Received: 1 March 2023 | Revised: 27 July 2023 | Accepted: 31 July 2023

DOI: 10.1111/sltb.12993

Suicide and Life-Threatening BEHAVIOR

ORIGINAL ARTICLE

Examination of proinflammatory activity as a moderator of the relation between momentary interpersonal stress and suicidal ideation

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Funding information
American Psychological Association; American Psychological Foundation; National Institute of Mental Health, Grant/Award Number: T32MH020061; Psi Chi

Abstract

Introduction: Peer-related interpersonal stress can increase risk for suicidal thoughts among adolescents and young adults. However, not all individuals who undergo peer-related interpersonal stressors experience suicidal thoughts. Heightened proinflammatory activity is one factor that may amplify the relation between interpersonal stress and suicidal thinking.

Methods: This pilot study examined the relation between interpersonal stress and suicidal ideation in real time, as well as whether proinflammatory cytokine (IL-6 and TNF-α) activity across a laboratory social stressor moderated this association in a sample of 42 emerging adults with recent suicidal ideation. Participants completed 28 days of 6×/daily ecological momentary assessment that assessed for suicidal ideation (presence vs. absence, ideation intensity), occurrence of negative peer events, and feelings of exclusion.

Results: There was a trend for within-person increases in feelings of exclusion to be associated with increases in *concurrent* suicidal ideation intensity. Additionally, within-person increases in negative peer events were associated with increased odds of *subsequent* suicidal ideation among individuals with very low IL-6 activity. However, this finding is considered preliminary.

Conclusion: Interventions targeting perceptions of exclusion and increasing social support may be of benefit. However, findings require replication in larger samples, and thus must be interpreted with caution.

KEYWORDS

emerging adults, interpersonal stress, proinflammatory activity, proinflammatory cytokines, suicidal ideation, suicide risk

INTRODUCTION

Suicide is the third leading cause of death among youth aged 15–24 (Centers for Disease Control and Prevention, 2022). The prevalence of suicidal ideation (SI) is highest among emerging adults aged 18–25, with 10.5% reporting suicidal thoughts in the past year (National Institute of Mental Health, 2019). Despite these high rates, relatively little is known about the short-term prediction of suicidal thinking (Franklin et al., 2017; Glenn & Nock, 2014). Recent research using experience sampling methodologies (e.g., ecological momentary assessment; EMA) suggests that the presence and intensity of SI for a given individual can fluctuate substantially throughout the day, and that presence of SI at one time point serves as a short-term predictor of SI at the next time point within the same day (Hallensleben et al., 2018, 2019; Kleiman et al., 2017). Such methodologies can also be used to examine other short-term predictors of suicidal thoughts and behaviors (STBs).

Interpersonal stress is one predictor that has received significant attention and holds the potential to increase short-term risk for suicide (Beautrais et al., 1997; Adams et al., 1994; Turecki & Brent, 2016). Peer victimization and rejection are two particularly salient interpersonal stressors for youth and young adults, and are reliably associated with both SI and suicide attempts in cross-sectional and longitudinal research (Hinduja & Patchin, 2010; Johnson et al., 2002; Massing-Schaffer et al., 2019; van Geel et al., 2014). Interpersonal stressors and SI have been associated at the daily level in predominantly middle-aged adult samples. For example, variability in several interpersonally related risk factors (hopelessness, loneliness, and burdensomeness) was correlated with variability in SI among psychiatrically hospitalized adults (Kleiman et al., 2017). In samples of adults with a recent suicide attempt, lower social support (Coppersmith et al., 2019) as well as increased social isolation and family-related interpersonal stress (Husky et al., 2017) have been associated with increased SI. Taken together, these studies demonstrate the importance of examining acute time frames to clarify the occurrence and timing of STBs relative to recent interpersonal precipitants or events.

Equally important is the study of factors that may help explain how, why, and for whom the short-term relation between interpersonal stress and STBs among youth exists. Recent research has begun to focus on the role of biomarkers (Glenn & Nock, 2014). One potentially promising line of research is the examination of proinflammatory activity, and whether an individual's biological response to interpersonal stress moderates the association between peer-related stress and STBs.

During acute stress, the biological stress response system is activated, including the immune system release of proinflammatory cytokines (Slavich & Irwin, 2014). Though it is well known that this proinflammatory response is triggered by acute physical threat and injury to promote healing, it can be prompted by social threat and acute interpersonal stress as well (Morey et al., 2015; Segerstrom, 2007; see Social Signal Transduction Theory of Depression: Slavich & Irwin, 2014). Chronic interpersonal stress may lead to lasting changes in proinflammatory activity (Slavich & Irwin, 2014). For example, a history of interpersonal stress and peer victimization has been associated with upregulated basal proinflammatory levels as well as a heightened proinflammatory response (Chiang et al., 2012; Copeland et al., 2014; Fuligni et al., 2009; Giletta et al., 2018). The ongoing interaction between interpersonal stress and proinflammatory activity transfers risk for negative behavioral effects through subsequent biological processes and sensitization of the brain to future social threats (Slavich & Irwin, 2014). Upregulated proinflammatory activity has been associated with mental health consequences (Jaremka et al., 2013; Walker et al., 2014) and may even serve as a biomarker for suicidal behaviors and death by suicide (Chang et al., 2016; Courtet et al., 2016; Serafini et al., 2013).

Increased proinflammatory activity may also be one condition under which the relation between interpersonal stress and STBs is strengthened. Research with youth who are *already* experiencing STBs could help clarify the moderating effect of upregulated proinflammatory activity. To our knowledge, no studies to date have examined this question in cross-sectional, longitudinal, or real-time research designs. However, a recent study with adolescents examined neural responses to a virtual peer rejection task as a moderator of the association between interpersonal stress and SI. Adolescents with greater experiences of interpersonal stress *and* increased activation of the right anterior insula to peer rejection had greater SI severity (Oppenheimer et al., 2020). Increased activation of the anterior insula is one possible neural mechanism associated with social rejection and the proinflammatory response to acute social stress (Slavich et al., 2010). These results therefore support examining proinflammatory activity as a potential moderator of the association between peer rejection and STBs. Moreover, given the heightened risk for peer rejection, victimization, and STBs during the adolescent and young adult years (Brendgen, 2018; Cha et al., 2018; Nock et al., 2008), investigation of this potential relation in this age group is warranted.

CURRENT STUDY

The relation between interpersonal stress and STBs among youth and young adults, herein referred to as emerging adults, is well-established. However, this relation has not

been studied with this younger population at the momentary level using EMA. This is important to do because it may otherwise be difficult to report on negative events retrospectively and research shows that SI varies considerably over just a few hours. It is equally important to understand the conditions under which this relation is most likely to exist. Though research suggests that proinflammatory cytokines may serve as a potential biomarker of STBs, it has yet to be studied as a moderator of the relation between interpersonal stress and SI. The current study addressed these gaps in the literature using a mixed methods approach. Using EMA, we examined the relation between the *real-time* occurrence of negative peer events and the presence of SI, as well as perceived exclusion severity and SI intensity, in a sample of emerging adults. We also examined whether proinflammatory activity measured across a laboratory peer rejection task moderated the association between interpersonal stress (i.e., negative peer events, exclusion severity) and SI. The current study is part of an overarching pilot study of interpersonal stress, proinflammatory activity, and STBs.

We hypothesized, (1A) a greater number of negative peer-related events would be associated with greater odds of the presence (vs. absence) of SI at the same time point and next time point; (1B) perceived exclusion severity from peers would be positively associated with degree of SI intensity at the same time point and next time point; and (2) the relation between negative peer-related events (hypothesis 1A) and exclusion severity (hypothesis 1B) and SI would be particularly strong for those with greater proinflammatory activity.

