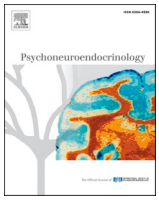
Psychoneuroendocrinology 178 (2025) 107498

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Spousal bereavement enhances proinflammatory cytokine production to acute, psychological stress

E. Lydia Wu-Chung [*,a], Ryan L. Brown [b], Robert Suchting [c], Jensine Paoletti-Hatcher [d], Michelle A. Chen [e], Angie S. LeRoy [f], Kyle W. Murdock [g], Cobi J. Heijnen [h], Christopher P. Fagundes [h,i,j,k]

[a] Department of Psychology, University of Pittsburgh, USA
[b] Human Development and Family Sciences, Texas Tech University, USA
[c] Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School at UTHealth, University of Texas Health Science Center at Houston, USA
[d] Department of Psychology, Portland State University, USA
[e] Department of Psychology, Texas Christian University, USA
[f] Department of Psychology, University of North Florida, USA
[g] Department of Biobehavioral Health, The Pennsylvania State University, USA
[h] Department of Psychological Sciences, Rice University, USA
[i] Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, USA
[j] Department of Psychology, University of Houston, USA
[k] Institute of Health and Resilience, Rice University, USA

ARTICLE INFO

Keywords:
Stressful life event
Inflammation
IL-6
Stress reactivity
Widowhood

ABSTRACT

Early widowhood is characterized by chronic stress and is associated with a higher risk of incident depression and cardiovascular-related morbidity and mortality. Peripheral inflammation is involved in the pathogenesis of major depressive disorder and atherothrombosis and may represent a common mechanism underlying widow(er)'s elevated risk for both health conditions. Chronic psychological stress sensitizes the release of proinflammatory cytokines during the peripheral stress response. The present study examined whether recent spousal bereavement enhances the inflammatory response to an acute, psychological stressor. Recently widowed older adults (n = 143) and non-widowed controls (n = 69) participated in a quasi-experimental study, during which they underwent the Trier Social Stress Test, provided multiple blood samples through an intravenous catheter (before stressor, 45 min post-stressor, 120 min post-stressor), and completed self-report questionnaires. Blood samples were assayed for serum Interleukin (IL)-6 levels. Mixed linear modeling was used to test hypotheses. There was a significant time × bereavement status effect on IL-6 after controlling for confounding variables. Widow(er)s showed a steeper increase in IL-6 per hour compared to non-bereaved adults. Findings suggest that the inflammatory stress response is heightened in widow(er)s, which may contribute to the mental and physical health risks associated with early widowhood.

1. Introduction

As one of life's most profound stressors (Holmes and Rahe, 1967), spousal bereavement significantly increases the risk of morbidity and mortality, especially during the first six months after the loss (Moon et al., 2014). Bereaved spouses experience significantly more cardiovascular events (Carey et al., 2014) and higher rates of major depressive disorder (Zisook et al., 1991) compared to non-bereaved adults. The mechanisms that underlie health differences between widow(er)s in early bereavement and non-bereaved individuals remain unclear.

Inflammation is closely intertwined with the stress response system and age-related disease pathology (Liu et al., 2017; Medzhitov, 2008). As the immune system's primary response to infection and injury, inflammation is characterized by increased immune cells and signaling molecules (e.g., cytokines, chemokines) (Medzhitov, 2008). Peripheral inflammation is involved in the pathogenesis of major depressive disorder (MDD), cardiovascular-related morbidity and mortality, and all-cause mortality (Franceschi and Campisi, 2014; Kiecolt-Glaser et al.,

* Correspondence to: 6500 Main St., 760B, Houston, TX 77030, USA.
E-mail address: lydiawuchung@pitt.edu (E.L. Wu-Chung).

https://doi.org/10.1016/j.psyneuen.2025.107498
Received 10 February 2025; Received in revised form 14 April 2025; Accepted 21 May 2025
Available online 22 May 2025

2015; Kinney et al., 2018; Ridker and Silvertown, 2008).

The magnitude of the inflammatory response to acute stress may represent an important index of inflammatory-related diseases and associated psychiatric disorders (Marsland et al., 2017). Medically healthy males with current MDD exhibited greater IL-6 production in response to a psychosocial stressor than non-depressed comparisons (Pace et al., 2006); compared with non-depressed comparisons, women with MDD were more desensitized to the anti-inflammatory effects of glucocorticoids after an acute, psychosocial stressor (Miller et al., 2005). Several studies show that larger stressor-induced increases in Interleukin-6 (IL-6), a proinflammatory cytokine, are associated with higher concurrent levels of systemic inflammation (Lockwood et al., 2016) and poorer cardiometabolic health over time (Brydon and Steptoe, 2005 May; Kiecolt-Glaser et al., 2020; Zannas et al., 2020). These findings suggest that exaggerated inflammatory responses to acute stress may be linked with higher depression risk and adverse physiological health.

Chronic stress enhances the inflammatory response to acute, psychological stressors (Pace et al., 2006; Miller et al., 2005; Fagundes et al., 2013; Kuhlman et al., 2022; Jaremka et al., 2013), a pattern that may be similarly observed during early bereavement. Adjustment to life without the romantic partner can be a source of chronic stress (Stroebe and Schut, 2010). Due to the evolutionary benefits of maintaining close, interpersonal relationships – which can include safety, emotional comfort, fulfillment, and support (Apostolou et al., 2023) – loss of a close, social bond, whether by bereavement or separation, evokes significant emotional distress (Paykel, 2003). In addition to typical everyday stressors (e.g., time-pressure hassles, rush hour traffic), widow(er)s experience stressors and role changes related to the loss, such as ruminating and yearning for the deceased individual and adjusting to new social roles as a single individual (Stroebe and Schut, 2010). Despite work suggesting that widow(er)s may be more psychologically reactive to daily stress than non-bereaved adults (Hahn et al., 2014), no studies have explored whether widow(er)s are physiologically more reactive to stress than their non-bereaved counterparts.

In the present study, we examined whether recent spousal bereavement enhances the inflammatory response to acute stress in serum. Based on the extant literature showing that the proinflammatory cytokine, IL-6, reliably increases in response to acute stressors and is a keystone cytokine in health and disease, we decided a priori to assess serum IL-6 (Marsland et al., 2017; Steptoe et al., 2007). We hypothesized that recently bereaved individuals would exhibit more significant stressor-induced increases in IL-6 than individuals not experiencing recent bereavement.

