Does Basal Inflammation Connote Vulnerability for Depression?

BY

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THESIS

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This thesis is dedicated to my parents, Ben Katz and Felice Fischer, who instilled and cultivated my love of learning and exploration, and to my partner, Max Green, for his enduring love and support. Without them, this may not have been accomplished.
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<td>TNF</td>
<td>Tumor Necrosis Factor</td>
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SUMMARY

The relationship between major depression and immune system functioning has increasingly been the subject of scientific inquiry, and several lines of research have pointed to the possibility of inflammatory processes playing a causal role in the development of depressive symptoms. If inflammatory processes are causal, then it is possible that basal markers of inflammation will connote vulnerability for major depression. Using a family study methodology, the present study therefore examined the relationship between depressive symptoms and markers of inflammation (specifically, C-reactive protein [CRP] and interleukin-6 [IL-6]) in 146 sibling pairs recruited from the greater Chicago community. Results showed that both CRP and IL-6 levels were stable over time and aggregated within families. There were significant positive associations between current depressive symptoms and inflammatory markers, replicating previous findings. However, familial risk analyses were inconclusive and were not able to demonstrate that CRP and IL-6 concentrations are associated with familial vulnerability for depression. Given the dynamic nature of the inflammatory system, it is possible that inflammatory stress reactivity, rather than basal levels of inflammation, is more indicative of vulnerability for depression.
I. INTRODUCTION

A. Depression and Health

Epidemiological studies have shown that approximately 15-20% of the US adult population will meet criteria for Major Depressive Disorder (MDD) at some point in their lifetime (Kessler et al., 2003; Hasin, Goodwin, Stinson & Grant, 2005; Kessler & Bromet, 2013). In addition to its high prevalence, MDD is one of the most costly psychiatric disorders: it surpasses almost every other chronic medical condition in burden of disease morbidity (Greden, 2001) and costs over $35 billion annually in the US alone (Greenberg, Stiglin, Finkelstein & Berndt, 1993; Kessler et al., 2006). In addition to psychosocial impairment and disability, MDD is also associated with poor health outcomes. For example, mortality rates are 25-39% higher in cancer patients with comorbid depressive disorders compared to those without depressive disorders (Satin, Linden & Phillips, 2009). The significant levels of disability, morbidity and mortality associated with MDD indicate that it is a major public health concern. As such, identification of vulnerability markers for MDD is crucial for early intervention and prevention efforts.

In addition to higher mortality rates in already-sick populations, MDD is also associated with increased rates of various medical conditions. Those with MDD are more likely to suffer from autoimmune disorders, such as Celiac disease (Carta et al., 2002) and rheumatoid arthritis (Bruce 2008; Matcham, Rayner, Steer & Hotopf, 2013), than healthy controls. In addition, depression is associated with inflammation-related diseases. For example, individuals with MDD are significantly more likely to have co-occurring coronary artery disease (Frasure-Smith & Lespérance, 2006) and diabetes (Anderson, Freedland, Clouse & Lustman, 2001) than the general population. The association between MDD and these diseases is not simply due to psychological distress that follows a diagnosis of these medical conditions, as there is ample evidence showing that MDD predates cardiovascular symptoms (Penninx, Melanschi, Lamers & Vogelzangs, 2013). Results from meta-analyses of several longitudinal studies have shown that disease-free individuals with MDD are at significantly greater risk for developing heart disease.
(Nicholson, Kuper & Hemingway, 2006), hypertension (Meng, Chen, Yang, Zheng & Hui, 2012), and diabetes (Mezuk, Eaton, Albrecht & Golden, 2008). The association between MDD and other chronic autoimmune and inflammatory diseases has led researchers in the field of immunology to examine immune system functioning in the context of MDD, paying particular attention to markers of inflammation.

**B. Overview of Inflammatory Processes**

Inflammation constitutes a major part of the body's nonspecific, innate immune response when exposed to an outside pathogen. In this context, *innate* immunity is held in contrast to *adaptive* immunity. The adaptive immune response (also called the specific or acquired immune response) is also mounted by exposure to infectious agents, but its primary function is to develop microbe-specific antibodies that confer lasting protection to the host organism via immunological memory. That is, the white blood cells of the adaptive immune system (broadly known as lymphocytes) adapt to the presence of extracellular microbes and “remember” their unique chemical signatures so that they can be neutralized and eliminated if the organism is re-infected (Barton, 2008; Murphy, 2011). Innate immunity (also called native or natural immunity), on the other hand, is always present in healthy individuals and defends against infection by blocking microbial entry and eliminating microbe-infected tissue (Abbas & Lichtman, 2009; Hoebe, Janssen, & Beutler, 2004).

Innate immunity is the host's first line of defense against infection. Once a pathogen penetrates the physical barriers that block out infectious microbes (i.e., the skin, and epithelia along the gastrointestinal and respiratory tracts), several cells work together to eliminate tissue infected with disease-causing microbes: namely, neutrophils, mononuclear phagocytes, and natural killer cells. Neutrophils and mononuclear phagocytes are two types of circulating phagocytes. Neutrophils are the first cells to respond to infection; they ingest microbes in the blood and extravascular tissue (Mantovani, Cassatella, Costantini & Jaillon, 2011). Mononuclear phagocytes take on two forms: monocytes and macrophages. Like neutrophils, blood
monocytes circulate through the vascular system and ingest microbes, and they differentiate into macrophages once they enter extravascular tissue. Unlike neutrophils, macrophages can survive in extravascular tissue for much longer periods, where they ingest microbes, similar to the way they do in the blood (Kantari, Pederzoli-Ribeil & Witko-Sarsat, 2008). Natural killer cells recognize host cells infected with microbes and initiate apoptosis (i.e., cell death; French & Yokoyama, 2003). The buildup of these three types of phagocytic cells (i.e., neutrophils, mononuclear phagocytes, and natural killer cells), along with surges of fluids and proteins in the tissue at the site of infection causes swelling, which is called inflammation. Taken together, the action of these components of the innate immune system is called the inflammatory response (Abbas & Lichtman, 2009).

The actions of the phagocytic cells described above are mediated by cytokines, a class of proteins that are secreted by macrophages and natural killer cells. There are several cytokines associated with innate immunity, and they function primarily to promote or inhibit further inflammation. Pro-inflammatory cytokines include interferon-γ (IFN-γ), tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-15 (IL-15), and interleukin-18 (IL-18). IFN-γ is produced by natural killer cells and activates macrophages (Biron, Nguyen, Pien, Cousens & Salazar-Mather, 1999). TNF is produced by activated mononuclear phagocytes and stimulates recruitment of neutrophils and monocytes at the site of infection (Zhang, Ramos & Jakschik, 1992). IL-1 is secreted by activated mononuclear phagocytes and mediates the inflammatory responses of innate immunity, including promoting endothelial cell adhesion and simulating chemokine (i.e., molecules that promote movement of the cells of innate immunity from blood to tissue) production by macrophages (Abbas & Lichtman, 2009). IL-6 is produced by many cells types and serves various functions in innate and adaptive immunity (Jones 2005). IL-12 is also produced by activated mononuclear phagocytes and activated natural killer cells and promotes the production of IFN-γ by natural killer cells (Biron et al., 1999). IL-15, too, is produced by
mononuclear phagocytes and in response to viral infections and stimulates propagation of natural killer cells (French & Yokoyama, 2003). IL-18 is produced by macrophages in response to lipopolysaccharide (LPS, a component of bacterial cell walls) and works together with IL-12 to stimulate the production of IFN-γ by natural killer cells (Puren, Razeghi, Fantuzzi & Dinarello, 1998).

C-reactive protein (CRP) is an acute-phase protein produced by the liver (Gabay & Kushner, 1999) in response to infection and tissue injury. It is named for its affinity for the phosphocholine (PCh) elements of C-polysaccharide, a component of many bacterial and fungal cell membranes. CRP also has selective receptors for the membranes of damaged or necrotic host cells (Kushner & Kaplan, 1961). Once bound to a cell membrane, CRP recruits the complement system and phagocytic cells to the site and initiates the removal of the pathogen or damaged host cell. Because of CRP’s ability to identify and a wide range of pathogens and damaged tissue, as well as its role in mediating their elimination, it is considered a key player in the innate immune system (Volanakis, 2001). CRP concentrations rise quickly during the acute phase of infection, and they return to their normal low levels equally quickly once a threat is removed. This process is governed primarily at the level of transcription of CRP genes, and IL-6 and IL-1 work synergistically to induce transcription (and therefore production) of CRP (Toniatti et al., 1990; Ganapathi, Rzewnicki, Samols, Jiang, & Kushner, 1991; Szalai, van Ginkel, Wang, McGhee, & Volanakis, 2000). Because of its central role in innate immunity, CRP concentrations in the blood can serve as proxies for activity of pro-inflammatory cytokines and thus serve as a marker of systemic inflammation.

