

Regular Article

Proinflammatory gene expression is associated with prospective risk for adolescent suicidal thoughts and behaviors over twelve months

Matthew G. Clayton¹ , Steve W. Cole^{2,3}, Matteo Giletta^{4,5}, Paul D. Hastings⁶ , Matthew K. Nock⁷,
Karen D. Rudolph⁸ , George M. Slavich³  and Mitchell J. Prinstein¹ 

¹Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, ²Division of Hematology-Oncology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA, ³Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA, ⁴Department of Psychology, Ghent University, Ghent, Belgium, ⁵Department of Developmental Psychology, Tilburg University, Tilburg, Netherlands, ⁶Center for Mind and Brain and Department of Psychology, University of California, Davis, CA, USA, ⁷Department of Psychology, Harvard University, Boston, MA, USA and ⁸Department of Psychology, University of Illinois at Urbana-Champaign, Urbana-Champaign, IL, USA

Abstract

Objective: Recent theories have implicated inflammatory biology in the development of psychopathology and maladaptive behaviors in adolescence, including suicidal thoughts and behaviors (STB). Examining specific biological markers related to inflammation is thus warranted to better understand risk for STB in adolescents, for whom suicide is a leading cause of death.

Method: Participants were 211 adolescent females (ages 9–14 years; $M_{\text{age}} = 11.8$ years, $SD = 1.8$ years) at increased risk for STB. This study examined the prospective association between basal levels of inflammatory gene expression (average of 15 proinflammatory mRNA transcripts) and subsequent risk for suicidal ideation and suicidal behavior over a 12-month follow-up period.

Results: Controlling for past levels of STB, greater proinflammatory gene expression was associated with prospective risk for STB in these youth. Similar effects were observed for CD14 mRNA level, a marker of monocyte abundance within the blood sample. Sensitivity analyses controlling for other relevant covariates, including history of trauma, depressive symptoms, and STB prior to data collection, yielded similar patterns of results.

Conclusions: Upregulated inflammatory signaling in the immune system is prospectively associated with STB among at-risk adolescent females, even after controlling for history of trauma, depressive symptoms, and STB prior to data collection. Additional research is needed to identify the sources of inflammatory up-regulation in adolescents (e.g., stress psychobiology, physiological development, microbial exposures) and strategies for mitigating such effects to reduce STB.

Keywords: adolescence; biomarkers; childhood trauma; inflammation; suicide

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Adolescent suicide is a national public health crisis and has been the second leading cause of death among individuals aged 10–34 years old for over a decade (Centers for Disease Control and Prevention, 2019). Data suggest a 17-fold increase in deaths by suicide (Centers for Disease Control and Prevention, 2014) between preadolescence and adolescence, indicating a critical developmental period during which time social-environmental and biological processes likely interact to greatly increase risk for suicidal behavior. Despite these alarming figures, suicide research has yet to identify specific biological processes that confer increased risk for suicidal thoughts and behaviors (STB) over time (Franklin et al., 2017), thus highlighting the need for additional research on this topic.

Recent theories of both adolescent suicide (see Miller & Prinstein, 2019) and stress biology (Slavich et al., 2023b; Slavich,

2020, 2022) have posited that persistent activation of stress-related biological systems may partially explain why some teens are uniquely vulnerable to psychopathology and at heightened risk for suicide. Given their greater exposure to social stress and biological sensitivity to such stress (Massing-Schaffer et al., 2019; Rose & Rudolph, 2006; Stroud et al., 2017), further knowledge of biological stress processes may be especially relevant for understanding risk for STB among adolescent girls. One domain that may be especially relevant in this context is the immune system, which is activated innately in the context of stress as an adaptive defense against perceived threats (Slavich et al., 2023a). Although such biological changes can be adaptive in the short term, when engaged chronically, these changes have been theorized to lead to increased risk for inflammatory disease and other maladaptive health outcomes (Dantzer et al., 2008; Miller, 2020; Slavich, 2020), including depression (Slavich & Irwin, 2014) and STB (Slavich & Auerbach, 2018). Furthermore, it is posited that deviations from normative immune functioning may play a role in risk for psychopathology in particular among vulnerable populations such as adolescents (Dantzer et al., 2011; Slavich et al., 2020), including inflammatory signaling pathways that influence brain function and

Corresponding author: Matthew G. Clayton; Email: mgc12@live.unc.edu

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behavioral processes involved in STB (Miller & Prinstein, 2019). For instance, the neuro-immune network hypothesis (Nusslock & Miller, 2016) highlights the influence of inflammatory processes on the prefrontal cortex, a brain region uniquely tied to impulse control, emotion regulation, and decision-making (Phillips et al., 2008), constructs with direct implications for risk for STB in adolescence (McHugh et al., 2019). Importantly, however, to date, no empirical research has assessed whether inflammatory gene expression may be a potential biological mechanism associated with increased risk for suicidal outcomes.

