Stress-Related Inflammation and Social Withdrawal in Mothers of a Child With Cancer: A 1-Year Follow-Up Study

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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 1 year. Three hypotheses tested whether a) initial levels of stress associate with initial levels of inflammation, b) initial levels of inflammation predict social network changes over time, and c) social network changes over time buffer changes in 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 interleukin [IL]-6) were assessed in 120 mothers three times after their child's cancer diagnosis: after diagnosis (T1), 6-month follow-up (T2), and 12-month follow-up (T3).

Results: Consistent with predictions, greater cancer-related stress after diagnosis (T1) was associated with higher IL-6 after diagnosis (T1; $b = 0.014$, standard error [SE] = 0.01, $p = .008$). In turn, higher IL-6 after diagnosis (T1) was associated with a decrease in social roles over time (T1 ➔ T3; $B = -0.030$, SE = 0.01, $p = .041$). Finally, dropping social roles over time (T1 ➔ T3) was associated with decreases in cancer-related stress ($B = 25.44$, SE = 12.31, $p = .039$) and slower increases in IL-6 ($B = 1.06$, SE = 0.52, $p = .040$) 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 after a major life stressor.

Key words: sickness behavior, inflammation, social behavior, stress, cancer.

INTRODUCTION

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., interleukin [IL]-1, IL-6, tumor necrosis factor-α) 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 after 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 with 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 (versus 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

IES = Impact of Events Scale, **IL-6** = interleukin-6, **MLM** = mixed linear model, **SNI** = Social Network Index

SDC Supplemental Digital Content

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Received for publication December 7, 2020; revision received July 28, 2021.

DOI: 10.1097/PSY.0000000000001037

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 (i.e., a wide network of social ties) 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 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 increase the likelihood for social support during times of stress, all facilitating adaptive physiological functioning (23,24). As such, building or maintaining a large network of social ties might buffer increases in stress and inflammation. Alternatively, in the year after a child's cancer diagnosis, selective social withdrawal may buffer increases in mothers' 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 after 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 after diagnosis (T1).
Hypothesis 2: Second, following the logic that inflammation causes role-specific changes in social behavior, higher systemic inflammation after 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 after 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 [standard deviation {SD}] age = 36 [8] years; see Table 1 for sample characteristics) recruited from the Division of Hematology and Oncology, Children's Hospital of Pittsburgh (see Supplemental Digital Content, http://links.lww.com/PSYMED/A805, 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 (25).

Briefly, the intervention, which involved six face-to-face sessions and six telephone sessions with a clinician over a 5- to 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 Institutional Review Board.

Procedure

Mothers were assessed at three time points over approximately 1 year after their child's diagnosis: T1 (mean [SD] = 1.84 [0.82] months after diagnosis), T2 (mean [SD] = 6.81 [1.94] months after diagnosis), and T3 (mean [SD] = 12.74 (2.20) months after 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 a) using Expectation-Maximization imputed T1 data to include all $n = 120$ subjects in analyses (see Analysis) and b) using all available data for each analysis (reported in Supplementary Tables, http://links.lww.com/PSYMED/A805). See Supplemental Digital Content, http://links.lww.com/PSYMED/A805, for detail.

TABLE 1. Sample Characteristics

Characteristic	Full Sample (n = 120)	T1 Data Available (n = 98)	T1 Data Missing (n = 22)	Difference
Age, y	35.94 (7.95)	34.92 (7.68)	40.50 (7.68)	$F(1,119) = 9.49$*
Education, y	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%)	
White	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 (standard deviation) or count (%). Note: T1 data were considered missing if any primary outcome variable or covariate was not available at T1.

*$p < .05$.

[a]$n = 119$.

[b]$n = 21$.

Measures

Cancer-Related Stress: Impact of Events Scale

The Impact of Events Scale (IES) is a 15-item measure assessing the psychological impact of a traumatic event (26), 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 α = .85, .89, and .93 for T1, T2, and T3, respectively.