The effects of pro-inflammatory cytokines are regulated by anti-inflammatory cytokines. Interleukin-10 (IL-10) is a primary anti-inflammatory cytokine activated by macrophages whose primary function is to inhibit activated macrophages and maintain homeostasis within the inflammatory system of the host (D’andrea, Aste-Amezaga, Valiante, Ma, Kubin & Trinchieri, 1993).
In addition to their roles in cell-mediated immunity, cytokines act on the brain via several neural pathways that ultimately produce cytokine expression in the brain (Gatti & Bartfai, 1993; Bret-Dibat, Bluthe, Kent, Kelley & Dantzer, 1995; Dantzer, O’Connor, Freund, Johnson & Kelley, 2008). Proinflammatory cytokines in the brain are responsible for producing sickness behaviors, a constellation of nonspecific behavioral symptoms that help the sick individual fight infection and prevent the infection of others. Sickness behaviors include weakness, malaise, lethargy, trouble concentrating, social withdrawal, and decreased interest in their surroundings (Dantzer et al., 2000). Although once thought to be trivial because they are not specific to a particular infection or class of infections, sickness behaviors are now understood as part of a motivational state to promote recovery from illness (Hart, 1991; Dantzer, 2001). For example, lethargy ensures that the body can devote its metabolic resources to fighting infection, rather than using energy for other activities.

Results from animal studies have shown that pro-inflammatory cytokines are the main purveyors of sickness behavior in mammals (Layé, Parnet, Goujon & Dantzer, 1994; Dantzer et al., 2000). Animals injected with IL-1β and TNF-α exhibit a variety of sickness behaviors, including reduced exploratory behavior, social withdrawal, reduced sexual behavior, decreased appetite, fatigue, hypersomnia, and decreased reward responsiveness (Bret-Dibat et al., 1995; Avitsur & Yirmiya, 1999; Dantzer, 2001; Konsman, Parnet & Dantzer, 2002; Carmichael et al., 2006). Further support for this relationship comes from studies showing that mice with deficiencies in IL-1 secretion (Segreti, Gheusi, Dantzer, Kelley & Johnson, 1997) or absorption (Bluthe et al., 2000) show decreased sickness behaviors compared to wild-type mice. Unlike IL-1β and TNF-α, which are directly responsible for sickness behaviors (Dantzer et al., 2000), IL-6 has been shown to have an indirect influence on sickness behaviors. Compared to wild type mice, IL-6-deficient mice display less sickness behavior in response to administration of LPS and IL-1 (Bluthe, Michaud, Poli & Dantzer, 2000; Sparkman et al., 2006). Similar results have been found when IL-6 signaling in the brain is disrupted (Burton, Sparkman & Johnson, 2011).
and when subjects receive an injection of an IL-6 antagonist prior to LPS administration (Harden, Plessis, Roth, Loram, Poole & Laburn, 2011). Taken together, these results suggest that IL-6 contributes to the production of sickness behavior.

C. Inflammation and Major Depression

The resemblance between sickness behaviors observed in animals and depressive symptoms in humans has led many researchers to examine the relationship between inflammation and MDD. Indeed, several studies have found that, compared to non-depressed individuals, those with diagnoses of MDD exhibit elevated levels of most pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, as well as CRP (Maes et al., 1995; Zorrilla et al., 2001; Alesci et al., 2005; Kuo et al., 2005; Thomas et al., 2005; Dowlati et al., 2010; Hiles, Baker, de Malmanche & Attia, 2012). Additionally, meta-analytic studies have shown that the effect sizes for the associations between pro-inflammatory cytokines and MDD were both significant and moderately sized (Howren, Lamkin & Suls, 2009; Liu, Ho & Mak, 2012). Another study found significant differences between the serum IL-6 levels in patients with antidepressant-resistant depression and antidepressant-responsive depression (Yoshimura et al., 2009). Results from other studies even suggested a dose-response relationship between markers of inflammation and depressive symptoms, as levels of IL-6 (Maes, 1995; Kim et al., 2007; Brietzke et al., 2009) and CRP (Panagiotakos et al., 2004) were positively correlated depression symptom severity. Interestingly, this dose-response relationship between cytokines (specifically IL-6) and depressive symptoms was observed even among patients admitted to a hospital for a suicide attempt, a group with a narrow range of depressive symptoms (Lindqvist et al., 2009).

One of the most compelling putative explanations for the cytokine abnormalities seen in the context of major depression may be the effect of stress on the innate immune response (Raison, Capuron & Miller, 2006). Psychosocial stress is one of the most common and robust risk factors for MDD (Kendler & Karkowski, 1999; Hammen, 2005; Monroe, Slavich &
Georgiades, 2009), and there is increasing evidence pointing to the effect of stress on the inflammatory system. In animal studies, psychological stress in the form of restraint, open field exposure, and social isolation has been shown to activate pro-inflammatory cytokines in the brain and bloodstream (Madrigal et al., 2002; O'Connor et al., 2003). Examinations of psychosocial stress in humans have also shown that both acute and chronic stress are associated with increases in pro-inflammatory cytokines and decreases in regulatory anti-inflammatory cytokines (Maes et al., 1998; Goebel et al., 2000; Deinzer et al., 2004; McDade, Hawkley & Cacioppo, 2006). That psychological stress is associated with both increased risk for depression and increased inflammation suggests that inflammation might mediate the relationship between psychosocial stress and development of major depression.

D. Inflammation and Vulnerability for Depression

Elevated levels of pro-inflammatory cytokines may not just be a concomitant of depressive symptoms, but they may play a causal role in depressive symptoms as well. In fact, the cytokine theory of depression (Smith, 1991) posits just that, and evidence from various avenues of research supports this hypothesis (Anisman, 2009). The above mentioned animal studies on cytokine-induced sickness behaviors is one model of how pro-inflammatory cytokines can play a role in the pathogenesis of MDD (Miller, Maletic & Raison, 2009). Immune-activating treatments (e.g., vaccines) given to healthy adults have also been shown to induce depressive symptoms, such as negative mood, and these symptoms were directly correlated with levels of IL-6 secretion (Reichenberg et al., 2001; Wright, Strike, Brydon & Steptoe, 2005). There is even evidence that pre- and immediately post-operative levels of CRP and IL-6 predict depressive symptoms at follow-up (Cremeans-Smith, Soehlen, Greene, Alexander, & Delahanty, 2009; Ai, Kabbaj, & Kathy, 2014). Furthermore, many studies have demonstrated that immunotherapy (i.e., treating some forms of cancer and hepatitis C with the cytokine interferon-α) in psychologically healthy individuals may cause MDD (Capuron, Ravaud & Dantzer, 2000;
Bonaccorso et al., 2002; Scalori et al., 2005). In some cases, the depressive episode has been severe enough to warrant termination of immunotherapy (Valentine, Meyers & Taipaz, 1995).

Taken together, these findings strongly suggest that hypersecretion of pro-inflammatory cytokines plays a role in the development of MDD in humans. A question that follows, then, is whether basal elevation in circulating pro-inflammatory cytokines is associated with vulnerability for depression. However, there has been relatively little research attempting to answer this question. Results from genetic studies indicate that polymorphisms in pro-inflammatory cytokine genes differentiate individuals with major depression from healthy controls (Traks et al., 2011; Bufalino, Hepgul, Aguglia & Pariante, 2013) and predict variation in antidepressant treatment response (Yu, Chen, Hong & Tsai, 2003; Baune et al., 2010; Bufalino et al., 2013; Cattaneo et al., 2013; although see Misener et al., 2008 for exceptions). Studies investigating whether indicators of inflammation longitudinally connote vulnerability for depression are limited and mixed. A few studies have found that higher levels of IL-6 and CRP at baseline predict later depressive symptoms in a variety of patient populations (Wichers et al., 2006; Gimeno et al., 2009; Hamer, Malloy, Oliveira & Demakakos, 2009; van Zuiden et al., 2011; Valkanova, Ebmeier & Allan, 2013; Au, Smith, Gariépy, & Schmitz, 2015). However, other studies have found no evidence of a longitudinal effect of inflammation on depression or that baseline depression predicted inflammation later (Stewart et al., 2009; Deverts et al., 2010; Duivis, de Jonge, Penninx, Na, Cohen, & Whooley, 2011; Copeland et al., 2012).

The findings described above are limited in a number of ways. Results from the genetic association studies are not consistent. Longitudinal findings have been mixed as well, and many of them are limited by small sample sizes and specialized populations (e.g., hepatitis C patients undergoing immunotherapy; Wichers et al., 2006). Additionally, these studies have all focused on whether elevated inflammation connotes risk for depression, whereas no study to date has examined whether markers of inflammation are associated with vulnerability for depressive symptoms. The difference between risk and vulnerability is subtle: both are variables (i.e.,
predictors or moderatoMrs) that increase the likelihood of a negative outcome. However, vulnerability factors are variables that imply a mechanism in their contribution to the negative outcome whereas risk factors do not (Ingram & Luxton, 2005). For example, being male is a risk factor for heart attacks, meaning that men are more likely to have heart attacks than women, whereas hypertension is a vulnerability factor for heart attacks because it implies a mechanism for the increased risk (i.e., that the heart requires more energy to pump blood through the body).