Preliminary evidence suggests that investigation of various inflammatory processes underlying STB may be a fruitful line of inquiry, and this is particularly true when considered from an adolescent perspective (Vargas-Medrano et al., 2020). A recent meta-analysis of the associations between altered immune system functioning and risk for suicidal behavior underscored the need to examine specific immunological pathways that confer increased risk for STB (Serafini et al., 2020). Subsequently, some empirical research examining proinflammatory cytokines (i.e., signaling proteins that mediate the immune cascade) has highlighted its potential relevance for adolescence in particular (Clayton et al., 2023), although there remains debate as to how cytokines confer risk for suicide (see Ducasse et al., 2015). An additional potential pathway is via the aforementioned inflammatory gene expression profile in circulating immune cells, and past research has identified how early-life adversity leads to changes in methylation of genes related to adolescent suicidal behaviors (Essex et al., 2013). Importantly, inflammatory gene expression appears to function in unique patterns when considered alongside other inflammatory biomarkers such as plasma proteins (Lindsay et al., 2024).

The present study examines an *a priori*, pre-specified set of proinflammatory mRNA markers in relation to STB in a clinically referred sample of adolescent girls. Analyses assessed the molecular signaling pathways underlying inflammation and risk for STBs over a 12-month period. Based on the research summarized above, it was hypothesized that upregulated inflammatory gene expression would be prospectively associated with greater risk for suicidal ideation and suicidal behavior, even after controlling for past STB. Data were also available to examine discriminant associations between inflammatory gene expression and nonsuicidal self-injury (NSSI) as a secondary analysis. Further sensitivity analyses controlled for race/ethnicity, BMI, pubertal development, nicotine use, alcohol use, and recent illness symptoms at the time of blood sampling, as well as past childhood trauma and depressive symptoms, respectively, to assess for the specificity of proinflammatory gene expression on prospective STB risk.

Method

Participants

Participants were 211 adolescent females ($M_{\text{age}} = 11.8$ years, $SD = 1.8$ years, range = 9–14-years-old) recruited from the southeastern United States, along with their primary caregiver. Demographic inclusion criteria were being assigned female at birth and being aged 9- to 14-years-old at time of recruitment. Clinical inclusion criteria were currently elevated depressive symptoms, prior suicidality, or a history of early life adversity as reported by the participant's primary caregiver (90% of participants were clinically referred), assessed via a phone-based prescreening using a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS;

Kaufman et al., 1997) and select items from the Youth Life Stress Interview (YLSI; Rudolph & Flynn, 2007). For this study, elevated depressive symptoms were defined as the endorsement of two or more depressive symptoms (e.g., feeling worthless or guilty, thinking about death or dying, not enjoying regular activities) in the past 2 years for 2 weeks or more prior to the start of data collection. This did not include individuals who endorsed these symptoms due to bereavement. Adolescents with a diagnostic history of psychosis, intellectual disability, or pervasive developmental disorder were deemed ineligible during prescreening. To participate, youth needed an available primary caregiver to provide consent and attend the baseline laboratory visit along with their adolescent. Participants were ethnically diverse, with 50.5% identifying as white, 28.6% identifying as Black or African American, 7.6% identifying as Latinx, and 13.3% identifying as mixed race or belonging to another ethnic group.

Data from four baseline samples were excluded due to invalid mRNA data (i.e., insufficient blood volume for reliable analysis), as well as 16 participants who were missing basal blood serum samples. No other exclusions were made.

Procedure

Following recruitment via phone screening with a trained research assistant, participants and their primary caregiver attended a baseline laboratory visit for initial data collection. After being acquainted to the study procedures, teens provided assent for their participation and their parents provided consent. Participants and their caregiver completed a series of questionnaires that assessed for participant history of life stress, pubertal development, and additional factors associated with inflammation. Trained research assistants assessed for historical and current participant suicidal ideation and behavior using a standardized semi-structured clinical interview with the participant. Finally, trained phlebotomists collected blood samples for the purposes of basal assays of participants' genetic markers of inflammation. All baseline blood samples were collected within a 2-hour period between 11am and 1 pm.

Over the 12 months following the baseline study visit, trained research assistants assessed for participant suicidal ideation and behavior, as well as NSSI, using an abbreviated version of the baseline clinical interview on follow-up calls at 4-, 8-, and 12-month intervals. The abbreviated interview removed items already assessed at baseline (e.g., lifetime history of SITB and NSSI). Participants represent 91.3% of the original sample, with 20 participants missing usable blood serum samples, thereby deeming them ineligible. All study procedures were approved by the research institution's human subjects committee, and all research was carried out in accordance with the Code of Ethics of the World Medical Association.