METHODS

Participants

The present sample included 42 emerging adults aged 18–23 years ($M = 19.55$, SD = 1.29) recruited from a large, diverse university in the Mid-Atlantic US. Participants were predominantly female (sex at birth: 83.3% female, 16.7% male; gender identity: 73.8% women, 16.7% men, 9.5% nonbinary), racially diverse (45.2% White, 16.7% African American, 16.7% Asian, 14.3% multiracial, 7.1% other), and predominantly non-Latino (88.1%; 11.9% Latino). Inclusion criteria were, (1) 18–23 years of age; (2) fluent in English; (3) current SI (i.e., self-reported presence of at least a wish to die within the past month during study screening)[1]; and (4) access to a smartphone during the study. Exclusion criterion was a self-reported health/developmental condition that impacts immune functioning.

Procedures

Prior to the start of data collection, all study procedures were approved by the university IRB. Of note, data were collected during the COVID-19 pandemic. Undergraduate students were recruited from the psychology department research pool via a study ad and from the broader university community via flyers. As part of the larger study, participants completed a laboratory visit wherein they provided informed consent to participate, completed an in-person laboratory social stressor task, the Yale Interpersonal Stressor (YIPS) (Stroud et al., 2000), and provided three salivary samples to measure proinflammatory activity across the task (see Defayette et al. (2023) for full description of recruitment and laboratory procedures). This measurement was used to approximate how each person's proinflammatory activity functions in everyday life. A pre- to post-task manipulation check supported that the YIPS resulted in increased feelings of sadness and exclusion, and decreased feelings of inclusion ($ps < 0.05$; Defayette et al., 2023). Participants were trained on EMA survey completion during the laboratory visit.

Participants completed 28 days of EMA via the HIPAA-compliant MetricWire (www.metricwire.com) app downloaded onto their smartphone. Each day, participants received one scheduled survey at 10:00 AM and five semirandom surveys between 11:00 AM and 10:00 PM. Semirandom surveys occurred at least 1 h apart, with no other specified time blocks. EMA surveys assessed three domains (peer-related interpersonal stressors, suicidal thoughts/behaviors, affect). Participants received an Amazon gift card worth up to $50 at the end of the EMA period. A payment schedule utilizing micro-incentives with bonus payments for high compliance was implemented (van Berkel et al., 2018). Participants received $0.25 for each EMA survey completed and a $2 bonus each week that their survey completion rate was at or above 80%. A multiphase suicide risk safety protocol was implemented and is available in Appendix S1.

EMA surveys

Participants reported on the presence/absence of a list of seven positive peer interactions (e.g., "invited to a party by a peer," "had a peer stick up for you") and seven negative peer events (e.g., "conflict/argument with a friend," "harassed by a peer online") since their last survey. The

[1]Note a delay between screening and the laboratory visit occurred for multiple participants due to scheduling and COVID-19 restrictions. Half of all participants eligible at screening reported that they had not experienced SI within the past month of their laboratory visit. As this was a pilot study, these participants were retained.

list of interpersonal stressors was developed for the present study. Relevant items were derived from validated assessments of peer experiences and stressors (De Los & Prinstein, 2004; Fuligni et al., 2009; Prinstein et al., 2001). A total score for number of negative peer events was calculated for each observation.

To assess for current affect, participants reported how strongly they felt happy, sad, angry, nervous, included, excluded, lonely, and hopeless since their last survey, on a 0 ("not at all") to 10 ("very strongly") Likert-type scale, with higher ratings indicating stronger affect. The present study used the "excluded" rating at each observation.

Finally, participants reported on any suicidal ideation and behaviors since their last EMA survey. Assessment of SI included presence/absence of any ideation ("Since your last survey, have you had thoughts about death or killing yourself?"), as well as SI intensity ("How intense was the thought?"), rated on a 0 ("not at all") to 10 ("very high"/"very much") Likert-type scale. Assessment of suicidal behaviors included presence/absence of a plan ("...considered a plan for killing yourself?") and of an attempt ("...tried to kill yourself?"). This survey was developed for the present study and informed by past EMA studies of self-injurious thoughts and behaviors (Kleiman et al., 2017; Nock et al., 2009). See Supporting Information for complete EMA survey.

Proinflammatory activity

Three saliva samples were collected across the course of a laboratory social stressor task (i.e., the YIPS), modified to comply with COVID-19 social distancing requirements. Whole unstimulated saliva was collected via passive drool after a 10-minute pre-task resting period, as well as immediately following, and 30 min following completion of the YIPS (see (Defayette et al., 2023) for full description of procedures). Salivary samples were assayed in duplicate with controls for IL-6 and TNF-α using proinflammatory cytokine 4-plex electrochemiluminescence immunoassays by Meso Scale Discovery. IL-6 and TNF-α cytokines were selected a priori based on their associations with interpersonal stress (Giletta et al., 2018; Marsland et al., 2017; Slavich & Irwin, 2014). Consistent with past work, two cytokines were included to allow for comparisons with other studies (Giletta et al., 2018; Marsland et al., 2017) and because no single proinflammatory cytokine is most reliably associated with interpersonal stress. Proinflammatory activity was calculated using area under the curve with respect to ground (AUCg) (Pruessner et al., 2003) for each cytokine to capture total proinflammatory cytokine output.

Data analysis plan

Analyses were conducted using R (R Core Team, 2020) with the RStudio development environment (RStudio Team, 2020). Specific R packages used are noted throughout.

Power analyses

Power estimates (*tidyverse* (Wickham et al., 2019) and *lmerTest* (Kuznetsova et al., 2017) R packages) were simulated based on six EMA prompts per day for 28 days, with an adjusted response rate of 70%, and $N = 42$ to evaluate how well this sample addresses the present research questions. Power estimates of observation-level main effects showed that the current sample is sufficiently powered (0.99; 1-β) to detect observation-level effect of $b = 0.20$. Power estimates of cross-level (i.e., observation-level × person-level) interactions showed that the current sample is nearly sufficiently powered (0.71; 1-β) to detect a cross-level interaction with an effect of $b = 0.15$. It was expected that cross-level interactions would be slightly underpowered (Aguinis et al., 2013), which is common in clinical research.

Preliminary analyses

Descriptive statistics and distributional properties of all study variables were examined using the *psych* R package (Revelle, 2022). To further examine variability in SI intensity, we fit an unconditional means model to derive and examine the ICC, calculated in the *lme4* R package (Bates et al., 2015) Data visualization, via time series plots of observation-level raw data, was used to capture variability in all continuous EMA variables using the *ggplot2* R package (Wickham et al., 2019).

Missing data

Missing data patterns were examined for overall degree of missingness using the *mice* R package (Van Buuren & Groothuis-Oudshoorn, 2011). In EMA research, a degree of missing data is expected due to missed survey notifications (Bolger & Laurenceau, 2013). In the present study, most missing data were due to missed observations (i.e., missed notifications; overall rate of missing survey data = 28.25%). Data were missing at the item level in five cases, and pairwise deletion was used to remove these cases from analyses as indicated. This resulted in removal of two cases in analyses of negative

peer events and presence versus absence of SI, and three cases in analyses of exclusion severity and SI intensity. Data for proinflammatory cytokine variables were complete.

Primary analyses

Analyses of primary hypotheses were conducted using the *brms* R package (Burkner, 2017) for binary outcomes and the *lme4* R package (Bates et al., 2015) for continuous outcomes. All models included time and estimation of random slopes. Estimation of random slopes allows for examination of between-subjects differences in the relation between within-subjects predictors and outcomes and should be included when examining person-level moderators (Germeys & Kuppens, 2021; Kleiman, 2017). Time-varying predictors (negative peer events, exclusion severity) were separated into their component parts at each level (i.e., within-subject/level 1 and between-subject/level 2) to prevent confounds due to differential relations between predictor and outcome at the different levels of the model (Bolger & Laurenceau, 2013).

