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Longitudinal changes of inflammatory biomarkers moderate the relationship between recent stressful life events and prospective symptoms of depression in a diverse sample of urban adolescents

Marin M. Kautz[a], Christopher L. Coe[b], Brae Anne McArthur[a], Naoise Mac Giollabhui[a], Lauren M. Ellman[a], Lyn Y. Abramson[b], Lauren B. Alloy[a,*]

[a] Department of Psychology, Temple University, United States
[b] Department of Psychology, University of Wisconsin-Madison, United States

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ABSTRACT

This study investigated whether longitudinal changes in inflammatory physiology moderated the relationship between recent stressful life events and subsequent depressive symptoms in adolescence. A diverse sample of adolescents representative of an urban community (N = 129; Age at baseline = 12.5 years; 48.8% female; 55.0% African American) completed measures of stressful life events, depressive symptoms, and two annual blood draws (BD1 and BD2). Controlling for inflammatory activity at BD1, depression at BD1, demographics and the time between assessments, increases in interleukin-6 (IL-6; $b = 0.878$, $p = .007$) and C-reactive protein (CRP; $b = 0.252$, $p = .024$) from BD1 to BD2 interacted with recent stressful life events before BD1 to predict severity of depressive symptoms at BD2. Similar associations were evident for IL-6 ($b = 2.074$, $p = .040$) and CRP ($b = 0.919$, $p = .050$) when considering acute stressful life events that had occurred within the two weeks before the first blood collection. More frequent stressful life events before BD1 predicted significantly more severe depressive symptoms at BD2, but only for adolescents with moderate (50th percentile) and high (84th percentile) levels of IL-6 and CRP at BD2. In conclusion, adolescents who experienced *both* recent stressful life events and larger increases in inflammatory activity following these stressors were at increased risk for more severe depressive symptoms after approximately one year. The findings indicate that the interaction of stress and larger changes in inflammatory activity following these stressors are prognostic risk factors for depression severity in adolescents.

1. Introduction

1.1. Prevalence of depression in adolescence

Depression is the fourth leading cause of overall global disease burden and a major cause of death for adolescents (Üstün et al., 2004; Windfuhr et al., 2008). From early to late adolescence, the cumulative prevalence of depression increases from 5% to 17% (Hankin et al., 1998; Lewinsohn et al., 1999b). Additionally, a recent national survey indicates that the past year prevalence of depressive episodes is highest for adolescents aged 12 to 17 (12.8%) (Ahrnsbrak et al., 2017). Prior to the first significant depressive episode, most adolescents exhibit subclinical depressive symptoms (van Lang et al., 2007), and even subclinical depressive symptoms are associated with some level of impaired functioning (Gotlib et al., 1995). Identifying risk factors for developing depressive symptoms in adolescence will allow for preemptive efforts to interrupt risk pathways and decrease the disease burden of depression (Thapar et al., 2012). In this study, we examined longitudinal changes in inflammatory activity as a factor that may moderate the influence of stressful life events on risk for depressive symptoms in adolescents.

1.2. Stress and depression

Adolescence has been characterized as a period of high stress (Nelson et al., 2005; O'Brien and Bierman, 1988; Silberg et al., 1999; Steinberg and Morris, 2001). Stressful life events and perceived stress are among the strongest risk factors for the development of depression, particularly interpersonal stressors (i.e., Brown and Harris, 1978; Hammen, 2005; Monroe et al., 2007; Slavich and Irwin, 2014; Slavich

* Corresponding author at: Department of Psychology, Temple University, Weiss Hall, 1701 N. 13th St., Philadelphia, PA 19122, United States.
E-mail address: lalloy@temple.edu (L.B. Alloy).

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et al., 2009). In fact, stressful events have been identified as the strongest risk factor for the occurrence of depression, even when compared to other prominent risk factors, such as familial depression, childhood and lifetime traumas, and poor social support (Kendler et al., 2002). In community samples, major life stressors were found to precipitate up to 80% of major depressive episodes across the life course (Harkness et al., 2010; Mazure, 1998). However, not everyone who experiences even major stressors becomes depressed. Individual differences in biological stress responses, such as inflammatory activation, may influence the likelihood that stress exposure leads to depression for a subgroup of individuals. Thus, understanding individual differences in biological stress responses that moderate whether stress exposure will lead to depression may present opportunities to intervene in the pathogenesis of depression.

The role of stress in depression is more complex in adulthood due to the secondary stressors generated by the experience of recurrent depression itself (Hammen, 1991). Therefore, it is of value to examine the antecedents of depression onset, such as stress, during adolescence. In adolescence, there is evidence that the severity of depressive symptoms is related to the frequency of stressful life events (Mac Giollabhui et al., 2018a). For female adolescents specifically, depressive symptoms were found to reflect the pattern of stressful life events over a four-year period (Ge et al., 1994). Moreover, the occurrence of multiple stressful events during adolescence is more strongly associated with first onset of depression than exposure to a single stressful event (Lewinsohn et al., 1999a). These findings provide a compelling rationale for investigating biological moderators that may influence reactivity to stressful life events and increase risk for depressive symptoms in specific subgroups of adolescents.

1.3. Stress and inflammation

When acute physical or psychological threats occur, there is parallel activation of the neuroendocrine axes as well as peripheral inflammatory neuroimmune pathways. Exposure to stressful life events can lead to increased inflammatory activity, including elevated levels of interleukin (IL)-6 and C-reactive protein (CRP) (Harkness et al., 2010; Hostinar et al., 2015; Kiecolt-Glaser et al., 2011; Marin et al., 2009; Miller and Chen, 2010; Slopen et al., 2010). Although fewer studies have examined stress–inflammation associations in adolescence, prior findings suggest that stressful events play a salient role in the elevation of inflammatory markers during adolescence. For example, the accumulation of negative interpersonal daily stressors over one to two weeks predicted elevated CRP, IL-6 and soluble TNF-α receptor (sTNFαRII) levels following a laboratory social stress test (Chiang et al., 2012; Fuligni et al., 2009). Higher levels of peer victimization during the prior year predicted elevated IL-6 and IL-1ß following a laboratory social stress test among adolescent females (Giletta et al., 2018). In the only longitudinal study to examine how early life stress predicts changes in inflammation in adolescence, Slopen et al. (2013) found that stressful events from birth to 1.5 years, from 6 to 8 years, and cumulatively from birth to 8 years of age all predicted increased CRP levels at age 15. These findings indicate that stress exposure may lead to increased inflammatory activity in adolescence. However, prior research has commonly relied on single assessments of inflammation co-occurring with contemporaneous stressful life events. We investigated whether longitudinal changes in inflammatory markers following stressful events prospectively modified risk for later depressive symptoms.

