Stress-related inflammation and social withdrawal in mothers after childhood cancer diagnosis

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Abstract

Objective: Acute inflammation-induced sickness behavior involves changes in social behavior that are believed to promote recovery. Whether chronic inflammation can influence social behaviors in ways that promote recovery is unknown. In a sample of mothers of a child with cancer, this report explores the relationship between inflammation that accompanies the stress of diagnosis and changes in social network, cancer-related stress, and inflammation across one year. Three hypotheses were tested, that (1) initial stress would associate with initial inflammation, (2) initial inflammation would predict social changes over time, and (3) social changes over time would buffer stress and inflammation over time.

Methods: Cancer-related stress (Impact of Events Scale), social network (social roles and contacts from the Social Network Inventory), and systemic inflammation (circulating IL-6) were assessed in 120 mothers three times after their child's cancer diagnosis: following diagnosis (T1), 6-month follow-up (T2), and 12-month follow-up (T3).

Results: Consistent with predictions, greater cancer-related stress following diagnosis (T1) was associated with higher IL-6 following diagnosis (T1; $b=.014, p=.008$). In turn, higher IL-6 following diagnosis (T1) was associated with a decrease in social roles over time (T1→T3; $B=-.030, p=.041$), particularly peripheral social roles. Finally, dropping social roles over time (T1→T3) was associated with decreases in cancer-related stress ($B=21.83, p=.040$) and slower increases in IL-6 ($B=.940, p=.036$) over time.

Conclusions: This study provides a first indication that chronic stress-related systemic inflammation may predict changes in social behavior that associate with stress recovery and slower increases in inflammation in the year following a major life stressor.

Keywords: sickness behavior; inflammation; social behavior; stress; cancer

Acronyms: IL-6 = Interleukin-6; IES = Impact of Events Scale; SNI = Social Network Index; CV = coefficient of variation; ANOVA = analysis of variance; MLM = mixed linear model

The innate immune system responds to pathogens and threat by producing cellular and behavioral changes that are thought to aid recovery. At the cellular level, proinflammatory cytokines (e.g., IL-1, IL-6, TNF-alpha) are released, which are widely accepted to signal motivated behavioral responses known as “sickness behavior” (1). Key among these are changes in social behaviors that are believed to promote rest and recovery, prevent the spread of disease, and provide an individual with care (2,3). In particular, social withdrawal behaviors may function to conserve energy and reduce the spread of infection by limiting physical contact, whereas social approach behaviors may prompt care and protection from others. However, outside of the acute experimental setting, no studies have examined inflammation and changes in social behavior in the context of a chronic major life stressor. The current study, therefore, provides an initial examination of associations between perceived stress, inflammation, and social network changes among mothers following the major life stressor of having a child diagnosed with cancer.

Inflammation and changes in social behavior

Experimental evidence from both animals and humans shows that acute inflammation can causally influence social behavior, but that changes depend on the social target. Social withdrawal behaviors have been observed in animals; compared to placebo conditions, those exposed to acute inflammatory challenge show less curiosity and responsiveness to potential social companions (4,5). Likewise in humans, experimentally-induced inflammation increases feelings of social disconnection (6) and amplifies neural threat responses to images of threatening strangers (7) and to negative social feedback from a stranger (8). However, acute inflammation has also been shown to cue social approach toward targets who may aid recovery (e.g., close others such as family members). Monkeys and rats exposed to inflammatory

challenge (vs. placebo) tend to huddle together with their cage mates while avoiding active social behavior with others (9,10). Humans too tend to selectively approach caregivers when sick (11), and acute inflammatory challenge increases psychological approach and neural reward sensitivity toward close others (12). Thus, acute, experimentally-induced inflammation can motivate both withdrawal and approach to specific social targets: it causes social withdrawal from strangers (i.e., peripheral others), but approach toward those who can provide support and care (i.e., close others) (13).

Chronic inflammation is also associated with social behavior. For example, in epidemiological samples, heightened systemic inflammation has been associated with chronic loneliness and social isolation (i.e., feeling or being socially disconnected) (14), whereas having a diverse social network is associated with lower systemic inflammation (15). Despite these associations, it is less clear whether chronic inflammation influences social behaviors in the long-term, and if so, whether inflammation-related changes in social behavior could serve an adaptive recovery function. There may be circumstances in which it is beneficial to simultaneously withdraw from peripheral others while also approaching close others. When major life stressors cause elevations in systemic inflammation, withdrawal from looser social ties—at least temporarily—may be beneficial for emotional and physical health. This possibility has never been explored in the context of a chronic stressor; here this idea is tested in a sample of mothers caring for a child newly diagnosed with cancer.

Childhood cancer and mothers' social network behavior and health

Having a child diagnosed with cancer is a life-altering stressor that impacts mothers' well-being (16), social life (17,18), and own health over time. Indeed, caring for a chronically ill child or loved one with cancer is associated with markers of compromised immune function,

including heightened inflammation (19–21). Members of mothers' social network have the potential to moderate the relationship between caregiving and inflammation. In light of previous literature, two possibilities are plausible. First, a diverse social network may buffer increases in stress and inflammation. Humans have a fundamental need for social connection (22), and having a diverse social network can promote positive health behaviors and emotions and provide social support during times of stress, all facilitating adaptive physiological functioning (23). Alternatively, selective social withdrawal may aid mothers' emotional recovery following cancer diagnosis, thereby buffering increases in stress and inflammation. Even with a strong social network, adjusting to cancer diagnosis is a major life stressor that can elevate inflammation, which could then cue social network changes. In particular, stress-induced inflammation may contribute to a tendency for mothers to devote energy to their closest family while dropping more peripheral social roles (13). Over time, dropping these social roles may help mothers to more effectively cope with this unique life change, which may buffer negative effects to their own health.

The current study

In a sample of mothers of a child newly diagnosed with cancer, this report explores the relationship between inflammation that accompanies the stress following diagnosis (T1) and changes in social network, inflammation, and cancer-related stress in the year after diagnosis (T2: 6-month follow-up; T3: 12-month follow-up). Three hypotheses were tested:

Hypothesis 1: First, greater psychological stress in response to cancer diagnosis was hypothesized to relate to higher levels of systemic inflammation (indexed by circulating levels of IL-6) in the first few weeks following diagnosis (T1).

Hypothesis 2: Second, following the logic that inflammation causes role-specific changes

in social behavior, higher systemic inflammation following diagnosis (T1) was hypothesized to predict decreases in social network roles and contacts over time (T1→T3), particularly toward peripheral social targets. An alternative possibility is that stress, rather than inflammation, predicts social network changes, implicating a more direct psychological pathway; as an alternative to Hypothesis 2, the possibility that higher cancer-related stress following diagnosis (T1) predicted decreases in social network roles and contacts over time (T1→T3) was tested.

Hypothesis 3: Third, exploring the possibility that inflammation-related social network changes may serve an adaptive function in the context of chronic caregiving stress, decreases in social network over time were hypothesized to buffer both cancer-related stress and systemic inflammation over time (T1→T3).

Methods

Participants

Participants were 120 female primary caregivers of a child (aged 0-17 years) newly diagnosed with cancer (mean age=36 years, SD=8; see Table 1 for sample characteristics) recruited from the Division of Hematology and Oncology, Children's Hospital of Pittsburgh (see *Supplementary Material* for eligibility criteria). This report describes secondary data analysis from a randomized controlled trial (NCT02022449) designed to assess the efficacy of a supportive stress management intervention on psychological distress and inflammation outcomes (24).

