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### Authors

Leschak, Carrienne J  
Dutcher, Janine M  
Haltom, Kate E Byrne  
[et al.](#)

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## Associations between Psychosocial Factors and Circulating Cytokines in Breast Cancer Survivors

Carrienne J. Leschak, M.A.<sup>a</sup>, Janine M. Dutcher, Ph.D.<sup>b</sup>, Kate E. Byrne Haltom, B.A.<sup>a</sup>, Elizabeth C. Breen, Ph.D.<sup>c</sup>, Julienne E. Bower, Ph.D.<sup>a,c,d</sup>, Naomi I. Eisenberger, Ph.D.<sup>a,\*</sup>

<sup>a</sup>Department of Psychology, University of California, Los Angeles

<sup>b</sup>Department of Psychology, Carnegie Mellon University

<sup>c</sup>Semel Institute for Neuroscience and Human Behavior, Cousins Center for Psychoneuroimmunology, University of California, Los Angeles

<sup>d</sup>Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles; Jonsson Comprehensive Cancer Center, University of California, Los Angeles

### Abstract

**Objective.**—Research has established links between social isolation and heightened levels of proinflammatory cytokines (e.g., interleukin-6 [IL-6], tumor necrosis factor alpha [TNF- $\alpha$ ]). Recent advances allow for the examination of cytokines that may also play a role in antiviral immunity (interferon-gamma [IFN- $\gamma$ ]). The present work explored how various features of social experience relate to circulating cytokines in breast cancer survivors, as inflammation has been tied to cancer recurrence and mortality.

**Design.**—Female breast cancer survivors ( $N=43$ ) completed a blood draw to assess circulating levels of proinflammatory cytokines (IL-6, TNF- $\alpha$ ) and levels of a cytokine that also relates to antiviral immunity (IFN- $\gamma$ ).

**Main Outcome Measures.**—We examined associations between cytokines and different aspects of social experience, including household size, psychosocial well-being, and social threat anxiety.

**Results.**—Circulating levels of IFN- $\gamma$  were associated with larger household size ( $r=0.32$ ,  $p=0.04$ ) and higher levels of psychosocial well-being ( $r=0.33$ ,  $p=0.04$ ). Additionally, heightened levels of IL-6 were associated with social threat anxiety ( $r=0.38$ ,  $p=0.01$ ). Heightened IL-6 was also associated with household size ( $r=0.33$ ,  $p=0.03$ ).

**Conclusion.**—These findings are consistent with work suggesting that antiviral immunity and inflammation may have distinct contributions to the links between social experience and health, particularly for those previously diagnosed with breast cancer.

\*Correspondence should be addressed to NIE: Naomi Eisenberger, University of California Los Angeles, Psych-Soc, Box 951563, 5514 Pritzker Hall, Los Angeles, CA 90095-1563, neisenbe@ucla.edu, Phone: 1-310-267-5196.

Disclosure of Interest

The authors report no conflict of interest.

## Keywords

inflammation; antiviral immunity; social threat; social contact; psychosocial well-being

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## 1. Introduction

Considerable research has highlighted the importance of social relationships for physical health. Those who report feeling more socially connected have higher survival rates (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015) and lower risk for a variety of diseases (Cohen, Doyle, Turner, Alper, & Skoner, 2003; Cole, Kemeny, Fahey, Zack, & Naliboff, 2003). A growing body of research has examined physiological and biological mechanisms underlying the link between social connection and health, and much of this work has focused on immune-related processes (Eisenberger & Cole, 2012; Leschak & Eisenberger, 2019). Most empirical research in this area over the last two decades has examined links between social experience and inflammation, such as circulating levels of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- $\alpha$ ) (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017; Uchino et al., 2018). However, recent advances in assaying procedures have now allowed us to examine cytokines, such as interferon gamma (IFN- $\gamma$ ), which also play a role in antiviral immunity. The present work aims to examine how various features of social relationships correlate with standard measures of inflammation (IL-6, TNF- $\alpha$ ) and with IFN- $\gamma$  in a sample of breast cancer survivors.