1.4. Inflammation and depression

Extensive evidence from population studies, meta-analytic reviews, and translational animal models indicates that elevated inflammation, particularly as indexed by CRP and IL-6, is positively associated with or predictive of future depression (Dowlati et al., 2010; Hodes et al., 2016; Howren et al., 2009; for reviews see Miller and Raison, 2016; Slavich and Irwin, 2014; Valkanova et al., 2013). Few studies have examined the role of inflammation in depression in younger individuals; however, the extant literature suggests a bidirectional association. One longitudinal study found higher levels of IL-6 at age 9 were associated with increased risk for developing depression at age 18 in a dose-dependent manner (Khandaker et al., 2014). However, there is inconsistent data about the association of CRP with depression in other adolescent samples. Duivis et al. (2015) reported that persistent depressive symptoms were associated with higher CRP levels at three later biennial assessments, whereas Copeland et al. (2012) did not find a significant relationship between CRP levels and depressive symptoms at follow-up. These studies relied on single assessments of inflammation and did not examine longitudinal changes in inflammation as potential predictors of later depressive symptoms.

The only study to utilize longitudinal measurements of inflammation *and* depression in an adolescent sample found that higher IL-6 levels preceded increased depressive symptoms six months later, but only for females with more stressors during childhood. Additionally, those with more frequent stressors and elevated CRP continued to have elevated CRP six months after a depressive episode, indicating a bidirectional relationship between inflammation and depression, highlighting the need for longitudinal study designs (Miller and Cole, 2012).

As important, recent studies have conveyed that only a subgroup of individuals with depression exhibits elevated inflammation (Raison and Miller, 2011). We hypothesized that differences in biological stress reactivity may help to account for previous mixed findings, and that inflammatory responses may help to explain why only some individuals become depressed following stressful events. We propose that adolescents who both experience stressful events and show increased inflammatory activity over time after high stress exposure will likely be at more risk for experiencing depressive symptoms.

1.5. The current study

Our study addresses the gap in the literature on the temporal associations between stress exposure, increases in inflammatory activity, and changes in depressive symptoms in adolescents. In a community sample of adolescents followed longitudinally, we examined whether change in inflammatory markers over approximately one year moderated the relationship between prior stressful life events and change in depressive symptoms. We hypothesized that: (1) a higher frequency of recent stressful events would prospectively predict increased depression severity, and (2) only those adolescents with an increase in inflammatory markers (IL-6 and CRP) following frequent recent stressful events would develop increased subsequent depressive symptom severity. Additionally, given prior evidence that the relationship between stress, inflammation, and depression may differ across demographic groups (Miller and Cole, 2012), we explored the possible influence of gender, race, and socioeconomic status.

2. Materials and methods

2.1. Participants

The participants were a subset of adolescents participating in a large prospective study examining the development of depressive disorders, the Adolescent Cognition and Emotion (ACE) study (Alloy et al., 2012). They were recruited from public and private middle schools and through advertisements in local newspapers in the Philadelphia area. Inclusion criteria were: (1) 12 or 13 years old at recruitment; (2) self-identified as Caucasian or white, African American or black, or biracial; and (3) their mother/primary female caregiver was willing to participate. Exclusion criteria included: (1) inability to read or speak English well enough to complete study assessments; and (2) presence of a severe cognitive or learning disability, cognitive impairment, psychotic disorder, developmental disorder, or any other psychiatric or medical

Table 1
Means, standard deviations, and correlations of stressful life events, inflammation, depressive symptoms, and covariates (N = 129).

Variable	*M/n*	*SD/%*	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. CDI - Total at BD1	6.37	5.76														
2. CDI - Total at BD2	6.68	5.92	0.56**													
3. LEI - Total at BD1	9.74	5.81	0.55**	0.51**												
4. LEI - Acute at BD1	1.23	1.84	0.15	0.27**	0.30**											
5. Time of BD2 [Hr:Min]	14:11	2:19	−0.04	0.06	0.14	0.03										
6. Inflammation Affecting Meds BD2 [a]	18	14.00	0.23**	0.08	0.07	0.16	0.03									
7. Alcohol & Drug (AADIS) at BD2	2.17	3.68	0.33**	0.32**	0.26**	0.04	−0.03	0.01								
8. Pubertal Timing (PDS) at BD2	−0.03	0.98	−0.04	−0.01	−0.02	−0.12	0.04	0.08	−0.06							
9. BMI at BD2 [b, c]	24.43	5.97	−0.09	0.14	0.04	−0.00	−0.01	0.02	−0.05	0.24*						
10. Birth Control Use at BD2 [b, d]	14	10.90	−0.04	−0.17	−0.03	0.02	0.05	0.21*	0.15	0.03	−0.02					
11. Female [b, c]	63	48.8	0.04	0.12	0.07	−0.10	0.03	0.10	−0.07	0.05	0.12	0.36**				
12. Eligible for free school lunch	52	40.3	0.06	0.02	0.04	0.10	0.14	0.07	−0.07	−0.06	−0.01	−0.08	−0.18*			
13. Age	12.45	0.71	−0.08	−0.00	−0.06	0.03	−0.02	0.00	0.04	0.82**	0.19*	0.09	−0.04	0.02		
14. Caucasian [d, e]	58	45.00	−0.05	−0.07	−0.02	−0.05	0.10	−0.05	−0.03	−0.18	−0.12	0.04	0.18*	−0.11	−0.20*	
15. Log CRP at BD1	1.71	0.59	−0.16	−0.05	−0.09	−0.20*	0.01	−0.04	0.00	0.21*	0.52**	0.16	0.27**	−0.03	0.06	0.05
16. Log CRP at BD2	1.78	0.57	−0.21*	−0.09	−0.15	−0.14	−0.04	0.03	−0.15	0.12	0.43**	0.19*	0.20*	−0.09	0.11	0.02
17. Log IL-6 at BD1	1.55	0.30	−0.05	0.08	0.01	−0.15	0.07	0.07	−0.01	0.15	0.34**	0.20*	0.35**	−0.02	0.03	0.10
18. Log IL-6 at BD2	1.44	0.24	0.18*	0.17	0.12	0.02	−0.01	0.07	−0.05	0.08	0.42**	0.07	0.22*	−0.07	−0.01	0.03
19. Log TNF at BD1	2.15	0.15	−0.11	0.03	−0.14	0.09	0.00	−0.01	−0.02	−0.23	−0.21*	−0.03	−0.10	−0.06	−0.20*	0.21*
20. Log TNF at BD2	2.12	0.11	−0.04	−0.02	−0.09	0.13	−0.06	−0.13	−0.17	−0.07	0.03	−0.20*	−0.16	0.05	−0.02	0.20*
21. Log IL-10 at BD1	1.34	0.21	−0.14	0.17	−0.09	0.13	−0.11	−0.10	0.01	−0.16	0.01	−0.17	0.02	−0.01	−0.09	0.11
22. Log IL-10 at BD2	1.29	0.20	0.04	0.11	0.04	0.26**	−0.10	0.07	−0.16	0.05	−0.03	−0.11	−0.05	0.05	0.04	0.04
23. Log IL-8 at BD1	2.58	0.33	−0.14	−0.10	−0.01	0.11	0.00	0.07	−0.05	−0.09	−0.22*	−0.08	−0.10	0.10	−0.05	0.10
24. Log IL-8 at BD2	2.46	0.20	0.07	0.09	0.05	0.03	0.05	0.00	0.08	0.11	−0.01	−0.07	−0.05	−0.04	0.08	0.17