Briefly, the intervention, which involved six face-to-face sessions and six telephone sessions with a clinician over a 5-6 month period, taught a range of cognitive behavioral coping skills (e.g., stress appraisal, problem solving, processing and talking about feelings, emotion regulation, relaxation, cognitive reappraisal, social support) intended to address challenges

related to caring for a child with cancer. Written informed consent was obtained in accordance with the University of Pittsburgh IRB.

Procedure

Mothers were assessed at three time points over approximately one year following their child's diagnosis: T1 ($M=1.84$ months ($SD=0.82$) post-diagnosis), T2 ($M=6.81$ months ($SD=1.94$) post-diagnosis), and T3 ($M=12.74$ months ($SD=2.20$) post-diagnosis). At each study appointment, blood was drawn for IL-6 assessment and participants were given questionnaires to complete and return within 3 weeks, including assessments of social network and cancer-related stress (see *Measures*). Seventeen mothers dropped out of the study after T1: $N=11$ mothers dropped out before T2 and an additional $N=6$ before T3 (dropout rate = 14%). To account for missing data, analyses were conducted (1) using Expectation-Maximization (EM) imputed T1 data to include all $N=120$ subjects in analyses (see *Analysis*) and (2) using all available data for each analysis (reported in *Supplementary Tables*). See *Supplementary Materials* for detail.

Measures

Cancer-related Stress: Impact of Events Scale (IES): The IES is a 15-item measure assessing the psychological impact of a traumatic event (25), in this case, cancer diagnosis. Items focus on intrusive emotions, images, and thoughts about the event, as well as attempts to avoid these thoughts and feelings. The frequency of these experiences during the last week is assessed on a 0 (not at all) to 5 (often) scale, and responses are summed to create a total score ranging from 0 to 75, with higher scores indicating higher cancer-related stress. Estimates of internal reliability in this sample were $\alpha=0.85$, 0.89, and 0.93 for T1, T2, and T3, respectively.

Social Network Index (SNI): In order to assess changes in social network over time, participants completed the Social Network Index (SNI) (26). The scale assesses the number of

high-contact social roles (referred to in this paper as ‘roles’) and the total number of people in one’s regular social network (referred to in this paper as ‘contacts’) from a list of 12 social role categories (spouse, parent, daughter, daughter-in-law, relative, friend, church member, student, employee, neighbor, volunteer, other group member). Importantly, the SNI accounts for frequency of contact; only people that participants see or talk to on a regular basis (at least once every two weeks) are counted as roles or contacts. For the measure of SNI *social roles*, the total number of high-contact role categories endorsed out of 12 was summed, and for the measure of SNI *social contacts*, the total number of people that participants regularly contact across all social roles was summed.

In order to explore potential changes in close vs. peripheral social roles and contacts, the total number of close family roles and contacts (spouse, parent, daughter) and the total number of peripheral roles and contacts (daughter-in-law, more distant relative, friend, church member, student, employee, neighbor, volunteer, other group member) were each summed. Roles and contacts were categorized based on: (1) previous theoretical perspectives from the social psychology literature suggesting that immediate social network members (principally family) are the closest and most powerful influences on health, well-being, and behavior (27), (2) large-scale social network analyses that close family members are heavily relied upon for support (28), and (3) previous research showing that experimental inflammatory challenge selectively alters responses to the same close network members (12).

Systemic Inflammation: Circulating plasma IL-6 levels were analyzed in batch using a high sensitivity quantitative sandwich enzyme immunoassay kit (R&D Systems, Cat # HS600B). Plasma samples from heparinized blood were stored at -80°C until assay. The range of detection for the assay was 0.156–10 pg/mL. Average intra- and inter-assay CVs were 7.5% and 8.5%. IL-

6 values were natural log transformed for analysis.

Covariates: Control variables included age, years of education, intervention condition, and the child's level of treatment intensity coded by a pediatric oncologist using the Intensity of Treatment Rating Scale-3 (29).

Statistical Analysis

Analyses were performed using StataSE Version 15.0 (StataCorp, College Station, Texas). Preliminary analyses characterized the full study sample and compared participants with complete data at T1 (N=98) to those with missing data at T1 (N=22) using chi-square (for categorical variables) and ANOVA tests (for continuous variables). Mixed linear models (MLMs; Stata's 'mixed' command) explored the relation between covariates (age, years of education, child's treatment intensity) and the primary outcomes (IL-6 and IES). Additionally, MLMs were used to test for intervention vs. no treatment control effects on IL-6 and IES across the study period (three time points from T1→T3). Finally, MLMs tested for changes in primary variables of interest across the study period (three time points from T1→T3), with time (coded as months since diagnosis at T1, T2, and T3) modeled as a random effect; MLM models used an unstructured covariance matrix and maximum likelihood estimation.

To test the primary hypotheses, data missing at T1 were imputed from all primary outcome variables and covariates (age, education, intervention condition, and treatment intensity; T1, T2, and T3 months since diagnosis, IES, SNI roles, SNI contacts, and IL-6) using SPSS's Expectation-Maximization (EM) algorithm (IBM SPSS Version 26). Specifically, data were estimated at T1 for treatment intensity (N=1), IES (N=2), and IL-6 (N=19), enabling all N=120 mothers to be included in primary analyses. Little's MCAR test suggests that these data were missing completely at random ($\chi^2(6)=4.16, p=.65$). Primary analyses conducted using all

available data are presented in Supplementary Tables 2-6.

Hypothesis 1: To test whether T1 stress would relate to higher T1 IL-6, a multiple regression model focused on the relationship between T1 IES score and T1 IL-6 while controlling for covariates.

Hypothesis 2: To test whether T1 inflammation would predict social network changes, in particular withdrawal from peripheral roles/contacts (or alternatively, whether T1 stress would predict social network changes), MLMs focused on the interaction between T1 IL-6 (or alternatively, T1 IES) and time since diagnosis (at T1, T2, and T3) to predict change in SNI roles/contacts and SNI close vs. peripheral roles/contacts subscales over time, controlling for covariates.

Hypothesis 3: Finally, to test whether social withdrawal would predict lower stress and slower increases in IL-6 over time, MLMs focused on the interaction between T1→T3 SNI roles/contacts slope and time since diagnosis (at T1, T2, and T3) to predict change in IES and IL-6 over time, controlling for T1 SNI roles/contacts intercept, T1 SNI roles/contacts intercept predicting change over time, and covariates. MLMs predicting change in SNI roles/contacts over time were used to estimate grand-mean centered SNI roles/contacts intercept and slope at the individual level. Specifically, Hypothesis 3 models followed the equation below¹; the interaction between SNI roles/contacts slope and time predicts change in the outcome (time variable) from change in the predictor (slope variable), and as such, is the primary predictor of interest:

$$IL-6_{it} = \gamma_{00} + \gamma_{01}(Condition_{it}) + \gamma_{02}(SNI_Intercept_{it}) + \gamma_{10}(Time_{it}) + \gamma_{11}(Condition_{it})*(Time_{it}) + \gamma_{12}(SNI_Intercept_{it})*(Time_{it}) + \gamma_{13}(SNI_Slope_{it})*(Time_{it}) + \gamma_{20}(Age_{it}) + \gamma_{30}(Education_{it}) + \gamma_{40}(TreatmentIntensity_{it}) + u_{0i} + u_{1i} + r_{it}$$

¹ The random effects of slope and intercept for SNI contacts were perfectly inversely correlated, such that an individual's change in number of social contacts did not explain any additional variance beyond number of social contacts at T1; thus, Hypothesis 3 models for SNI contacts focused on the interaction between T1→T3 SNI contacts slope and time to predict change in IES and IL-6 over time, but did not include the T1 SNI contacts intercept predicting change over time.

