Published in final edited form as:

Brain Behav Immun. 2015 February ; 44: 137–147. doi:10.1016/j.bbi.2014.09.008.

Depressogenic vulnerability and gender-specific patterns of neuro-immune dysregulation: What the ratio of cortisol to C-reactive protein can tell us about loss of normal regulatory control

Edward C. Suarez, PhD¹, John S. Sundry, MD, PhD², and Alaattin Erkanli, PhD³

¹Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

²Department of Medicine, Duke University Medical Center, Durham, NC, USA

³Department of Biostatistics, Duke University Medical Center, Durham, NC, USA

Abstract

We examined whether the ratio of cortisol (CORT) to high-sensitivity C-reactive protein (hsCRP), an index that captures the integrity of homeostatic regulation between the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory processes, is associated with vulnerability to depression in a gender specific manner and whether glucocorticoid receptor (GR) sensitivity plays a role in these associations. Fasting blood samples were collected between 0845 and 0915 and assayed for CORT, hsCRP, and leukocyte count in 213 healthy, medication-free men and women. The NEO-Personality Inventory was used to assess neuroticism, extraversion and anxiety. We used the Hamilton Depression Interview to assess depressive symptoms, the Buss-Perry anger subscale to measure anger, and the Pittsburgh Sleep Quality Index to evaluate subjective sleep quality and its components. Log-transformed CORT/CRP values were analyzed using multiple regression with Holms' adjusted p-values and age, body mass index (BMI), and race as covariates. GR sensitivity was estimated using the log-transformed ratio of neutrophils (N)-to-monocytes (M). The log-transformed ratio of CORT/CRP did not differ between men and women but was significantly and negatively associated with age and BMI. Severity of depressive symptoms, extraversion, anxiety, and sleep quality were associated with the CORT/CRP ratio in a gender-specific manner. For women, decreasing CORT/CRP ratios, suggestive of an insufficient release of CORT coupled with a heightened inflammatory state, were associated with increasing severity of depressive symptoms, decreasing quality of sleep, increasing frequency of sleep disturbance, and decreasing extraversion. For men, increasing frequency of daytime disturbance and levels of anxiety were associated with increasing CORT/CRP ratio, suggestive of an enhanced release of CORT relative

© 2014 Elsevier Inc. All rights reserved.

Corresponding author: Edward C. Suarez, PhD, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, PO Box 3328, Durham, NC, USA 27710; Tel: +1 919 684 2941; Fax: +1 919 668 6419; suare001@mc.duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

to attenuated levels of hsCRP. For both genders, increasing anger was associated with decreasing CORT/CRP ratios. Although results suggested GR downregulation in women but not men, such differences did not mediate the observed associations. With the use of the CORT/CRP ratio, we showed that vulnerability factors for depression are associated with a loss of normal regulatory controls resulting in gender-specific patterns of neuro-immune dysregulation. That GR downregulation did not influence these associations suggests that the loss of regulatory controls in at risk individuals is primarily at the level of the hormone. Beyond the individual contribution of each component of the CORT/CRP ratio, disruption of normal neuroimmune regulatory feedback provides a plausible biological framework useful in understanding biobehavioral vulnerabilities to depression in a gender specific manner. The CORT/CRP ratio may be a viable biomarker not only for delineating risk for MDD but also progression and treatment responses among patients with MDD; possibilities that are testable in future studies.

Keywords

Inflammation; Hypothalamic-pituitary-adrenal axis; Regulatory feedback mechanisms; Cortisol; C-reactive protein; Neuroticism; Anxiety; Depression; Sleep disturbances; Gender differences

1. INTRODUCTION

The etiology of major depressive disorder (MDD) is thought to involve the dysregulation various biological systems including the hypothalamic-pituitary-adrenal (HPA) axis and the immune system (Howren et al., 2009) with emerging evidence suggesting potential gender differences (Owens et al., 2014; Sanches et al., 2013). Moreover, altered function of the HPA axis and elevated levels of inflammatory biomarkers have also been associated with severity of depressive symptoms and a spectrum of vulnerability factors among individuals without a history of depression and those who are symptom-free (Capuron et al., 2011; Feinberg et al., 2012; Kirschbaum et al., 1995; Klok et al., 2011; Portella et al., 2005; Roy et al., 2010; Sutin et al., 2010b; Zobel et al., 2004) again with some evidence of gender differences (e.g., Poanta et al., 2010; Polk et al., 2005; Prather et al., 2013; Suarez, 2008). The combined evidence suggests that dysregulation of the HPA axis and immune system is associated not only with clinical diagnosis but also with the heightened risk of depression with emerging evidence suggesting that the risk of depression reflects both psychological vulnerabilities and biological dysregulation (Owens et al., 2014).

It is well understood that the HPA axis and inflammatory systems are inherently intertwined in a reciprocal manner; a relationship that is integral in maintaining health and preventing disease (Johnson et al., 1992; Pace et al., 2009). The normal sequence of regulatory events and the preservation of bidirectional feedback signaling are key aspects of homeostasis (Besedovsky and del Rey, 1996). Distinguishing it from normal regulatory processes, derangements of the HPA axis-immune interface result in a disproportionate (e.g., either too much or too little) secretion of adrenal hormones relative to levels of pro-inflammatory proteins (Straub et al., 2011). Although the importance of homeostasis in health and disease is widely acknowledged, most published studies have applied methodologies and analytic strategies that aim at evaluating HPA axis and immune-inflammatory factors independently. To determine whether impairment of feedback mechanisms plays a critical role in the

cascade of events contributing to MDD (Bonne et al., 2004), it is necessary to develop new methodologies and assessment tools to evaluate the inter-relationship between the HPA axis and immune systems. To accomplish this goal, we introduce the ratio of CORT to CRP as one approach to assess regulatory status.

The current study aimed to evaluate the status of the negative feedback loop between the HPA axis and inflammatory system. To accomplish this goal required the development of a metric that encapsulates and quantifies the interplay between specified components. To achieve this goal, a number of published studies have employed ratios to capture and operationalize inter-related activities between components within a system (e.g., Th1/Th2; Huang and Lee, 2007) and between systems (e.g., CRH/NE and 5HT/NE, respectively; Gold and Chrousos, 2002; Martino et al., 2012). In the current study, we employed the CORT/CRP ratio. The CORT/CRP ratio has been previously used in studies of patients with rheumatic diseases such as polymyalgia rheumatica (PMR) (e.g., Demir et al., 2006). Studies have shown that, relative to healthy controls, patients with PMR exhibit significantly lower CORT/CRP ratio values suggestive of HPA axis hyporesponsivity relative to elevated levels of CRP (Demir et al., 2006; Narvaez et al., 2006). Although differences between patients and healthy controls are noteworthy, the validity of the CORT/CRP rests upon a large body of evidence for the bidirectional influences between the HPA axis and the immune system (Mastorakos et al., 1993; Mendelson and Glasgow, 1966; Tsigos et al., 1997). Thus, the interpretation of the CORT/CRP ratio that makes it a useful metric for evaluating the underlying biological perturbations associated with increased vulnerability to depression.

As described above, the use of CORT/CRP ratio has been limited to studies of inflammatory conditions where it is likely that the ratio values are low. Similarly, low ratio values may also be observed in depressed patients given previous evidence suggesting higher inflammation in the presence of lower CORT levels among depressed women relative to health controls (Miller et al., 2005). Depression, however, is multifactorial in its origins with underlying putative mechanisms encompassing various patterns of biological perturbations. Thus high ratio values, suggestive of excessive CORT release accompanied by attenuated levels of CRP, are also likely to be as informative given that higher CORT levels have been reported among depressed patients. As a measure, the CORT/CRP ratio appears to be unique in that it captures distinct patterns of dysregulation implicated in the etiology of depression; excessive inflammation with insufficient CORT release and excessive CORT release relative to low inflammation. Interpreting high and low values in such a manner allows moderate values to be suggestive of homeostasis; a state not often assigned when a single factor is assessed isolation. Additional details and related background on the CORT/CRP ratio are found in the supplementary material.

While regulatory feedback dysregulation between the HPA axis and inflammatory system may emerge at the level of the end-hormones, we note that the loss of bidirectional signaling may also occur at the level of the receptor (Barnes and Barnes, 2010; Nemeroff et al., 1984). Downregulation of glucocorticoid (GR) and mineralocorticoid (MR) receptors effectively diminishes negative feedback signaling resulting in an over-activation of the HPA axis and attenuation of the anti-inflammatory effects of glucocorticoids (Barnes and Barnes, 2010;

Silverman and Sternberg, 2012). GR downregulation has been reported in patients with MDD (McQuade and Young, 2000; Pariante and Miller, 2001), most often in women with MDD (Jarcho et al., 2013). Although limited, there is evidence to suggest GR downregulation among individuals predisposed to MDD (McCleery and Goodwin, 2001) and healthy individuals reporting high levels of chronic stress (Cohen et al., 2012). Given the paucity of evidence, a secondary aim of the current study was to examine whether GR downregulation moderated the association between loss of regulatory feedback and vulnerability to depression.