Measures

Self-injurious thoughts and behaviors

During the baseline laboratory visit, trained research assistants conducted the Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock et al., 2007) with each participant to assess for historical and current participant suicidal ideation and suicidal behavior, as well as NSSI. Responses were dichotomized for the presence (1) or absence (0) of lifetime suicidal ideation, the presence (1) or absence (0) of lifetime suicidal behaviors, and the presence (1) or absence (0) of lifetime NSSI. Suicidal behaviors included prior suicide attempts, as well as aborted or

interrupted suicide attempts. This dichotomization of ideation, attempts, and NSSI is consistent with past adolescent STB research (e.g., Eisenlohr-Moul *et al.*, 2018). At the follow-up intervals of 4, 8, and 12 months, research assistants conducted an abbreviated version of the SITBI to assess for presence (1) or absence (0) of any suicidal ideation, suicidal behaviors, or NSSI at any point over the interim 12-month period. For the purposes of this study, prospective suicidal ideation, suicidal behaviors, and NSSI were the endorsement of any ideation or behavior over the entirety of the follow-up period.

Proinflammatory gene expression

Gene expression data were assessed in 2.5 mL whole blood samples collected into PAXgene RNA tubes by standard antecubital venipuncture. Sample tubes were frozen for storage and batch shipment to the UCLA Social Genomics Core Laboratory for genome-wide transcriptional profiling by RNA sequencing, as previously described (see Cole *et al.*, 2020). Briefly, total RNA was extracted (Qiagen RNeasy), and polyadenylated RNA was converted to cDNA (Lexogen QuantSeq 3' FWD with low-mass buffer) and sequenced on an Illumina NextSeq instrument (Lexogen Services, GmbH), all following the manufacturers' standard protocols for low-mass samples. Samples were assayed in a single batch and yielded an average of 4.7 million sequencing reads, each of which was mapped to the reference human transcriptome using the STAR aligner (99% average mapping rate) (Dobin *et al.*, 2013). The total number of reads for each human gene was normalized to transcripts per million mapped reads, floored at 1 read per million to suppress spurious variability, and log₂ transformed for analysis by linear statistical models as described below. Samples were collected from 215 participants. Four samples (1.9%) failed cDNA synthesis or endpoint data quality control screening and were omitted from subsequent analyses, leaving a total of 211 baseline RNA samples for analysis as described below.

Covariates

In subsequent sensitivity analyses, this study assessed and controlled *a priori* for several factors that have been associated with inflammation and STB in prior research (e.g., Reid *et al.*, 2020; Slavish *et al.*, 2015). These factors included pubertal development (PDS; Petersen *et al.*, 1988), body mass index (BMI; calculated from height and weight measurements by a trained research assistant during the lab visit; Zeller *et al.*, 2013), recent illness symptoms at time of blood sampling, alcohol use, and nicotine use. The selection of these covariates was based in theoretical linkages between such factors and inflammatory gene expression (Slavich & Cole, 2013), as well as empirical work (e.g., Cole *et al.*, 2020; Gil *et al.*, 2007) and associations with STB (e.g., Eaton *et al.*, 2005; Korhonen *et al.*, 2018; Schilling *et al.*, 2009). Illness symptoms were aggregated from two items asked of the participant and the participant's caregiver (i.e., "In the past 7 days, have you/your child had any signs or symptoms of being sick [this could include itchy/sore throat, fever, fatigue, runny or stuffy nose, headaches, chills, etc.]"), dichotomized for presence or absence of any symptoms. Regular alcohol and nicotine use were assessed for using selected items from the Youth Risk Behavior Surveillance Survey (YRBS; Centers for Disease Control and Prevention, 2021). Additional details are included in the Appendix.

Additionally, participants completed the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.*, 2003) to assess for lifetime history of major and traumatic stress. As mentioned prior,

experiences of childhood trauma may contribute to maladaptive inflammatory profiles (Slavich & Cole, 2013) and heightened risk for STB (e.g., Angelakis *et al.*, 2020). The CTQ is a 28-item measure that is well-validated for use in adolescent samples (for a review, see Georgieva *et al.*, 2021) and uses a 5-point Likert scale (1 = *Never True* to 5 = *Very Often True*) to assess for various major lifetime stressors or supports (e.g., "People in my family called me things like stupid, lazy or ugly," "I believe that I was physically abused," "My family was a source of strength of support (reverse scored)"). Sum scores of the CTQ were computed (Cronbach's $\alpha = .79$), and the resulting scores were used in sensitivity analyses following primary data analyses.

