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Examining systemic inflammation as a pathway linking peer victimization to depressive symptoms in adolescence

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Background: Adolescents exposed to victimization are at an increased risk for a variety of adverse mental health outcomes, including depressive symptoms. Yet, the biological pathways underlying these associations remain poorly understood. Focusing on within-person processes, we examined whether low-grade systemic inflammation mediated the longitudinal associations between peer victimization and depressive symptoms in adolescence. **Methods:** 207 adolescents (at baseline M_{age} = 12.69 years; *SD* = 0.49; 43.5% female) participated in a multi-wave longitudinal study, with assessments repeated every 6 months over 1.5 years. At each assessment wave, participants self-reported their peer victimization experiences and depressive symptoms. Dried blood spots were collected at each wave using a finger prick procedure to assay a key marker of low-grade systemic inflammation, interkeukin-6 (IL-6). Data were analyzed using random-intercept cross-lagged panel models. **Results:** The cross-lagged paths from IL-6 to depressive symptoms were significant across all models and waves (β_{12} = .13; β_{23} = .12; β_{34} = .08), indicating that when adolescents' levels of low-grade systemic inflammation were above their person-specific average, they reported increased levels of depressive symptoms in the subsequent months. However, no significant cross-lagged within-person associations emerged between peer victimization and either IL-6 or depressive symptoms. **Conclusions:** The findings provide no evidence for the hypothesized mediating role of inflammation in the within-person associations between peer victimization and depressive symptoms. Nevertheless, they extend prior research by indicating that elevated levels of low-grade systemic inflammation predict the development of depressive symptoms in adolescence. **Keywords:** Adolescence; depression; inflammation; interleukin-6; peer victimization; social stress.

Introduction

Adolescence is a critical period for shaping health trajectories, in part because it encompasses major biological growth and social role transitions. This developmental stage is characterized by significant physical and hormonal changes, which impact adolescents' emotionality and stress reactivity (Romeo, 2010). At the same time, adolescents place increased importance on their perception by, and integration with, peers (Somerville, 2013). This focus on peer inclusion coupled with a malleable physiology may render adolescents particularly vulnerable to the adverse effects of social stressors.

A significant source of social stress for many adolescents is peer victimization, which affects approximately 20%–30% of youths (Afifi et al., 2020; González-Cabrera et al., 2021; Söderberg & Björkqvist, 2020). Adolescents victimized by their peers are at increased risk for various negative health outcomes, including somatic complaints, sleep disturbances, and notably, symptoms of depression (Bowes, Joinson, Wolke, & Lewis, 2015; Burke, Sticca, & Perren, 2017; Herge, La Greca, & Chan, 2016; Kotchick, Papadakis, Nettles, & Jobe, 2020; Li, Huebner, & Tian, 2021; Massing-Schaffer et al., 2019; Nixon, Linkie, Coleman, & Fitch, 2011; Stapinski, Araya, Heron, Montgomery, & Stallard, 2015). Depressive symptoms have been linked to greater personal distress, lower educational attainment, social adjustment problems, and an elevated risk for subsequent psychiatric diagnoses, such as major depressive disorder (Musliner, Munk-Olsen, Eaton, & Zandi, 2016; Weavers et al., 2021). Efforts to better understand the pathogenesis of depression have led to theoretical models such as the *Social Signal Transduction Theory of Depression*, which highlights inflammation as a key biological pathway linking social stressors to increased risk for depression and comorbid physical health problems (e.g. Slavich & Irwin, 2014; Slavich & Sacher, 2019). However, rigorous investigations of the role of inflammation in the association between peer victimization and depressive symptoms – particularly during adolescence – are presently missing in the literature. To address this gap and advance our understanding of risk pathways linking social stressors and depression, we examined whether low-grade systemic inflammation mediated the longitudinal associations between peer victimization and depressive symptoms in adolescence.

Increasingly, researchers have turned to studying low-grade systemic inflammation as a plausible

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biological pathway linking social stressors to depression. Inflammation involves an acute response by neutrophils, monocytes, and dendritic cells to pathogen invasion or cell injury that release inflammatory cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α; Robles, 2021). These cytokines help remove the pathogen and repair damaged cells. Once the threat is eliminated, the inflammation is typically resolved (Furman et al., 2019). According to the *Social Signal Transduction Theory of Depression* (Slavich & Irwin, 2014; Slavich & Sacher, 2019), social stressors can also upregulate inflammatory activity. Social threats such as social rejection and exclusion can activate brain regions that process negative affect and distress, especially in otherwise vulnerable individuals. These brain regions, in turn, project to lower-level neural networks that modulate the activity of the hypothalamus–pituitary–adrenal axis and autonomic nervous system, which can affect inflammation by regulating gene expression activity in leukocytes. Once activated, these social signal transduction pathways may induce transient somatic, affective, and behavioral alterations that closely resemble symptoms of depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Although adaptive in the short term, as the induced biobehavioral responses protect the body from the (presumed) impending threat, repeated activation of these pathways may be harmful. Specifically, prolonged or excessive social threat exposure may sensitize the inflammatory response, leading to chronic low-grade systemic inflammatory activity and, in turn, an increased risk for inflammation-related mental health problems, such as depression (Miller, Chen, & Parker, 2011; Slavich, 2020, 2022; Slavich et al., 2023).

