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Abstract

Although evidence suggests that loneliness may increase risk for health problems, the mechanisms responsible are not well understood. Immune dysregulation is one potential pathway: Elevated proinflammatory cytokines such as interleukin-6 (IL-6) increase risk for health problems. In our first study ($N = 134$), lonelier healthy adults exposed to acute stress exhibited greater synthesis of tumor necrosis factor- α (TNF- α) and IL-6 by peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS) than their less lonely counterparts. Similarly, in the second study ($N = 144$), lonelier posttreatment breast-cancer survivors exposed to acute stress exhibited greater synthesis of IL-6 and interleukin-1 beta (IL-1 β) by LPS-stimulated PBMCs than their counterparts who felt more socially connected. However, loneliness was unrelated to TNF- α in Study 2, although the result was in the expected direction. Thus, two different populations demonstrated that lonelier participants had more stimulated cytokine production in response to stress than less lonely participants, which reflects a proinflammatory phenotype. These data provide a glimpse into the pathways through which loneliness may affect health.

Keywords

loneliness, inflammation, psychoneuroimmunology, stress reactions, health, neuroendocrinology

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The desire for social connection is a strong impetus behind human behavior (Leary & Cox, 2008; Maslow, 1968). The importance of the need to belong is not surprising given the significance of group living for humans' survival throughout their evolutionary past; humans were most likely to thrive when they were part of a network of people who were invested in their welfare and who looked out for their well-being (Tooby & Cosmides, 1996). Over time, this ultimately led to a fundamental need to form close and caring bonds with other people (Baumeister & Leary, 1995).

Because the need for social connection is central to human nature, the failure to fulfill this need should be detrimental to mental and physical health. Indeed,

loneliness is strongly linked to poor health (Hawkley & Cacioppo, 2010). For example, people who were lonelier reported worse physical health, experienced more chronic diseases, and were more likely to develop coronary heart disease than people who felt more socially connected (Sugisawa, Liang, & Liu, 1994; Thurston & Kubzansky, 2009). Another study found that lonely people had 45% lower odds of survival compared with

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people who were not lonely, even after accounting for important sociodemographic and health-relevant risk factors (Holt-Lunstad, Smith, & Layton, 2010). This effect is on par with the negative health effects of obesity and inactivity (Holt-Lunstad et al., 2010), which provides compelling evidence for the importance of close relationships for well-being.

Immune dysregulation is one potential pathway through which loneliness may influence health. In fact, recent theoretical work suggests that the links among loneliness, stress, and inflammation (a key immunological mechanism) are critical to understanding the health implications of loneliness (Hawkley, Bosch, Engeland, Marucha, & Cacioppo, 2007). Inflammation is modulated by stress and has strong ties to health; excessive and chronic inflammation is linked to age-related diseases, such as cardiovascular and neurodegenerative disorders, and frailty (Ershler & Keller, 2000; Hansson, 2005).

A growing body of evidence suggests that loneliness may be linked to dysregulated immune function, including elevated inflammation. Compared with people who felt more socially connected, lonelier medical students had higher levels of Epstein-Barr virus (EBV) antibody titers (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985). Similarly, lonelier HIV-infected men had higher human herpesvirus 6 (HHV-6) antibody titers than people who felt more socially connected (Dixon et al., 2006). Because elevated herpesvirus antibody titers reflect poor cellular immune system control over the latent virus, the EBV and HHV-6 data provide evidence of dysregulated cellular immunity among lonely people. Lonelier medical students and lonelier psychiatric inpatients also exhibited less natural-killer-cell activity, an important antitumor and antiviral defense, than their counterparts who felt more socially connected (Kiecolt-Glaser, Garner, et al., 1984; Kiecolt-Glaser, Ricker, et al., 1984). People who were lonelier had a poorer immune response to an influenza vaccine than those who were less lonely (Pressman et al., 2005). Compared with people who felt more socially connected, lonelier people had higher monocyte chemotactic protein-1 (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012), a cytokine implicated in inflammatory diseases such as rheumatoid arthritis and atherosclerosis (Deshmane, Kremlev, Amini, & Sawaya, 2009). In addition, lonelier individuals exhibited more up-regulation of proinflammatory genes and down-regulation of anti-inflammatory genes compared with people who were less lonely (Cole et al., 2007).

Much less is known about the links between loneliness and inflammation in the context of acute stress. However, related evidence suggests that lonelier people are more psychologically reactive to stress than those who are less lonely. For example, although loneliness was not associated with the frequency of major life

stressors or traumatic events, lonelier individuals felt more stressed and reported greater anxiety than individuals who were less lonely (Cacioppo et al., 2000). Similarly, lonelier people experienced everyday activities as more stressful and threatening, even though there were no loneliness-related differences in the type or frequency of daily activities (Hawkley, Burleson, Berntson, & Cacioppo, 2003). Because lonely people are highly stress reactive and stress modulates inflammation (Glaser & Kiecolt-Glaser, 2005), loneliness may be linked to proinflammatory cytokine production in response to an acute stressor. Indeed, initial evidence demonstrated that the proinflammatory cytokine interleukin-6 (IL-6) and the interleukin-1 receptor antagonist (IL-1Ra) were elevated after acute stress among people experiencing greater loneliness compared with those who were less lonely (Hackett et al., 2012).

