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Interpersonal life stress, inflammation, and depression in adolescence: Testing Social Signal Transduction Theory of Depression

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Abstract

Background: Depression rates increase markedly for girls across the adolescent transition, but the social-environmental and biological processes underlying this phenomenon remain unclear. To address this issue, we tested a key hypothesis from Social Signal Transduction Theory of Depression, which posits that individuals who mount stronger inflammatory responses to social stress should exhibit greater increases in depressive symptoms following interpersonal life stress exposure than those who mount weaker inflammatory responses to such stress.

Method: Participants were 116 adolescent girls (M_{age} = 14.71) at risk for psychopathology, defined as having a history of mental health concerns (e.g., psychiatric treatment, significant symptoms) over the past 2 years. At baseline, we characterized their inflammatory reactivity to social stress by quantifying their salivary proinflammatory cytokine responses to a laboratory-based social stressor. Then, 9 months later, we assessed the interpersonal and noninterpersonal stressful life events that they experienced over the prior 9 months using an interview-based measure of life stress.

Results: As hypothesized, greater interpersonal life stress exposure was associated with significant increases in depression over time, but only for girls exhibiting stronger salivary tumor necrosis factor-α and interleukin-1β reactivity to social stress. In contrast, noninterpersonal stress exposure was unrelated to changes in depression longitudinally, both alone and when combined with youths' cytokine reactivity scores.

Discussion: These results are consistent with Social Signal Transduction Theory of Depression and suggest that heightened inflammatory reactivity to social stress may increase adolescents' risk for depression. Consequently, it may be possible to reduce depression risk by modifying inflammatory responses to social stress.

KEYWORDS

cytokines, development, disease, inflammation, major depressive disorder, risk, social stress, vulnerability

1 | INTRODUCTION

Depression is a very common, often recurrent psychiatric condition that frequently emerges in early adolescence and is associated with substantial social and economic costs across the lifespan (Auerbach, Admon, & Pizzagalli, 2014; Monroe, Slavich, & Georgiades, 2014). Cognitive and affective symptoms of depression such as sad mood, hopelessness, and suicidal ideation can greatly impact an individual's life, but this impact is further compounded by the fact that depression is associated with increased risk for developing several serious somatic and physical health problems that have an immunologic basis, including asthma, chronic pain, cardiovascular disease, and autoimmune and neurodegenerative disorders (Slavich, 2020). Together, these clinical characteristics combine to make depression a leading cause of nonfatal disease burden worldwide (Ferrari et al., 2013).

Although depression can impact all persons, females are disproportionately affected. During childhood, only 3% of boys and girls meet criteria for major depressive disorder (MDD) over the past year (Merikangas et al., 2010). Following the pubertal transition, though, depression rates increase nearly fivefold overall and, in addition, girls suddenly become twice as likely to develop MDD on average relative to boys (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015). Researchers have identified a wide variety of mechanisms that may underlie this dramatic increase in depression risk for adolescent girls, including stress generation, heightened neurocognitive sensitivity to threat, and exaggerated hypothalamic-pituitary-adrenal axis reactivity (Allen & Dahl, 2015; Gibb, Beevers, & McGeary, 2013; Gold, 2015; Hammen, 2006; Hankin, 2015; Rudolph, 2008). For the most part, though, this work has examined processes that are not mechanistically capable of directly inducing depressive symptoms. As a result, additional research is needed to examine how social-environmental factors interact with biological processes to predict changes in depression. This work would benefit from carefully assessing the different life stressors that youth experience, by characterizing stress-induced biological changes that can evoke depressive symptoms, and by the following youth longitudinally to investigate how stress-biology interactions predict the emergence of depressive symptoms over time.

1.1 | Interpersonal life stress and depression

One of the strongest proximal risk factors for depression involves experiencing a recent interpersonal stressful life event (Slavich, 2016; Slavich, Monroe, & Gotlib, 2011; Slavich, O'Donovan, Epel, & Kemeny, 2010a). In a recent study that carefully dated both the occurrence of different stressful life events and youths' development of depression, for example, interpersonal life events were found to be statistically unique predictors of subsequent onset of MDD across two adolescent samples; in contrast, noninterpersonal events were unrelated to depression (Vrshek-Schallhorn et al., 2015). In a second longitudinal study, exposure to interpersonal life events interacted with a multilocus genetic profile score to prospectively predict increases in depressive symptoms in adolescents but, again, these effects were specific to interpersonal stressors (Feurer et al., 2017; see also Starr et al., 2017; Starr, Dienes, Li, & Shaw, 2019). Finally, a third study found that interpersonal life events involving targeted rejection precipitated onset of depression three times faster than other types of major life events (Slavich, Thornton, Torres, Monroe, & Gotlib, 2009; see also Massing-Schaffer et al., 2019). Moreover, when the impact of these stressors has been examined in youth assessed longitudinally, only interpersonal life events involving targeted rejection have been found to predict within-person changes in intracellular signaling molecules that are implicated in depression pathogenesis (Murphy, Slavich, Chen, & Miller, 2015; Murphy, Slavich, Rohleder, & Miller, 2013).

Relatedly, three lines of research suggest that interpersonal life stress may be especially relevant for understanding risk for depression in adolescent girls. First, adolescent girls have been found to experience more interpersonal stressors than both preadolescent girls and adolescent boys (Hankin, Mermelstein, & Roesch, 2007). Second, adolescent girls exhibit greater investment in intimate peer relationships and sensitivity to relational conflict than adolescent boys (Larson, 2001; Rudolph, 2002). Finally, adolescent girls show greater neural sensitivity to negative social information than adolescent boys (Guyer, McClure-Tone, Shiffron, Pine, & Nelson, 2009; Somerville, 2013). Consistent with this research, several studies have found that interpersonal stressors are more strongly related to MDD in adolescent girls versus boys (e.g., Hankin et al., 2007; Rudolph, Flynn, Abaied, Groot, & Thompson, 2009). In one of the most well-controlled studies on this topic, for example, an analysis of 1,057 opposite-sex dizygotic twin pairs revealed that four out of the five factors that significantly predicted greater liability for MDD in females versus males involved the continuity and quality of interpersonal relationships (Kendler & Gardner, 2014).

1.2 | Inflammation and depression

These literatures provide converging evidence indicating that interpersonal life stress exposure is an especially strong predictor of depression for adolescent girls. However, research has generally struggled to identify biological processes that are both upregulated by interpersonal stress *and* mechanistically involved in evoking depression. Stress reliably increases cortisol production in many individuals (Zorn et al., 2017), for example, but does not itself induce depressive symptoms. One of the most important discoveries in depression research has thus involved the recent realization that components of the immune system involved in inflammation are strongly upregulated by social stress and that inflammatory mediators can, in turn, induce depressive symptoms (Slavich & Irwin, 2014). Consequently, there is now substantial interest in better understanding the etiologic role that inflammatory processes may play in depression (Miller, Maletic, & Raison, 2009; Mills, Scott, Wray, Cohen-Woods, & Baune, 2013).