Finally, participants reported on their baseline depressive symptoms using the Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988). Depressive symptoms are consistently associated with variations in inflammatory processes (Colasanto *et al.*, 2020) and STB (Gili *et al.*, 2019) in adolescence. The MFQ is a 33-item measure of depressive symptoms, with participants responding using a 3-point Likert scale (0 = *not true*, 1 = *sometimes true*, 2 = *mostly true*) indicating the presence of symptoms in the 2 weeks prior to the study visit. Sum scores were computed using 29 items from the full measure (Cronbach's $\alpha = .93$), used in sensitivity analyses. Four items assessing for suicidal ideation were excluded to avoid overlap with the SITBI measure.

Data analysis

Mixed effect linear models were applied to quantify the association between STB and NSSI measures during the 12-month follow-up period and average expression of 15 proinflammatory indicator genes. The 15 transcripts derived were chosen *a priori* from a list of 19 proinflammatory genes used in prior research, with removal of 4 transcripts that showed minimal levels or variance in mRNA expression in this data set ($SD < .5$ log₂ mRNA abundance; Cole *et al.*, 2020) while controlling for baseline STB. The 15 transcripts analyzed were *CXCL8*, *FOS*, *FOSL2*, *IL1B*, *JUN*, *JUNB*, *JUND*, *NFKB1*, *NFKB2*, *PTGS1*, *PTGS2*, *REL*, *RELA*, *RELB*, and *TNF*. All primary analyses without additional covariates were tested by a single *p*-value of .05 for significance. As indicated, subsequent sensitivity analyses additionally controlled for race/ethnicity (white, Latinx, Black or African American, multi-racial), BMI, pubertal development, nicotine use, alcohol use, recent illness symptoms at the time of blood sampling, history of trauma, and depressive symptoms.

This approach is consistent with prior research relating gene expression to behavioral processes (e.g., Cole *et al.*, 2005), because genes (unlike Likert scale items) are fairly heteroscedastic (variances differ by >10-fold). Treating them akin to a repeated measures "outcome" allows the specification of a variance-covariance matrix in the mixed effect linear model that accommodates both the heteroscedasticity across genes and the correlations among those genes, driven by their common regulation by shared proinflammatory transcription factors. While possible to average the 15 genes together to form a single composite summary score (in which case the number of observations would equal number of subjects), the composite would be biased by the heteroscedasticity across genes, and it would end up reflecting primarily the few genes with greatest variance while under-representing the many genes with lesser variance.

However, an alternative is to standardize the genes' variance and then compute a 1-number composite. Therefore, secondary logistic regression analyses were conducted to verify results from

Table 1. Sample rates of suicidal ideation, suicidal behavior, and nonsuicidal injury

	Prior to Baseline	4-Month Follow-Up	8-Month Follow-Up	12-Month Follow-Up	Follow-Up Aggregate
Suicidal Ideation	46.7% (<i>n</i> = 98)	18.3% (<i>n</i> = 36)	18.4% (<i>n</i> = 34)	14.3% (<i>n</i> = 33)	27.1% (<i>n</i> = 57)
Suicidal Behavior	29.0% (<i>n</i> = 61)	2.6% (<i>n</i> = 6)	2.6% (<i>n</i> = 6)	1.7% (<i>n</i> = 4)	6.7% (<i>n</i> = 14)
Nonsuicidal Self-Injury	34.2% (<i>n</i> = 77)	12.6% (<i>n</i> = 29)	9.1% (<i>n</i> = 21)	10.4% (<i>n</i> = 24)	20.9% (<i>n</i> = 48)

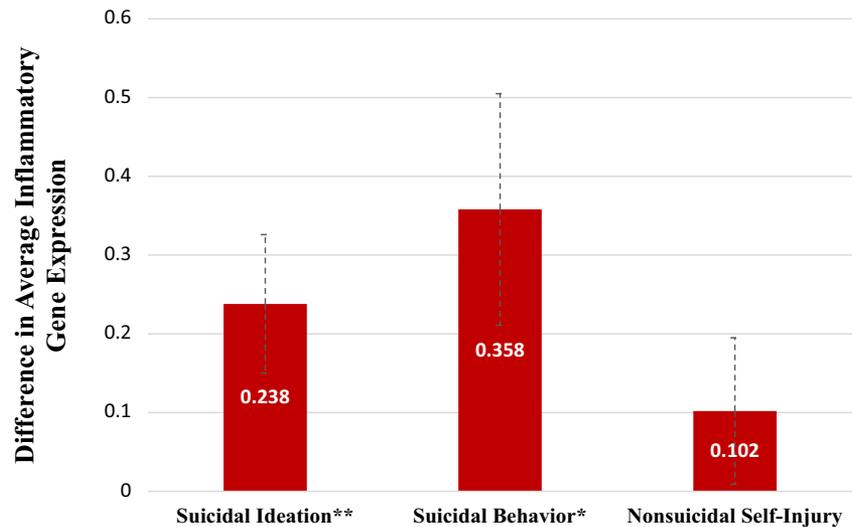


Figure 1. Difference inflammatory gene expression in adolescents reporting SITB relative to those not reporting SITB over 12-months. SITB = self-injurious thoughts and behaviors. * $p < .05$; ** $p < .01$.