One way to examine vulnerability markers for psychopathology is the family study method (Kendler, 2006; Robins & Guze, 1970). Although the family study method cannot separate genetic from environmental effects, it allows researchers to examine familial vulnerability for a particular psychopathology. The logic behind the family study method is that if variable X is a vulnerability marker for MDD, which is highly familial and heritable condition (Weissman et al., 2006; Joormann, Eugène & Gotlib, 2008; Hammen, 2009; Gotlib, Joormann, & Foland-Ross, 2014), then it should be present in the low-symptom family members of depressed individuals and relate more strongly to family history of depressive symptoms (e.g., Gottesman and Gould, 2003). Stated another way, if “depressed” (i.e., high-symptom) probands and their “healthy” (i.e. low-symptom) family members both exhibit abnormal levels of that variable, then variable X is understood to be a vulnerability marker for MDD. Additionally, if variable X is a vulnerability marker, then it should also be stable over time, aggregate in families, and be present even in the absence of current depressive symptoms. To that end, the present study examined the concentrations of circulating IL-6 and CRP in a sample of full biological siblings with a wide range of depressive symptoms to see if elevations in IL-6 and CRP connote vulnerability for depression. Specifically, the family study method was used to examine: 1) whether the levels of IL-6 and CRP are abnormal in the healthy relatives of depressed probands, while accounting for the relatives’ current mood symptoms, 2) whether IL-6 and CRP levels remain elevated in those with remitted depression, compared to never-
depressed individuals, 3) whether IL-6 and CRP levels are stable over time within people, and 4) whether IL-6 and CRP levels in probands predict the IL-6 and CRP levels in their full siblings.

Another limitation of prior studies on whether markers of inflammation are vulnerability factors for depression is how depression was operationalized. Major depressive disorder is a broad and heterogeneous syndrome, and inflammation may be associated with vulnerability for particular dimensions of the disorder. Several models that have been proposed to parse the heterogeneity of depression (Clark & Watson, 1991; Simms, Grös, Watson & O’Hara, 2008; Watson, 2009; Treadway & Zald, 2011). Many of these models agree that MDD contains two broad affective factors: low positive affect (PA) and high negative affect (NA; Clark & Watson, 1991). PA reflects a person’s zest for life and tendency to engage in or approach pleasurable stimuli, and NA represents a person’s unpleasant feelings and tendency to avoid aversive stimuli. Whereas high NA is conceptualized as an indicator of general distress and a nonspecific factor across internalizing psychopathology, low PA is thought to be more related to MDD than other internalizing psychopathologies. These dimensions of mood are reflected in the two cardinal symptoms of depression: anhedonia is the deficit in PA, and depressed mood is the deficit in NA. However, these are not the only symptoms of depression (or internalizing psychopathology) as the syndrome contains numerous other symptoms that may be related to the inflammatory process (e.g., insomnia, etc). Thus, depression will be assessed with the Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012), an empirically derived measure that yields multiple dimensions of depression and internalizing psychopathology more broadly.

There is some evidence to suggest that inflammation may have a stronger association with anhedonia than other symptom dimensions. Higher levels of pro-inflammatory cytokines have been found to be associated with a decrease in preference for saccharin and attenuate neural responding to rewarding brain stimulation in animals (Dantzer et al., 1999) and reduce activity in the ventral striatum (a region implicated in reward processing, Haber & Knutson,
2010) following receipt of rewards in humans (Eisenberger et al., 2010). In addition, different inflammatory profiles have been found in a subtype of depression characterized by anhedonia (i.e., melancholic depression), although results have been inconsistent (Rothermundt et al., 2001; Maes, Mihaylova, Kubera & Ringel, 2012; Lamers et al., 2013).

E. The Present Study

The goal of the present study was to examine whether baseline inflammation predicts familial vulnerability for depression. Specifically, we compared peripheral levels of pro-inflammatory cytokines in full biological siblings, focusing particularly on symptom-discordant siblings. If elevated inflammation is a marker of vulnerability for major depression, then higher levels of IL-6 and CRP should be observed in “sick” probands, as well as their “healthy” siblings. Depression was examined both dimensionally, defining siblings as “sick” and “healthy” based on relative scores on the IDAS-II, as well as categorically, using a diagnosis of MDD to determine “sick” and “healthy” siblings, as is consistent with classic family study methodology. It is noteworthy that examining psychopathology in a dimensional way is more in line with the goals of the Research Domain Criteria (RDoC; Cuthbert & Insel, 2010, 2013; Cuthbert, 2014), an initiative put forth by the National Institute of Mental Health to examine transdiagnostic dimensions of psychopathology, rather than categorical diagnoses. A second aim of the current study was to look at whether differences in the inflammatory cytokine profiles are associated with vulnerability for a particular dimension of major depression, such as negative affect or anhedonia. Thus, investigated the relationship between CRP and IL-6 levels and scores on the IDAS in sets of full siblings to test the following hypotheses:

1) Concentrations of CRP and IL-6 will be stable across two measurement points
2) Concentrations of IL-6 and CRP will be similar (i.e., correlated) among full siblings
3) In the whole sample, elevated levels of CRP and IL-6 should be associated with greater depressive symptoms
4) IL-6 and CRP concentrations should be elevated in those with remitted depression, compared to those who have never been depressed.

5) The concentrations of IL-6 and CRP in the low-symptom siblings of high-symptom probands will be abnormal.
II. METHOD

A. Participants

The sample consisted of 146 young adult sibling pairs enrolled in a larger study on familial emotional processes. Individuals were recruited for the broader study from the greater Chicago metropolitan area via advertisements designed to capture a wide-range of psychopathology. As part of the inclusion criteria for the larger study, which sought to assess individuals in the peak risk window for psychopathology, participants were required to be between the ages of 18 and 30 and have at least one full biological sibling within the same age range who was eligible to enroll. Individuals were excluded if they had a personal or first-degree family history of manic, hypomanic, or psychotic symptoms. These individuals were excluded because the primary aim of this larger study was examining internalizing psychopathology, and prior structural studies of psychopathology have shown that mania and psychosis load onto different factors from the internalizing disorders (Krabbendam et al., 2004; Bedford & Deary, 2006; Markon, 2010). Additionally, individuals were excluded if they could not read or write English, had a history of head trauma with loss of consciousness, or were left-handed. The rationale for these criteria included ensuring ability to provide consent and complete all measures and minimizing potential confounds to psychophysiological data. Please see Table 1 for demographic information.

B. Measures

1. Current depressive symptoms (dimensional assessment)

Current depression symptoms were assessed in all participants using the expanded Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012). The IDAS-II is a 99-item factor-analytically derived self-report inventory of 11 empirically distinct dimensions of depression and anxiety symptoms. Each item assesses symptoms over the past two weeks on a 5-point Likert scale ranging from 1 (Not at all) to 5 (Extremely). The IDAS-II has demonstrated good internal consistency, test-retest reliability, and convergent and discriminant validity with
diagnoses and self-report measures in similar populations (Watson et al., 2007; Watson et al., 2012). The scales of the IDAS-II that are of primary interest for this study are the Well-Being scale, which assesses positive affect, and is defined by items reflecting high energy and positive affect specifically relating to depression (Watson et al., 2007; Watson et al., 2012) and the Dysphoria scale, which taps negative affect and general distress. There are five other scales reflecting specific symptom clusters of MDD: Insomnia, Lassitude (i.e., fatigue, low energy, and hypersomnia), Suicidality, Appetite Loss, and Appetite Gain. Ill Temper assesses anger and hostility that can serve as an alternative expression of depressed mood. Finally, The General Depression scale provides an index of overall depressive symptoms.

2. **Diagnosis of MDD (categorical assessment)**

In addition to assessing current depressive symptoms dimensionally, current and lifetime diagnoses of depression were assessed via the Structured Clinical Interview for the DSM (SCID; First, Spitzer, Gibbon, & Williams, 1996). Diagnosticians were trained to criterion on the SCID and supervised by Dr. Shankman. In addition to depression symptoms, interviewers assessed functional impairment and subjective distress dimensionally. Interviewers made separate ratings for impairments in the domains of social, occupational, and daily life, as well as perceived distress, along a nine-point scale ranging from 0 (None) to 8 (Severe). The anchors for the scale were adopted from the Anxiety Disorders Interview Schedule (ADIS-IV; Brown, DiNardo, & Barlow, 1994) in which a two or higher was clinically significant distress or impairment.

3. **Systemic Inflammation**

To examine basal levels of inflammation in the sample, peripheral levels of the pro-inflammatory cytokine IL-6 and the acute phase protein CRP were collected from drops of whole blood and preserved on a Whatman blood spot card. This collection method is less invasive than a full blood draw and equivalent in terms of providing information on markers of
inflammation (McDade, Williams & Snodgrass, 2007). The samples were assayed using Dr. Thomas McDade's laboratory at Northwestern University.