Inflammatory activity has been most commonly assessed in depression research by quantifying levels of the three proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines are often derived from serum. An alternative approach that involves assessing cytokines in saliva has been criticized for being only moderately correlated with serum levels (Byrne et al., 2013), reflective of local immune activity (Riis, Granger, DiPietro, Bandeen-Roche, & Johnson, 2015), and sensitive to several factors including sleep quality, oral health/hygiene, sampling method, assay technique, and salivary flow rate (Slavish, Graham-Engeland, Smyth, & Engeland, 2015). However, several lines of research support their use in studies of stress, inflammation, and depression. First, salivary cytokines are both upregulated by laboratory-based social stressors (Newton et al., 2017; Shields, Young Kuchenbecker, Pressman, Sumida, & Slavich, 2016) and are also associated with the same types of naturalistic stressors that strongly predict depression (Szabo, Fernandez-Botran, & Newton, 2019; Tyrka, Parade, Valentine, Eslinger, & Seifer, 2015). Second, individual differences in salivary cytokine reactivity are strongly correlated with individuals' neural, emotional, and physiological responses to acute social stress (Izawa et al., 2013; Newton et al., 2017; Quinn, Stanton, Slavich, & Joormann, 2020; Slavich, Way, Eisenberger, & Taylor, 2010b), suggesting that they are not simply a reflection of local inflammation in the oral cavity. Third, salivary cytokines are associated with several somatic disease conditions (e.g., asthma, rheumatoid arthritis, cardiovascular disease, diabetes, and cancer; Zhang et al., 2016) in addition to depressive symptoms (Keller, El-Sheikh, Vaughn, & Granger, 2010). Finally, intervention studies have shown that salivary cytokine levels subside during mindfulness training for depression (Walsh, Eisenlohr-Moul, & Baer, 2016).

In turn, multiple findings suggest a link between life stress, inflammatory activity, and depression more broadly. First, interpersonal stressors are known to strongly upregulate proinflammatory cytokine activity (Segerstrom & Miller, 2004; Steptoe, Hamer, & Chida, 2007), and such levels have, in turn, been found to mediate stress-related changes in depression over time (Kautz et al., in press). Second, experimental animal model and human studies have shown that these inflammatory mediators alter neurobiological processes that are implicated in depression, and that they promote depression-like symptoms in rodents and MDD in humans (Capuron & Miller, 2011; Miller et al., 2009). Finally, concentrations of the sex hormones estrogen and progesterone, which undergo major changes as girls become more pubertally developed, can enhance the depressogenic potential of cytokines (Oertelt-Prigione, 2012; Schwarz & Bilbo, 2012), and this may explain why rates of MDD increase so substantially for adolescent girls who have recently experienced interpersonal life stress (Derry, Padin, Kuo, Hughes, & Kiecolt-Glaser, 2015).

1.3 | Social Signal Transduction Theory of Depression

In an attempt to integrate these findings and develop a multilevel working model of how life stress promotes inflammation and risk for depression, Slavich and Irwin (2014) proposed Social Signal Transduction Theory of Depression, which posits that interpersonal life stressors activate inflammatory processes that, in turn, play a role in the development of depressive symptoms for at least some people. According to this theory, individuals who mount stronger inflammatory responses to social stress should exhibit greater increases in depressive symptoms following recent interpersonal life stress exposure as compared to those who mount weaker inflammatory responses to social stress. Testing this hypothesis requires combining measures of life stress exposure and social stress-induced inflammatory reactivity with longitudinal methods to assess changes in depressive symptoms over time, but to date, only a limited number of longitudinal studies have been conducted that combine assessments of both recent life stress exposure and youths' proinflammatory cytokine reactivity to social stress.

1.4 | Present study

To address this issue, we examined how recent life stress exposure and social stress-induced inflammatory reactivity were associated with changes in depressive symptoms over 9 months in a longitudinal study of adolescent girls oversampled to be at risk for psychopathology. The study design thus provided an opportunity to investigate associations between different types of life stress exposure and depression-relevant biological processes in a population of maximal clinical relevance. We used a well-validated, interview-based measure of life stress to identify the recent interpersonal and noninterpersonal life events that youth experienced during the study. In addition, we characterized each adolescent's inflammatory reactivity to social stress by collecting oral measures of the key inflammatory cytokines TNF-α, IL-1β, and IL-6 before and after each participant completed a standardized, laboratory-based social stress task.

Consistent with Social Signal Transduction Theory of Depression, we hypothesized that greater interpersonal life stress exposure would be associated with significant increases in depressive symptoms over time for girls exhibiting stronger salivary cytokine responses to social stress, but not for girls exhibiting weaker salivary cytokine responses to social stress. In contrast, we hypothesized that noninterpersonal life stress exposure would be unrelated to changes in depressive symptoms over time.

2 | METHOD

2.1 | Participants

Participants were 116 adolescent girls (M_{age} = 14.71, standard deviation [*SD*] = 1.40; range: 12–16 years old), drawn from a larger study of girls at risk for psychopathology. The sample was ethnically diverse, with 65.5% self-identifying as Caucasian, 24.1% as African American, 9.5% as multiracial, and 0.9% as Hispanic/Latina.

Following NIMH/RDoC recommendations (Sanislow et al., 2010), we adopted a transdiagnostic approach that involved studying adolescents exhibiting various levels of symptoms across different diagnostic categories. According to primary caregiver reports on the Behavioral Assessment System for Children (Reynolds & Kamphaus, 1992), at study entry, 41.4% of youth exhibited clinical symptoms of psychopathology (i.e., *T* scores ≥70; 20.7% attention problems, 17.2% conduct disorder, 17.2% hyperactivity, 12.1% anxiety, and 8.6% depression). Additional descriptive characteristics are presented in Table 1.

2.2 | Recruitment and selection

Participants were recruited from local high schools, community advertisements, community mental health agencies, and inpatient and outpatient clinics. A telephone screening interview using a modified Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present (K-SADS; Kaufman et al., 1997) was administered to caregivers by trained interviewers. To be eligible, girls had to (a) be 12–16 years old and (b) have a history of mental health concerns over the past 2 years, defined as having significant symptoms or a prior diagnosis of, or prior treatment for, mood or anxiety disorders, disruptive behavior disorders, or attention-deficit/hyperactivity disorder (ADHD), as indicated by the K-SADS. Girls exhibiting any indication of prior or current psychosis, mental retardation, or a pervasive developmental disorder were excluded. Other factors that could have influenced cytokine or depression levels were assessed and evaluated as potential covariates—specifically, age, ethnicity, pubertal status, body mass index (BMI), same-day caffeine intake, general (i.e., nonpsychotropic) medication use, psychotropic medication use, oral contraceptive use, sleep problems, smoking status, and recent illness symptoms (see below).