Prior work has highlighted the link between social experience and inflammation. Specifically, many studies have shown links between increased inflammation and both objective (e.g. small social networks) (Ford, Loucks, & Berkman, 2006; Yang, McClintock, Kozloski, & Li, 2013) and subjective (e.g. loneliness) measures of social isolation (Cole et al., 2015; Vingeliene, Hiyoshi, Lentjes, Fall, & Montgomery, 2019). Further, those who perceive themselves as socially isolated tend to have more robust inflammatory responses following a stressor (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012; Jaremka et al., 2013). In addition to this correlational work, experimental studies directly manipulating social experience (e.g. Trier Social Stress Test) have shown that experiences related to social threat (e.g. negative social evaluation) can causally increase proinflammatory activity (Dickerson, Gable, Irwin, Aziz, & Kemeny, 2009; Kemeny, 2009). Interestingly, research has also shown that experimental manipulations of inflammation can lead to changes in social perception and behavior. Specifically, experimentally increasing inflammation (via injection of low-dose endotoxin) leads to enhanced neural sensitivity to social evaluative feedback and social threat (e.g. rejection) (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009; Muscatell, Moieni, et al., 2016). In sum, past work points to a bidirectional relationship in which socially threatening experiences can increase inflammation and inflammation can increase sensitivity to social threat.

Though the recent focus in this domain has been on the relationship between social factors and inflammation, earlier work suggests that social experience may have important consequences for antiviral immunity as well. For example, correlational work has shown

that, for those without high levels of life stress, individuals with more diverse social ties or more supportive social networks tend to have lower incidences of upper respiratory infections (Cobb & Steptoe, 1996; Hamrick, Cohen, & Rodriguez, 2002). Research utilizing experimental protocols such as the common cold paradigm, in which healthy participants are exposed to the common cold virus and subsequently monitored for signs of infection and illness, has similarly found that individuals with larger social networks are less susceptible to upper respiratory infections (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). In addition, within the context of experimental common cold paradigms, those high in traits that may facilitate increased social contact, such as sociability and extraversion, appear to have increased resistance to upper respiratory infections (Cohen et al., 2003), as well as less severe infections as measured by viral shedding (Broadbent, Broadbent, Phillpotts, & Wallace, 1984). In addition to the common cold paradigm, studies have assessed immune competence by examining the extent to which antibodies are produced in response to a viral vaccine (e.g. influenza). Such work has found that those with higher levels of loneliness tend to have a lower antibody response, suggesting poorer *in vivo* functional immunity (Pressman et al., 2005). Together, this correlational work suggests that certain aspects of social experience are related to antiviral immunity, though causal studies in this area are lacking.

Recent animal work has demonstrated that changes in interferon-gamma (IFN- $\gamma$ ), a pleiotropic cytokine that plays a role in both innate and adaptive immunity (Müller et al., 1994), can alter social behavior. Although IFN- $\gamma$  is now known to play a role in immune and inflammatory responses as well as tumor immunosurveillance (Ivashkiv, 2018), it was originally discovered as a factor that interferes with viral replication. While Type I interferons, such as interferon-alpha and interferon-beta, are the primary interferon responders to viral threats, IFN- $\gamma$ , as a Type II interferon, works alongside other interferons to supplement defenses to antiviral and microbial threats (Kang, Brown, & Hwang, 2018). Specifically, IFN- $\gamma$  obstructs nearly every stage of the viral life cycle: inhibiting viral entry during both extracellular and intracellular stages, interrupting viral replication, inhibiting viral gene transcription, weakening the stability of expressed viral genes, inhibiting viral shedding, and interfering with viral reactivation (Kang et al., 2018).

Indeed, IFN- $\gamma$ 's role in anti-viral immunity has been posited as critical for its effect on social behavior. Specifically, mice that have been genetically altered to have deficiencies in IFN- $\gamma$  show impairments in social behavior, displaying a preference for non-social versus social stimuli (Filiano et al., 2016), behavior considered typical of autistic phenotypes (Werner, Dawson, Osterling, & Dinno, 2000). Remarkably, after reversing the IFN- $\gamma$  deficiencies via injections of recombinant IFN- $\gamma$  into the cerebrospinal fluid, social behavior was restored such that it was indistinguishable from wild type mice (with no immune deficiencies) (Filiano et al., 2016). In sum, past work points to a bidirectional relationship in which greater social contact can increase antiviral immunity and certain cytokines that contribute to antiviral immunity are critical for social interaction.