2. Methods

2.1. Participants

Recently bereaved spouses and non-bereaved adults were recruited for a longitudinal observational study examining the biobehavioral mechanisms underlying increased cardiovascular risk during the first year of spousal bereavement. Participants were recruited from obituary listings, community events, and online postings. The parent study adopted a phased recruitment approach, such that most bereaved participants were recruited before nonbereaved participants. Inclusion criteria were as follows: 1) individual recently lost a spouse within the last three months OR was an age-matched nonbereaved adult and 2) individual was able to read and write in English. Non-bereaved adults were not required to be married/partnered. Participants were excluded if they met one or more of the following exclusion criteria: 1) experienced bereavement of a loved one during the past year; 2) were pregnant or nursing; 3) divorced within the past year; 4) had autoimmune, inflammatory, obstructive pulmonary, and/or heart diseases; 5) had significant auditory or visual impairment; or 6) lost a spouse within the last 5 years (nonbereaved adults). Study procedures were approved by Rice University's Institutional Reviewer Board. All participants provided informed consent. Participants who completed a laboratory social stressor, which took place approximately 1–2 months after the baseline visit of the longitudinal study, were included in the present study. Bereaved participants completed the laboratory stressor approximately four months after spousal death ($M = 138$ days, $SD = 16$). Non-bereaved comparisons completed the laboratory stressor after an arbitrary baseline visit for the parent study.

From February 2016 to March 2020, 230 participants (151 bereaved and 79 controls) completed a laboratory social stressor. Of the 230 participants, 18 were excluded from analyses either because blood draws were not administered or blood draw complications rendered the blood samples insufficient, resulting in a final sample size N = 212 ($n_{bereaved} = 143$, $n_{control} = 69$). This sample size was sufficiently powered to test hypotheses using unadjusted and adjusted models: Power analyses determined that a sample size of 123 was necessary to have 80 % power to detect a medium effect size ($f^2 = .15$) with 11 predictors in the model. The total analytic sample was 212.

2.2. Study design

Blood samples, anthropometric measures, and self-reported health measures were acquired at the visit. Self-report questionnaires were completed at the end of the visit, after all behavioral and physiological assessments had concluded. Participants underwent the Trier Social Stress Test (TSST), a standardized social stressor known to induce reliable increases in proinflammatory cytokine production (Marsland et al., 2017; Kirschbaum et al., 1993); the protocol has been described previously (Brown et al., (2022). Blood samples were acquired three times throughout the visit and were specifically timed to capture serum IL-6 response patterns to acute stress, which occur over a two-hour observation period post-stressor (Marsland et al., 2017; Steptoe et al., 2007). The baseline blood sample was acquired before the TSST and after a 30-min relaxation period following the initial catheter insertion (median time relative to start of TSST: −24 min). After the TSST, participants continued the relaxation period and received their 2nd and 3rd blood draws, approximately 45 min (median time since start of TSST: 47 min) and 120 min post-TSST (median time since start of TSST: 122 min). During relaxation periods, participants watched one of three Ken Burn documentaries of their choosing (i.e., national parks, baseball, Abraham Lincoln). Notably, every participant started their visit before 9 AM in order to minimize variations attributed to the diurnal variation of IL-6 (Nilsonne et al., 2016); thus, any stress-induced changes in IL-6 occurred outside the effect of circadian rhythmicity.

2.3. Measures

Proinflammatory biomarker. Whole blood was drawn into a serum separator tube. After 30 min of clotting, tubes were subsequently centrifuged for 10 min at 3000 x g at 4 °C. Serum aliquots were stored at −80 °C until assayed in duplicates for levels of IL-6 using high-sensitivity enzyme-linked immunosorbent assays (Quantikine, R&D Systems, Minneapolis, MN). The detection sensitivity of these assays was 0.16–10 pg/ml. Intra- and inter-assay coefficients of variation were 3.6–4.7 % and 3.9–10.8 %, respectively. Immunoassays were run in five separate batches. In preliminary testing, each subsequent batch was positively associated with higher levels of IL-6 ($p < .001$, see Supplemental Material). Thus, batch number was included as a random effect in all models to account for the influence of batch number on serum IL-6 levels, consistent with prior validation studies (Liao, 2005; Whitcomb et al., 2010). Notably, observed patterns did not change when batch number was modeled as a fixed effect, and these results can be found in supplemental material. Serum tumor necrosis factor (TNF) alpha was also assayed but it was not part of primary aims or hypotheses; readers interested in stress-induced TNF alpha levels can find these post-hoc results in Supplemental Material.

Depressive symptomology. Depressive symptoms were measured using the *Center for Epidemiological Studies Depression Scale* (CES-D) (Radloff, 1977). Higher scores indicate more severe depressive symptomology and scores ≥ 16 indicate clinically significant depression. The reliability of the CES-D scale was high (α =.91).

Comorbid conditions. Comorbid health conditions were assessed using the *Charlson Comorbidity Index*, an index commonly used for predicting mortality (Charlson et al., 1994). Comorbid conditions are designated weights based on their potential influence on one-year mortality. Higher values indicate more severe comorbidity.

Perceived stress. A 3-item survey probed stress severity toward the TSST. Using a 7-point Likert scale, participants rated their degree of perceived stress towards the 1) speech portion, 2) math portion, and 3) whole experience (speech and math portions combined). Higher values indicate higher levels of perceived stress.

Sleep quality. The *Pittsburgh Sleep Quality Index Sleep* (PSQI) was designed to measure sleep quality in clinical populations (Buysse et al., 1989). It has good reliability and validity across diverse sample populations, including psychiatric and sleep disorder patients and healthy elderly subjects (Buysse et al., 1989). A global sleep quality score (range: 0–21) is computed from the sum of the seven components. Higher scores indicate poorer overall sleep quality (Buysse et al., 1989). The reliability of the PSQI was acceptable (α =.71).

Sociodemographic and clinical characteristics. Age, sex (male or female), education, use of anti-inflammatory medication, and body mass index (BMI) were also included as covariates. Participants self-reported age, sex, education, and medication use. Education levels were given the following codes: 6 = graduate/professional training, 5 = 3 or more years of college, 4 = up to 3 years of college, 3 = high school graduate, 2 = 7–12 years (non-graduate), 1 = less than 7 years. Anti-inflammatory medication consisted of statins, metformin, non-steroidal anti-inflammatory drugs (NSAIDS), and COX-2 inhibitor drugs; for data analysis, anti-inflammatory medication was coded as a binary variable. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared.

2.4. Statistical analyses

Preliminary analyses evaluated normality, skewness, and kurtosis of all study variables. Serum IL-6 values were positively skewed, as commonly observed for inflammatory biomarkers (e.g., Fagundes et al., 2018). Natural log transformation was applied to handle potential non-normal residuals during statistical modeling with IL-6 as the outcome variable, and subsequent examination of Q-Q plots were evaluated to confirm that residuals were approximately normally distributed.