C. Procedure

1. Data collection

Participants provided written informed consent after review of the protocol, and all procedures were approved by the University of Illinois at Chicago Institutional Review Board. Following informed consent, participants underwent a structured clinical interview, completed an electronic battery of questionnaires, and provided a small blood sample on bloodspot cards to examine inflammatory markers. Participants' height and weight were also measured to determine their body mass index (BMI), as it is often associated with inflammation (Festa et al., 2001; Khaodhia, Ling, Blackburn & Bistrian, 2004). Finally, participants were asked if they had been sick in the last two weeks—specifically, they were asked whether they had experienced nasal congestion, a productive cough, fever, or vomiting. Their temperature was taken, and collection of blood spots was deferred to the following visit if individuals had a temperature greater than 99° or if they reported having had any of the symptoms listed above in the past two weeks. A subsample of participants (n = 27) provided a second set of dried blood spots during a second laboratory visit, when they completed various behavioral tasks as part of the larger study. On average, participants provided their second blood sample 9 days after their first one. All precautions taken with the first sample (i.e., temperature, assessment of infection) were taken during the second dried blood spot collection.

2. Dried blood spot storage and immunoassays

After blood spots had dried, they were stored at room temperature with desiccant packets for no more than 7 days before being transferred to a laboratory-grade freezer at the University of Illinois Biorepository. The samples were transferred on dry ice to Dr. McDade’s laboratory to avoid sample degradation from thaw-refreeze cycles. For the immunoassays, the dried blood spots were reconstituted as hemolyzed whole blood and analyzed using the
enzyme-linked immunosorbent assay (ELISA) protocol (see McDade, Burhop & Donhal, 2007). The CRP and IL-6 ELISA protocols require different amounts of blood, and some participants did not provide sufficient sample amounts to examine both CRP and IL-6. In addition, some of the samples could not be run in duplicate, so those data are not presented here. In total, 347 individuals produced usable CRP data, and 308 participants provided usable IL-6 data. There were 135 families in which both siblings provided usable CRP data, and there were 114 families in which both siblings provided usable IL-6 data.

D. Data Analysis Plan

To normalize the data, both CRP and IL-6 ratios were square root-transformed for all analyses (see Figure 1 for histograms). All data were analyzed using SPSS 22.0.

1. **Hypotheses 1 and 2**

To test the first hypothesis of stability of immune markers over time, one-way random intraclass correlations (ICCs) were calculated for CRP and IL-6 concentrations at time 1 and time 2. In order to examine familial aggregation of cytokine concentrations, ICCs were calculated for proband and sibling IL-6 and CRP concentrations. ICCs are more appropriate for this context than Pearson correlations as the latter allows for linear trends, and goal of testing agreement of measures cannot be well predicted from a linear model.

2. **Hypotheses 3 and 4**

Mixed-effect regression models were used to test the third and fourth hypotheses, which were that those with current and remitted depression would show higher levels of inflammation compared to non-depressed and never-depressed individuals, respectively. Mixed effects regression models (rather than standard hierarchical linear regression models) were used to account for the non-independent cases within families in this nested family design.

3. **Hypothesis 5**

The fifth hypothesis, which was that cytokine concentrations would be elevated in the low-symptom siblings of high-symptom probands, was examined in two ways: dimensionally,
using IDAS scores, and categorically, using diagnosis of MDD. For the dimensional analyses, each individual within a sibling pair was designated as either the ‘proband’ or the ‘sibling.’ Specifically, the member of the pair that reported more current depressive symptoms (i.e., higher score on the IDAS-II General Depression Scale) was labeled ‘proband’, and the member of the pair that reported fewer current depressive symptoms was labeled ‘sibling.’ If the two siblings reported the same level of depressive symptoms, they were assigned at random to ‘proband’ and ‘sibling’. The analyses using categorical diagnosis employed a similar approach for designating probands and siblings. In sibling pairs discordant for MDD, the individual diagnosed with MDD was designated the proband, and the healthy individual was designated as the sibling. For sibling pairs concordant for MDD (i.e., either both individuals were depressed or neither were depressed), the proband vs. sibling designation was assigned randomly.

To test whether the proband’s current depressive symptoms predicted sibling’s systemic inflammation, two hierarchical linear regression models were conducted—one for CRP and one for IL-6. In each model, proband depressive symptoms was the predictor, and inflammation marker was the criterion variable. Sibling depressive symptoms were included as a covariate to examine whether proband depressive symptoms predicts sibling inflammation, over and above the effect of the sibling’s own depressive symptoms. In accordance with published guidelines for conducting analyses with inflammation data (O’Connor et al., 2009), sibling’s gender, age, BMI, current smoking status, drinking status, insomnia, and whether a female sibling was taking birth control were also included as covariates.

To test whether proband MDD diagnosis predicted sibling inflammation levels, two multivariate analyses of covariance (ANCOVAs) were conducted comparing sibling levels of CRP and IL-6 in three types of families - (1) siblings concordant for current depression, (2) MDD-discordant siblings, and (3) siblings concordant for no current depression. Sibling CRP and IL-6 were the criterion variables (in separate analyses), and a three-level categorical variable for family type was the predictor. These models had the same covariates as the
dimensional analyses: sibling gender, age, BMI, smoking status, drinking status, insomnia, and birth control use.

4. **Exploratory parent-child analyses**

For a subset of families ($N = 22$ for CRP; $N = 18$ for IL-6), history of major depressive disorder was available for one or both parents. Therefore, two sets of exploratory analyses were conducted examining the association between parent depression and child inflammation. To test these associations, two hierarchical linear regression models were conducted, wherein CRP and IL-6 concentrations for proband and sibling were regressed (in separate regressions) onto parent lifetime major depressive disorder, with proband and sibling covariates included as detailed above.

To examine if the never-depressed children of parents with lifetime major depression differed from the never-depressed children of never-depressed parents, ANCOVAs were conducted comparing proband and sibling levels of CRP and IL-6 in three types of families - (1) never-depressed children of never-depressed parents, (2) never-depressed children of parents with lifetime diagnosis of MDD, and (3) children with lifetime diagnosis of MDD of parents with lifetime diagnosis of MDD. Proband and sibling CRP and IL-6 were the criterion variables (in separate analyses), and a three-level categorical variable for family type was the predictor. These models had the same covariates as all other analyses: sibling gender, age, BMI, smoking status, drinking status, insomnia, and birth control use.
III. RESULTS

A. Temporal Stability of Inflammatory Markers

The mean levels of CRP ($N = 27$) at time 1 and time 2 were 0.774 ($SD = 0.563$; median = 0.583) and 0.742 ($SD = 0.546$; median = .490), respectively. Paired-samples t-tests indicated no significant difference in CRP between time 1 and time 2, $t(26) = .290$, n.s. The mean levels of IL-6 ($N = 21$) at time 1 and time 2 were 1.038 ($SD = .366$) and 1.060 ($SD = .351$), respectively. As with CRP, there was no significant difference in IL-6 between time 1 and time 2, $t(20) = -.309$, n.s. Repeated-measures ANOVAs controlling for gender, age, BMI, smoking status, drinking status, birth control, and current insomnia showed that there was no significant effect of time on either CRP ($F[1, 19] = .519$, n.s.) or IL-6 ($F[1, 13] = .395$, n.s.). Furthermore, one-way random intraclass correlations (ICCs) between CRP and IL-6 samples collected at two separate time points indicated significant associations over time (CRP: ICC[1,1] = .625, $p < .01$; IL-6: ICC[1,1] = .738, $p < .01$).

B. Familial Aggregation of Inflammation

The mean levels of CRP for sibling 1 and sibling 2 were 0.749 ($SD = 0.488$; median = 0.573) and 0.781 ($SD = 0.529$; median = 0.601), respectively. Paired-samples t-tests indicated no significant difference in CRP between sibling 1 and sibling 2, $t(138) = -.561$, n.s. The mean levels of IL-6 for sibling 1 and sibling 2 were 1.117 ($SD = .393$; median = 1.037) and 1.104 ($SD = .338$; median = 1.016), respectively. As with CRP, there was no significant difference in IL-6 between sibling 1 and sibling 2, $t(104) = .282$, n.s. Repeated-measures ANOVAs showed that there was no significant effect of sibling on either CRP ($F[1, 138] = .314$, n.s.) or IL-6 ($F[1, 104] = .079$, n.s.). Furthermore, one-way random ICCs between proband and siblings for CRP and IL-6 demonstrated significant familial association of markers of inflammation (CRP: ICC[1,1] = .283, $p < .05$; IL-6: ICC[1,1] = .307, $p < .05$).
C. Effects of Covariates

To determine which covariates to use in the remaining analyses, mixed-effects regression models were run examining the effects of each putative covariate, one at a time, on CRP and IL-6 levels. For CRP, significant effects were found for BMI and birth control use, and trend-level effects were found for sex and current smoking. For IL-6, significant effects were found for BMI, drinking, and current insomnia. See Table 2 for coefficient estimates.

D. Association between Current Depression and Inflammation

Current depression was operationalized four ways to examine the relationship between depression and markers of inflammation: current categorical diagnosis of depression and four subscale scores of the IDAS: Depression, Dysphoria, Lassitude, and Well-Being.

