Title

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Journal

Research on Child and Adolescent Psychopathology, 51(7)

ISSN

2730-7166

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Publication Date

2023-07-01

DOI

10.1007/s10802-023-01033-4

Peer reviewed

Published in final edited form as:

Res Child Adolesc Psychopathol. 2023 July ; 51(7): 977–987. doi:10.1007/s10802-023-01033-4.

Interpersonal Life Stress and Inflammatory Reactivity as Prospective Predictors of Suicide Attempts in Adolescent Females

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Abstract

Adolescents' suicidal behavior frequently is preceded by interpersonal stress, but not all who experience distress attempt to end their lives. Recent theories have posited individual differences in stress-related inflammatory reactivity may be associated with psychopathology risk; this study examined inflammatory reactivity as a moderator of the prospective association between interpersonal stress and adolescents' suicidal behavior. Participants included 157 at-risk adolescent females (ages 12 to 16 years) and assessed individual differences in proinflammatory cytokine responses to a brief laboratory-based social stressor, both interpersonal and non-interpersonal life events, and suicidal behavior over an 18-month follow-up period. Measuring levels of the key proinflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) before and after an experimentally-induced social stressor, results revealed that blunted cytokine reactivity heightened the effect of high interpersonal stress exposure on risk for suicidal behaviors over the subsequent 9 months. Significant effects were not revealed for non-interpersonally themed stress. Finding highlight the urgent need for more research examining inflammation reactivity among adolescents.

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10802-023-01033-4.

Conflict of Interest The authors declare no potential conflicts of interest.

Keywords

Life stress; Social stress; Cytokines; Inflammation; Suicide; Adolescence

Suicide is a public health crisis and the second leading cause of death among 10 to 34-year-olds in the United States (CDC, 2019). Recent theories of depression (Slavich & Irwin, 2014) and adolescent suicide (Miller & Prinstein, 2019) have highlighted the role of conjoint interpersonal stress exposure and biological stress reactivity on risk for suicidal thoughts and behaviors (STB), aiming to address the current gap in the suicide literature that has seen relatively little advancement over the past 50 years (Franklin et al., 2017). Unfortunately, remarkably little prospective research has been conducted to examine these theories stringently. This study examined individual differences in inflammatory reactivity to experimentally-induced social stress as a moderator of the association between interpersonal life stress exposure and suicidal behavior in a sample of adolescent females at high risk for suicide.

It is well known that suicide attempts among adolescents, particularly adolescent females, are often precipitated by experiences of acute interpersonal stress, such as social devaluation and rejection (Massing-Schaffer et al., 2019). Although social stressors are common during this developmental period, a majority of distressed adolescents do not attempt suicide. Research examining potential moderators of the association between interpersonal stress exposure and suicidal behavior is needed to help identify youth who are at the greatest risk for exhibiting social stress-related increases in suicidal behavior.

Recent theories have implicated differences in biological stress reactivity in the development of numerous chronic diseases and psychopathology across the lifespan (Slavich, 2020; Slavich & Cole, 2013). More specifically, recent theories of suicidal behavior have postulated that risk for engaging in STBs may increase in the context of failures in acute biological stress regulation (Miller & Prinstein, 2019). One possibility is that stressful experiences in general—and interpersonal stressors in particular (Slavich et al., 2010)—upregulate components of the immune system involved in inflammation via the sympathetic nervous system and hypothalamic–pituitary–adrenal axis signaling (Slavich, 2020). Although this response is adaptive in the short term, if heightened and engaged chronically, it can result in physiological and epigenetic dysregulation that confers higher risk for deleterious psychological outcomes (e.g., Miller 2020). At the cellular level, this dysregulation may be indexed as the aberrant release of social stress-induced proinflammatory cytokines (e.g., interleukin (IL)-1β [IL-1β]), which are signaling proteins that mediate key aspects of the inflammatory cascade (Dantzer et al., 2008). Within an adolescent sample prior research suggests that some may exhibit elevated cytokine responses to stress, others may exhibit blunted response, and still others may have little reactivity at all (Szabo et al., 2020); indeed, prior studies examining related physiological stress responses among adolescents often suggest no mean change from pre- to post-stressor (Stroud et al., 2009; Yim et al., 2010). In contrast, *within-sample individual differences* may be meaningful. Specifically, it may be that individual differences in acute inflammatory

responses act as biological markers of vulnerability, which in turn increases the risk for outcomes like suicide, in the context of interpersonal life stress.

