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Stress and chronic illness: The inflammatory pathway☆

Rebecca L. Acabchuk [a, b, *], Jayesh Kamath [c], John D. Salamone [a, b], Blair T. Johnson [a, b]

[a] Department of Psychological Sciences, The University of Connecticut, Storrs, CT 06269-1020, USA
[b] Institute for Collaboration on Health, Intervention, and Policy (InCHIP), University of Connecticut, 2006 Hillside Road, Unit 1248, Storrs, CT 06269-1248 USA
[c] Department of Psychiatry, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030-1410, USA

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1. Introduction

A recent study published in *Social Science & Medicine* provides a compelling example of how psychoneuroimmunology and epigenetics are being utilized in the field of health psychology to tackle important questions. Understanding the biological mechanisms of how social adversity (e.g., poverty, unemployment, low education and lack of social support) gets "under the skin" is essential to help reduce socioeconomic disparities in health. Simons, Lei, Beach, Barr, Cutrona, Gibbons, and Philibert's (2017) study investigated the impact of social adversity on the immune system and chronic disease in a vulnerable population using a novel technique that broadens the array of biomarkers for immune function. Building on immune system research of Cole and colleagues (e.g., Cole, 2014) and methods developed by Houseman et al. (2012), Simons et al. introduced a new multiplex biomarker to assess the dual nature of immune function alterations in response to chronic stress. Their results show that the link between social disadvantage and chronic illness is mediated in part by changes in immune cell distribution.

2. Two components of the immune system

The immune system can be generally divided into two main components: (1) the innate immune system and (2) the adaptive or 'acquired' immune system. The innate immune system provides a nonspecific, rapid response in the body's first line of defense, which includes not only barriers such as skin cells, but also inflammatory and antimicrobial responses that work through monocytes and natural killer cells. Chronic inflammation is a major factor in almost all of today's chronic diseases. The major leading causes of death in the developed world, such as Alzheimer's Disease, heart disease, diabetes, chronic obstructive pulmonary disease, and cancer, all involve chronic inflammation to some degree. Understanding how, when, and where chronic inflammation contributes to disease can help lead to better interventions and treatments to stop or slow it. The link between inflammation and health issues is so robust that scholars sum it up with the succinct label *inflammaging*. Major cell components of the innate immune system include natural killer cells and monocytes, which release proinflammatory cytokines such as IL-6, TNF alpha, and C-reactive protein. In turn, elevated levels of proinflammatory cytokines are linked to symptoms of depression (Felger and Treadway, 2017), changes in body composition, neurological decline, and many other negative signs of aging, including premature aging itself, as gauged by telomere length (Simons et al., 2016).

The immune system's adaptive program provides a slower, specific response that retains memory to provide antiviral response through antibody synthesis (Repetti et al., 2011). Stress impairs the adaptive immune system and reduces the body's ability to produce antibodies to fight off intracellular pathogens and viruses. The link between stress and impaired adaptive immune function has been well established using both human and animal studies; stress impairs wound healing, reduces antibody response to vaccinations, and increases susceptibility to illness such as the common cold

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* Corresponding author. Institute for Collaboration on Health, Intervention, and Policy (InCHIP), University of Connecticut, 2006 Hillside Road, Unit 1248, Storrs, CT 06269-1248, USA.
E-mail address: rebecca.acabchuk@uconn.edu (R.L. Acabchuk).

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(e.g., Cohen et al., 1991; Glaser and Kiecolt-Glaser, 2005). Major cell components of the adaptive immune system include B- and T-lymphocytes.

3. ITACT ratio: A biomarker for inflammatory dominance

Stress impairs the immune system in a dualistic fashion; the innate immune system upregulates pro-inflammatory genes, while the adaptive immune system down-regulates expression of Type I interferon- and antibody-related genes, weakening the antiviral response (Cole, 2014). Cole labeled this pattern of change in the two components of the immune system *conserved transcriptional response to adversity* (CTRA). CTRA pattern can be thought of as the immune system leaning towards "inflammatory dominance," as it reflects increased inflammation and reduced antiviral response. Cole's research has linked the CTRA pattern to social-environmental adversity (i.e., low socioeconomic status, social isolation, low social status).

Simons et al. (2017) build on Cole's work on the dualistic pattern of immune response by using the ratio of leukocyte cell types associated with increased innate immunity marked by proinflammatory cells (monocytes and natural killer cells), on the one hand, to reduced levels of the adaptive, antiviral program (B-lymphocytes and CD4-and CD8-lymphocytes), on the other (see Fig. 1). Simons et al. label this measurement the *ITACT Ratio*, as it compares **I**nnate **T**o **A**cquired **C**ell **T**ypes as a ratio. Simons' team tested their mediation hypothesis using a random sampling of African American female primary caregivers from the Family and Community Health Study (FACHS), which commenced with residents living in small town and rural areas in Iowa and Georgia ranging from relatively poor to quite affluent. As the authors report, many studies have linked social adversity to both inflammation and illness. Yet, few have investigated the often-hypothesized mediation of the impact of socioeconomic disadvantage on changes in chronic illness by inflammatory response systems. Simons and colleagues' use of the ITACT Ratio provides the first direct support for the mediation hypothesis, setting the stage for future research to identify predictors of resilience that ameliorates the socioeconomic adversity → inflammation → chronic illness pathway.

