



Stress and chronic illness: The inflammatory pathway[☆]



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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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(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 **Innate To Acquired Cell Types** 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

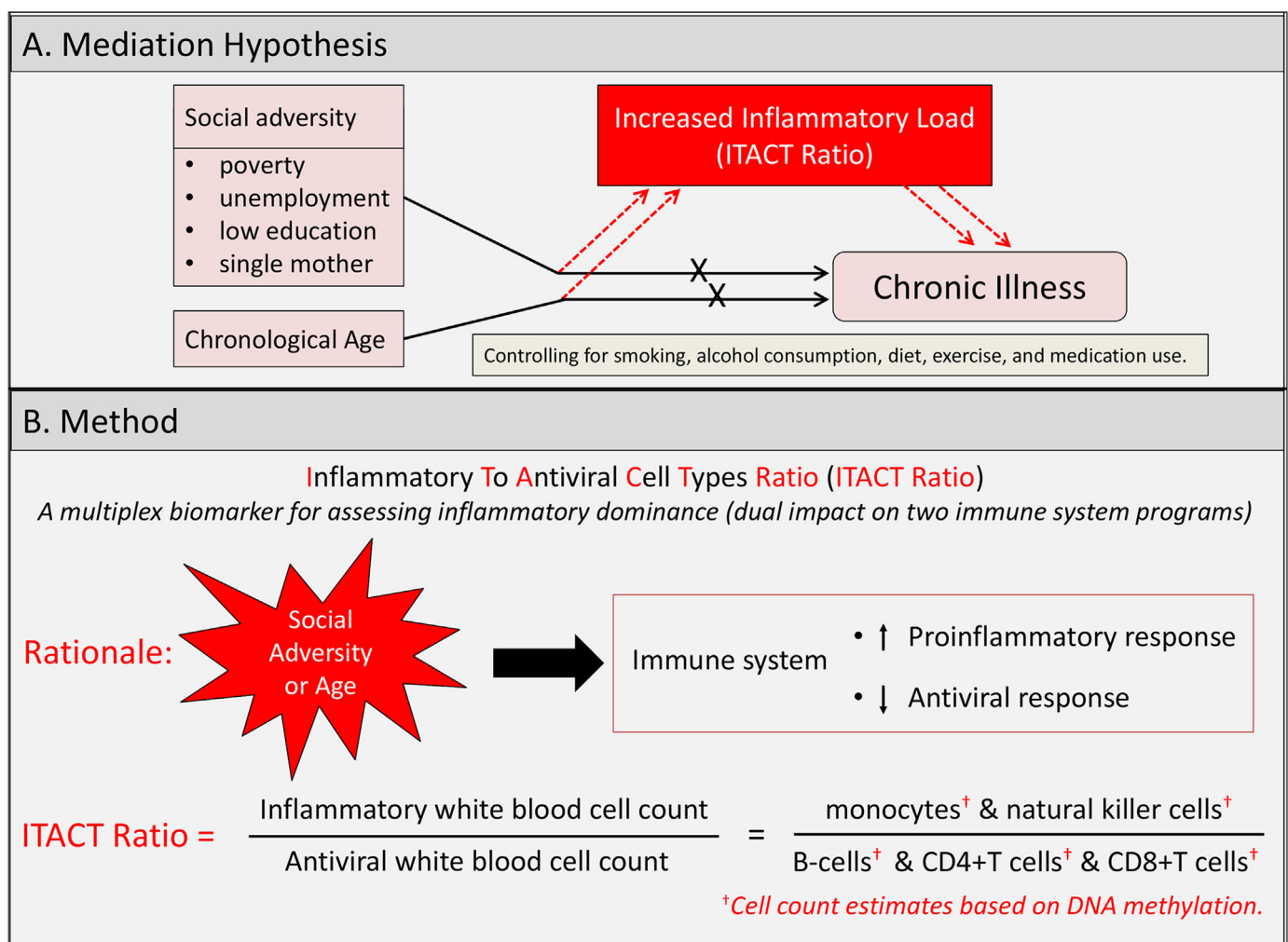


Fig. 1. Overview of hypothesis and methods in Simons et al. (2017). **A.** Mediation hypothesis suggests the influence of social adversity and age on chronic illness is mediated by increased inflammatory load. ‘Chronic Illness’ was measured by the following eight items: heart trouble, diabetes, kidney 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.