Missing data comprised 1.26 % of the dataset. Missingness on the outcome variable (i.e., IL-6) was handled by maximum likelihood estimation. Missing values among continuous predictors were handled by random forest imputation, a machine-learning technique that uses decision trees and bootstrap aggregation (i.e., bagging) to develop a single predictive model (Breiman, 2001). Random forest imputation addresses limitations imposed by traditional multiple imputation by accommodating nonlinear variables and complex interactions, with strong performance under moderate and high levels of missingness (Tang and Ishwaran, 2017). Observed patterns remained the same when listwise deletion was used (see Supplemental Material).

Generalized linear mixed modeling was used to test hypotheses. The −2 log-likelihood value, Akaike information criterion [AIC], and Bayesian information criterion [BIC] were used to determine whether fixed, random and/or a polynomial effects should be included in the model. The best-fitting model allowed for a random intercept for the immunoassay batch, random intercept for person, and the random slope of time to vary by person.

To examine whether IL-6 levels over time differ by bereavement status, serum IL-6 (log-transformed) was regressed on time since TSST (hours) × bereavement status (bereaved or non-bereaved) and main effects. A significant interaction term would suggest that the relationship between time since the TSST and IL-6 (i.e., change in IL-6 or IL-6 reactivity) is significantly different at each level of bereavement status (i.e., bereaved, non-bereaved). Mixed models were run with (adjusted) and without (unadjusted) covariates. In adjusted models, covariates included age, sex, BMI, education, medication, comorbid conditions, sleep quality, and depressive symptoms. Depressive symptoms were modeled as a continuous variable but model results did not change when modeled as a categorical variable. Simple slopes tests were conducted at each level of the moderator (i.e., bereavement status) if the interaction term between time (hours) and bereavement status was significant. To enhance interpretability, coefficients for simple slopes were exponentiated to provide the percent increase in raw units of the outcome (see Brown et al., 2022 for detailed explanation). To determine whether IL-6 levels at a given time point were different by group, pairwise contrasts were conducted.

All analyses were conducted in R Studio (RStudio Team, 2021). The following packages were used for multilevel models, data visualization, tables, random forest imputation, or simple slopes testing: *lme4* (Bates et al., 2022), *ggplot2* (Wickham, 2016), *ggeffects* (Lüdecke, 2018), *rvg* (Gohel and set_attr, 2020), *officer* (Gohel, 2022), *sjPlot* (Lüdecke, 2021), *arsenal* (Heinzen et al., 2021), *apaTables* (Stanley, 2020), *caret* (Kuhn, 2020), and *emmeans* (Length, 2022).

3. Results

Descriptive information by bereavement status can be found in Table 1. Bereaved individuals reported more depressive symptoms ($F(1, 210) = 24.94$, $p < .001$) and poorer sleep quality ($F(1, 210) = 7.93$, $p < .01$) than nonbereaved comparisons. More bereaved individuals identified as White than non-bereaved individuals. The groups did not differ on all other demographic characteristics, BMI, age, sex, comorbid conditions, and medication. Correlations between variables of interest can be found in Table 2.

In unadjusted and adjusted models, the interaction term (hours since TSST × bereavement status) was a significant predictor of IL-6 ($p < .01$, see Table 3). Simple slopes tests revealed that bereaved and controls exhibited significant increases in IL-6 production over time, with bereaved individuals showing a 25 % increase in IL-6 per hour ($\exp(b) = 1.25$, 95 % $CI[1.19, 1.30]$, $p < .001$) and controls showing a 10 % increase in IL-6 per hour ($\exp(b) = 1.10$, 95 % $CI[1.04, 1.17]$, $p < .01$) (See Fig. 1). Pairwise comparisons demonstrated that bereaved and control participants showed no differences in IL-6 levels at baseline ($p = .15$), 45 min post-TSST ($p = .75$) and 120 min post-TSST ($p = .32$). In ancillary models controlling for baseline IL-6 levels, patterns remained unchanged, except that bereaved adults showed higher levels of IL-6 than non-bereaved adults at 120 min post-TSST ($p = .002$) (see Supplemental Material).

4. Discussion

Recently bereaved spouses in this study exhibited larger stress-induced increases in serum IL-6 compared to adults not experiencing recent bereavement. The finding remained robust after controlling for other factors known to influence inflammation (i.e., age, sex, body mass index, education, comorbid conditions, anti-inflammatory medication, depressive symptoms, and sleep quality). This study suggests that those experiencing recent bereavement may be more physiologically reactive to acute stress than those not experiencing bereavement.

By comparing widow(er)s to a nonwidowed comparison group and controlling for depressive symptom severity, we demonstrate that beyond individual differences in psychological distress (Brown et al., 2022), exposure to a recent life stressor can enhance one's immune response to an innocuous, acute psychosocial stressor. The observation that widow(er)s are more "reactive" to acute stressors than non-widow

Table 1
Sample description at the time of the trier social stress test (n = 212).

	Nonbereaved adults (*N* = 69)	Bereaved adults (*N* = 143)	Total (*N* = 212)	p value
Age				0.966
Mean (SD)	68.28 (13.11)	68.21 (8.79)	68.23 (10.36)	
Range	23.00–86.00	35.00–87.00	23.00–87.00	
Gender				0.163
Female	51 (73.91 %)	92 (64.34 %)	143 (67.45 %)	
Race				0.003
White	50 (72.46 %)	127 (88.81 %)	177 (83.49 %)	
Ethnicity				0.784
Non-Hispanic	55 (91.67 %)	123 (90.44 %)	178 (90.82 %)	
Education				0.956
< 12 years high school	0 (0.00 %)	1 (0.70 %)	1 (0.48 %)	
High school graduate	10 (14.71 %)	19 (13.38 %)	29 (13.81 %)	
Up to 3 years of college	10 (14.71 %)	20 (14.08 %)	30 (14.29 %)	
3 + years of college	9 (13.24 %)	17 (11.97 %)	26 (12.38 %)	
Graduate/professional training	39 (57.35 %)	85 (59.86 %)	124 (59.05 %)	
Body mass index (BMI)				0.148
Mean (SD)	28.85 (6.64)	27.63 (5.29)	28.03 (5.77)	
Range	17.97–46.04	16.01–50.14	16.01–50.14	
Comorbid				0.726
Mean (SD)	0.45 (2.78)	0.36 (1.00)	0.39 (1.78)	
Range	0.00–23.00	0.00–8.00	0.00–23.00	
Anti-inflammatory medication				0.878
Yes	33 (47.83 %)	70 (48.95 %)	103 (48.58 %)	
CES-D (depressive symptoms)				< 0.001
Mean (SD)	7.77 (7.16)	14.34 (9.74)	12.20 (9.48)	
Range	0.00–30.00	0.00–46.00	0.00–46.00	
CESD ≥ 16	9 (13.04)	56 (39.16)	65 (30.66)	
PSQI (sleep quality)				0.006
Mean (SD)	5.85 (3.45)	7.37 (3.79)	6.88 (3.75)	
Range	0.00–15.00	2.00–19.00	0.00–19.00	
Perceived stress of TSST				0.684
Mean (SD)	5.13 (1.14)	5.05 (1.44)	5.07 (1.35)	
Range	2.00–7.00	1.00–7.00	1.00–7.00	
Time at baseline draw				0.377
Mean (SD)	−25.10 (4.41)	−24.48 (4.62)	−24.67 (4.56)	
Range	−41.00 - −17.00	−45.00 - −13.00	−45.00 - −13.00	
Time at 2nd draw				0.707
Mean (SD)	47.42 (3.16)	47.19 (4.67)	47.26 (4.24)	
Range	42.00–61.00	41.00–92.00	41.00–92.00	
Time at 3rd draw				0.642
Mean (SD)	122.57 (3.79)	122.31 (3.67)	122.39 (3.70)	
Range	116.00–137.00	116.00–148.00	116.00–148.00	
IL−6 levels at baseline				0.071
Mean (SD)	2.87 (2.22)	2.32 (2.01)	2.50 (2.09)	
Range	0.17–10.00	0.11–10.00	0.11–10.00	
IL−6 levels at 2nd draw				0.223
Mean (SD)	3.03 (2.36)	2.64 (2.06)	2.77 (2.16)	
Range	0.18–10.00	0.11–10.00	0.11–10.00	
IL−6 levels at 3rd draw				0.706
Mean (SD)	3.58 (2.64)	3.73 (2.68)	3.68 (2.66)	
Range	0.18–11.57	0.39–10.00	0.18–11.57	