Meta-analysis (Vasupanrajit et al., 2021) examining the relevance of immune activation to suicidal behavior high-lights the role of cytokines in contributing to risk for suicide attempts via increased neurotoxicity and decreased neuro-protective factors. This mechanism is proposed to be similar to the pathophysiological underpinnings seen in individuals with mood disorders and schizophrenia (Maes & Carvalho, 2018; Maes et al., 2021). Further, although cytokines play a critical role in regulating the inflammatory response and have been studied extensively in relation to other mental health concerns (e.g., depression; see Slavich & Irwin 2014), remarkably little work has been conducted in the context of suicide, particularly among adolescents. Prior research suggests that elevated basal levels of inflammatory cytokines (such as IL-2, IL-1β, IL-6, and tumor necrosis factor-α (TNF-α)) are associated with suicidal behavior among adults (Janelidze et al., 2011; Serafini et al., 2020), as well as in post-mortem samples of patients with suicidality (see Black & Miller 2015). Among adolescents, elevated IL-1β, IL-6, and TNF-α were found in the prefrontal cortex of recent teenage suicide completers as compared to non-suicided matched controls (Pandey et al., 2012), but results have been equivocal (cf., Gabbay et al., 2009; Jha et al., 2020).

The examination of basal differences in markers of inflammatory responses as putative risk factors for adolescents' suicidal behavior may be limited, however. It is well known that adolescents' suicidal behavior most often occurs in the content of an acute crisis (Miller & Prinstein, 2019), and thus, the study of inflammatory reactivity in the context of stress is sorely needed. Indeed, meta-analysis of this literature underscores the importance of (1) examining *cytokine reactivity* in the context of stress (Szabo et al., 2020), and (2) examining prospective risk for suicide based on *individual differences* in cytokine reactivity following social stress (Ducasse et al., 2015). Consistent with other work on stress response biomarkers more broadly (e.g., cortisol; Johnson et al., 2021), it may be that reactive dysregulation (i.e., hypo- and/or hyper-reactive profiles) of inflammatory cytokines might serve to exacerbate the effects of social stress on risk for suicide.

Inflammatory reactivity to interpersonally-themed stress may be particularly relevant during adolescence, a developmental period of increased sensitivity to social stressors (Somerville, 2013). The present study thus provided a unique opportunity to examine whether interpersonal life stress exposure is associated with increased risk for subsequent suicidal behavior more strongly for females who exhibit a non-normative inflammatory response to social stress.

Interpersonal stress exposure and inflammatory cytokine reactivity were examined in the context of a laboratory-based social stressor using a prospective longitudinal design. It was hypothesized that after controlling for both lifetime suicidal behavior and suicidal ideation, interpersonal stress exposure would be associated prospectively with suicidal behavior more strongly for individuals with maladaptive stress profiles that may be observed as hyper- or hypo-reactive inflammatory cytokine responsivity to acute social stress (see Miller & Prinstein 2019). Prior work suggests unique trajectories and predictors of suicidal behavior

over short- (i.e., 1–9 month) and longer-term (12–18 month) periods (Goldston et al., 1999; Prinstein et al., 2008; Spirito et al., 1992). It was postulated that the effects of interpersonal stress and cytokine reactivity would be associated with suicidal behavior within this short-term, 9-month prospective period; therefore, secondary analyses were included for 18-months follow-up. Additionally, to test the specificity of hypotheses regarding interpersonal stress, we examined the hypothesis that non-interpersonal stress exposure would not be a relevant predictor of suicidal behavior, nor moderated by cytokine reactivity.

Methods

Participants

Participants were 157 adolescent females (M_{age} = 14.73, SD = 1.38, range = 12–16 years old) from the southeastern United States exhibiting elevated risk for psychopathology and suicide based on a screen with adolescents' primary caregiver. Recruitment screening was conducted using items adapted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al., 1997), assessing for the presence of at least one mental health concern (i.e., mood, anxiety, disruptive behavior) over the past 2 years, thus yielding an enriched sample that was more likely to be at risk for suicide (see Franklin et al., 2017). Nearly half of the sample was recruited from clinical sources, with 33% of participants from local psychiatric inpatient units and 12% from outpatient mental health practices. The remainder of the sample was recruited from online advertisements (40%) and emails to university staff and community personnel (15%). Specific inclusion criteria required that participants were: (a) biologically female at birth, (b) between 12 and 16 years old, (c) presenting with mental health symptoms in the past 2 years, and (d) with an available primary caregiver to consent for data collection. Exclusionary criteria were active psychosis, intellectual disability, or any pervasive developmental disorder at initial screening using the K-SADS.

Participants were ethnically diverse, with 65% of participants identifying as white, 24.2% as Black or African American, 1.9% as Latina, and 8.9% as mixed ethnicity or belonging to another ethnic group. An assessment of guardian's highest levels of education revealed that 1.3% of participants had guardians with some high school education, 13.3% high school degree or GED, 12.8% trade degree, 17.8% some college education, 24.7% bachelor's degree, 11% some graduate school education, 13.3% master's degree, and 5.5% doctoral degree.