Note. M and *SD* are used to represent mean and standard deviation, respectively. Pearson correlation coefficients are displayed; AADIS = Adolescent Alcohol and Drug Involvement Scale; PDS = Pubertal Development Scale, Self-Report (Z-standardized score); BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; [a]These included using at BD: bronchodilator and other asthma medications, ADHD medications, SSRIs/SNRIs, Mood stabilizers/Anti-psychotics/Anti-convulsant, Nonsteroidal anti-inflammatory drugs, Acne medication, Pain killers; Covariates at BD2 ($p < .05$): CRP[b], IL-6[c], TNF-α [d], IL-8[e] (No significant covariates for IL-10); *$p < .05$, **$p < .01$.

problem that would prevent the adolescents or their caregivers from completing the study. See Alloy et al. (2012) for further details about the Project ACE study.

Adolescent participants were included in the current analytic sample if they completed: (1) at least two optional blood draws (BD) for measurements of peripheral inflammatory markers (BD1 and BD2), (2) a life events interview 3–12 months prior to BD1, and (3) the Children's Depression Inventory at BD1 and BD2. One hundred thirty-four participants met these criteria (42.3% low socioeconomic status; 49.3% female; 55.2% African American).

Adolescents were excluded from the current analyses if they had: a blood clotting condition (n = 1, 0.8%), an autoimmune disease (n = 3, 2.3%), diabetes (0%), or were pregnant (n = 1, 0.8%) at the time of either blood draw. These criteria left 129 participants for the present analytic sample. Excluded participants were examined to determine whether the analytic sample of 129 adolescents differed significantly from the full longitudinal ACE sample. The analytic sample was representative of the whole sample with respect to gender and racial composition. However, the socioeconomic status of the analytic sample did differ from the full ACE sample, $\chi^2(1) = 4.73$, $p = .030$, with significantly fewer participants of lower SES backgrounds (standardized residual = −1.4).

2.2. Assessments

At baseline, participants' demographics, lifetime history and current psychiatric diagnoses, and family psychiatric history were assessed initially and updated annually. Stressful life events and depressive symptoms were assessed approximately every six months. In this analytic sample (N = 129), participants were on average 12.5 years old at baseline (standard deviation [SD] = 0.7 years), 16.1 years old at BD1 (SD = 1.3 years), and 17.5 years old at BD2 (SD = 1.3 years; See supplementary Fig. A.1 for the study design and timeline).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbi.2019.02.029.

2.2.1. Stressful life events.

Stressful life events were assessed with a combined questionnaire and interview procedure approximately every six months (Range = 3 to 12 months) depending on participant availability. Adolescents and their mothers completed the 63-item Adolescent Life Events Questionnaire (ALEQ; Hankin and Abramson, 2002), assessing a broad range of stressors in familial, social, relationship, appearance, and school/achievement domains during the previous six months. Following completion of the ALEQ, adolescents completed the Life Events Interview (LEI; Safford et al., 2007), which generated detailed information about events endorsed on the ALEQ and when they occurred. LEI interviewers were blind to participants' diagnoses and depressive symptoms. The LEI uses manualized, event-specific definitions to maintain consistency. Events not meeting definitional criteria are excluded to reduce subjective reporting biases. Reliability and validity are established for the ALEQ (Abela et al., 2011; Hankin, 2008; Hankin and Abramson, 2002) and the LEI (Francis-Raniere et al., 2006; Safford et al., 2007). For this study, the number of LEI stressful events over the 3–12 months prior to BD1 was summed to create a "total stressors" score, and stressful events over the two weeks prior to BD1 were summed to create an "acute stressors" score.

2.2.2. Depressive symptoms.

The Children's Depression Inventory (CDI; Kovacs, 1981) measures current depressive symptomatology (i.e., over the past two weeks) in youth. This scale has 27 items assessing affective, cognitive, and somatic symptoms of depression. Reliability and validity are established for the CDI for diverse community and clinical samples of adolescents (Lee et al., 2017; Masip et al., 2010; Saylor et al., 1984; Smucker et al., 1986). CDI scores have been found to be unaffected by socioeconomic status and racial differences (Twenge and Nolen-Hoeksema, 2002).

2.2.3. Inflammatory biomarkers.

Blood was obtained annually at a regularly scheduled lab visit in the late afternoon to control for diurnal variation in inflammatory physiology. Samples were collected via antecubital venipuncture by a certified phlebotomist in special 10 mL vacutainers designed for freezing after centrifugation (BD Vacutainer, Ref: 362788). Potentially confounding variables such as medication use, medical disorders, time of last meal, and time of blood collection (see Table 1) were recorded at each blood draw and participants' height and weight were measured to allow calculation of body mass index (BMI). After sitting at room temperature for at least 20 min., the blood samples were centrifuged and then stored in an ultracold −80 °C freezer until thawed on the day of assay. Blood was shipped frozen on dry ice by overnight courier to the University of Wisconsin, where the assays were conducted.