Vulnerability Factors of Depression

A wide-array of psychological factors is associated with an increased risk of depression. Recent evidence, however, has suggested that pathways leading to depression may differ for men and women (Goodwin and Gotlib, 2004; Grav et al., 2012a; Kendler and Gardner, 2014; Zinbarg et al., 2010). Thus, a factor associated with an increased risk of depression in women may not incur a similar level of risk in men and vice-a-versa. An example of such gender differences is the relation of personality factors to depression. For example, neuroticism is a stable personality trait that reflects the extent to which individuals tend to experience negative emotional states (Costa and McCrae, 1992). Neuroticism has been associated with an increased risk of MDD (Bienvenu et al., 2004; Goodwin and Gotlib, 2004; Hirschfeld et al., 1989; Huprich, 2000; Jylhä and Isometsä, 2006; Kendler et al., 1993; Sutin et al., 2010a) with some studies suggesting that neuroticism has a greater influence on the risk of depression in women than in men (Goodwin and Gotlib, 2004; Kendler and Gardner, 2014). Similarly, anxiety, a component of neuroticism, has also been associated with an increased risk of depression (Bromberger and Matthews, 1996; Parker et al., 1999; Potvin et al., 2013) with anxiety preceding the onset of depressive symptoms (Alloy et al., 1990) and anxiety disorders predating the onset of a depressive episode (Parker et al., 1999). In studies that have examined gender differences, a diagnosis of generalized anxiety disorder appears to increase the risk of depression more so in men and adolescent boys than in women and adolescent girls (Gallerani et al., 2010; Hettema et al., 2006).

In contrast to neuroticism and anxiety, other personality traits such as extraversion are associated with a lower risk of depression. Extraversion is the extent to which individuals are sociable and outgoing (Costa and McCrae, 1992). Although less robust than the association between neuroticism and depression, low extraversion has been associated with an increased prevalence of depression in adults and adolescents (Chioqueta and Stiles, 2005; Grav et al., 2012b; Jylhä and Isometsä, 2006; Klein et al., 2011) with some studies suggesting that the relationship between depression and extraversion is moderated by level of neuroticism (Kendler et al., 2006b) as well as gender (VanDyke and Gore, 2012).

In addition to trait factors, increased risk of MDD has also been associated with state-related factors such as severity of depressive symptoms and subclinical symptoms of depression (Judd et al., 1997), poor sleep quality, insomnia and daytime sleepiness (Alvaro et al., 2013; Baglioni et al., 2011; Eaton et al., 1995; Franzen et al., 2010; Lustberg and Reynolds, 2000) and anger (Besharat et al., 2013; Fava et al., 1993; Judd et al., 2013) with emerging evidence

suggesting gender differences in the relation of depression to some, but not all, of these factors (Gillespie et al., 2012).

The current study examined the relation of the CORT/CRP ratio to psychological and behavioral traits and states associated with vulnerability to depression. As briefly described in the preceding sections, there is sufficient evidence to suggest gender-differences in: (1) HPA axis function, (2) inflammatory processes, and (3) psychological traits and states associated with increased risk of depression. Thus, the current study tested the hypothesis that vulnerability to depression, operationalized by individual differences in trait and state factors associated with increased risk of MDD, is associated with a loss of normal regulatory controls between the HPA axis and inflammatory system in a gender dependent manner. In this study, the CORT/CRP ratio was used to assess regulatory feedback between the HPA axis and inflammation.

METHODS

Participants

Participants were 213 healthy, un-medicated men and women between the ages of 18 and 65. Subjects were enrolled in a study of the relation of inflammatory biomarkers to psychosocial factors associated with increased risk of cardiovascular disease (Suarez, 2004). Participants were recruited from the general community via advertisements placed in newspapers, online websites, and fliers distributed throughout the community. Interested individuals were screened using a self-report health questionnaire with potential subjects participating in a more in-depth interview. Individuals were excluded if they were smokers, reported a history or current diagnosis of psychiatric conditions, had been treated with antidepressants, or had any chronic medical conditions related to inflammation, such as asthma, allergies, arthritis, diabetes, all forms of cancer, and cardiovascular diseases including hypertension. Women were excluded if they reported use of oral contraceptives or hormone replacement during the 6 months prior to screening. Individuals taking medications on a prescribed daily regimen (e.g., low dose aspirin, allergy medications, statins, blood pressure medication) were excluded.

Once scheduled for their laboratory visit, subjects were instructed not to use any prescription medications and over-the-counter medications including low-dose aspirin for two weeks prior to the study visit. Subjects requiring treatment for acute conditions that occurred during the 2-week prior to study visit were rescheduled 2-weeks (or more) after treatment was completed or medication was discontinued by their physician. At the study visit, three 7-ml fasting blood samples were collected at approximately 0845–0915. For premenopausal women, samples were collected during the follicular phase of the menstrual cycle, when ovarian hormones are at their nadir.

The principal investigator (ECS) extensively interviewed participants to verify health status including the presence of acute infections and illnesses, recent injuries, and medical/dental procedures conducted in the prior two weeks. Each subject's temperature was taken orally and subjects were queried on any current physical symptoms. Informed consent was

obtained prior to the study. Subjects were compensated for their participation. The Institutional Review Board of Duke University Health System approved this protocol.

Depression

The Hamilton Depression (HAM-D) scale was used to assess severity of depressive symptoms. The HAM-D was administered following the Structure Interview Guide for the HAM-D (Williams, 1988) by a trained staff member. The scale is composed of 21 items of which the first 17 are used to calculate the score (Brown et al., 1995; Rehm and O'Hara, 1985). Higher scores represent greater severity of depressive symptoms.

Anger

To assess anger, we used the anger subscale of the Buss-Perry Aggression Questionnaire (BPAQ) (Buss and Perry, 1992). The BPAQ anger subscale consists of 8 items (e.g., "Some of my friends think I'm a hothead") answered on a Likert scale. Nine-week test-retest correlation for the anger subscale shows relative stability ($r = 0.72$) with a similar magnitude of internal consistency ($\alpha = 0.83$).

Sleep Quality

We used the Pittsburgh Sleep Quality Index (PSQI) to assess overall sleep quality and aspects of poor sleep (Buysse et al., 1989). The PSQI is a well-established and validated self-report scale used to assess overall subjective sleep quality and sleep-related symptoms over the previous 1-month period. The 19 items yield seven component scores that reflect the frequency of sleep problems in the areas of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The sum of the seven components scores yields a global score that ranges from 0 to 21 with poor sleep quality associated with higher scores (Buysse et al., 1989). A PSQI global score of five and above has a diagnostic sensitivity of 89.6% and specificity of 86.5% in differentiating "poor sleepers" from "good sleepers").

Personality Measures

We used the NEO-Personality Inventory to assess the five domains (e.g., traits) of normal personality: neuroticism, extraversion, openness, conscientiousness, and agreeableness (Costa and McCrae, 1992). Evidence suggests that extraversion and neuroticism, alone or in combination with conscientiousness, are associated with a reduced or increased risk, respectively, of future depressive episodes (Jylhä and Isometsä, 2006).

Blood Assays

Blood samples were collected between 0845 and 0915 following an overnight fast. Samples were centrifuged and stored frozen at -80°C until assayed. Two blood samples, collected within a 30-min period, were assayed for morning levels of plasma CORT using a commercially available radioimmunoassay kit (Radioassay System Laboratories, Carson City, CA). The resulting two values were averaged and the mean CORT level was used in the reported analysis. The intra- and inter-assay coefficients of the assay were 5.3% and 8.4%, respectively. CRP was assayed in duplicate with an ultrasensitive, enzyme-linked,

immunometric latex-enhanced assay (Diagnostic Products Corporation, Los Angeles, CA) using purified protein and polyclonal anti-CRP antibodies (Diagnostic Products Corporation, Los Angeles, CA). This system has a lower detection threshold of < 0.10 mg/L with coefficients of variation ranging from 6.6% to 9.3%.

Glucocorticoid receptor sensitivity

The effect of GC on leukocyte number has been well characterized, with increasing concentrations of CORT associated with increasing numbers of circulating neutrophils and decreasing numbers of lymphocytes, monocytes, eosinophils, and basophils. It has been suggested that the association of CORT concentration to leukocyte trafficking, and specifically the ratios of neutrophils-to-lymphocytes (N/L) and neutrophils-to-monocytes (N/M), can be used as an indirect measure of GR sensitivity with a lack of an association between CORT and leukocyte ratios suggestive of GR resistance (Blacksher, 2012; Cole et al., 2007). Following the procedures described in Cohen et al. (2012), we examined the relationship between CORT and log-transformed N/M ratio as an indirect measure of GR sensitivity. Unlike the N/L ratio, the N/M ratio appears not to be associated with potential confounders such as BMI while being more strongly associated with circulating CORT levels (Cole et al., 2007).

Statistical Analysis

Data analyses were conducted using SAS software (version 9.3, Research Triangle Park, NC). To derive the mathematical ratio we followed the procedure described by Demir et al (Demir et al., 2006). Mean baseline (unstressed) CORT ($\mu\text{g/dl}$) was divided by hsCRP (mg/L) and the resulting ratio was log-transformed (see Figure 1). and used in all analyses.

Scores on the individual instruments were used as continuous predictor variables. The HAM-D score was log-transformed due to a skewed distribution with all other scores were left untransformed. Tests of the relation of predictor variables to the log-transformed CORT/CRP ratio were conducted using general linear modeling (PROC GLM in SAS) with age, body mass index (BMI), and race as covariates. Estimates of effect size are provided using partial η_p^2 whose value represents the proportion of the total variability attributed to a given predictor. Interpretation of the effect size for values for η_p^2 in multivariate analysis are small ($\eta_p^2 = .01$), medium ($\eta_p^2 = .06$) and large ($\eta_p^2 = .13$). To test gender differences, the gender by psychological scale interaction was included in the initial model. If the two-way interaction proved to be significant, we probed the interaction by conducting analysis centering all appropriate variables and examining the relation of psychological scale score to log-transformed CORT/CRP for men and women separately. If the gender by vulnerability interaction was not significant, the interaction was removed and we tested the main effect with gender as an additional covariate. Primary analyses were conducted using NEO neuroticism, extraversion, and anxiety, HAMD severity of depressive symptoms, Buss-Perry anger and PSQI overall sleep quality. Six predictor variables (HAMD depression, NEO neuroticism, extraversion and anxiety, PSQI total score and anger) were considered the primary variables of interests. The step-down method of Holm's sequentially rejective multiple test was used to adjust the p-value for multiple testing. The Holm procedure requires first ranking resulting p-values and then using the following adjusted p-values for

six comparisons (.008, .01, .0125, .0167, .025, .05). Additional analyses are considered exploratory. For brevity, we used the term CORT/CRP ratio to refer to the log-transformed CORT/CRP ratio.