TABLE 1 Descriptive characteristics of the sample and main study variables

	Mean (*SD*) or # of participants [%]	Range	Skewness
Demographic characteristics			
Age	14.71 (1.40)	12–17[a]	−0.27
Ethnicity			
White	76 [65.5]	–	–
Non-white	40 [34.5]	–	–
Life stress			
Interpersonal life stress exposure	22.2 (13.25)	0–59	0.74
Noninterpersonal life stress exposure	9.49 (5.37)	0–27.50	0.64
Proinflammatory cytokines[b]			
Tumor necrosis factor-α (TNF-α)			
Presocial stress task	0.60 (0.43)	−0.96–1.65	−0.60
Postsocial stress task	0.58 (0.42)	−0.70–1.46	−0.74
Interleukin-1β (IL-1β)			
Presocial stress task	2.57 (0.45)	1.10–3.43	−0.56
Postsocial stress task	2.60 (0.47)	−0.16–3.60	−1.96
Interleukin-6 (IL-6)			
Presocial stress task	0.59 (0.43)	−0.43–1.87	0.36
Postsocial stress task	0.62 (0.45)	−0.43–1.83	0.31
Pubertal status	3.41 (0.49)	1.60–4.00	−1.41
Depressive symptoms			
Baseline	0.54 (0.42)	0–1.79	0.85
Follow-up (9 months later)	0.43 (0.38)	0–1.59	1.00
Covariates evaluated			
Salivary assessment timing (hours)[c]	5.57 (1.61)	3–11	0.76
Body mass index	22.88 (5.83)	15.36–41.81	1.17
Same-day caffeine intake	11 [9.5][d]	–	–
General medication use	44 [37.9]	–	–
Psychotropic medication use	65 [56]	–	–
Oral contraceptive use	17 [14.7]	–	–
Sleep problems (severity)	1.27 (0.98)	0–3	0.34
Smoking status	8 [6.9]	–	–
Recent illness symptoms	13 [11.2]	–	–

Abbreviation: *SD*, standard deviation.

[a]One participant turned 17 years old during the study. Participants' ages thus ranged from 12 to 17 years old.

[b]Cytokines values were log-transformed to correct for skewness.

[c]Calculated by subtracting youths' awakening time from the time of their first saliva assessment.

[d]Bracketed percentages here and below refer to the % of participants endorsing the covariate, alongside the corresponding *n*.

2.3 | Study design

Written informed consent was obtained from caregivers, and assent from adolescents, during the baseline study visit. Adolescents then completed a baseline depression assessment and underwent a laboratory-based social stress task, before and after which their cytokine levels were quantified (see below). Nine months later, telephone-based follow-up interviews were conducted by trained interviewers to assess participants' depressive symptoms at follow-up and all of the stressful life events that they experienced from baseline to follow-up (i.e., 9 months later). Participants were compensated for their time, and all procedures were approved by the Institutional Review Board.

Given the goals of this study, we included in analyses all participants with life stress data at follow-up and depression data at baseline and follow-up who had also completed the cytokine assessment protocol ($N = 116$). Complete life stress and depression data were available for 73.9% of adolescents with available cytokine data, with missing data being due to youth withdrawing from the study ($n = 13$) or not completing the follow-up life stress interview ($n = 28$). Youth with ($n = 116$) and without ($n = 41$) complete data did not differ on age, ethnicity, depressive symptoms, salivary cytokine levels, or pubertal status ($ps > 0.08$).

2.4 | Life stress assessment

The stressful life events that adolescents experienced between baseline and the 9-month follow-up visit were assessed using the Youth Life Stress Interview (YLSI; Rudolph & Flynn, 2007). YLSI-trained interviewers conducted a 1–2 hr semi-structured interview with each adolescent to obtain extensive factual and contextual information about each life event that the youth experienced, in addition to all of the personal biographical details that would be necessary to make independent, contextually based stressor severity and content ratings. Following each session, the YLSI interviewer constructed a detailed stress exposure profile that summarized each participant's unique biographical information and the specific characteristics of each of the life events experienced. These detailed narratives were then presented to an independent panel of three to six expert YLSI raters who were kept blind to all factors that could potentially bias the life stress ratings, including participants' emotional reactions to the stressors, and their depressive symptom and cytokine scores. Consistent with YLSI guidelines, each rater independently judged the degree of negative impact/stress associated with each life event on a scale ranging from 1 (*no impact/stress*) to 5 (*severe impact/stress*); then, a final consensus rating was obtained for each life event following extensive group discussion, with higher scores representing greater life stress exposure.

Next, based on previously established procedures (Rudolph & Flynn, 2007), we employed a team-based consensus rating approach to code each life event as interpersonal (i.e., life events involving significant interaction between the youth and another person that directly affected their relationship) or noninterpersonal (i.e., all other events). Prototypic interpersonal life events included things like a serious argument, relationship breakup, or death of a close friend or loved one, whereas noninterpersonal life events included things like failing out of school, losing money, or getting laid off of work. Consistent with prior research (e.g., Hammen, Kim, Eberhart, & Brennan, 2009), events rated "1" were excluded because they had no impact or stress and are therefore not considered stressors. All of the remaining stress severity scores were, in turn, summed separately for interpersonal and noninterpersonal life events. The final scores used in analyses thus represented the sum of all of the final team-rated, consensually derived severity scores for interpersonal and noninterpersonal life events for each participant. To ensure the quality of these scores, 30% of all cases were randomly selected and then rerated by two independent life stress rating teams. This cross-check revealed that excellent reliability was achieved for both the life event severity scores (intraclass correlation coefficient [ICC] = 0.95) and for the coding of interpersonal versus noninterpersonal life stress (Cohen's $\kappa = 0.92$).

2.5 | Laboratory social stress task

Participants' salivary cytokine reactivity to social stress was quantified using a modified version of the laboratory-based Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) that was similar to what we and others have previously used in several studies (e.g., Giletta et al., 2018; Yim, Quas, Rush, Granger, & Skoluda, 2015). Participants were asked not to consume any caffeine, including chocolate or coffee, or to take any ADHD medication (if applicable) during the day of their study visit. Approximately 3 hr after beginning the visit, participants rinsed their mouths out under the direction of study staff and then entered a lab room where they were instructed to audition for a fictional reality show about how adolescents interact and make friends. A 1-min preparation period was followed by a 3-min speech. While preparing and delivering the speech, adolescents were seated facing a camera that was connected to a closed-circuit television screen that displayed their own live image. To enhance the social-evaluative nature of the experience, a young adult male "judge" was in the room while each girl gave her speech. The judge was trained to maintain eye contact and a neutral facial expression during the speech planning and delivery phase, and to write notes at regularly timed intervals during the speech, ostensibly evaluating the participant's performance. Compared to the standard TSST, we used the speech (but not math) task and a young adult male judge (instead of three raters) to make the stressor briefer and more interpersonally intimate and developmentally relevant. In prior studies, the TSST has been shown to trigger a 1.2–2.0 fold increase in proinflammatory cytokine activity at the group level, as well as substantial differences in cytokine reactivity across individuals (e.g., Quinn et al., 2020; Slavich et al., 2010b; for reviews, see Marsland, Walsh, Lockwood, & John-Henderson, 2017; Rohleder, 2014).