To address hypothesis 1A, a series of two-level Bayesian generalized linear mixed models (GLMMs)[2] were conducted with observations nested within people. Observation-level number of negative peer events at time *T* was used to predict presence (1) versus absence (0) of SI at time *T* (same time point). Observation-level number of negative peer events (at time *T*) was also used to predict presence versus absence of SI at time *T* + *1* (next time point). Models were estimated via the Markov chain Monte Carlo algorithm and no-U-turn sampler extension (Burkner, 2017; Hoffman & Gelman, 2014). We selected the default priors set in the *brms* R package, which are designed to be minimally influential on the outcomes of the analysis (i.e., uninformative priors). Each model used four Markov chains, each with 1000 warm-up iterations and 1000 inference iterations, for a total of 4000 posterior samples. The *brms* R package summarizes parameter estimates using the mean (*b*) and standard deviation (estimate error; *SE*) of the posterior distribution, along with two-sided 95% credible intervals (CrIs) (Burkner, 2017). Parameter estimates in which 95% CrIs do not cross zero are considered significant.

To address hypothesis 1B, a series of two-level multilevel models (MLMs) were conducted with observations nested within people. Observation-level exclusion severity at time *T* was used to predict SI intensity at time *T* as well as at time *T* + *1*. Models were fitted using a maximum likelihood estimator. Effect sizes were examined as indicated using the *EMAtools* R package (Kleiman, 2021).

To address hypothesis 2, proinflammatory activity (AUCg score) was added to the series of two-level GLMMs (hypothesis 1A) and two-level MLMs (hypothesis 1B). Separate models were conducted to examine IL-6 and TNF-α activity. One proinflammatory cytokine was entered into the level 2 equation for level 1 slope for examination of the direct effect of that proinflammatory cytokine on the outcome variable. This also allowed for examination of the interaction between proinflammatory activity and the between-subject component of the interpersonal stress predictor. The given proinflammatory cytokine was also entered into the level 2 equation for the level 1 interpersonal stress predictor for examination of the cross-level interaction between proinflammatory activity and the within-subject component of the interpersonal stress predictor. Proinflammatory activity variables were grand mean centered.

RESULTS

Descriptive statistics

Average compliance with EMA assessments was 71.84% (SD = 29.60%, range = 4.76%–100%). Participants completed a total of 5063 unique assessment prompts. An average of 120.76 prompts were completed per participant (SD = 49.81, range = 8–168, 168 possible prompts per person). Descriptive statistics for all study variables are presented in Table 1. Time series plots for observation-level raw data reports of SI intensity, exclusion, and negative peer events are presented in Figure 1. Clinical characteristics of the sample are described in Defayette et al. (Defayette et al., 2023) Overall endorsement of SI was low (present at 2.29% of total assessment prompts), with only 18 participants reporting at least one instance of SI. No suicide attempts were reported during the study period. SI intensity was recoded to capture both those who did not endorse any SI as well as those who endorsed ideation but no intensity; SI intensity was rescaled to a possible range of 1–11 (instead of 0–10) and missing data due to the absence of SI were recoded as 0. Finally, results of the ICC for SI intensity demonstrated that 9.91% of the total variance in SI intensity in this sample can be attributed to between-subjects differences and 90.09% can be attributed to within-subjects differences.

Examination of random slopes

The random effect for level 1 negative peer events was examined in both the main effects and moderation

[2] A Bayesian estimator was used here because model non-convergence can occur when using maximum likelihood estimators for binary outcomes in multilevel models with a random slope.

TABLE 1 Descriptive statistics of study variables.

	M	SD	Range	Skew	Kurtosis
Observation level variables					
Negative peer events	0.96	1.22	0–7	1.25	1.01
Exclusion	0.87	1.91	0–10	2.72	7.61
Suicidal ideation intensity	0.09	0.66	0–10	8.48	80.18
Any suicidal ideation					
No	4947[a]	97.71%[b]	–	–	–
Yes	116[a]	2.29%[b]	–	–	–
Suicidal ideation intensity[c]	3.97	1.92	1–10	0.83	0.18
Person level model variables					
Average negative peer events[d]	0.91	0.53	0.12–1.93	0.50	−0.92
Average exclusion[d]	0.96	1.56	0–8.99	3.57	14.61
IL-6 activity	8.93	8.93	1.00–49.37	2.66	9.78
TNF-α activity	6.61	4.39	0.21–18.66	0.71	−0.02
Person level suicidal ideation					
Average instances of suicidal ideation ($N = 42$)	2.76	6.80	0–35	3.43	11.91
Average instances of suicidal ideation ($n = 18$)[e]	6.44	9.29	1–35	1.98	2.89
Average suicidal ideation intensity[c]	4.25	1.51	2–8	0.62	−0.12

Note: Proinflammatory values are in pg/mL.

[a]Corresponds to *n* out of total responses.

[b]Corresponds to percentage out of total responses.

[c]Based on suicidal ideation intensity ratings for only those observations in which suicidal ideation was present (scale = 1–11).

[d]Corresponds to each participant's average across observations.

[e]Corresponds to the subset of the sample that reported presence of suicidal ideation on at least one EMA survey.

GLMMs. There were sizeable between-person differences in the within-person association between negative peer events and the odds of SI at the same time point and at the next time point (see Tables 2–4). The random effect for level 1 exclusion severity was also examined in both the main effects and moderation MLMs. Between-person differences in the within-person association between exclusion severity and SI intensity at the same time point were sizeable, and at the next time point were somewhat smaller yet notable (see Tables 5–7). Together, there was considerable variability in the effect of interpersonal stress variables on SI outcomes at the same time point and the next time point across people.

Main effect models

Negative peer events and presence versus absence of SI

Results of the GLMMs to examine hypothesis 1A are presented in Table 2. Number of negative peer events was not associated with the odds of presence versus absence of SI at the *same* time point at either the within-subject ($b = 0.00$, 95% CrI [−0.54, 0.48]) or between-subject ($b = 0.84$, 95% CrI [−1.12, 2.93]) level. Likewise, number of negative peer events was not associated with the odds of SI at the *next* time point at either the within-subject ($b = 0.09$, 95% CrI [−0.42, 0.44]) or between-subject ($b = 1.26$, 95% CrI [−0.63, 3.40]) level.

Exclusion and SI intensity

Results of the MLMs to examine hypothesis 1B are presented in Table 5. The association between within-subject changes in exclusion severity and SI intensity at the *same* time point was marginally significant ($b = 0.04$, $p = 0.059$, 95% CI [−0.001, 0.07]), with a medium effect ($d = 0.58$). That is, when an individual's exclusion severity rating was higher than usual, there was a trend for SI intensity also to be higher. The association between within-subject changes in exclusion severity and SI intensity at the *next* time point was not significant ($b = -0.003$, $p = 0.66$, 95% CI [−0.02, 0.01]). Between-subject changes in exclusion severity was not associated with SI intensity at the *same* time point ($b = 0.01$, $p = 0.78$, 95% CI [−0.04, 0.05]) or the *next* time point ($b = 0.02$, $p = 0.50$, 95% CI [−0.03, 0.06]).

FIGURE 1 Observation-level time series plots of exclusion, negative peer events, and suicidal ideation intensity. (A) Exclusion. (B) Negative peer events. (C) Suicidal ideation intensity.