Note: p-values indicate significant differences between groups testing using Linear ANOVA (continuous variables) or Pearson Chi-square testing (categorical), without controlling for extraneous variables.

(er)s dovetails with work showing that widow(er)s are more sensitive to daily stressors than non-bereaved individuals (Hahn et al., 2014). Indeed, even though they may not necessarily experience more stress, widow(er)s report more daily negative affect than their non-bereaved counterparts on days with and without stressors (Hahn et al., 2014). Moreover, widow(er)s, but not married individuals, report more physical symptoms on days with a home-related stressor than on days without a home-related stressor (Hahn et al., 2014). Previously, Cohen et al. (2012) demonstrated that, relative to not experiencing a recent life stressor, being exposed to a chronic life stressor was associated with glucocorticoid resistance, which was in turn associated with elevated risk of developing a cold and a larger inflammatory response to a physical stressor (e.g., viral infection) (Cohen et al., 2012). Together, our findings alongside prior work suggest that stressful life events heighten reactivity to acute physical or psychological stress, which may be one pathway by which stressful life events increase disease risk.

In the broader stress reactivity literature, the magnitude of the stress response has future clinical relevance, regardless of health differences at baseline (Turner et al., 2020; Whittaker et al., 2021). For example, among people with normal blood pressure levels at baseline, heightened blood pressure reactivity to acute stress predicted future hypertension status 13 years later, after controlling for resting blood pressure levels at baseline (Matthews et al., 2004). Indeed, exaggerated and blunted cardiovascular responses to stress are associated with increased risk factors for cardiovascular disease (e.g., ambulatory blood pressure, hypertension status, carotid intima-media thickness, coronary artery calcification) (Turner et al., 2020; Chida and Steptoe, 2010). However, considerably less research has examined the prospective health implications of stress-induced inflammation. Across two studies, exaggerated IL-6 responses to acute stress (e.g., TSST, cognitive stress tests) predicted larger increases in blood pressure over a 3-year period (Brydon and Steptoe, 2005) and worsening cardiometabolic health over a 12-month period (Zannas et al., 2020); these findings were observed after accounting for baseline cardiovascular health and inflammation.

Table 2
Pearson correlations of variables of interest.

Variable	1	2	3	4	5	6	7	8	9
1. IL−6 (1st draw: before TSST)									
2. IL−6 (2nd draw: 45 min post-TSST)	.89 * * [.86,.91]								
3. IL−6 (3rd draw: 120 min post-TSST)	.70 * * [.63,.77]	.80 * * [.75,.85]							
4. Age	.32 * * [.20,.44]	.32 * * [.19,.44]	.19 * * [.06,.32]						
5. BMI	.29 * * [.16,.41]	.29 * * [.16,.41]	.24 * * [.10,.36]	−.06 [−.20,.07]					
6. Education	−.13 [−.26,.01]	−.15 * [−.28, −.01]	−.10 [−.24,.04]	−.06 [−.19,.08]	−.28 * * [−.40, −.15]				
7. Comorbidities	.11 [−.02,.24]	.12 [−.01,.26]	.05 [−.09,.18]	.12 [−.02,.25]	.02 [−.12,.15]	−.07 [−.20,.07]			
8. CES-D	−.08 [−.21,.06]	−.01 [−.15,.12]	.10 [−.04,.23]	−.17 * [−.30, −.04]	.07 [−.07,.20]	.02 [−.11,.16]	.04 [−.09,.18]		
9. PSQI	.06 [−.07,.20]	.04 [−.10,.18]	.15 * [.01,.28]	−.11 [−.24,.03]	.13 [−.01,.26]	.05 [−.09,.18]	.07 [−.06,.21]	.52 * * [.41,.61]	
10. Perceived stress of TSST	.02 [−.12,.17]	.02 [−.12,.16]	−.04 [−.18,.11]	−.07 [−.21,.07]	.10 [−.04,.24]	−.20 * * [−.33, −.05]	.10 [−.04,.24]	.14 [−.00,.28]	.03 [−.12,.17]

Note. Values in square brackets indicate the 95 % confidence interval for each correlation. The confidence interval is a plausible range of population correlations that could have caused the sample correlation (Cumming, 2014). * indicates $p < .05$. * * indicates $p < .01$. BMI = body mass index. Education = higher values indicate more years of education; CES-D = Center for Epidemiological Studies Depression Scale (higher scores indicate more depressive symptoms). PSQI = Pittsburgh Sleep Quality Index (higher values indicate poorer sleep quality). Perceived stress of TSST = ratings between 1 and 7 with higher values indicating more perceived stress.

Table 3
Mixed linear model depicting serum IL-6 as a function of bereavement status, time since the TSST, and other covariates (n = 212).