To ensure that the TSST induced a negative emotional response, we assessed participants' negative affect before and after the stressor using negative affect words from the Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988). Responses to each item were provided on a 1 (*very slightly or not*

at all) to 5 (*extremely*) scale and then averaged to create an index of negative affect, with higher scores indicating more negative affect. Internal consistency was acceptable for the pre-TSST scale ($\alpha = .72$) and very good for the post-TSST scale ($\alpha = .86$).

2.6 | Proinflammatory cytokine reactivity to social stress

Consistent with prior research describing the timing of inflammatory responses to acute social stress, we assessed each adolescent's salivary cytokine levels immediately before the social stress task and 40 min after the task when social stress-related cytokine levels have been shown to peak (Marsland et al., 2017), thus providing an index of participants' cytokine reactivity to social stress (Slavish et al., 2015; Steptoe et al., 2007). The cytokines TNF-α, IL-1β, and IL-6 were selected *a priori*, given their known responsivity to stress, involvement in the acute phase response, and relevance for depression (Schett, Elewaut, McInnes, Dayer, & Neurath, 2013; Slavich & Irwin, 2014). To control for possible diurnal rhythm effects on participants' cytokine levels, a timing variable was computed by subtracting adolescents' awakening time from the time of their first saliva assessment.

Saliva samples were obtained using a SalivaBio Oral Swab (Salimetrics, State College, PA) and were transferred to a −25°C freezer immediately after collection. Immunoassays were later conducted in a complete batch using a Bio-Plex 200 (Bio-Rad, Hercules, CA). Salivary cytokines were measured using high-sensitivity multiplex immunoassay kits (R&D Systems, Minneapolis, MN), which have a mean minimal detectable dose of 0.29 pg/ml for TNF-α, 0.08 pg/ml for IL-1β, and 0.14 pg/ml for IL-6. The mean intra-assay coefficients of variation reported by the manufacture are 5.3% for TNF-α and IL-1β, and 5.2% for IL-6, and the mean inter-assay coefficients of variation are 9.6% for TNF-α and IL-6, and 12.8% for IL-1β. Log-transformed cytokine values were used in analyses to correct for skewness.

To create a social stress-induced cytokine reactivity score for each participant, we computed standardized residual scores regressing adolescents' postsocial stress task cytokine levels on their presocial stress task levels. Compared to simple difference scores, which are an absolute measure of change, standardized residual scores indicate change *relative to the sample mean*. This statistical approach is preferred over using cytokine change scores or area under the curve because it accounts for differences in each person's baseline cytokine levels and thus enables investigators to examine associations between biological reactivity and depression levels "free of the influence of individual differences in baseline arousal" (Burt & Obradović, 2013, p. 39). Consistent with prior research (e.g., Slavich et al., 2010b) and suggested statistical protocol (Tabachnick & Fidell, 2013), reactivity scores >3 *SD*s from the mean ($n = 2$) were winsorized to improve the normality of the cytokine data distributions and limit the undue influence that extreme values could have on analyses.

2.7 | Depressive symptoms

Participants' levels of depression were assessed at baseline and at the 9-month follow-up visit with the well-validated Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988). Three items about suicide were excluded due to sensitivity. Participants indicated how often they experienced each symptom over the past 2 weeks on a 3-point scale, with higher scores representing greater depression severity. Responses were then averaged to obtain a depressive symptom severity score at each timepoint for each participant. Internal consistency for the MFQ was excellent at both baseline and at the 9-month follow-up visit ($\alpha = .94$ at both time-points).

2.8 | Covariates

Prior research has shown that inflammatory and depression levels can both differ substantially as a function of age, ethnicity, and pubertal status (Stowe, Peek, Cutchin, & Goodwin, 2010; Strine et al., 2008). We, therefore, included participants' age and ethnicity (White, non-White) as *a priori* covariates in all models testing our primary hypotheses, as well as pubertal status, which was assessed at baseline with the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988). The PDS includes items describing key aspects of development (i.e., body hair, skin changes, growth spurt, breast development, and menarche), and adolescents rated each item on a 4-point scale, ranging from 1 (*no development*) to 4 (*development seems complete*), with the exception of the menarche item, which was rated as 1 (*no*) or 4 (*yes*). Responses were then averaged to create an overall pubertal status score for each girl ($\alpha = .71$). Finally, we evaluated salivary assessment timing, as well as youths' current BMI, same-day caffeine intake, general medication use (e.g., for asthma, allergies, pain, cold symptoms), psychotropic medication use (e.g., for depression, anxiety), oral contraceptive use (yes/no), sleep problems (e.g., trouble getting to sleep), smoking status (yes/no), and recent illness symptoms as potential covariates. However, none of these factors were significantly related to youths' cytokine reactivity scores and were thus omitted (see Table S1). Importantly, however, models including these covariates yielded the same results.

2.9 | Statistical analysis

Primary analyses involved conducting two-step hierarchical linear regression models with depression scores at follow-up as the outcome in all models. Separate regression models were run for each cytokine. As described above, each model adjusted for three a priori covariates—namely, age, ethnicity, and pubertal status—by including these factors in Step 1 of the regression models. In Step 1, we also included participants' presocial stress task cytokine levels to control for the effect of individual differences in inflammatory activity before the social stressor on youths' depression scores at follow-up (Burt &

Obradović, 2013). Finally, baseline (i.e., Time 1) depression levels were also included in Step 1 so that the results would reflect *changes* in depressive symptoms over the 9-month study period.

To test our primary hypothesis that interpersonal life stress exposure interacts with social stress-induced cytokine reactivity to predict increases in depressive symptoms over time, we introduced two-way Interpersonal (or Noninterpersonal) Life Stress Exposure × Cytokine Reactivity to Social Stress interaction terms in Step 2 of each two-step hierarchical linear regression model. Multivariate outliers were inspected using Mahalanobis distance ($p < .001$), Cook's *D*, and standardized residuals (values >3 *SD*s from the mean), and cases containing outliers according to two or more of these methods ($n = 1$ for TNF-α; $n = 2$ for IL-1β) were removed to prevent the cases from unduly influencing the results. Significant interactions were probed by calculating simple slopes using previously developed tools (Preacher, Curran, & Bauer, 2006), and all predictors were grand-mean centered before analysis. Below, we present preliminary analyses first, followed by tests of the primary hypotheses.