primary analyses by generating a z-score standardized composite score that averaged across the 15 analyzed mRNA transcripts and testing for association with dichotomized follow-up STB and NSSI (present/absent) while controlling for baseline STB or NSSI, race/ethnicity, BMI, pubertal development, nicotine use, alcohol use, recent illness symptoms at the time of blood sampling, and where indicated, depressive symptoms and history of trauma. In these logistic models, prospective STB and NSSI were treated as dependent variables in contrast to the mixed linear effect models. It is important to note that the primary analysis using unstandardized data is typically more accepted due to its higher degree of correlation with other measures of inflammation (e.g., Cole et al., 2020), and therefore secondary analyses were used largely to corroborate the primary findings. Secondary analysis models were fit using SAS PROC LOGISTIC.

Additionally, to determine whether any observed differences in proinflammatory gene expression might stem from differences in monocyte abundance within the circulating blood cell pool, parallel analyses of *CD14* mRNA abundance were also conducted. Models were estimated using SAS PROC MIXED with mRNA abundance data mean-centered to facilitate maximum likelihood estimation and a compound symmetry covariance matrix to control for correlation among residuals across the 15 gene transcripts analyzed.

Results

Descriptive statistics

Baseline depressive symptoms of the present sample were mostly in the minimal to moderate range of severity ($M = 13.12$, $SD = 10.68$), with 13.7% of adolescents scoring above the cutoff point suggestive of clinical depression (Thabrew et al., 2018). Regarding childhood trauma ($M_{total} = 48.02$, $SD = 16.44$), 54.8% of

participants reported having experienced one or more type of early-life traumatic event (Bernstein et al., 2003), with subtype rates varying in prevalence: 15.3% for emotional neglect, 19.9% for physical abuse, 22.6% for sexual abuse, 26.3% for physical neglect, and 30.9% for emotional abuse.

Rates of suicidal ideation at baseline ($n = 98$, 46.7% of total sample) and across the 12-month follow-up assessment ($n = 57$, 27.1% of total sample), were high, reflecting the elevated risk for suicide in the sample. This was also true of suicidal behavior at baseline ($n = 61$, 29.0% of total sample) and across the 12-month follow-up period ($n = 14$, 6.7% of total sample), as well as NSSI at baseline ($n = 77$, 34.2% of total sample) and across 12-months follow-up ($n = 48$, 20.9% of total sample). Sample-wide rates of suicidal ideation, suicidal behavior, and nonsuicidal self-injury over each follow-up interval were fairly consistent (Table 1), with 80.7%, 14.3%, and 33.7% of these participants reporting suicidal ideation, suicidal behavior, or NSSI respectively at two or more timepoints. Of note, rates of suicidal ideation, suicidal behavior, and NSSI displayed some variability across the three timepoints. While some appear to be slightly declining (e.g., suicidal ideation), there is some prior evidence to suggest that these may reflect temporary remission in STB following an acute crisis (Prinstein et al., 2008), making it difficult to fully characterize the trajectory of STB in the current sample.

Risk for future suicidal ideation

Primary analyses identified a significant association between average expression of 15 proinflammatory genes at baseline and suicidal ideation during the 12-month follow-up period while controlling for suicidal ideation at baseline (.238 log₂ mRNA abundance / [SI unit] \pm .088 SE, $t(2926) = 2.71$, $p = .007$; Figure 1). Similar results emerged from sensitivity analyses that controlled for youths' CTQ scores (.244 \pm .087, $t(2842) = 2.79$, $p = .005$),