	Serum IL-6					
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.77	0.33 – 1.21	**0.001**	−1.75	−2.79 – −0.71	**0.001**
Time since TSST (hours)	0.10	0.04 – 0.16	**0.002**	0.10	0.04 – 0.16	**0.002**
Bereavement status [Bereaved]	−0.20	−0.45 – 0.04	0.102	−0.13	−0.36 – 0.10	0.265
Time since TSST x Bereaved	0.12	0.05 – 0.20	**0.001**	0.12	0.05 – 0.20	**0.001**
Age				0.02	0.01 – 0.03	**< 0.001**
Female				0.08	−0.11 – 0.27	0.399
Body mass index				0.04	0.03 – 0.06	**< 0.001**
Comorbidity				0.02	−0.03 – 0.07	0.445
Anti-inflammatory medication				0.04	−0.14 – 0.21	0.690
Education				−0.01	−0.09 – 0.07	0.759
Depressive symptoms				−0.00	−0.01 – 0.01	0.704
Sleep quality				0.01	−0.02 – 0.04	0.509
Random Effects						
σ^2	0.09			0.09		
τ_{00}	0.54_{id}			0.43_{id}		
	0.19_{batch}			0.16_{batch}		
τ_{11}	$0.04_{id.time}$			$0.04_{id.time}$		
ρ_{01}	-0.47_{id}			-0.42_{id}		
ICC	0.89			0.87		
N	212_{id}			212_{id}		
	5_{batch}			5_{batch}		
Observations	623			623		
Marginal R^2 / Conditional R^2	0.048 / 0.894			0.172 / 0.891		

Note: TSST = Trier Social Stress Test; Anti-inflammatory medication (coded as binary) consists of statins, metformin, non-steroidal anti-inflammatory drugs, and COX-2 inhibitor drugs. Comorbidity was assessed using the Charlson Comorbidity Index. Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale. Sleep quality was assessed using the Pittsburgh Sleep Quality Index. Education: higher values indicating more education.

Exaggerated inflammatory reactivity to stress also explained the relationship between interpersonal stress and future depressive symptom severity, such that more interpersonal stress was associated with higher future depressive symptom severity among individuals who exhibited larger stress-induced increases in IL-6 (Madison et al., 2022). Altogether, the stress reactivity literature suggests that the degree of stress-induced physiological change can independently predict future health, even among people whose resting physiological levels and health status do not differ at baseline. Notably, the stress reactivity literature provides some perspective for understanding the clinical implications of the

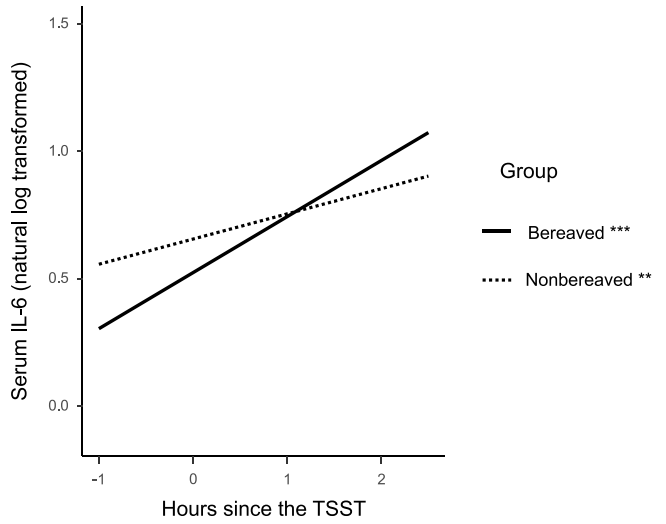


Fig. 1. Inflammatory response to acute stress over time by bereavement status (n = 212)Note: * **p < .001, * * p < .01, *p < .05; TSST = Trier Social Stress Test. Time is modeled continuously with Time = 0 representing the start of the TSST. Figure represents the adjusted model (covariates: age, gender, BMI, education, comorbidity, depressive symptoms, sleep quality, anti-inflammatory medication).

present study's findings. Despite bereaved and non-bereaved individuals showing comparable levels of serum IL-6 levels, bereaved individuals, relative to non-bereaved individuals, did show exaggerated stress-induced increases in serum IL-6 – a pattern that has been prospectively linked with adverse health in prior work (Brydon and Steptoe, 2005; Zannas et al., 2020). Whether stress reactivity patterns can explain long-term health differences between bereaved and non-bereaved remains a topic for future research.

The profound health impact of spousal bereavement may partially stem from its disruption of coregulatory patterns typically afforded by attachment relationships. Co-regulation, the reciprocal maintenance of psychobiological homeostasis within dyads, is a defining feature of attachment bonds (Sbarra and Hazan, 2008). Indeed, relationship partners reflect increasingly similar stress reactivity patterns over time (Laws et al., 2015). As the attachment bond is deemed safe and secure, distress alleviation patterns become embedded within homeostatic systems. Previous work has shown that supportive attachment bonds attenuate stress appraisals and cardiovascular reactivity to acute stress (Bourassa et al., 2019). Notably, the regulatory functions of attachment bonds are most evident when bonds are disrupted (Sbarra and Hazan, 2008). The biobehavioral function of close attachment bonds in humans manifests potently when the bond is severed: the loss of coregulation facilitates a state of emotional and physiological dysregulation (Sbarra and Hazan, 2008; LeRoy et al., 2020), which is especially evident during the early stages of bond separation (Fagundes et al., 2018; Buckley et al., 2011).

These findings prompt new directions for research. Future studies could investigate whether inflammatory stress reactivity patterns provide an early indication of future health status. Inflammatory stress reactivity patterns predicted changes in cardiometabolic markers in a sample of premenopausal women (Zannas et al., 2020). Whether stress-induced inflammatory responses can predict future depressive symptoms or physical health in recently bereaved individuals remains unknown. Currently, time since the loss is the primary determinant of pathological or normal grief coping (Bui et al., 2015). Although depressive and grief symptoms are commonly observed during the grieving process, some may experience these symptoms at high severity and chronicity and may benefit from early treatment (Shear et al., 2011). Early intervention may prevent the downstream risk of morbidity and mortality among at-risk widow(er)s. Second, while spousal bereavement is unique from depression and other chronic stressors (e.g., work stress, chronic illness), stressors that involve attachment disruption (e.g., divorce, dementia spousal caregiving) may evoke similar inflammatory reactivity patterns, given the profound effects that social loss has on health (Slavich, 2020). Examining stress-induced inflammatory activity in different stress contexts may clarify the generalizability of our findings to other stressors in adulthood. Third, evaluating inflammatory reactivity patterns toward personally relevant stressors may enhance clinical translatability and is an important future direction.

Some discrepancies between this study and related work should be noted. First, we did not find baseline differences in serum IL-6 between bereaved spouses and non-bereaved adults; however, prior work observing differences in serum IL-6 were either found in a small sample (n = 64; 36 widow(er)s) (Schultze-Florey et al., 2012) or in a mixed bereavement sample (bereaved relative or friend) (Cohen et al., 2015). Recently, Fagundes et al. (2018) observed differences in stimulated proinflammatory cytokine production between bereaved spouses and controls. Similar to the current study, Fagundes et al. (2018) evaluated cytokine production to a physical stimulus, which resembles stress-induced changes in serum IL-6 more than baseline levels of serum IL-6. Second, despite bereaved individuals showing sharper increases over time, bereaved and nonbereaved adults did not exhibit differences in IL-6 at any time point post-stressor; however, after controlling for baseline IL-6 levels, bereaved individuals had higher levels of IL-6 at 120 min post-stressor compared to controls. Prior studies reported significant differences in circulating IL-6 between high vs. low distress groups at 45–120 min post-stressor (Fagundes et al., 2013; Kuhlman et al., 2022; Jaremka et al., 2013). While immune dysregulation is evident in bereavement (Knowles et al., 2019), more work is needed to understand the nuanced relationships between the bereavement experience and immune function.