3 | RESULTS

3.1 | Preliminary analyses

Descriptive statistics for the sample and main study variables are presented in Table 1, and zero-order correlations are presented in Table 2. A total of 1,432 YLSI-defined stressful life events were identified during the 9-month study period, 68.2% of which were rated as interpersonal and 31.8% of which were rated as non-interpersonal. Participants experienced an average of 8.42 life events (*SD* = 4.52), which included an average of 3.92 interpersonal life events (*SD* = 2.02) and 12.34 noninterpersonal life events (*SD* = 5.37). Almost all participants experienced at least one interpersonal life event (99.1%) and one noninterpersonal life event (98.3%).

With regard to the laboratory-based social stressor, as expected, the TSST successfully induced a negative emotional state, with negative emotions increasing significantly from pre-TSST ($M = 2.49$, $SD = 4.73$) to post-TSST ($M = 17.52$, $SD = 16.11$), $t(103) = -10.36$, $p < .001$. In terms of the inflammatory data, no significant effects were observed at the group level for changes in the three salivary cytokines in response to the laboratory-based social stressor [TNF-α: $t(112) = 1.49$, $p = .14$; IL-1β: $t(116) = -1.13$, $p = .26$; IL-6: $t(113) = -0.98$, $p = .33$]. As expected, however, many adolescents exhibited increased salivary cytokine levels in response to the stressor (% exhibiting an increase: TNF-α: 38.4%; IL-1β: 52.6%; IL-6: 51.3%). Moreover, substantial variability was observed in youths' social stress-induced cytokine reactivity (*SD*s for raw change scores: TNF-α: 5.26 pg/ml; IL-1β: 420.75 pg/ml; IL-6: 11.19 pg/ml). These cytokine responses did not differ as a function of youths' demographic characteristics, depressive symptoms, or pubertal status (all *p*s > 0.10). Finally, as would be expected, social stress-induced changes for the three salivary cytokines were all significantly inter-correlated (*r*s = .44–.48, *p*s < 0.001).

TABLE 2 Bivariate correlations among the main study variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	–												
2. Ethnicity	0.04	–											
3. Interpersonal life stress exposure	0.30**	0.13	–										
4. Noninterpersonal life stress exposure	0.25**	−0.12	0.28**	–									
5. Presocial stress TNF-α	0.02	0.21*	0.09	−0.03	–								
6. TNF-α reactivity to social stress	0.03	0.15	0.06	−0.02	0.000	–							
7. Presocial stress IL-1β	−0.05	0.23*	0.11	0.03	0.45***	0.06	–						
8. IL-1β reactivity to social stress	0.06	0.08	0.01	0.05	−0.19*	0.44***	−0.09	–					
9. Presocial stress IL-6	−0.05	0.12	0.13	0.03	0.31**	0.10	0.33***	−0.08	–				
10. IL-6 reactivity to social stress	−0.03	0.004	0.13	−0.04	−0.03	0.48***	0.07	0.45***	0.001	–			
11. Pubertal status	0.52***	0.05	0.22*	0.10	0.10	−0.01	0.13	0.03	0.02	0.02	–		
12. Depressive symptoms at baseline	0.20*	−0.04	0.18†	0.17†	−0.05	−0.03	0.07	−0.13	0.20*	0.001	0.06	–	
13. Depressive symptoms at follow-up	0.26**	0.04	0.46***	0.20*	−0.05	0.21*	0.03	0.05	0.13	0.07	0.28**	0.40***	–

Abbreviations: TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.
†$p < .10$.
*$p < .05$.
**$p < .01$.
***$p < .001$.

3.2 | Primary analyses

Next, we tested the primary *a priori* hypothesis that greater interpersonal life stress exposure would be associated with significant increases in depressive symptoms over time for girls exhibiting stronger cytokine responses to social stress, but not for those exhibiting weaker cytokine responses to social stress. The hierarchical linear regression models for interpersonal life stress exposure are presented in Table 3 and the models for noninterpersonal life stress exposure are shown in Table 4.

Focusing first on interpersonal life stress exposure, analyses revealed a significant Interpersonal Life Stress Exposure × Cytokine Reactivity to Social Stress interaction effect for TNF-α (see Table 3, Step 2). As hypothesized, and as depicted in Figure 1, greater interpersonal life stress exposure was associated with significant increases in depressive symptoms over time for girls exhibiting high TNF-α reactivity to social stress (simple slopes [standard error, *SE*]: 0.019 [0.003], $p < .001$) but not for girls exhibiting low TNF-α reactivity to social stress (simple slopes [*SE*]: 0.01 [0.003], $p = .08$). As shown in Table 3, Step 2, a similar effect was found for IL-1β. Specifically, greater interpersonal life stress exposure was associated with significant increases in depressive symptoms over time for girls exhibiting high IL-1β reactivity to the laboratory-based social stressor (simple slopes [*SE*]: 0.017 [0.003], $p < .001$) but not for girls exhibiting low IL-1β reactivity to the social stressor (simple slopes [*SE*]: 0.01 [0.002], $p = .101$). In contrast to TNF-α and IL-1β, no two-way interaction effect was found for IL-6 (see Table 3, Step 2). In sum, therefore, greater exposure to recent interpersonal life stress predicted increases in depressive symptoms over 9 months, but only for girls exhibiting heightened inflammatory reactivity to social stress, as indexed by TNF-α and IL-1β.

It is possible that noninterpersonal stressors also interact with cytokine reactivity to predict changes in depression over time. We thus re-ran the hierarchical linear regression models described above using noninterpersonal life stress exposure instead of interpersonal life stress exposure. As hypothesized, however, noninterpersonal stress exposure was not related to depressive symptoms in any of the models, either alone or in combination with adolescents' cytokine reactivity scores (see Table 4, Step 2).

Finally, we examined whether the significant effects observed above for interpersonal stress exposure were specific to participants' cytokine *reactivity* profiles. To do this, we re-ran the hierarchical linear regression models described above that included interpersonal life stress exposure, but instead of including participants' cytokine *reactivity* scores, we included their presocial stress task (i.e., basal) cytokine levels. As shown in Table 5, Step 2, however, no significant two-way interaction effects emerged, indicating that it is adolescents' inflammatory reactivity to social stress, not their basal inflammatory levels, that is relevant for predicting interpersonal stress-related increases in depressive symptoms over time.