Results

Preliminary Analyses

Sample characteristics are described in Table 1. Participants with missing data at T1 were significantly older than those with complete data at T1, but these groups did not otherwise differ on educational attainment, race, intervention condition, or child's treatment intensity (Table 1).

The primary outcome, IL-6, was negatively related to age ($B=-.028, p<.0005$), years of education ($B=-.089, p=.002$), and child's treatment intensity ($\chi^2(2)=17.96, p=.0001$). The secondary outcome, IES, was negatively related to age ($B=-.342, p=.034$), but not years of education ($B=-1.047, p=.086$) or child's treatment intensity ($\chi^2(2)=2.22, p=.33$). Across the study period (T1→T3), the intervention did not significantly change IL-6 ($B=.013, p=.20$) or IES ($B=.008, p=.98$) compared to no treatment, but was additionally included as a covariate to control for any intervention effects. In sum, age, education, treatment intensity, and intervention condition were included as covariates in primary analyses. Correlations between the primary outcomes are shown in Supplementary Table 7.

Finally, preliminary analyses tested for changes in primary variables of interest across the study period (T1→T3). Across participants, cancer-related stress decreased over time, as did numbers of social roles and contacts, while IL-6 increased (see Table 2). Notably, mothers maintained close social roles ($B=0.001, p=.85$) and tended to drop more peripheral social roles ($B=-0.023, p=.063$) over time; likewise, mothers maintained the same number of close social contacts ($B=0.007, p=.41$) and dropped peripheral social contacts ($B=-0.155, p=.008$) over time (Table 2). Descriptively, mothers were most likely to drop neighbor, more distant relative, in-law, church, work, and other group roles across the study period, and dropped the highest number of work, friend, more distant relative, church, neighbor, and other group contacts.

Significant residual variance was present for all variables after accounting for the effect of time, indicating the presence of individual-level variation in changes in stress, social network, and IL-6 (Table 2). Thus, primary analyses explored the relationship between changes in mothers' social network, cancer-related stress, and IL-6 in the year following their child's cancer diagnosis.

Primary Analyses

Hypothesis 1: Does initial stress predict initial inflammation?

Multiple regression analyses supported the prediction that greater psychological stress related to cancer diagnosis was associated with higher IL-6 at T1 ($b=.014, p=.008$; Table 3). Consistent with prior work and current hypotheses, mothers who reported greater cancer-related stress within the weeks following their child's cancer diagnosis also had higher systemic inflammation (Figure 1).

Hypothesis 2: Does initial inflammation predict changes in social network over time?

MLMs focused on the interaction between T1 IL-6 and time since diagnosis (at T1, T2, and T3) supported the prediction that higher IL-6 at T1 was associated with a decrease in overall social roles from T1 through T3 ($B=-.030, p=.041$; Table 4; Figure 2). More specifically, consistent with literature showing acute inflammation-induced withdrawal from peripheral others and approach toward close others, higher T1 IL-6 tended to associate with a decrease in peripheral social roles ($B=-.023, p=.084$), whereas close social roles were maintained ($B=-.002, p=.60$).

In contrast, higher IL-6 at T1 was not significantly associated with changes in overall number of social contacts from T1 to T3 ($B=-.053, p=.42$; Table 4), either peripheral social contacts ($B=-.036, p=.58$) or close social contacts ($B=-.012, p=.23$). Higher IL-6 within the weeks following diagnosis was associated with withdrawal from social *roles*, particularly

peripheral roles, but not with the number of social *contacts*.

Alternative Hypothesis 2: Does initial stress predict changes in social network over time?

The alternative to hypothesis 2 was not supported: higher stress at T1 was not associated with a decrease in overall social roles ($B=.001$, $p=.29$; Table 5) or social contacts ($B=.006$, $p=.12$; Table 5) from T1 to T3. Thus, greater cancer-related stress was not directly associated with withdrawal from one's social network over time. However, higher stress at T1 was related to having a smaller social network at T1 (social roles $B=-.026$, $p=.018$, social contacts $B=-.159$, $p=.002$; Supplementary Table 1); in other words, having a larger social network following diagnosis was associated with lower initial cancer-related stress.

Hypothesis 3: Do changes in social network predict changes in stress and inflammation?

Hypothesis 3 tested whether maintaining a larger social network throughout the year following diagnosis continued to be helpful for buffering stress and increases in inflammation, or whether dropping social roles and/or contacts was more beneficial. MLMs tested for an interaction between SNI T1→T3 slope and time since diagnosis. In regard to SNI social roles, both predictions were supported; a decrease in social roles overall was associated with a decrease in cancer-related stress from T1→T3 ($B=25.442$, $p=.039$; Figure 3a) as well as a slower increase in IL-6 from T1→T3 ($B=1.060$, $p=.040$; Figure 3b) (see Table 6a for full MLM results).

Decreases in overall SNI social contacts were not significantly associated with decreases in cancer-related stress or IL-6 over time (see Table 6b). Whereas withdrawal from social *roles* was associated with decreased stress and slower increases in IL-6 over the year following diagnosis, withdrawal from individual social *contacts* was not associated with changes in stress or IL-6.

Discussion

A growing literature supports an evolutionary function of acute inflammation-induced sickness behavior. Animals and humans alike show withdrawal from regular social activity and approach toward close others who can provide care (2,3,13); together, these changes in social behavior are believed to function to conserve energy, promote recovery, and curb the spread of disease. However, whether chronic stress-related inflammation changes social behaviors in ways that promote recovery is an open question. In a sample of mothers with a child recently diagnosed with cancer, this study provides the first indication that chronic stress-related systemic inflammation predicts social network changes, especially withdrawal from peripheral social roles. Further, these changes in social network were associated with stress recovery and slower increases in inflammation in the year following cancer diagnosis, a major stressful life event.

An open question for future research is to clarify the bidirectional communication pathways between the brain and peripheral immune system that give rise to such findings (30,31). Specifically, chronic stressors are thought to activate threat-related pathways in the brain (32), which signal changes in peripheral autonomic and neuroendocrine activity that modulate the innate immune system to upregulate the production and release of proinflammatory cytokines into peripheral circulation (33). In turn, these cytokines access the central nervous system either directly by crossing the blood-brain barrier (34) or indirectly, for example, by activating the vagus nerve (35) (e.g., Marsland et al., 2017). Centrally, this inflammation induces sickness behaviors, including social approach and withdrawal behaviors, by influencing neural sensitivity to social cues (13). These changes in social behavior may further signal peripheral and central changes, the same bidirectional pathways supporting stress recovery and slowing further increases in inflammation over time. Overall, the present findings are supported by complex biological circuits linking brain, body, and behavior that are believed to promote recovery.

Additional research would benefit from integrating brain pathways hypothesized to support inflammation-induced social changes and recovery over time.