A total of 220 adolescents participated in this study; however, cytokine measurements began after the first 63 adolescents participated. No significant differences emerged between those with/out cytokine data on any study variables. Over the 18-month follow-up period, missingness of suicidal behavior data was 9% at 3 months, 12% at 6 months, 9% at 9 months, 16% at 12 months, 16% at 15 months, and 20% at 18 months. Aggregate follow-up assessment scores (i.e., participants missing one or more follow-up assessments) were coded as missing and addressed with full information maximum likelihood (FIML; see below). Attrition analyses revealed no significant differences in baseline or follow-up variables for those with complete versus missing data.

Procedure

Participants and their primary caregiver participated in a laboratory-based data collection session; caregivers gave informed consent and participants provided assent. As part of the study visit, participants completed a series of self-report questionnaires, underwent a clinical interview to assess for suicidal behavior, and participated in a modified version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), an in vivo social stress task. The modified TSST instructs participants to prepare and present a speech to a cohort of two trained research assistants, instructed to be non-responsive to the participant's speech to elicit a stress response. The TSST is currently the most frequently used social stress task in psychological research across all age groups (for additional details, please see Goodman et al., 2017; Seddon et al., 2020). Using the Positive and Negative Affect Schedule for Children (PANAS-C; Laurent et al., 1999), participants in the current study reported a large and statistically significant negative affective response to the TSST (Owens et al., 2019). Saliva samples were collected immediately before and 40 min after the speech task to adequately capture cytokine stress reactivity (Carpenter et al., 2010; Newton et al., 2017).

To control for diurnal variation in physiological stress responses (Nilsonne et al., 2016; Petrovsky et al., 1998), 95% of all study visits began on Saturdays during the same two-hour window, between 11am and 1pm. Follow-up assessments of participants' suicidal behavior were administered during follow-up phone calls every three months for 18 months post-baseline using an abbreviated version of the baseline clinical interview; only the adolescent participants provided follow-up data. Study design did not include measures of follow-up interpersonal stress in these analyses to avoid bias by contemporaneous depressive symptoms via the depression-distortion hypothesis (Richters & Pellegrini, 1989), confounding effects that may particularly relevant for adolescents reporting interpersonal stress (De Los Reyes & Prinstein, 2004). All study procedures were approved by the University of North Carolina at Chapel Hill's human subjects committee, and all research was carried out in accordance with the Code of Ethics of the World Medical Association.

Measures

Suicidal Ideation and Behavior—At baseline and all follow up time points, trained research assistants utilized the semi-structured Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock et al., 2007) to assess participant suicidal ideation and behavior. Research assistants were originally trained in the administration of the SITBI by a licensed clinician on the research team, and throughout data collection, the research assistants and clinician met weekly to review SITBI data and questions about administration. The SITBI yields dichotomous (i.e., presence (1) or absence (0)) scores for lifetime and recent (i.e., over last three months) suicidal ideation and suicidal behavior. Suicidal ideation was defined as the presence of any lifetime thoughts of killing oneself ("Have you ever had thoughts of killing yourself?"), while suicidal behavior for the present study was defined as the presence of suicide attempts, aborted attempts, or interrupted attempts. Participants were interviewed every three months to bolster accurate retrospective recall and data from 3, 6, and 9 month time points were coded to yield outcome measures for *any* suicidal behavior (i.e., suicide attempts or interrupted/aborted attempts) over the follow-up period (coded as presence or absence, as above). Participants' missing data at one or more of the 3, 6, or 9-month

interviews were treated as missing data for the follow-up period, and these missing data points were later addressed in the analytic procedure (see below). An identical procedure was used to compute suicidal behavior from 12 to 18 months post-baseline.

Proinflammatory Cytokine Reactivity—Three proinflammatory cytokines were assayed to index each participant's inflammatory reactivity to the acute social stressor: TNF-α, IL-1β, and IL-6. These three particular cytokines were chosen *a priori* due to their role in the acute phase immune response (Slavich & Irwin, 2014; Slavish et al., 2015) and their associations with the development of subsequent mental health symptoms including suicidal behavior (Slavich, 2020). Cytokine levels were assayed immediately pre-stressor and 40 min post-stressor via saliva samples by trained research assistants.