4 | DISCUSSION

It has been hypothesized that social stress-related increases in inflammatory activity play a role in the emergence of depressive symptoms for some individuals (Slavich & Irwin, 2014). To date, however, no study has examined whether differences in inflammatory

TABLE 3 Hierarchical linear regression models predicting depressive symptom severity at follow-up separately by cytokine for interpersonal life stress exposure

	TNF-α ($n = 111$)[a]			IL-1β ($n = 114$)[b]			IL-6 ($n = 113$)[c]		
Step and predictor	***β***	**95% CI**	***b***	***β***	**95% CI**	***b***	***β***	**95% CI**	***b***
Step 1	Total $R^2 = 0.44^{***}$			Total $R^2 = 0.37^{***}$			Total $R^2 = 0.35^{***}$		
Age	−.03	[−0.22, 0.15]	−0.01	−.04	[−0.23, 0.14]	−0.01	−.02	[−0.21, 0.18]	−0.01
Ethnicity	−.05	[−0.20, 0.10]	−0.04	−.01	[−0.16, 0.15]	−0.004	−.02	[−0.18, 0.14]	−0.01
Pubertal status	.20*	[0.03, 0.37]	0.15	.21*	[0.03, 0.39]	0.16	.19*	[0.01, 0.38]	0.15
Presocial stress cytokine levels	−.10	[−0.25, 0.05]	−0.09	−.08	[−0.24, 0.09]	−0.06	.02	[−0.15, 0.18]	0.01
Baseline depressive symptoms	.36***	[0.21, 0.51]	0.32	.29***	[0.13, 0.46]	0.26	.32***	[0.16, 0.49]	0.29
Interpersonal life stress exposure	.41***	[0.25, 0.57]	0.01	.39***	[0.23, 0.57]	0.01	.37***	[0.19, 0.54]	0.01
Cytokine reactivity to social stress	.22**	[0.07, 0.37]	0.08	.15	[−0.004, 0.33]	0.07	.02	[−0.14, 0.18]	0.01
Step 2	Total $R^2 = 0.49^{***}$, $\Delta R^2 = .05^{**}$			Total $R^2 = 0.37^{***}$, $\Delta R^2 = .03^{*}$			Total $R^2 = 0.35^{***}$, $\Delta R^2 = 0.000$		
Interpersonal life stress exposure × Cytokine reactivity to social stress	.23**	[0.08, 0.37]	0.01	.18*	[0.04, 0.49]	0.01	−.02	[−0.18, 0.14]	−0.01

Note: 95% CI = 95% confidence intervals for standardized coefficients (βs).

Abbreviations: TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

[a]Models with TNF-α included 111 participants because TNF-α values were not available for four participants and one multivariate outlier case was excluded.

[b]Models with IL-1β included 114 participants because two multivariate outlier cases were excluded.

[c]Models with IL-6 included 113 participants because IL-6 values were not available for three participants.

*$p < .05$.

**$p < .01$.

***$p < .001$.

TABLE 4 Hierarchical linear regression models predicting depressive symptom severity at follow-up separately by cytokine for noninterpersonal life stress exposure

	TNF-α (n = 111)[a]			IL-1β (n = 115)[b]			IL-6 (n = 111)[c]		
Step and predictor	***β***	**95% CI**	***b***	***β***	**95% CI**	***b***	***β***	**95% CI**	***b***
Step 1	Total $R^2 = 0.29^{***}$			Total $R^2 = 0.25^{***}$			Total $R^2 = 0.28^{***}$		
Age	.04	[−0.17, 0.24]	0.01	.02	[−0.18, 0.22]	0.01	.05	[−0.16, 0.26]	0.01
Ethnicity	.05	[−0.12, 0.22]	0.04	.04	[−0.15, 0.21]	0.03	.06	[−0.11, 0.23]	0.05
Pubertal status	.23*	[0.03, 0.42]	0.17	.28**	[0.08, 0.48]	0.21	.22*	[0.02, 0.41]	0.17
Presocial stress cytokine levels	−.03	[−0.20, 0.14]	−0.03	−.06	[−0.23, 0.12]	−0.05	.09	[−0.08, 0.26]	0.08
Baseline depressive symptoms	.33***	[0.16, 0.50]	0.29	.32***	[0.16, 0.51]	0.29	.37***	[0.19, 0.54]	0.33
Noninterpersonal life stress exposure	.11	[−0.06, 0.29]	0.01	.09	[−0.08, 0.26]	0.01	.14	[−0.04, 0.31]	0.01
Cytokine reactivity to social stress	.26**	[0.10, 0.44]	0.10	.12	[−0.05, 0.30]	0.05	.06	[−0.11, 0.22]	0.03
Step 2	Total $R^2 = 0.29^{***}$, $\Delta R^2 = 0.000$			Total $R^2 = 0.26^{***}$, $\Delta R^2 = 0.01$			Total $R^2 = 0.28^{***}$, $\Delta R^2 = 0.000$		
Noninterpersonal life stress exposure × Cytokine reactivity to social stress	.02	[−0.09, 0.25]	0.002	.09	[−0.15, 0.20]	0.01	.004	[−0.17, 0.18]	0.000

Note: 95% CI = 95% confidence intervals for standardized coefficients (βs).

Abbreviations: TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

[a]Models with TNF-α included 111 participants because TNF-α values were not available for four participants and one multivariate outlier case was excluded.

[b]Models with IL-1β included 115 participants because one multivariate outlier case was excluded.

[c]Models with IL-6 included 111 participants because IL-6 values were not available for three participants and two multivariate outlier cases were excluded.

*$p < .05$.