Social Network Index

To assess changes in social network over time, participants completed the Social Network Index (SNI) (27). The scale assesses the number of high-contact social roles (referred to in this article as "roles") and the total number of people in one's regular social network (referred to in this article 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 2 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.

To explore potential changes in close versus 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 a) 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 (28), b) large-scale social network analyses that close family members are heavily relied upon for support (29), and c) 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, catalog no. HS600B). Plasma samples from heparinized blood were stored at −80°C until assay. The range of detection for the assay was 0.156 to 10 pg/ml. Average intra- and interassay coefficients of variation were 7.5% and 8.5%. IL-6 values were natural log transformed for analysis.

Covariates

Potentially confounding variables adjusted for in statistical analyses included age, years of education, intervention condition, and the child's level of treatment intensity based on diagnosis, stage, and treatment data coded by a pediatric oncologist using the Intensity of Treatment Rating Scale-3 ((30); also see Ref. (31) for detail on treatment intensity coding criteria).

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) with those with missing data at T1 (n = 22) using χ^2 (for categorical variables) and analysis of variance 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). In addition, MLMs were used to test for intervention versus 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 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 missing completely at random 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 2–7, http://links.lww.com/PSYMED/A805.

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 adjusting 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 versus peripheral roles/contacts subscales over time, adjusting 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, adjusting 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 below; 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:

$$\begin{aligned} \mathrm{IL{-}6}_{ti} = {} & \gamma_{00} + \gamma_{01}(\mathrm{Condition}_i) + \gamma_{02}\left(\mathrm{SNI}_{\mathrm{Intercept}_i}\right) + \gamma_{10}(\mathrm{Time}_{ti}) \\ & + \gamma_{11}(\mathrm{Condition}_i)^*(\mathrm{Time}_{ti}) + \gamma_{12}\left(\mathrm{SNI}_{\mathrm{Intercept}_i}\right)^*(\mathrm{Time}_{ti}) \\ & + \gamma_{13}\left(\mathrm{SNI}_{\mathrm{Slope}_i}\right)^*(\mathrm{Time}_{ti}) + \gamma_{20}(\mathrm{Age}_{ti}) + \gamma_{30}(\mathrm{Education}_{ti}) \\ & + \gamma_{40}(\mathrm{TreatmentIntensity}_{ti}) + u_{0i} + u_{1i} + r_{ti} \end{aligned}$$

However, 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.

To clearly illustrate results from Hypothesis 3, mothers were categorized into groups based on whether they dropped, maintained, or added SNI roles from T1 ➔ T3. Then, additional models estimated the interaction between SNI roles group (drop, add, maintain) and time since diagnosis to predict change in IES and IL-6, adjusting for covariates. As such, Figure 3 depicts patterns of change in stress and inflammation among women who dropped social roles in the year after their child's cancer diagnosis compared with women who maintained or added social roles.

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 ($B = -0.028$, $p < .0005$), years of education ($B = -0.089$, $p = .002$), and child's treatment intensity ($\chi^2(2) = 17.96$, $p = .0001$). The secondary outcome, IES, was negatively related to age ($B = -0.342$, $p = .034$), 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 ($B = 0.013$, $p = .20$) or IES ($B = 0.008$, $p = .98$) compared with 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 8, http://links.lww.com/PSYMED/A805.

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, whereas IL-6 increased (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 after their child's cancer diagnosis.

Primary Analyses

Hypothesis 1: Association Between Initial Stress and Initial Inflammation

Multiple regression analyses supported the prediction that greater psychological stress related to cancer diagnosis was associated