Although considerable work has examined the link between social measures and inflammatory markers, to date, few studies in humans have examined how social measures relate to IFN- $\gamma$ . Past work in this area has typically examined stimulated production

of IFN- $\gamma$ , which has been shown to increase in response to acute psychological stress (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998; Buske-Kirschbaum, Kern, Ebrecht, & Hellhammer, 2007). Until recently, assays have not been sensitive enough to detect circulating concentrations of IFN- $\gamma$ , in part, because IFN- $\gamma$  is produced at lower levels relative to other cytokines (Aziz et al., 1999; Breen et al., 2011; Reed et al., 2016; Shen et al., 1998). Because of the measurement difficulties with circulating IFN- $\gamma$ , prior work has not been able to simultaneously examine circulating measures of proinflammatory cytokines alongside circulating measures of IFN- $\gamma$  within one sample. However, work examining a composite pattern of leukocyte gene expression known as the conserved transcriptional response to adversity (CTRA) has examined the expression of genes related to inflammation and antiviral immunity simultaneously (although CTRA focuses on Type-1 interferons, rather than IFN- $\gamma$ , which is a Type-2 interferon). Research on the CTRA pattern suggests that factors associated with psychosocial well-being relate to differences in immunity at the gene expression level. Specifically, loneliness is associated with the downregulation of antiviral genes and upregulation of proinflammatory genes (Cole et al., 2015), whereas eudaimonic well-being is associated with the opposite pattern—upregulation of antiviral genes and downregulation of proinflammatory genes (Fredrickson et al., 2013). The present work will explore whether similar associations exist between social factors such as loneliness and immune outcomes when measured at the protein level.

The current study explored these associations within breast cancer survivors given that alterations in immune status have been tied to important clinical outcomes within this population. For example, inflammation is associated with increased risk for recurrence and survival (Boen et al., 2018), as well as with negative side effects of cancer treatment (e.g., fatigue) (Bower, 2007). Additionally, several cancer treatment options, such as chemotherapy and radiation may increase risk for secondary infections or reactivation of latent viruses (Castón et al., 2016; Lai, Su, Kao, & Liang, 2019). Furthermore, psychosocial factors such as social isolation and lack of social support are predictive of poorer outcomes in breast cancer patients (Hinzey, Gaudier-Diaz, Lustberg, & Devries, 2016; Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006; Kroenke et al., 2013). Thus, understanding the social coregulation of the immune system may be particularly relevant for patients who are at risk for poorer health outcomes (e.g. following radiation treatment).

## 2. Methods

### 2.1. Participants

Participants consisted of 45 female breast cancer survivors. Participants were recruited via the University of California Los Angeles (UCLA) Tumor Registry, newspaper advertisements, re-contacting participants from past research studies, and word-of-mouth referrals. In order to be eligible for the study, participants had to have been diagnosed with early stage breast cancer (stages 0-III), completed any radiation or chemotherapy between 3 months and 10 years ago, and have no evidence of residual or recurrent disease. In addition, participants had to have no metallic implants (due to safety restrictions for a neuroimaging portion of the larger study, not reported here) and be right-handed (due to the neuroimaging

session). The UCLA Institutional Review Board approved all study procedures, and all participants provided written informed consent.

Two participants were excluded from analyses due to missing blood draw data ( $n = 1$ ) or missing household size data ( $n = 1$ ), leaving  $N = 43$  participants. This sample size is sufficient to detect medium-to-large Pearson correlations ( $r = 0.41$ ,  $\alpha = 0.05$ ,  $\beta = 0.20$ ) (Hulley, Cummings, Browner, Grady, & Newman, 2013), and thus suitable for the present work. The remaining 43 participants were, on average, 52.7 years of age ( $SD = 8.2$  years; range: 32–65 years), and the majority of women identified as Caucasian (79.1%). Over half (62.8%) of participants were employed at the time of the study, and an additional 16.3% were retired. About half of participants reported that they had previously undergone radiation (48.8%), endocrine therapy (53.5%), and/or chemotherapy (48.8%), and 16.3% of participants reported having taken Herceptin.<sup>1</sup>

## 2.2. Measures

Eligible women came to UCLA for a single study visit between 8:00 AM and 12:00 PM. Participants completed a blood draw to assess baseline levels of circulating cytokines, and then completed eight separate self-report measures related to social experience.

**2.2.1. Social experience measures.**—Participants completed various measures of social support, loneliness, depression, well-being, social anxiety, and rejection sensitivity. These constructs were selected given the previous associations of these psychosocial dimensions and physical health, including immune outcomes.

**2.2.1.1. Household size.**: Participants self-reported the number of individuals (besides themselves) who reside in their household. Household members represent a consistent and frequent source of social contact, and therefore a source of pathogen exposure. Prior studies investigating pathogen transmission have reported larger household size as a risk factor for the spread of communicable disease (Almuneef et al., 2004; Blake et al., 1993) and thus may relate to antiviral processes.