**$p < .01$.

***$p < .001$.

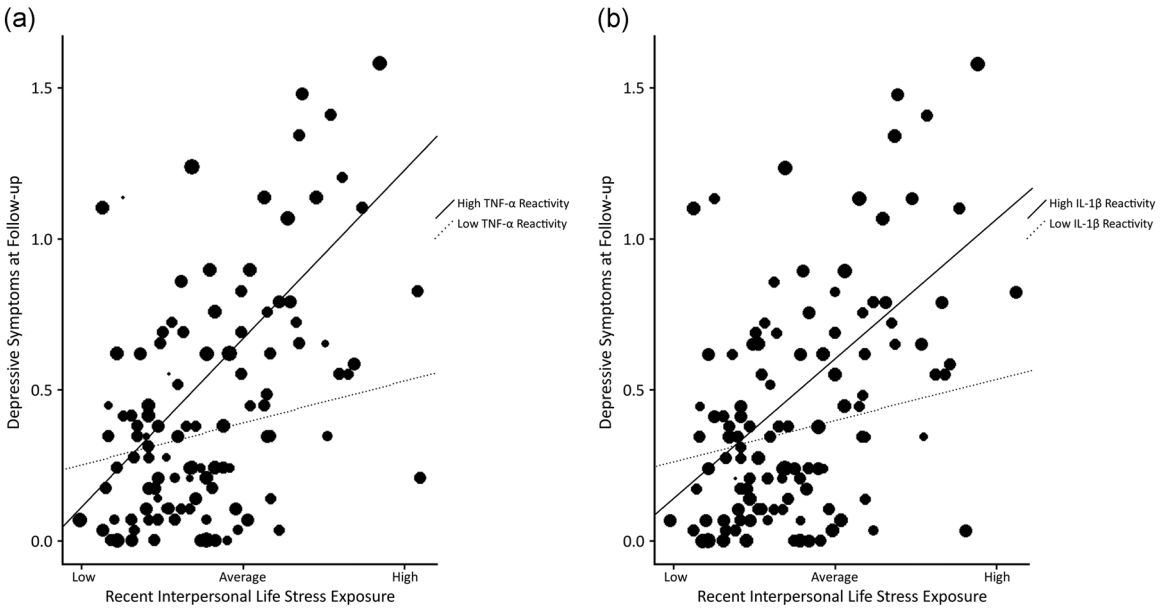

FIGURE 1 Interpersonal life stress exposure, inflammation, and depressive symptoms. Hierarchical linear regression models revealed that recent interpersonal life stress exposure interacted with youths' social stress-induced salivary cytokine reactivity to predict significant increases in depressive symptoms over 9 months, while controlling for age, ethnicity, and pubertal status. Results for TNF-α are shown in panel (a), where greater interpersonal life stress exposure predicted significant increases in depressive symptoms over time for girls exhibiting high TNF-α reactivity to social stress (simple slopes [*SE*]: 0.019 [0.003], $p < .001$) but not for girls exhibiting low TNF-α reactivity to social stress (simple slopes [*SE*]: 0.01 [0.003], $p = .08$). As shown in panel (b), similar effects were found for IL-1β, where greater interpersonal life stress exposure predicted significant increases in depressive symptoms over time for girls exhibiting high IL-1β reactivity to social stress (simple slopes [*SE*]: 0.017 [0.003], $p < .001$) but not for girls exhibiting low IL-1β reactivity to social stress (simple slopes [*SE*]: 0.01 [0.002], $p = .101$). In contrast to these results, noninterpersonal stress exposure was not related to changes in depressive symptoms longitudinally, either alone or in combination with participants' salivary cytokine reactivity scores. Dot sizes represent the magnitude of participants' cytokine reactivity to the social stress task, with larger dots indicating greater reactivity. TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; *SE*, standard error

TABLE 5 Hierarchical linear regression models predicting depressive symptom severity at follow-up using presocial stress cytokine levels and interpersonal life stress exposure

	TNF-α (n = 112)[a]			IL-1β (n = 113)[b]			IL-6 (n = 113)[c]		
	β	95% CI	b	β	95% CI	b	β	95% CI	b
Step 1	Total R^2 = 0.39***			Total R^2 = 0.38***			Total R^2 = 0.35***		
Age	−.03	[−0.22, 0.16]	−0.01	−.05	[−0.23, 0.13]	−0.01	−.02	[−0.21, 0.18]	−0.01
Ethnicity	−.01	[−0.17, 0.15]	−0.01	−.03	[−0.18, 0.12]	−0.02	−.02	[−0.18, 0.14]	−0.01
Pubertal status	.21*	[0.03, 0.39]	0.16	.23*	[0.04, 0.40]	0.17	.19*	[0.10, 0.38]	0.15
Presocial stress cytokine levels	−.09	[−0.25, 0.07]	−0.08	−.04	[−0.20, 0.12]	−0.03	.02	[−0.15, 0.18]	0.01
Baseline depressive symptoms	.32***	[0.16, 0.48]	0.29	.33***	[0.18, 0.50]	0.30	.32***	[0.16, 0.49]	0.29
Interpersonal life stress exposure	.36***	[0.19, 0.53]	0.01	.38***	[0.21, 0.54]	0.01	.37***	[0.19, 0.54]	0.01
Cytokine reactivity to social stress	.20*	[0.05, 0.36]	0.08	.13	[−0.02, 0.28]	0.06	.02	[−0.14, 0.18]	0.01
Step 2	Total R^2 = 0.40***, ΔR^2 = 0.01			Total R^2 = 0.38***, ΔR^2 = 0.001			Total R^2 = 0.35***, ΔR^2 = 0.000		
Interpersonal life stress exposure × Presocial stress cytokine levels	.10	[−0.06, 0.27]	0.01	−.04	[−0.22, 0.13]	−0.003	.001	[−0.16, 0.16]	0.000

Note: 95% CI = 95% confidence intervals for standardized coefficients (βs).

Abbreviations: TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

[a]Models with TNF-α included 112 participants because TNF-α values were not available for four participants.

[b]Models with IL-1β included 113 participants because three multivariate outlier cases were excluded.

[c]Models with IL-6 included 113 participants because IL-6 values were not available for three participants.

*p < .05.

**p < .01.

***p < .001.

reactivity to social stress might help explain who develops depressive symptoms following recent life stress exposure. The present study is novel in this regard as it is the first to show that social stress-induced increases in TNF-α and IL-1β significantly moderate the effects of recent interpersonal stress exposure on the development of depressive symptoms in adolescent girls, even after controlling for several relevant covariates. In contrast, noninterpersonal life stress exposure was unrelated to changes in depression over time, both alone and when combined with youths' cytokine reactivity scores. These findings are consistent with Social Signal Transduction Theory of Depression (Slavich & Irwin, 2014) and suggest that propensity for developing depressive symptoms following interpersonal life stress may be particularly high for adolescents who exhibit heightened TNF-α or IL-1β responses to social stress.

In contrast with TNF-α and IL-1β, IL-6 reactivity scores were unrelated to changes in depressive symptoms over time. This may have occurred because TNF-α and especially IL-1β are the predominant mediators of sickness behavior in the brain, and, therefore, could potentially be better markers of stress-related vulnerability for depression than IL-6 (Dantzer, 2009; Slavich, 2020). A second possibility is that because TNF-α and IL-1β are released earlier in the inflammatory cascade than IL-6 (Medzhitov, 2008; Yamakawa et al., 2009), our postsocial stressor cytokine sampling timepoint may have been more well suited for detecting depression-relevant changes in IL-1β and TNF-α than IL-6 (Irwin & Slavich, 2017).

No prior studies have examined how interpersonal life stress exposure and social stress-induced cytokine reactivity jointly predict the emergence of depressive symptoms over time. However, the present results are consistent with existing research showing that interpersonal stressors are more strongly associated with depression than noninterpersonal stressors (Feurer et al., 2017; Slavich et al., 2009; Vrshek-Schallhorn et al., 2015). They are also consistent with an abundance of animal model and human studies showing that interpersonal stressors strongly upregulate inflammatory activity, and with research showing that proinflammatory cytokines can promote depressive symptoms via multiple neurobiological pathways (for reviews, see Miller et al., 2009; Slavich & Irwin, 2014). Finally, one study has shown that self-reported stressful life events interact with changes in basal inflammatory levels over time to predict depression (Kautz et al., in press).