Proinflammatory activity as a moderator

Negative peer events and presence versus absence of SI

Results of the GLMMs to examine hypothesis 2A are presented in Tables 3 and 4 for IL-6 and TNF-α, respectively. IL-6 activity was not associated with the odds of presence versus absence of SI in either models of the *same* time point ($b = -0.02$, 95% CrI [−0.15, 0.11]) or the next *time* point ($b = -0.03$, 95% CrI [−0.16, 0.11]). Additionally, IL-6 activity did not moderate the relation between number of negative peer events and the odds of SI at the *same* time point ($b = 0.01$, 95% CrI [−0.02, 0.05]) at the within-person level. However, it did moderate the relation between number of negative peer events and the odds of SI at the *next* time point at the within-person level ($b = -0.06$, 95% CrI [−0.14, −0.01]).

A Johnson-Neyman plot was constructed (*interactions* R package; Long, 2021) to further explore the nature of the interaction (see Figure 2). Examination of the plot indicated that at very low levels of IL-6 activity, within-person increases in number of negative peer events were associated with increased odds of SI at the next time point. However, at average IL-6 levels, number of negative peer events was not associated with odds of SI. Importantly, this plot also indicated that the region of significance falls outside of the observed range of data. Thus, this finding should be interpreted with considerable caution.

In contrast to the within-subject level, IL-6 activity did not moderate the relation between number of negative peer events and the odds of SI at the *same* time point ($b = 0.28$, 95% CrI [−0.13, 0.78]) or the *next* time point ($b = 0.36$, 95% CrI [−0.08, 0.91]) at the between-subject level.

TNF-α activity was not associated with the odds of presence versus absence of SI in either models of the *same* time point ($b = 0.06$, 95% CrI [−0.19, 0.34]) or the *next* time point ($b = -0.01$, 95% CrI [−0.28, 0.27]). TNF-α activity also did not moderate the relation between number of negative peer events and the odds of SI at the *same* time point ($b = 0.00$, 95% CrI [−0.07, 0.08]) or *next* time point ($b = -0.03$, 95% CrI [−0.11, 0.03]) at the within-subject level. Likewise, TNF-α activity did not moderate the relation between number of negative peer events and the odds of SI at the *same* time point ($b = 0.12$, 95% CrI [−0.38, 0.65]) or *next* time ($b = 0.26$, 95% CrI [−0.25, 0.81]) at the between-subject level.

(b) Negative Peer Events

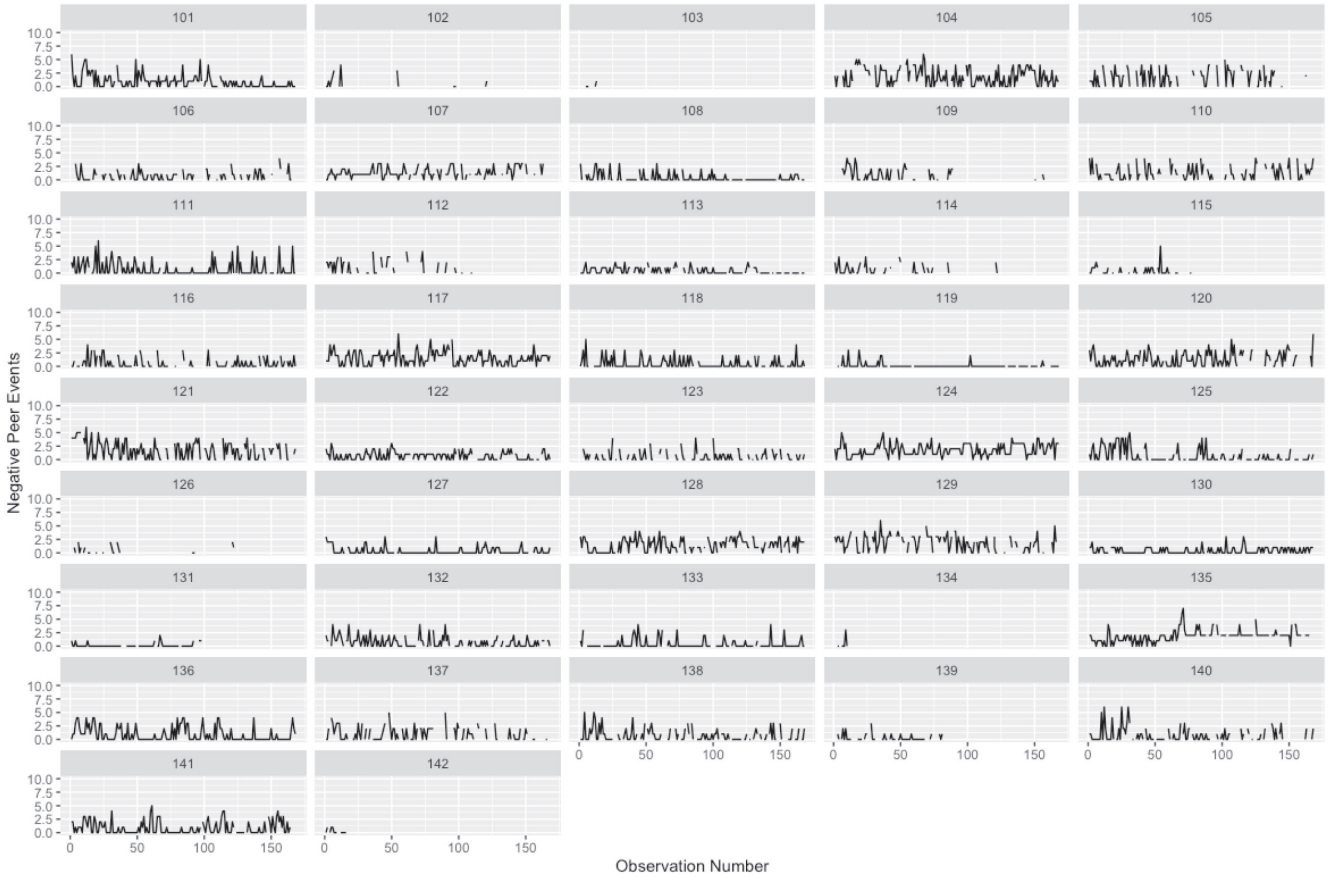

FIGURE 1 (Continued)

Exclusion and SI intensity

Results of the MLMs to examine hypothesis 2B are presented in Tables 6 and 7 for IL-6 and TNF-α, respectively. IL-6 activity was not associated with SI intensity in either models of the *same* time point ($b = -0.002$, $p = 0.60$, 95% CI [−0.01, 0.01]) or the *next* time point ($b = -0.002$, $p = 0.60$, 95% CI [−0.01, 0.01]). Additionally, IL-6 activity did not moderate the relation between exclusion severity and SI intensity at the *same* time point ($b = -0.001$, $p = 0.74$, 95% CI [−0.01, 0.004]) or the *next* time point ($b = 0.001$, $p = 0.32$, 95% CI [−0.001, 0.003]) at the within-subject level. Likewise, IL-6 activity did not moderate the relation between exclusion severity and SI intensity at the *same* time point ($b = 0.003$, $p = 0.63$, 95% CI [−0.01, 0.01]) or the *next* time point ($b = 0.002$, $p = 0.67$, 95% CI [−0.01, 0.01]) at the between-subject level. Of note, the model of exclusion severity, IL-6 activity, and *next* time point SI intensity resulted in a singular fit, which indicates near-zero estimates on some dimensions of the variance–covariance matrix. The *lme4* package is capable of handling singular fits (Bates et al., 2015), and as such, this model can still be interpreted.