RESULTS

Sample Characteristics

The sample was multi-ethnic and was composed of 116 men and 97 women aged 18–65 years. Table 1 presents the means (SD) and medians (interquartile range) of measured variables by gender and tests of gender differences. While women scored significantly higher on the NEO agreeableness and conscientiousness scales, the differences between men and women were relatively small in comparison to gender-specific variances. Due to poor sample quality, three men and five women had missing CORT values; thus, analyses were conducted on 205 subjects. There were no significant gender differences in CORT and hsCRP levels.

To illustrate the contribution of each component of the CORT/CRP ratio to the ratio value, we examined group means for the upper and lower quartiles of the CORT/CRP distribution (top 25% of ratio scores: 29 men, 26 women; lower 25% of ratio scores: 30 men, 29 women). As expected, we observed significant differences between the upper and lower quartiles of the CORT/CRP ratio for CORT ($F(1,113) = 13.89$, $p < .0003$, $\eta^2 = .118$) and hsCRP ($F(1,113) = 565.8$, $p < .0001$, $\eta^2 = .843$). As illustrated in Figure 2, subjects with higher CORT/CRP ratios exhibited significantly higher CORT levels and lower CRP levels. The opposite was true for those in the bottom quartile of the distribution, who showed significantly higher CRP levels and lower CORT levels.

Men and women did not differ on CORT/CRP ratio ($t = -0.07$; men: 32.4 ± 3.7 vs. women: 36.5 ± 4.2), and the overall mean for the sample was similar in magnitude to the mean CORT/CRP ratio previously reported by Kreiner and Galbo (2012) for healthy controls. Univariate analysis revealed that the CORT/CRP ratio was negatively associated with age ($r = -0.34$, $p < .0001$) and BMI ($r = -0.48$, $p < .0001$), suggesting that increasing age and BMI were associated with a shift toward a more pronounced inflammatory state coupled with insufficient CORT release. Such associations are consistent with previous findings of age-related decreases in HPA axis activity (Kudielka and Kirschbaum, 2003) and increases in inflammation (Youm et al., 2013). We found no evidence for gender differences in the relation of age and BMI to the CORT/CRP ratio. In analysis adjusting for age and BMI, we failed to detect significant gender differences in hsCRP ($F(1, 199) = 0.03$, $p = .77$) and CORT ($F(1, 199) = 0.17$, $p = .48$).^{footnote 1}

Additional univariate analysis revealed that CORT/CRP ratio was not associated with education ($r = -0.08$, ns), race ($r = -0.03$, ns) and leisure time physical activity ($r = 0.09$, ns). Waist and hip measurements were collected on a subgroup of subjects ($n = 85$). Regression models controlling for age and gender revealed that increasing waist circumference ($\beta = -0.111$, $t(86) = -5.00$, $p < .0001$), hip circumference ($\beta = -0.114$, $t(86) = -4.76$, $p < .0001$), and waist-to-hip ratio ($\beta = -5.27$, $t(86) = -2.83$, $p = .006$) were associated

with lower CORT/CRP ratios. Gender did not moderate any of these associations. A table of zero-order correlations among variables of interest is provided in the supplement.

Although the two blood samples used to assess CORT were collected within a 30-min period (0845–0915), we nevertheless examined the relation of log-transformed CORT to time when samples were collected. Results revealed that mean CORT levels were not associated with time of collection for the total sample ($r = -0.07$, ns), for men ($r = -0.10$, ns), or for women ($r = -0.01$, ns). Moreover, the two CORT samples showed a strong association ($r = 0.95$, $p < .0001$).

Of the 206 subjects, 13.2% had hsCRP levels of 3.00 mg/L or above but no subjects had CRP above 10.0 mg/L, most likely the results of our stringent health screening and injury assessment. According to *a priori* published criteria for risk stratification (Ridker and Ridker, 2010), levels at or above 3.0 mg/L are associated with an increased risk of future heart disease and stroke (Ridker et al., 2000; Rifai and Ridker, 2003).

Depression

Regression analysis with log-transformed ratio of CORT/CRP as the dependent variable revealed a significant gender by log-transformed HAM-D interaction ($F(1, 191) = 6.47$, $p = .010$, adjusted Holm's $p = .0125$, $\eta_p^2 = .04$). For women, increasing severity of depressive symptoms ($\beta = -0.327$, $t(87) = -2.22$, $p = .03$) was associated with a shift from homeostasis (moderate CORT/CRP) toward a pronounced inflammatory state coupled with an insufficient release of CORT resulting in lower CORT/CRP values. For men, this association was not significant ($\beta = 0.135$, $t(99) = 1.08$, ns) although increases in symptom severity were associated with increases in CORT/CRP ratios. No main effect for log-transformed HAM-D was observed in analysis with gender, age, BMI, and race as covariates.

¹The primary dependent variable was the log-transformed ratio of CORT-to-CRP. Nevertheless, we examined the independent relation of log-transformed CORT and hsCRP values to those factors that significantly predicted the CORT/CRP ratio. For CORT analyses, none of the gender by vulnerability factor interactions was significant or approached significance. However, we did find significant main effects for HAM-D ($b = -0.07$, $t(191) = -2.27$, $p = .025$, adjusted Holm's $p = .01$, $\eta_p^2 = .02$) and extraversion ($b = 0.004$, $t(191) = 3.02$, $p = .003$, adjusted Holm's $p = .025$, $\eta_p^2 = .05$) for CORT. For CRP, no other main effects were significant. In contrast, log-transformed hsCRP was associated with HAM-D ($F(1, 191) = 6.37$, $p = .01$, adjusted Holm's $p = .01$, $\eta_p^2 = .029$), neuroticism ($F(1, 191) = 3.13$, $p = .08$, adjusted Holm's $p = .025$, $\eta_p^2 = .014$), extraversion ($F(1, 191) = 7.90$, $p = .006$, adjusted Holm's $p = .008$, $\eta_p^2 = .04$), anxiety ($F(1, 192) = 6.52$, $p = .010$, adjusted Holm's $p = .0125$, $\eta_p^2 = .03$), and sleep quality ($F(1, 191) = 5.90$, $p = .02$, adjusted Holm's $p = .0167$, $\eta_p^2 = .04$) in a gender specific manner. Inspection of regression coefficients revealed that higher CRP was associated with increased vulnerability to depression and current depressive symptoms in women, results that are consistent with the observations by Azar et al. (2012) in apparently healthy men and women. For men, most of the aforementioned associations were non-significant, with the exception of HAM-D and PSQI total, for which decreasing CRP levels were associated with increasing severity of depressive symptoms and decreasing sleep quality. Even in the absence of significant associations between CORT and vulnerability factors, the CORT/CRP remains a significant correlate.

Given the above findings, we examined whether gender-specific associations between CRP and vulnerability factors drove the primary findings using the log-transformed ratio of CORT-to-CRP. To test this assumption, we conducted a series of regression analysis with psychological factors as the dependent measures and examined the effect of the CORT/CRP ratio by sex interaction (along with the main effects) with age, race, and log-transformed hsCRP (and CORT) as covariates. If the gender-specific effects of the CORT/CRP significantly persists, the findings would suggest that the relationship between vulnerability scores and the CORT/CRP ratio is above and beyond any relationship vulnerability scores have with hsCRP. Without exception, the inclusion of hsCRP (and CORT) as a covariate failed to alter our primary findings: (a) HAM-D (without adjusting for hsCRP: $F(1, 191) = 4.06$, $p = .045$, $\eta_p^2 = .02$; adjusting for hsCRP: $F(1, 190) = 4.24$, $p = .059$, $\eta_p^2 = .02$); (b) neuroticism (without adjusting for hsCRP: $F(1, 193) = 3.15$, $p = .08$, $\eta_p^2 = .01$; adjusting for hsCRP: $F(1, 192) = 3.11$, $p = .08$, $\eta_p^2 = .01$); (c) extraversion (without adjusting for hsCRP: $F(1, 192) = 8.55$, $p = .004$, $\eta_p^2 = .04$; adjusting for hsCRP: $F(1, 191) = 7.64$, $p = .006$, $\eta_p^2 = .04$); (d) anxiety (without adjusting for hsCRP: $F(1, 192) = 6.18$, $p = .014$, $\eta_p^2 = .03$; adjusting for hsCRP: $F(1, 191) = 6.27$, $p = .013$, $\eta_p^2 = .03$); and (e) sleep quality ($F(1, 192) = 10.68$, $p = .002$, $\eta_p^2 = .05$; adjusting for hsCRP: $F(1, 191) = 10.63$, $p = .001$, $\eta_p^2 = .05$). The results failed to support the notion that the relation of hsCRP to vulnerability factors drove the relationship between CORT/CRP ratio and risk factors.

Anger

The anger by gender interaction was not significant; therefore, we examined the main effect of anger on CORT/CRP with gender as a covariate. Results indicated that increasing anger ($\beta = -0.029$, $t(200) = -2.08$, $p = .036$, adjusted Holm's $p = .025$) was associated with decreasing CORT/CRP ratio.