Overview of the Current Research

The goal of the current research was to fill an important gap in the literature by examining whether loneliness is linked to stress-related proinflammatory cytokine production. We selected tumor necrosis factor-alpha (TNF- α) and IL-6 as our primary inflammation measures because of their pervasive use in the psychoneuroimmunology (PNI) literature and their strong ties to age-related diseases (Ershler & Keller, 2000; Hansson, 2005).

In the current research, we utilized two samples: (a) healthy middle-aged adults and (b) breast-cancer survivors who had completed cancer treatment—except for selective estrogen-receptor modulators (SERMs) and aromatase inhibitors—between 2 months and 3 years prior to enrollment in the study. We hypothesized that, compared with their counterparts who felt more socially connected, lonelier people would exhibit greater TNF- α and IL-6 production in response to an acute laboratory stressor.

Study 1

The sample in Study 1 was purposefully selected on the basis of health; only healthy, sedentary, overweight people without major comorbidities were eligible to participate. This sample allowed us to examine our hypothesis in a relatively homogeneous sample free of health problems that could influence cytokine production.

Method

Participants. Participants ($N = 134$) were drawn from the baseline prerandomization sample of a clinical trial assessing the potential health benefits of omega-3; all were recruited through advertisements and media

announcements. Individuals were ineligible to participate if they had a convulsive, autoimmune, or inflammatory disease or if they had diabetes, chronic obstructive pulmonary disease, symptomatic ischemic heart disease, liver or kidney failure, gastroesophageal reflux disease, a prior history of cancer (except basal or squamous cell), excessively high triglycerides or low-density lipoprotein cholesterol, or a body mass index (BMI) under 22.5 or over 40. People were also excluded if they engaged in more than 3 hr of vigorous physical exercise per week; were taking medications for depression, anxiety, cholesterol, or cardiovascular problems; or were pregnant, nursing, vegetarians, alcoholics, drug abusers, or smokers. Additional characteristics of the sample are listed in Table 1. The Ohio State University Institutional Review Board approved the project; all subjects provided written informed consent prior to participation.

Procedure. Participants arrived at the Clinical Research Center (CRC; a hospital research unit) at 7:45 a.m., and a catheter was inserted in their arm. After eating a standardized breakfast and resting for 20 min, participants gave blood so we could assess baseline levels of stimulated cytokine production. Next, participants completed the Trier Social Stress Test, a well-validated stressor consisting of an impromptu speech and a mental arithmetic task (Kirschbaum, Pirke, & Hellhammer, 1993). Participants spent 10 min preparing a speech about why they were the best candidate for a job. Then they delivered a

5-min speech (without notes or aids) in front of a video camera and two panel members who were trained to remain neutral and unresponsive. Participants also completed a 5-min serial-subtraction task out loud in front of the same panel. Additional blood samples were collected 45 min and 2 hr after the stressor.

Questionnaires. Loneliness was measured with the UCLA Loneliness Scale, which assessed perceptions of social isolation and loneliness (Russell, 1996). The scale is highly reliable, demonstrates construct and convergent validity, and is one of the most commonly used loneliness measures.

The Pittsburgh Sleep Quality Index (PSQI) measured sleep quality over the month prior to the study by assessing a combination of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI can distinguish between people with and without sleep disturbances, indicating acceptable discriminant validity. The measure provided a way to assess the links between loneliness and stimulated cytokine production independent of sleep, which can influence cytokine levels (Faraut, Boudjeltia, Vanhamme, & Kerkhofs, 2012).

Exercise was measured with a combination of one item about hours of vigorous exercise per week and a shortened version of the Community Healthy Activities Model Program for Seniors questionnaire, a well-validated measure of physical activity among middle-aged and older adults (Stewart et al., 2001). High levels of exercise are associated with low levels of inflammation (Shephard, 2002). Accordingly, the exercise index allowed us to disentangle the relationships among loneliness, inflammation, and exercise.

Participants answered questions about their age, smoking status, weekly average alcohol consumption, current medication use, and highest level of education. Education level was used as an index of socioeconomic status because some women in our sample did not work outside of the home. In addition, education is less vulnerable to current economic conditions than income and job status. We also assessed participants' sagittal abdominal diameter (SAD), an index of abdominal fat measured via a person's abdominal height while laying flat. SAD was used as an adiposity measure because belly fat is one major source of proinflammatory cytokines (Mohamed-Ali et al., 1997). In addition, SAD is more precise than BMI, another common adiposity measure, because BMI can be influenced by muscle mass.