The present study includes some limitations. First, the sample consisted of 83 % non-Hispanic White participants. It is critical to study social loss and stress processes in more diverse groups. Second, although controlling for psychiatric medication use at the time of assessment did not alter main findings (see supplemental material), we are limited by not knowing if participants were actively undergoing psychotherapy or had a history of psychiatric illness prior to bereavement, both of which may have influenced inflammatory processes. Third, we have limited information surrounding the cause of death or whether the widow(er) was a spousal caregiver, which may contribute to individual differences in health following bereavement (Elwert and Christakis, 2008; Tal et al., 2017; Wilson et al., 2020). Fourth, we do not have information about IL-6 activity beyond 120 min post-stressor, and, thus, may incompletely capture how the bereavement experience affects IL-6 reactivity and recovery from acute stress. However, given that circulating IL-6 levels remain elevated at 300 min post-stressor (Madison et al., 2022), examining IL-6 recovery presents a logistical challenge. Moreover, examining IL-6 activity during a two hour period post-stressor is standard protocol within the literature (Marsland et al., 2017). Nevertheless, future studies that follow subjects for longer periods may clarify the significance of bereavement on stress-related inflammatory patterns. Lastly, inflammatory reactivity patterns were determined from one-time exposure to acute stress. It is likely that exaggerated reactivity to repeated or chronic stress exposure drives stress-related disease risk. While the TSST has ecological validity (Henze et al., 2017) and serves as a proxy of what multiple exposures to acute stress may do to a bodily system, future studies that characterize stress reactivity patterns to repeated stressors are warranted.

These limitations are offset by key strengths, including a relatively large sample of bereaved adults who were assessed relatively early in the bereavement process. The months following the death of a spouse provide unique insights into the psychoneuroimmunological underpinnings of social loss experiences (Brown et al., 2022; Fagundes et al., 2018; LeRoy et al., 2020; Chirinos et al., 2019; Wu et al., 2021; Wu et al., 2021). Moreover, control participants did not differ from our bereaved

participants across any of the following parameters: age, sex, BMI, co-morbid conditions, education, or medications. The only key difference between groups was depressive symptoms and sleep disturbance, which were predictably elevated among the bereaved participants. However, study findings remained even after accounting for sleep disturbance and depressive symptom severity.

Inflammatory mechanisms are increasingly recognized as one mechanistic pathway linking stressful life events to increased disease risk (Fagundes and Wu, 2020). The present study demonstrated that individuals experiencing recent spousal bereavement exhibited sharper increases in stress-induced proinflammatory cytokine production compared to those not experiencing bereavement. This study advances a growing literature aimed at understanding how stressful life events, such as death of a spouse, get "under the skin" to precipitate future illness.

Supplementary information is available at Psychoneuroendocrinology website.

CRediT authorship contribution statement

Wu-Chung E-Lim Lydia: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ryan L. Brown:** Writing – review & editing, Writing – original draft. **Robert Suchting:** Writing – review & editing, Formal analysis. **Jensine Paoletti-Hatcher:** Writing – review & editing. **Michelle A. Chen:** Writing – review & editing, Data curation. **Angie S. LeRoy:** Writing – review & editing. **Kyle W. Murdock:** Writing – review & editing. **Cobi J. Heijnen:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Christopher P. Fagundes:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

None.

Acknowledgements

We are grateful to the participants who offered their valuable time to be in this study. This work was supported by the National Heart, Lung, and Blood Institute (Fagundes: 1R01HL127260). At the time of writing, authors were supported by the following funders: National Heart, Lung, and Blood Institute (Chen: F32HL164050), National Institute on Aging (Wu-Chung 1F31AG074648; Paoletti: 1F32AG079624; LeRoy 1K01AG073824-01A1), and National Institute of Mental Health grant (Brown: T32MH019391). We would like to acknowledge Ms. Kristi English and Ms. Patricia Morales for project management.

Disclosures

We have no conflict of interest to disclose. Generative AI or AI-assisted technology were not used in the writing process.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2025.107498.

References

Apostolou, M., Christoforou, C., Lajunen, T.J., 2023 Oct 1. What are romantic relationships good for? An explorative analysis of the perceived benefits of being in a relationship. Evol. Psychol. 21 (4), 14747049231210245.

Bates, D., Maechler, M., Bolker, B., Walker, S., Christensen, R.H.B., Singmann, H., et al., 2022. lme4: Linear Mixed-Eff. Models Using "Eig. " S4 [Internet] [cited 2022 Sep 13].Available from: ⟨https://CRAN.R-project.org/package=lme4⟩.

Bourassa, K.J., Ruiz, J.M., Sbarra, D.A., 2019. The impact of physical proximity and attachment working models on cardiovascular reactivity: comparing mental activation and romantic partner presence. Psychophysiology 56 (5), e13324.

Breiman, L., 2001. Random forests. Mach. Learn. 45 (1), 5–32.

Brown, R.L., LeRoy, A.S., Chen, M.A., Suchting, R., Jaremka, L.M., Liu, J., et al., 2022 Jun 1. Grief symptoms promote inflammation during acute stress among bereaved spouses. Psychol. Sci. 33 (6), 859–873.

Brydon, L., Steptoe, A., 2005 May. Stress-induced increases in interleukin-6 and fibrinogen predict ambulatory blood pressure at 3-year follow-up. J. Hypertens. 23 (5), 1001–1007.

Buckley, T., Mihailidou, A.S., Bartrop, R., McKinley, S., Ward, C., Morel-Kopp, M.C., et al., 2011 Feb 1. Haemodynamic changes during early bereavement: potential contribution to increased cardiovascular risk. Heart Lung Circ. 20 (2), 91–98.

Bui, E., Mauro, C., Robinaugh, D.J., Skritskaya, N.A., Wang, Y., Gribbin, C., et al., 2015 Jul 1. The structured clinical interview for complicated grief: reliability, validity, and exploratory factor analysis. Depress Anxiety 32 (7), 485–492.

Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 28 (2), 193–213.

Carey, I.M., Shah, S.M., DeWilde, S., Harris, T., Victor, C.R., Cook, D.G., 2014 Apr 1. Increased risk of acute cardiovascular events after partner bereavement: a matched cohort study. JAMA Intern. Med. 174 (4), 598–605.