Subjective Quality of Sleep

The relation of PSQI total score to the CORT/CRP ratio was moderated by gender ($F(1, 193) = 8.38$, $p = .005$, adjusted Holm $p = .008$, $\eta_p^2 = .04$). Decreasing ratio of CORT/CRP in women was associated with increasing PSQI total score ($\beta = -0.108$, $t(88) = -2.27$, $p = .026$). Increasing scores are indicative of decreasing sleep quality. For men, increasing CORT/CRP ratios were associated with poor sleep quality, but the results were marginally significant ($\beta = 0.066$, $t(111) = 1.79$, $p = .07$). A main effect only model revealed no significant main effect for PSQI total score on CORT/CRP ratio when adjusting for gender, BMI, age, and race.

Personality Traits

We examined the independent relation of the CORT/CRP ratio to individual differences for normal personality traits of neuroticism and extraversion, the two domains of the NEO-PI that have been previously associated with an increased risk of depression. Given the relation of anxiety to increased risk of depression, we also examined its relation to CORT/CRP. Gender moderated the relation of extraversion to CORT/CRP ratio ($F(1, 192) = 7.40$, $p = .007$, adjusted Holm $p = .0167$, $\eta_p^2 = .04$). For women, decreasing scores on the extraversion scale ($\beta = 0.021$, $t(88) = 3.47$, $p = .0008$) were associated with decreasing ratio values of the CORT/CRP ratio. Extraversion was not associated with the CORT/CRP ratio in men ($\beta = -0.0002$, $t(111) = -0.02$, ns). There was also a trend for gender to moderate the relation of CORT/CRP ratio to neuroticism ($F(1, 193) = 3.71$, $p = .056$, adjusted Holm $p = .05$, $\eta_p^2 = .02$). Probing of the interaction revealed that decreasing CORT/CRP ratios were associated with increasing scores on the neuroticism ($\beta = -0.009$, $t(88) = -1.96$, $p = .053$) in women with no association observed in men ($\beta = 0.003$, $t(111) = 0.09$, ns). We failed to find a significant main effect for neuroticism but did observe a significant main effect for extraversion ($\beta = 0.10$, $t(199)$, $p = .01$) when gender was used as a covariate.

The anxiety by gender interaction was significant ($F(1, 193) = 8.87$, $p < .004$, adjusted Holm $p = .01$, $\eta_p^2 = .04$). The anxiety subscale of the NEO-Personality Inventory measures levels of free-floating anxiety. For men, increasing scores on anxiety ($\beta = 0.046$, $t(111) = 2.49$, $p = .0143$) were associated with increasing CORT/CRP ratios (see Figure 4). For women, higher anxiety scores ($\beta = -0.038$, $t(88) = -1.87$, $p = .065$) were associated with decreasing CORT/CRP ratio. When gender was entered as a covariate, we failed to find a significant main effect for anxiety.

Exploratory Analyses

Components of PSQI—Given the significant findings with the total score on the PSQI, we conducted exploratory analyses to examine the independent relation of each component

of the PSQI to the CORT/CRP ratio. The CORT/CRP ratio was significantly associated with greater frequency of sleep disturbance ($F(2, 191) = 3.65, p = .028, \eta_p^2 = .04$) and daytime dysfunction ($F(2, 191) = 4.37, p = .014, \eta_p^2 = .04$) in a gender dependent manner. Higher scores on sleep disturbance are indicative of an inability to breath comfortably, coughing or snoring loudly, feeling too hot or too cold, having bad dreams, pain, and waking up in the middle of the night. For daytime dysfunction, higher scores represent problems staying awake while engaging in daily life activities and problems keeping up enough enthusiasm to get things done. For women, increasing severity of sleep disturbance ($\beta = -0.455, t(88) = -1.81, p = .074$) was associated with a shift toward lower CORT/CRP ratios. For men, sleep disturbance ($\beta = 0.246, t(111) = 0.97, ns$) was not associated with CORT/CRP ratio. Increasing severity of daytime dysfunction ($\beta = 0.389, t(111) = 2.49, p = .014$), however, was significantly associated with increasing CORT/CRP in men. For women, the association was negative ($\beta = -0.367, t(88) = -2.14, p = .035$). Tests of main effects failed to show significant relationships between CORT/CRP and scores on sleep disturbance and daytime dysfunction as well as other PSQI component scores (subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency).

Personality Facets of the NEO-PI—Given the observed gender-differences in the relation of extraversion and neuroticism to CORT/CRP ratio, we conducted exploratory analysis to examine relation of individual facets of extraversion and neuroticism to CORT/CRP ratio as a function of gender. For extraversion, only the assertiveness facet by gender interaction was significant ($F(1, 190) = 3.90, p = .049, \eta_p^2 = .02$) with lower CORT/CRP ratios associated with lower assertiveness ($\beta = 0.0629, t(89) = 2.81, p = .006$) for women but not men ($\beta = .009, t(111) = 0.12, ns$). Higher scores on the assertiveness subscale are suggestive of greater forcefulness of expression and social ascendancy. Entering gender as a covariate, we observed a significant main effect for assertiveness ($\beta = 0.036, t(201) = 2.43, p = .016$), an effect most likely driven by the strength of the association found in women.

We also examined whether the interaction between extraversion and neuroticism predicted CORT/CRP and if this relationship was moderated by gender. Neither the three-way interaction between neuroticism, extraversion, and gender ($F(1, 185) = 1.23, ns$) nor the two-way neuroticism by extraversion interaction ($F(1, 188) = 1.16, ns$) were significant.

The neutrophil/monocyte ratio as an index of GC receptor responsiveness: test of gender differences and moderation

We explored whether gender-specific associations were due, in part, to gender differences in GR downregulation. Results of regression analysis of log-transformed N/M with age and BMI as covariates revealed a significant CORT by gender interaction ($F(1, 190) = 4.16, p = .043, \eta_p^2 = .02$). Gender-specific analysis centering all covariates revealed that for men, CORT ($\beta = 0.20, t(108) = 2.05, p = .04$) was positively associated with the log-transformed N/M ratio, suggesting normal GCR sensitivity. For women, however, CORT ($\beta = -0.09, t(90) = -0.82, ns$) did not predict the N/M ratio, suggesting down-regulation of GR. In light of these findings, we examined whether the CORT/CRP ratio predicted the N/M ratio.

Results indicated that log-transformed N/M ratio was not associated with the CORT/CRP ratio in men, and in the total sample suggesting independence between these two indices.

We examined whether GR downregulation moderated the relation of vulnerability factors to the CORT/CRP ratio in women. Regression analyses were conducted with log-transformed N/M ratio, age, BMI, and race as covariates and the primary vulnerability factors as independent variables. Inclusion of the log N/M ratio did not alter the associations between vulnerability factors and the CORT/CRP ratio (results not presented), suggesting that the observed associations in women were independent of GR down-regulation.

DISCUSSION

Inflammation and HPA axis dysregulation have been independently linked to vulnerability factors associated not only with an increase the risk of depression but also progression, treatment response and remission of MDD. Although these two systems are intrinsically inter-related and their activities controlled through inhibitory feedback signals, few studies have employed an integrated systems approach with no studies examining potential gender-differences. By evaluating the status of the regulatory feedback loop, we identified two distinct and unique patterns of feedback dysregulation that are in line with the individual role of the HPA axis and inflammation in the etiology of depression. Although the CORT/CRP ratio has been used previously in studies of patients with rheumatologic conditions (Demir et al., 2006; Kreiner and Galbo, 2012), this study is the first to use the CORT/CRP ratio to examine whether factors associated with an increased risk of MDD are associated with patterns of feedback dysregulation and whether these associations differed in men and women.

Using the Holm's sequentially rejective multiple test procedure (Holm, 1979), we observed significant gender-specific relationships between vulnerability factors and the CORT/CRP ratio that were independent of potential confounders. For women, increasing severity of depressive symptoms, diminishing sleep quality as well as higher neuroticism and lower extraversion, were associated with the loss of normal regulatory influences characterized by greater inflammation relative to an insufficient release of CORT. For men, however, the loss of normal regulatory feedback reflected an imbalance characterized by an enhanced release of CORT coupled with attenuated inflammation, a pattern that was associated with increasing trait anxiety, diminishing quality of sleep, and increasing frequency of daytime dysfunction. Although previous studies have reported gender differences in the relation of the individual components of the CORT/CRP ratio to MDD, severity of depressive symptoms, and vulnerability factors (e.g., Maes et al., 1988; Shivpuri et al., 2011; Zobel et al., 2004), to our knowledge these are the first data to suggest gender specificity in the relation of vulnerability factors to distinct and gender-specific uncoupling of neuro-immune feedback mechanisms.

The current study extends the use of the CORT/CRP ratio to research in behavioral sciences and the area of mood disorders. In previous studies, researchers used the CORT/CRP ratio to characterize not only the degree of dysregulation between the HPA axis and inflammatory processes in untreated patients with PMR but also treatment responses to antiinflammatory

agents (Demir et al., 2006; Ennis et al., 1993; Straub and Cutolo, 2006). Given the target patient population of those studies, the magnitude of the reported ratios was generally restricted to the lower half of the CORT/CRP distribution noted in this study. In the current study, calculated values ranged from low to high with higher values suggestive of excessive release of CORT relative to attenuated levels of CRP, an imbalance not likely to occur in patients with PMR. The use of the CORT/CRP ratio allowed us not only to quantify the degree of dysregulation but also to characterize the pattern of dysregulation within the framework of normal homeostatic controls. Thus, the CORT/CRP ratio is a metric whereby circulating levels are interpreted in relation to each other and not in isolation. This allowed for conclusion to be made about the regulatory demands necessary to maintain homeostasis, an approach recommended by Capitanio et al. (2011).