Several studies have found support for this theory. A recent meta-analysis revealed small, but robust positive associations between childhood psychosocial stressors and low-grade systemic inflammation during adolescence (Chiang, Lam, Chen, & Miller, 2022), which echoes prior evidence of a link between early-life adversity and greater inflammatory activity during both adolescence and adulthood (e.g. O'Shields, Patel, & Mowbray, 2022; cf. Lacey et al., 2020; Latham et al., 2022). Similar results have been found for peer victimization. For example, there is evidence suggesting that victimized adolescents have higher levels of inflammatory markers than their non-victimized peers (Arana et al., 2018; Giletta et al., 2018). Additionally, a history of victimization during adolescence has been shown to predict higher levels of low-grade systemic inflammation in early and late adulthood (Copeland, Wolke, Angold, & Costello, 2013; Takizawa, Maughan, & Arseneault, 2014). Peer victimization – and, more broadly, social adversity during the adolescent years – may thus portend an increase in inflammation-related health problems across the life span.

Inflammatory processes are likewise implicated in the pathophysiology of depression. Large population-based studies have linked medical conditions involving increased inflammatory activity to depressive symptoms, which may be alleviated with anti-inflammatory medication (Köhler, Krogh, Mors, & Benros, 2016; Köhler-Forsberg et al., 2019; Park et al., 2018). Regardless of comorbid medical conditions, higher levels of low-grade systemic inflammation have also consistently been found in individuals with clinical depression (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014), as well as in adolescents with elevated depressive symptoms (Toenders et al., 2022). Yet, few studies have examined these associations using within-person designs, which substantially strengthen causal inferences. To our knowledge, only one study used a multi-wave design to investigate bi-directional effects between inflammation and depressive symptoms among adolescents over time (Moriarity et al., 2020). This study found that when adolescents had person-specific increases in markers of inflammation (i.e. IL-10, TNF-α), they reported higher than their typical levels of depressive symptoms 1 year later. Vice versa, adolescents with higher than their typical level of dysphoric symptoms had person-specific increases in markers of inflammation (i.e. IL-6, IL-10, TNF-α).

Despite the theoretical convergence of research on social adversity and inflammation on the one hand, and inflammation and depression on the other, few empirical studies have directly linked social adversity to depressive symptoms via inflammation. A recent systematic review indicated weak evidence in support of a model of inflammation mediating the association between early-life adversity and depression, with approximately half of the investigated studies identifying an effect (Maayan & Maayan, 2024). Offering preliminary evidence for inflammation as a potential pathway, prior longitudinal research, for example, found an inflammatory marker (i.e. C-reactive protein) to underlie the association between retrospective recall of exposure to adverse childhood experiences and depressive symptoms in late adulthood (Iob, Lacey, & Steptoe, 2020). Additionally, a cross-sectional study indirectly indicated that childhood maltreatment and depressive symptoms may be associated via markers of systemic low-grade inflammation (latent variable derived from multiple cytokines; O'Shields et al., 2022). However, other studies did not find evidence for low-grade systemic inflammation as a biological pathway linking social stressors and inflammation. For example, low-grade systemic inflammation (as indexed by C-reactive protein) during late childhood to late adolescence did not appear to underlie the association between adverse childhood experiences and early-adulthood depression, although bullied adolescents emerged to have elevated markers of inflammation (Iob, Lacey, Giunchiglia, & Steptoe, 2022). Similarly, a

cross-sectional study examining associations between peer victimization, inflammation, and depressive symptoms during adolescence found no evidence for inflammation as a mediating pathway (Arana et al., 2018). Rather, peer victimization was indirectly associated with a marker of low-grade systemic inflammation (i.e. IL-6) via depression.