Psychologically, a child's cancer diagnosis is a particularly potent chronic stressor that can take a toll on mothers' health over time. The current results raise the possibility that increases in inflammation that accompany the stress of diagnosis motivate selective social network changes that allow mothers to focus energy on supportive family roles and away from the maintenance of peripheral social roles. Of course, sensitivity analyses showing specific withdrawal from peripheral roles were not statistically significant and should therefore be interpreted with caution and replicated in future research. Still, the current findings are consistent with other evidence that the year following cancer diagnosis is a transitional period in which mothers draw closer to family for emotional and instrumental support (18,37), leaving less time to maintain previous social roles. Mothers in particular often take on new responsibilities surrounding day-to-day treatment and emotional care while needing to delegate other responsibilities at home (38). This changed role within the family may alter mothers' identities in ways that disconnect them from more peripheral social roles (39). Thus, in the context of childhood cancer, there are many reasons why temporary, selective social withdrawal may be beneficial that could be tested in future research (e.g., maintaining a variety of social roles may feel overwhelming or some roles may feel less important to maintain). The current results provide intriguing initial evidence that systemic inflammation may contribute to changes in social function that support mothers' mental and physical health.

Notably, the benefits of social withdrawal were specific to social roles rather than total number of social contacts; these mothers may have developed a more focused self-identity spread over fewer domains. Selectively dropping entire, less supportive role categories (e.g.,

work, distant relatives), at least temporarily, may relieve more burden than losing contact with people across several roles. Although not directly measured, it is also possible that mothers find support from new social contacts through the course of treatment (e.g., the medical team; families of other children with cancer), thus replacing lost social contacts while still dropping specific roles. However, the health benefits of having fewer social roles that are evident in the short-term may have negative consequences if mothers do not re-integrate with the broader social community over time (40). For example, spousal caregivers whose social networks continue to shrink over the course of six years show steeper increases in inflammation compared to non-caregivers (41), suggesting that social re-integration is important for long-term health.

A large epidemiological literature shows that greater social integration is associated with lower systemic inflammation (15) and a longer, healthier life (26,42,43), but the present results demonstrate one context in which maintaining a large number of social roles may not be beneficial. It will be important to replicate and extend these findings over longer periods of time and in other populations faced with major life stress, stress-induced inflammation, and changing values and identities. Selective social withdrawal may be adaptive for other types of chronic stressors (e.g., natural disaster recovery, adult caregiving), but it is also possible that caring for an ill child is a unique life event that warrants social adjustments. In light of these findings, future intervention research might incorporate strategies that allow mothers to set aside peripheral social roles as they adjust to their new caregiving responsibilities (e.g., delegating a relative to maintain online health updates and communication with peripheral ties). Future research may also explore when it is beneficial to re-engage with peripheral social ties and how mothers establish new, values-consistent social roles.

Limitations

The results presented here provide a first examination of associations between the inflammation that accompanies the onset of an overwhelming life stressor and social network changes that may contribute to recovery. However, there are several noteworthy limitations and alternatives. First, this study is limited by missing data; it may be that the 14% of the sample that dropped out of the study were employing social withdrawal that may or may not relate to adaptive psychological and physical health outcomes as observed here. Second, data from this report comes from a behavioral intervention RCT targeting stress and inflammation; although intervention-related changes in the primary outcomes were not observed (24) and analyses controlled for intervention condition, the intervention adds noise to the interpretation of the longitudinal results observed here. In particular, the intervention addressed the topic of social support, among other coping skills, a component that could plausibly have impacted the outcomes observed here. Third, an alternative possibility is that a third variable, rather than inflammation-related sickness behavior, is driving the changes in social roles observed here. However, exploratory analyses testing the possibility that mothers who experienced the highest levels of stress following cancer diagnosis may drop social roles as a means of coping (i.e., that T1 stress predicts social withdrawal over T1→T3) did not support this alternative explanation. Instead, consistent with prior literature, the data here shows that a larger social network following diagnosis related to lower cancer-related stress following diagnosis, but that dropping some social roles in the year after diagnosis was associated with stress recovery.

Finally, the clinical significance of the results observed here is unknown. On average, the mean change in mothers' social roles was small; however, 43% of mothers dropped social roles across the study period (while 38% showed no changes and 19% added social roles), suggesting that social network changes are a common and potentially important phenomenon in this

population. Similarly, although mean IL-6 levels were within the normal limits at all time points in this sample, mean IL-6 levels increased by 42% in the year following cancer diagnosis; small increases in systemic IL-6 levels have been associated with risk for cardiometabolic disease (44). Understanding processes that may buffer these increases inflammation could have meaningful implications for caregivers. Moreover, the observed reductions in cancer-related stress have clinical significance, as many mothers show mental health symptoms for years after childhood cancer diagnosis (45). Additionally, from the perspective of biological mechanisms, these results suggest that chronic stress-related inflammation may drive similar sickness behaviors to those observed following acute increases.

Conclusion

Overall, these findings provide new insight into a complex adaptation process following childhood cancer diagnosis, whereby mothers' stress-induced inflammation may influence social network changes that are adaptive for their psychological and physical health over time.

References

1. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain, behavior, and immunity*. 2007;21:153–160.
2. Cole SW. The Complexity of Dynamic Host Networks. In: Deisboeck TS, Kresh JY, editors. *Complex Systems Science in Biomedicine*. Boston, MA: Springer; 2006. p. 605–29.
3. Hennessy MB, Deak T, Schiml PA. Sociality and sickness: Have cytokines evolved to serve social functions beyond times of pathogen exposure? *Brain, Behavior, and Immunity*. 2014;37:15–20.
4. Bluthé R-M, Dantzer R, Kelley KW. Effects of interleukin-1 receptor antagonist on the behavioral effects of lipopolysaccharide in rat. *Brain Research*. 1992;573:318–20.
5. Bluthé RM, Pawlowski M, Suarez S, Parnet P, Pittman Q, Kelley KW, Dantzer R. Synergy between tumor necrosis factor α and interleukin-1 in the induction of sickness behavior in mice. *Psychoneuroendocrinology*. 1994;19:197–207.
6. Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain, behavior, and immunity*. 2010;24:558–563.
7. Inagaki TK, Muscatell KA, Irwin MR, Cole SW, Eisenberger NI. Inflammation selectively enhances amygdala activity to socially threatening images. *NeuroImage*. 2012;59:3222–26.
8. Muscatell KA, Moieni M, Inagaki TK, Dutcher JM, Jevtic I, Breen EC, Irwin MR, Eisenberger NI. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. *Brain, behavior, and immunity*. 2016;57:21–29.
9. Willette AA, Lubach GR, Coe CL. Environmental context differentially affects behavioral, leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus monkey. *Brain, Behavior, and Immunity*. 2007;21:807–15.
10. Yee JR, Prendergast BJ. Sex-specific social regulation of inflammatory responses and sickness behaviors. *Brain, behavior, and immunity*. 2010;24:942–951.
11. Bowlby J. *A secure base: Parent-child attachment and healthy human development*. Basic books; 2008.
12. Inagaki TK, Muscatell KA, Irwin MR, Moieni M, Dutcher JM, Jevtic I, Breen EC, Eisenberger NI. The role of the ventral striatum in inflammatory-induced approach toward support figures. *Brain, behavior, and immunity*. 2015;44:247–252.
13. Eisenberger NI, Moieni M, Inagaki TK, Muscatell KA, Irwin MR. In *Sickness and in Health: The Co-Regulation of Inflammation and Social Behavior*. *Neuropsychopharmacology*. 2017;42:242–53.