Immune assays. Production of TNF- α and IL-6 by peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS, a bacterial endotoxin) was

Table 1. Characteristics of the Study 1 Sample ($N = 134$)

Characteristic	Number or mean
Race	
White	$n = 105$ (77.8%)
Black	$n = 22$ (16.3%)
Other	$n = 7$ (5.2%)
Education	
High school or below	$n = 7$ (5.2%)
Some college or college graduate	$n = 81$ (60%)
Graduate or professional training	$n = 46$ (34%)
Marital status	
Single	$n = 18$ (13.4%)
Married	$n = 92$ (68.6%)
Separated, divorced, or widowed	$n = 24$ (17.8%)
Sex	
Male	$n = 42$ (31.1%)
Female	$n = 92$ (68.1%)
Age (years)	$M = 51.01$ ($SD = 7.75$)
Body mass index	$M = 30.83$ ($SD = 4.7$)
Sagittal abdominal diameter (cm)	$M = 22.96$ ($SD = 3.14$)
Loneliness ^a	$M = 17.78$ ($SD = 9.53$)

^aLoneliness was scored from 0, lowest, to 60, highest, using the UCLA Loneliness Scale (Russell, 1996).

measured using an electrochemiluminescence method with kits from Meso Scale Discovery (Rockville, MD) and read using the Meso Scale Discovery Sector Imager 2400. The stored culture supernatant samples for each subject were assayed for all the cytokine markers in one run, thus using the same controls for all three time points for each person. To assess LPS-stimulated cytokine production, we incubated PBMC cultures, 1×10^6 cells/ml, for 24 hr in 3 ml RPMI-1640 media (Sigma-Aldrich, St. Louis, MO) containing 10% human male serum either with or without 1.0 $\mu\text{g/ml}$ LPS. After 24 hr, the cells were pelleted by centrifugation (2,000 rpm for 5 min) and the supernatants removed and stored at -80°C . The dose and duration were based on evidence that the effects of dietary n-3 supplementation (which was part of the parent randomized controlled trial) are best demonstrated through the use of low LPS concentrations to stimulate PBMCs (Calder, 2004; Fritsche, 2006). Sensitivity for LPS-stimulated cytokine production is 2.4 pg/ml . The intraassay coefficient of variation was 3.16% for TNF- α and 4.56% for IL-6. The interassay coefficient of variation was 15.35% for TNF- α and 12.13% for IL-6.

Data-analysis strategy. The distributions of the immune data were checked for normality and the presence of outliers. Participants whose immune values were more than 4 standard deviations from the mean were dropped from the corresponding analyses. Specifically, we dropped three TNF- α and three IL-6 values, which were less than 1% of all samples. The results did not differ whether the outliers were included or excluded. The data for TNF- α and IL-6 were highly skewed. Accordingly, each measure was \log_{10} transformed prior to analyses.

Mixed models were utilized to account for correlations within subjects because several observations were obtained for each participant. An unstructured variance-covariance matrix was fitted to estimate the error variance. We hypothesized that loneliness would be linked to stimulated cytokine production in response to the stressor, such that higher levels of loneliness would be associated with greater increases in stimulated cytokine production. To test reactivity to the stressor, we investigated whether loneliness predicted poststress levels of stimulated cytokine production, controlling for baseline levels of the corresponding cytokine. Adjusting for baseline created scores reflecting change in the outcome from before to after the stressor.

Potential confounds were selected based on their theoretical and empirical relationships to cytokine levels and kept the same within and across studies when possible. Every model was adjusted for SAD, age, and gender. Models also included a random effect for the plate on which the assay was conducted when results suggested that plate number produced additional variability not

explained by other predictors. All models were analyzed with SPSS Version 19.0 (IBM, New York, NY) using a repeated and a random statement (when plate was included as a random effect). In ancillary analyses, we examined health behaviors (e.g., sleep and exercise) as additional confounds.

We initially included the three-way Loneliness \times Measurement Time \times Gender interaction and the corresponding two-way interactions in each model. None of the two-way or three-way interactions involving gender were significant, and thus the gender interaction terms were omitted from all analyses.

Results

Results reported here are unstandardized coefficients; results for TNF- α and IL-6 reactivity are presented graphically in Figures 1a and 1b, respectively. Loneliness was unrelated to baseline synthesis of TNF- α or IL-6 by PBMCs stimulated with LPS (both $ps > .623$).

Primary analyses. To analyze the stimulated TNF- α production stress-reactivity data, we used a mixed model that included the covariates listed in the Data-Analysis Strategy section, baseline levels of stimulated TNF- α production, the main effects of loneliness and measurement time (45 min after stress vs. 2 hr after stress), and the interaction between loneliness and measurement time. In response to acute stress, participants who were lonelier exhibited significantly greater increases in the synthesis of TNF- α production by LPS-stimulated PBMCs than participants who were less lonely, $b = 0.004$, $F(1, 108) = 7.70$, $p = .007$. The nonsignificant interaction between loneliness and measurement time indicated that the strength of the relationship between loneliness and stimulated TNF- α production was the same at both poststress assessments, $p = .124$.

In the next model, we examined stimulated IL-6 production using a similar analytic strategy. In response to acute stress, lonelier participants exhibited significantly greater increases in IL-6 production by LPS-stimulated PBMCs than participants who were less lonely, $b = 0.004$, $F(1, 113) = 5.00$, $p = .027$. The nonsignificant interaction between loneliness and time indicated that the strength of the relationship between loneliness and stimulated IL-6 production was the same at both poststress assessments, $p = .807$.