Similarly, TNF-α activity was not associated with SI intensity at the *same* time point ($b = -0.003$, $p = 0.75$, 95% CI [−0.02, 0.01]). TNF-α activity did not moderate the relation between exclusion severity and SI intensity at the *same* time point at the within-subject level ($b = -0.002$, $p = 0.57$, 95% CI [−0.01, 0.01]). TNF-α activity also did not moderate the relation between exclusion severity and SI intensity at the *same* time point at the between-subject level ($b = 0.004$, $p = 0.58$, 95% CI [−0.01, 0.01]). The model examining TNF-α activity as a moderator for the relation between exclusion severity and SI intensity at the *next* time point did not converge. As such, while results of this model are presented in Table 7, parameter estimates cannot be interpreted further.

DISCUSSION

The present study examined the relation between interpersonal stress (i.e., negative peer events, exclusion severity) and the presence and intensity of suicidal ideation in real time, as well as the impact of proinflammatory activity (IL-6 and TNF-α cytokines) during social stress on this

(c) Suicidal Ideation Intensity

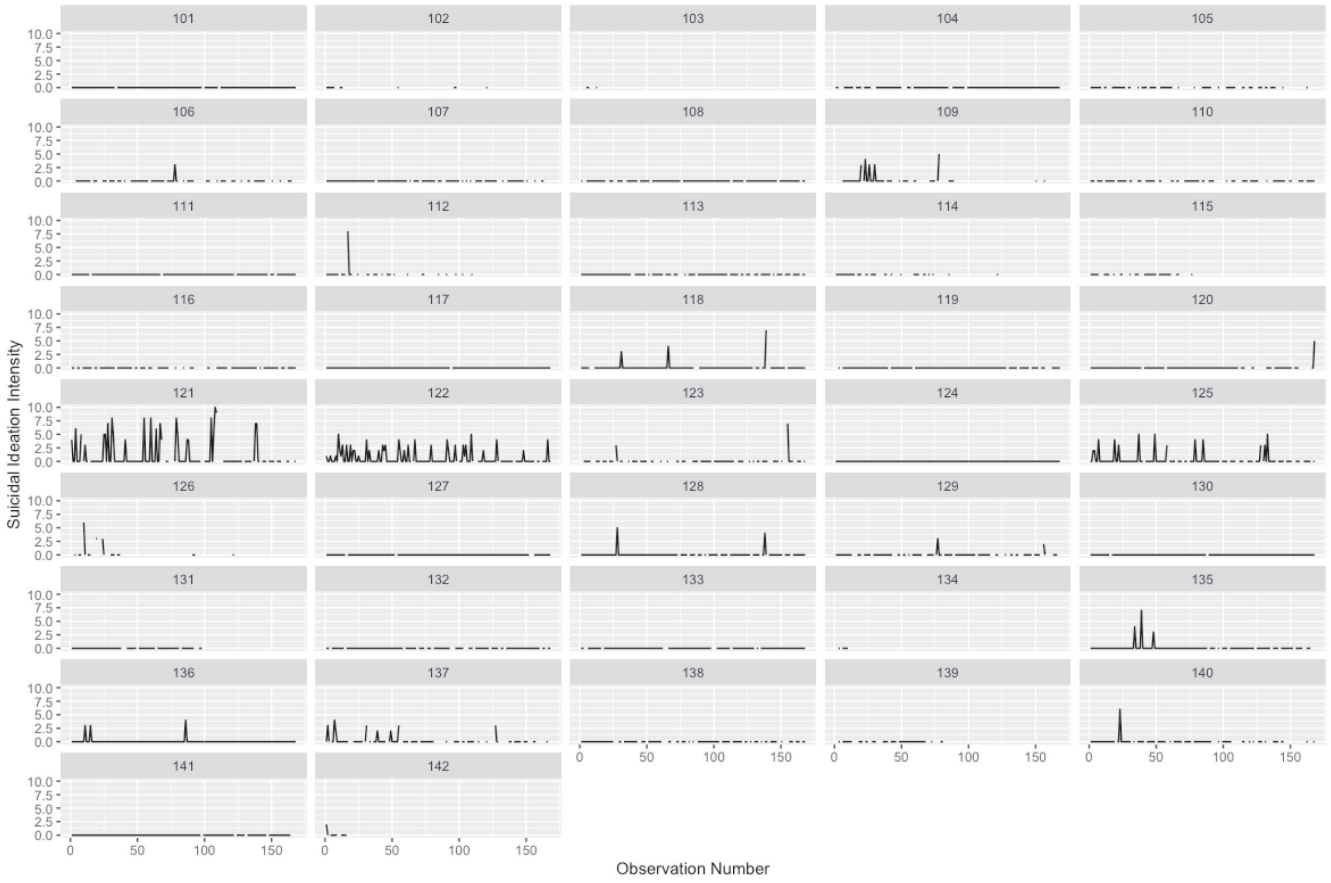

FIGURE 1 (Continued)

TABLE 2 Main effects models of the relation between number of negative peer events and presence versus absence of suicidal ideation at the same time point and next time point.

	Presence vs. absence suicidal ideation at *T*			Presence vs. absence suicidal ideation at *T* + 1		
Dependent variable	***b***	**SE**	**95% CrI (*b*)**	***b***	**SE**	**95% CrI (*b*)**
Fixed effects						
Intercept	−5.22	0.63	[−6.64, −4.14][a]	−5.62	0.68	[−7.09, −4.44][a]
Time (observation)	−0.01	0.00	[−0.02, −0.01][a]	−0.001	0.00	[−0.01, 0.00]
Between neg. peer events	0.84	1.01	[−1.12, 2.93]	1.26	1.02	[−0.63, 3.40]
Within neg. peer events	0.00	0.25	[−0.54, 0.48]	0.09	0.21	[−0.42, 0.44]
Between neg. peer events by within neg. peer events	−0.05	0.30	[−0.60, 0.61]	0.05	0.23	[−0.37, 0.56]
Random effects						
Intercept	2.66	0.59	[1.77, 4.03][a]	2.58	0.59	[1.65, 3.93][a]
Within neg. peer events	0.35	0.21	[0.02, 0.83][a]	0.18	0.15	[0.01, 0.57][a]

Note: Effect estimates and CrIs are presented as log-odds.

Abbreviations: Between neg. peer events, between-person component of number of negative peer events; CrI, credible interval; *T*, same time point; *T* + 1, next time point; Within neg. peer events, within-person component of number of negative peer events.

[a]Credible intervals that do not cross zero are considered significant effects.

relation, in a sample of emerging adults with past-month passive or active SI at the time of recruitment. Hypotheses regarding the association between exclusion severity and SI intensity were partially supported. Though not statistically significant, increases in a participant's own rating of exclusion had a moderate effect on *concurrent* increases

TABLE 3 Models of IL-6 activity as a moderator of the relation between number of negative peer events and presence versus absence of suicidal ideation at the same time point and next time point.

	Presence vs. absence suicidal ideation at *T*			Presence vs. absence suicidal ideation at *T* + 1		
Dependent variable	***b***	**SE**	**95% CrI (*b*)**	***b***	**SE**	**95% CrI (*b*)**
Fixed effects						
Intercept	−5.34	0.68	[−6.82, −4.18][a]	−5.87	0.75	[−7.53, −4.61][a]
Time (observation)	−0.01	0.00	[−0.02, −0.01][a]	−0.001	0.00	[−0.01, 0.00]
Between neg. peer events	1.30	1.13	[−0.77, 3.69]	1.74	1.21	[−0.51, 4.32]
IL-6 activity	−0.02	0.06	[−0.15, 0.11]	−0.03	0.07	[−0.16, 0.11]
Within neg. peer events	−0.09	0.29	[−0.76, 0.44]	−0.05	0.25	[−0.62, 0.38]
Between neg. peer events by IL-6	0.28	0.23	[−0.13, 0.78]	0.36	0.25	[−0.08, 0.91]
Between neg. peer events by within neg. peer events	0.02	0.37	[−0.64, 0.83]	0.20	0.30	[−0.34, 0.85]
Within neg. peer events by IL-6	0.01	0.02	[−0.02, 0.05]	−0.06	0.03	[−0.14, −0.01][a]
Within neg. peer events by between neg. peer events by IL-6	0.02	0.08	[−0.14, 0.19]	−0.02	0.09	[−0.18, 0.16]
Random effects						
Intercept	2.76	0.63	[1.80, 4.26][a]	2.71	0.68	[1.70, 4.35][a]
Within neg. peer events	0.41	0.25	[0.03, 0.97][a]	0.19	0.16	[0.01, 0.62][a]

Note: Effect estimates and CrIs are presented as log-odds.