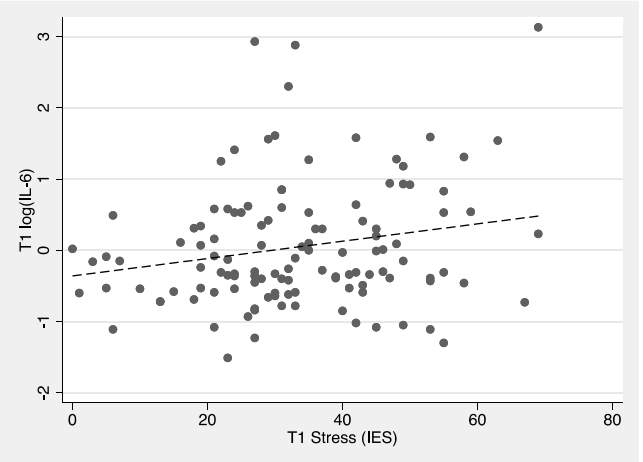

FIGURE 1. Relationship between cancer-related stress and IL-6 in the first several weeks after cancer diagnosis. Higher initial stress was associated with higher initial inflammation. IES = Impact of Events Scale; IL-6 = interleukin 6.

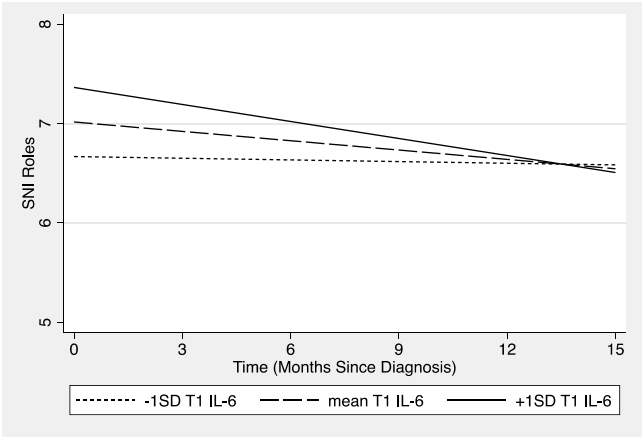

FIGURE 2. Model-predicted change in SNI roles by T1 IL-6 at mean and ±1 SD log IL-6. Higher initial inflammation (solid line) was associated with greater withdrawal from social roles. IL-6 = interleukin 6; SNI = Social Network Index; SD = standard deviation.

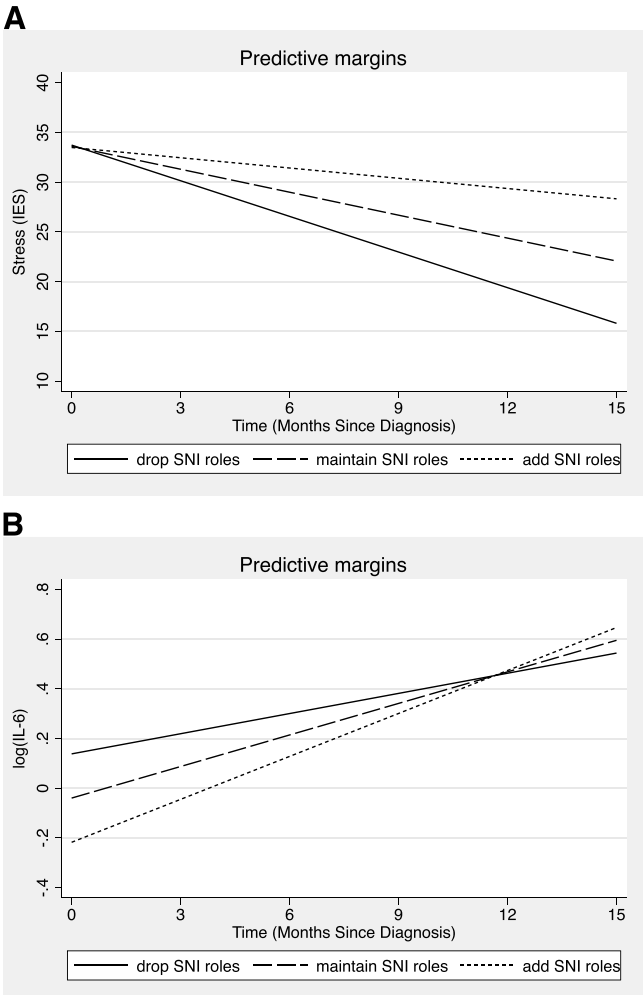

FIGURE 3. A, Change in cancer-related stress (T1 ➔ T3) grouped by whether mothers dropped, maintained, or added SNI roles from T1 ➔ T3. Mothers who drop social roles in the year after their child's cancer diagnosis show greater reductions in cancer-related stress over time. B, Change in IL-6 (T1 ➔ T3) grouped by whether mothers dropped, maintained, or added SNI roles from T1 ➔ T3. Mothers who drop social roles in the year after their child's cancer diagnosis show slower increases in inflammation over time. IES = Impact of Events Scale; IL-6 = interleukin 6; SNI = Social Network Index.