A key limitation of existing research is its reliance on cross-sectional data (e.g. Arana et al., 2018) and two-time-point designs, mostly with very long intervals between assessments, spanning one or more years (e.g. Iob et al., 2022). These designs are not well suited to examine mechanistic processes, which instead require repeated assessments over shorter time periods. Additionally, the hypothesized processes, such as the impact of inflammation on depressive symptoms, imply within-person *change*, which has often been examined by looking at between-person differences (Moriarity & Slavich, 2023). This may lead to misinterpretations, as associations found at the population level may not be applicable at the individual level (Fisher, Medaglia, & Jeronimus, 2018). Using within-subject designs instead may substantially strengthen causal inferences, as participants serve as their own control, which largely removes unmeasured vulnerabilities across participants. Prior research, therefore, offers only limited insights into the dynamic associations between peer victimization, inflammation, and depressive symptoms.

The present study

We aimed to address these critical issues in the present study by examining the mediating role of low-grade systemic inflammation in the longitudinal associations between peer victimization and depressive symptoms during adolescence. To this end, we examined data collected over four waves, spanning 1.5 years, which began during adolescents' transition to secondary school. This enabled us to capture a time of increased social sensitivity, as students formed new peer relations and entered different peer groups. We focused on levels of circulating IL-6, a key marker of low-grade systemic inflammation (Chiang et al., 2022). Based on the research summarized above, we hypothesized that, when adolescents reported higher than their person-specific average of peer victimization, they would have higher than their typical levels of low-grade systemic inflammation 6 months later. Inflammation, in turn, was hypothesized to predict greater person-specific increases in levels of depressive symptoms over time.

Method

Preregistration and transparency

This study's hypotheses and analyses were preregistered on the Open Science Framework (OSF; https://osf.io/5647j). However, we deviated from the preregistered analytic plan in a number of ways. The deviations as well as the results of the originally planned analyses are reported in the Supporting Information (Appendices S1–S3, Table S1).

Participants and procedure

Data were available for 233 participants who took part in a larger longitudinal project aimed at investigating the effects of adolescents' peer experiences on their physical and mental health (see e.g. de Bruine, Denissen, & Giletta, 2022). In two secondary schools in the Netherlands, data were collected approximately every 6 months for a total of four waves, starting when students were in the first year of secondary school until the end of their second year. All first-year students (n = 459) and their parents were introduced to the project via informational meetings, during which they were handed information letters and informed consents. Approximately half of the attending parents provided consent for their child to participate in the study. Out of those with parental consent, thirteen adolescents did not participate in the first wave of data collection because they either opted out of the study (n = 7), were sick on the day of recording (n = 5), or had transferred to another school (n = 1). Adolescents who did not participate in wave 1 could join the study at a later wave. For further details on the recruitment procedure, see prior publications (de Bruine, Denissen, & Giletta, 2022; Kellij et al., 2024).

For the present study, participants were included if they had valid data for all key variables for at least one of the four waves of data collection, resulting in a final analytic sample of 207 participants aged approximately 12 years at baseline (M = 12.69 years; SD = 0.49; 43.5% female). Detailed information about the retention rate over time and missing data for the key variables is provided in the Supporting Information (Appendix S4). Participants primarily identified themselves as Dutch (92.3%) and lived with both of their biological parents (81.8%).

Adolescents provided written assent for participation at the start of each wave of assessment. They then completed a battery of online questionnaires during school hours, with no more than six students in the room at a time. Afterward, participants individually took part in a physical health assessment, which included measurements of the adolescent's height and weight, as well as the collection of dried blood spots to assess inflammatory levels. Completing all assessments took approximately 60 min. At the end of each wave, participants received a 10€ gift card. The study was approved by the Medical Ethics Committee Brabant, the Netherlands (NL56418.028.16).

Measures

Peer victimization. Peer victimization was measured with the Revised Peer Experiences Questionnaire (Prinstein, Boergers, & Vernberg, 2001), which includes items assessing overt, relational, and reputational peer victimization experienced over the past 6 months. This self-report measure consists of thirteen statements (e.g. 'A peer hit, kicked or pushed me in a mean and harmful way'), to which responses are given on a 5-point Likert scale ranging from 1 (*never*) to 5 (*a few times a week*). A total peer victimization score was computed for each wave by averaging across the 13 items, with higher scores indicating higher levels of peer victimization. Internal consistency was high across all waves (Cronbach's $\alpha > .83$). Given high skewness and kurtosis, all peer victimization values were log transformed (natural logarithm).

Depressive symptoms. Depressive symptoms were measured using the Short Mood and Feelings Questionnaire (SMFQ; Messer et al., 1995). The questionnaire asks

participants to indicate the degree to which they agree with a total of thirteen items on their feelings and actions of the past 2 weeks (e.g. 'I felt miserable or unhappy'). Responses are given on a 3-point Likert scale ranging from 1 (*Not true*) to 3 (*True*). A total depressive symptom score was calculated for each wave by averaging across items, with higher scores reflecting higher levels of depressive symptoms. The SMFQ has previously been shown to correlate with measures of clinical depression (Rhew et al., 2010). Internal consistency of the SMFQ was high across all waves (Cronbach's $\alpha > .85$). Given high skewness and kurtosis, all depressive symptoms values were log transformed (natural logarithm).

