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Short Communication

Early-life socioeconomic disadvantage, not current, predicts accelerated epigenetic aging of monocytes

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ABSTRACT

Low socioeconomic status (SES) in early-life and adulthood independently contribute to increased risk for aging-related chronic diseases. One mechanistic hypothesis for these associations involves faster cellular aging of immune cells, which could plausibly contribute to chronic disease pathogenesis by compromising host resistance and/or up-regulating inflammation. However, little is known about the association between life-course SES and cellular aging. The present study examines the association of early-life and current SES with a novel biomarker of cellular aging termed the "epigenetic clock," in monocytes. Additionally, we examine health behaviors and depressive symptoms as potential explanatory pathways. The study involved 335 participants between the ages of 15 and 55 from Vancouver, Canada and surrounding areas. Enrolled participants had to fit into four life-course SES trajectories, corresponding to low-low, low-high, high-low and high-high combinations of early-life (ages 0 to 5) and current SES respectively. Cellular aging of monocytes was measured using Horvath's DNA methylation derived measure of epigenetic age acceleration. Results indicated that socioeconomic disadvantage during early-life, but not later in life, was associated with accelerated epigenetic aging of monocytes. No early-life SES by current SES interaction was detected, suggesting that socioeconomic mobility is unrelated to epigenetic age acceleration. In path analyses, neither current health behaviors nor current depressive symptoms emerged as mediators of the early-life SES effect. These findings suggest socioeconomic disadvantage in early-life is independently predictive of cellular aging of immune cells, with potential implications for aging-related diseases later in life.

1. Introduction

Aging-related chronic diseases such as heart disease, diabetes, and cancer are among the leading causes of death worldwide. Morbidity and mortality from these conditions are disproportionately high among socioeconomically disadvantaged individuals (Braveman and Barclay, 2009). Although much evidence comes from studies of socioeconomic status (SES) during adulthood, accumulating data suggest early-life SES is also associated with age-related health problems. Independent of adulthood SES, early-life SES confers increased risk for upper respiratory infection, premature death, and morbidity and mortality from cardiovascular disease and cancer (reviewed in Miller et al., 2011). These findings suggest early-life and adulthood disadvantage increase vulnerability to aging-related diseases through at least partially independent mechanisms.

There is considerable interest in elucidating biological mechanisms underlying socioeconomic disparities. Given the array of health problems associated with low SES, it is tempting to speculate a common mechanistic pathway. Identifying one has been challenging, because conditions that pattern by SES have diverse pathogenic features. One possibility is that disadvantage affects a general biological process, like cellular aging, and thus manifests in multiple tissues, interacting with other liabilities to increase disease risk. However, studies of telomere length, an established cellular aging metric, and life-course SES have yielded inconsistent findings (Robertson et al., 2013). Mounting evidence suggests Horvath's "epigenetic clock" is a more sensitive and

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prognostic indicator of cellular aging than telomere length, and independently predicts mortality (for detailed comparison, see Horvath, 2013; Marioni et al., 2016). Horvath's clock aggregates DNA methylation (DNAm) at 353 age-associated CpG sites to quantify DNAm age. Epigenetic age acceleration represents variance in DNAm age not accounted for by chronological age. Positive values on this metric suggest accelerated cellular aging – i.e., that an individual is biologically older than expected – and have been associated with all-cause mortality, some cancers, and morbidity and mortality from cardiometabolic disease (Horvath, 2013; Jones et al., 2015; Marioni et al., 2016; Perna et al., 2016). One study of adults found that low SES across the life-course was associated with epigenetic age acceleration (Fiorito et al., 2017). While this was a large, multi-cohort study, it focused on older adults, a sizeable minority of whom had a history of cancer or heart disease. Here, we examined epigenetic age acceleration patterns in younger adults who were free of chronic diseases.

We hypothesized that low early-life and current SES would be associated with positive epigenetic age acceleration. We focus on early-life, based on evidence suggesting the immune system is particularly sensitive to environmental stimulation during the first years of life (Miller et al., 2011). Additionally, we considered how life-course SES *trajectories,* of stability or mobility, might relate to epigenetic age acceleration. We used a 2 × 2 design, which crossed level of disadvantage (low vs. high) with stage of life-course (early-life vs. current) and measured the epigenetic aging of participants' monocytes. We also explored potential mediating pathways. These include lifestyle characteristics – smoking, alcohol, abdominal adiposity, and inactivity – which are linked to epigenetic age acceleration (Lam et al., 2012). and depressive symptoms, a known correlate of immune dysregulation (Haroon et al., 2012).

2. Methods

Between 2009 and 2012 we enrolled 360 healthy participants from the Vancouver, British Columbia, Canada area. Recruitment and eligibility criteria are extensively detailed elsewhere (Hostinar et al., 2017). The University of British Columbia's Research Ethics Board approved this study. All adult participants provided written informed consent; for those under 18, guardians provided consent.