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[a]
IES	33.28 (14.93)	27.13 (16.82)	23.09 (17.98)	B = −0.869 (0.14), z = −6.24*	113.6 [93, 139]
SNI roles	7.00 (1.83)	6.71 (1.92)[b]	6.84 (1.79)[b]	B = −0.031 (0.01), z = −2.29*	1.00 [0.74, 1.34]
Close roles	2.60 (0.63)	2.63 (0.58)[b]	2.68 (0.54)[c]	B = 0.001 (0.00), z = 0.19	0.06 [0.05, 0.09]
Peripheral roles	4.20 (1.50)	3.96 (1.60)[b]	4.02 (1.44)[c]	B = −0.023 (0.01), z = −1.86	0.75 [0.56, 1.00]
SNI contacts	17.85 (8.52)	16.20 (7.90)[v]	17.06 (8.31)[d]	B = −0.153 (0.06), z = −2.61*	21.24 [17.0, 26.5]
Close contacts	4.60 (1.58)	4.56 (1.41)[b]	4.85 (1.57)[c]	B = 0.007 (0.01), z = 0.82	0.48 [0.39, 0.60]
Peripheral contacts	13.25 (8.42)	11.51 (7.74)[b]	12.17 (7.76)[c]	B = −0.155 (0.06), z = −2.65*	20.64 [16.8, 25.4]
IL-6, pg/ml	1.88 (3.23)	1.80 (2.66)[c]	2.67 (3.57)[e]	B = 0.039 (0.01), z = 6.05*[f]	0.15 [0.10, 0.21]

IES = Impact of Events Scale; SNI = Social Network Index; IL-6 = interleukin 6.

Data reported as means (standard deviation) or slope coefficient (standard error).

*p < .05.

[a] Individual-level residual variance [95% confidence interval] after accounting for the effect of time.

[b] n = 96.

[c] n = 81.

[d] n = 83.

[e] n = 72.

[f] Slope calculated from log-transformed data.

with higher IL-6 at T1 (b = 0.014, p = .008; Table 3). Consistent with prior work and current hypotheses, mothers who reported greater cancer-related stress within the weeks after their child's cancer diagnosis also had higher systemic inflammation (Figure 1).

Hypothesis 2: Association Between Initial Inflammation and 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 to T3 (B = −0.030, 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 = −0.023, p = .084), whereas close social roles were maintained (B = −0.002, 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 = −0.053, p = .42; Table 4), either peripheral social contacts (B = −0.036, p = .58) or close social contacts (B = −0.012, p = .23). Higher IL-6 within the weeks after diagnosis was associated with withdrawal from social *roles*, particularly peripheral roles, but not with the number of social *contacts*.

TABLE 3. Hypothesis 1: Association Between T1 Stress and T1 IL-6

	T1 IES ➔ T1 IL-6
	B (SE)
Intercept (β_0)	1.821 (0.65)*
T1 IES (β_1)	0.014 (0.01)*
Age (β_2)	−0.008 (0.01)
Education (β_3)	−0.082 (0.04)*
Treatment intensity (β_4)	−0.330 (0.12)*
T1 time since diagnosis (β_5)	0.110 (0.09)

IL-6 = interleukin 6; IES = Impact of Events Scale; SE = standard error.

n = 120.

*p < .05.