An important feature of the present sample involves the fact that many participants were clinically referred teenagers at risk for psychopathology. This sampling strategy has the benefit of revealing processes that may underlie the emergence of depression among those who experience the greatest psychosocial impact and disease burden over the lifespan. However, it also provides context that is important for interpreting our results. It is possible, for example, that at-risk girls may experience more interpersonal stressors—or may be more reactive to such stressors—than their lower-risk counterparts (Hankin et al., 2007; Rudolph, 2002). Likewise, at-risk girls may have psychological, neural, or genetic characteristics that make them more likely to exhibit stronger cytokine responses to social stress or to develop depression more frequently following such responses (Crone & Dahl, 2012; Hankin et al., 2015; Somerville, 2013). As a result, additional research is needed to examine the generalizability of the present results to other groups of adolescents (e.g., low-risk girls and boys), as well as to adults at varying risk for psychopathology. It will also be important to replicate the present findings in adolescents and adults at varying risk specifically for depression.

Another remaining question concerns how social stress-related increases in inflammatory activity actually lead to depressive symptoms.

The present data do not address this important issue, but as alluded to above, recent research has shown that interpersonal stressors can activate molecular signaling pathways that drive proinflammatory cytokine production (Slavich & Cole, 2013). Cytokines can, in turn, induce depressive symptoms in several ways including by influencing hypothalamic-pituitary-adrenal axis activity and glucocorticoid receptor signaling (Slavich et al., 2010a); altering the metabolism, synthesis, and reuptake of the monoamines serotonin, norepinephrine, and dopamine (Raison et al., 2009); affecting the release and reuptake of glutamate (Müller & Schwarz, 2007); and increasing oxidative stress that leads to excitotoxicity and the loss of glial elements (McNally, Bhagwagar, & Hannestad, 2008; Miller et al., 2009). Resulting effects include altered metabolic or neural activity in several depression-relevant brain regions that regulate mood, motivation, and behavior, including the basal ganglia, cerebellum, anterior cingulate cortex, and ventral striatum (Capuron & Miller, 2011; Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011). Additional research that combines measures of life stress exposure, cytokine activity, and neural activity is ultimately needed to better understand how interpersonal stressors alter neuro-immune dynamics that, in turn, promote depression.

4.1 | Strengths

This study has several strengths. First, we used an interview-based system for assessing life stress exposure that included a 1–2-hr interview and independent panel of expert raters who judged the objective severity and interpersonal nature of each life event that was reported. Second, we employed a stressor characteristics perspective on the life event data obtained, and based on this perspective, we examined the effects of both interpersonal and noninterpersonal stressors on youths' propensity to develop depressive symptoms over time. Third, we used a well-validated laboratory-based task to characterize participants' biological reactivity to social stress. Fourth, we focused on specific biological mechanisms (i.e., cytokines) that are known to induce depressive symptoms. Finally, we followed participants longitudinally for 9 months, which enabled us to examine for the first time how interpersonal and noninterpersonal stress exposure interacts with youths' social stress-induced inflammatory reactivity to predict changes in depressive symptoms over time.

4.2 | Limitations

Several limitations should also be noted. First, we characterized participants' social stress-induced inflammatory reactivity using salivary cytokines. Although these biomarkers have good measurement properties (Shields, Slavich, Perlman, Klein, & Kotov, 2019), salivary cytokines are not interchangeable with serum levels. Additionally, they can be sensitive to sample acquisition/processing method and salivary flow rate, and can be influenced by several factors including oral hygiene and health, mouth rinsing and teeth brushing, smoking, and sleep quality and duration (Byrne et al., 2013; Riis et al., 2015; Slavish et al., 2015). Second, the percentage of participants who exhibited a social stress-induced increase in salivary cytokine activity was modest (38.4–52.6%, depending on cytokine), prompting the question of whether a different social stress task might be more effective in eliciting an inflammatory response. Relatedly, we did not assess social stress-induced cytokine *recovery* levels, which future studies could examine as an additional marker of resilience to interpersonal life stress exposure (Slavich, 2015). Third, we carefully assessed youths' recent life stress exposure, but we did not assess their inflammatory reactivity to naturalistic (e.g., daily) stressors as they occurred nor did we assess their lifetime stress exposure (Slavich & Shields, 2018; Slavich, Stewart, Esposito, Shields, & Auerbach, 2019), both of which would provide convergent information (Monroe & Slavich, 2020). Fourth, we employed the well-validated MFQ to assess longitudinal changes in depressive symptoms, but such reports could be biased, and future research using independent assessments of youths' depressive symptoms and diagnostic status are needed. Similarly, because we employed a NIHM/RDoC-informed approach, additional research using diagnostic interviews is needed to examine whether the effects described here differ by diagnosis.

Fifth, research has shown that estrogen and progesterone regulate inflammation (Oertelt-Prigione, 2012; Schwarz & Bilbo, 2012), and it is possible that these sex hormones may help explain how interpersonal stressors increase inflammation leading to depression (see Slavich & Sacher, 2019). However, these hormones were not assessed here and should thus be measured in future research. Sixth, because all participants were relatively young, female, and at risk for psychopathology, additional research is needed to examine the generalizability of these findings to other groups of individuals, including persons specifically at risk for depression and community samples with less severe psychopathology. Finally, an abundance of research has shown that social stressors can upregulate proinflammatory cytokine activity and that cytokines can, in turn, induce depression (Slavich & Irwin, 2014), but the main associations described here are correlational and causation cannot be assumed.

4.3 | Clinical implications and conclusions

In conclusion, the present data provide important new insights into the stress-biology-depression relationship by showing that differences in inflammatory reactivity to social stress moderate the effects of recent interpersonal life stress exposure on the development of depressive symptoms over time. The findings thus have implications for understanding individual differences in risk for depression following interpersonal life stress and may help explain why MDD frequently co-occurs with other inflammation-related disease conditions, such as asthma, chronic pain, cardiovascular disease, and autoimmune and neurodegenerative disorders (Furman et al., 2019; Slavich & Auerbach, 2018). To the extent that interventions can be developed to modify negative stress-related cognitions that drive inflammatory reactivity, such interventions

may be helpful for reducing inflammation-related depression and physical disease risk. Looking forward, additional research is needed to examine these effects in other populations, to confirm the present results using other inflammatory markers, and to elucidate psychological, neural, molecular, and genomic pathways linking interpersonal stress exposure with heightened inflammatory activity and risk for depression.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data supporting the findings are available from the authors upon request.

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SUPPORTING INFORMATION

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