**2.2.1.2. Social support.**: To capture various dimensions of social support, including both emotional and instrumental support, as well as support received as well as provided to others, participants completed the Social Provisions Scale (Cutrona & Rusell, 1987) and the 2-Way Social Support Scale (Shakespeare-Finch & Obst, 2011). The Social Provisions Scale consists of 24 items (e.g. “I have close relationships that provide me with a sense of emotional security and well-being”) measured on a 4-point Likert scale (1 = *strongly disagree*, 4 = *strongly agree*). The 2-Way Social Support Scale consists of 21 items (e.g. “I feel that I have a circle of people who value me”) measured on a 6-point Likert scale (0 = *not at all*, 5 = *always*). Both the Social Provisions Scale and the 2-Way Social Support Scale demonstrated high internal reliability ( $\alpha = 0.90$  and  $\alpha = 0.89$ , respectively).

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<sup>1</sup>Treatment percentages do not sum to 100%, as participants often indicated that they had undergone more than one treatment.

**2.2.1.3. Eudaimonic well-being:** Eudaimonic well-being was measured using 11 items (e.g. “How often did you feel that you had warm and trusting relationships with others?”) from the Mental Health Continuum-Short Form (Keyes, 2009). Items were assessed using a 6-point Likert scale (0 = *never*, 5 = *everyday*). The scale demonstrated high internal reliability ( $\alpha = 0.87$ ).

**2.2.1.4. Loneliness:** Loneliness was assessed with the 20-item UCLA Loneliness Scale-Version 3 (Russell, 1996), where participants responded to items such as “How often do you feel that you lack companionship?” using a 4-point Likert scale (1 = *never*, 4 = *always*). The scale demonstrated high internal reliability ( $\alpha = 0.93$ ).

**2.2.1.5. Depression:** Depression was assessed with the Center for Epidemiological Studies Depression Scale (Radloff, 1977), which consists of 20 items (e.g. “I felt lonely”) using a 4-point Likert scale (0 = *rarely or none of the time*, 3 = *most or all of the time*). The scale demonstrated high internal reliability ( $\alpha = 0.92$ ).

**2.2.1.6. Social anxiety:** The Social Interaction Anxiety Scale (Leary, 1983) consists of 15 items (e.g. “I often feel nervous even in casual get-togethers”) assessed on a 5-point Likert scale (1 = *not at all characteristic of me*, 5 = *extremely characteristic of me*). The measure demonstrated high internal reliability ( $\alpha = 0.93$ ).

**2.2.1.7. Rejection sensitivity:** The Sensitivity to Rejection Scale (Mehrabian, 1970) consists of 24 items (e.g. “I am very sensitive to any signs that a person might not want to talk to me”) assessed on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*). The scale demonstrated acceptable internal reliability ( $\alpha = 0.74$ ).

**2.2.2. Cytokine assessment.**—Blood samples were collected by venipuncture into tubes containing ethylenediaminetetraacetic acid, immediately chilled at 4°C, then centrifuged for acquisition of plasma and stored at –80°C for subsequent batch testing. Cytokine concentrations were quantified using an MSD MULTI-SPOT® Assay System (Meso Scale Discovery [MSD], Rockville, MD). Plasma samples were thawed and prepared by the recommended 2-fold dilution, then assayed in duplicate on a custom 5-plex (Proinflammatory Panel 1 Human Kit: IL-6, IL-8, IL-10, TNF- $\alpha$ , IFN- $\gamma$ ). Assays were performed according to the manufacturer’s protocol, with an expanded 8-point standard curve utilizing serial 3-fold dilutions, beginning with a 3-fold dilution of the multianalyte calibrator provided. Electrochemiluminescence signals were measured on the SECTOR Imager 2400 instrument (MSD), and the Discovery Workbench (MSD) software was used to generate a 4-parameter logistic fit curve for all analytes. Analyte-specific lower limits were determined based on the lowest calculated sample or calibrator concentration for each analyte, taking the two-fold sample dilution into account (0.1 pg/mL for IL-10 and TNF- $\alpha$ , 0.2–0.3 pg/mL for IL-6, IL-8, and IFN- $\gamma$ ). Mean intra-assay coefficient of variation (CV) percentages for duplicate determinations on an internal laboratory quality control sample were less than or equal to 8% for all cytokines. Inter-assay CV percentages across two assay plates were less than 15% for all cytokines (range 5.9% to 14.7%).

Although it would have been interesting to also examine Type I interferons, the MSD assay system being used has been shown to be unable to detect IFN- $\alpha$ 2 in a majority of human plasma samples (Meissner et al., 2014). Moreover, while MSD does produce components to measure human IFN- $\beta$  as part of a combination kit for IFN- $\gamma$ , - $\alpha$ 2a, and - $\beta$ , the manufacturer only reports on human plasma levels of IFN- $\gamma$ . This combination assay also requires customization and configuration by the user, and does not have the same degree of quality control as the validated assays completely manufactured by MSD, which our laboratory utilizes. Therefore, we have chosen to perform studies such as the one reported here with the 5-plex described, but recognize that as technology improves, there may be options in future studies to explore circulating levels of both Type I and Type II interferons in human subjects.