In addition to gender differences in the patterns of dysregulation, we also noted fewer significant associations between CORT/CRP ratio and vulnerability factors in men. Prior evidence suggests that the risk of depression is more strongly associated with personality factors in women than in men (Goodwin and Gotlib, 2004; Kendler and Gardner, 2014; Oquendo et al., 2013) with adverse acute stressors, alone or in combination with psychobiological factors, having a greater impact on risk of depression in adolescent boys relative to girls (Uddin et al., 2011; Uddin et al., 2010) and in men relative to women (Kendler and Gardner, 2014). In this study, anxiety, poor sleep quality and greater daytime disturbance were significantly correlated with the increasing CORT/CRP ratio values in men. In line with our findings, longitudinal studies have shown that insomnia and anxiety significantly predict the onset of depression in men (Chang et al., 1997; Paffenbarger et al., 1994) with poor sleep not predicting depression in women (Gillespie et al., 2012). In one longitudinal study, the increased risk of depression in young men with insomnia was shown to persist up to a 30-year period follow-up period (Chang et al., 1997). Although it is well-recognized that women are at twice the risk for depression than men, this is not the case when gender comparisons are made among those with generalized anxiety disorder where the risk of depression is significantly greater in men (Hettema et al., 2006). In one longitudinal study of adolescents, history of anxiety increased the risk of depression for boys but not for girls (Gallerani et al., 2010). The effects of anxiety are such that controlling for prior anxiety reduced by more than 50% the coefficient between gender and major depression (Breslau et al., 1996). The effects of anxiety may also go beyond risk of depression, with one study showing that increased anxiety among adults diagnosed with bipolar depression was associated with a decreased gray matter volume in the ventral prefrontal cortex but only in men (Almeida et al., 2009). In light of such evidence, the fact that only anxiety and sleep-related factors emerged as significant correlates of the CORT/CRP ratio in men is consistent with the vulnerability models of depression for men.

That vulnerability factors were associated with distinct patterns of dysregulation in men and women led us to explore whether such gender differences could be due to GR downregulation (Bourke et al., 2012). As part of the negative feedback loop, the GR plays an important part in normalizing HPA axis output (Marques et al., 2009). If GR sensitivity differs in men and women, such differences may account for our gender specific associations. Our findings suggest that, at basal conditions, GR downregulation was apparent in women but not in men, differences that are consistent with previous findings

suggesting that stress promotes GR downregulation in healthy women but increases GR sensitivity in men (Rohleder et al., 2001). Although we observed GR downregulation in women, we found no evidence to suggest that GR downregulation played a role in observed gender specific associations. While encouraging, our findings require replication using a full-scale receptor study of GR function.

The novel nature of our findings led us to review published data to determine whether our findings generalize to patient populations. In a published study of women with and without a clinical diagnosis of MDD, Miller et al. (2005) assessed both CORT and hsCRP levels prior to and in response to a laboratory stressor. Review of the published tabulated means suggests that, if calculated, the CORT/CRP ratio at baseline would be lower for depressed women relative to healthy controls. Moreover, for depressed women, it appears that the laboratory stressor evoked a mean increase in hsCRP level with a concomitant mean decrease in CORT, response trajectories suggestive of further reduction in the values of the CORT/CRP ratio. In contrast, for non-depressed women, the stressor evoked a slight increase in CORT that was coupled with a slight increase in hsCRP, a pattern of increases likely to yield similar ratio values at baseline and post-stress. Based on our inspection of tabulated means, women with MDD, relative to healthy controls, appear to have lower CORT/CRP, an observation in line with the current findings. What is intriguing is the possibility that acute stress leads to further loss of regulatory feedback in depressed women whereas for non-depressed women, normal homeostatic controls remained intact during and following stress. That the current findings generalize to women with MDD is highly encouraging. That stress may evoke further dysregulation of homeostasis in women with MDD but not healthy controls calls for additional studies and re-analysis of existing data. If demonstrated, such observations would further the argument that depression is reflective of both individual differences and responses to life stressors.

The only vulnerability factor associated with CORT/CRP and not moderated by gender was anger. Although irritability is no longer a diagnostic symptom of MDD in adults, studies have shown that among adults with MDD, approximately 50% report increased irritability (Fava et al., 2010; Judd et al., 2013). Increased irritability/anger in patients with MDD has been associated with anxiety, early age of onset, and lifetime persistence (Fava et al., 2010), observations recently replicated and extended by Judd et al (2013). Judd et al. (2013) also reported that increases in irritability/anger were associated with greater severity of depressive symptoms, a more chronic and severe long-term course of illness, and higher rates of anxiety disorders, but not with increased suicidal ideation or behaviors. The current observations add to the growing body of evidence suggesting that inflammation is associated with anger and related behaviors (Suarez et al., 2002; Zalcman and Siegel, 2006). It is interesting to note that patients undergoing cytokine treatment with interferon- γ or IL-2 report increases in anger (Dan et al., 2007) and most notably among those with a polymorphism in the promoter region of TNF- α (Kraus et al., 2003), findings that suggest that inflammation may precede anger. Interestingly, animal studies have shown that mice with the combined deletion of TNF receptors show no aggressive behaviors and increased non-aggressive exploration of an intruder mouse (Patel et al., 2010). Whether stress-induced arousal of anger furthers the dysregulation of the neuro-immune interface is a provocative possibility.

The current study has several limitations. First, the cross-sectional design did not allow us to determine cause and effect. Whether vulnerability factors precede dysregulation of regulatory pathways or whether loss of regulatory controls between the HPA axis and inflammatory processes that precedes the onset of depression in at-risk individuals remains to be determined. Secondly, although blood samples were collected during a narrow timeframe, unstressed CORT levels were measured only twice in the morning after an overnight fast. While it is encouraging that our findings are consistent with other studies that have assessed unstressed levels of CORT more frequently (Miller et al., 2005), it is not known to what extent, if any, our sampling rate influenced ratio values and overall findings. In contrast, hsCRP has been reported to be relatively stable, with most studies evaluating concentration at a single time point (Shemesh et al., 2009). Thirdly, blood samples were collected during the follicular phase of the menstrual cycle, when ovarian hormones are at their nadir and CRP is at levels that are relatively lower than those reported for luteal and mid-cycle (Jilma et al., 1997). Whether our findings generalize across the menstrual cycle remains to be determined. Lastly, our sample was relatively young with an average age of approximately 30 years. Given the likelihood that gonadal hormones play a significant role in the dysregulation of the neuro-immune interface, our observations may not generalize to older men and post-menopausal women. In other words, gender differences observed in this study may not emerge when comparisons are made between men over 50 years of age and post-menopausal women. In our sample, age was significantly associated with lower CORT/CRP thus it may be that the pattern of greater inflammation coupled with an insufficient CORT release is similar for depressed older men and women, a speculation already reported among depressed adults over the age of 55 years (Bremner et al., 2008; Taylor et al., 2006).

With the exception of extraversion and anger, we failed to find any significant main effects when gender was used as a covariate. Such findings underscore the need for careful consideration of how gender is treated in statistical modeling and more so for conditions where gender differences in prevalence are well-established, such as MDD (Weinberger et al., 2010). In view of the differences in the results when gender was used as a moderator and as a covariate, it is reasonable to raise the question whether the lack of significant associations in prior studies was due, in part, to the use of gender as a covariate. In light of our findings, it is recommended that future studies directly test the moderating effect of gender before using gender as a covariate.

The wealth of evidence for gender differences in the prevalence of MDD is sufficient to justify examining gender differences in pathophysiological mechanisms implicated in susceptibility, onset, and progression of depression (Owens et al., 2014; Piccinelli and Wilkinson, 2000), as well as treatment responses (Weinberger et al., 2010). That gender differences in brain morphology, hard wiring, and function outcomes have been reported (Cosgrove et al., 2007) provide additional support for the development of gender-specific models of disease etiology—in this case, clinical depression. Development of comparative gender-specific models does not pose insurmountable scientific obstacles. On the contrary, such approaches have the potential to provide greater insight for understanding gender differences in the etiology of MDD and underlying pathophysiology (Kendler et al., 2002, 2006a). Interestingly, some have suggested that researcher explore separate models for

biological substrates of depressive subtypes (Gold and Chrousos, 2013); an approach that has already led to uncovering distinct patterns of regulatory activity between the HPA axis and inflammatory processes in atypical depression versus melancholia (Karlovič et al., 2012; Lamers et al., 2013). Not surprisingly, gender differences in the prevalence of these two depressive subtypes have been reported, with more men diagnosed with melancholia (Hildebrandt et al., 2003) and a threefold higher prevalence of atypical depression in women (Halbreich and Kahn, 2007).