Ancillary analyses. We used a series of mixed models to examine whether the relationships between loneliness and stimulated cytokine production held after controlling for sleep quality over the month prior to the study, numbers of hours slept the night before the visit, smoking status, exercise levels, alcohol consumption, education

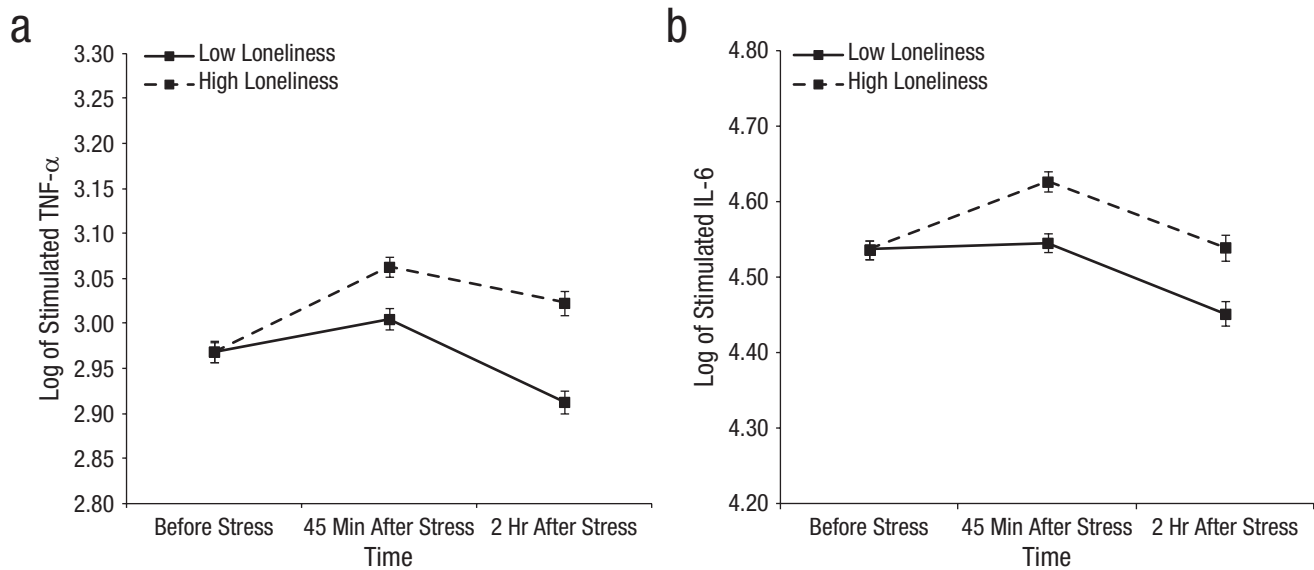


Fig. 1. Results from Study 1: mean stimulated production of (a) tumor necrosis factor-alpha (TNF- α) and (b) interleukin-6 (IL-6) as a function of measurement time and loneliness (low = 1 *SD* below the mean; high = 1 *SD* above the mean). All dependent measures were \log_{10} transformed. Error bars show standard errors of the mean.

level, and medication use. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common type of medication used in this sample ($n = 24$). The results were unchanged after adjusting for these variables.

Study 2

The sample we used in Study 2 was chosen with the goal of generalizing the Study 1 findings to a more diverse sample. In particular, the Study 2 sample was more heterogeneous in terms of overall health, health behaviors, and medication use. Using a sample of breast-cancer survivors also allowed us to assess the links between loneliness and stress-related proinflammatory cytokine production among a group who recently experienced a major life stressor (i.e., cancer diagnosis and treatment). We made one addition to the Study 2 inflammation measures, interleukin-1 beta (IL-1 β). We added IL-1 β to expand our cytokine repertoire; stimulated IL-1 β production is reliably modulated by acute stress (Steptoe, Hamer, & Chida, 2007). We hypothesized that, compared with their counterparts who felt more socially connected, lonelier people would exhibit greater stimulated TNF- α , IL-6, and IL-1 β production in response to an acute laboratory stressor, which would reflect a proinflammatory phenotype among lonely individuals.

Method

Participants. Participants were breast-cancer survivors ($N = 144$) between Stages 0 and IIIA from the baseline

prerandomization sample of an ongoing clinical trial about cancer-related fatigue. Survivors were recruited through cancer clinics and media announcements if they had completed cancer treatment (except for SERMs and aromatase inhibitors) between 2 months and 3 years prior to enrollment in the study. Individuals were ineligible if they engaged in over 5 hr of vigorous physical activity per week or if they had a BMI over 44, chronic obstructive pulmonary disease, symptomatic ischemic heart disease, uncontrolled hypertension, liver or kidney failure, or a prior history of cancer (except basal or squamous cell). The average age of participants was 51.44 years ($SD = 9.17$, range = 28–76), and the majority of participants were White (86%). Additional sample characteristics are listed in Table 2. The project was approved by The Ohio State University Institutional Review Board; all participants provided written informed consent before participating.