### 2.3. Analysis Approach

Analyses were conducted using SPSS 25. All cytokine data were natural log transformed prior to analysis to correct for non-normal distributions. Descriptive information for the non-transformed cytokine data is reported in Supporting Information (Table S1). All associations were examined via partial Pearson correlations, controlling for body mass index (BMI) due to known effects of BMI on cytokines (Himmerich et al., 2006). Controlling for age did not affect any of the reported results; thus, results controlling only for BMI are reported.

## 3. Results

### 3.1. Examination of social experience measures

First, we examined correlations between the self-report measures (Supporting Information, Table S2). Given substantial correlations between several of the measures, we submitted the eight social experience measures to a principal components analysis in order to reduce redundancy. This approach also aimed to minimize the number of statistical tests conducted, thereby controlling the Type I error rate.

The principal components analysis identified three orthogonal factors that explained 78% of the variance (eigenvalues  $> 1$ ; see Table). The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.73 (exceeding the recommended value of 0.6). Bartlett's test of sphericity was significant ( $\chi^2(.28) = 147.08, p < 0.001$ ), confirming adequate correlations between the variables, thus allowing for successful data reduction. All variables had a primary factor loading above 0.7 (exceeding the minimum criterion of 0.4), and no variables had a cross-loading of 0.3 or above, indicating all variables contributed to a simple factor structure. Thus, composite measures were created based on the self-report measures that loaded onto each factor. The raw scores for each measure were standardized, and the measures were averaged together for each component, resulting in three measures which were further examined in analyses.

Based on the constructs included in each component, we refer to these three measures as a single-item measure of household size, a composite score of psychosocial well-being, and a composite score of social threat anxiety. These three components were not significantly correlated with each other (Supporting Information, Table S3).



**3.1.1. Household size.**—Household size was examined separately, as it was not correlated with any other self-report measure, and did not significantly load onto the other two factors, described below.

**3.1.2. Psychosocial well-being.**—The composite score for psychosocial well-being was created by combining measures of social support, eudaimonic well-being, loneliness (reverse-coded), and depression (reverse-coded). Thus, this composite captured aspects of social well-being (e.g. social support, loneliness) as well as broader psychological well-being (e.g. depression, eudaimonic well-being), which can often stem from social well-being. Measures of loneliness and depression were reverse-scored prior to composite creation so that higher values reflected better psychosocial well-being. One participant was missing depression data, and therefore the psychosocial well-being composite for this subject was computed excluding depression. (Removing this participant did not significantly change the results.)

**3.1.3. Social threat anxiety.**—A composite score for social threat anxiety was created utilizing scores from the Social Interaction Anxiety Scale and the Sensitivity to Rejection Scale, two scales associated with hypervigilance and anxiety regarding potential social threats. These two measures were positively correlated with each other,  $r(41) = 0.58$ ,  $p < 0.001$ .

### 3.2. Correlations between cytokines and social experience measures

Correlations between individual scale measures and each cytokine are reported in Table S4 in Supporting Information. There were no significant associations between any of the social composite measures and TNF- $\alpha$  ( $p$ 's  $> 0.17$ ). Since the focus of this investigation was on IL-6, TNF- $\alpha$ , and IFN- $\gamma$ , results from analyses with IL-10 and IL-8 are reported in Supporting Information (Table S3). Thus, below we present associations between the remaining cytokines of interest, IL-6 and IFN- $\gamma$ , and the social composite measures.

Household size was positively correlated with plasma levels of IFN- $\gamma$  ( $r(40) = 0.32$ ,  $p = 0.04$ ), such that women who lived with a greater number of individuals tended to have higher levels of circulating IFN- $\gamma$  (Figure, Panel A). Household size was also positively correlated with plasma levels of IL-6 ( $r(40) = 0.33$ ,  $p = 0.03$ ) (Figure, Panel B).

The composite measure of psychosocial well-being was positively correlated with IFN- $\gamma$  ( $r(40) = 0.33$ ,  $p = 0.04$ ), such that women with higher levels of psychosocial well-being had higher levels of circulating IFN- $\gamma$  (Figure, Panel C). In contrast, psychosocial well-being was not significantly associated with IL-6 ( $r(40) = 0.10$ ,  $p = 0.53$ ) (Figure, Panel D).