14. Hawkey LC, Cacioppo JT. Loneliness Matters: A Theoretical and Empirical Review of Consequences and Mechanisms. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*. 2010;40:218–27.
15. Uchino BN, Trettenvik R, Kent de Grey RG, Cronan S, Hogan J, Baucom BR. Social support, social integration, and inflammatory cytokines: A meta-analysis. *Health Psychology*. 2018;37:462.
16. Svavarsdottir EK. Caring for a child with cancer: a longitudinal perspective. *Journal of Advanced Nursing*. 2005;50:153–61.
17. Da Silva FM, Jacob E, Nascimento LC. Impact of Childhood Cancer on Parents' Relationships: An Integrative Review: Childhood Cancer and Parents' Relationship. *Journal of Nursing Scholarship*. 2010;42:250–61.
18. Long KA, Marsland AL. Family Adjustment to Childhood Cancer: A Systematic Review. *Clinical Child and Family Psychology Review*. 2011;14:57–88.
19. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences*. 2004;101:17312–17315.
20. Rohleder N, Marin TJ, Ma R, Miller GE. Biologic cost of caring for a cancer patient: dysregulation of pro-and anti-inflammatory signaling pathways. *J Clin Oncol*. 2009;27:2909–2915.
21. Walsh CP, Ewing LJ, Cleary JL, Vaisleib AD, Farrell CH, Wright AG, Gray K, Marsland AL. Development of glucocorticoid resistance over one year among mothers of children newly diagnosed with cancer. *Brain, behavior, and immunity*. 2018;69:364–373.
22. Baumeister RF, Leary MR. The need to belong: Desire for interpersonal attachments as a fundamental human motivation. *Psychological Bulletin*. 1995;117:497–529.
23. Cohen S. Social relationships and health. *American psychologist*. 2004;59:676.
24. Marsland AL, Walsh CP, Cleary JL, Vaisleib AD, Farrell C, Woods W, Tersak J, Wright AGC, Ewing LJ. A randomized controlled pilot trial examining efficacy of a stress management intervention for mothers of children newly diagnosed with cancer. submitted;
25. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosomatic Medicine*. 1979;41:209–18.
26. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. *Jama*. 1997;277:1940–1944.
27. Bowlby J. Attachment. In: *Attachment and Loss*. New York, NY: Basic Books; 1969.

28. Dunbar RI, Spoors M. Social networks, support cliques, and kinship. *Human nature*. 1995;6:273–290.
29. Kazak AE, Hocking MC, Ittenbach RF, Meadows AT, Hobbie W, DeRosa BW, Leahey A, Kersun L, Reilly A. A revision of the intensity of treatment rating scale: classifying the intensity of pediatric cancer treatment. *Pediatric blood & cancer*. 2012;59:96–99.
30. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology*. 2011;11:625–32.
31. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological review*. 1998;105:83.
32. Gianaros PJ, Wager TD. Brain-body pathways linking psychological stress and physical health. *Current directions in psychological science*. 2015;24:313–321.
33. Eisenberger NI, Cole SW. Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health. *Nature Neuroscience*. 2012;15:669–74.
34. Erickson MA, Banks WA. Neuroimmune Axes of the Blood–Brain Barriers and Blood–Brain Interfaces: Bases for Physiological Regulation, Disease States, and Pharmacological Interventions. Dantzer R, editor. *Pharmacological Reviews*. 2018;70:278–314.
35. Maier SF, Goehler LE, Fleshner M, Watkins LR. The Role of the Vagus Nerve in Cytokine-to-Brain Communication. *Annals of the New York Academy of Sciences*. 1998;840:289–300.
36. Marsland AL, Kuan DC-H, Sheu LK, Krajina K, Kraynak TE, Manuck SB, Gianaros PJ. Systemic inflammation and resting state connectivity of the default mode network. *Brain, Behavior, and Immunity*. 2017;62:162–70.
37. McCubbin M, Balling K, Possin P, Friedrich S, Bryne B. Family resiliency in childhood cancer. *Family Relations*. 2002;51:103–111.
38. Lutgendorf SK, Laudenslager ML. Care of the caregiver: stress and dysregulation of inflammatory control in cancer caregivers. *Journal of Clinical Oncology*. 2009;27:2894–95.
39. Jetten J, Haslam C, Haslam SA, Dingle G, Jones JM. How groups affect our health and well-being: the path from theory to policy. *Social Issues and Policy Review*. 2014;8:103–130.
40. Lovell B, Moss M, Wetherell M. The psychosocial, endocrine and immune consequences of caring for a child with autism or ADHD. *Psychoneuroendocrinology*. 2012;37:534–42.
41. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences*. 2003;100:9090–95.

42. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and Social Isolation as Risk Factors for Mortality: A Meta-Analytic Review. *Perspectives on Psychological Science*. 2015;10:227–37.
43. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS medicine*. 2010;7:e1000316.
44. Bakhshi H, Ostovaneh MR, Ambale VB, Allison M, Herrington, Cushman M, Szklo M, Wu CO, Blaha M, Budoff M, Tracy R, Bluemke DA, Lima JA. Abstract 14731: Association of Longitudinal Changes in CRP, IL-6, and Fibrinogen Level With Cardiovascular Disease Events: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2015;132:A14731–A14731.
45. Ljungman L, Cernvall M, Grönqvist H, Ljótsson B, Ljungman G, von Essen L. Long-Term Positive and Negative Psychological Late Effects for Parents of Childhood Cancer Survivors: A Systematic Review. Stemmer SM, editor. *PLoS ONE*. 2014;9:e103340.

Table 1. Sample characteristics.

Characteristic	Full Sample (N=120)	T1 data available (N=98)	T1 data missing (N=22)	Difference
Age in years	35.94 (7.95)	34.92 (7.68)	40.50 (7.68)	$F(1,119)=9.49^*$
Education in years	13.99 (2.12)	14.08 (2.12)	13.59 (2.12)	$F(1,119)=0.97$
Race				$\chi^2(1)=0.57$
African American + Other	17 (14%)	15 (15%)	2 (9%)	
Caucasian	103 (86%)	83 (85%)	20 (91%)	
Treatment Intensity	^a		^b	$\chi^2(1)=2.08$
Moderate	34 (28%)	30 (31%)	4 (18%)	
Very	67 (56%)	55 (56%)	12 (55%)	
Most	18 (15%)	13 (13%)	5 (23%)	
Intervention Condition	60 (50%)	52 (53%)	8 (36%)	$\chi^2(1)=2.00$

Data are presented as means (SD) or count (%). Note: T1 data were considered missing if any primary outcome variable or covariate was not available at T1. ^aN=119, ^bN=21. * $p<.05$.

Table 2. Descriptive statistics of primary predictor and outcome variables.