Samples were obtained using SalivaBio Oral Swabs (Salimetrics, State College, PA) and stored at −25 °C until analysis using Bio-Plex 200 (Bio-Rad, Hercules, CA) at the UNC Cytokine and Biomarker Analysis Facility. Assays followed guidelines established by the manufacturer (R&D Systems, Minneapolis, MN) and used high-sensitivity multiplex immunoassay kits. Such kits allow for mean minimal detectable doses of 0.29 pg/mL for TNF-α, 0.08 pg/mL for IL-1β, and 0.14 pg/mL for IL-6. All assays were run at a negligible 2x dilution, and all three chosen cytokines performed well upon assaying. According to the manufacturer, no IL-1β samples were below the detection limit, 3 out of 314 (0.95%) IL-6 samples were below the detection limit, and 10 out of 314 (3.18%) TNF-α samples were below the detection limit. These missing values were later estimated via FIML (see below). In addition, mean intra-assay coefficients of variation are 5.3% for TNF-α, 5.3% for IL-1β and 5.2% for IL-6, whereas mean inter-assay coefficients of variation are 9.6% for TNF-α, 12.8% for IL-1β, and 9.8% for IL-6. Given evidence of diurnal variation in the biomarkers assessed in this study (Nilsonne et al., 2016; Petrovsky et al., 1998), the biomarker assessment timepoint was standardized across individuals, and mean time of initial sampling occurred at 2:29pm (*SD* = 1 h and 6 min; on average, 3 h after arrival). There were no observed correlations between pre- or post-stressor cytokine expression and time of sampling. All cytokine values were logarithmically transformed to adjust for skewness and the impact of extreme outliers (Burt & Obradović, 2013; Horn et al., 2018), as well as to allow for their use as indicators for the Confirmatory Factor Analysis (CFA) in the creation of latent factors of inflammation (Brown & Moore, 2012). An extreme outlier was identified post-transformation (6 *SD*s from the mean for post-stress IL-1) and was subsequently winsorized to the next highest value in the distribution lying within 3 *SD*s. Analyses excluding this participant yielded identical results.

Substantial data support the validity of salivary cytokines for the assessment of cytokine reactivity in response to acute stress (Slavich et al., 2020; Szabo et al., 2020), including studies utilizing the TSST (Newton et al., 2017). Particularly relevant for the present population, collection of salivary cytokines is a painless, non-invasive procedure that is easier to use than collection of a blood sample (Granger et al., 2007) and is recommended for pediatric populations (Ouellet-Morin et al., 2011). Additionally, research has demonstrated that salivary cytokine activity, while localized in the oral cavity, can reach throughout the body, including the CNS, via multiple pathways (Hasturk & Kantarci, 2015). Such activity is also associated with activity in brain regions involved in emotional processes

(O'Connor et al., 2009). However, it is important to additionally note that there remains relatively limited knowledge about the relevance of salivary markers of inflammation in the context of mental health outcomes (Fernandez-Botran et al., 2011; Szabo & Slavish, 2021).

Life Stress Exposure—Exposure to interpersonal and non-interpersonal stressful life events occurring during the six months prior to the initial study visit were assessed using a 43-item, modified version of the Life Events Checklist (LE-C; Coddington 1972). A summed score for the number of (1 = yes, 0 = no) interpersonally themed stressful life events (out of 31 items) or non-interpersonal life events (12 items) was computed for each adolescent. Indices of internal consistency are not relevant due to the checklist nature of the measure.

Depressive Symptoms—To account for associations with suicidal ideation and behavior, as well as inflammatory responses to acute stressors (Fagundes et al., 2013), depressive symptoms were assessed at baseline with the 33 item Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988) using a 3-point Likert scale (0 = *not true*, 1 = *sometimes true*, 2 = *mostly true*). Four items related to suicidal ideation were excluded from analyses to avoid overlap with dependent variables and a mean score was computed across the remaining 29 items (Cronbach's $\alpha = 0.92$).

Covariates—We assessed and controlled *a priori* for several factors that have been associated with inflammation in prior research (e.g., Slavish et al., 2015). These factors included: ethnicity, age, parent report of their adolescent's socioeconomic status, recent illness, birth control and medication use, and physical indices including body mass index (BMI), same-day caffeine intake, and smoking.

Data Analysis—Descriptive analyses examined differences in the primary, untransformed study variables between participants with and without a prior history of suicidal behavior at baseline (Table 1a) and over the follow-up period (Table 1b). Bivariate correlations of the transformed primary study variables, excluding covariates, were then examined (see Table 2).

Consistent with prior work demonstrating that composite scores of inflammation have stronger associations with neural responsivity and psychological outcomes than individual scores (e.g., Miller et al., 2020), following transformation, the three proinflammatory cytokines were combined in a composite measure of inflammation. A latent factor for inflammation first was constructed using confirmatory factor analysis (CFA; see Giletta et al., 2018). CFA evaluated measurement models, including measurement invariance, with the three cytokines as observed indicators, which loaded onto a common latent factor of inflammation at pre- and post-stress. Next, computation of the latent change factor adjusted for individual differences in levels of pre-stress cytokines that may have influenced participant reactivity to the TSST. A path from pre- to post-stress was freely estimated and the covariance between the pre-stress latent factor and the second-order factor was set to zero (Burt & Obradovic, 2013), resulting in a latent change factor. Further description of the CFA procedure is included in the appendix. Finally, individual latent factor scores for

pre-stress and change, respectively, were extracted and subsequently used as predictors in the final model.