chronic disease while controlling for as many confounders as possible. Simons et al. controlled for several lifestyle factors that are known to contribute to cellular inflammation, notably smoking, alcohol consumption, diet, exercise, and medication use, all recorded with self-reports.

4. Methodological advances

Advances in clinical biomarkers are especially vital for conditions that are marked only by a set of symptoms in order to aid early diagnosis and to monitor disease progression. Combining biomarkers can often be much more effective than any single biomarker alone. For example, a recent study found the combination of three biomarkers (lymphocytes, monocytes, and C-reactive protein) predicted Gulf War Illness with 90% accuracy (Johnson et al., 2016); Gulf War Illness is a chronic multi-symptom illness that is troublesome to diagnose.

Although numerous studies have demonstrated the relation between elevation of circulating markers of inflammation and a wide variety of chronic diseases associated with age, many have employed single markers of inflammation (e.g., IL-1, IL-6, TNF-alpha), often resulting in modest or conflicting effects. The ITACT Ratio may be useful in helping to reveal why pro-inflammatory cytokines such as IL-6 are upregulated following adverse experiences or depression; the ITACT Ratio incorporates changes in immune cell distribution upstream from cytokines. Past inflammation studies have modeled dependent variables such as motivational symptoms of depression or neurological decline in relation to plasma markers for inflammation (Felger and Treadway, 2017). Yet, a robust multiplex biomarker of immune dysregulation would be extremely useful if it can accurately capture the dualistic impact of stress on immune function. Thus, future studies using the ITACT Ratio would benefit by also including existing proinflammatory markers in their analysis.

Simons et al.'s (2017) study contains several additional methodological advances over previous research that should be noted. First, the researchers use an innovative method to estimate the proportions of leukocyte (white blood cell) types in a peripheral blood draw based on the unique DNA methylation signatures of each leukocyte type. This method for quantifying leukocytes developed by Houseman et al. (2012) provides a marked advantage over more direct measures of cell counts, such as flow cytometry, in that it is more efficient and less costly. Second, unlike many studies that focus on a single illness (e.g., cardiovascular disease; diabetes), the dependent variable in this study was an index of eight illnesses associated with age and disadvantage (listed in legend of Fig. 1). In addition, the authors controlled for prior diagnosis of chronic illnesses, which allowed them to predict changes in illness over a three-year period rather than the more typical one-time assessment of illness. Likewise, the authors have employed an index of five indicators of disadvantage collected over a seven-year time span. Moreover, few studies of the effects of disadvantage on illness have included adults, and even fewer have this extensive assessment of chronic illness.

5. Biological pathways

The relationship between social adversity and chronic disease is highly complex, bidirectional, and often self-reinforcing. Simons et al.'s study is important in that it shows changes in immune cell distribution leading to a reduced antiviral response and excessive production of proinflammatory cytokines play a mediating role between social adversity and chronic disease. Yet, it is important to note that the ITACT Ratio did not mediate the entire relationship between either age or adversity and illness, as it was found to

account for less than 50% for each. Thus, additional biological pathways are also involved. Another mechanism by which social and environmental factors along with perceived stress can affect the body at a biological level is through epigenetic changes, leading to alterations in gene expression. Health psychology is expanding to include the emerging field of human social genomics, providing biological evidence that external social conditions and perceived stress interact to influence gene expression (Slavich and Cole, 2013).

