Health & Place 16 (2010) 1104–1112

Contents lists available at ScienceDirect

Health & Place

journal homepage: www.elsevier.com/locate/healthplace

Cross-sectional and longitudinal associations of neighborhood characteristics with inflammatory markers: Findings from the multi-ethnic study of atherosclerosis ☆, ☆☆

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ARTICLE INFO

Article history:
Received 23 December 2009
Received in revised form
7 July 2010
Accepted 12 July 2010

Keywords:
Inflammation
Fibrinogen
Interleukin-6
C-reactive protein
Neighborhood

ABSTRACT

We investigated cross-sectional associations of neighborhood deprivation, problems, safety, and cohesion with circulating levels of fibrinogen, interleukin-6, and C-reactive protein ($n=5370$) and longitudinal associations with changes in IL-6 over a 3–4 year period ($n=946$). In cross-sectional analyses, higher levels of neighborhood deprivation and problems were associated with higher levels of all three inflammatory markers, whereas higher levels of safety were associated with lower levels. Fibrinogen remained associated with all neighborhood characteristics except cohesion and IL-6 remained associated with safety after adjustment for race and SES. In longitudinal analyses, higher levels of neighborhood deprivation and problems, and lower levels of safety were associated with greater longitudinal increases in IL-6 after adjustment for age, sex, race, and SES. These findings were not substantially modified by further risk factor adjustment. Although findings regarding different inflammatory markers were mixed, the longitudinal results that are less limited by race confounding suggest that inflammatory pathways may contribute to neighborhood differences in cardiovascular disease risk.

1. Introduction

A number of studies have documented associations of neighborhood characteristics with cardiovascular outcomes that persist after accounting for individual-level measures of socioeconomic position (Cubbin and Winkleby, 2005; Leclere et al., 1998; Sundquist et al., 2004; Diez Roux et al., 2001, 1995; Franzini and Spears, 2003; Chaix et al., 2007; Winkleby et al., 2007). However, considerable debate exists on whether these associations are causal and the mechanisms mediating these associations have not been fully identified. In some cases, associations of neighborhood characteristics with cardiovascular outcomes appear to persist after additional control for established cardiovascular risk factors, suggesting that other mediators may be involved (Diez Roux et al., 2001).

Systemic inflammation, as indexed by various circulating markers, has emerged as a possible cardiovascular risk factor (Willerson and Ridker, 2004). The inflammatory markers fibrinogen, interleukin-6 (IL-6), and C-reactive protein (CRP) are known to be inversely associated with individual-level socioeconomic factors (Jousilahti et al., 2003; Wilson et al., 1993; Nazmi and Victora, 2007; Ranjit et al., 2007a; Ramsay et al., 2008) but there are plausible mechanisms through which neighborhood context may affect levels of inflammatory markers independently of individual-level socioeconomic indicators. These include possible effects of neighborhood context on behavioral factors (such as diet, physical activity, or smoking) (Diez Roux and Mair, 2010) linked to inflammation, neighborhood differences in the risk of acquiring infectious diseases linked to inflammatory processes (Acevedo-Garcia, 2000), neighborhood differences in air pollution levels (O'neill et al., 2003) as well as effects of neighborhood environments on stress-related physiological processes hypothesized to play a role in the inflammatory process (Mcdade et al., 2006; Ranjit et al., 2007b).

Very few studies have investigated associations of neighborhood characteristics with inflammatory markers (Pollitt et al., 2007; Petersen et al., 2008) and no studies of which we are aware

☆This manuscript was presented as an abstract at the 42nd Annual Society for Epidemiologic Research Meeting in Anaheim, CA in June 2009.

☆☆Funded by NIH.

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doi:10.1016/j.healthplace.2010.07.001

have moved beyond neighborhood socioeconomic characteristics to investigate more specific neighborhood attributes, or have examined associations of neighborhood characteristics with changes in inflammatory markers over time. Finding that neighborhood-level factors are associated with biological precursors of cardiovascular risk would strengthen evidence for causal effects of neighborhoods on the development of cardiovascular disease.

Using data from an ancillary study to the multi-ethnic study of atherosclerosis (MESA), we investigated cross-sectional associations of several neighborhood characteristics (deprivation, safety, cohesion, and problems) with circulating levels of inflammatory markers and longitudinal changes in inflammatory markers in a large population-based multi-ethnic sample with detailed measures of neighborhood characteristics, inflammatory markers, and potential confounders.

2. Methods

The multi-ethnic study of atherosclerosis (MESA) is a population-based longitudinal study of the prevalence, correlates, and progression of subclinical cardiovascular disease (CVD). The cohort comprised 6814 individuals aged 45–84 years with 38% white, 28% black, 22% Hispanic, and 12% Chinese. Participants were recruited from six US communities using a variety of population-based approaches and were free of clinical CVD at the time of the baseline visit. Detailed information on the study objectives and design has been published elsewhere (Bild et al., 2002). Cross-sectional analyses reported here employed data collected as part of the baseline examination conducted between 2000 and 2002. Longitudinal analyses used follow-up data available 3–4 years after baseline (2004–2006) collected on a subsample of white, black, and Hispanic participants from the New York and Los Angeles sites. The follow-up sample was composed of participants in an ancillary study to MESA, which collected follow-up information on approximately 1000 white, black, and Hispanic participants at two of the MESA sites (Ranjit et al., 2009). Participants were invited to enroll in the ancillary study in the order in which they attended the visit resulting in an approximately random sample (Ranjit et al., 2009).