IL-6, IL-8, IL-10, and TNF-α were quantified by multi-cytokine array, and high-sensitivity CRP (hs-CRP) was determined in a singleplex assay, using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for quantification of both cytokines and CRP (Meso Scale Discovery, Rockville, MD). Each specimen was assayed in duplicate, with intra-assay coefficients of variation between 1.94 and 4.38%, and values referenced to a standard curve generated from 7 calibrators with known concentrations. The lower limit of cytokine detection (LLOD) was 0.1 pg/mL, with a large dynamic range up to 2000 pg/mL. CRP is present in higher concentrations, and thus, needed to be assayed separately; after running diluted plasma so that it corresponded to the reference curve, values were converted to mg/L units to be consistent with the clinical literature, and calculated down to 0.1 mg/L. A natural log transformation was applied to cytokines and CRP to normalize the distribution of values.

2.2.4. Other potential confounders.

The elapsed times between the main measurements (stress, inflammation, and depression) for each individual were included as covariates. Alcohol, cigarette, and other drug use was assessed for the 6 months prior to BD1 with the Adolescent Alcohol and Drug Involvement Scale (AADIS; Moberg and Hahn, 1991). The AADIS includes 14 self-report items assessing the frequency of use of tobacco, alcohol, marijuana, and multiple other substances. Higher scores represent greater substance involvement, with scores ≥ 37 indicating a possibly clinical level of substance use. Pubertal timing was assessed at BD1 using a z-standardized score of pubertal development from the Pubertal Development Scale, Self-Report (PDS; Petersen et al., 1988). The PDS asks about five different aspects of development (i.e., growth, body hair, skin change, breast change [girls]/voice change [boys], and menstruation [girls]/facial hair growth [boys]) and has demonstrated good psychometric properties and convergent validity with physician-rated Tanner stages (Petersen et al., 1988). AADIS and PDS scores were assessed as possible covariates in the inflammatory analyses (see Table 1).

2.3. Statistical analysis

Linear regressions were conducted to assess whether the frequency of total stressful events (3–12 months before BD1) and acute stressful events (2 weeks before BD1) significantly predicted elevated depression symptoms (CDI scores) at BD2, controlling for depression symptoms at BD1 (Hypothesis 1). To account for the presence of current acute illnesses (Landry et al., 2017; Pearson, 2003), for the CRP analyses, participants with CRP > 10 mg/L were excluded and, for cytokine analyses, log-transformed cytokine values ≥ 3 SDs above the mean were excluded. The excluded inflammatory values were found in 18 participants (CRP: $n = 5$, 3.9%; IL-6: $n = 2$, 1.6%; TNF-α: $n = 4$, 3.1%; IL-10: $n = 6$, 4.7%; IL-8: $n = 6$, 4.7%). There were no undetectable values below the limits of assay sensitivity.

For analyses involving changes in inflammation levels, initial bivariate correlations were conducted to examine which demographic, health, medication, substance use, and psychosocial variables (i.e., eligibility for free school lunches, a measure of financial need that accounts for the number of dependents being supported on the family's income) were significantly associated with inflammatory markers at BD2, and therefore, should be included as covariates in the final models (Howren et al., 2009; O'Connor et al., 2009; see Table 1). To assess the conditional effect of changes in inflammation on the relationship between recent life stress prior to BD1 and depressive symptoms at BD2, moderation analyses were conducted (Hypothesis 2). In these moderation analyses, CDI scores at BD2 were the outcome, total stressors and acute stressors prior to BD1 were the predictors, and changes in cytokines and CRP from BD1 to BD2 were the moderators, controlling for cytokines at BD1 to assess change in inflammation, holding constant all significant covariates and CDI scores at BD1 to assess change in depressive symptoms (Slopen et al., 2013). These analyses were completed using SPSS Version 24 (IBM) and the PROCESS macro Version 3 (Model 1; Hayes, 2017). This model establishes high, moderate, and low levels of the moderator, which were assessed as the 84th, 50th, and 16th percentiles, respectively. Johnson-Neyman analyses were conducted for each moderation analysis to assess the value of the moderator for which the slope of the predictor was statistically significant.

Exploratory *post hoc* analyses were conducted using three-way interactions in linear regression models to examine whether gender, race, or SES (i.e., free school lunch) further influenced the interactive relationship between recent stressful events and change in inflammation over time predicting change in depressive symptoms over time. These analyses examined whether depression at BD2 was predicted by the interaction of gender, race, or SES with each of the five inflammatory markers from BD1 to BD2 and with both total and acute recent stressors prior to BD1. To probe the conditional effects of any significant three-way interactions, the sample was split by the dichotomous demographic characteristic (e.g., males and females) and the two-way interactions between recent stressful events prior to BD1 and change in inflammatory response over time predicting depression at BD2 were examined.

3. Results

3.1. Initial analyses

Race, gender, BMI, and birth control use all were found to be significantly associated with at least one of the inflammatory markers at BD2 (see Table 1), and thus, were controlled in the subsequent regression analyses. As shown in Table 1, frequent total and acute stressful events were positively correlated with higher depressive symptoms at BD2, indicating a relationship between high stress exposure and increased severity of depressive symptoms one year later. Acute stressful events prior to BD1 also were positively associated with IL-10 at BD2. Additionally, higher depressive symptoms at BD1 were negatively correlated with log-transformed CRP, but positively correlated with log-transformed IL-6 levels at BD2. The mixed results with inflammatory biomarkers may be explained by the failure of unadjusted correlations to account for critical confounds assessed in multivariate analyses. The potentially moderating role of inflammatory changes from BD1 to BD2 accounting for these critical covariates were explored further in the following analyses.

3.2. Recent life stressors and depressive symptoms

The stressful events that occurred most frequently in this sample were: arguments/fights (between family members), unpleasant household responsibilities (e.g., chores), insufficient leisure time (e.g., too much work), not completing a homework assignment, and being very unsatisfied with their physical appearance. A higher frequency of stressful events reported on the LEI for the 3–12 months prior to BD1 predicted significantly higher CDI scores at BD2, controlling for CDI

Table 2
Regression models of recent total stressful life events predicting depressive symptoms.