Abbreviations: Between neg. peer events, between-person component of number of negative peer events; CrI, credible interval; IL-6, IL-6 proinflammatory activity; *T*, same time point; *T* + 1, next time point; Within neg. peer events, within-person component of number of negative peer events.

[a]Credible intervals that do not cross zero are considered significant effects.

in SI intensity but not at a subsequent time point. There was no association between participants' average perceived experience of exclusion and SI intensity. These findings suggest that the relation between an individual's perception of social exclusion and SI varies across time, and are similar to prior research in this area. In adult samples, a concurrent, but not temporal, real-time association has been found at the individual level between related interpersonal constructs such as perceived loneliness, burdensomeness (Kleiman et al., 2017), and low social support (Coppersmith et al., 2019) and SI. As social exclusion represents experiences of rejection and social loss, rather than simply an absence of social connection (Slavich et al., 2009), this preliminary finding adds to existing research. It also adds to a growing body of literature which suggests that subjective interpersonal factors may influence present-moment SI intensity but may not aid in short-term *prediction* of increased SI. However, it is also possible that the transition from feeling isolated and excluded to an increase in suicidal thoughts occurs more quickly than can be captured with current real-time monitoring techniques.

Counter to hypotheses, a relation was not found between number of negative peer events and the presence of SI, either concurrently or temporally in real time. Broadly, neither individual changes in negative peer events, or differences between participants' average experience of negative peer events, were associated with likelihood of SI. These results are inconsistent with the established body of literature that documents a relation between occurrence of negative interpersonal events, such as loss, conflict, and bullying, and STBs, using more traditional cross-sectional and longitudinal research designs (Beautrais et al., 1997; Adams et al., 1994; Hinduja & Patchin, 2010). Findings are also inconsistent with prior findings of an acute relation between interpersonal negative life events and increased odds of a suicide attempt (Bagge et al., 2013). Cumulatively, study results may suggest that the *perception* of exclusion and rejection is more potent than the mere occurrence of a negative interpersonal event. While the presence of one or more negative interpersonal events may not be impactful enough to result in SI, the subjective experience of being rejected or excluded appears to play a role in intensity of SI.

In analyses of proinflammatory activity, neither cytokine examined (IL-6 or TNF-α) was directly associated with increased odds of SI or SI intensity. While emerging

TABLE 4 Models of TNF-α activity as a moderator of the relation between number of negative peer events and presence versus absence of suicidal ideation at the same time point and next time point.

	Presence vs. absence suicidal ideation at *T*			Presence vs. absence suicidal ideation at *T* + 1		
Dependent variable	***b***	**SE**	**95% CrI (*b*)**	***b***	**SE**	**95% CrI (*b*)**
Fixed effects						
Intercept	−5.50	0.72	[−7.05, −4.27][a]	−5.89	0.77	[−7.58, −4.63][a]
Time (observation)	−0.01	0.00	[−0.02, −0.01][a]	−0.001	0.00	[−0.01, 0.00]
Between neg. peer events	0.87	1.12	[−1.21, 3.32]	1.34	1.18	[−0.81, 3.79]
TNF-α activity	0.06	0.13	[−0.19, 0.34]	−0.01	0.14	[−0.28, 0.27]
Within neg. peer events	−0.04	0.30	[−0.69, 0.50]	0.05	0.25	[−0.55, 0.45]
Between neg. peer events by TNF-α	0.12	0.26	[−0.38, 0.65]	0.26	0.27	[−0.25, 0.81]
Between neg. peer events by within neg. peer events	−0.001	0.34	[−0.64, 0.74]	0.13	0.27	[−0.37, 0.74]
Within neg. peer events by TNF-α	0.00	0.04	[−0.07, 0.08]	−0.03	0.04	[−0.11, 0.03]
Within neg. peer events by between neg. peer events by TNF-α	−0.04	0.10	[−0.24, 0.15]	0.00	0.08	[−0.15, 0.16]
Random effects						
Intercept	2.94	0.67	[1.90, 4.54][a]	2.76	0.66	[1.73, 4.29][a]
Within neg. peer events	0.45	0.25	[0.04, 1.01][a]	0.22	0.20	[0.01, 0.71][a]

Note: Effect estimates and CrIs are presented as log-odds.

Abbreviations: Between neg. peer events, between-person component of number of negative peer events; CrI, credible interval; *T*, same time point; *T* + 1, next time point; TNF-α, TNF-α proinflammatory activity; Within neg. peer events, within-person component of number of negative peer events.

[a]Credible intervals that do not cross zero are considered significant effects.

TABLE 5 Main effects models of the relation between exclusion severity and suicidal ideation intensity at the same time point and next time point.

Dependent variable	**Suicidal ideation intensity at *T***				**Suicidal ideation intensity at *T* + 1**			
Fixed effects	***b***	**SE**	**95% CI (*b*)**	***p***	***b***	**SE**	**95% CI (*b*)**	***p***
Intercept	0.137	0.037	[0.067, 0.208]	0.0004***	0.127	0.039	[0.052, 0.203]	0.002**
Time (observation)	−0.0005	0.0002	[−0.001, −0.0001]	0.007**	−0.0004	0.0002	[−0.001, 0.00003]	0.068[†]
Between exclusion	0.006	0.022	[−0.037, 0.050]	0.777	0.016	0.023	[−0.029, 0.061]	0.499
Within exclusion	0.037	0.019	[−0.001, 0.073]	0.059[†]	−0.003	0.008	[−0.019, 0.013]	0.660
Between exclusion by within exclusion	0.008	0.012	[−0.014, 0.031]	0.484	−0.004	0.005	[−0.014, 0.006]	0.456
Random effects	**Variance**	**SD**	**95% CI (Variance)**		**Variance**	**SD**	**95% CI (Variance)**	
Intercept	0.044	0.210	[0.027, 0.067]		0.044	0.209	[0.025, 0.071]	
Within exclusion	0.011	0.110	[0.006, 0.018]		0.0003	0.016	[0.00004, 0.001]	
Residual	0.354	0.590	[0.340, 0.368]		0.379	0.616	[0.363, 0.396]	

Note: [†]$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Abbreviations: Between exclusion, between-person component of exclusion severity; CI, confidence interval; *T*, same time point; *T* + 1, next time point; Within exclusion, within-person component of exclusion severity.

research suggests that proinflammatory cytokines may serve as a biomarker for suicidal *behaviors* and death by suicide (Chang et al., 2016; Courtet et al., 2016; Serafini et al., 2013), these findings may suggest that the association between proinflammatory cytokines and suicidal *ideation* is not as strong.

TABLE 6 Models of IL-6 activity as a moderator of the relation between exclusion severity and suicidal ideation intensity at the same time point and next time point.