Alternative Hypothesis 2: Association Between Initial Stress and 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 = 0.001, p = .29; Supplementary Table 1, http://links.lww.com/PSYMED/A805) or social contacts (B = 0.006, p = .12; Supplementary Table 1, http://links.lww.com/PSYMED/A805) 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 = −0.026, p = .018, social contacts: B = −0.159, p = .002; Supplementary Table 1, http://links.lww.com/PSYMED/A805); in other words, having a larger social network after diagnosis was associated with lower initial cancer-related stress.

Hypothesis 3: Association Between Changes in Social Network and Changes in Stress and Inflammation

Hypothesis 3 tested whether maintaining a larger social network throughout the year after diagnosis continued to be helpful for buffering stress and increases in inflammation, or whether dropping social roles and/or contacts was more beneficial. MLMs were used to test the 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 5 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 (Table 6). Whereas withdrawal from social *roles* was associated

TABLE 4. Hypothesis 2: Association Between T1 IL-6 and Changes in Social Network From T1 ➔ T3

	T1 IL-6 ➔ Δ SNI Roles		T1 IL-6 ➔ 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 (0.28)	1.61	0.129 (1.28)	0.10
T1 IL-6 (γ_{02})	0.399 (0.19)	2.08*	0.797 (0.89)	0.89
Time since diagnosis (γ_{10})	−0.030 (0.01)	−2.32*	−0.154 (0.06)	−2.63*
T1 IL-6 × time since diagnosis (γ_{11})	−0.030 (0.01)	−2.04*	−0.053 (0.07)	−0.81
Age (γ_{20})	0.008 (0.02)	0.43	0.210 (0.08)	2.47*
Education (γ_{30})	0.326 (0.07)	4.59*	0.890 (0.32)	2.77*
Treatment intensity (γ_{40})	−0.203 (0.22)	−0.91	−0.528 (1.01)	−0.52
	Estimate	95% CI	Estimate	95% CI
Within-subject error (r_{ti})	1.01 (0.15)	0.75–1.35	21.13 (2.28)	17.10–26.11
Between-subject error (u_{0i})	1.87 (0.40)	1.23–2.86	41.62 (6.39)	30.80–56.24
Random slope variance (u_{1i})	0.00 (0.00)	0.00–0.00	0.00 (0.00)	0.00–0.01

IL-6 = interleukin 6; SNI = Social Network Index; SE = standard error; CI = confidence interval.

$n = 120$.

*$p < .05$.

with decreased stress and slower increases in IL-6 over the year after 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 withdrawal from social roles, with a

TABLE 5. Hypothesis 3: Association Between Changes in Social Roles From T1 ➔ T3 and Changes in Stress and IL-6 From T1 ➔ T3

	ΔSNI Roles ➔ ΔIES		ΔSNI Roles ➔ ΔIL-6	
	B (SE)	*z*	*B* (SE)	*z*
Intercept (γ_{00})	38.29 (9.63)	3.98*	2.918 (0.52)	5.58*
Condition (γ_{01})	−2.949 (2.58)	−1.14	−0.193 (0.15)	−1.29
SNI intercept (γ_{02})	−2.007 (0.96)	−2.09*	0.076 (0.06)	1.37
Time since diagnosis (γ_{10})	−0.798 (0.20)	−3.92*	0.033 (0.01)	3.74*
Condition × time since diagnosis (γ_{11})	−0.071 (0.28)	−0.26	0.011 (0.01)	0.87
SNI intercept × time since diagnosis (γ_{12})	−0.151 (0.10)	−1.56	0.007 (0.00)	1.53
SNI slope × time since diagnosis (γ_{13})	25.442 (12.31)	2.07*	1.060 (0.52)	2.06*
Age (γ_{20})	−0.357 (0.15)	−2.37*	−0.017 (0.01)	−2.05*
Education (γ_{30})	−0.115 (0.60)	−0.19	−0.095 (0.03)	−2.91*
Treatment intensity (γ_{40})	4.006 (1.77)	2.26*	−0.308 (0.10)	−3.22*
	Estimate	95% CI	Estimate	95% CI
Within-subject error (r_{ti})	111.52 (11.66)	90.86 to 136.88	0.14 (0.03)	0.10 to 0.20
Between-subject error (u_{0i})	75.96 (22.79)	42.19 to 136.76	0.50 (0.09)	0.35 to 0.71
Random slope variance (u_{1i})	0.07 (0.08)	0.01 to 0.68	0.00 (0.00)	0.00 to 0.00
Intercept-slope covariance	2.34 (1.14)	0.10 to 4.57	−0.02 (0.01)	−0.03 to −0.00

IL-6 = interleukin 6; SNI = Social Network Index; IES = Impact of Events Scale; SE = standard error; CI = confidence interval.