2.1. Design

This 2 × 2 design only enrolled participants who met criteria for one of four life-course SES trajectories: low early-life/low current, low early-life/high current, high early-life/low current, and high early-life/high current SES. SES was operationalized as occupational status, using the extensively validated United Kingdom's National Statistics Socioeconomic Classification (NS-SEC) (Rose et al., 2005). Early-life SES was defined as maximum parental occupational status from years 0-5. Current SES was defined as maximum household occupational status within 5 years before study enrollment. In the NS-SEC, occupational status is graded on an 8-point scale, which breaks down into three broader categories (low, middle, high). To qualify as low-SES, participants needed an NS-SEC score of > 5, which corresponds to service and manual occupations, e.g., cleaners and transportation operatives. To qualify as high-SES, an NS-SEC score < 2, was required, which corresponds to higher managerial and professional occupations, e.g., architects and physicians.

2.2. Measures

2.2.1. Epigenetic age acceleration

Most studies of epigenetic age acceleration focus on heterogeneous pools of cells, creating uncertainty about which leukocyte sub-population(s) are involved. To circumvent this problem we focused on monocytes, a cell population sensitive to life-course SES and implicated in multiple age-related diseases (Miller et al., 2011). Following an overnight fast, antecubital blood was collected into Cell Preparation Tubes (BD Biosciences). Peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation. From the resulting pellet, monocytes were isolated by immune-magnetic capture using antibodies against CD14 (Miltenyi AutoMACS). Monocytes were lysed, homogenized, and stored at −80 °C. Next, genomic DNA was isolated using a column-based method and assessed for quality and quantity using a NanoDrop. Approximately 750 ng of genomic DNA was used for bisulfite treatment for sequence-based differentiation of methylated cytosine nucleotides. Bisulfite converted DNA samples were randomized and processed using the Illumina 450 K array. Horvath's clock was estimated with a publicly available R script. Epigenetic age acceleration was calculated by extracting residuals from a linear model wherein DNAm age was regressed onto chronological age (Horvath, 2013).

2.2.2. Potential mediators

Past month depressive symptoms were assessed with the Center for Epidemiologic studies Depression scale (CES-D) brief version (Andresen, 1994). (Chronbach's alpha = 0.84). Participants reported daily number of cigarettes smoked and weekly alcoholic drinks, coded as none (0), < 10 (1), or > 10 (2). Physical activity was measured as weekly minutes of brisk activity (Paffenbarger et al., 1993). Abdominal adiposity was operationalized as continuous waist circumference. Participants self-reported their age, sex, and race/ethnicity.

2.3. Data preparation

Variables were examined for outliers before analyses. Values exceeding four mean standard deviations were Winsorized with the value at the 99.9th percentile (waist circumference: n = 3). Physical activity was skewed and normalized with a square-root transformation.

2.4. Missing data

Of 360 participants, 25 (6.9%) were missing data for epigenetic aging due to technical problems with venipuncture, sample processing, or assay procedures. Between 0.3% and 4.5% of participants were missing data for smoking: n = 15, alcohol use: n = 10, physical activity: n = 10, waist circumference: n = 1, and depressive symptoms: n = 8. Therefore, analytic Ns ranged from 320 to 335.

3. Results

Table 1 provides characteristics of the sample. Consistent with previous studies, chronological age and DNAm age were strongly correlated ($r(333) = 0.93$, $p = 1.1 \times 10^{-144}$). As expected, the derived epigenetic age acceleration metric was uncorrelated with chronological age, $r(333) = 0.00$, $p = 0.996$.

Next, we used ANOVAs to address whether life-course SES was associated with epigenetic age acceleration. Crude models contained variables reflecting early-life SES, current SES, and their interaction; adjusted ANCOVA models also included the covariates age, race, and sex. Hypotheses about low SES were partially supported. We observed a main effect of early-life SES in both unadjusted, F(1, 334) = 4.50, p = .035, d = .24, and adjusted models F(1, 334) = 4.33, p = .038, d = .23. Participants with low early-life SES showed more epigenetic age acceleration compared to those with high early-life SES (Fig. 1). The difference corresponded to an epigenetic age acceleration of 0.93 years. In contrast, there was no main effect of current SES in unadjusted, $F(1, 333) = 0.10$, $p = .748$, $d = 0.03$ or adjusted models, $F(1, 333) = 0.07$ $p = 0.790$, $d = 0.03$. There also was no significant interaction between early-life and current SES in either unadjusted, $F(1, 333) = 0.17$, $p = 0.693$, $d = 0.06$, or adjusted models, $F(1, 333) = 0.26$, $p = 0.61$, $d = 0.06$.