Inflammation. The inflammatory cytokine IL-6 was derived from dried blood spots via a finger prick procedure. This minimally invasive procedure is particularly advantageous to use with adolescents for whom repeated venipuncture may otherwise be problematic (Fischer, Obrist, & Ehlert, 2019; McDade, 2014). Trained research assistants collected blood spots following a standardized protocol (see McDade, 2014). After a slight prick to the middle or ring finger using single-use micro lancets (BD Microtainer® lancets 1.5 mm blade, 2.00 mm depth), between 2 and 5 drops of blood (approximately 50 μl per drop) were collected on filter paper (Whatman #903). The filter papers were then allowed to air dry before they were stored at −30°C in a freezer at the University. Once data collection was completed, all samples were flown to the Laboratory for Human Biology Research at Northwestern University for assay. Following a validated protocol (McDade, Miller, Tran, Borders, & Miller, 2020), assays were done using the ultrasensitive S-PLEX Human IL-6 Kit (Meso Scale Diagnostics), which has a minimum detection threshold of 0.042 pg/mL. Whenever possible, samples were assayed in duplicate (79%), revealing acceptable mean intra- and inter-assay coefficients of variability (CV; 7.5% and 7.7%, respectively). Given high skewness and kurtosis, all IL-6 values were log transformed (natural logarithm).

Covariates. Participants' sex and body mass index (BMI; adjusted for age and sex) were included as covariates given prior research pointing to their potential influence on inflammatory mechanisms (e.g. Gregor & Hotamisligil, 2011; Schachter et al., 2018; Slavich & Sacher, 2019). We also considered including smoking and alcohol use as covariates (O'Connor et al., 2009). However, at any given wave, only few participants smoked (< 3.4%) or consumed alcohol on a weekly basis (<1.7%). With little variance in these variables, modeling their effects may have come at the cost of inflating the Type I error rate (Ribbing & Jonsson, 2004). We therefore decided a priori not to include these variables in the models.

Statistical analyses

We first ran descriptive analyses, correlations, and Intraclass Correlations Coefficients (ICC) for key variables using RStudio version 1.4.1717 (R Core Team, 2022). We then conducted random-intercept cross-lagged panel models (RI-CLPMs; Hamaker, Kuiper, & Grasman, 2015; Mulder & Hamaker, 2021) in Mplus version 8.8 (Muthén & Muthén, 1998-2017) to examine whether IL-6 mediated the associations between peer victimization and depressive symptoms over time. RI-CLPMs decompose the score of each observed variable (i.e. peer victimization, IL-6, and depressive symptoms) into stable between-person components and fluctuating within-person components. Therefore, this approach enabled us to investigate within-person cross-lagged effects while accounting for stable between-person differences.

We estimated four main models that included autoregressive effects, bi-directional cross-lagged effects, and concurrent within-time associations (i.e. residual covariances and variances). The first RI-CLPM (Model 1) examined the within-person effects of peer victimization on IL-6 over time. Then, the second RI-CLPM (Model 2) examined the within-person effects of IL-6 on depressive symptoms. The third RI-CLPM (Model 3) examined the full hypothesized model including peer victimization, IL-6, and depressive symptoms. Lastly, we conducted bootstrapped mediation analyses to estimate the indirect within-person effect of peer victimization (t) on depressive symptoms ($t + 2$) via IL-6 ($t + 1$; Model 4). This step-wise model-building strategy was chosen to ensure that estimates were robust across models.

All models used robust maximum likelihood estimation (MLR) and included participants' sex and BMI as time-invariant predictors of the random intercepts (see Mulder & Hamaker, 2021). Missing data were handled using full information maximum likelihood (FIML). To estimate the most parsimonious models and test for time invariance of estimates, for each of the main models, we compared a fully unconstrained baseline model to models in which constraints were gradually imposed on the autoregressive paths, cross-lagged paths, residual covariances and variances, and grand means. Examining time invariance in this way was particularly important, given recent evidence suggesting that immune markers – and their associations with stress – may vary by season (Gassen, Mengelkoch, & Slavich, 2024). The final models retained for analyses included equality constraints for the various paths only if imposing the constraints did not significantly worsen model fit (i.e. non-significant chi-square difference test). Model fit indices and model fit comparisons of all evaluated models are provided in the Supporting Information (Appendices S5–S7, Tables S3–S5). The final dataset and syntax are available on OSF (Lorenz, Michels, & Giletta, 2024).