Outcome	T1 (N=120)	T2 (N=97)	T3 (N=87)	T1→T3 Slope (N=120)	Variance^f
IES	33.28 (14.93)	27.13 (16.82)	23.09 (17.98)	<i>B</i>=-0.869 (.14), <i>z</i>=-6.24*	113.6 [93, 139]
SNI Roles	7.00 (1.83)	6.71 (1.92) ^a	6.84 (1.79) ^c	<i>B</i>=-0.031 (.01), <i>z</i>=-2.29*	1.00 [0.74, 1.34]
Close Roles	2.60 (0.63)	2.63 (0.58) ^a	2.68 (0.54) ^b	<i>B</i> =0.001 (.00), <i>z</i> =0.19	0.06 [0.05, 0.09]
Peripheral Roles	4.20 (1.50)	3.96 (1.60) ^a	4.02 (1.44) ^b	<i>B</i> =-0.023 (.01), <i>z</i> =-1.86	0.75 [0.56, 1.00]
SNI Contacts	17.85 (8.52)	16.20 (7.90) ^a	17.06 (8.31) ^c	<i>B</i>=-0.153 (.06), <i>z</i>=-2.61*	21.24 [17.0, 26.5]
Close Contacts	4.60 (1.58)	4.56 (1.41) ^a	4.85 (1.57) ^b	<i>B</i> =0.007 (.01), <i>z</i> =0.82	0.48 [0.39, 0.60]
Peripheral Contacts	13.25 (8.42)	11.51 (7.74) ^a	12.17 (7.76) ^b	<i>B</i>=-0.155 (.06), <i>z</i>=-2.65*	20.64 [16.8, 25.4]
IL-6 (pg/mL)	1.88 (3.23)	1.80 (2.66) ^b	2.67 (3.57) ^d	<i>B</i>=0.039 (.01), <i>z</i>=6.05*^e	0.15 [0.10, 0.21]

Data reported as means (SD) or slope coefficient (SE). ^aN=96, ^bN=81, ^cN=83, ^dN=72, ^eSlope calculated from log-transformed data, ^findividual-level residual variance [95% CI] after accounting for the effect of time. ***p<.05**.

Table 3. Hypothesis 1: Does T1 stress predict higher T1 IL-6?

	T1 IES $\rightarrow$ T1 IL-6
	<i>B</i> (SE)
Intercept (β_0)	1.821 (.65)*
T1 IES (β_1)	0.014 (.01)*
Age (β_2)	-0.008 (.01)
Education (β_3)	-0.082 (.04)*
Treatment Intensity (β_4)	-0.330 (.12)*
T1 Time Since Diagnosis (β_5)	0.110 (.09)
N=120. * p<.05.	

Table 4. Hypothesis 2: Does T1 IL-6 predict decrease in social network?

	T1 IL-6 $\rightarrow$ Δ SNI Roles		T1 IL-6 $\rightarrow$ Δ SNI Contacts	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	2.470 (1.23)	2.01*	-0.838 (5.54)	-0.15
Condition (γ_{01})	0.456 (.28)	1.61	0.129 (1.28)	0.10
T1 IL-6 (γ_{02})	0.399 (.19)	2.08*	0.797 (.89)	0.89
Time Since Diagnosis (γ_{10})	-0.030 (.01)	-2.32*	-0.154 (.06)	-2.63*
T1 IL-6*Time Since Diagnosis (γ_{11})	-0.030 (.01)	-2.04*	-0.053 (.07)	-0.81
Age (γ_{20})	0.008 (.02)	0.43	0.210 (.08)	2.47*
Education (γ_{30})	0.326 (.07)	4.59*	0.890 (.32)	2.77*
Treatment Intensity (γ_{40})	-0.203 (.22)	-0.91	-0.528 (1.01)	-0.52
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	1.01 (.15)	0.75, 1.35	21.13 (2.28)	17.10, 26.11
Between-subjects error (u_{0i})	1.87 (.40)	1.23, 2.86	41.62 (6.39)	30.80, 56.24
Random slope variance (u_{1i})	0.00 (.00)	0.00, 0.00	0.00 (.00)	0.00, 0.01

N=120. ***p<.05**.

Table 6a. Hypothesis 3: Do decreases in social roles from T1 → T3 predict decreases in stress and IL-6 from T1 → T3?

	Δ SNI Roles → Δ IES		Δ SNI Roles → Δ IL-6	
	<i>B</i> (SE)	<i>z</i>	<i>B</i> (SE)	<i>z</i>
Intercept (γ_{00})	38.29 (9.63)	3.98*	2.918 (.52)	5.58*
Condition (γ_{01})	-2.949 (2.58)	-1.14	-0.193 (.15)	-1.29
SNI Intercept (γ_{02})	-2.007 (.96)	-2.09*	0.076 (.06)	1.37
Time Since Diagnosis (γ_{10})	-0.798 (.20)	-3.92*	0.033 (.01)	3.74*
Condition*Time Since Diagnosis (γ_{11})	-0.071 (.28)	-0.26	0.011 (.01)	0.87
SNI Intercept*Time Since Diagnosis (γ_{12})	-0.151 (.10)	-1.56	0.007 (.00)	1.53
SNI Slope*Time Since Diagnosis (γ_{13})	25.442 (12.31)	2.07*	1.060 (.52)	2.06*
Age (γ_{20})	-0.357 (.15)	-2.37*	-0.017 (.01)	-2.05*
Education (γ_{30})	-0.115 (.60)	-0.19	-0.095 (.03)	-2.91*
Treatment Intensity (γ_{40})	4.006 (1.77)	2.26*	-0.308 (.10)	-3.22*
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	111.52 (11.66)	90.86, 136.88	0.14 (.03)	0.10, 0.20
Between-subjects error (u_{0i})	75.96 (22.79)	42.19, 136.76	0.50 (.09)	0.35, 0.71
Random slope variance (u_{1i})	0.07 (.08)	0.01, 0.68	0.00 (.00)	0.00, 0.00
Intercept-Slope Covariance	2.34 (1.14)	0.10, 4.57	-0.02 (.01)	-0.03, -0.00

N=120. * $p < .05$.

Table 6b. Hypothesis 3: Do decreases in social contacts from T1 → T3 predict decreases in stress and IL-6 from T1 → T3?

	Δ SNI Contacts → Δ IES		Δ SNI Contacts → Δ IL-6	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	35.155 (9.54)	3.68*	2.753 (.52)	5.25*
Condition (γ_{01})	-3.778 (2.51)	-1.51	-0.166 (.15)	-1.11
SNI Intercept (γ_{02})	-0.658 (.21)	-3.16*	0.007 (.01)	0.56
Time Since Diagnosis (γ_{10})	-0.835 (.21)	-4.00*	0.032 (.01)	3.62*
Condition*Time Since Diagnosis (γ_{11})	-0.025 (.28)	-0.09	0.013 (.01)	1.05
SNI Slope*Time Since Diagnosis (γ_{13})	2.565 (3.67)	0.70	-0.300 (.17)	-1.80
Age (γ_{20})	-0.232 (.15)	-1.53	-0.018 (.01)	2.12*
Education (γ_{30})	-0.240 (.57)	-0.42	-0.082 (.03)	2.59*
Treatment Intensity (γ_{40})	4.304 (1.75)	2.46*	-0.310 (.10)	-3.25*
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	112.47 (11.72)	91.70, 137.95	0.15 (.03)	0.10, 0.21
Between-subjects error (u_{0i})	66.42 (21.22)	35.51, 124.21	0.50 (.10)	0.34, 0.71
Random slope variance (u_{1i})	0.13 (.11)	0.03, 0.70	0.00 (.00)	0.00, 0.00
Intercept-Slope Covariance	2.96 (1.02)	0.97, 4.96	-0.02 (.01)	-0.03, -0.00

N=120. *p<.05.