In summary, vulnerability factors associated with an increased risk of depression are associated with gender-specific and distinct patterns of dysregulation of normal regulatory influences between the HPA axis and inflammatory processes. For women, the loss of regulatory feedback is characterized by enhanced inflammation accompanied by an insufficient release of CORT whereas for men, the pattern is one of greater release of CORT and attenuated inflammation. These observations were independent of various potentially confounding factors including race, BMI, and age as well as the associations found for the individual component of the ratio (see supplemental material). Two major themes emerged from the current study. First, the current findings underscored the critical nature of examining regulatory pathways beyond evaluation of individual system components in isolation. Secondly, approaches used to understand MDD might benefit from the development of gender-specific models that have the potential to guide the development of prevention strategies and treatments. That underlying pathophysiology associated with increased risk of depression is best framed as patterns of dysregulation stemming from loss of normal regulatory influences is not only promising but also useful given the technology to measure both CORT and CRP at point-of-care. The CORT/CRP ratio may prove to be a reliable biomarker useful in quantifying and synthesizing the regulatory interactions implicated in the etiology of MDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- Alloy, LB.; Kelly, KA.; Mineka, S.; Clements, CM., editors. Comorbidity of anxiety and depressive disorders: A helplessness-hopelessness perspective. Arlington, VA, US: American Psychiatric Association; 1990.
- Almeida JRC, Akkal D, Hassel S, Travis MJ, Banihashemi L, Kerr N, Kupfer DJ, Phillips ML. Reduced gray matter volume in ventral prefrontal cortex but not amygdala in bipolar disorder: Significant effects of gender and trait anxiety. *Psychiatry Research: Neuroimaging*. 2009; 171:54–68.
- Alvaro PK, Roberts RM, Harris JK. A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep*. 2013; 36:1059–1068. [PubMed: 23814343]
- Azar R, Nolan RP, Stewart DE. Listening to the heart-brain talk: persistent depressive symptoms are associated with hsCRP in apparently healthy individuals at high risk for coronary artery disease. *European Journal of Preventive Cardiology*. 2012; 19:857–863. [PubMed: 21729973]
- Baglioni C, Battagliese G, Feige B, Spiegelhalter K, Nissen C, Voderholzer U, Lombardo C, Riemann D. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *J. Affect. Disord*. 2011; 135:10–19. [PubMed: 21300408]

- Barnes PJ, Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. *Journal of Steroid Biochemistry & Molecular Biology*. 2010; 120:76–85. [PubMed: 20188830]
- Besedovsky HO, del Rey A. Immune-Neuro-Endocrine Interactions: Facts and Hypotheses. *Endocr. Rev.* 1996; 17:64–102. [PubMed: 8641224]
- Besharat MA, Nia ME, Faharan H. Anger and major depressive disorder: the role of emotion regulation and anger rumination. *Asian J Psychiatry*. 2013; 6:36–41.
- Bienvenu OJ, Samuels JF, Costa PT, Reti IM, Eaton WW, Nestadt G. Anxiety and depressive disorders and the five-factor model of personality: A higher- and lower-order personality trait investigation in a community sample. *Depress. Anxiety*. 2004; 20:92–97. [PubMed: 15390211]
- Blacksher E. Redistribution and Recognition. *Camb. Q. Healthc. Ethics*. 2012; 21:320–331. [PubMed: 22624535]
- Bonne O, Grillon C, Vythilingam M, Neumeister A, Charney DS. Adaptive and maladaptive psychobiological responses to severe psychological stress: implications for the discovery of novel pharmacotherapy. *Neurosci. Biobehav. Rev.* 2004; 28:65–94. [PubMed: 15036934]
- Bourke CH, Harrell CS, Neigh GN. Stress-induced sex differences: Adaptations mediated by the glucocorticoid receptor. *Horm. Behav.* 2012; 62:210–218. [PubMed: 22426413]
- Bremner MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, Hoogendijk WJ. Inflammatory markers in late-life depression: results from a population-based study. *J. Affect. Disord.* 2008; 106:249–255. [PubMed: 17716746]
- Breslau N, Roth T, Rosenthal L, Adreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiologic study of young adults. *Biol. Psychiatry*. 1996; 39:41–48.
- Bromberger JT, Matthews KA. A longitudinal study of the effects of pessimism, trait anxiety, and life stress on depressive symptoms in middle-aged women. *Psychol. Aging*. 1996; 11:207–213. [PubMed: 8795049]
- Brown C, Shulberg HC, Madonia MJ. Assessing depression in primary care practice with the Beck Depression Inventory and the Hamilton Rating Scale for Depression. *Psychological Assessment*. 1995; 7:59–65.
- Buss AH, Perry M. The aggression questionnaire. *J. Pers. Soc. Psychol.* 1992; 63:452–459. [PubMed: 1403624]
- Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989; 28:193–213. [PubMed: 2748771]
- Capitanio JP, Mendoza SP, Cole SW. Nervous temperament in infant monkeys is associated with reduced sensitivity of leukocytes to cortisol's influence on trafficking. *Brain, Behavior, and Immunity*. 2011; 25:151–159.
- Capuron L, Poitou C, Machaux-Tholliez D, Frochot V, Bouillot J-L, Basdevant A, Layé S, Clément K. Relationship between adiposity, emotional status and eating behaviour in obese women: role of inflammation. *Psychol. Med.* 2011; 41:1517–1528. [PubMed: 20961476]
- Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression: The Johns Hopkins Precursors Study. *Am. J. Epidemiol.* 1997; 146:105–114. [PubMed: 9230772]
- Chioqueta AP, Stiles TC. Personality traits and the development of depression, hopelessness, and suicide ideation. *Personality and Individual Differences*. 2005; 38:1283–1291.
- Cohen, S.; Janicki-Deverts, D.; Doyle, WJ.; Miller, GE.; Frank, E.; Rabin, BS.; Turner, RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk; Proceedings of the National Academy of Sciences; 2012. p. 5995-5999.
- Cole S, Hawkey L, Arevalo J, Sung C, Rose R, Cacioppo J. Social regulation of gene expression in human leukocytes. *Genome Biology*. 2007; 8:R189. [PubMed: 17854483]
- Cosgrove KP, Mazure CM, Staley JK. Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biol. Psychiatry*. 2007; 62:847–855. [PubMed: 17544382]
- Costa PT, McCrae RR. Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychological Assessment*. 1992; 4:5–13.

- Dan AA, Crone C, Wise TN, Martin LM, Ramsey L, Magee S, Sjogren R, Ong JP, Younossi ZM. Anger Experiences Among Hepatitis C Patients: Relationship to Depressive Symptoms and Health-Related Quality of Life. *Psychosomatics*. 2007; 48:223–229. [PubMed: 17478591]
- Demir H, Tanriverdi F, Ozogul N, Calis M, Kirnap M, Durak A, Kelestimur F. Evaluation of the hypothalamic-pituitary-adrenal axis in untreated patients with polymyalgia rheumatica and healthy controls. *Scand. J. Rheumatol*. 2006; 35:217–223. [PubMed: 16766369]
- Eaton WW, Badawi M, Melton B. Prodromes and precursors: Epidemiologic data for primary prevention of disorders with slow onset. *The American Journal of Psychiatry*. 1995; 152:967–972. [PubMed: 7793466]
- Ennis JH, LeClair JK, Wadas L, Patterson C. Polymyalgia rheumatica presenting as depression: the role of the history and physical examination in psychiatric assessment. *Jefferson J Psychiatry*. 1993; 11:29–33.
- Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. *Mol. Psychiatry*. 2010; 15:856–867. [PubMed: 19274052]
- Fava M, Rosenbaum J, Pava J, McCarthy M, Steingard R, Bouffides E. Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *Am J Psychiatry*. 1993; 150:1158–1163. [PubMed: 7848377]
- Feinberg ME, Jones DE, Granger DA, Bontempo DE. Anxiety and chronic couple relationship stress moderate adrenocortical response to couple interaction in expectant parents. *Br. J. Psychol.*, n/a-n/a. 2012
- Franzen PL, Buysse DJ, Rabinovitz M, Pollock BG, Lotrich FE. Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment. *Psychiatry Research*. 2010; 177:240–245. [PubMed: 20381876]
- Gallerani CM, Garber J, Martin NC. The temporal relation between depression and comorbid psychopathology in adolescents at varied risk for depression. *J. Child Psychol. Psychiatry*. 2010; 51:242–249. [PubMed: 19874429]
- Gillespie NA, Gehrman P, Byrne EM, Kendler KS, Heath AC, Martin NG. Modeling the direction of causation between cross-sectional measures of disrupted sleep, anxiety and depression in a sample of male and female Australian twins. *J. Sleep Res*. 2012; 21:675–683. [PubMed: 22738694]
- Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol. Psychiatry*. 2002; 7:254–275. [PubMed: 11920153]
- Gold PW, Chrousos GP. Melancholic and atypical subtypes of depression represent distinct pathophysiological entities: CRH, neural circuits, and the diathesis for anxiety and depression. *Mol. Psychiatry*. 2013; 18:632–634. [PubMed: 23698316]
- Goodwin RD, Gotlib IH. Gender differences in depression: the role of personality factors. *Psychiatry Research*. 2004; 126:135–142. [PubMed: 15123392]
- Grav S, Stordal E, Romild UK, Hellzen O. The relationship among neuroticism, extraversion, and depression in the HUNT Study: in relation to age and gender. *Issues Ment. Health Nurs*. 2012a; 33:777–785. [PubMed: 23146012]
- Grav S, Stordal E, Romild UK, Hellzen O. The relationship among neuroticism, extraversion, and depression in the HUNT study: In relation to age and gender. *Issues Ment. Health Nurs*. 2012b; 33:777–785. [PubMed: 23146012]
- Halbreich U, Kahn LS. Atypical depression, somatic depression and anxious depression in women: Are they gender-preferred phenotypes? *J. Affect. Disord*. 2007; 102:245–258. [PubMed: 17092565]
- Hettema JM, Kuhn JW, Prescott CA, Kendler KS. The impact of generalized anxiety disorder and stressful life events on risk for major depressive episodes. *Psychol. Med*. 2006; 36:789–795. [PubMed: 16515735]
- Hildebrandt MG, Stage KB, Kragh-Soerensen P. Gender differences in severity, symptomatology and distribution of melancholia in major depression. *Psychopathology*. 2003; 36:204–212. [PubMed: 14504455]