Results

Descriptive analyses

Descriptive information for the primary study variables is provided in Table S2. Bivariate correlations among key variables are reported in Table 1. ICCs were 0.49 for peer victimization, 0.18 for IL-6, and 0.57 for depressive symptoms, indicating that 51%, 82%, and 43% of the variance observed in peer victimization, IL-6, and depressive symptoms, respectively, were attributable to within-person fluctuations over time. Therefore, there was sufficient within-person variance to investigate within-person processes.

Associations between peer victimization, Interleukin-6, and depressive symptoms

Models 1 and 2 examined associations between peer victimization and IL-6, and IL-6 and depressive symptoms, respectively. The final RI-CLPMs retained for analyses had acceptable model fit (Model 1: $\chi^2(29) = 36.07$, $p = .17$, TLI = 0.96, CFI = 0.98, RMSEA = 0.03, SRMR = 0.06; Model 2: $\chi^2(32) = 52.52$, $p = .01$, TLI = 0.92, CFI = 0.94, RMSEA = 0.06, SRMR = 0.07). Figures S1 and S2 present the RI-CLPMs. As shown in Figure S1 (Model 1), no significant within-person associations emerged between peer victimization and IL-6. There was thus no evidence suggesting that person-specific increases in peer victimization predicted higher levels of IL-6 6 months later. Moreover, the random

Table 1 Bivariate correlations among key variables

	Peer victimization				IL-6			Depressive symptoms			BMI					
Variable	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
PV																
Wave 1																
Wave 2	.60***															
Wave 3	.47***	.60***														
Wave 4	.44***	.54***	.59***													
IL-6																
Wave 1	−.02	.09	.06	.08												
Wave 2	.06	.05	.003	.12	.22**											
Wave 3	−.08	−.06	−.03	.01	.28***	.33***										
Wave 4	.02	−.11	−.002	−.02	.10	.08	.15									
DS																
Wave 1	.56***	.51***	.36***	.39***	−.01	.07	−.12	−.21*								
Wave 2	.39***	.57***	.41***	.39***	.10	−.02	−.10	−.17*	.65***							
Wave 3	.29***	.48***	.50***	.36***	.07	−.03	−.05	−.14	.49***	.64***						
Wave 4	.27***	.38***	.34***	.45***	.001	−.05	−.05	−.14	.48***	.56***	.65***					
BMI																
Wave 1	.01	.05	.13	.14	.23**	.04	.08	.18*	.07	.06	.05	−.01				
Wave 2	.09	.12	.17*	.21**	.19*	.06	.08	.06	.09	.12	.10	.02	.92***			
Wave 3	.02	.07	.12	.12	.10	.11	.09	.17	.03	.05	.05	−.03	.88***	.90***		
Wave 4	−.07	−.01	−.001	.11	.07	.04	.05	.07	−.05	−.02	.003	−.06	.87***	.91***	.93***	
Sex (0 = female)	.10	−.07	−.02	−.05	−.03	.18*	.17*	.16	−.04	−.24***	−.17*	−.17*	−.06	−.10	−.09	−.17*

Bivariate correlations are for transformed variables. Sex was dummy-coded (0 = female, 1 = male). BMI scores are based on percentiles and were standardized for age and sex (< 5th percentile, underweight; between 5th and 85th percentile, healthy weight; between 85th and 95th percentile, overweight; > 95th percentile, obesity; CDC).
BMI, body mass index; DS, depressive symptoms; IL-6, interleukin-6; PV, peer victimization.
*$p < .05$; **$p < .01$; ***$p \leq .001$.

intercepts were not significantly correlated, indicating that peer victimization and IL-6 were also not associated at the between-person level. However, as shown in Figure S2 (Model 2), the cross-lagged paths from IL-6 to depressive symptoms were significant across all waves (*p*s = .03), with medium-to-large effect sizes (β_{12} = .16, β_{23} = .14, β_{34} = .09; Orth et al., 2024). The results indicated that person-specific increases in levels of IL-6 predicted higher levels of depressive symptoms 6 months later. In the other direction, the lagged paths from depressive symptoms to IL-6 were not significant.

The final RI-CLPM for Model 3 examined the associations between peer victimization, IL-6, and depressive symptoms. Model fit was good for this model as well ($\chi^2(64) = 78.76$, $p = .10$, TLI = 0.97, CFI = 0.98, RMSEA = 0.03, SRMR = 0.06). Model results (Figure 1) generally reflected those of the prior models. Similar to Model 1, no significant within- or between-person associations emerged between peer victimization and IL-6. Additionally, although there were significant concurrent within-person associations between peer victimization and depressive symptoms (*p*s < .05), cross-lagged associations were not significant. There was therefore no evidence suggesting that person-specific increases in peer victimization predicted higher levels of either IL-6 or depressive symptoms 6 months later. Similar to Model 2, the cross-lagged paths from IL-6 to depressive symptoms were significant across all waves (*p*s = .049), with medium-to-large effect sizes (β_{12} = .13, β_{23} = .12, β_{34} = .08). Additionally, a significant cross-lagged path from depressive symptoms to IL-6 was observed from wave 1 to wave 2 ($p = .01$; β_{12} = .27).