All continuous predictors were centered prior to analyses. Little's (1998) Missing Completely at Random (MCAR) test yielded nonsignificant results, $X^2(39, n = 157) = 47.31$, $p = .170$, and logistic regression analyses examining all predictors among those with/out outcome data similarly yielded nonsignificant results. Full information maximum-likelihood (FIML) estimation with robust standard errors thus was utilized to address missing data. The final model estimated the means and variances of all predictors and sensitivity analyses using listwise deletion yielded an identical pattern of results.

Primary hypotheses were tested using a binary logistic regression analysis with adolescents' suicidal behavior during follow-up as the primary outcome. After controlling for covariates (i.e., ethnicity, age, SES, recent illness, birth control use, medication use, BMI, smoking, same-day caffeine intake) in Step 1, baseline symptoms of depression, interpersonal stress exposure, non-interpersonal stress exposure, suicidal ideation, and suicidal behavior were entered in Step 2. The third step examined the main effects of latent basal cytokine activity and latent cytokine reactivity on youths' engagement in future suicidal behavior. The final step tested how recent interpersonal and non-interpersonal stress exposure interacted with youths' latent cytokine reactivity scores to predict subsequent suicidal behavior. All analyses were conducted in Mplus Version 8.4 (Muthén & Muthén, 2017).

Significant interactions were examined using post-hoc probing procedures in accordance with prior work for non-linear interactions, utilizing online post-hoc probing utilities created by Dawson (2014). Note that slopes are non-linear because these analyses yield model-implied odds ratios. Simple slopes were calculated at low and high levels (+/− 1 SD from the mean) of social-stress induced latent cytokine reactivity.

Results

Preliminary Analyses

Descriptive statistics and bivariate correlations among the primary study variables are presented in Table 1a, Table 1b, and Table 2. Rates of suicidal ideation at baseline (n = 87, 55.4% of total sample), as well as suicidal behavior at baseline (n = 43, 27.4% of total sample) and suicidal behavior over the 9-month (n = 24, 15% of total sample) and 18-month (n = 21, 13% of total sample) were relatively high, reflecting the elevated risk for suicide in the sample. Six of the 24 participants reporting suicidal behavior over the 9-month follow-up period were new onset (i.e., did report lifetime suicidal behavior at baseline), as well as four of 21 participants at 18-months. As anticipated and consistent with prior research, there were no significant sample-level mean differences pre- to post-stressor for the assayed inflammatory cytokines (either as individual cytokines or as latent factors). However, as expected, there was significant individual variability around the latent factor mean ($b = 0.03$, *95% CI* = [0.01, 0.05], $p = .003$), consistent with this paper's focus on individual differences in stress responses.

As compared to adolescents who did not report suicidal behaviors at baseline, adolescents who did report suicidal behaviors reported significantly higher levels of depressive symptoms and both interpersonal and non-interpersonal stress exposure (see Table 1a). Further, individuals who reported suicidal behavior over the 9-month follow-up period reported significantly higher levels of interpersonal stress at baseline (see Table 1b). All individual cytokine assays pre- and post-stress were significantly and positively correlated with one another, with higher pre-stress IL-6 levels being significantly correlated with higher levels of baseline depressive symptoms. Finally, higher baseline depressive symptoms were significantly correlated with higher interpersonal and non-interpersonal life stress exposure at baseline, and the two stress indices were significantly positively correlated (see all in Table 2).

Predicting Future Suicidal Behavior

A significant interaction effect between adolescents' interpersonal stress exposure and proinflammatory cytokine reactivity scores was revealed. Post hoc analyses revealed that interpersonal stress exposure was associated with greater likelihood of suicidal behavior over the 9-month follow-up for adolescents exhibiting *blunted* cytokine reactivity ($b = 0.03$, 95% CI = [0, 0.05], $p = .021$), but not for those with heightened reactivity ($b = -0.02$, 95% CI = [−0.04, 0], $p = .313$; see Figure 1). Lastly, as hypothesized, the significant interaction was specific to interpersonal stressors and cytokine reactivity, and there was no significant interaction effect between non-interpersonal stressors and cytokine reactivity (see Table 3). To examine possible suppressor effects, the analysis was additionally run in the absence of covariates, and results remained robust and consistent.