Low socioeconomic status (SES) can lead to chronic health issues by direct means such as increased exposure to lead, asbestos, noise, and pollution, and by indirect pathways including stress, behavior and lifestyle. To reduce growing health disparities, it is critical to uncover the mechanisms that underlie the link between SES and

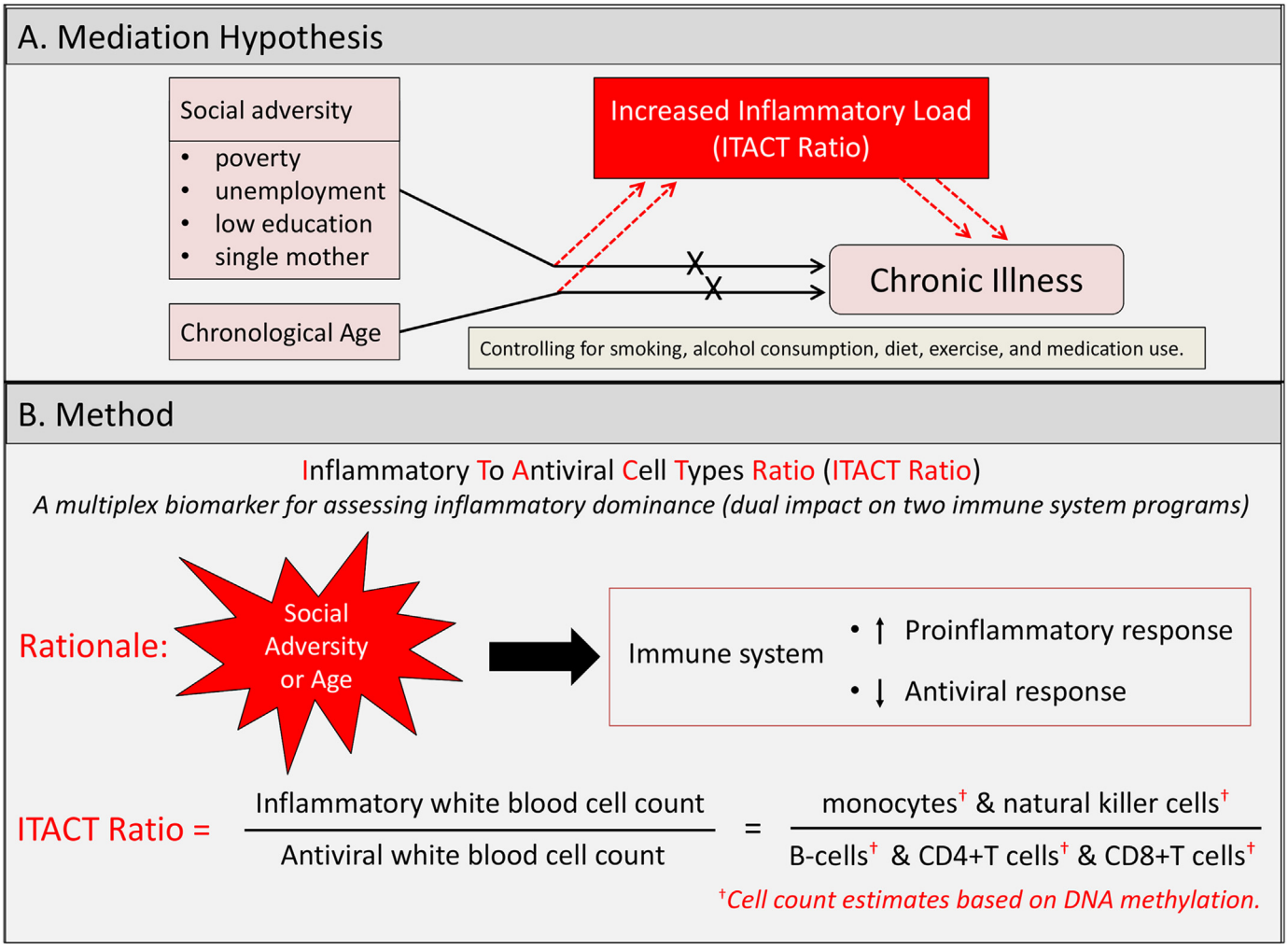

Fig. 1. Overview of hypothesis and methods in Simons et al. (2017). **A**. Mediation hypothesis suggests the influence of social adversity and age on chronic illness is mediated by increased inflammatory load. 'Chronic Illness' was measured by the following eight items: heart trouble, diabetes, kidney disease, cancer, effects of stroke, circulation trouble in arms and legs, emphysema or chronic bronchitis, and cataracts. **B**. Rationale and methods employed in Simons et al. (2017) used to evaluate inflammatory dominance vis-à-vis the ITACT Ratio.