Research in this emerging field has begun to isolate which genes are susceptible to social-environmental regulation, including those that regulate immune functioning. Evidence suggests that social context and early life adversity may be associated with gene-specific epigenetic modifications (e.g., via DNA methylation) that may confer a proinflammatory epigenetic signature mediating a heightened inflammatory state (Saban et al., 2014). Such epigenetic “priming” of inflammatory pathways increases the risk for developing proinflammatory diseases (e.g., cardiovascular and cerebrovascular diseases; Saban et al., 2014). In addition to epigenetic changes, chronic stress and changes in immune function interact with other systems of the body as well as mood and behavior. Whether from social adversity, early childhood adverse experiences, trauma, lack of support, or a variety of other sources, chronic stress can impair optimal function and health. These effects include increased pain sensitivity and impairments in memory, cognition, and self-regulation; altered intestinal flora; increased flare-ups of other existing conditions (e.g., multiple sclerosis or other autoimmune disorders, migraines, IBS, thyroid conditions, etc.); changes in body composition or mood (such as anxiety and depression); or behavioral changes that further impair health.

These pathways interact with each other as well as the immune system and illness and disease. The interactions between social adversity, inflammation, and chronic diseases such as cardiovascular diseases are further complicated by psychosocial factors known to play an important role in pathophysiology, including such factors as smoking, substance use, and diet. Social adversity and related poverty can compromise certain lifestyle factors (e.g., diet) and increase the risk of unhealthy behaviors such as smoking. Social adversity increases risk of stress-related psychiatric disorders (e.g., post-traumatic disorders, depression). Stress-related disorders, in turn, are known to compromise lifestyle factors and are frequently associated with unhealthy behaviors. Thus, self-reinforcing loops can perpetuate the impact of social and environmental stress by working synergistically with behavioral factors and stress-related disorders to increase the risk of chronic disease.

Recent studies show evidence for links between stress-related psychiatric disorders such as depression/PTSD and chronic inflammation, dysfunction in the psycho-neuro-endocrine systems and their interactions with each other (Haroon et al., 2012; Raison and Miller, 2003). Single mothers have higher rates of reported chronic stress and depression, which has been attributed to less social support and higher exposure to stress (Cairney et al., 2003). Additionally, low parental education is associated with an increased risk for depression (Ritscher, 2001). Elevated proinflammatory cytokines such as IL-6 and TNF-alpha have been linked to depression (Felger and Treadway, 2017), and clinical administration of the proinflammatory cytokine interferon alpha, which is used to treat some forms of cancer and hepatitis-C, has been shown to induce depressive symptoms, with fatigue being seen in 80% of patients (Miller, 2009). Taken together, increases in inflammatory dominance following social adversity is likely not only linked to chronic conditions such as heart disease, but also to a broader set of symptoms that include depression, fatigue, sleep disturbances and cognitive dysfunction. Simons et al.'s study did not examine

depressive symptoms as part of their clinical outcome measurements, but future studies should examine whether the ITACT Ratio is a useful biomarker for depression.

6. Stress, cortisol, the immune system, and aging

From an evolutionary standpoint, stress has a paradoxical effect in that the short-term response is designed to protect the organism from disease and attack, but in the long-term, it exposes the body to damaging factors if not properly ceased. Chronic stress, such as in the form of social adversity, may expose a person to consistently elevated levels of stress hormones from the hypothalamic-pituitary-adrenal (HPA) axis and adrenergic system, including cortisol. Elevated cortisol levels have long been associated with morbidity, mortality, and even increases in apparent age gauged in photographs (Noordam et al., 2012). High cortisol levels are associated as much as a five-fold greater risk of dying from cardiovascular disease (Vogelzangs et al., 2010). While Simons et al.'s study did not measure cortisol, it is important to consider the role that cortisol may play in orchestrating the relationship between social adversity, immune function and chronic disease in future studies. Elevated cortisol levels suppress immune function and reduce inflammation. How then, might inflammatory dominance occur despite high levels of cortisol?