As no significant lagged associations with other key variables emerged for peer victimization, we did not test for significant indirect paths.

Discussion

Prior studies have linked adolescent peer victimization to concurrent depressive symptoms as well as future symptom escalation (e.g. Bernasco, van der Graaff, Meeus, & Branje, 2022; Davis et al., 2019; Li et al., 2021); yet, there is still limited knowledge about the biological mechanisms underlying these associations. To address this gap, we investigated the role of low-grade systemic inflammation, as measured by IL-6 levels, in the within-person associations between peer victimization and future depressive symptoms in adolescence. Our results provide no evidence for the hypothesized mediating role of inflammation. However, they reveal potential within-person effects from IL-6 to later depressive symptoms.

The findings indicate that when adolescents' levels of low-grade systemic inflammation are above their person-specific average, they may report increased levels of depressive symptoms 6 months later. These results extend prior research on the association between inflammation during late childhood to early adolescence and depressive symptoms, most of which focused on between-person differences (e.g. Chu et al., 2019; Khandaker et al., 2018). Only one prior study has taken a similar approach to the present study by examining within-person associations over time (Moriarity et al., 2020). The study identified a potential causal role particularly for TNF-α in the development of depressive symptoms after 1 year. The present study highlights the role of another marker of inflammation, IL-6, in predicting depressive symptoms among adolescents. Considering that depressive symptoms predicted increased levels of IL-6 at only one instance in one model, low-grade systemic inflammation may be a risk factor for depression, rather than a consequence of it.

Peer victimization, however, predicted neither low-grade systemic inflammation nor depressive symptoms at the within-person level, providing no evidence for inflammation as a biological pathway linking peer victimization to depressive symptoms. These findings are surprising given prior literature suggesting that peer victimization may be causally related to the development of depressive symptoms (e.g. Davis et al., 2019; Li et al., 2021; cf. Bernasco et al., 2022), and research linking psychosocial stressors to low-grade systemic inflammation (for a meta-analysis see Chiang et al., 2022). Yet, prior studies have often focused on longitudinal associations with large time frames, for example linking victimization experiences during adolescence to markers of inflammation during adulthood (Copeland et al., 2013; Takizawa et al., 2014). It may thus be that associations with circulating markers of low-grade systemic inflammation emerge over longer periods of time (see also Scott & Manczak, 2021), becoming evident only after cumulative exposure to chronic stress or with full biological maturation. Our measure of peer victimization asked about the frequency of adolescents' exposure to victimization over the past months, which may not have sufficiently captured the chronicity of the experiences. Moreover, all key measures were assessed during adolescence in the present study. We were therefore unable to investigate the potential effects of peer victimization in adulthood. Future research may benefit from repeating assessments over multiple years during adolescence to early adulthood to tap into the chronicity of the psychosocial stressor as well as capture larger maturation periods.

Interestingly, the present study revealed high within-person variation as well as relatively low stability in IL-6 over the span of 6 month. These findings contrast those of prior meta-analytic work (Walsh et al., 2023), which showed at least moderate stability of IL-6 in adults over periods of up to 3 years. Although our findings may not fully represent the broader literature (e.g. Miller &