	Dependent variable: CDI - Total at BD2				
	Model 1 (Life Events as predictor)	Model 2 (Change in CRP as moderator)	Model 3 (Inter. of stress, CRP, & gender)	Model 4 (Change in IL-6 as moderator)	Model 5 (Inter. of stress, IL-6, & gender)
LEI - Total at BD1	0.301***	−0.186	−0.256	−1.016*	−0.771
	(0.086)	(0.208)	(0.315)	(0.482)	(0.489)
CDI - Total at BD1	0.407***	0.454***	0.450***	0.436***	0.454***
	(0.087)	(0.089)	(0.087)	(0.088)	(0.086)
Gender (Reference group: Male)		0.848	1.044	0.560	4.525
		(0.937)	(5.397)	(0.910)	(5.198)
Log CRP at BD1		0.123	1.206		
		(1.005)	(1.055)		
Log CRP at BD2		−2.274	−1.075		
		(1.465)	(1.910)		
LEI - Total at BD1 × Log CRP at BD2		0.252*	0.186		
		(0.110)	(0.195)		
LEI - Total at BD1 × Log CRP at BD2 × Gender			0.060		
			(0.245)		
Log IL-6 at BD1				1.222	2.082
				(1.679)	(1.660)
Log IL-6 at BD2				−9.843**	−5.427
				(3.814)	(4.413)
LEI - Total at BD1 × Log IL-6 at BD2				0.878**	0.592
				(0.324)	(0.347)
LEI - Total at BD1 × Log IL-6 at BD2 × Gender					0.163
					(0.105)
Observations	129	113	113	127	127
R^2	0.373	0.454	0.496	0.446	0.492
Residual Std. Error	4.723 (df = 126)	4.450 (df = 101)	4.337 (df = 98)	4.583 (df = 116)	4.449 (df = 113)
F Statistic	37.404*** (df = 2;126)	7.622*** (df = 11;101)	6.896*** (df = 14;98)	9.357*** (df = 10;116)	8.410*** (df = 13;113)

Note. Unstandardized beta displayed; Standard errors shown in parentheses; BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; Additional covariates included in Model 2, 3, 4, and 5 are BMI at BD2, birth control at BD2 (only for Model 2 and 3), time between CDI and BD2, time between BD1 and BD2, time between LEI and BD1, Gender X LEI - Total at BD1 and Gender X Log CRP/IL-6 (only for Model 3 and 5); *$p < .05$, **$p < .01$, ***$p < .001$.

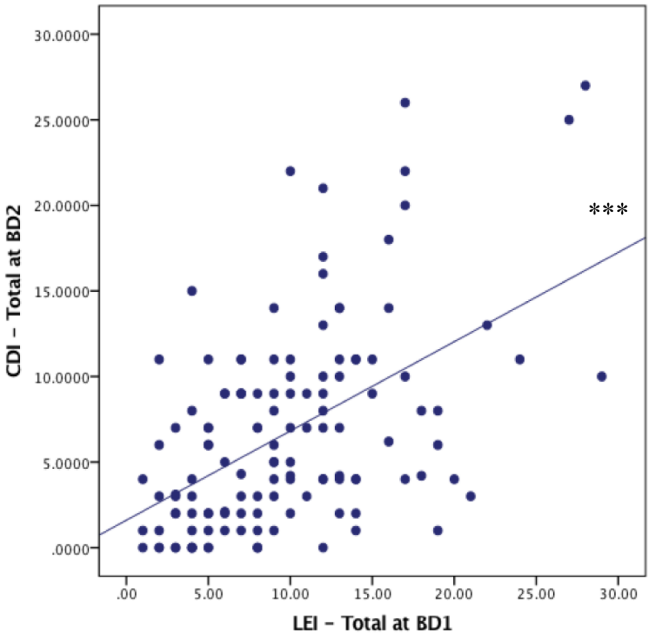

Fig. 1. Stressful Life Events for 3–12 Months Prior to BD1 Predict Change in Depressive Symptoms from BD1 to BD2. CDI total score at BD1 was included as a covariate; BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; *$p < .05$, **$p < .01$, ***$p < .001$.

scores at BD1 (see Table 2 and Fig. 1). This finding was replicated when examining the acute stressors that occurred in just the two weeks prior to BD1 as a predictor (see Table 3).

3.3. Change in inflammation as a moderator of the recent life stressors – Depression association

Moderation analyses were conducted to assess whether the change in cytokines and CRP from BD1 to BD2 moderated the relationship between total and acute stressful events prior to BD1 and symptoms of depression at BD2, an average of one year later, controlling for depressive symptoms at BD1. CRP and IL-6 at BD2 (controlling for CRP and IL-6 at BD1, respectively) were found to significantly moderate this relationship, whereas changes in TNF-α (n = 114, $b = 0.977$, $SE = 0.767$, $p = .206$; $b = -2.442$, $SE = 2.430$, $p = .317$), IL-8 (n = 122, $b = 0.679$, $SE = 0.373$, $p = .071$; $b = 0.386$, $SE = 1.141$, $p = .736$), and IL-10 (n = 122, $b = 0.613$, $SE = 0.423$, $p = .150$; $b = -0.314$, $SE = 1.135$, $p = .783$) did not moderate this relationship.

3.3.1. CRP as moderator

CRP levels at BD2 interacted with the total number of stressful events for the 3–12 months prior to BD1 to predict depression at BD2, controlling for CRP levels at BD1, depression at BD1, BMI at BD2, birth control at BD2, gender, the time between the initial CDI and BD2, the time between the LEI and BD1, and the time between BD1 and BD2 (see Table 2). Conditional effects of this relationship indicated that a greater total number of stressful life events prior to BD1 predicted a greater severity of depression at BD2 at moderate ($b = 0.249$, $SE = 0.087$, $p = .005$) and high ($b = 0.451$, $SE = 0.124$, $p < .005$) levels of CRP at BD2 (see Fig. 2). Johnson-Neyman analyses indicated that the

Table 3
Regression models of recent acute stressful life events predicting depressive symptoms.