The composite score for social threat anxiety was positively correlated with IL-6 ( $r(40) = 0.38$ ,  $p = 0.01$ ), such that individuals with higher levels of social threat anxiety had higher levels of circulating IL-6 (Figure, Panel F). However, social threat anxiety was not significantly correlated with IFN- $\gamma$  ( $r(40) = 0.17$ ,  $p = 0.29$ ) (Figure, Panel E).

## 4. Discussion

The current work examined associations between various social constructs and quantitative measurements of circulating levels of cytokines (IL-6, TNF- $\alpha$ , IFN- $\gamma$ ) in a sample of breast cancer survivors. Results show that IFN- $\gamma$  was positively associated with psychosocial well-being, whereas IL-6 was positively associated with social threat anxiety. Both IFN- $\gamma$  and IL-6 were positively associated with household size. No significant associations were found between any of the three social measures and TNF- $\alpha$ .

Although IFN- $\gamma$  is involved in both innate and adaptive immunity, the association observed here between higher circulating levels of IFN- $\gamma$  and better psychosocial well-being is in line with past work linking increased eudaimonic well-being and decreased loneliness (two components of this psychosocial well-being measure) with upregulated antiviral gene expression (though this work has focused on Type I rather than Type II interferons) (Cole et al., 2015; Fredrickson et al., 2013). Importantly, similar associations between higher eudaimonic well-being and increased antiviral gene expression have been found in breast cancer survivors (Boyle, Cole, Dutcher, Eisenberger, & Bower, 2019). Given the nature of the psychosocial well-being composite here, our results suggest that other psychosocial measures, such as low levels of depression, may be similarly related to bolstered antiviral immunity.

In contrast to household size and psychosocial well-being, social threat anxiety was not significantly associated with IFN- $\gamma$ . Instead, social threat anxiety was significantly associated with IL-6, such that individuals who are more hypervigilant about social threats or perceive them as more likely to occur (e.g. those high in rejection sensitivity) tended to have higher circulating levels of IL-6. This fits with prior work linking psychosocial stress and negative social experiences more generally with increased levels of inflammation (Kemeny, 2009; Steptoe, Hamer, & Chida, 2007). Additionally, this finding is in line with the theory that perceptions of social threat may serve as an indicator of potential wounding, thereby necessitating elevated levels of inflammation (Leschak & Eisenberger, 2019). Although TNF- $\alpha$ , another proinflammatory cytokine, has previously been linked with factors related to social functioning (Marucha, Crespin, Shelby, & Andersen, 2005), including social threat (Dickerson et al., 2009), the circulating levels observed in this study population were not associated with any of the social measures examined here. This may partially be due to the fact that associations between social measures and TNF- $\alpha$  are typically less robust than for IL-6 (Steptoe et al., 2007).

Finally, the observed association between household size and in vivo levels of IFN- $\gamma$  is in line with recent theoretical models suggesting that increased social contact is associated with a bolstered antiviral response in order to protect from the potential associated increase in viral pathogen exposure (Cole, 2019; Leschak & Eisenberger, 2019). Household size was also positively associated with circulating levels of IL-6. One potential explanation for this finding is that living with more household members, in addition to increasing pathogen exposure, also presents more consistent opportunities for social conflict or interpersonal stress, conditions that have been shown to upregulate inflammatory responses (Steptoe et al.,

2007). Future work could further probe this finding by assessing household levels of stress or interpersonal conflict.

The present study population consisted of a community sample of mostly Caucasian and relatively affluent adult females who had been previously diagnosed with and treated for breast cancer. Thus, it is possible that some aspect of the associations observed here may be unique to this population. Indeed, we do not have a comparison group to examine if this same pattern of associations is also present in a sample that has not gone through breast cancer. While this is a limitation of this study, these findings provide preliminary insights regarding links between social functioning and in vivo immune status, and suggest that social measures may be linked to IFN- $\gamma$  in ways different from the more commonly assessed circulating cytokines (e.g., IL-6). Though existing work within similar patient populations has often examined links between inflammation and social measures (Marucha et al., 2005; Muscatell, Eisenberger, Dutcher, Cole, & Bower, 2016), direct investigations of associations between correlates of antiviral immunity and social measures remain sparse. Future research should focus on how social experience relates to both inflammatory and antiviral immunity in other population types.