1. Current MDD

Across the entire sample, there was a positive relationship between diagnosis of current major depression and inflammation. Specifically, results from mixed-effects regression models showed a significant fixed effect of MDD diagnosis on CRP level \( b = 1.680, SE = 0.794, p < .05 \) and a trend-level association between current MDD and IL-6 level \( b = 0.823, SE = 0.473, p < .09 \); see Figure 1).

2. IDAS General Depression

Across the entire sample, there was a significant positive relationship between IDAS Depression subscale score and CRP level \( b = 0.014, SE = 0.007, p < .05 \). There was not a significant effect of IDAS Depression subscale score on IL-6 level \( b = 0.002, SE = 0.005, n.s. \).

3. IDAS Dysphoria

There was a trend-level positive relationship between scores on the IDAS Dysphoria subscale and CRP levels \( b = 0.021, SE = 0.011, p < .07 \). There was a significant negative relationship between scores on the IDAS Dysphoria subscale and IL-6 levels \( b = -0.015, SE = 0.005, p < .05 \).
4. **IDAS Lassitude**

There was a significant effect of IDAS Lassitude on CRP level \((b = 0.111, SE = 0.054, p < .05)\). There was no significant effect of IDAS Lassitude on IL-6 concentration \((b = 0.021, SE = 0.038, n.s.)\).

5. **IDAS Well-Being**

There was no effect of IDAS Well-Being subscale score on CRP level \((b = 0.028, SE = 0.018, n.s.)\). There was a significant positive relationship between scores on the IDAS Well-Being subscale and IL-6 levels \((b = 0.056, SE = 0.025, p < .05)\).

E. **Association between Remitted Depression and Inflammation**

Unlike current depression, remitted depression was not associated with elevated levels of inflammation. Specifically, neither CRP nor IL-6 concentrations were significantly associated with remitted depression \((CRP: b = -0.051, SE = 0.061, n.s.; IL-6: b = -0.071, SE = 0.053, n.s.)\).

F. **Familial Vulnerability Analyses**

1. **IDAS subscales and inflammation**

Results from six hierarchical linear regression models examining the relationship between IDAS subscale scores and inflammation did not find a relationship between proband IDAS subscale score (i.e., IDAS Depression, Dysphoria, and Well-Being) and sibling inflammation level (i.e., CRP and IL-6; all \(p > .500\)).

2. **MDD Diagnosis**

Two sets of ANCOVAs were conducted to examine the differences in inflammation across sibling type. Because there were no families in the sample in which both siblings had current depression, the first set compared CRP and IL-6 in healthy siblings of healthy probands to the healthy siblings of currently depressed probands. Results from these ANOVAs did not show significant differences in inflammation between the two groups of healthy siblings (CRP: \(F[1, 111] = 0.769, n.s.; IL-6: F[1, 94] = 2.608, n.s.)\). To compare all three sibling types (i.e., healthy siblings of healthy probands, healthy siblings of depressed probands, and depressed
siblings of depressed probands), “proband” was determined by lifetime diagnosis of depression. Results from the two ANOVAs comparing IL-6 and CRP levels across these three sibling types did not reveal significant differences in inflammation across the sibling types (CRP: \( F[2, 115] = 1.721, \text{n.s.} \); IL-6: \( F[2, 94] = 1.606, \text{n.s.} \); see Figure 2).

3. **Exploratory parent-child analyses**

Four hierarchical linear regression models were conducted examining the effect of parent MDD on proband and sibling CRP and IL-6. Four ANCOVAs were conducted examining proband and sibling CRP and IL-6 across family type.

a. **Regression analyses**

There was a significant positive effect of parent lifetime MDD on offspring IL-6, over and above the effect of offspring lifetime MDD (\( \beta = .493, t = 3.079, p < .05 \)). That is, the children of parents with a history of MDD had higher levels of IL-6, even after adjusting for the children’s own MDD histories. Similarly, the parallel analysis with sibling CRP yielded a positive significant coefficient for the effect of parent lifetime MDD on sibling CRP level (\( \beta = .494, t = 2.408, p < .05 \)). There were no significant associations between parental history of MDD and proband inflammation level (i.e., CRP and IL-6, all \( p > .250 \)).

b. **ANCOVA analyses**

Results from the first set of ANCOVAs demonstrated that both sibling CRP and IL-6 differed across type of family (CRP: \( F[2, 18] = 6.378, p < .05 \); IL-6: \( F[2, 15] = 6.091, p < .05 \)). Follow-up analyses comparing only the never-depressed children of never-depressed parents to the never depressed children of parents with a lifetime MDD diagnosis showed that the latter group (i.e., the “high risk” group) had higher levels of CRP (\( F[1, 9] = 4.387, p = .05 \)) and IL-6 (\( F[1, 8] = 2575.612, p < .05 \)) than the former (i.e., the “low risk” group). There were no significant differences in proband inflammation across family type (i.e., CRP and IL-6, all \( p > .450 \)).
IV. DISCUSSION

Results from this investigation showed that basal markers of inflammation are stable over time and run in families. Overall, basal markers of inflammation were associated with current symptoms of depression, although the nature of these effects varied by inflammation marker and definition of depression. The two sets of analyses examining whether basal inflammatory markers were vulnerability factors for (rather than comcominants of) depression yielded null results. Markers of inflammation were not associated with remitted depression. The results from the familial vulnerability analyses—assessed both dimensionally and categorically—did not suggest a relationship between proband depression and sibling inflammation.

A. Inflammation as Vulnerability for Depression

In order for a construct that is associated with a particular disorder to be considered a vulnerability marker for that disorder, it must meet several criteria: 1) the marker should be relatively stable over time, 2) to the extent that the disorder runs in families, the putative vulnerability marker should run in families, as well, 3) it should be present in the healthy relatives of individuals with the disorder at greater frequencies than the general population, 4) the marker should remain even in the absence of symptoms of the disorder, and 5) healthy individuals with the marker should be more likely to develop the disorder than those without the marker. In the context of this framework, the current findings serve as mixed evidence for the hypothesis that elevated basal inflammation is indicative of vulnerability for depressive symptoms.

The first two hypotheses, which were that markers of inflammation should be stable over time and that they should run in families, were confirmed for both CRP and IL-6. These results are consistent with the idea that inflammation is a vulnerability marker for depression and with previous studies examining similar questions (Lang et al., 2006; Wessel et al., 2007; Singh, Hawkley, McDade, Cacioppo, & Masi, 2009; Platz et al., 2010; Epstein et al., 2013). Results
from this study replicated previous findings for the association between CRP and current depression, both measured categorically and dimensionally (Howren et al., 2009; Liu, et al., 2012). However, the relationship between IL-6 and current depression varied by the definition of depression. That is, the present study found that IL-6 was positively associated with current MDD diagnosis at a trend level but that it was associated with lower scores on the IDAS Dysphoria scale and higher scores (i.e., less general distress) on the IDAS Well-Being subscale. Given these data, CRP level seems to be a better candidate as a vulnerability marker for major depression than IL-6. However, the fourth and fifth hypotheses, which were that proband depression would predict sibling CRP and IL-6 and that CRP and IL-6 would be elevated in those with remitted depression, were not supported by the data. Results from exploratory analyses showed some positive associations between parental history of major depressive disorder and levels of inflammation in the children. However, these results were run in a small subsample of the data and were not consistent across probands and siblings, which limits their interpretability.

There are several possible explanations as to why CRP and IL-6 were not consistently shown to be familial vulnerability markers of depression in this sample. First, although the ICCs between siblings for CRP and IL-6 levels were significantly different from 0, they were both somewhat modest in magnitude. Thus, there are likely more influential situational and/or environmental factors that contribute to levels of inflammation than genetics or the familiality/heritability of basal inflammation. Second, it is possible that inflammation does not constitute a vulnerability marker for depression at all, and may merely be concomitant of depressive symptoms.

B. Inflammatory Reactivity as Vulnerability Marker for Depression

However, it is more likely that elevated basal levels of inflammation might not be associated with risk for depression, the way they have been shown to predict risk for other diseases, like cardiovascular disease (e.g., Lagrand et al., 1999). Given the dynamic nature of
the inflammatory system, as well as the evidence that inflammation may be a crucial mechanism in the relationship between stressful life events and the development of major depression (Raison, Caupron, & Miller, 2006; Miller, Maletic, & Raison, 2009; Slavich & Irwin, 2014), it is possible that abnormalities in inflammatory reactivity might be more indicative of vulnerability for depression. In this next section, we discuss the evidence that suggests various aspects of the inflammatory stress response are associated with depressive symptoms.

1. **Peak cytokine level during stress response**

Perhaps individuals who are predisposed to depression have higher peaks in their levels of pro-inflammatory cytokines in response to acute stress. Studies have shown that individuals with depression display greater inflammatory reactions to immune challenges (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003; Christian, Franco, Iams, Sheridan, & Glaser, 2010). For example, Christian and colleagues (2010) found that pregnant women with greater depressive symptoms had exaggerated inflammatory responses to an influenza vaccine than low-symptom women. There is even evidence that greater immune response, specifically IL-6 and IL-1β, to ex vivo antigen stimulation is associated with greater depressive symptoms (Stieglitz et al., 2015). That is, when whole blood samples were exposed to two different types of infectious agents, elevated cytokine responses were associated with increased depressive symptoms.