Dependent variable	Suicidal ideation intensity at *T*				Suicidal ideation intensity at *T*+1[a]			
Fixed effects	***b***	**SE**	**95% CI (*b*)**	***p***	***b***	**SE**	**95% CI (*b*)**	***p***
Intercept	0.142	0.038	[0.069, 0.216]	0.0006***	0.131	0.041	[0.054, 0.208]	0.002**
Time (observation)	−0.0005	0.0002	[−0.001, −0.0001]	0.007**	−0.0003	0.0002	[−0.001, 0.00005]	0.086†
Between exclusion	0.020	0.040	[−0.057, 0.097]	0.621	0.029	0.042	[−0.050, 0.108]	0.489
IL-6 response	−0.002	0.004	[−0.011, 0.006]	0.596	−0.002	0.004	[−0.011, 0.006]	0.622
Within exclusion	0.039	0.020	[0.001, 0.076]	0.058†	−0.003	0.008	[−0.019, 0.014]	0.735
Between exclusion by IL-6	0.003	0.005	[−0.008, 0.013]	0.628	0.002	0.006	[−0.008, 0.013]	0.668
Within exclusion by	0.013	0.023	[−0.030, 0.057]	0.562	−0.014	0.010	[−0.034, 0.006]	0.178
Between exclusion								
Within exclusion by IL-6	−0.0008	0.002	[−0.005, 0.004]	0.736	0.001	0.001	[−0.001, 0.003]	0.316
Within exclusion by between exclusion by IL-6	0.001	0.003	[−0.005, 0.007]	0.750	−0.166	0.001	[−0.004, 0.001]	0.231
Random effects	**Variance**	**SD**	**95% CI (Variance)**		**Variance**	**SD**	**95% CI (Variance)**	
Intercept	0.046	0.214	[0.026, 0.067]		0.046	0.214	[0.025, 0.069]	
Within exclusion	0.012	0.108	[0.006, 0.017]		0.0002	0.016	[0.00002, 0.001]	
Residual	0.354	0.595	[0.340, 0.368]		0.379	0.616	[0.363, 0.396]	

Abbreviations: Between exclusion, between-person component of exclusion severity; CI, confidence interval; IL-6, IL-6 proinflammatory activity; Within exclusion, within-person component of exclusion severity; *T*, same time point; *T* + 1, next time point.

[a]Model resulted in a singular fit.

Note: †$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 7 Models of TNF-α activity as a moderator of the relation between exclusion severity and suicidal ideation intensity at the same time point and next time point.

Dependent variable	Suicidal ideation intensity at *T*				Suicidal ideation intensity at *T*+1[a]			
Fixed effects	***b***	**SE**	**95% CI (*b*)**	***p***	***b***	**SE**	**95% CI (*b*)**	***p***
Intercept	0.140	0.038	[0.069, 0.212]	0.0005***	0.131	0.039	[0.056, 0.205]	0.002**
Time (observation)	−0.0005	0.0002	[−0.001, −0.0001]	0.006**	−0.0003	0.0002	[−0.001, 0.00005]	0.086†
Between exclusion	0.021	0.036	[−0.048, 0.091]	0.559	0.051	0.038	[−0.022, 0.124]	0.191
TNF-α response	−0.003	0.008	[−0.018, 0.013]	0.748	−0.375	0.008	[−0.019, 0.012]	0.653
Within exclusion	0.038	0.019	[0.0004, 0.074]	0.057†	−0.0005	0.008	[−0.017, 0.016]	0.954
Between exclusion by TNF-α	0.004	0.008	[−0.010, 0.019]	0.581	0.009	0.008	[−0.006, 0.025]	0.251
Within exclusion by between exclusion	0.028	0.020	[−0.011, 0.066]	0.179	−0.021	0.010	[−0.040, −0.001]	0.066†
Within exclusion by TNF-α	−0.002	0.004	[−0.011, 0.006]	0.574	0.002	0.002	[−0.002, 0.006]	0.319
Within exclusion by between exclusion by TNF-α	0.005	0.004	[−0.003, 0.013]	0.238	−0.004	0.002	[−0.008, 0.00001]	0.075†
Random effects	**Variance**	**SD**	**95% CI (Variance)**		**Variance**	**SD**	**95% CI (Variance)**	
Intercept	0.046	0.215	[0.027, 0.068]		0.045	0.212	[0.024, 0.067]	
Within exclusion	0.011	0.106	[0.006, 0.017]		0.0003	0.016	[0.00003, 0.001]	
Residual	0.354	0.595	[0.340, 0.368]		0.379	0.616	[0.363, 0.395]	

Note: †$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Abbreviations: Between exclusion, between-person component of exclusion severity; CI, confidence interval; Within exclusion, within-person component of exclusion severity; *T*, same time point; *T* + 1, next time point; TNF-α, TNF-α proinflammatory activity.

[a]Model did not converge and thus, estimates cannot be interpreted.

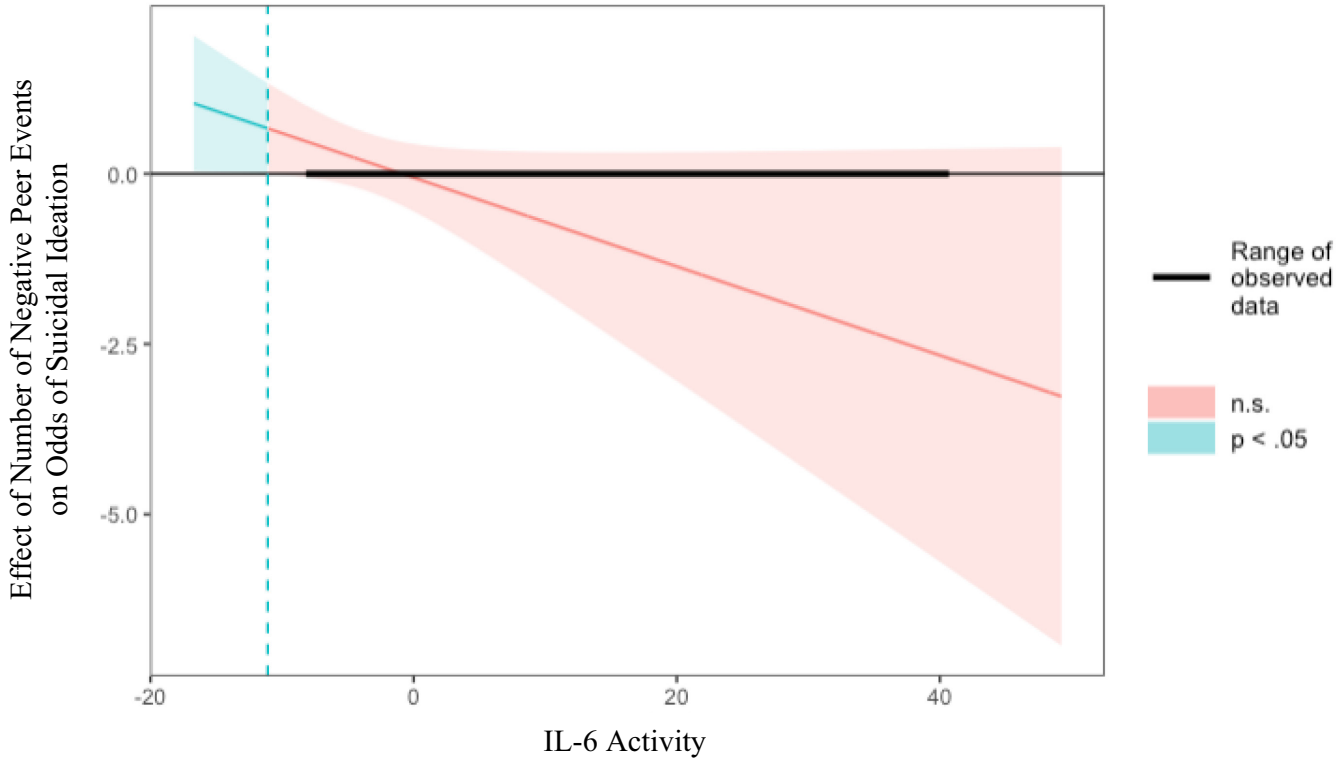

FIGURE 2 Johnson-Neyman plot of the relation between IL-6 activity and the effect of number of negative peer events on odds of suicidal ideation at next time point. Y-axis displays the relation between number of negative peer events at time *T* and odds of presence versus absence of SI at time *T* + 1. Region of significance represents the IL-6 activity values at which there is an association between number of negative peer events and the odds of presence versus absence of SI. Nonsignificant region indicates the IL-6 activity values at which there is no association between number of negative peer events and the odds of presence versus absence of SI.