	Dependent variable: CDI - Total at BD2				
	Model 1 (Life Events as predictor)	Model 2 (Change in CRP as moderator)	Model 3 (Inter. of stress, CRP, & gender)	Model 4 (Change in IL-6 as moderator)	Model 5 (Inter. of stress, IL-6, & gender)
LEI - Acute at BD1	0.594*	−0.918	0.429	−2.287	−0.450
	(0.235)	(0.762)	(1.021)	(1.367)	(1.773)
CDI - Total at BD1	0.544***	0.553***	0.530***	0.542***	0.558***
	(0.075)	(0.077)	(0.076)	(0.079)	(0.078)
Gender (Reference group: Male)		1.214	5.326	1.173	7.267
		(0.961)	(3.469)	(0.937)	(6.361)
Log CRP at BD1		0.268	0.902		
		(1.040)	(1.039)		
Log CRP at BD2		−0.726	1.030		
		(1.094)	(1.353)		
LEI - Acute at BD1 × Log CRP at BD2		0.919*	−0.140		
		(0.463)	(0.644)		
LEI - Acute at BD1 × Log CRP at BD2 × Gender			1.973*		
			(0.934)		
Log IL-6 at BD1				1.450	2.149
				(1.736)	(1.734)
Log IL-6 at BD2				−4.127	−0.641
				(2.450)	(3.433)
LEI - Acute at BD1 × Log IL-6 at BD2				2.074*	0.485
				(0.960)	(1.284)
LEI - Acute at BD1 × Log IL-6 at BD2 × Gender					2.627
					(2.012)
Observations	129	113	113	127	127
R^2	0.345	0.428	0.480	0.418	0.451
Residual Std. Error	4.827 (df = 126)	4.554 (df = 101)	4.409 (df = 98)	4.701 (df = 116)	4.624 (df = 113)
F Statistic	33.118*** (df = 2;126)	6.858*** (df = 11;101)	6.449*** (df = 14;98)	8.320*** (df = 10;116)	7.142***(df = 13;113)

Note. Unstandardized beta displayed; Standard errors shown in parentheses; BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; Additional covariates included in Model 2, 3, 4, and 5 are BMI at BD2, birth control at BD2 (only for Model 2 and 3), time between CDI and BD2, time between BD1 and BD2, time between LEI and BD1, Gender X LEI - Total at BD1 and Gender X Log CRP/IL-6 (only for Model 3 and 5); *$p < .05$, **$p < .01$, ***$p < .001$.

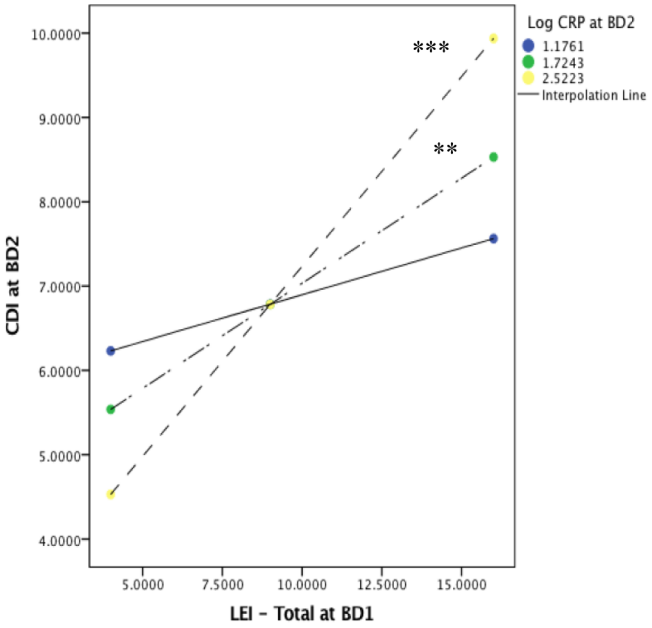

Fig. 2. Change in CRP from BD1 to BD2 Moderates the Relationship Between Total Stressors Prior to BD1 and Depressive Symptoms at BD2. BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; Displays ŷ for each combination of x and moderator level; *$p < .05$, **$p < .01$, ***$p < .001$.

conditional effect of change in CRP began to significantly moderate the relationship between total stressful events and prospective depressive symptoms at log-transformed CRP = 1.455 mg/L (hs-CRP raw value of 4.284 mg/L; 70.80% of the sample was above this value).

This relationship was replicated when we examined the number of acute stressful events for the two weeks prior to BD1, controlling for all of the same covariates (see Table 3). Conditional effects of this relationship were significant at moderate ($b = 0.667$, $SE = 0.261$, $p = .012$), and high ($b = 1.401$, $SE = 0.512$, $p = .007$) levels of CRP at BD2, such that a greater number of acute stressors prior to BD1 predicted greater depression severity at BD2. Johnson-Neyman analyses indicated that the conditional effect of change in CRP began to significantly moderate the relationship at log-transformed CRP = 1.536 mg/L (hs-CRP raw value of 4.646 mg/L; 64.60% of the sample was above this value).

3.3.2. IL6 as moderator

IL-6 levels at BD2 also interacted with the total number of stressful events for the 3–12 months prior to BD1 to predict depression at BD2, controlling for IL-6 levels at BD1, depression at BD1, BMI at BD2, gender, the time between the initial CDI and BD2, the time between the LEI and BD1, and the time between BD1 and BD2 (see Table 2). Conditional effects of this relationship suggested that a higher number of stressful events prior to BD1 predicted greater depression severity at BD2 at moderate ($b = 0.226$, $SE = 0.086$, $p = .010$) and high ($b = 0.472$, $SE = 0.113$, $p < .0005$) levels of IL-6 at BD2 (see Fig. 3). Johnson-Neyman analyses indicated that the conditional effect of change in IL-6 began to significantly moderate the relationship at log-transformed IL-6 = 1.362 mg/L (IL-6 raw value of 3.904; 59.843% of the sample was above this value).

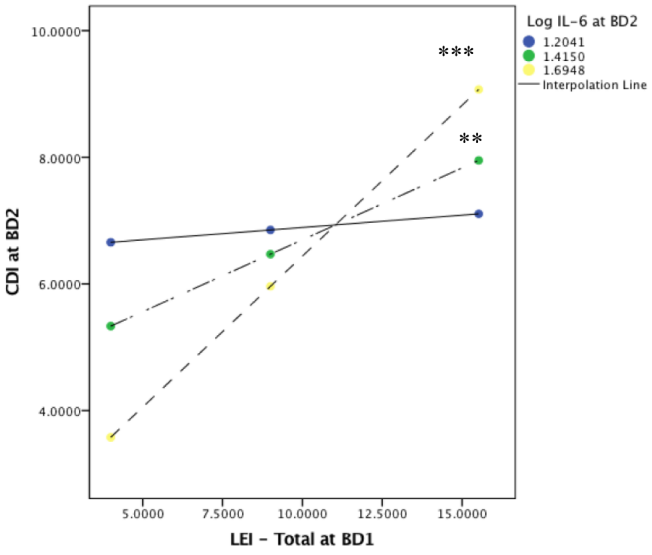

Fig. 3. Change in IL-6 from BD1 to BD2 Moderates the Relationship Between Total Stressors Prior to BD1 and Depressive Symptoms at BD2. BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; Displays ŷ for each combination of x and moderator level; *$p < .05$, **$p < .01$, ***$p < .001$.