There is also considerable evidence that depression is associated with a heightened inflammatory response to social stress. Indeed, studies have shown that individuals with depression secrete higher levels of pro-inflammatory cytokines following laboratory tasks that induce social stress than non-depressed controls (Miller, Rohleder, Stetler, & Kirschbaum, 2005; Pace et al., 2006; Weinstein et al., 2010; Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013). Naturalistic studies have also found associations between chronic psychosocial stress (e.g., caregiving, work stress/burnout, etc.) and greater inflammatory responses (see Rohleder, 2014 for review). Although no study has examined whether elevated inflammatory
responses to acute stress prospectively predict depression, there is evidence that individuals with risk alleles in the serotonin transporter gene (which is associated with risk for depression) demonstrate greater acute inflammatory responses to social stress tasks (Fredericks et al., 2010; Yamakawa, Matsunaga, Isowa, & Ohira, 2015). The findings from these cross-sectional investigations would need to be extended by examining the longitudinal relationship between inflammatory stress reactivity and development of depressive symptoms.

2. **Chronometry of inflammatory stress response**

   Alternatively, chronometric aspects of the inflammatory stress response may be better predictors of risk for depression. Chronometry refers to the temporal aspects of the stress response, specifically the rise time to peak and recovery time associated with particular response systems (Davidson, 1998; 2015). It is possible that individuals who reach peak levels of pro-inflammatory cytokines following a stressor or are slower to return to baseline levels of pro-inflammatory cytokines are more vulnerable to the development of depression. Very few experimental studies have examined the chronometry of the inflammatory stress response, particularly with regard to its relationship to depression. However, one study found that depressed women’s CRP levels continued to rise even after they completed an acute social stress task, whereas non-depressed women’s CRP levels had already returned to baseline (Miller et al., 2005).

3. **Sensitivity of inflammatory response**

   Third, maybe it is the sensitivity of the inflammatory response to stressors that is associated with risk or vulnerability for depression. That is, individuals with either hyper- or hypo-sensitive inflammatory responses may be more vulnerable to depression. For instance, people whose inflammatory stress responses are activated similarly in response to both minor and major stressors might (in either direction) have higher risk for developing depression in their lifetime. Although no studies have examined this question with the inflammatory stress response, this has been demonstrated with HPA axis responding, particularly for cortisol.
Specifically, studies have found both blunted and hyper-reactive cortisol responses to laboratory and daily stressors to be pathogenic (McQuade & Young, 2000; Holsboer, 2001; Peeters, Nicholson, & Berkhof, 2003; Dickerson & Kemeny, 2004; Burke, Davis, Otte, & Mohr, 2005; Morris, Rao, Wang, & Garber, 2014; Mazurka, Wynne-Edwards, & Harkness, 2015). It possible that a similar pattern could be the case in inflammation.

4. **Differential units of analysis for stress**

In addition, much of the research summarized thus far has focused on the mediating role that the inflammatory stress response plays in the relationship between psychosocial stress and depression. However, it is important to consider that the inflammatory response to physiochemical and microbial stressors might also be related to one’s propensity to develop depression. The positive associations between inflammation and depressive symptoms during *in vivo* and *ex vivo* immunological challenge studies described earlier lend support to this idea (Christian et al., 2010; Steiglitz et al., 2015). In addition, there is evidence that early microbial environment moderates the relationship between stress and elevated inflammation (McDade, Hoke, Borja, Adair, & Kuzawa, 2013) and that malnutrition is associated with risk for inflammation-related disease (Guerrant, DeBoer, Moore, Scharf, & Lima, 2013).

It is also possible that the subjective experience of an event as stressful might contribute to elevated inflammation. Perhaps individual variation in the inflammatory stress response is related to cognitive factors, like attributing a situation as stressful or negative. For example, models of resilience, such as the “shift-and-persist” model suggest that adverse sequelae of life stress—including poor health outcomes—can be mitigated by “shifting” (i.e., accepting stressors and adapting oneself through reappraisals) and “persisting” (i.e., persevering by holding on to meaning and maintaining optimism; Chen & Miller, 2012). Relately, there is evidence that those who are able to derive benefits from negative or traumatic experiences experience better mental and physical health than those who cannot (Bower, Moscowitz, & Epel, 2009). It is purported that these health outcomes arise from more adaptive and efficient responses to future
stressors, which, in turn, subject these individuals to less exposure to stress hormones that can have deleterious effects on physical health. All together, these findings highlight the necessity of broad definitions of “stress” and the “stress response” in the investigation of the role of the inflammatory stress response in the development of depression.

5. **Set-point for inflammatory reactivity**

Finally, it is possible that inflammation, particularly with regard to its relationship with risk for depression, has a set point, similar to body weight. The set-point theory for body weight posits that different bodies are programmed to function best (i.e., optimal metabolic performance) at different body weights (Mrovsky & Powley, 1977; Keesey & Hirvonen, 1997). The set-point theory has been used to explain weight regain in previously obese persons following weight loss. That is, their body weight might change substantially, but their set-point remains the same, which is why they return to their pre-diet weight so often. In addition, a person’s set-point for weight, rather than his current weight, might actually be more indicative of his risk for various cardiovascular and metabolic diseases (Armitage, Taylor & Poston, 2005).

Applying this logic to inflammation, perhaps the appropriate risk factor to examine when investigating the relationship between inflammation and depression is actually inflammatory reactivity, rather than resting inflammation.

C. **Role of Anti-inflammatory Cytokines in Depression Vulnerability**

Healthy immune functioning requires a balance between pro- and anti-inflammatory cytokines. Anti-inflammatory cytokines, like IL-10, inhibit activated macrophages and maintain homeostasis within the inflammatory system of the host (D'andrea, Asté-Amezaga, Valiante, Ma, Kubin & Trinchieri, 1993). Given IL-10’s regulatory role of IL-6 and other pro-inflammatory cytokines, researchers have proposed that IL-10 might also play a key role in MDD (Roque, Correia-Neves, Mesquita, Palha & Sousa, 2009). The rationale behind examining IL-10 is that a robust inflammatory response is not particularly harmful on its own; rather, it is the lack of
homeostatic control by anti-inflammatory cytokines (i.e., IL-10) that contributes to depressive symptoms.

Although not examined in the present study, it is possible that abnormal levels of basal IL-10 are vulnerability factors for depression. Studies in both animals and humans have implicated IL-10 (and other anti-inflammatory cytokines) in the development of depressive symptoms. Animal studies have demonstrated that anti-inflammatory cytokines are critical for the regulation of the duration and intensity of sickness behaviors by inhibiting production of pro-inflammatory cytokines and mitigating pro-inflammatory cytokine signaling in the brain (Heyen, Finck & Johnson, 2000; Strle et al., 2007). A study by Mesquita and colleagues (2008) even found a dose-response relationship between IL-10 and sickness behavior, such that altering IL-10 expression in mice yielded changes in observed sickness behaviors.

In humans, various investigations have found links between anti-inflammatory cytokines and depression. One study found that individuals with a diagnosis of major depression had significantly lower levels of circulating IL-10, as well as a weaker ratio between IL-6 and IL-10 than never-depressed controls (Dhabhar et al., 2009). Similarly, others have found major depression to be associated with increased levels of IL-1β and decreased levels of IL-10 (Song, Halbreich, Han, Leaonard & Luo, 2009). Finally, pharmacological treatment studies have demonstrated that several classes of antidepressants stimulate production of IL-10 (Maes et al., 1999; Kubera, Kenis, Bosmans, Scharpe & Maes, 2000; Kubera et al., 2001). These findings suggest that a loss of regulatory association between pro- and anti-inflammatory cytokines is a correlate of depressive symptoms in adults. Therefore, in an examination of the putative role of inflammation in risk for developing depression, perhaps it is too simplistic to examine pro-inflammatory cytokines and CRP only and more attention should be paid to anti-inflammatory cytokines and the ratio of pro- to anti-inflammatory cytokines.
D. Heterogeneity of Depression and Inflammation

Depression is also a heterogeneous syndrome with various symptom clusters and clinical presentations. Therefore, another aim of this study was to explore which aspects of depression might be related to inflammation. Towards this aim, depression was operationalized in several different ways: categorical diagnosis, dimensional depressive symptoms (IDAS General Depression), low positive affect (IDAS Well-Being), high negative affect (IDAS Dysphoria), and low motivation (IDAS Lassitude). Indeed, we found that inflammation was related to some of these constructs more than others.