Three inflammatory markers (fibrinogen, IL-6, and CRP) linked to cardiovascular events in prior work (Pahor et al., 1999; Tracy, 1999) were investigated in cross-sectional analyses. Fibrinogen (mg/dL) and CRP (mg/L) were measured using the BNII nephelometer (N high sensitivity CRP and N antiserum to human fibrinogen, Dade Behring, Deerfield, IL). IL-6 (pg/mL) was measured by ultrasensitive ELISA (R&D Systems, Minneapolis, MN). Analytic coefficients of variation were 2.6%, 6.3%, and 3.6% for fibrinogen, IL-6, and CRP, respectively. CRP and IL-6 were log-transformed prior to analyses due to skewed distributions. Follow-up measures of IL-6 were available on a subsample of 946 white, black, and Hispanic participants from the New York and Los Angeles MESA sites (mean follow-up time 3.9 years). All assays were performed at the MESA Central Laboratory located at the University of Vermont.

Neighborhood of residence (proxied by census tract) was assigned to each MESA participant based on residential addresses at baseline. Four neighborhood domains were investigated: neighborhood deprivation, safety, cohesion, and problems. Neighborhood deprivation was used as a summary measure of the neighborhood environment. A deprivation score for each neighborhood was created based on a factor analysis of 19 census tract-level variables reflecting dimensions of race/ethnicity, family structure, housing, residential stability, crowding, education, employment, occupation, and income/wealth available in the 2000 US Census. Six variables, which accounted for 61% of the variance (percent vacant housing, percent with no telephone, percent with no vehicle, percent unemployed, median household income, and percent poverty) loaded on the first factor were used in these analyses. The deprivation factor was the weighted sum of the six standardized variables (Mujahid et al., 2007). The factor score was converted to z scores.

The three other neighborhood domains investigated – problems, safety, and cohesion – were assessed using questionnaires administered to MESA participants. These three domains were selected for investigation because they capture aspects of neighborhoods that may be related to levels of inflammatory markers through their effects on health behaviors or psychosocial processes related to inflammation. Each domain was assessed using scales linked to cardiovascular-related outcomes in prior work (Mujahid et al., 2007; Auchincloss et al., 2008; Echeverría et al., 2008). Seven questions were used to determine the neighborhood problems score. These items referred to the state of the neighborhood sidewalks, trash and litter in the neighborhood, playgrounds/parks, adequate shopping, heavy traffic/speeding, excessive noise and violence in the neighborhood. For each item participants were asked to indicate whether the issue in question was a problem using a 4 point Likert scale (“often” to “never”). The neighborhood safety score was based on three items (using a 5 point Likert scale: “strongly agree” to “strongly disagree”) regarding neighborhood violence, crime, and the ability to walk in the neighborhood without fear. Neighborhood cohesion was scored according to five items (using a 5 point scale as above) on neighbors’ willingness to help each other, neighbors getting along, neighbors trusting each other and shared/common values. Likert scales used to collect data on individual items were summed to create composite scores. Higher scores for each characteristic referred to more neighborhood problems, greater safety, and greater social cohesion. The scales had acceptable validity and reliability for the measurement of neighborhood-level domains (Mujahid et al., 2007; Echeverria et al., 2004).

Because aggregation across multiple respondents may reduce error arising from individual subjectivities and improve the validity of the measure (Mujahid et al., 2007), the neighborhood characteristics of each MESA participant was estimated by averaging the responses of all other MESA participants living within the same census tract. All neighborhood variable values were converted to z scores for analysis.

Baseline covariates included age, race/ethnicity, socioeconomic status, use of anti-inflammatory medications, recent history of acute infection, physical activity, smoking, alcohol drinking, body mass index (BMI), waist circumference, impaired fasting glucose, and diabetes. All of these variables have been linked to levels of inflammatory markers and could plausibly confound and/or mediate any neighborhood effects on inflammation. Race/ethnicity was self-reported based on questions modeled on the year 2000 census. Education was collected in nine categories (no schooling, 1–8 years, 9–11 years, high school graduate or GED certificate, some college but no degree, technical school certificate, associate’s degree, bachelor’s degree, graduate/professional degree) and income in 13 categories (ranging from $\$ < 5000$ to 100000+). Some of these categories were collapsed for descriptive analyses. Use of hormone replacement therapy, aspirin, oral anti-inflammatory agents, lipid-lowering drugs, and non-steroidal anti-inflammatory drugs during the baseline visit was grouped into a single dichotomous variable (yes to any vs. none). Having had an acute infection (bronchitis, cold/flu, fever, pneumonia, sinusitis, urinary, or tooth infection) in the 2 weeks previous to the baseline interview was coded as positive for recent infection. Physical activity was assessed using a standardized questionnaire (Ainsworth et al., 1999). Level of intentional