- Hirschfeld RM, Klerman GL, Lavori P, Keller MB, Griffith P, Coryell W. Premorbid personality assessments of first onset of major depression. *Arch. Gen. Psychiatry*. 1989; 46:345–350. [PubMed: 2649038]
- Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979; 6:65–70.
- Howren MB, Lamkin DM, Suls J. Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. *Psychosom. Med*. 2009; 71:171–186. [PubMed: 19188531]
- Huang TL, Lee CT. T-helper 1/T-helper 2 cytokine imbalance and clinical phenotypes of acute-phase major depression. *Psychiatry Clin. Neurosci*. 2007; 61:415–420. [PubMed: 17610667]
- Huprich SK. Describing depressive personality analogues and dysthymics on the NEO-Personality Inventory--Revised. *J. Clin. Psychol*. 2000; 56:1521–1534. [PubMed: 11132568]
- Jarcho MR, Slavich GM, Tylova-Stein H, Wolkowitz OM, Burke HM. Dysregulated diurnal Cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. *Biol. Psychol*. 2013; 93:150–158. [PubMed: 23410758]
- Jilma B, Dirnberger E, Loscher I, Rumplmayr A, Hildebrandt J, Eichler H-G, Kapiotis S, Wagner OF. Menstrual cycle-associated changes in blood levels of interleukin-6, α_1 acid glycoprotein, and C-reactive protein. *J Lab Clinical Med*. 1997; 130:69–75. [PubMed: 9242368]
- Johnson EO, Kamilaris TC, Chrousos GP, Gold PW. Mechanisms of stress: a dynamic overview of hormonal and behavioral homeostasis. *Neurosci. Biobehav. Rev*. 1992; 16:115–130. [PubMed: 1630726]
- Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *J. Affect. Disord*. 1997; 45:5–18. [PubMed: 9268771]
- Judd LL, Schettler PJ, Coryell W, Akiskal HS, Fiedorowicz JG. Overt irritability/anger in unipolar major depressive episodes: Past and current characteristics and implications for long-term course. *JAMA Psychiatry*. 2013; 70:1171–1180. [PubMed: 24026579]
- Jylhä P, Isometsä E. The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. *Depress. Anxiety*. 2006; 23:281–289. [PubMed: 16688731]
- Karlovič D, Serretti A, Vrkai N, Martinac M, Marinko D. Serum concentrations of CRP, IL-6, TNF- α and Cortisol in major depressive disorder with melancholic or atypical features. *Psychiatry Research*. 2012; 198:74–80. [PubMed: 22386567]
- Kendler KS, Gardner CO. Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. *Am J Psychiatry*. 2014; 171:426–435. [PubMed: 24525762]
- Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. *Am J Psychiatry*. 2002; 159:1133–1145. [PubMed: 12091191]
- Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in men. *Am J Psychiatry*. 2006a; 163:115–124. [PubMed: 16390898]
- Kendler KS, Gatz M, Gardner CO, Pedersen NL. Personality and major depression: a Swedish longitudinal, population-based twin study. *Arch. Gen. Psychiatry*. 2006b; 63:1113–1120. [PubMed: 17015813]
- Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A longitudinal twin study of personality and major depression in women. *Arch. Gen. Psychiatry*. 1993; 50:853–862. [PubMed: 8215811]
- Kirschbaum C, Prussner JC, Stone AA, Federenko I, Gaab J, Lintz D, Schommer N, Hellhammer DH. Persistent high Cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosom. Med*. 1995; 57:468–474. [PubMed: 8552738]
- Klein DN, Kotov R, Bufferd SJ. Personality and depression: explanatory models and review of the evidence. *Annu Rev Clin Psychol*. 2011; 7:269–295. [PubMed: 21166535]
- Klok MD, Giltay EJ, Van der Does AJW, Geleijnse JM, Antypa N, Penninx B, de Geus EJC, Willemsen G, Boomsma DI, van Leeuwen N, Zitman FG, de Kloet ER, DeRijk RH. A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females. *Transl. Psychiatr*. 2011; 1:8.
- Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *J. Clin. Psychiatry*. 2003; 64:708–714. [PubMed: 12823087]

- Kreiner F, Galbo H. Activity of the neuroendocrine axes in patients with polymyalgia rheumatica before and after TNF-alpha blocking etanercept treatment. *Arthritis Research & Therapy*. 2012; 14:R186. [PubMed: 22894827]
- Kudielka BM, Kirschbaum C. Awakening Cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. *Psychoneuroendocrinology*. 2003; 28:35–47. [PubMed: 12445835]
- Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol. Psychiatry*. 2013; 18:692–699. [PubMed: 23089630]
- Lustberg L, Reynolds CF. Depression and insomnia: questions of cause and effect. *Sleep Medicine Reviews*. 2000; 4:253–262. [PubMed: 12531168]
- Maes M, De Ruyter M, Claes R, Suy E. Sex-related differences in the relationships between self-rated depression and biological markers. *Journal of Affective Disorders*. 1988; 15:119–125. [PubMed: 2975681]
- Marques AH, Silverman MN, Sternberg EM. Glucocorticoid Dysregulations and Their Clinical Correlates. *Ann. N. Y. Acad. Sci.* 2009; 1179:1–18. [PubMed: 19906229]
- Martino M, Rocchi G, Escelsior A, Fornaro M. Immunomodulation Mechanism of Antidepressants: Interactions between Serotonin/Norepinephrine Balance and Th1/Th2 Balance. *Current neuropharmacology*. 2012; 10:97–123. [PubMed: 23204981]
- Mastorakos G, Chrousos G, Weber J. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *Journal of Clinical Endocrinology and Metabolism*. 1993; 77:1690–1694. [PubMed: 8263159]
- McCleery JM, Goodwin GM. High and low neuroticism predict different cortisol responses to the combined dexamethasone-CRH test. *Biol. Psychiatry*. 2001; 49:410–415. [PubMed: 11274652]
- McQuade R, Young AH. Future therapeutic targets in mood disorders: the glucocorticoid receptor. *British J Psychiatry*. 2000; 177:390–395.
- Mendelson J, Glasgow LA. The in Vitro and in Vivo Effects of Cortisol on Interferon Production and Action. *The Journal of Immunology*. 1966; 96:345–352. [PubMed: 4286754]
- Miller GE, Rohleder N, Stetler C, Kirschbaum C. Clinical Depression and Regulation of the Inflammatory Response During Acute Stress. *Psychosom. Med*. 2005; 67:679–687. [PubMed: 16204423]
- Narvaez J, Bernad B, Diaz Torne C, Momplet J, Montpel J, Nolla J, Valverde-Garcia J. Low serum levels of DHEAS in untreated polymyalgia rheumatica/giant cell arteritis. *J. Rheumatol*. 2006; 33:1293–1298. [PubMed: 16783861]
- Nemeroff C, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts C, Loosen P, Vale W. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*. 1984; 226:1342–1344. [PubMed: 6334362]
- Oquendo MA, Turret J, Grunebaum MF, Burke AK, Poh E, Stevenson E, Mann JJ, Galfalvy H. Sex differences in clinical predictors of depression: A prospective study. *J. Affect. Disord*. 2013; 150:1179–1183. [PubMed: 23735213]
- Owens, M.; Herbert, J.; Jones, PB.; Sahakian, BJ.; Wilkinson, PO.; Dunn, VJ.; Croudace, TJ.; Goodyer, IM. Elevated morning cortisol is a stratified population-level biomarker for major depression in boys only with high depressive symptoms; *Proceedings of the National Academy of Sciences*; 2014.
- Pace, TWW.; Raison, CL.; Miller, AH. Neuroendocrine-Immune Interactions: Implications for Health and Behavior. In: Donald, WP.; Arthur, PA.; Susan, EF.; Anne, ME.; Robert, TR., editors. *Hormones, Brain and behavior*. San Diego: Academic Press; 2009. p. 2597-2632.
- Paffenbarger RS, Lee IM, Leung R. Physical activity and personal characteristics associated with depression and suicide in American college men. *Acta Psychiatrica Scandinavica*. 1994; 89:16–22. [PubMed: 8053361]
- Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol. Psychiatry*. 2001; 49:391–404. [PubMed: 11274650]
- Parker G, Wilhelm K, Mitchell P, Austin M-P, Roussos J, Gladstone G. The influence of anxiety as a risk to early onset major depression. *J. Affect. Disord*. 1999; 52:11–17. [PubMed: 10357013]

