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Associations of salivary cortisol levels with inflammatory markers: The Multi-Ethnic Study of Atherosclerosis

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Summary Socioeconomic and psychosocial factors have been found to be associated with systemic inflammation. Although stress is often proposed as a contributor to these associations, no population studies have investigated the links between inflammation and biomarkers of stress. The current study examines associations between daily cortisol profiles and inflammatory markers interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor (TNF-a) in a population-based sample of 869 adults with repeat measures of cortisol over multiple days. Persons with higher levels of IL-6 had a less pronounced cortisol awakening response, a less steep daily decline, and higher cortisol area under the curve for the day with associations persisting after controls for risk factors and other cytokines. Persons with higher levels of TNF-a had lower cortisol levels upon waking, and flatter daily decline, although associations with decline were attenuated when controlling for inflammatory risk factors. Higher levels of IL-10 were associated with marginally flatter daily cortisol decline ($p < .10$). This study is the first to identify associations of basal cortisol activity and inflammatory markers in a population based sample. Findings are consistent with the possibility that HPA axis activity may mediate associations between psychosocial stressors and inflammatory processes. Additional prospective data are necessary to clarify the directionality of associations between cortisol and inflammatory markers.

There is a growing body of evidence linking socioeconomic and psychosocial stress to inflammation and immune function (Black, 2003; Kiecolt-Glaser et al., 2002; Segerstrom and Miller, 2004). The physiologic mechanisms underlying these associations have not been fully explained, but chronic

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activation of the hypothalamic–pituitary–adrenal (HPA) axis, a stress-responsive biological system, has been proposed as a potential contributor to observed links between adverse psychosocial influences and immune or inflammatory processes.

The HPA axis is responsible for mobilizing the body's resources when an individual encounters psychological or physical stressors (Sapolsky et al., 1986). Cortisol, a hormone produced by the HPA axis, increases in response to stress in both naturalistic and laboratory settings (Adam et al., 2006; Dickerson and Kemeny, 2004) and varies according to a circadian rhythm in which levels are typically high upon awakening, increase sharply within 30–40 min of waking (a phenomenon referred to as the cortisol awakening response or CAR) (Pruessner et al., 1997), and decline across the remainder of the waking day (Kirschbaum and Hellhammer, 1989). Because the HPA axis is known to interact in complex ways with immune system activity (Petrovsky et al., 1998; Sapolsky et al., 2000; Sternberg, 2001), it is reasonable to expect that HPA axis activity could contribute to immune system or inflammatory alterations in the face of psychosocial stress.

Elevated levels of inflammation-related cytokines, including interleukin-6 (IL-6), have been associated with increased levels of chronic and acute stress and anxiety levels (Kiecolt-Glaser et al., 2003; Maes et al., 1998, 1999). Higher levels of pro-inflammatory cytokines have been found among racial/ethnic minorities in the US and individuals of low socioeconomic status in the US and UK (Gimeno et al., 2007; Koster et al., 2006; Ramsay et al., 2008; Ranjit et al., 2007). A parallel body of work has also linked racial/ethnic minority status, socioeconomic disadvantage, and adverse psychosocial profiles to alteration of the levels and circadian rhythm of cortisol (Cohen et al., 2006; DeSantis et al., 2007; Hajat et al., 2010). Taken together, these results suggest that alteration of the levels or the circadian rhythm of cortisol may serve as a mechanism underlying associations between psychosocial stress and inflammation. However, few if any studies have examined the direct links between HPA axis activity and systemic levels of inflammatory markers in population-based samples.

Associations between cortisol levels and inflammation-related cytokines are likely to be complex and bidirectional: pro-inflammatory cytokines stimulate activity in the HPA axis, leading to increases in cortisol, but cortisol and other glucocorticoids (GCs) typically act as immuno-suppressants (Riechlin, 1993). Much early research focused on the role of GCs as immuno-suppressants (Chrousos, 1995; Elenkov and Chrousos, 1999; Petrovsky et al., 1998). However, recent research has increasingly found that GCs are immuno-modulatory, rather than simply immunosuppressive (Elenkov, 2008; Elenkov and Chrousos, 2002; McEwen et al., 1997). Although in the short-term, cortisol acts as an immunosuppressant (Chrousos, 1995; Elenkov and Chrousos, 2002), long-term chronic activation of the HPA axis has been hypothesized to contribute to inflammation (Chrousos, 1995; Elenkov and Chrousos, 1999, 2002; Miller et al., 2002; DeRijk et al., 1997). For example, there is some evidence that white blood cells may respond to excessive exposure to GCs by downregulating the expression and/or function of GC receptors (Miller et al., 2002). These results suggest that chronic stress may impair the immune system's capacity to respond to hormonal signals that terminate inflammation, and that this pathway could be one of the mechanisms through which chronic stress contributes to inflammation-related conditions (Ibid., 2002).

A number of clinical and experimental studies have analyzed associations between cytokine activity and GCs (DeRijk et al., 1997; Elenkov and Chrousos, 2002; Miller et al., 2002; Riechlin, 1993; Steensburg et al., 2003). However, the extent to which cortisol activity in naturalistic settings (e.g., levels at various points in the day, rates of decline across the waking day, and cortisol responses to awakening) is related to cytokine activity in non-clinical population-based samples has not been extensively investigated. We used data from a large population based sample to investigate associations between daily cortisol levels and circulating levels of three cytokines, IL-6, interleukin-10 (IL-10), and tumor necrosis factor-α (TNF–α).

We investigated these three cytokines because each participates in a different aspect of the inflammatory process. IL-6 is increasingly recognized as a pleiotropic cytokine that serves both to activate as well as suppress inflammatory activity. It is an important mediator of the acute phase response (Feghali and Wright, 1997) and has been found to be particularly sensitive to exogenous corticosteroids in experimental research (DeRijk et al., 1997). The principal function of IL-10 appears to be limiting and terminating inflammatory responses (Moore et al., 2001). Because levels of IL-10 been found to increase in response to psychological stress, IL-10 has been proposed as a potential key mediator of stress-induced immune-suppression (Curtin et al., 2009). TNF-α has pro-inflammatory properties and plays a key role in the initial stages of the APR (Feghali and Wright, 1997). It stimulates the synthesis of several other pro-inflammatory cytokines, as well as the release of corticotropin releasing hormone (CRH) from the hypothalamus. Through its effects on the release of CRH, TNF-α plays a key role in modulating the immuno-suppressive response of the HPA axis.

Prior work from this sample has examined associations of socioeconomic and psychosocial factors with inflammatory markers and with HPA axis activity (Ranjit et al., 2007, 2009; Hajat et al., 2010). This report focuses on direct associations between cortisol activity and inflammatory markers.

Specifically, we address the following questions:

1. Is there an association between diurnal cortisol rhythms (wake-up levels, the cortisol awakening response (CAR), or the decline in cortisol over the day) and IL-6, IL-10, or TNF-α levels?
2. Is there an association between total cortisol output measured by area under the curve (AUC) and IL-6, IL-10, or TNF-α levels?

Specifically, we hypothesized that higher levels of IL-6 and TNF-α would be related to higher cortisol AUC, flatter cortisol decline and higher bedtime cortisol levels. In contrast, we hypothesized that higher levels of IL-10 would be related to lower cortisol AUC, more pronounced declines, and lower bedtime values.

1. Methods

The data utilized in these analyses come from an ancillary study to the Multi-Ethnic Study of Atherosclerosis (MESA), the