$n = 120$.

*$p < .05$.

TABLE 6. Hypothesis 3: Association Between Changes in Social Contacts From T1 ➔ T3 and Changes in Stress and IL-6 From T1 ➔ T3

	ΔSNI Contacts ➔ ΔIES		ΔSNI Contacts➔ΔIL-6	
	B (SE)	*z*	*B* (SE)	*z*
Intercept (γ_{00})	35.155 (9.54)	3.68*	2.753 (0.52)	5.25*
Condition (γ_{01})	−3.778 (2.51)	−1.51	−0.166 (0.15)	−1.11
SNI intercept (γ_{02})	−0.658 (0.21)	−3.16*	0.007 (0.01)	0.56
Time since diagnosis (γ_{10})	−0.835 (0.21)	−4.00*	0.032 (0.01)	3.62*
Condition × time since diagnosis (γ_{11})	−0.025 (0.28)	−0.09	0.013 (0.01)	1.05
SNI slope × time since diagnosis (γ_{13})	2.565 (3.67)	0.70	−0.300 (0.17)	−1.80
Age (γ_{20})	−0.232 (0.15)	−1.53	−0.018 (0.01)	2.12*
Education (γ_{30})	−0.240 (0.57)	−0.42	−0.082 (0.03)	2.59*
Treatment intensity (γ_{40})	4.304 (1.75)	2.46*	−0.310 (0.10)	−3.25*
	Estimate	95% CI	Estimate	95% CI
Within-subject error (r_{ti})	112.47 (11.72)	91.70 to 137.95	0.15 (0.03)	0.10 to 0.21
Between-subject error (u_{0i})	66.42 (21.22)	35.51 to 124.21	0.50 (0.10)	0.34 to 0.71
Random slope variance (u_{1i})	0.13 (0.11)	0.03 to 0.70	0.00 (0.00)	0.00 to 0.00
Intercept-slope covariance	2.96 (1.02)	0.97 to 4.96	−0.02 (0.01)	−0.03 to −0.00

IL-6 = interleukin 6; SNI = Social Network Index; IES = Impact of Events Scale; SE = standard error; CI = confidence interval.

$n = 120$.

*$p < .05$.

trend toward selective withdrawal from peripheral roles. Furthermore, these changes in social network were associated with stress recovery and slower increases in inflammation in the year after cancer diagnosis, a major stressful life event.

An open question for future research is to clarify the bidirectional communication pathways between the brain and the peripheral immune system that give rise to such findings (32,33). Specifically, chronic stressors are thought to activate threat-related pathways in the brain (34), 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 (35). In turn, these cytokines access the central nervous system either directly by crossing the blood-brain barrier (36) or indirectly, for example, by activating the vagus nerve (37) (e.g., (38)). 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 after cancer diagnosis is a transitional period in which mothers draw closer to family for emotional and instrumental support (18,39), 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 (40). This changed role within the family may alter mothers' identities in ways that disconnect them from more peripheral social roles (41). 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 reintegrate with the broader social community over time (42). For example, as their social networks shrink over the course of 6

years, spousal caregivers show drastically steeper increases in inflammation compared with noncaregivers (43,44), suggesting that social reintegration is important for long-term health.