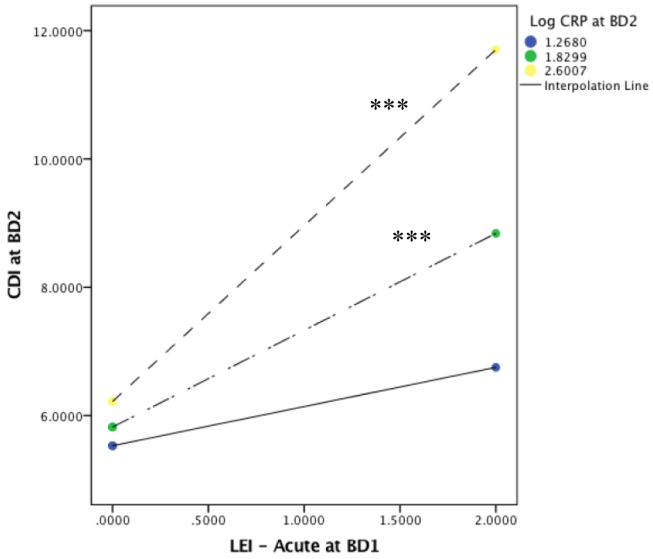

Fig. 4. For adolescent females, change in CRP from BD1 to BD2 Moderates the Relationship Between Acute Stressors Prior to BD1 and Depressive Symptoms at BD2. BD = Blood draw; CDI = Children's Depression Inventory; LEI = Life Events Interview; Displays ŷ for each combination of x and moderator level; *$p < .05$, **$p < .01$, ***$p < .001$.

We found that IL-6 also moderated this relationship for just the number of acute stressors in the two weeks prior to BD1, including the same covariates (see Table 3). Conditional effects of this relationship were significant at moderate ($b = 0.647$, $SE = 0.249$, $p = .014$) and high ($b = 1.227$, $SE = 0.376$, $p = .002$) levels of IL-6 at BD2, such that a greater number of acute stressful events prior to BD1 predicted greater depression severity at BD2. Johnson-Neyman analyses indicated that the change in IL-6 began to significantly moderate the relationship at log-transformed IL-6 = 1.345 mg/L (IL-6 raw value of 3.838; 63.78% of the sample was above this value).

3.3.3. Exploratory analyses of gender, race, and socioeconomic status

To further explore the role of key demographic factors in these temporal associations, the three-way interactions of gender, race, or SES with each of the five inflammatory markers, and both total and acute recent stressors were assessed as predictors of depression at BD2. As shown in Tables 2 and 3, the interaction of gender, acute (but not total) stressors, and change in CRP, but not IL-6, was found to significantly predict depression severity at BD2, including the same covariates as used in the previous models. Also, the interactions of gender, total and acute stressors, and change in TNF-α ($b = 0.019$, $SE = 1.555$, $p = 0.990$; $b = 0.361$, $SE = 5.571$, $p = 0.948$), IL-10 ($b = -1.244$, $SE = 0.836$, $p = 0.140$; $b = 0.600$, $SE = 2.534$, $p = 0.813$), and IL-8 ($b = -0.278$, $SE = 0.797$, $p = 0.728$; $b = 1.394$, $SE = 2.957$, $p = 0.638$) did not significantly predict depression severity at BD2, including the same covariates. Neither race nor SES was found to significantly interact with any of the five inflammatory markers and acute or total stressors to predict depression at BD2.

When the sample was split into females and males, the two-way interaction between acute stressors and change in CRP did not significantly predicted depression for the male adolescents. For females, only the interaction of acute stressors prior to BD1 and change in CRP significantly predicted depression at BD2, including the same covariates ($F(10, 46) = 11.443$, $p < .0005$, $R^2 = 0.713$). In this model, neither the main effect of acute stressors prior to BD1 nor CRP at BD2 significantly predicted depression at BD2. However, we found that the two-way interaction of these predictors was significantly associated with depression at BD2 ($b = 1.599$, $SE = 0.544$, $p = .005$). We estimated the simple slopes for female adolescents (n = 57), and the acute stressors prior to BD1 were significantly associated with depression at BD2 only at moderate and high levels of CRP at BD2 ($b = 1.509$, $SE = 0.405$, $p = .0005$; $b = 2.741$, $SE = 0.671$, $p = .0002$), controlling for the same covariates (see Fig. 4).

4. Discussion

This study is the first to show that the well-established relationship between stressful life events and risk for depressive symptoms depends in part on increased inflammatory activity, as indexed by CRP and IL-6. Our results replicate previous research showing a prospective relationship between stressful life events and increases in depressive symptoms (e.g., Ge et al., 1994; Hankin et al., 2015; Lewinsohn et al., 1999b; Mac Giollabhui et al., 2018a; Monroe et al., 1999). However, in a diverse urban sample, this relationship was significant only for those adolescents with increases in IL-6 and CRP levels over time following stress exposure. For those adolescents with lower levels of inflammatory activity, there appeared to be more psychological resilience even after exposure to frequent stressful life events. Although these adolescents did experience some depressive symptoms, the severity from BD1 to BD2 fluctuated very little (see Figs. 2 and 3) regardless of the number of stressors they experienced. Our findings indicate that a differential susceptibility model may best explain the linkage between inflammation and stress reactivity (Belsky et al., 2009). The subgroup with elevated inflammatory activity following stress exposure appears to be at heightened risk. Simultaneously, this group experienced less depression in the absence of stressors than did those without elevated inflammatory activity. Our findings suggest that stress may be a critical explanatory factor accounting for prior reports linking IL-6 and CRP to the emergence of depression in adolescents (Duivis et al., 2015; Khandaker et al., 2014).