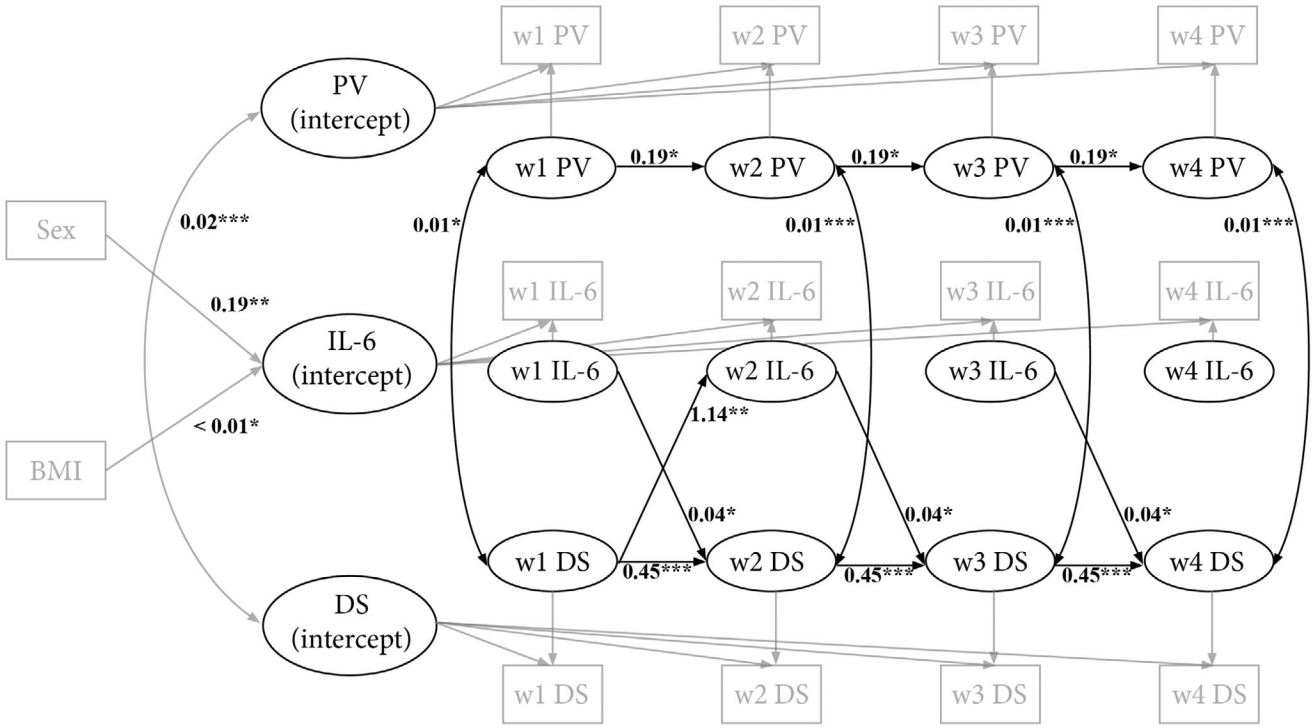

Figure 1 Final random-intercept cross-lagged panel model for peer victimization, interleukin-6 and depressive symptoms. For ease of interpretation, only significant paths are shown. Estimates are unstandardized. Observed variables are shown in gray. BMI, body mass index; PV, peer victimization; IL-6, interleukin-6; DS, depressive symptoms; w1–w4, waves 1–4. *$p < .05$, **$p < .01$, ***$p < .001$

Wrosch, 2007), they may suggest that exclusive reliance on circulating markers of systemic inflammation provides only a limited view of the complex inflammatory response. To gain a more dynamic understanding of immune activity, future studies may benefit from using alternative approaches, such as ex vivo cell culture methods (see Ehrlich, Miller, Rohleder, & Adam, 2016). These methods involve assessing the intensity of the inflammatory response to microbial challenges. They may offer a more detailed examination of the inflammatory process compared to the analysis of circulating markers of systemic inflammation, providing insights into how immune cells respond to pathogens in a controlled setting (McDade et al., 2021).

An alternative reason for some of our null effects may be that low-grade systemic inflammation modulates the associations between peer victimization and depressive symptoms, rather than serves as an underlying pathway. For example, prior research has revealed that the interaction between a history of childhood adversity and low-grade systemic inflammation predicted depression (Miller & Cole, 2012). We examined the potential modulating role of low-grade systemic inflammation in some of our own analyses, but were unable to detect significant associations (see Appendix S2), likely because of a lack of power. The *Social Signal Transduction Theory of Depression* also predicts a link between social stress, inflammation and depressive symptoms particularly for vulnerable individuals (Slavich & Irwin, 2014). Given our low sample size, we were underpowered to investigate the potential modulating effect of early-life adversity or cognitive vulnerability, which may be critical for detecting associations between social stressors, inflammation, and depression. We recommend that future research oversample high-risk adolescents and use larger sample sizes when investigating within-person associations of psychobiological processes.

Strengths and limitations

The present study extends prior research on the within-person associations between low-grade systemic inflammation and depressive symptoms in adolescents. Using a within-person design, we were able to examine potential causal associations, rather than solely focus on average differences between adolescents. Nevertheless, our study has several limitations. First, although our sample size is comparable to that of other studies examining within-person associations between social stressors, inflammatory markers, and health outcomes among adolescents (Kautz et al., 2023; Miller & Cole, 2012; Moriarity et al., 2020), the sample size was too small to identify small effects (for results of our power simulation, see Appendix S8; see also Mulder, 2023). Moreover, although the lagged effects of IL-6 on depressive symptoms were consistent across models and waves, we cannot entirely rule out the possibility that the relatively

small sample size resulted in biased estimates. It is therefore crucial that future studies use larger sample sizes to validate and build upon our findings. Second, average levels of reported peer victimization and depressive symptoms were generally low in our study, similar to findings in other research using community samples (e.g. Ehrhardt, Hoffman, & Schacter, 2022; Stapinski et al., 2015). Even though using a normative sample offered us baseline data on the prevalence and natural variation in peer victimization, levels of circulating IL-6 and depressive symptoms, our sample choice may have contributed to some of our null findings. Third, we used self-reports for our peer victimization and depressive symptoms measures, which allowed us to tap into adolescents' own perceptions of adversity and symptom severity. However, using clinical interviews for depression in particular may have improved clinical relevance.