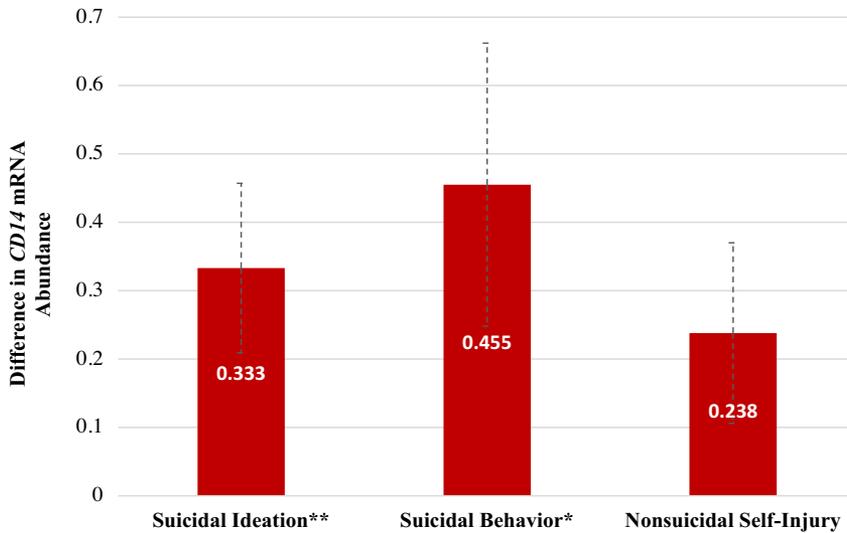


Figure 2. Difference in CD14 mRNA abundance in adolescents reporting SITB relative to those not reporting SITB over 12-months. SITB = self-injurious thoughts and behaviors. * $p < .05$; ** $p < .01$.

depressive symptoms ($.225 \pm .080$, $t(2926) = 2.53$, $p = .012$), and race/ethnicity, pubertal development, BMI, nicotine use, alcohol use, and recent illness symptoms prior to blood sampling ($.181 \pm .086$, $t(2814) = 2.11$, $p = .035$). Similar results also emerged from secondary logistic regression analyses that formed a single z-score composite of the 15 proinflammatory gene expression measures and tested for prediction of suicidal ideation during the 12-month follow-up period while controlling for suicidal ideation at baseline (OR = 1.61, 95% CI [1.12, 2.31], $X^2(1) = 6.68$, $p = .010$), or additionally controlling for race/ethnicity, pubertal development, BMI, nicotine use, alcohol use, and recent illness symptoms prior to blood sampling (1.51 [1.01, 2.05], $X^2(1) = 4.06$, $p = .044$), or the same covariates supplemented by CTQ scores (1.54 [1.03, 2.31], $X^2(1) = 4.43$, $p = .035$) or depressive symptoms (1.51 [1.00, 2.27], $X^2(1) = 3.86$, $p = .050$).

Risk for future suicidal behavior

Analyses also identified a significant association between proinflammatory gene expression at baseline and suicidal behavior during the 12-month follow-up period while controlling for suicidal behavior at baseline ($.358 \pm .147$, $t(2786) = 2.43$, $p = .015$; Figure 1). Similar results emerged from sensitivity analyses that controlled for CTQ scores ($.329 \pm .149$, $t(2715) = 2.21$, $p = .027$), depressive symptoms ($.350 \pm .148$, $t(2786) = 2.36$, $p = .019$), and race/ethnicity, pubertal development, BMI, nicotine use, alcohol use, and recent illness symptoms prior to blood sampling ($.323 \pm .145$, $t(2673) = 2.22$, $p = .026$). Similar results also emerged from secondary logistic regression analyses predicting suicidal behavior during the 12-month follow-up period from proinflammatory mRNA abundance while controlling for suicidal behavior at baseline (2.24 [1.12, 4.49], $X^2(1) = 10.23$, $p = .001$), or additionally controlling for race/ethnicity, pubertal development, BMI, nicotine use, alcohol use, and recent illness symptoms prior to blood sampling (2.68 [1.14, 6.32], $X^2(1) = 5.10$, $p = .024$), or the same covariates supplemented by CTQ scores (2.86 [1.16, 7.03], $X^2(1) = 5.24$, $p = .022$) or depressive symptoms (2.89 [1.18, 7.06], $X^2(1) = 5.40$, $p = .020$).

Risk for future nonsuicidal self-injurious behavior

To determine the specificity of associations between inflammatory gene expression and STB, secondary analyses examined risk for NSSI during the 12-month follow-up period while controlling for

NSSI at baseline. Results showed no significant association ($.102 \pm .093$, $t(2926) = 1.09$, $p = .277$; Figure 1), and similar findings emerged from sensitivity analyses that controlled for CTQ scores ($.089 \pm .094$, $t(2842) = 0.95$, $p = .344$), depressive symptoms ($.087 \pm .094$, $t(2926) = 0.92$, $p = .355$), and race/ethnicity, pubertal development, BMI, nicotine use, alcohol use, and recent illness symptoms prior to blood sampling ($.058 \pm .092$, $t(2814) = 0.63$, $p = .529$). Similar nonsignificant results emerged from secondary logistic regression analyses predicting nonsuicidal self-injury during the 12-month follow-up period from proinflammatory mRNA abundance while controlling for nonsuicidal self-injury at baseline (1.23 [0.85, 1.77], $X^2(1) = 1.19$, $p = .276$), or additionally controlling for race/ethnicity, pubertal development, BMI, nicotine use, alcohol use, and recent illness symptoms prior to blood sampling (1.15 [0.75, 1.75], $X^2(1) = 0.39$, $p = .531$), or the same covariates supplemented by CTQ scores (1.11 [0.72, 1.70], $X^2(1) = 0.21$, $p = .648$) or depressive symptoms (1.12 [0.73, 1.72], $X^2(1) = 0.25$, $p = .615$).