The present work consisted of examining correlations between cytokines and self-reported social measures from a single timepoint. Thus, we cannot make claims about the causality of these effects. However, based on past work documenting the coregulation of the immune system and social behavior (Eisenberger et al., 2017), the associations observed here are likely similarly bidirectionally influenced. Developing experimental laboratory models and protocols with human subjects that may allow direct manipulation of reliable biomarkers of antiviral immunity (as has been done with inflammation using low-dose endotoxin) at the same time that social experience can be evaluated, will likely require creative interdisciplinary collaborations with immunologists and/or virologists, but will be critical for further examining the causality of effects related to antiviral immunity and social behavior. When causal approaches are not possible, levels of circulating IFN- $\gamma$  can be measured in humans, as was done here, to examine potential associations with psychological factors and social behavior. As mentioned, little work has previously examined levels of circulating IFN- $\gamma$  in humans as, until recently, assays have not been sensitive enough to reliably detect levels in plasma. The continued development of more sensitive assays that include IFN- $\gamma$  will enable researchers to further investigate IFN- $\gamma$  and its correlates in human populations.

In sum, the current work is among the first to examine circulating markers that relate to both inflammation and antiviral immunity, and their distinct associations with various dimensions of social experience. Household size and psychosocial well-being measures, which are likely to predict exposure to viral pathogens, were associated with higher levels of circulating IFN- $\gamma$ , which has been associated with antiviral immunity. In contrast, social threat anxiety, believed to signal the perceived likelihood of wounding from hostile conspecifics, was associated with higher circulating IL-6, associated with heightened inflammatory activity, in order to prepare the body for possible wound healing. These findings support recent theoretical models suggesting distinct roles for inflammation and antiviral processes as they relate to social behavior.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Biographies

Carrienne J. Leschak is a doctoral candidate in Psychology at the University of California, Los Angeles (UCLA). Her research aims to understand the bidirectional relationship between social interactions and physical health, focusing on neuroimmune interactions.

Janine M. Dutcher is a Research Scientist (Special Faculty) in Psychology and the Lab Director for the Health & Human Performance Lab at Carnegie Mellon University. Her research seeks to understand how positive interventions and experiences (e.g., self-affirmation, mindfulness meditation, social support) may lead to reductions in threat and stress responding.

Kate E. Byrne Haltom is a senior staff Research Associate and lab manager for the Social and Affective Neuroscience Laboratory and the Social Cognitive Neuroscience Laboratory at the University of California, Los Angeles (UCLA).

Elizabeth C. Breen is a Professor Emerita of the Cousins Center for Psychoneuroimmunology at University of California, Los Angeles (UCLA). She began her career as a Clinical Laboratory Scientist, and transitioned to human immunology research in the Department of Microbiology & Immunology in the UCLA School of Medicine. She served for more than a decade as Co-Director of the Center's Inflammatory Biology Core Laboratory.

Julienne E. Bower is a Professor in the Departments of Psychology and Psychiatry/ Biobehavioral Sciences at the University of California, Los Angeles (UCLA). She examines the interrelationships among psychological and behavioral parameters, biological factors, and disease, including specific pathways from psychological responses through to the biological processes that influence disease and health outcomes.

Naomi I. Eisenberger is a Professor of Psychology and Director of the Social and Affective Neuroscience Laboratory at the University of California, Los Angeles (UCLA). She specializes in social neurocognitive aspects of emotion and behavior and how these processes relate to health-relevant biomarkers.

## Data Availability Statement

The data that support the findings of this study are openly available in the Open Science Framework at <http://doi.org/10.17605/OSF.IO/KQ984>. Because participants may be identified by the combination of demographic and/or cancer diagnosis or treatment variables, some data are not publicly available in order to protect the privacy of research participants.