Another limitation of our study is that, to investigate adolescents' levels of low-grade systemic inflammation, we relied on dried blood spot assays rather than assays of cytokines derived from plasma samples – the current gold standard (McDade, 2014). However, using dried blood spots was advantageous for the current sample, as the procedure is minimally invasive and allowed us to prick adolescents repeatedly without inducing significant discomfort. Additionally, as detailed in prior validation research, cytokines derived from dried blood spots samples are generally highly correlated with cytokines from plasma samples (McDade et al., 2020). Finally, although our within-subject design helped to partial out potentially unmeasured vulnerabilities shared across participants, the possibility remains that unmeasured confounders influenced our effects (e.g. other life stressors, sleep health, medical history). Relatedly, we did not have reliable information about participants' socio-economic status (SES), and therefore could not control for its potential effects. The extent to which our findings can be generalized across various SES levels remains unknown.

Conclusion

In conclusion, the present data revealed significant within-person associations between low-grade systemic inflammation and depressive symptoms among adolescents. The results are primarily suggestive of a directional association from inflammation to depressive symptoms, but not the other way around, thus pointing to low-grade systemic inflammation as a potential risk process implicated in the pathogenesis of depressive symptoms. Although we did not find evidence suggesting a significant role for peer victimization in these associations, it remains important to identify risk factors for the coupling of inflammation and depression to better identify vulnerable adolescents.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Deviations From the Preregistration (https://osf.io/5547j).

Appendix S2. Preregistered Analyses.

Table S1. Longitudinal Mediation and Moderation Analyses to Assess Direct and Indirect Within-Person Effects of Peer Victimization on Depressive Symptoms via, or in Interaction With, Interleukin-6.

Appendix S3. RStudio Code for the Preregistered Analyses.

Appendix S4. Retention Rate and Missing Data.

Table S2. Descriptive Information for Key Variables.

Appendix S5. Random-Intercept Cross-Lagged Panel Models for Peer Victimization and Interleukin-6.

Table S3. Model Fit Indices and Model Fit Comparisons of all Random-Intercept Cross-Lagged Panel Models for Peer Victimization and Interleukin-6.

Appendix S6. Random-Intercept Cross-Lagged Panel Models for Interleukin-6 and Depressive Symptoms.

Table S4. Model Fit Indices and Model Fit Comparisons of Random-Intercept Cross-Lagged Panel Models for Interleukin-6 and Depressive Symptoms.

Appendix S7. Random-Intercept Cross-Lagged Panel Models for Peer Victimization, Interleukin-6 and Depressive Symptoms.

Table S5. Model Fit Indices and Model Fit Comparisons of Random-Intercept Cross-Lagged Panel Models for Peer Victimization, Interleukin-6, and Depressive Symptoms.

Figure S1. Final Random-Intercept Cross-Lagged Panel Model for Peer Victimization and Interleukin-6.

Figure S2. Final Random-Intercept Cross-Lagged Model for Interleukin-6 and Depressive Symptoms.

Appendix S8. Power Simulation.

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Ethical approval

All participants and their primary caregivers provided informed consent and assent for participation in the project. The study was approved by the Medical Ethics Committee Brabant, the Netherlands (NL56418.028.16).

Data availability statement

The data that support the findings of this study are openly available in OSF at http://doi.org/10.17605/OSF.IO/JMFET.

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Key points

- Despite the known link between peer victimization and depression during adolescence, the underlying biological mechanisms remain largely unknown.
- The present study examined whether a key marker of low-grade systemic inflammation (i.e. interleukin-6) mediated the within-person associations between peer victimization and depressive symptoms in 207 adolescents, with assessments repeated every 6 months over 1.5 years.
- Analyses of random-intercept cross-lagged panel models revealed a significant cross-lagged path from interleukin-6 to depressive symptoms. However, no significant cross-lagged within-person associations emerged between peer victimization and either interleukin-6 or depressive symptoms.
- Findings suggest that inflammation may predict the development of adolescent depressive symptoms. Future research should use designs that are better suited to identify the short-term effects of peer victimization on inflammation, especially among cognitively vulnerable youth.

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