Cellular mechanisms

Finally, to investigate whether the observed associations involving proinflammatory gene expression might stem from differences in monocyte abundance within the circulating blood cell pool, we analyzed the abundance of *CD14* transcripts encoding the primary cell surface protein marker for monocytes. Monocytes represent the predominate cell type expressing proinflammatory gene transcripts among peripheral blood mononuclear cells and serve as key mediators of the stress-induced inflammatory response. Results indicated elevated *CD14* mRNA abundance in association with both suicidal ideation (controlling for baseline suicidal ideation, $.333 \log_2$ CD14 mRNA abundance / [SI unit] $\pm .124$, $t(207) = 2.69$, $p = .008$) and suicidal behavior ($.455 \pm .207$, $t(197) = 2.20$, $p = .029$), but no significant association with NSSI ($.238 \pm .132$, $t(207) = 1.80$, $p = .073$), indicating possible biological mediation of suicidal ideation and behavior by activation of innate immune cells. These results highlighting differences in *CD14* mRNA abundance are illustrated in Figure 2. Similar results emerged from logistic regression analyses that used standardized *CD14* mRNA abundance to predict follow-up suicidal ideation (controlling for baseline suicidal ideation; OR 1.74 per SD *CD14*, 95% CI [1.17, 2.58], $X^2(1) = 7.43$, $p = .006$), suicidal behavior (2.53

[1.13, 5.67], $X^2(1) = 5.07$, $p = .024$), and NSSI (1.46 [0.98, 2.17], $X^2(1) = 3.43$, $p = .064$), respectively. Results showed no significant prediction of any suicidality outcome by *CD16* (above and beyond general monocyte abundance marked by *CD14*), suggesting that general monocyte abundance is more predictive of suicidality outcomes than is the relative prevalence of classical vs non-classical monocyte subsets. Results also showed no significant prediction of any suicidality outcome by markers of other leukocyte subsets (*T* cells, including *CD4+* and *CD8+* *T* cells subsets, *B* cells, *NK* cells; all tested in parallel and adjusted for multiple testing).

Discussion

The present study represents a novel investigation of the role of inflammatory biology in prospectively predicting risk for STB among adolescent girls. Consistent with theories suggesting that dysregulated stress biology confers increased risk for poor mental and physical health in general (Slavich et al., 2023b; Slavich, 2020, 2022) and suicide in particular (Miller & Prinstein, 2019), we examined whether upregulated inflammatory gene expression was related to STB in a diverse adolescent sample. Using a longitudinal, multi-method design with a population at high-risk for STB, it was examined whether the expression of indicator proinflammatory genes at baseline was associated with heightened risk for prospective STB over 12 months, after controlling for lifetime suicidality.

Confirming study hypotheses, we found that elevated expression of proinflammatory genes in circulating blood cells was associated with elevated risk of suicidal ideation and suicidal behavior over the 12-month follow-up period in a sample of adolescent girls at increased risk for suicide. These associations were specific to STB, as no similar association was observed for NSSI. Moreover, these effects were robust while controlling for a variety of other risk factors that affect the risk of STB, including childhood trauma, current depressive symptoms, and demographic and health-behavior covariates. Consistent with a key role for myeloid lineage immune cells in mediating stress-induced transcriptional responses (Heidt et al., 2014; Powell et al., 2013; Slavich & Cole, 2013), these data also link STB to elevated prevalence of monocytes within the circulating leukocyte pool, as indicated by elevated *CD14* mRNA abundance. These findings are consistent with the theory that increased inflammatory signaling is one possible pathway conferring heightened risk for STB (Slavich & Auerbach, 2018), and this may be particularly true in the vulnerable population of adolescent girls. Future work specifically examining this mediation pathway is a critical next step for this literature. Additional secondary analyses using logistic regression models with standardized composite *z*-score to represent average mRNA transcript expression confirmed the present findings. Odds ratios in these models ranged from 1.5 to 3.0, further underscoring the significant differences in prospective risk for STB depending on inflammatory gene signaling.