In studies of adults, both CRP and IL-6 have consistently been linked to depression and stress (Beach et al., 2017; Danese et al., 2011; Danese et al., 2009). Consistent with prior findings, elevated IL-10 also was found to be initially associated with more frequent recent stressors. But, unlike IL-6 and CRP, IL-10 levels following stressors did not predict change in depressive symptom severity. IL-6 also has been consistently implicated in the development of depression-like behaviors in animal models; for review see Hodes et al. (2016). IL-6 can directly stimulate the hepatic release of the acute-phase protein CRP which, together with

other proinflammatory cytokines, can trigger changes in the central nervous system (CNS) through more porous regions of the blood-brain-barrier or by stimulating the afferent vagus nerve (Ricciotti and FitzGerald, 2011). Upregulated inflammatory activity alters neural activity in several brain regions linked to depression, including anterior cingulate and insular cortex, and limbic circuitry (Brydon et al., 2008; Capuron et al., 2007; Capuron et al., 2012; Eisenberger et al., 2010; Harrison et al., 2009). These neural alterations can induce cognitive, emotional, and behavioral changes, including depressive symptoms and feelings of fatigue (Byrne et al., 2016; Hodes et al., 2016). Additionally, a single nucleotide polymorphism on the IL-6 promoter region has been linked to increased inflammatory response to stressful life events (Cole et al., 2010). These genetic and neurobiological pathways may help to explain why IL-6 and CRP were the only inflammatory moderators sensitive enough to predict the emergence of depression in our analyses.

Our findings using a longitudinal study design replicate previous cross-sectional studies showing that stress is associated with elevated inflammatory activity (Chiang et al., 2012; Fuligni et al., 2009). One prior study found that a higher cumulative frequency of adverse events predicted changes in inflammatory activity (Slopen et al., 2013), although that analysis did not control for depression after inflammation. Another study found that elevations in IL-6 levels predicted depression only for female adolescents who experienced high levels of childhood adversity (Miller and Cole, 2012). However, more recent stressful events were not integrated into those longitudinal analyses, unlike in our study. More specifically, our findings identified adolescents at increased risk for developing depressive symptoms using interview-based techniques to assess recent stressful events and changes in peripheral inflammatory activity over an average of 1.4 years. Our results concur with the conclusion from prior work that greater biological reactivity to acute stressors is predictive of later depression for female, but not male, adolescents. Although race and SES did not further identify those at risk in our sample, the influence of gender on this relationship may be especially salient and should be explored further.

Utilizing inflammatory activity to identify adolescents at higher risk also could improve the efficacy of targeted interventions. A common criterion of subclinically elevated CRP level is a value over 3 mg/L and physicians usually rely on values over 10 mg/L as a criterion of acute infection (Pearson, 2003). In a research setting, clinical trials testing the value of anti-inflammatory medications for the treatment of depression in adults often use a CRP cutoff value of 5 mg/L (Raison et al., 2018; Raison et al., 2013). However, our Johnson-Neyman analyses indicated that a smaller increment of CRP, even below 5 mg/L (hsCRP raw value of 4.284–4.646 mg/L) in adolescents may convey some risk for depressive symptoms following increased stress. Although adolescents with higher levels of CRP had increasingly severe symptoms of depression, it is important to recognize that inflammatory activity appears to increase the risk of developing depressive symptoms even at lower levels of inflammation. Because CRP is also routinely measured in primary care settings, it would be possible to include it in evaluating the prospective health and well-being of adolescents and identify those who would benefit most from psychological interventions and cognitive behavioral therapies following periods of increased stress.

4.1. Study limitations and future directions

Our conclusions are still limited by the fact that the inflammatory biomarkers were measured at only two timepoints and we did not assess change in stressors, preventing more definitive demonstrations of causality over time. Future studies should utilize additional time points enabling more sensitive temporal resolution. Do increases in inflammatory activity precede (and perhaps cause) increases in depression symptoms following a stressful life event? Alternatively, does increased inflammation and increased depression occur together in the aftermath of stressors? These findings also were limited by the self-reporting of depressive symptoms rather than diagnosed depressive episodes. However, we did use objective interview-based assessment of life events rather than retrospective self-report. Additionally, adolescents from lower SES family backgrounds were slightly less likely to be retained in this analytic sample than represented in the full ACE sample. Thus, our findings derive from a somewhat higher SES sample. However, the retained participants still include a diverse sample comprised of a racially and socioeconomically mixed group of female and male adolescents from a large urban setting (48.8% female, 55.0% African-American, 40.3% low SES), which does enhance the generalizability of these results.

Our analyses did not begin with stressful events during childhood. However, childhood stressors have been found to contribute to the likelihood of depression onset in adolescents through stress-sensitization. The stress-sensitization model posits that adolescents who experience more childhood stressors have an increased susceptibility to developing depressive symptoms in response to lower levels of subsequent stressors compared to their peers without a history of high childhood adversity (Hammen et al., 2000; Harkness et al., 2006). Additionally, among young adults, those who experienced extreme stress during childhood, such as maltreatment, had higher IL-6 and CRP levels with and without provocation by a laboratory social stress test (Carpenter et al., 2010; Carroll et al., 2013; Danese et al., 2007; c.f. Carpenter et al., 2012). Given the effect of childhood stressors on stress-related cognitive and biological processes that contribute to the risk of depression, future studies should explore the impact of childhood stress, in addition to the influence of recent life stress, on longitudinal patterns of inflammation.

Cognitive functioning is a potential pathway linking stress and inflammation with depression. Premorbid general intellectual functioning (IQ) assessed in childhood is predictive of a subsequent diagnosis of major depressive disorder (Koenen et al., 2009) and worse executive functioning prospectively predicts higher depressive symptoms during adolescence (Mac Giollabhui et al., 2018b). Lower IQ may increase risk for depression because it is associated with maladaptive coping styles, thereby reducing one's ability to cope in the face of acute stressors (Joormann and Gotlib, 2010; Martel et al., 2007). This risk may, in turn, be exacerbated by the effect of both stress (Lupien et al., 2009) and inflammation (Harrison et al., 2014) on cognitive functioning, although it should be noted that research also has suggested that inflammation and IQ may be independent risk factors for subsequent depression (Khandaker et al., 2018). Future research could profitably benefit from an examination of the role of cognitive functioning, which could exacerbate biological stress reactivity, the capacity to manage life stress, and subsequent risk for depression.

4.2. Conclusion

In summary, as hypothesized, stressful life events, both within the prior two weeks and prior 3–12 months, were associated with increased severity of depressive symptoms approximately one year later in a diverse sample of urban adolescents. Moreover, increases in the two inflammatory biomarkers most commonly associated with risk for depression, IL-6 and CRP, following stress exposure exacerbated the association between stress exposure and severity of depressive symptoms. Our findings suggest that increased inflammatory responsiveness following stress act as a vulnerability for depression and may provide a modifiable target that could ameliorate the path from stress to depression during adolescence.

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Conflict of interest

The authors declare no conflict of interest.

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