval of updated proposal.

4. Rationale:

Various studies have found an association between lifetime SES and risk of CVD [1-9]. Hart et al. (1998) found that poor socioeconomic circumstances experienced at different stages of the lifecourse significantly increased risk of CVD in adulthood. Heslop et al. (2001) found significant associations between several lifetime SES indicators and various physiological risk factors for CVD in women. Lynch et al. (1997) reported that SES at various points in the lifecourse was associated with adult health behaviors including smoking, physical activity, and obesity, each of which are risk factors for CVD. SES throughout the life course may be associated with increased risk of CVD partly through an increase in sustained inflammatory burden. Low socioeconomic status has been associated with poor health behaviors (which may lead to obesity, insulin resistance and the multiple metabolic syndrome, type 2 diabetes, dyslipidemia, blood pressure elevation, and other metabolic impairments) associated with increased systemic inflammation [9-11]. Exposure to poor socioeconomic environments throughout the life course may lead to poor health behaviors and/or poor dental care, resulting in periodontitis. Mediated through an increase in monocyte cytokines, endotoxins from these bacteria can induce vascular smooth muscle proliferation, inflammatory cell infiltration into blood vessels and intravascular coagulation [12, 13]. These processes may lead to and/or

augment the inflammatory process of atherosclerosis [14]. In addition to the association between low SES and health behaviors which may result in accelerated development of inflammation, studies indicate that the stress of (and depression/hopelessness/hostility caused by) low SES and negative environmental factors leads to chronic activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system, increased release of corticosteroids, abnormal platelet function, and other conditions which may potentially result in increased levels of inflammation [15-17]. Work done by Barker and others also suggests that malnutrition and other physiological insults (which may be associated with low parental SES) may negatively influence the organism during a critical developmental period, resulting in elevated risk of physiologic dysfunction in adulthood, of the type found to be associated with increased levels of markers of inflammation [18-20]. To our knowledge, however, no studies have examined the influence of SES factors throughout the lifecourse on markers of inflammation in adulthood.

We thus propose to investigate, as part of an ARIC ancillary study, the association of SES, neighborhood SES, and deprivation/hardship indicators throughout the lifecourse with the profile of inflammatory marker levels in adulthood.

The significance of the proposed work rests on the central role of inflammation in cardiovascular disease – particularly at all stages of atherosclerosis –as supported from basic science [21, 22] and from epidemiology. From epidemiology, numerous prospective epidemiologic studies have reported associations between cytokines, acute-phase proteins, or other systemic markers of inflammation and cardiovascular events, including ischemic coronary heart disease, stroke, and peripheral arterial disease, in middle aged men and women [4, 8, 23-37]. Additionally, emerging evidence links the systemic inflammatory response to the prevalence of the component elements of the metabolic syndrome and of their clustered occurrence [38-41].

ARIC data from the baseline examination includes measures of the inflammatory markers fibrinogen, white blood cell (WBC) count, Factor VII, and von Willebrand factor (vWF), allowing the examination of the hypothesized association between life course SES experience and level of inflammation. The availability of serum CRP measurements in a random sample of the ARIC participants who participated in the Dental ARIC study permits the inclusion of CRP levels as a further inflammatory marker. Newly available serum immunoglobulin G (IgG) levels of antibodies to 17 different periodontal organisms in members of the Dental ARIC study cohort, provided by Dr. James Beck, will provide a measure of systemic exposure to these organisms.

5. Main Hypothesis/Study Questions:

A. Low individual-level SES, number of deprivation/hardship indicators, and exposure to low SES neighborhood/community environments are associated with higher adult levels of markers of inflammation (cross-sectional analysis).

B. Short-term changes in individual-level SES, as indicated by changes in occupation and income across the repeated ARIC visit measures, are associated with increases in adult levels of markers of inflammation.

C. Low SES in childhood, adolescence, and adulthood, number of deprivation/hardship indicators, amount of time spent living in a low-SES community/neighborhood, and number of times measured below 150% of the poverty line are all associated with higher adult levels of markers of inflammation.

6. Data (variables, time window, source, inclusions/exclusions):

Measures of individual-level SES, neighborhood SES, and life course SES measures will be obtained from the Life Course SES ancillary study and ARIC study visits. ARIC data to be included in this proposal include history of infectious and inflammatory diseases, WBCs, vWF, fibrinogen, Factor VII activity, use of medication, and the "established" risk factors associated with atherosclerosis and CHD events, as available from each cohort examination visit. CRP levels will be requested from the Dental ARIC study.

Serum levels of immunoglobulin G (IgG) antibodies specific to 17 different periodontal organisms have become available for a subset (n = 4585) of the ARIC participants examined during the Dental ARIC substudy at Visit 4 (1996-1998).

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X____ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

ARIC proposal # 926: Carson AP. Individual and area-level lifecourse socioeconomic status and subclinical Atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) study.

ARIC proposal # 960: Shoham DA. Individual and area-level life-course SES and decline in renal function: the Atherosclerosis Risk in Communities Study.

11. Manuscript preparation is expected to be completed in one to three years. If a

manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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