Multiple interpretations may explain why upregulated inflammatory gene expression is associated with risk for suicide among adolescents. For example, elevated inflammatory signaling is implicated in the occurrence of dysregulated neural processes, such as poorer executive functioning and emotion regulation (Nusslock & Miller, 2016), within the prefrontal cortex. Executive functioning deficits, directly implicated in impulsive behaviors and decision-making abilities, are posited to contribute to risk for self-injurious behavior among adolescents (Fikke et al., 2011; Onat et al., 2019). This is especially true for emotion regulation and risk for STBs

(for review, see Colmenero-Navarrete et al., 2022) given that adolescents are developmentally predisposed to such difficulties. Another possibility is that inflammation, elsewhere prospectively linked to depression and behavioral correlates of depression (Kuhlman et al., 2020), may predispose adolescents to maladaptive behaviors such as STB. Put another way, although immune system activation is designed to help prepare and protect individuals in the face of threat (e.g., social stress), exaggerated proinflammatory activity in response to interpersonal stressors may prompt further and higher intensity emotional, cognitive, and behavioral responses. Adolescents who might otherwise ignore or adequately cope with interpersonal difficulties could experience heightened emotional reactivity, cognitive perseveration, or need to behaviorally respond to such threats. Suicidal thoughts and behaviors, as well as self-harm, could be conceptualized as a means of coping with this increased physiological arousal and associated inflammatory processes. Although perhaps counterintuitive, self-harm can be used by individuals as a relief or distraction from high intensity emotions, while STB could play a role akin to avoidant coping in the face of stress. However, such hypotheses and associated empirical support requires further examination, particularly in adolescence.

Several limitations of this study should be noted. First, STBs were assessed longitudinally but inflammatory gene expression was only at baseline. Second, life stressors between baseline and the 12-month follow-up period were not included in the present analyses, and it is possible that these stressors, as well as other biobehavioral factors, could have moderated the association between inflammatory gene expression and STBs (Alley et al., *in press*). Third, the assessments of inflammatory biology were based on peripheral assessments. It is possible that sampling neuroinflammation could yield different results, although this approach is presently very difficult. Fourth, additional research is needed to investigate the generalizability of these findings to males as well as to other populations and age groups. Given the exceptionally high rates of STB among gender diverse youth in particular (e.g., Toomey et al., 2018), studies examining the role of proinflammatory gene expression on suicide risk in this subpopulation is needed. Finally, while consistent with prior work with similar data, the present paper collapsed its longitudinal STB data over the entirety of the 12-month follow-up period due to its limited sample size and relatively low rates of STB at each follow-up point. Future work with more data points would ideally utilize repeated measures STB data at varied intervals to examine and differentiate how STB risk varies longitudinally in relation to inflammatory gene expression over time.

Notwithstanding these limitations, this study is the first to examine whether proinflammatory gene expression is related to prospective suicide risk in an adolescent sample. The findings are consistent with recent adolescent suicide theory (Miller & Prinstein, 2019) and broader theories of human social genomics (Slavich & Cole, 2013), and they extend the literature on inflammation and suicide risk by focusing on the molecular signaling pathways underlying inflammatory activity and by demonstrating prospective associations between inflammation and STBs. Inflammatory gene expression is distinct and non-redundant from other existing biomarkers of related inflammatory mechanisms (e.g., plasma proteins such as proinflammatory cytokines) and therefore requires future inquiry. Interestingly, patterns of results from other related work suggest that inflammatory processes (e.g., cellular mechanisms vs. plasma proteins) function in unique ways that are not always correlated

(Lindsay et al., 2024). This point further underscores the importance of investigation of various biomarkers related to inflammation, as they are in fact diverse, distinct, and non-redundant from one another. Finally, looking forward, an additional point of inquiry would be to examine how inflammatory biology interacts with recent acute life stressors to precipitate STB, as research has found that adolescent suicidal crises often follow socially distressing life events (e.g., Massing-Schaffer et al., 2019) and sudden increases in depressive symptoms (Murphy et al., 2013; Slavich et al., 2009).

In sum, the present results support that inflammatory biology, as represented by the average expression of genes related to proinflammatory immunological processes, may be one potential mechanism that confers risk for suicide in adolescence. Further, inflammatory gene expression, whether considered as the expression of multiple genes or site specific-genes related to monocyte abundance in the circulating leukocyte pool (i.e., *CD 14*), may help connect the currently disparate fields of human social genomics and suicide research. Specifically, these findings indicate that inflammatory biology may confer heightened risk for STB among adolescents at high risk for suicide, and this extends existing research by focusing on the molecular signaling pathways underlying inflammatory biology and by demonstrating these associations prospectively. These results thus represent an important step forward in service of better understanding biological processes that are associated with increases in suicidal ideation, suicidal behavior, and deaths by suicide in adolescence.

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