Charlson, M., Szatrowski, T.P., Peterson, J., Gold, J., 1994. Validation of a combined comorbidity index. J. Clin. Epidemiol. 47 (11), 1245–1251.

Chida, Y., Steptoe, A., 2010 Apr. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status. Hypertension 55 (4), 1026–1032.

Chirinos, D.A., Ong, J.C., Garcini, L.M., Alvarado, D., Fagundes, C., 2019. Bereavement, self-reported sleep disturbances, and inflammation: results from Project HEART. Psychosom. Med. 81 (1), 67.

Cohen, M., Granger, S., Fuller-Thomson, E., 2015 Apr. The association between bereavement and biomarkers of inflammation. Behav. Med. 41 (2), 49–59.

Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., et al., 2012 Apr 17. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad. Sci. 109 (16), 5995–5999.

Elwert, F., Christakis, N.A., 2008 Nov. The effect of widowhood on mortality by the causes of death of both spouses. Am. J. Public Health 98 (11), 2092–2098.

Fagundes, C.P., Glaser, R., Hwang, B.S., Malarkey, W.B., Kiecolt-Glaser, J.K., 2013 Jul 1. Depressive symptoms enhance stress-induced inflammatory responses. Brain Behav. Immun. 31, 172–176.

Fagundes, C.P., Murdock, K.W., LeRoy, A., Baameur, F., Thayer, J.F., Heijnen, C., 2018 Jul 1. Spousal bereavement is associated with more pronounced ex vivo cytokine production and lower heart rate variability: mechanisms underlying cardiovascular risk? Psychoneuroendocrinology 93, 65–71.

Fagundes, C.P., Wu, E.L., 2020 May 7. Matters of the heart: grief, morbidity, and mortality. Curr. Dir. Psychol. Sci., 0963721420917698

Franceschi, C., Campisi, J., 2014 Jun 1. Chronic inflammation (Inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. A Biol. Sci. Med Sci. 69 (_1), S4–S9.

Gohel D. officer: Manipulation of Microsoft Word and PowerPoint Documents [Internet]. 2022. Available from: ⟨https://davidgohel.github.io/officer/⟩.

Gohel, D., set_attr), B.R., 2020. Javascript Code Use Funct., Algorithms) FB (Clipp. rvg: R. Graph. Devices Vector Graph. Output [Internet] [cited 2022 Sep 13].Available from: ⟨https://CRAN.R-project.org/package=rvg⟩.

Hahn, E.A., Cichy, K.E., Small, B.J., Almeida, D.M., 2014 Jan 1. Daily emotional and physical reactivity to stressors among widowed and married older adults. J. Gerontol. Ser. B 69B (1), 19–28.

Heinzen, E., Sinnwell, J., Atkinson, E., Gunderson, T., Dougherty, G., Votruba, P., et al., 2021. Arsenal: Arsenal "R. " Funct. Large-Scale Stat. Summ. [Internet]. ⟨https://CRAN.R-project.org/package=arsenal⟩ [cited 2022 Jul 19]. Available from.

Henze, G.I., Zänkert, S., Urschler, D.F., Hiltl, T.J., Kudielka, B.M., Pruessner, J.C., et al., 2017 Jan 1. Testing the ecological validity of the trier social stress test: association with real-life exam stress. Psychoneuroendocrinology 75, 52–55.

Holmes, T.H., Rahe, R.H., 1967. The social readjustment rating scale. J. Psychosom. Res. 11 (2), 213–218.

Jaremka L.M., Fagundes C.P., Peng J., Bennett J.M., Glaser R., Malarkey W.B., et al. Loneliness promotes inflammation during acute stress. Psychological Science [Internet]. 2013 [cited 2018 Jun 24];24(7). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3825089/.

Kiecolt-Glaser, J.K., Derry, H.M., Fagundes, C.P., 2015 Sep 11. Inflammation: depression fans the flames and feasts on the heat. AJP 172 (11), 1075–1091.

Kiecolt-Glaser, J.K., Renna, M.E., Shrout, M.R., Madison, A.A., 2020 Sep 9. Stress reactivity: what pushes us higher, faster, and longer—and why it matters. Curr. Dir. Psychol. Sci. [Internet] [cited 2022 Nov 20]; Available from: ⟨http://journals.sagepub.com/doi/full/10.1177/0963721420949521⟩.

Kinney, J.W., Bemiller, S.M., Murtishaw, A.S., Leisgang, A.M., Salazar, A.M., Lamb, B.T., 2018 Jan 1. Inflammation as a central mechanism in Alzheimer's disease. Alzheimer'S. Dement. Transl. Res. Clin. Interv. 4, 575–590.

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. NPS 28 (1–2), 76–81.

Knowles, L.M., Ruiz, J.M., O'Connor, M.F., 2019. A systematic review of the association between bereavement and biomarkers of immune function. Psychosom. Med 81 (5), 415–433.

Kuhlman K.R., Cole S.W., Craske M.G., Fuligni A.J., Irwin M.R., Bower J.E. Enhanced Immune Activation Following Acute Social Stress Among Adolescents With Early-