Procedure. Participants arrived at the CRC at 8:30 a.m., and a catheter was inserted in their arm. After eating a standardized breakfast and relaxing for 20 min, participants gave blood so we could assess baseline stimulated cytokine production. Next, participants completed the same Trier Social Stress Test as described in Study 1. Two additional blood samples were collected 45 min and 2 hr after the stressor.

Questionnaires. Loneliness and sleep quality were measured with the same questionnaires as in Study 1. Exercise was assessed with one item about hours of

Table 2. Characteristics of the Study 2 Sample ($N = 144$)

Characteristic	Number or mean
Race	
White	$n = 124$ (86%)
Black	$n = 15$ (10%)
Other	$n = 5$ (4%)
Education	
High school or below	$n = 8$ (5.5%)
Some college or college graduate	$n = 80$ (55.5%)
Graduate or professional training	$n = 56$ (39%)
Marital status	
Single	$n = 20$ (14%)
Married	$n = 103$ (71.5%)
Separated, divorced, or widowed	$n = 21$ (14.5%)
Stage of cancer	
0	$n = 11$ (7.5%)
I	$n = 63$ (44%)
II	$n = 56$ (39%)
III	$n = 14$ (9.5%)
Age (years)	$M = 51.44$ ($SD = 9.17$)
Months since treatment	$M = 11.35$ ($SD = 7.84$)
Body mass index	$M = 27.82$ ($SD = 5.64$)
Sagittal abdominal diameter (cm)	$M = 20.74$ ($SD = 3.23$)
Loneliness ^a	$M = 18.69$ ($SD = 8.45$)

^aLoneliness was scored from 0, lowest, to 60, highest, using the UCLA Loneliness Scale (Russell, 1996).

vigorous activity in a typical week. Participants answered questions about their age, smoking status, weekly average alcohol consumption, current medication use, and highest level of education.

To account for potential links between comorbidities and immune function, we administered the Charlson index, a widely utilized comorbidity measure originally developed for breast-cancer patients and later extended to cancer and noncancer populations (Charlson, Szatrowski, Peterson, & Gold, 1994). The measure uses participants' self-reported health information to assign weights to 19 medical conditions based on their ability to influence 1-year mortality.

Immune assays. Synthesis of TNF- α , IL-6, and IL-1 β by LPS-stimulated PBMCs were assayed using the same method as in Study 1.

Data-analysis strategy. The distributions of the immune data were checked for normality and the presence of outliers. Similar to the procedure in Study 1, participants whose immune values were more than 4 standard deviations from the mean were dropped from the corresponding analyses. Specifically, we dropped three TNF- α

values and one IL-1 β value, which were less than 1% of all samples. The results did not differ whether the outliers were included or excluded. The distributions of TNF- α , IL-6, and IL-1 β were moderately skewed and were thus square root transformed prior to analyses.

To test reactivity to the stressor, we employed the same mixed-model analytic strategy as in Study 1. The control variables were the same as in Study 1, except for the following changes: Gender was omitted because all participants were women, and time since completion of cancer treatment, type of cancer treatment, and major medical comorbidities were added to tailor the covariates to a cancer population. Models also included a random effect for the plate on which the assay was conducted when results suggested that plate number produced additional variability not explained by other predictors. In ancillary analyses, we examined health behaviors as additional confounds.

Results

Results for TNF- α , IL-6, and IL-1 β are presented in Figures 2a, 2b, and 2c, respectively. There were no loneliness-related baseline differences in the synthesis of TNF- α , IL-6, or IL-1 β by PBMCs stimulated with LPS (all $ps > .768$).

Primary analyses. To analyze the stimulated TNF- α production stress-reactivity data, we used a mixed model that included the covariates listed in the Data-Analysis Strategy, baseline levels of stimulated TNF- α production, the main effects of loneliness and measurement time (45 min after stress vs. 2 hr after stress), and the interaction between loneliness and measurement time. Loneliness was unrelated to changes in stimulated TNF- α production from before to after stress, $b = 0.14$, $F(1, 129) = 2.33$, $p = .130$. However, the pattern was in the expected direction, with lonelier participants exhibiting greater stimulated TNF- α production than less lonely participants in response to stress. The nonsignificant interaction between loneliness and measurement time indicated that the strength of the relationship between loneliness and stimulated TNF- α production was the same at both poststress assessments, $p = .137$.

In the next set of models, we analyzed the stimulated IL-6 and IL-1 β production data using a similar mixed-model strategy. In response to acute stress, lonelier participants exhibited greater synthesis of IL-6 and IL-1 β by PBMCs stimulated with LPS than participants who were less lonely—IL-6: $b = 0.53$, $F(1, 129) = 4.48$, $p = .036$; IL-1 β : $b = 0.42$, $F(1, 131) = 7.21$, $p = .008$. The nonsignificant interactions between loneliness and measurement time indicated that the strength of the relationships between loneliness and stimulated IL-6 and IL-1 β