- Patel A, Siegel A, Zalcman SS. Lack of aggression and anxiolytic-like behavior in TNF receptor (TNF-R1 and TNF-R2) deficient mice. *Brain, Behavior, and Immunity*. 2010; 24:1276–1280.
- Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. *Br. J. Psychiatry*. 2000; 177:486–492.
- Poanta L, Craciun A, Dumitrascu DL. Professional stress and inflammatory markers in physicians. *Rom. J. Intern. Med*. 2010; 48:57–63. [PubMed: 21180242]
- Polk DE, Cohen S, Doyle WJ, Skoner DP, Kirschbaum C. State and trait affect as predictors of salivary cortisol in healthy adults. *Psychoneuroendocrinology*. 2005; 30:261–272. [PubMed: 15511600]
- Portella MJ, Harmer CJ, Flint J, Cowen P, Goodwin GM. Enhanced early morning salivary cortisol in neuroticism. *Am J Psychiatry*. 2005; 162:807–809. [PubMed: 15800161]
- Potvin O, Bergua V, Swendsen J, Meillon C, Tzourio C, Ritchie K, Dartigues JF, Amieva H. Anxiety and 10-year risk of incident and recurrent depressive symptomatology in older adults. *Depress. Anxiety*. 2013; 30:554–563. [PubMed: 23532935]
- Prather AA, Epel ES, Cohen BE, Neylan TC, Whooley MA. Gender differences in the prospective associations of self-reported sleep quality with biomarkers of systemic inflammation and coagulation: Findings from the Heart and Soul Study. *J. Psychiatr. Res*. 2013; 47:1228–1235. [PubMed: 23746737]
- Rehm LP, O'Hara MW. Item characteristics of the hamilton rating scale for depression. *J. Psychiatr. Res*. 1985; 19:31–41. [PubMed: 3989736]
- Ridker PM, Hennekens CH, Buring J, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N. Engl. J. Med*. 2000; 342:836–843. [PubMed: 10733371]
- Ridker PM, Ridker PM. Establishing a clinical basis for hsCRP in the prevention and treatment of cardiovascular disease. *Clin. Chem*. 2010; 56:1186–1187. [PubMed: 20360125]
- Rifai N, Ridker PM. Population distributions of C-reactive protein in apparently healthy men and women in the United States: Implication for clinical interpretation. *Clin. Chem*. 2003; 49:666–669. [PubMed: 12651826]
- Rohleder N, Schommer NC, Hellhammer DH, Engel R, Kirschbaum C. Sex differences in glucocorticoid sensitivity of proinflammatory cytokine production after psychosocial stress. *Psychosomatic Medicine*. 2001; 63:966–972. [PubMed: 11719636]
- Roy B, Diez-Roux AV, Seeman T, Ranjit N, Shea S, Cushman M. Association of optimism and pessimism with inflammation and hemostasis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Psychosom. Med*. 2010; 72:134–140. [PubMed: 20100888]
- Sanches M, Zunta-Soares GB, Hatch JP, Soares JC. Gender differences in serum cortisol levels among patients with major depressive disorder. *Neuropsychiatry Neuropsychologia*. 2013; 8:89–93.
- Shemesh T, Rowley KG, Jenkins AJ, Best JD, O'Dea K. C-reactive protein concentrations are very high and more stable over time than the traditional vascular risk factors total cholesterol and systolic blood pressure in an Australian aboriginal cohort. *Clin. Chem*. 2009; 55:336–341. [PubMed: 19074519]
- Shivpuri S, Gallo L, Crouse J, Allison M. The association between chronic stress type and C-reactive protein in the multi-ethnic study of atherosclerosis: does gender make a difference? *J. Behav. Med*. 2011; 1–12.
- Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann. N. Y. Acad. Sci*. 2012; 1261:55–63. [PubMed: 22823394]
- Straub R, Buttgerit F, Cutolo M. Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases: a role for misguided energy regulation. *Clin. Rheumatol*. 2011; 29:S23–S31.
- Straub RH, Cutolo M. Further evidence for insufficient hypothalamic-pituitary-glandular axes in polymyalgia rheumatica. *The Journal of Rheumatology*. 2006; 33:1219–1223. [PubMed: 16821261]
- Suarez EC. C-reactive protein is associated with psychologic risk factors of cardiovascular disease in apparently healthy adults. *Psychosom. Med*. 2004; 66:684–691. [PubMed: 15385692]

- Suarez EC. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: Evidence for gender disparity. *Brain, Behavior, and Immunity*. 2008; 22:960–968.
- Suarez EC, Lewis JG, Kuhn CM. The relation of aggression, hostility, and anger to lipopolysaccharide-stimulated tumor necrosis factor (TNF)- α by blood monocytes of normal men. *Brain, Behavior and Immunity*. 2002; 16:675–684.
- Sutin AR, Beason-Held LL, Dotson VM, Resnick SM, Costa PT Jr. The neural correlates of Neuroticism differ by sex prospectively mediate depressive symptoms among older women. *J. Affect. Disord*. 2010a; 127:241–247. [PubMed: 20599276]
- Sutin AR, Terracciano A, Deiana B, Naitza S, Ferrucci L, Uda M, Schlessinger D, Costa PT Jr. High neuroticism and low conscientiousness are associated with interleukin-6. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences*. 2010b; 40:1485–1493.
- Taylor CB, Conrad A, Wilhelm FH, Neri E, DeLorenzo A, Kramer MA, Giese-Davis J, Roth WT, Oka R, Cooke JP, Kraemer H, Spiegel D. Psychophysiological and cortisol responses to psychological stress in depressed and nondepressed older men and women with elevated cardiovascular disease risk. *Psychosom. Med*. 2006; 68:538–546. [PubMed: 16868262]
- Tsigos C, Papanicolaou D, Defensor R, Mitsiadis C, Kyrou I, Chrousos G. Dose effects of recombinant human interleukin-6 on pituitary hormone secretion and energy expenditure. *Neuroendocrinology*. 1997; 66:54–62. [PubMed: 9258919]
- Uddin M, de los Santos R, Bakshis E, Cheng C, Aiello AE. Building conditions, 5-HTTLPR genotype, and depressive symptoms in adolescent males and females. *J. Adolesc. Health*. 2011; 49:379–385. [PubMed: 21939868]
- Uddin M, Koenen KC, de Los Santos R, Bakshis E, Aiello AE, Galea S. Gender differences in the genetic and environmental determinants of adolescent depression. *Depress. Anxiety*. 2010; 27:658–666. [PubMed: 20336806]
- VanDyke CL, Gore JS. Using Personality Profiles and Gender to Predict Affect. *Undergraduate Research Journal for the Human Sciences*. 2012:11.
- Weinberger AH, McKee SA, Mazure CM. Inclusion of women and gender-specific analyses in randomized clinical trials of treatments for depression. *Journal of women's health*. 2010; 19:1727–1732. (2002).
- Williams JW. A structured interview guide for the hamilton depression rating scale. *Arch. Gen. Psychiatry*. 1988; 45:742–747. [PubMed: 3395203]
- Youm Y-H, Grant Ryan W, McCabe Laura R, Albarado Diana C, Nguyen Kim Y, Ravussin A, Pistell P, Newman S, Carter R, Laque A, Münzberg H, Rosen Clifford J, Ingram Donald K, Salbaum JM, Dixit Vishwa D. Canonical Nlrp3 Inflammasome Links Systemic Low-Grade Inflammation to Functional Decline in Aging. *Cell Metabolism*. 2013; 18:519–532. [PubMed: 24093676]
- Zalcman SS, Siegel A. The neurobiology of aggression and rage: Role of cytokines. *Brain, Behavior, and Immunity*. 2006; 20:507–514.
- Zinbarg R, Mineka S, Griffith JW, Sutton J, Rose RD, Nazarian M, Mor N, Waters AM. The Northwestern-UCLA Youth Emotion Project: Associations of cognitive vulnerabilities, neuroticism and gender with past diagnoses of emotional disorders in adolescents. *Behav. Res. Ther*. 2010; 48:347–358. [PubMed: 20070951]
- Zobel A, Barkow K, Schulze-Rauschenbach S, Von Widdern O, Metten M, Pfeiffer U, Schnell S, Wagner M, Maier W. High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in healthy volunteers. *Acta Psychiatrica Scandinavica*. 2004; 109:392–399. [PubMed: 15049775]

Figure 1.

Mean log value of the CORT/CRP for the lowest quartile, the second and third quartiles combined, and highest quartile of the CORT/CRP distribution

Figure 2.
Mean CORT and hsCRP levels for low, moderate and high CORT/CRP groups

Figure 3.
Relation of log(CORT/CRP) to log(Hamilton Depression Score) as a function of gender

Figure 4.
Relation of log(CORT/CRP) to NEO-Personality Inventory anxiety facet score as a function of gender

Table 1

Subject characteristics for total sample and by gender

	Men	Women	Total
Age (y)	28 (9.7)	29.6 (9.5)	28.4 (9.6)
BMI (kg/m ²)	25.4 (4.7)	25.0 (4.9)	25.5 (4.8)
Waist Circumference (cm) ^b	90.1 (1.6)	80.8 (1.7)	85.8 (12.1)
Race (% non-white)	43	58	45
NEO Personality Inventory			
Domains			
Neuroticism	79.6 (20.8)	79.1 (22.8)	79.4 (21.7)
Extraversion	113.7 (17.4)	117.5 (17.0)	115.4 (17.3)
Openness	119.2 (18.9)	122.2 (20.1)	120.5 (19.5)
Conscientiousness ^b	46.3 (9.0)	49.5 (7.6)	47.6 (8.6)
Agreeableness ^b	47.1 (6.0)	50.4 (7.8)	48.6 (7.0)
Facets			
Assertiveness	16.8 (4.7)	16.9 (5.1)	19.9 (4.9)
Anxiety	14.4 (4.9)	15.0 (5.4)	14.7 (5.1)
Buss-Perry Anger	14.6 (9.3)	14.1 (4.9)	14.2 (5.1)
PSQI Total	4.5 (2.4)	4.0 (2.3)	4.2 (2.4)
Hamilton Depression ^c	3 (1–9)	3 (1–9)	3 (1–9)
Cortisol (µg/dl)	14.4 (5.0)	14.6 (6.6)	14.5 (5.8)
C-Reactive Protein (mg/L) ^c	0.72 (0.29–1.64)	0.74 (0.28–1.65)	0.72 (0.28–1.65)

Caption: Data are mean (SD) except where noted. *Abbreviations:* BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index.^aGender difference: p<0.05.^bGender difference: p<0.01.^cMedian (IQR).