There was consistent evidence for the relationship between overall depression and higher levels of inflammation, as elevated CRP and IL-6 were both associated with a categorical diagnosis of depression, and elevated CRP was associated with higher scores on the IDAS General Depression scale. This replicates previous findings of the relationship between depression and inflammation (e.g., Slavich & Irwin, 2014) and extends them by demonstrating the relationship between CRP and a dimensional measure of depressive symptoms using an empirically derived scale. To the best of our knowledge, no study has examined a relationship between CRP and the IDAS General Depression scale.

Findings for the relationship between inflammation and negative affect/depressed mood, as measured by the IDAS Dysphoria subscale, were mixed. Whereas there was a trend-level positive association between CRP concentration and IDAS Dysphoria score (i.e., greater dysphoria predicts higher CRP level), there was a significant negative relationship between IL-6 and IDAS dysphoria score (i.e., lower dysphoria predicted higher IL-6). There is not consensus in the literature about the relationship between inflammation and broad distress/negative affect. Whereas some studies have found no association between inflammation and self-reported negative affect (measured by participants’ endorsement of depression, anxiety, and anger items on a 5-point Likert scale; Janicki-Deverts, Cohen, Doyle, Turner, & Treanor, 2007), others have shown that differences in trait negative affect (Marsland, Sathanoori, Muldoon, & Manuck, 2007;
Prather, Marsland, Muldoon, & Manuck, 2007) and negative affective response to a laboratory task (Carroll et al., 2011) are associated with increased pro-inflammatory cytokines. The current findings suggest that inflammatory dysregulation is either not specific to dysregulation in negative affect, or that CRP and IL-6 are differentially associated with negative affect. One study found that insulin resistance moderated the relationship between inflammation and negative affect (Suarez, Boyle, Lewis, Hall, & Young, 2006), and there may be a moderating variable at play here, too.

Another potential explanation for the mixed findings are how negative affect is defined in these studies. Some definitions might emphasize the deactivating components of negative affect (such as sadness), whereas others might accentuate the more arousing components (such as anger and anxiety). The IDAS-II Dysphoria subscale includes a balance of the deactivating (e.g., “I felt discouraged about things”) and arousing components of negative affect (e.g., “I found myself worrying all the time”), although it does not include items related to anger (these are found in the Ill Temper subscale). This mix might also contribute to the mixed findings observed here if inflammation, or just CRP or IL-6, is associated with negative affect.

The findings were similarly mixed for the IDAS Lassitude subscale. Whereas there was a positive relationship between Lassitude score and CRP level, there was no significant relationship between Lassitude and IL-6 concentration. The IDAS Lassitude subscale measures low energy (e.g., “I felt exhausted”) as well as diminished motivation ("It took a lot of effort for me to get going"). These items most closely match sickness behaviors, which function as a motivational state to conserve energy so an animal can ward off infection (Hart, 1991; 2011; Dantzer, 2001). The observed positive association between Lassitude and CRP is consistent with the idea that elevated levels of inflammation contribute to the diminished motivation and activity levels seen in MDD. However, given that pro-inflammatory cytokines have been demonstrated to be the purveyors of sickness behaviors (Dantzer, 2000), it is surprising that no relationship was found between IL-6 and scores on the Lassitude subscale of the IDAS-II.
Finally, the results were also mixed regarding the relationship between positive affect (i.e., IDAS Well-Being score) and inflammation. On the one hand, there was no significant relationship between CRP level and IDAS Well-Being scale; on the other hand, there was a significant positive relationship between IDAS Well-Being score and IL-6 concentration. That is, greater well-being (more positive affect) was associated with higher levels of IL-6. This is surprising given previous studies’ findings of the positive association between anhedonia and inflammation (Eisenberger et al., 2010), negative associations between positive affect and inflammation (Prather et al., 2007; Steptoe et al., 2008; Stellar et al., 2015).

Major Depressive Disorder is a heterogenous syndrome, with over 1,000 different possible symptom permutations (Fried & Nesse, 2015). Although the evidence for the relationship between depression, broadly, and inflammation is well-established, it is not true that every individual with depression also has elevated inflammation. It follows logically that elevations in pro-inflammatory cytokines and CRP are associated with certain types of depression (Kiecolt-Glaser et al., 2015). Research, for example, has shown that melancholic and non-melancholic depression are associated with different inflammatory profiles (Rothermundt et al., 2001). In addition, there is evidence that markers of inflammation are positively correlated with depression symptom severity in MDD with melancholic features, whereas they are negatively correlated in MDD with atypical features (Karlović, Serretti, Vrkić, Martinac, & Marčinko, 2012). There is also evidence that particular symptoms of depression, such as suicidality, are associated with elevations in inflammatory markers (Köhler-Forsberg et al., 2017). The current findings highlight the need for multifaceted definitions and assessments of depression when examining depression and inflammation to best capture the nuanced relationship.

E. Strengths and Limitations

This study contained some limitations that might have contributed to the pattern of results that was observed. First, the sample was overall, quite healthy. Although 116 of the 347
individuals who participated had a lifetime diagnosis of MDD, there were only 15 with current diagnoses of MDD. Even when using the IDAS General Depression scale, which would account for individuals with significant subthreshold depressive symptoms, the mean was 36.72 ($SD = 12.26$), and only 4% of the sample had scores above 65, a score that is consistent with current clinical levels of depression (Watson, O'Hara, & Chmielewski, 2008). Thus, the limited range of depressive symptoms observed in this sample might have made it difficult to detect a relationship between depression and inflammatory markers. Second, siblings with equal symptom levels were randomized to “proband” and “sibling” for the analyses. Although this allowed for the retention of more data, it was not ideal for examining inflammatory markers in the “high risk” siblings of probands with significant depressive symptoms. Third, there are many factors that affect inflammation that were not measured or could not be accounted for in the present study. In addition to more stable factors like diet, exercise, and socioeconomic status, there are several momentary factors that contribute to variation in inflammation throughout the day, such as acute stress, having eaten recently, and time of day. Although the present study attempted to control for these factors by ensuring that participants had been seated for several hours before the blood spots were collected, the samples were taken at various points throughout the day. In addition, because of the timing of the blood spot collection (at the end of a 3- to 4-hour laboratory visit), some participants ended up eating or drinking something, and this was not noted in the data. As a result, these uncontrolled factors might have caused variance in the data that could not be accounted for during analyses.

Despite these limitations, the study contained several strengths. First of all, it contained multiple assessments of depressive symptoms—reliable clinician ratings from a diagnostic interview as well as self-reported symptoms using an empirically derived scale. Second, this research study was conducted in an ethnically diverse community sample, so the findings are be more generalizable than they would be if they had come from an undergraduate sample.
F. **Clinical Implications and Future Directions**

The results of this investigation showed that markers of peripheral inflammation, namely CRP and IL-6, are stable over time and familial concomitants of depression, although they do not represent familial vulnerability factors for depression. That being said, elevated inflammation may still play a mechanistic role in the pathogenesis of depression, or it may be an important component of the maintenance of depressive symptoms. If this is the case, then additional examination of the relationship between inflammation and depressive symptoms could clarify the etiology of depression (or at least a particular type of depression), explain the mechanism of various efficacious treatments, and inform development and testing of new treatments for depression. In this next section, we highlight some of these future directions.

1. **Clarifying the pathogenesis of depression**

   Based on prior studies and the present results, as mentioned above, it is possible that the inflammatory stress response, rather than basal inflammation, is key in the pathogenesis of depression. As discussed above, there are a variety of cross-sectional studies that have examined this connection and found that greater inflammatory reactivity to acute and chronic stress is associated with negative mood (Reichenberg et al., 2001; Wright et al., 2005; Harrison et al., 2009) and full-threshold depression (Miller et al., 2005; Pace et al., 2006; Weinstein et al., 2010; Fagundes et al., 2013). Longitudinal studies examining the inflammatory stress response, as opposed to basal levels of inflammation, could clarify this question. As an alternative, cross-sectional studies could benefit from examining the moderating role of life stress in the association between inflammation and depression. If inflammation is a key component of the association between life stress and depression, then life stress may moderate the relationship between depressive symptoms and inflammation (Slavich & Irwin, 2014). Additionally, researchers have been paying increasing attention to the role of anti-inflammatory cytokines (Roque et al., 2009), and specifically on the ratio of pro- to anti-inflammatory cytokines in depression (Dhabhar et al., 2009; Song et al., 2009). Additional research focused on
understanding the role of anti-inflammatory cytokines in the pathogenesis of depression would augment our understanding of this pathway.

Based on the evidence that the stress response seems to play a key role in the relationship between inflammation and depression, examining how other aspects of the stress response relate to both depression and inflammation is important. There is already a significant body of evidence linking the activity of the inflammatory system with HPA axis functioning in both acute and chronic stress (Black, 2002; Leonard, 2005; Hughes, Connor, & Harkin, 2016). As technology for data collection continues to improve, larger-scale studies that investigate the interaction between both systems—particularly in response to stressful laboratory stress paradigms—would help answer these questions.