Secondary Analysis

A secondary analysis was run to test the specificity of effects to the 9-month follow-up period. Specifically, an additional logistic regression model utilizing all study variables examined the prospective effect of stress exposure and cytokine reactivity on suicidal behavior in the subsequent 9 months (i.e., 12 to 18 months). This secondary analysis yielded nonsignificant results, suggesting specificity to relatively short-term effects.

Discussion

The present study used a longitudinal, multimethod design to investigate whether social-stress induced proinflammatory cytokine reactivity moderated the prospective association between interpersonal life stress exposure and suicidal behavior in an at-risk, adolescent female sample over a 9-month period. Adolescence is a period of increased sensitivity to social stressors (Somerville, 2013), which have been found to often precede suicidal thoughts and behaviors, particularly among adolescent females (Massing-Schaffer et al., 2019). Despite this association, only a subset of females who experience interpersonal stress go on to engage in suicidal behavior, which has led to recent theoretical frame-works suggesting that that suicidal behavior may occur in the context of both social stressors and dysregulated stress responsivity (Miller & Prinstein, 2019).

Results from this study provided support for this hypothesis. Individual differences in youths' proinflammatory cytokine reactivity moderated the association between their interpersonal life stress exposure and suicidal behavior over the subsequent nine months while controlling for prior lifetime suicidal behavior. Additionally, this interaction was specific to interpersonal (vs. non-interpersonal) stress exposure, further highlighting the importance of interpersonally themed stressors in the context of risk for suicide. Interestingly, post-hoc probing revealed significant associations between interpersonal stress and increased risk for suicidal behavior only under conditions of *blunted* proinflammatory cytokine reactivity (Figure 1). Note that while initial research revealed preliminary associations between suicidal behavior and higher basal levels of cytokine inflammation (Pandey et al., 2012; Serafini et al., 2020), other research on suicide revealed no associations with basal proinflammatory markers (Jha et al., 2020) or even lower levels of TNF-α in suicidal adolescents when compared to nonsuicidal controls (Gabbay et al., 2009). Further, these studies did not examine individuals' proinflammatory cytokine *reactivity*, which likely has differing implications in the context of sensitivity to interpersonal life stress. Additionally, no prior study has examined the effect of inflammatory cytokine reactivity on *prospective* suicidal behaviors.

Findings are consistent with several theories and prior work. Recent research has revealed blunted sympathetic reactivity during interpersonal interactions among adolescents at risk for depression (Nelson et al., 2021), as well as an association between blunted parasympathetic reactivity (e.g., heart rate variability) and suicidal ideation in young adults (Chesin et al., 2020). In addition, research has found that *both* excessive and blunted physiological reactivity (i.e., an inverse u-shaped curve) confer higher risk for suicide and other psychopathology, suggesting multiple indices of immune *dysregulation* may relevant as risk predictors (Del Giudice et al., 2011). In other words, although moderate acute biological stress reactivity can be protective in the short-term and better prepare an individual to meet environmental demands, excessive activation may contribute to different maladaptive response profiles, including both sensitized and hyperactive (i.e., "vigilant"), as well as de-sensitized and hyporesponsive. Consistent with the Adaptive Calibration Model (ACM) of stress responses (Del Giudice et al., 2011), this blunted profile may have emerged in the present sample, as participants were selected for having a history of risk for psychopathology, which is often accompanied by elevated lifetime stress exposure. Importantly, participants who endorsed prior suicidal behavior at baseline also had significantly greater recent life stress exposure and depressive symptoms. Future research is needed to understand how physiological changes in response to stress may hinder adaptive, and promote maladaptive, behavioral responses. Such findings could prove to have highly needed clinical implications for at-risk youth, including knowledge that blunted acute proinflammatory responses may increase likelihood of physical *as well as* mental health problems. Additionally, these findings may indicate the importance of studying psychosocial and psychopharmacological therapies that have the ability to normalize immune system function to reduce risk for negative health outcomes, including suicide (Shields et al., 2020).

Future research would benefit by addressing several study limitations. First, although remarkably little research has examined the prospective effect of cytokines on adolescent suicidal behavior and no prior work has examined cytokine reactivity in relation to suicide,

the findings in this study should be interpreted cautiously in light of ongoing debate regarding the use of salivary samples to assess cytokine reactivity. Future research might overcome this limitation via use of blood samples, or via the incorporation of salivary data that controls for dental hygiene, body temperature, or oral flow rates. Nevertheless, the approach used in this study is consistent with past research (Granger et al., 2007; Ouellet-Morin et al., 2011; Slavich et al., 2020) and offers an important advance in the study of a leading public health crisis. Future work may also consider sample collection at points shorter or longer than the 40-minute post-stressor sample used in this study; empirical work is needed to understand peak inflammatory response (Szabo et al., 2020) as well as inflammatory recovery following an experimentally induced stressor (Newton et al., 2017; Szabo et al., 2020). Future studies also may benefit from the use of a contextual life stress interview in addition to the approach used in this study to understand various types of interpersonal stress exposure most relevant to adolescent suicide (Liu & Miller, 2014). Further, while the study design did not include follow-up measures of interpersonal stress to mitigate confounding effects via the depression-distortion hypothesis (Richters & Pellegrini, 1989; De Los Reyes & Prinstein, 2004), future studies might alternatively elect to include measures of stress at follow-up to capture the potential effects of prospective stress on prospective risk for suicide. Last, although this study offers an important focus on adolescent girls who are at greater risk for adolescent suicidal behavior than boys, additional research with males is needed to understand the role of stress and stress-related physiology.