Life Adversity. Biological Psychiatry: Global Open Science [Internet]. 2022 Mar 12 [cited 2022 Sep 20];0(0). Available from: https://www.bpsgos.org/article/S2667-1743(22)00026-X/fulltext.
Kuhn M. caret: Classification and Regression Training [Internet]. 2020. Available from: ⟨https://CRAN.R-project.org/package=caret⟩.
Laws, H.B., Sayer, A.G., Pietromonaco, P.R., Powers, S.I., 2015. Longitudinal changes in spouses' HPA responses: convergence in cortisol patterns during the early years of marriage. Health Psychol. 34, 1076–1089.
Length R.V. emmeans: Estimated Marginal Means, aka Least-Squares Means [Internet]. 2022. Available from: ⟨https://github.com/rvlenth/emmeans⟩.
1991 Zisook S, Shuchter SR. Depression through the first year after the death of a spouse. Am. J. Psychiatry 148 (10), 1991, 1346–1352.
LeRoy, A.S., Gabert, T., Garcini, L., Murdock, K.W., Heijnen, C., Fagundes, C.P., 2020 Feb 1. Attachment orientations and loss adjustment among bereaved spouses. Psychoneuroendocrinology 112, 104401.
Liao, J.J.Z., 2005. A linear mixed-effects calibration in qualifying experiments. J. Biopharm. Stat. 15 (1), 3–15.
Liu, Y.Z., Wang, Y.X., Jiang, C.L., 2017. Inflammation: the common pathway of stress-related diseases. Front. Hum. Neurosci. [Internet] [cited 2023 May 1];11. Available from: ⟨https://www.frontiersin.org/articles/10.3389/fnhum.2017.00316⟩.
Lockwood, K.G., Marsland, A.L., Cohen, S., Gianaros, P.J., 2016 Nov 1. Sex differences in the association between stressor-evoked interleukin-6 reactivity and C-reactive protein. Brain, Behav., Immun. 58, 173–180.
Lüdecke, D., 2018. ggeffects: tidy data frames of marginal effects from regression models. J. Open Source Softw. 3 (26), 772.
Lüdecke D. sjPlot: Data visualization for statistics in social science [Internet]. 2021. Available from: ⟨https://CRAN.R-project.org/package=sjPlot⟩.
Madison, A.A., Andridge, R., Shrout, M.R., Renna, M.E., Bennett, J.M., Jaremka, L.M., et al., 2022. Frequent interpersonal stress and inflammatory reactivity predict depressive-symptom increases: two tests of the social-signal-transduction theory of depression. Psychol. Sci. 33 (1), 152–164.
Marsland, A.L., Walsh, C., Lockwood, K., John-Henderson, N.A., 2017 Aug 1. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. Brain Behav. Immun. 64, 208–219.
Matthews, K.A., Katholi, C.R., McCreath, H., Whooley, M.A., Williams, D.R., Zhu, S., et al., 2004 Jul 6. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. Circulation 110 (1), 74–78.
Medzhitov, R., 2008 Jul. Origin and physiological roles of inflammation. Nature 454 (7203), 428–435.
Miller, G.E., Rohleder, N., Stetler, C., Kirschbaum, C., 2005 Oct. Clinical depression and regulation of the inflammatory response during acute stress. Psychosom. Med. 67 (5), 679.
Moon, J.R., Glymour, M.M., Vable, A.M., Liu, S.Y., Subramanian, S.V., 2014 Sep 1. Short- and long-term associations between widowhood and mortality in the United States: longitudinal analyses. J. Public Health (Oxf.) 36 (3), 382–389.
Nilsonne, G., Lekander, M., Åkerstedt, T., Axelsson, J., Ingre, M., 2016 Nov 10. Diurnal variation of circulating interleukin-6 in humans: a meta-analysis. PLOS ONE 11 (11), e0165799.
Pace, T.W.W., Mletzko, T.C., Alagbe, O., Musselman, D.L., Nemeroff, C.B., Miller, A.H., et al., 2006 Sep. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. AJP 163 (9), 1630–1633.
Paykel, E.S., 2003. Life events and affective disorders. Acta Psychiatr. Scand. 108 (s418), 61–66.
Radloff, L.S., 1977 Jun. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1 (3), 385–401.
Ridker, P.M., Silvertown, J.D., 2008. Inflammation, C-reactive protein, and atherothrombosis. J. Periodontol. 79 (8S), 1544–1551.
RStudio Team, 2021. RStudio: Integrated Development Environment for R [Internet]. Boston, MA. RStudio, PBC. Available from: ⟨http://www.rstudio.com/⟩.
Sbarra, D.A., Hazan, C., 2008 May 1. Coregulation, dysregulation, self-regulation: an integrative analysis and empirical agenda for understanding adult attachment, separation, loss, and recovery. Pers. Soc. Psychol. Rev. 12 (2), 141–167.
Schultze-Florey, C.R., Martinez-Maza, O., Magpantay, L., Breen, E.C., Irwin, M.R., Gündel, H., et al., 2012 Oct. When grief makes you sick: Bereavement induced systemic inflammation is a question of genotype. Brain Behav. Immun. 26 (7), 1066–1071.
Shear, M.K., Simon, N., Wall, M., Zisook, S., Neimeyer, R., Duan, N., et al., 2011. Complicated grief and related bereavement issues for DSM-5. Depress Anxiety 28 (2), 103–117.
Slavich, G.M., 2020 May 7. Social safety theory: a biologically based evolutionary perspective on life stress, health, and behavior. Annu. Rev. Clin. Psychol. 16 (1), 265–295.
Stanley D. apaTables: Create American Psychological Association (APA) Style Tables [Internet]. 2020. Available from: ⟨https://github.com/dstanley4/apaTables⟩.
Steptoe, A., Hamer, M., Chida, Y., 2007 Oct 1. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav. Immun. 21 (7), 901–912.
Stroebe, M., Schut, H., 2010. The dual process model of coping with bereavement: a decade on. OMEGA-J. Death Dying 61 (4), 273–289.
Tal, I., Mauro, C., Reynolds, I.I.I., CF, Shear, M.K., Simon, N., Lebowitz, B., et al., 2017 May 28. Complicated grief after suicide bereavement and other causes of death. Death Stud. 41 (5), 267–275.
Tang, F., Ishwaran, H., 2017 Dec. Random forest missing data algorithms. Stat. Anal. Data Min. 10 (6), 363–377.
Turner, A.I., Smyth, N., Hall, S.J., Torres, S.J., Hussein, M., Jayasinghe, S.U., et al., 2020 Apr. Psychological stress reactivity and future health and disease outcomes: a systematic review of prospective evidence. Psychoneuroendocrinology 114, 104599.
Whitcomb, B.W., Perkins, N.J., Albert, P.S., Schisterman, E.F., 2010 Jul. Treatment of batch in the detection, calibration, and quantification of immunoassays in large-scale epidemiologic studies. Epidemiology 21 (4), S44–S50.
Whittaker, A.C., Ginty, A., Hughes, B.M., Steptoe, A., Lovallo, W.R., 2021 Sep. Cardiovascular stress reactivity and health: recent questions and future directions. Psychosom. Med. 83 (7), 756–766.
Wickham, H., 2016. ggplot2: Elegant graphics for data analysis [Internet]. Springer-Verlag New York. Available from: ⟨https://ggplot2.tidyverse.org⟩.
Wilson, S.J., Padin, A.C., Bailey, B.E., Laskowski, B., Andridge, R., Malarkey, W.B., et al., 2020 Aug 1. Spousal bereavement after dementia caregiving: a turning point for immune health. Psychoneuroendocrinology 118, 104717.
Wu, E.L., Brown, R.L., Chirinos, D.A., Chen, M.A., de Dios, M.A., Taylor, D.M., et al., 2021 Aug 1. Socioeconomic disparities in health: changes in sleep quality and inflammation during bereavement. Compr. Psychoneuroendocrinology 7, 100056.
Wu, E.L., LeRoy, A.S., Heijnen, C.J., Fagundes, C.P., 2021 Jun 1. Inflammation and future depressive symptoms among recently bereaved spouses. Psychoneuroendocrinology 128, 105206.
Zannas, A.S., Gordon, J.L., Hinderliter, A.L., Girdler, S.S., Rubinow, D.R., 2020 Oct 1. IL-6 response to psychosocial stress predicts 12-month changes in cardiometabolic biomarkers in perimenopausal women. J. Clin. Endocrinol. Metab. 105 (10), e3757–e3765.