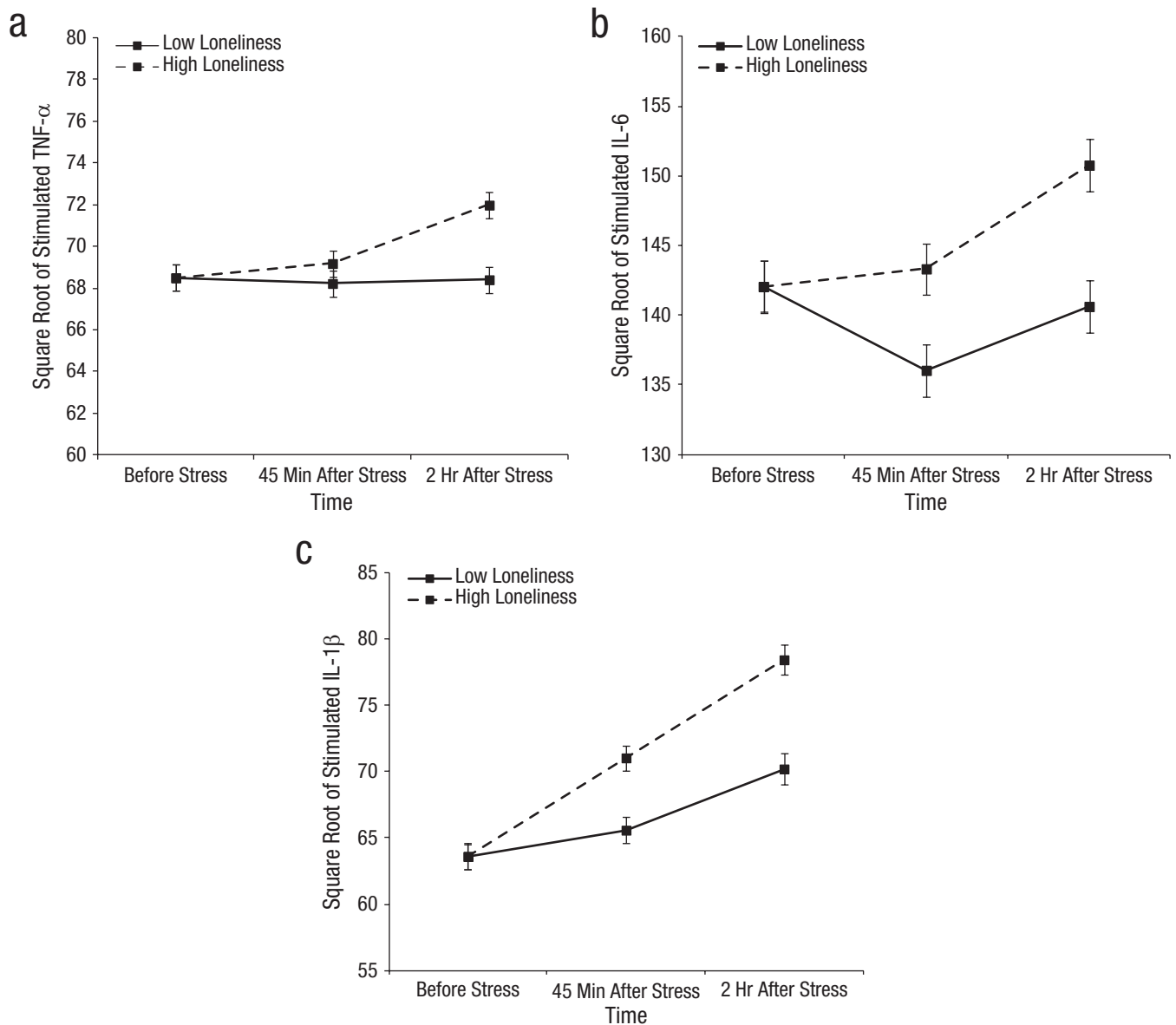


Fig. 2. Results from Study 2: mean stimulated production of (a) tumor necrosis factor- α (TNF- α), (b) interleukin-6 (IL-6), and (c) interleukin-1 beta (IL-1 β) as a function of measurement time and loneliness (low = 1 *SD* below the mean; high = 1 *SD* above the mean). All dependent measures were square root transformed. Error bars show standard errors of the mean.

production were the same at both poststress assessments, $p = .602$ and $p = .359$, respectively.

Ancillary analyses. Similar to Study 1, we used a series of mixed models to examine whether the relationships between loneliness and stimulated cytokine production held after controlling for sleep quality over the past month, number of hours slept the night before the visit, smoking status, exercise levels, alcohol consumption, education level, and medication use. NSAIDs ($n = 65$), cancer-related medications (SERMs and aromatase

inhibitors; $n = 133$), and depression medications ($n = 64$) were the most common type of medications used in this sample. The patterns were unchanged after adjusting for these variables.

Discussion

In accord with psychological data demonstrating that lonely people are highly stress reactive, the results of the current studies showed that people who were lonelier exhibited more stimulated TNF- α , IL-6, and IL-1 β

production in response to an acute stressor than those who were less lonely. Furthermore, the results were highly consistent across two different populations—healthy overweight adults and breast-cancer survivors¹—which suggests that lonely individuals exhibit a proinflammatory phenotype.