Finally, the results of this study showed that different aspects of depression relate to aspects of inflammation in different ways. Although there is some evidence that inflammatory dysregulation may be more related to anhedonia/low positive affect than depressed mood/high negative affect (Janicki-Deverts et al., 2007), the data is still mixed in regard to this question (Marsland et al., 2007; Prather et al., 2007). In addition, newer conceptualizations of inflammation and depression point to a depression subtype which is more affected by inflammation and is characterized by melancholia, fatigue, and somatic symptoms (Maes et al., 2012; Penninx et al., 2013). Factor analytic studies including depressive symptoms and various markers of inflammation would help answer questions about which types of depression and depressive symptoms load on to which aspects of inflammatory dysregulation.

2. Explaining current treatments

If inflammatory cytokines indeed play a role in the pathogenesis of MDD, then this might also help explain why certain psychotherapies are effective. For example, behavioral activation is one the most efficacious psychotherapeutic interventions for major depression (Dimidjian et al., 2006; Cuijpers, Van Straten & Warmerdam, 2007) and seeks to achieve antidepressant effects by increasing activity (e.g., exercise, hobbies, and self-care) and engaging in more
prosocial behaviors (Lejuez, Hopko & Hopko, 2001; Beck & Alford, 2009). Perhaps the mechanism driving the relationship between increased activity and depressive symptom reduction is reduced inflammation. That is, as physical activity and engaging in prosocial behavior are both associated with decreases in inflammation (Kasapis & Thomson, 2005; Uchino, 2006), it is possible that a decrease in inflammation is a biological mechanism through which behavioral activation achieves efficacy.

Cognitive-behavioral therapy, the goal of which is for patients to identify and modify maladaptive thinking patterns which emerge in stressful situations, might also help reduce the inflammatory stress response, in addition to the subjective emotional response to stressful situations. Indeed, there is some evidence that better cognitive control of emotional information is associated with reduced pro-inflammatory cytokine response to emotional stressors (Shields, Kuchenbecker, Pressman, Sumida, & Slavich, 2016). Mindfulness-based approaches, such as mindfulness-based stress reduction and mindfulness-based cognitive therapy emphasize enhancing the mind-body connection and reducing the emotional impact of cognitions, and these interventions have been shown to be efficacious for reducing depressive symptoms (Goyal et al., 2014). Because these treatments specifically target stress reduction and stress management, they may also help attenuate the inflammatory stress response as part of their active ingredient. Intervention studies with non-clinical samples have demonstrated that individuals who participate in mindfulness-based treatments show reduced inflammatory responses to social stressors compared to those who participate in education-based control treatments (Pace et al., 2009; Rosenkranz et al., 2013). Incorporating biometric and inflammatory data into randomized control treatment studies for depression could begin to answer these questions about treatment mechanisms.

3. Developing novel treatment approaches

This information could also inform novel treatment strategies, even targeting the inflammation itself as a way of reducing depressive symptoms. There is some evidence that
anti-inflammatory diet can help alleviate mood symptoms in hospital settings (Allison & Ditor, 2015), and physical activity interventions have demonstrated efficacy for treating MDD (Blake, Mo, Malik, & Thomas, 2009; Josefsson, Lindwall, & Archer, 2014). Finally, there is growing evidence that augmenting antidepressant medication with an anti-inflammatory medications, such as infliximab, help treat depressive symptoms in those who do not respond to antidepressants alone (Raison et al., 2012; Maciel, Silva, Morrone, Calixto, & Campos, 2013).
V. CONCLUSION

The findings from the current study indicate that markers of basal inflammation are relatively stable over time, run in families, and are associated with specific components of current depression. However, basal peripheral inflammation did not predict familial vulnerability for depression or particular depressive symptoms. These results do not rule out the putative mechanistic role of elevated inflammation, particularly during the inflammatory stress response—in the pathogenesis and/or maintenance of depression. Longitudinal studies examining whether cytokine levels during the inflammatory stress response predict later depressive symptoms could help answer this question. Clarifying the role of inflammation in depression could also shed light on the mechanisms of current treatments and the development of novel treatment approaches.
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### Table 1

**Sample Characteristics and Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Proband</th>
<th>Sibling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>22.28 (3.14)</td>
<td>22.22 (3.23)</td>
</tr>
<tr>
<td>N Female (%)</td>
<td>84 (57.5)</td>
<td>81 (55.5)</td>
</tr>
<tr>
<td>N Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>20 (13.7)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Asian</td>
<td>16 (11)</td>
<td>18 (12.3)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>73 (50)</td>
<td>71 (48.6)</td>
</tr>
<tr>
<td>Latino/a</td>
<td>25 (17.1)</td>
<td>27 (18.5)</td>
</tr>
<tr>
<td>Mixed Race/Other</td>
<td>9 (6.2)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>24.88 (5.44)</td>
<td>24.89 (5.43)</td>
</tr>
<tr>
<td>Mean IDAS Score (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>42.29&lt;sup&gt;a&lt;/sup&gt; (12.285)</td>
<td>31.14&lt;sup&gt;b&lt;/sup&gt; (7.29)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>20.50&lt;sup&gt;a&lt;/sup&gt; (8.02)</td>
<td>13.96&lt;sup&gt;b&lt;/sup&gt; (4.34)</td>
</tr>
<tr>
<td>Well-Being</td>
<td>21.30&lt;sup&gt;a&lt;/sup&gt; (6.28)</td>
<td>28.17&lt;sup&gt;b&lt;/sup&gt; (5.66)</td>
</tr>
<tr>
<td>N Lifetime MDD diagnosis (%)</td>
<td>75&lt;sup&gt;a&lt;/sup&gt; (53)</td>
<td>20&lt;sup&gt;b&lt;/sup&gt; (14)</td>
</tr>
<tr>
<td>N Current MDD diagnosis (%)</td>
<td>11&lt;sup&gt;a&lt;/sup&gt; (8)</td>
<td>0&lt;sup&gt;b&lt;/sup&gt; (0)</td>
</tr>
<tr>
<td>N Lifetime Anxiety Disorder (%)</td>
<td>68&lt;sup&gt;a&lt;/sup&gt; (49)</td>
<td>57&lt;sup&gt;b&lt;/sup&gt; (39)</td>
</tr>
<tr>
<td>N Current Anxiety Disorder (%)</td>
<td>40 (27)</td>
<td>33 (22)</td>
</tr>
<tr>
<td>N Current Antidepressants (%)</td>
<td>11 (7.5)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>N Current Psychotherapy (%)</td>
<td>9 (6.1)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>N Past Psychiatric Hospitalization (%)</td>
<td>10 (6.8)</td>
<td>4 (2.7)</td>
</tr>
</tbody>
</table>

*Note. Values with non-common superscripts indicate significant differences between proband and sibling according to paired samples t-tests and χ² tests.*
Table 2

Estimates of Fixed Effects of Covariates on CRP and IL-6

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (0 = female)</td>
<td>-0.086*</td>
<td>0.011</td>
</tr>
<tr>
<td>Age</td>
<td>0.006</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI</td>
<td>0.037**</td>
<td>0.014**</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.199*</td>
<td>-0.015</td>
</tr>
<tr>
<td>Past smoking</td>
<td>-0.012</td>
<td>-0.015</td>
</tr>
<tr>
<td>Current Drinking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear effect of drinking status</td>
<td>-0.139</td>
<td>-0.195*</td>
</tr>
<tr>
<td>Quadratic effect of drinking status</td>
<td>0.032</td>
<td>0.086*</td>
</tr>
<tr>
<td>Current Insomnia</td>
<td>0.047</td>
<td>0.138*</td>
</tr>
<tr>
<td>Birth control use</td>
<td>0.428**</td>
<td>-0.089</td>
</tr>
</tbody>
</table>

Note. Values marked with an asterisk (*) indicate significant effects at \( p < .05 \). Values marked with two asterisks (**) indicate significant effects at \( p < .01 \). Values marked with a plus (+) indicate trend-level effects at \( p < .10 \). Because drinking has been shown to have a curvilinear effect, such that both non-drinkers and heavy drinkers (i.e., 8+ drinks/week) have elevated inflammation (O’Connor et al., 2009), both the linear and quadratic effects of drinking status were included as covariates.
Figure 1. Distributions of raw and square root-transformed CRP and IL-6 concentrations.
Figure 2. Associations between CRP and IL-6 concentrations.
Figure 3. Inflammation by current depression diagnosis. Across the whole sample, the CRP levels of depressed individuals \((n = 15)\) were significantly higher than those without current depression \((n = 332)\). Across the whole sample, the IL-6 levels of depressed individuals \((n = 13)\) were higher than those of non-depressed individuals \((n = 295)\) at a trend level.
Figure 4. Sibling inflammation levels by family type. There were no significant differences in CRP level between never-depressed siblings of never-depressed probands \((n = 51)\), never-depressed siblings of probands with lifetime depression \((n = 46)\), and siblings with lifetime depression of probands with lifetime depression \((n = 18)\). Similarly, there were no significant differences in IL-6 level between never-depressed siblings of never-depressed probands \((n = 44)\), never-depressed siblings of probands with lifetime depression \((n = 35)\), and siblings with lifetime depression of probands with lifetime depression \((n = 15)\).
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