Brain, Behavior, and Immunity 34 (2013) 31–38

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

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

Childhood socioeconomic status, telomere length, and susceptibility to upper respiratory infection ☆

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ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form 25 June 2013
Accepted 29 June 2013
Available online 8 July 2013

Keywords:
Socioeconomic status
Childhood socioeconomic status
Telomere length
$CD8^+CD28^-$
Infection
Upper respiratory infection
Rhinovirus
Host resistance
Common cold
Viral-challenge

ABSTRACT

Low socioeconomic status (SES) during childhood and adolescence has been found to predict greater susceptibility to common cold viruses in adults. Here, we test whether low childhood SES is associated with shorter leukocyte telomere length in adulthood, and whether telomere length mediates the association between childhood SES and susceptibility to acute upper respiratory disease in adulthood.

At baseline, 196 healthy volunteers reported whether they currently owned their home and, for each year of their childhood, whether their parents owned the family home. Volunteers also had blood drawn for assessment of specific antibody to the challenge virus, and for $CD8^+CD28^-$ T-lymphocyte telomere length (in a subset, $n = 135$). They were subsequently quarantined in a hotel, exposed to a virus (rhinovirus [RV] 39) that causes a common cold and followed for infection and illness (clinical cold) over five post-exposure days.

Lower childhood SES as measured by fewer years of parental home ownership was associated with shorter adult $CD8^+CD28^-$ telomere length and with an increased probability of developing infection and clinical illness when exposed to a common cold virus in adulthood. These associations were independent of adult SES, age, sex, race, body mass, neuroticism, and childhood family characteristics. Associations with infections and colds were also independent of pre-challenge viral-specific antibody and season. Further analyses do not support mediating roles for smoking, alcohol consumption or physical activity but suggest that $CD8^+CD28^-$ cell telomere length may act as a partial mediator of the associations between childhood SES and infection and childhood SES and colds.

1. Introduction

Lower levels of socioeconomic status (SES) in childhood and adolescence, as measured by living conditions, family income, and parental education and employment, have repeatedly been found to be associated with poorer health and greater risk for premature mortality in adulthood (Aber et al., 1997; Cohen et al., 2010; Gissler et al., 1998; Nelson, 1992; Roberts and Power, 1996). Although this literature has primarily focused on mortality (Galobardes et al., 2004; Galobardes et al., 2008) and cardiovascular health (Pollitt et al., 2005), there has been increasing interest in the impact of low early childhood SES on adult immune competence and susceptibility to infectious diseases (Cohen et al., 2004; Miller et al., 2009; Ziol-Guest et al., 2012).

The aim of the present study is to investigate the possibility that low childhood SES contributes to shorter leukocyte telomere length that, in turn, increases susceptibility to virus infection. Shorter white blood cell telomere lengths have been suggested as markers of decreased immunocompetence (Effros and Pawelec, 1997; Effros, 2001). Consistent with this view, human adults with shorter peripheral blood mononuclear cell (PBMC) telomere lengths, especially in $CD8^+CD28^-$ T lymphocytes, have been found to be at greater risk for experimentally-induced upper respiratory infections (Cohen et al., 2013). $CD8^+$ T lymphocytes that have lost the capacity to express CD28, a costimulatory molecule important for antiviral function, exhibit an accelerated rate of telomere attrition (Schmid et al., 2002; Valenzuela and Effros, 2002). Shorter average telomere length in this cell population indicates a greater proportion of cells nearing replicative senescence and hence

☆ Please see Brief Commentary by Kiecolt-Glaser et al. (2013) 34, 29–30.

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http://dx.doi.org/10.1016/j.bbi.2013.06.009

comparatively fewer effector cells available to respond to viral insult (Cohen et al., 2013).

Although childhood SES has not been directly associated with adult leukocyte telomere length, childhood exposures to stressful environments that are characteristic of the low childhood SES experience have been associated with shorter average PBMC telomere lengths measured decades later (e.g., Kiecolt-Glaser et al., 2011; Tyrka et al., 2010; reviewed by Price et al. (2013)). Moreover, low childhood SES (parental education) has been related to shorter telomere length in children aged 7–13 years (Needham et al., 2012). That exposures during childhood may result in concurrent changes in telomere length that persist through adulthood is suggested by evidence that telomere length is quite stable over 10 or more years (Chen et al., 2011; Ehrlenbach et al., 2009) and is thought to operate as a stable marker of disease susceptibility over much of the life course (Cohen et al., 2013).