IL-6 activity moderated the relation between number of negative peer events and *subsequent*, but not *concurrent*, presence of SI. The direction of this effect, however, was contrary to expectations. Specifically, individual increases in negative peer events were associated with increased odds of the presence of SI at the next time point among those with very *low* levels of IL-6 activity. This interaction effect should be interpreted with extreme caution, as the effect was only significant at IL-6 values that were below the range of observed data. That is, while the statistical pattern suggests that the interaction effect exists at very low levels of IL-6 activity, the interaction cannot be *directly* observed using this dataset. Some argue that conclusions should not be drawn under these conditions (Finsaas & Goldstein, 2021), and thus this finding requires replication.

No other moderation hypotheses were supported in the present study. Models examining moderation hypotheses may have been too complex relative to the sample size to detect effects, resulting in nonsignificant results and, in one case, nonconvergence of parameter estimates (Brauer & Curtin, 2018). It is also possible that hypotheses were not supported because no true interaction effect exists. Future research with larger samples is needed to examine this question.

Implications

Findings from the present study hold potential implications. Clinically, these results suggest that individual changes in feelings of exclusion, rather than instances of negative peer interactions, may be associated with SI. Thus, when working with emerging adults who experience SI in the context of therapy, use of evidence-based approaches e.g., identifying negative thought patterns that fuel feelings of exclusion and subsequently assisting them in the development of an effective counter thoughts (Beck, 2005; Beck, 2020); skills that aid in recovery from experiences of invalidation (Linehan, 2014) may help decrease short-term SI intensity. Incorporating feelings of exclusion as a warning sign for possible SI into safety plans (Stanley & Brown, 2012) may also help young people to use healthy coping strategies to reduce distress *before* SI arises. Additionally, the relative importance of exclusion over negative peer interactions may also align with social safety perspectives, which argue that for those with histories of interpersonal stress, feelings of exclusion (or other forms of social threat) may arise in the absence of social safety cues (e.g., lack of connection, belonging, inclusion), rather than from a clear negative stressor

(Diamond & Alley, 2022; Slavich, 2020). This is especially relevant for young people who have experienced stigma and marginalization, who may also be at increased risk for STBs (e.g., as related to sexually diverse and gender-diverse populations; see Diamond & Alley (Diamond & Alley, 2022) for a review).[3]

On a larger scale, just as rates of STBs have increased and been identified as a public health concern (Hedegaard, 2018) so too has social isolation and loneliness, even prior to the COVID-19 pandemic (Holt-Lunstad, 2021). Social isolation and loneliness, which are linked to feelings of exclusion, can have both short- and long-term negative implications for both physical and mental health more broadly, as well as risk for premature mortality (Holt-Lunstad, 2018). Building social connection may offer a protective buffer against this myriad of potential negative health effects. The results of the present study therefore may offer additional support to the strong arguments made by others to take a multisystem approach to implementing preventive intervention strategies (see Holt-Lunstad (Holt-Lunstad, 2018; Holt-Lunstad, 2021) for a review and recommendations).

Limitations

This is one of the first studies to examine proinflammatory activity across social stress as a moderator of the relation between real-time interpersonal stress and SI, and to document an effect between exclusion severity and SI intensity. Moreover, the overall response rate to EMA surveys was relatively high. Despite the novelty of the present study and relative strengths, it also includes several limitations. First, the overall rate of SI in the present sample was low (i.e., SI was reported on only 2.29% of surveys), with only 18 of 42 participants reporting at least one instance of SI. This may have reduced power and resulted in erroneous null effects. The present study therefore warrants replication in a sample of participants with greater SI frequency and severity. Second, because this was a pilot study and the sample size was smaller, models examining SI at time $T+1$ did not control for SI at time T. Future studies with larger samples should consider including SI at T when predicting SI at $T+1$ to better examine short-term changes in SI.

Third, data were collected between October 2020 and June 2021, during the COVID-19 pandemic. While the checklist of negative peer events included digital peer interactions, local restrictions and safety guidelines reduced opportunities for in-person interactions and may have also resulted in atypical experiences of interpersonal stress. It is also possible that COVID-19 influenced the laboratory social stressor and resulting proinflammatory activity. Specifically, use of face masks may have impacted participants' interpretation of verbal and nonverbal rejection cues, and social distancing may have decreased the social intimacy of the interaction. Fourth, while the list of negative peer events was drawn from measures that assess conceptually similar constructs, items were administered as a checklist (vs. on a Likert scale for frequency or severity), and psychometric tests were not conducted on the scale used here. Future work may therefore require confirming that this scale is unidimensional.

Finally, we had to approximate how proinflammatory activity might occur in real time through a laboratory measure as we are not aware of an intensive longitudinal measurement of proinflammatory activity. Additionally, while pre- to post-task self-reported changes in feelings of sadness, exclusion, and inclusion were reported, we did not explicitly ask participants whether they perceived the task to be a negative or socially stressful event or whether the experience was akin to other times they have experienced interpersonal stress. Therefore, it is possible that the laboratory stressor did not manipulate proinflammatory activity exactly as intended. We also were limited to analysis of only two proinflammatory cytokines and were not able to account for coordination of multiple stress response systems (e.g., hypothalamic–pituitary–adrenal axis, degree of individual glucocorticoid resistance). Future research with more complex biopsychosocial models of stress responsivity is needed to more thoroughly examine the transactional nature of interpersonal stress and stress responsivity, and the subsequent impact on suicide risk.

CONCLUSION

The present study extends prior research on the relation between interpersonal stress, proinflammatory activity, and SI among emerging adults with past-month passive or active SI at recruitment. Individual increases in exclusion severity had a moderate, although not statistically significant, effect on concurrent increases in SI intensity. Individual increases in negative peer events were associated with increased odds of the presence of subsequent SI at very *low* levels of IL-6 activity. No other hypotheses were supported. Evidence-based interventions targeting perceptions of exclusion may help decrease short-term SI intensity. Additionally, interventions that build social connection may offer protective effects. More research is needed to clarify the potential role of proinflammatory activity in the relation between interpersonal stress and SI before further conclusions are drawn.

[3]We thank the reviewer who highlighted this perspective.

ACKNOWLEDGMENTS

This research was supported by the American Psychological Foundation/Council of Graduate Departments of Psychology Graduate Student Research Scholarship, the Mamie Phipps Clark Diversity Research Grant from Psi Chi, and the American Psychological Association Dissertation Research Award, all awarded to the first author. This work was also partially supported by the National Institute of Mental Health (T32MH020061). We would like to thank the University of California Irvine Institute for Interdisciplinary Salivary Bioscience Research for conducting salivary assays for this study.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Defayette, A. B., Esposito-Smythers, C., Cero, I., Kleiman, E. M., López, R. Jr, Harris, K. M., & Whitmyre, E. D. (2023). Examination of proinflammatory activity as a moderator of the relation between momentary interpersonal stress and suicidal ideation. *Suicide and Life-Threatening Behavior*, *53*, 922–939. https://doi.org/10.1111/sltb.12993