The current results are consistent with theoretical speculation and empirical evidence demonstrating that close and caring relationships are essential to mental and physical well-being (Baumeister & Leary, 1995); lonelier participants had larger stimulated cytokine production responses to acute stress than less lonely participants, and inflammation is linked to a variety of age-related diseases (Ershler & Keller, 2000; Hansson, 2005). Indeed, compared with their counterparts who feel more socially connected, lonelier people experience a wide array of health problems ranging from increased incidence of coronary heart disease to premature mortality (Holt-Lunstad et al., 2010; Thurston & Kubzansky, 2009). Accordingly, inflammation driven by excessive cytokine production may be one key mechanism linking loneliness to poor health.

Other factors may work independently or in tandem with changes in inflammation to influence health. For example, compared with people who felt more socially connected, lonelier people reported poorer sleep quality, a strong predictor of negative health outcomes (Cacioppo et al., 2002; Strine & Chapman, 2005). In the current studies, ancillary analyses demonstrated that lonelier people exhibited greater stimulated proinflammatory cytokine production in response to stress than less lonely people regardless of sleep quality. These data suggest that sleep quality does not explain loneliness-related immune alterations. Accordingly, loneliness may independently influence health via both sleep and immune dysregulation.

Mechanistically, both the autonomic and neuroendocrine systems influence stress-related inflammation. Norepinephrine stimulates the release of proinflammatory cytokines by inducing nuclear factor- κ B (NF- κ B) transcription, an intracellular signaling molecule that regulates proinflammatory cytokine-gene expression (Bierhaus et al., 2003; Kohm & Sanders, 2000). Furthermore, parasympathetic activity can reduce inflammation via the cholinergic anti-inflammatory pathway that induces acetylcholine release (Tracey, 2009). Because it reduces parasympathetic activity, stress ultimately results in elevated cytokine production. Accordingly, research incorporating the autonomic, neuroendocrine, and immune consequences of loneliness would help provide a more complete picture about the ways that these physiological systems influence each other to affect health.

In sum, loneliness was linked to exaggerated proinflammatory cytokine production following an acute

stressor, which reflects a proinflammatory phenotype among lonely individuals. The current studies demonstrate that loneliness has immune consequences and provide a glimpse into the pathways through which social relationships can affect health and well-being.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Note

1. The one exception is that, although in the expected direction, the results for stimulated TNF- α production were nonsignificant in Study 2.

References

- Baumeister, R. F., & Leary, M. R. (1995). The need to belong: Desire for interpersonal attachments as a fundamental human motivation. *Psychological Bulletin, 117*, 497–529. doi:10.1037/0033-2909.117.3.497
- Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P. M., Petrov, D., . . . Nawroth, P. P. (2003). A mechanism converting psychosocial stress into mononuclear cell activation. *Proceedings of the National Academy of Sciences, USA, 100*, 1920–1925. doi:10.1073/pnas.0438019100
- Buyse, D. J., Reynolds, C. F., III, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research, 28*, 193–213.
- Cacioppo, J. T., Ernst, J. M., Burleson, M. H., McClintock, M. K., Malarkey, W. B., Hawkley, L. C., . . . Berntson, G. G. (2000). Lonely traits and concomitant physiological processes: The MacArthur social neuroscience studies. *International Journal of Psychophysiology, 35*, 143–154.
- Cacioppo, J. T., Hawkley, L. C., Berntson, G. G., Ernst, J. M., Gibbs, A. C., Stickgold, R., & Hobson, J. A. (2002). Do lonely days invade the nights? Potential social modulation of sleep efficiency. *Psychological Science, 13*, 384–387.
- Calder, P. C. (2004). n-3 fatty acids, inflammation, and immunity: Relevance to postsurgical and critically ill patients. *Lipids, 39*, 1147–1161.
- Charlson, M., Szatrowski, T. P., Peterson, J., & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of Clinical Epidemiology, 47*, 1245–1251.
- Cole, S. W., Hawkley, L. C., Arevalo, J. M., Sung, C. Y., Rose, R. M., & Cacioppo, J. T. (2007). Social regulation of gene expression in human leukocytes. *Genome Biology, 8*, R189. doi:10.1186/gb-2007-8-9-r189