Home ownership is a comprehensive SES indicator, reflecting wealth, income and social status (Long and Caudill, 1992) and is thought to be a more sensitive measure of SES in women than husband's occupation or income (Pugh et al., 1991). Parental home ownership has been widely used as an indicator of childhood SES with ownership associated with less psychological and emotional distress (e.g., Boyle, 2002; Cairney, 2005), less of an inflammatory profile in asthmatics (Chen et al., 2006) and greater resistance to upper respiratory infection (Cohen et al., 2004). An advantage of home ownership as a retrospective marker of *childhood* SES is that people are confidently able to recall whether their parents owned the family home from fairly early childhood (Cohen et al., 2004). In this study, we operationalized childhood SES as the number of years during participants' childhoods (through age 18 years) that their parents owned the family home.

Here, we evaluate whether childhood SES, measured as years of parental home ownership, is associated with $CD8^+CD28^-$ T cell telomere length in young to mid-life adults. We further ask whether childhood SES predicts susceptibility to infection and upper respiratory illness as previously reported (Cohen et al., 2004) and whether these associations are wholly or partly mediated by $CD8^+CD28^-$ T cell telomere length. In all of these cases, we test whether the associations are independent of current (adult) SES and of other childhood family characteristics such as parental divorce, number of children in the home, number of residence moves, and mother's age when the participant was born.

2. Methods

2.1. Participants

Participants were drawn from 212 healthy volunteers ages 18–55 from greater Pittsburgh, PA. Of these, the last 152 had blood drawn for assessment of telomere length. The participants were recruited by newspaper and posted advertisements, and each was paid $1000. The study was conducted between 2007 and 2011 and was approved by the Institutional Review Boards of both Carnegie Mellon University and the University of Pittsburgh and all participants provided signed informed consent.

2.2. Overview

Healthy adult participants answered questions about their childhood and current socioeconomic status, and had blood drawn for measurement of rhinovirus (RV) 39 antibody titer and $CD8^+CD28^-$ telomere length (subsample only). They were subsequently quarantined, administered nasal drops containing a rhinovirus that causes the common cold (RV39), and monitored in quarantine over 5 days for infection and objective signs of a cold.

2.3. Procedures

Volunteers presenting for possible enrollment underwent medical screenings and were excluded if they were treated in the past year or hospitalized in the last 5 years for psychiatric illness; had a history of major nasal or otologic surgery, respiratory disorders, or cardiovascular disease; had abnormal urinalysis, complete blood count, or blood enzymes; were currently pregnant or lactating; tested seropositive for human immunodeficiency virus; or regularly taking medication other than birth control. Specific serum neutralizing antibody titer to RV39 was assessed at screening, and, in order to maximize the rate of infection, volunteers were also excluded if that titer was greater than 4. This assay was repeated on a blood sample taken 2–3 days before quarantine to be defined as the pre-viral challenge titer for use as a covariate. The last 152 participants also had their blood drawn during the pre-quarantine baseline interval between screening and viral challenge to be assayed for lymphocyte telomere length.

Qualifying volunteers were isolated in a local hotel for a 6-day period. During the first 24 h of quarantine (before viral exposure), volunteers had a nasal examination and a nasal lavage, and baseline symptoms, nasal mucociliary clearance and nasal mucus production were assessed. Volunteers were dismissed from the study if they displayed signs or symptoms of a cold on that day, and data for any participant in whom a virus was isolated from the nasal lavage fluids collected on that day were excluded from all analyses. Then, participants were given nasal drops containing approximately 100 tissue culture infectious dose ($TCID_{50}$)/mL of RV39. The quarantine continued for five days. On each day, volunteers were assessed for nasal mucociliary clearance and nasal mucus production, and nasal lavage samples were collected for virus culture. Approximately 28 days after virus exposure, blood was collected for serological testing. Investigators were blinded to all predictor variables at all points of the trial. Telomere length was assayed after the trial was completed by technicians blinded to all other study data.

2.4. Socioeconomic status

2.4.1. Childhood SES

Data on parental home ownership were collected by self-report questionnaire during the baseline day in quarantine. For each year of their lives from age 1 through 18, participants were asked whether their parents owned their family home. Response alternatives included *yes*, *no*, and *I don't know*. Many ($n = 33$) participants were unable to provide information on parental home ownership for the first 4 years of their childhoods. For this reason, our primary analyses in the parent study were limited to childhood SES based on data provided for ages 5–18. By assessing parental home ownership on a yearly basis, we were able to calculate the total number of years of home ownership from ages 1 through 18, as well as to assess exposure at specific ages.

2.4.2. Current (adult) SES

Current SES was assessed by self-report questionnaire during the baseline interval between screening and viral challenge. Participants were asked to report the highest level of educational attainment that they had completed. Nine response options were provided, ranging from didn't finish high school to doctoral degree. For analysis, education was coded into three indicator variables with bachelor's degree or higher as the referent category: high school or less; less than two years of college; 2 years of college + associate's degree. Participants also were asked whether