Figure 1.
Relationship between cancer-related stress and IL-6 in the first several weeks following cancer diagnosis. Higher initial stress was associated with higher initial inflammation.

Figure 2.
Model-predicted change in SNI Roles by T1 IL-6 concentration. Higher initial inflammation (green line) was associated with greater withdrawal from social roles.

Figure 3.

A. Relationship between change in SNI Roles (T1→T3 slope) and change in cancer-related stress (T1→T3 slope). Mothers who drop social roles in the year following their child's cancer diagnosis show reductions in cancer-related stress over time.

B. Relationship between change in SNI Roles (T1→T3 slope) and change in IL-6 (T1→T3 slope). Mothers who drop social roles in the year following their child's cancer diagnosis show slower increases in inflammation over time.

Supplementary Material

Participants: Participants were 120 female primary caregivers of a child (aged 0-17 years) newly diagnosed with cancer. Eligible participants were at least 18 years of age and fluent in English. Baseline exclusion criteria included: clinical history of psychotic or bipolar disorder, neurological disorder, or chronic disease known to influence immune function; use of medication that interferes with immune system functioning; and exclusive night shift work. Participants were recruited between 2010 and 2014 and paid \$75 for participation.

Procedure: Study appointments were conducted in the pediatric oncology outpatient clinic or in the inpatient unit. Before each appointment, participants were instructed to limit physical activity and alcohol intake for 24 hours and caffeine intake for 3 hours. A research nurse administered a medical history and medication use interview, and drew a blood sample for IL-6 assessment (see *Measures*). Participants with symptoms of acute illness and those who had taken antibiotics or were vaccinated in the previous two weeks were rescheduled; IL-6 was excluded for participants who reported an immune-related disease or current medication use for that diagnosis. To the extent possible, all 3 visits were scheduled at the same time of day to control for diurnal variation in IL-6. After each study appointment, participants were given questionnaires to complete and return within 3 weeks, including assessments of social network and cancer-related stress (see *Measures*).

Missing data: Seventeen mothers dropped out of the study after T1: N=11 mothers dropped out before T2 and an additional N=6 before T3 (dropout rate = 14%). Reasons for dropping out included child passing away or in palliative care (N=4), mother no longer involved in child's treatment (N=2), mother overwhelmed (N=2), family moved (N=1), or mother noncompliant with the protocol (N=8). Additional data were missing for primary outcome

measures and covariates. IES data were missing from N=2 mothers at T1 and from N=1 mother at all three time points. All mothers (N=120) provided SNI data at one or more time points. IL-6 data were missing at all three time points for N=19 mothers. Treatment intensity data was missing for N=1 mother; age, education, and intervention condition were available for all mothers. Supplementary Tables 2-6 show results of primary analyses conducted using all available data for each analysis (Hypothesis 1: N=98; Hypothesis 2: N=100; alternative Hypothesis 2: N=117; Hypothesis 3a: N=118; Hypothesis 3b: N=100).

Supplementary Tables

Supplementary Table 1. Alternative Hypothesis 2: Does T1 stress predict decrease in social network?

	T1 IES → Δ SNI Roles		T1 IES → Δ SNI Contacts	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	4.039 (1.20)	3.36*	6.140 (5.34)	1.15
Condition (γ_{01})	0.332 (.28)	1.19	-0.396 (1.24)	-0.32
T1 IES (γ_{02})	-0.026 (.01)	-2.36*	-0.159 (.05)	-3.14*
Time Since Diagnosis (γ_{10})	-0.062 (.03)	-1.96*	-0.356 (.14)	-2.54*
T1 IES*Time Since Diagnosis (γ_{11})	0.001 (.00)	1.07	0.006 (.00)	1.56
Age (γ_{20})	-0.004 (.02)	-0.21	0.150 (.08)	1.79
Education (γ_{30})	0.298 (.07)	4.34*	0.825 (.31)	2.70*
Treatment Intensity (γ_{40})	-0.129 (.22)	-0.57	0.054 (1.00)	0.05
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	1.00 (.15)	0.75, 1.35	20.96 (2.21)	17.05, 25.78
Between-subjects error (u_{0i})	1.86 (.40)	1.22, 2.83	37.70 (7.63)	25.35, 56.07
Random slope variance (u_{1i})	0.00 (.00)	0.00, 3.26	0.00 (.00)	0.00, 7.46

N=120. *p<.05.

Supplementary Table 2. Descriptive statistics of primary predictor and outcome variables using all available data.

Outcome	T1 (N=120)	T2 (N=97)	T3 (N=87)	T1→T3 Slope (N=120)	Variance ^h
IES	33.17 (15.01) ^a	27.13 (16.82)	23.09 (17.98)	B=-0.866 (.14), z=-6.19^a	114.8 [93,141]
SNI Roles	7.00 (1.83)	6.71 (1.92) ^b	6.84 (1.79) ^c	B=-0.031 (.01), z=-2.29*	1.00 [.74,1.34]
Close Roles	2.60 (0.63)	2.63 (0.58) ^b	2.68 (0.54) ^c	B=0.000 (.00), z=0.06	0.07 [.05,.09]
Peripheral Roles	4.20 (1.50)	3.96 (1.60) ^b	4.02 (1.44) ^c	B=-0.023 (.01), z=-1.93	0.79 [.61,1.02]
SNI Contacts	17.85 (8.52)	16.20 (7.90) ^b	17.06 (8.31) ^c	B=-0.153 (.06), z=-2.61*	21.24 [17.0,26.5]
IL-6 (pg/mL)	1.93 (3.48) ^d	1.80 (2.66) ^e	2.67 (3.57) ^f	B=0.039 (.01), z=5.69^{d,g}	0.15 [.10,.22]

Data reported as means (SD) or slope coefficient (SE). ^aN=118, ^bN=96, ^cN=83, ^dN=101, ^eN=81, ^fN=72, ^gSlope calculated from log-transformed data, ^hindividual-level residual variance [95% CI] after accounting for the effect of time. *p<.05.

Supplementary Table 3. H1: Does T1 stress predict higher T1 IL-6?

	T1 IES → T1 IL-6
	B (SE)
Intercept (β_0)	1.822 (.77)*
T1 IES (β_1)	0.014 (.01)*
Age (β_2)	-0.007 (.01)
Education (β_3)	-0.087 (.05)
Treatment Intensity (β_4)	-0.300 (.15)*
T1 Time Since Diagnosis (β_5)	0.102 (.11)

N=98. IES data missing for N=2; IL-6 data missing for N=19; treatment intensity missing for N=1. *p<.05.

Supplementary Table 4. H2: Does T1 IL-6 predict decrease in social network?

	T1 IL-6 → Δ SNI Roles		T1 IL-6 → Δ SNI Contacts	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	2.616 (1.25)	2.10*	-0.022 (5.66)	-0.00
Condition (γ_{01})	0.273 (.30)	0.91	-0.333 (1.36)	-0.24
T1 IL-6 (γ_{02})	0.291 (.19)	1.55	0.495 (.87)	0.57
Time Since Diagnosis (γ_{10})	-0.029 (.01)	-1.97*	-0.135 (.06)	-2.17*
T1 IL-6*Time Since Diagnosis (γ_{11})	-0.030 (.02)	-1.95	-0.050 (.07)	-0.76
Age (γ_{20})	-0.001 (.02)	-0.02	0.117 (.10)	1.18
Education (γ_{30})	0.337 (.08)	4.39*	0.982 (.35)	2.82*
Treatment Intensity (γ_{40})	-0.152 (.23)	-0.65	-0.149 (1.06)	-0.14
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	0.97 (.16)	0.70, 1.34	20.34 (2.34)	16.23, 25.48
Between-subjects error (u_{0i})	1.77 (.42)	1.11, 2.83	37.20 (8.26)	24.07, 57.48
Random slope variance (u_{1i})	0.00 (.00)	0.00, 0.11	0.00 (.00)	0.00, 82.93

N=100. IL-6 data missing for N=19; treatment intensity missing for N=1. * $p < .05$.