Conclusion

This study investigated differences in social stress-induced proinflammatory cytokine reactivity that may elucidate why only some girls experiencing interpersonal stress engage in suicidal behavior. Results offer an important step towards understanding the conjoint effects of biological vulnerability and interpersonal contexts on adolescents' development and risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Preparation of this manuscript was supported by grants from the National Science Foundation Graduate Research Fellowship Program to Matthew Clayton (1,000,255,141), and from the National Institute of Mental Health to Mitchell Prinstein (R01 MH107479) and George Slavich (K08 MH103443).

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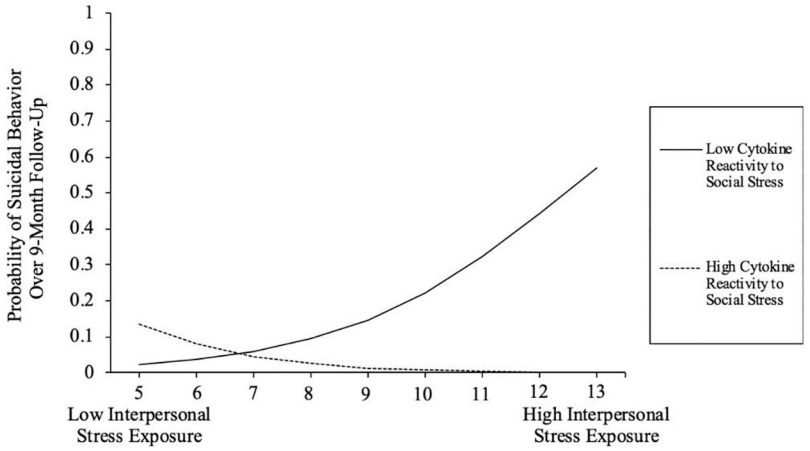

Fig. 1.

Longitudinal associations of the interaction of interpersonal life stress exposure and proinflammatory cytokine reactivity to social stress on prospective risk for suicidal behavior over 9-months. Probing revealed that high interpersonal stress exposure was associated with increased prospective risk for suicidal behavior for adolescents with blunted cytokine reactivity to social stress. Note: Post-hoc probing analyses utilized procedures for logistic regression created by Dawson (2014)

Table 1a

Means (and standard deviations) for the primary study variables

	No suicidal behavior at baseline (*n* = 114)	Suicidal behavior at baseline (*n* = 43)	*t*(155)
Depressive symptoms	0.50(0.44)	0.75(0.39)	3.30**
Interpersonal stress	7.04(4.52)	10.00(5.94)	3.34**
Non-interpersonal stress	3.42(1.76)	2.52(1.94)	2.66**
Pre-stress IL-6	0.61(0.45)	0.67(0.40)	0.77
Post-stress IL-6	0.64(0.48)	0.72(0.35)	1.01
Pre-stress IL-1β	2.58(0.41)	2.63(0.41)	0.68
Post-stress IL-1β	2.61(0.41)	2.62(0.40)	0.20
Pre-stress TNF-α	0.59(0.44)	0.63(0.38)	0.63
Post-stress TNF-α	0.58(0.44)	0.60(0.31)	0.35

Note. IL-6 = interleukin-6; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α

* $p < .05$;

** $p < .01$;

*** $p < .001$

Table 1b

Means (and standard deviations) for the primary study variables

	No suicidal behavior over 9-month follow-up (*n* = 109)	**Suicidal behavior over 9-month follow-up (*n* = 24)**	***t*(131)**
Depressive symptoms	0.53(0.41)	0.89(0.52)	3.71
Interpersonal stress	7.52(4.82)	9.21(5.99)	1.48 *
Non-interpersonal stress	2.56(1.86)	3.25(1.92)	1.64
Pre-stress IL-6	0.63(0.41)	0.67(0.44)	0.42
Post-stress IL-6	0.70(0.44)	0.60(0.32)	1.05
Pre-stress IL-1β	2.58(0.41)	2.68(0.41)	1.11
Post-stress IL-1β	2.65(0.38)	2.49(0.38)	1.88
Pre-stress TNF-α	0.60(0.43)	0.64(0.34)	0.49
Post-stress TNF-α	0.58(0.43)	0.55(0.42)	0.25