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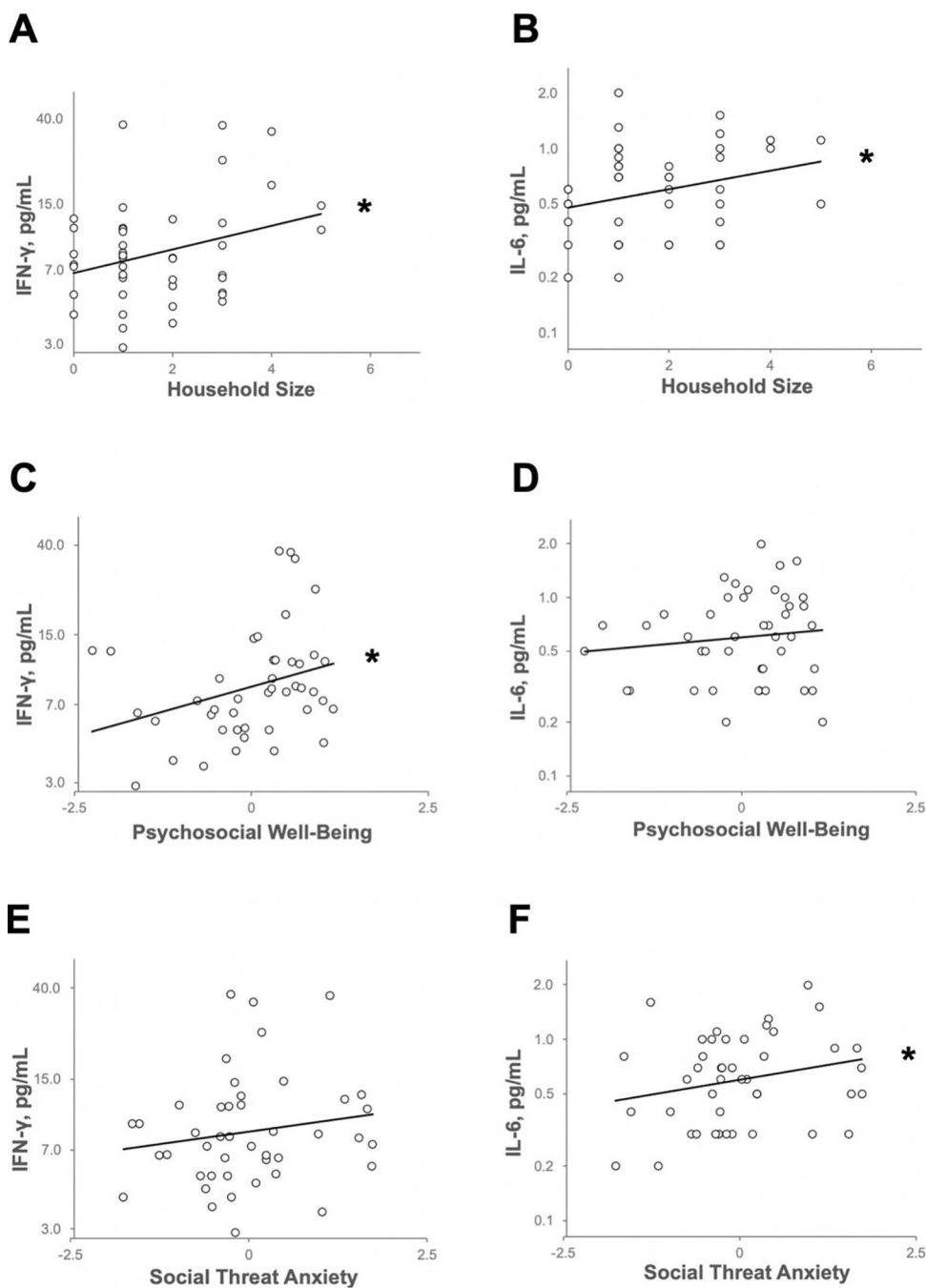
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**Figure. Associations between social experience and IFN- $\gamma$  and IL-6 cytokines.** Raw correlations are shown between measures of household size (A, B), psychosocial well-being (C, D), and social threat anxiety (E, F), and plasma levels of IFN- $\gamma$  and IL-6. Horizontal axes for psychosocial well-being and social threat anxiety are standardized z-scores. Plotted cytokines values (vertical axes) are natural log transformed but axes are labeled with non-transformed values for ease of interpretation. \* $p < 0.05$ .

**Table.**

Summary of principle components analysis.

Measures	Factor 1: Household size	Factor 2: Psychosocial well-being	Factor 3: Social threat anxiety
Number of household members	<b>0.931</b>		
Social provisions (SPS)		<b>0.851</b>	
Social support (2-WSSS)		<b>0.790</b>	
Eudaimonic well-being (MHC-SF)		<b>0.810</b>	
Loneliness (UCLA)		<b>-0.900</b>	
Depression (CES-D) <sup>a</sup>		<b>-0.785</b>	
Social anxiety (SIAS)			<b>0.801</b>
Rejection sensitivity (SRS)			<b>0.884</b>
<b>Eigenvalue</b>	1.065	3.560	1.625
<b>% of Variance</b>	13.307	44.503	20.317

Note. SPS = Social Provisions Scale; 2-WSSS = 2-Way Social Support Scale; UCLA = UCLA Loneliness scale (version 3); MHC-SF = Mental Health Continuum-Short Form; CES-D = Center for Epidemiologic Studies Depression; SIAS = Social Interaction Anxiety Scale; SRS = Sensitivity to Rejection Scale. *N* = 43.