- Deshmane, S. L., Kremlev, S., Amini, S., & Sawaya, B. E. (2009). Monocyte chemoattractant protein-1 (MCP-1): An overview. *Journal of Interferon & Cytokine Research*, *29*, 313–326. doi:10.1089/jir.2008.0027
- Dixon, D., Cruess, S., Killbourn, K., Klimas, N., Fletcher, M. A., Ironson, G., . . . Antoni, M. H. (2006). Social support mediates loneliness and human herpesvirus type 6 (HHV-6) antibody titers. *Journal of Applied Social Psychology*, *31*, 1111–1132. doi:10.1111/j.1559-1816.2001.tb02665.x
- Ershler, W. B., & Keller, E. T. (2000). Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annual Review of Medicine*, *51*, 245–270. doi:10.1146/annurev.med.51.1.245
- Faraut, B., Boudjeltia, K. Z., Vanhamme, L., & Kerkhofs, M. (2012). Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Medicine Reviews*, *16*, 137–149. doi:10.1016/j.smr.2011.05.001
- Fritsche, K. (2006). Fatty acids as modulators of the immune response. *Annual Review of Nutrition*, *26*, 45–73. doi:10.1146/annurev.nutr.25.050304.092610
- Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology*, *5*, 243–251. doi:10.1038/nri1571
- Glaser, R., Kiecolt-Glaser, J. K., Speicher, C. E., & Holliday, J. E. (1985). Stress, loneliness, and changes in herpesvirus latency. *Journal of Behavioral Medicine*, *8*, 249–260. doi:10.1007/BF00870312
- Hackett, R. A., Hamer, M., Endrighi, R., Brydon, L., & Steptoe, A. (2012). Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology*, *37*, 1801–1809. doi:10.1016/j.psyneuen.2012.03.016
- Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine*, *352*, 1685–1695.
- Hawkey, L. C., Bosch, J. A., Engeland, C. G., Marucha, P. T., & Cacioppo, J. T. (2007). Loneliness, dysphoria, stress, and immunity: A role for cytokines. In N. P. Plotnikoff, R. E. Faith, A. J. Murgo, R. A. Good (Eds.), *Cytokines: Stress and immunity* (2nd ed., pp. 67–85). Boca Raton, FL: CRC Press.
- Hawkey, L. C., Burleson, M. H., Berntson, G. G., & Cacioppo, J. T. (2003). Loneliness in everyday life: Cardiovascular activity, psychosocial context, and health behaviors. *Journal of Personality and Social Psychology*, *85*, 105–120. doi:10.1037/0022-3514.85.1.105
- Hawkey, L. C., & Cacioppo, J. T. (2010). Loneliness matters: A theoretical and empirical review of consequences and mechanisms. *Annals of Behavioral Medicine*, *40*, 218–227.
- Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine*, *7*(7), e1000316. Retrieved from <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000316>
- Kiecolt-Glaser, J. K., Garner, W., Speicher, C., Penn, G. M., Holliday, J., & Glaser, R. (1984). Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine*, *46*, 7–14.
- Kiecolt-Glaser, J. K., Ricker, D., George, J., Messick, G., Speicher, C., Garner, W., & Glaser, R. (1984). Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. *Psychosomatic Medicine*, *46*, 15–23.
- Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'—A tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*, 76–81.
- Kohm, A. P., & Sanders, V. M. (2000). Norepinephrine: A messenger from the brain to the immune system. *Immunology Today*, *21*, 539–542. doi:10.1016/S0167-5699(00)01747-3
- Leary, M. R., & Cox, C. B. (2008). Belongingness motivation: A mainspring of social action. In W. L. Gardner & J. Y. Shah (Eds.), *Handbook of motivation science* (pp. 27–40). New York, NY: Guilford Press.
- Maslow, A. H. (1968). *Toward a psychology of being* (2nd ed.). Oxford, England: D. Van Nostrand.
- Mohamed-Ali, V., Goodrick, S., Rawesh, A., Katz, D. R., Miles, J. M., Yudkin, J. S., . . . Coppel, S. W. (1997). Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *The Journal of Clinical Endocrinology and Metabolism*, *82*, 4196–4200.
- Pressman, S. D., Cohen, S., Miller, G. E., Barkin, A., Rabin, B. S., & Treanor, J. J. (2005). Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology*, *24*, 297–306. doi:10.1037/0278-6133.24.3.297
- Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. *Journal of Personality Assessment*, *66*, 20–40.
- Shephard, R. J. (2002). Cytokine responses to physical activity, with particular reference to IL-6: Sources, actions, and clinical implications. *Critical Reviews in Immunology*, *22*, 165–182.
- Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*, *21*, 901–912. doi:10.1016/j.bbi.2007.03.011
- Stewart, A. L., Mills, K. M., King, A. C., Haskell, W. L., Gillis, D., & Ritter, P. L. (2001). CHAMPS physical activity questionnaire for older adults: Outcomes for interventions. *Medicine & Science in Sports & Exercise*, *33*, 1126–1141.
- Strine, T. W., & Chapman, D. P. (2005). Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. *Sleep Medicine*, *6*, 23–27. doi:10.1016/j.sleep.2004.06.003
- Sugisawa, H., Liang, J., & Liu, X. (1994). Social networks, social support, and mortality among older people in Japan. *Journal of Gerontology*, *49*, S3–S13. doi:10.1093/geronj/49.1.S3
- Thurston, R. C., & Kubzansky, L. D. (2009). Women, loneliness, and incident coronary heart disease. *Psychosomatic Medicine*, *71*, 836–842. doi:10.1097/PSY.0b013e3181b40efc
- Tooby, J., & Cosmides, L. (1996). Friendship and the banker's paradox: Other pathways to the evolution of adaptations for altruism. In W. G. Runciman, J. M. Smith, & R. I. M. Dunbar (Eds.), *Evolution of social behaviour patterns in primates and man* (pp. 119–143). New York, NY: Oxford University Press.
- Tracey, K. J. (2009). Reflex control of immunity. *Nature Reviews: Immunology*, *9*, 418–428. doi:10.1038/nri2566