A large epidemiological literature shows that greater social network diversity is associated with lower systemic inflammation (15) and a longer, healthier life (27,45,46), but the present results demonstrate one context in which maintaining a large number of social roles may not be beneficial. Typically, although social relationship constructs often overlap, social network diversity as assessed here promotes health independent of stress, by encouraging health behaviors, positive affect, and a sense of stability, purpose, and identity, whereas social support—which can be provided by a single confidant—is more important for health during times of stress (23). Here, a diverse social network at diagnosis related to lower initial stress, perhaps by increasing the likelihood for social support, which has been widely shown to buffer stress (24). However, *dropping* social roles throughout the year buffered stress and increases in inflammation. These results suggest an intriguing possibility that reducing the diversity of their social networks during a time of major life stress may allow mothers to focus more on supportive roles to cope with stress. Furthermore, consolidating one's social network to match changes in identity resulting from major life stress may be adaptive. 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 some social roles as they adjust to their new caregiving responsibilities (e.g., delegating a relative to maintain online health updates and communication with looser social ties). Future research may also explore when it is beneficial to reengage with one's full social network and whether 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 using social withdrawal that may or may not relate to adaptive psychological and physical health outcomes as observed here. Second, data from this report come from a behavioral intervention randomized controlled trial targeting stress and inflammation; although intervention-related changes in the primary outcomes were not observed (25) 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, drove the changes in social roles observed here. However, exploratory analyses testing the possibility that mothers who experienced the highest levels of stress after 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 show that a larger social network after diagnosis related to lower cancer-related stress after diagnosis, but that dropping some social roles in the year after diagnosis was associated with stress recovery. Fourth, although results are largely consistent with the hypothesis that inflammation motivates people to draw closer to those who can provide support while withdrawing from peripheral others, in practice, it may be more difficult for mothers to completely withdraw from their closest roles. It is possible that inflammation altered psychological correlates of withdrawal behavior (e.g., decreasing perceived closeness) that were not measured by the SNI. Instead, the SNI assesses the number of high-contact social roles, allowing us to observe a trend toward withdrawal from peripheral roles, but does not measure approach behavior (e.g., increasing physical proximity) or perceived closeness toward close roles. Thus, whether mothers drew closer to their immediate family members or simply maintained these close roles because they are more difficult to drop is unknown.

Finally, the clinical significance of the results observed here is unknown. On average, the number of social roles mothers reported at study entry is within the normal range (27,47) and the mean change in mothers' social roles was small; however, 43% of mothers dropped one or more social roles across the study period (whereas 38% showed no changes and 19% added social roles), suggesting that social network changes are a common and potentially important phenomenon in this population. One possibility is that the benefits of dropping social roles are more apparent among mothers with larger social networks at diagnosis; maintaining a diverse network of social connections may be burdensome during cancer treatment. Similarly, although mean IL-6 levels were within the normal limits at all time points in this sample, IL-6 increased by 42% in the year after cancer diagnosis; increases in circulating IL-6 levels of a similar magnitude are commonly used in laboratory paradigms to selectively induce psychological sickness symptoms (48), lending plausibility to the results observed here. Moreover, small increases in systemic IL-6, akin to the changes observed in the current sample, have been associated with an increased risk of cardiometabolic disease (49). Understanding processes that may buffer these increases in 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 (50). In addition, from the perspective of biological mechanisms, these results suggest that chronic stress–related inflammation may drive similar sickness behaviors to those observed after acute increases.

Conclusion

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

The authors would like to thank all the mothers who participated in this study and the staff in the hematology and Oncology Program at Children's Hospital of Pittsburgh for their help with the study. In particular, the authors would like to thank Veronica Ekeroth, CRNP, for assistance in recruiting subjects; Jennifer L. Cleary, BS, Alina D. Vaisleib, MA, and Chelsea Farrell, MA, for

coordinating the study; and Katarina Gray, BS, for running all of the immune assays and general technical assistance. They also thank all of the clinical interns and undergraduate research assistants, without whom the study would not have been possible.

Source of Funding and Conflicts of Interest: The authors report no conflicts of interest. This research was supported by a grant from the American Cancer Society RSG118367 awarded to Linda J. Ewing, PhD, RN. This funding source had no involvement in study design; data collection, analysis, or interpretation; writing of this report; or the decision to submit this article for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Cancer Society.

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