Note. IL-6 = interleukin-6; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α

* $p < .05$;

** $p < .01$;

*** $p < .001$

Table 2

Bivariate correlations among the main study variables

	1	2	3	4	5	6	7	8	9
1. Depressive symptoms	-								
2. Interpersonal stress	0.370**	-							
3. Non-interpersonal stress	0.376**	0.645**	-						
4. Pre-stress IL-6	0.194*	0.150	0.143	-					
5. Post-stress IL-6	0.152	0.173*	0.117	0.769***	-				
6. Pre-stress IL-1β	0.038	− 0.078	0.037	0.325***	0.339***	-			
7. Post-stress IL-1β	− 0.039	− 0.108	0.024	0.291**	0.472***	0.751***	-		
8. Pre-stress TNF-α	− 0.060	− 0.017	− 0.022	0.249**	0.225**	0.419***	0.256**	-	
9. Post-stress TNF-α	− 0.069	− 0.051	− 0.007	0.257**	0.384***	0.389***	0.465***	0.732***	-

Note. IL-6 = interleukin-6; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-α

* $p < .05$;

** $p < .01$;

*** $p < .001$

Table 3

Prediction of future suicidal behavior by interpersonal life stress exposure, latent change score of inflammatory cytokine reactivity, and their interaction

	Step Statistics				Final Statistics			
Predictors	**β**	**Wald**	***OR* [95% CI]**	***p***	**β**	**Wald**	***OR* [95% CI]**	***p***
Step 1: Covariates								
Age	0.491	4.485*	1.634 [1.037, 2.574]	0.034	0.960	5.323*	2.611 [1.155, 5.900]	0.021
Ethnicity	0.544	0.656	1.723 [0.462, 6.421]	0.418	1.176	1.275	3.240 [0.421, 24.918]	0.259
SES	0.422	0.591	1.525 [0.520, 4.473]	0.422	0.581	0.423	1.787 [0.311, 10.283]	0.516
BMI	0.023	5.173*	1.023 [1.003, 1.043]	0.023	0.041	4.691*	1.042 [1.004, 1.082]	0.030
Smoking	0.047	0.003	1.048 [0.187, 5.867]	0.957	−0.710	0.220	0.492 [0.025, 9.537]	0.639
Caffeine intake	−0.076	0.007	0.927 [0.161, 5.339]	0.933	1.726	1.131	5.619 [0.233, 135.285]	0.288
Birth control	0.287	0.162	1.332 [0.330, 5.373]	0.687	−1.299	1.233	0.273 [0.028, 2.701]	0.267
Medication use	1.422	4.896*	4.147 [1.176, 14.616]	0.027	0.998	0.727	2.714 [0.273, 26.930]	0.394
Proinflammatory illness	−0.718	0.645	0.488 [0.085, 2.812]	0.422	−1.871	1.719	0.154 [0.009, 2.525]	0.190
Step 2: Baseline symptoms								
Depressive symptoms	1.454	3.281	4.279 [0.888, 20.626]	0.070	1.493	1.645	4.451 [0.455, 43.577]	0.200
Interpersonal stress	−0.035	0.225	0.965 [0.835, 1.117]	0.635	0.012	0.015	1.012 [0.840, 1.218]	0.902
Non-interpersonal stress	−0.264	1.123	0.768 [0.472, 1.251]	0.289	−0.379	1.290	0.685 [0.356, 1.317]	0.256
Baseline suicidal ideation	1.936	2.317	6.929 [0.573, 83.767]	0.128	1.179	0.594	3.250 [0.162, 65.169]	0.441
Baseline suicidal behavior	2.059	7.147**	7.838 [1.732, 35.467]	0.008	3.886	7.454**	48.699 [2.993, 792.377]	0.006
Step 3: Inflammatory cytokines								
Latent pre-stress cytokines	−0.625	0.071	0.535 [0.005, 52.975]	0.790	2.027	0.440	7.591 [0.019, 3031.628]	0.507
Latent cytokine reactivity	−0.098	7.950**	0.906 [0.846, 0.970]	0.005	−0.068	0.713	0.934 [0.798, 1.094]	0.399
Step 4: Interactions								
Interpersonal stress × Cytokine reactivity					−0.033	5.466*	0.967 [0.941, 0.995]	0.019
Non-interpersonal stress × Cytokine reactivity					−0.009	0.152	0.991 [0.946, 1.038]	0.696

Note. SES = socioeconomic status; BMI = body mass index; Ethnicity as nonwhite = 0 and white = 1

* $p < .05$;

** $p < .01$;

$^{***}p < .001$