A recent animal study that exposed macaques to social stress found the new leukocyte distribution generated from social stress conditions is primed for inflammation and insensitive to cortisol (Cole et al., 2015a, b). Such reduced responsiveness to glucocorticoids and dysfunctional glucocorticoid signaling has been documented in stress-related disorders such as post-traumatic stress disorder and depression (Raison and Miller, 2003). In these disorders, the impaired feedback regulation of stress-response has been associated with heightened inflammation, high sympathetic nervous system tone, and hypersecretion of corticotropin-releasing hormone (Raison and Miller, 2003). It is important to note that such dysfunctional interactions between neuro-immune-endocrine systems may have other consequences such as adverse effects on insulin resistance and bone metabolism (Raison and Miller, 2003). Together, these studies highlight critical considerations for future investigations assessing the biological impact of social stress by combining ITACT Ratio with other known biomarkers of stress and autonomic nervous system activity (e.g., cortisol and heart rate variability, respectively).

Simons et al.'s (2017) results suggest socioeconomic disparities translate into negative health effects similar to premature aging. A variety of biopsychosocial factors contribute to the rate of biological aging, including environment, stress, lifestyle and genetics. Studies have linked psychological stress to cellular aging of blood mononuclear cells, which include the leukocyte cell types used in ITACT. Blackburn's team found women with highest levels of perceived stress have lower telomerase activity and shorter telomere length in peripheral blood mononuclear cells, suggesting that stress can promote earlier onset of age-related chronic disease at the cellular level (Epel et al., 2004). Horvath's (e.g., 2013) 353-clock model provides a biomarker method to distinguish between chronological age and biological age that may allow researchers to determine if certain cell types are aging faster due to perceived stress; future studies using the ITACT Ratio may profit by integrating this model.

7. Clinical implications

Multiple genetic and environmental factors play a role in the etiology and pathophysiology of chronic diseases. It appears that social adversity plays a critical role in the development and/or maintenance of these factors, which include physiological changes,

poor health-related behaviors (e.g., unhealthy diet, smoking), and stress-related psychiatric disorders. Together, these factors interact in a complex bidirectional fashion increasing the risk of chronic diseases, especially in vulnerable populations (Nusslock and Miller, 2016), and are complicated by such other variables as genetic vulnerability, psychosocial factors, and interactions between multiple biological systems. Decades of research focusing on individual organs, systems, or diseases have delineated the role of chronic inflammation and dysfunction in psycho-neuro-endocrine systems in the pathophysiology of these diseases. Emerging research is identifying the impact of social adversity on several biological systems simultaneously and via multiple pathways (Nusslock and Miller, 2016): Chronic, low-grade inflammation appears to play a key role and may be the common mediator for these pathways and interactions. The integrative model emerging from this work has important clinical implications in terms of our understanding of chronic diseases and their link to social-environmental stress. Further, it gives us opportunities to investigate new points of target for intervention. The FACHS sample selection, which included single mothers of low socioeconomic status with low levels of education, make this study even more relevant to the urgent issues facing public health and our healthcare system. Interventions and preventive measures, such as programs designed to build resilience, should address the specific needs and barriers of vulnerable populations to help reduce health equity gaps.

8. Conclusion

In their study, Simons et al. (2017) have provided important insight into how immune system responses mediate the effects of social adversity and age on chronic illness. The ITACT Ratio is a novel assessment of immune functioning that helps expand the toolkit of health psychology. Not only is this study noteworthy in showing how socioeconomic disadvantage may influence immune cell profile, but also it may prompt future work in other domains to use this new index of inflammatory dominance, the ITACT Ratio. Simons et al.'s demonstration that social adversity gets “under the skin” through the immune system has much potential for expansion: combining ITACT with other common markers for stress and inflammation, including additional measurements for perceived stress, and expanding the investigation of the link between ITACT and chronic disease in additional populations. Results of future studies will determine if ITACT will emerge as an important new biomarker tying inflammatory dominance to chronic disease.

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