Supplementary Table 5. Alternative H2: Does T1 stress predict decrease in social network?

	T1 IES → Δ SNI Roles		T1 IES → Δ SNI Contacts	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	4.180 (1.21)	3.45*	6.525 (5.38)	1.21
Condition (γ_{01})	0.320 (.28)	1.13	-0.555 (1.26)	-0.44
T1 IES (γ_{02})	-0.027 (.01)	-2.38*	-0.160 (.05)	-3.14*
Time Since Diagnosis (γ_{10})	-0.064 (.03)	-2.00*	-0.361 (.14)	-2.58*
T1 IES*Time Since Diagnosis (γ_{11})	0.001 (.00)	1.05	0.006 (.00)	1.55
Age (γ_{20})	-0.006 (.02)	-0.31	0.151 (.08)	1.78
Education (γ_{30})	0.289 (.07)	4.11*	0.789 (.31)	2.53*
Treatment Intensity (γ_{40})	-0.092 (.23)	-0.40	0.176 (1.01)	0.17
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	1.01 (.15)	0.75, 1.35	21.06 (2.23)	17.11, 25.93
Between-subjects error (u_{0i})	1.87 (.41)	1.22, 2.87	38.02 (7.78)	25.46, 56.77
Random slope variance (u_{1i})	0.00 (.00)	0.00, 3.46	0.00 (.00)	0.00, 6.16

N=117. IES data missing for N=2; treatment intensity missing for N=1. * $p < .05$.

Supplementary Table 6a. H3: Do decreases in social roles from T1 → T3 predict decreases in stress and IL-6 from T1 → T3?

	Δ SNI Roles → Δ IES ^a		Δ SNI Roles → Δ IL-6 ^b	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	38.31 (9.72)	3.94*	2.951 (.58)	5.10*
Condition (γ_{01})	-3.173 (2.62)	-1.21	-0.241 (.18)	1.37
SNI Intercept (γ_{02})	-2.061 (.97)	-2.12*	0.056 (.07)	0.83
Time Since Diagnosis (γ_{10})	-0.808 (.20)	-3.95*	0.031 (.01)	3.29*
Condition*Time Since Diagnosis (γ_{11})	-0.058 (.28)	-0.21	0.014 (.01)	1.06
SNI Intercept*Time Since Diagnosis (γ_{12})	-0.154 (.10)	-1.59	0.008 (.00)	1.59
SNI Slope*Time Since Diagnosis (γ_{13})	21.826 (10.62)	2.06*	0.957 (.45)	2.13*
Age (γ_{20})	-0.364 (.15)	-2.39*	-0.020 (.01)	-1.98*
Education (γ_{30})	-0.077 (.61)	-0.13	-0.085 (.08)	4.41*
Treatment Intensity (γ_{40})	3.966 (1.81)	2.19*	-0.322 (.11)	-3.00*
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	112.30 (11.79)	91.41, 137.96	0.14 (.03)	0.10, 0.20
Between-subjects error (u_{0i})	77.99 (23.39)	43.33, 140.39	0.61 (.11)	0.42, 0.87
Random slope variance (u_{1i})	0.07 (.08)	0.01, 0.70	0.00 (.00)	0.00, 0.00
Covariance	2.28 (1.17)	-0.02, 4.57	-0.02 (.01)	-0.04, -0.00

^aN=118 (IES data missing for N=1; treatment intensity missing for N=1); ^bN=100 (IL-6 data missing for N=19; treatment intensity missing for N=1). ***p<.05**.

Supplementary Table 6b. H3: Do decreases in social contacts from T1 → T3 predict decreases in stress and IL-6 from T1 → T3?

	Δ SNI Contacts → Δ IES ^a		Δ SNI Contacts → Δ IL-6 ^b	
	B (SE)	z	B (SE)	z
Intercept (γ_{00})	35.178 (9.64)	3.65*	2.791 (.58)	4.85*
Condition (γ_{01})	-4.049 (2.55)	-1.59	-0.228 (.18)	-1.30
SNI Intercept (γ_{02})	-0.670 (.21)	-3.18*	0.004 (.01)	0.24
Time Since Diagnosis (γ_{10})	-0.849 (.21)	-4.04*	0.030 (.01)	3.17*
Condition*Time Since Diagnosis (γ_{11})	-0.009 (.28)	-0.03	0.016 (.01)	1.24
SNI Slope*Time Since Diagnosis (γ_{13})	2.483 (3.74)	0.66	-0.329 (.18)	-1.83
Age (γ_{20})	-0.235 (.15)	-1.53	-0.020 (.01)	1.98*
Education (γ_{30})	-0.213 (.58)	-0.36	-0.074 (.04)	2.05*
Treatment Intensity (γ_{40})	4.283 (1.79)	2.40*	-0.320 (.11)	-2.99*
	Estimate	95% CI	Estimate	95% CI
Within-subjects error (r_{ii})	113.29 (11.86)	92.28, 139.09	0.15 (.03)	0.10, 0.22
Between-subjects error (u_{0i})	68.19 (21.77)	36.47, 127.48	0.60 (.11)	0.41, 0.87
Random slope variance (u_{1i})	0.13 (.11)	0.02, 0.70	0.00 (.00)	0.00, 0.00
Covariance	2.92 (1.04)	0.88, 4.96	-0.02 (.01)	-0.04, -0.00

^aN=118 (IES data missing for N=1; treatment intensity missing for N=1); ^bN=100 (IL-6 data missing for N=19; treatment intensity missing for N=1). ***p<.05**.

Supplementary Table 7a. Correlations between primary outcomes at T1.

	T1 IES	T1 SNI Roles	T1 SNI Contacts	T1 IL-6
T1 IES	1.00			
T1 SNI Roles	-0.22*	1.00		
T1 SNI Contacts	-0.29**	0.82**	1.00	
T1 IL-6	0.21*	0.06	-0.04	1.00

* $p < .05$. ** $p < .01$.*Supplementary Table 7b. Correlations between primary outcomes at T2.*

	T2 IES	T2 SNI Roles	T2 SNI Contacts	T2 IL-6
T2 IES	1.00			
T2 SNI Roles	-0.35*	1.00		
T2 SNI Contacts	-0.41**	0.75**	1.00	
T2 IL-6	0.07	0.18	0.11	1.00

* $p < .05$. ** $p < .01$.*Supplementary Table 7c. Correlations between primary outcomes at T3.*

	T3 IES	T3 SNI Roles	T3 SNI Contacts	T3 IL-6
T3 IES	1.00			
T3 SNI Roles	-0.22	1.00		
T3 SNI Contacts	-0.18	0.76**	1.00	
T3 IL-6	0.01	0.08	0.03	1.00

* $p < .05$. ** $p < .01$.