Title

IL-6 predicts non-suicidal self-injury over 3 months in high-risk adolescents.

Journal

BJPsych Open, 10(2)

ISSN

2056-4724

Authors

Bai, Sunhye
Asarnow, Joan
Babeva, Kalina
et al.

Publication Date

2024-02-26

DOI

10.1192/bjo.2023.656

Peer reviewed

BJPsych Open (2024)
10, e51, 1–6. doi: 10.1192/bjo.2023.656

IL-6 predicts non-suicidal self-injury over 3 months in high-risk adolescents

Sunhye Bai, Joan R. Asarnow, Kalina N. Babeva and Michael R. Irwin

Background

Suicide is the second leading cause of death in 12- to 17-year-old adolescents in the USA. Research on biological mechanisms contributing to self-harm risk that could be targeted in treatment could help to prevent suicide and self-harm episodes.

Aims

We aimed to evaluate whether markers of inflammation, interleukin-6 (IL-6) and C-reactive protein (CRP), predict self-harm over 3 months within a sample selected for elevated suicide/self-harm risk at project entry.

Method

Fifty-one adolescents aged 12–19 years selected for elevated suicide/self-harm risk completed three clinical interviews about suicide attempts and non-suicidal self-injury, 3 months apart. At baseline and 3 months, youth also provided blood samples, from which we assayed levels of IL-6 and CRP.

Results

Using generalised mixed models, we found that greater levels of IL-6 predicted more self-harm episodes (odds ratio [OR] = 3.3, 95% CI: 1.1, 10.0) and specifically, non-suicidal self-injury (OR = 3.5, 95% CI: 1.1, 11.2), over 3 months.

Conclusions

The study findings increase our understanding of whether and how inflammation may be implicated in risk of self-harm. IL-6 may be a viable biological marker of short-term risk for self-harm.

Keywords

Non-suicidal self-injury; inflammation; interleukin-6; C-reactive protein; self-harm.

Suicide prevention is recognised as a national imperative by the US National Strategy for Suicide Prevention.[1] In 2020, suicide was the second leading cause of death in 12- to 17-year-old adolescents in the USA.[2] Prior self-harm (defined to include suicide attempts and non-suicidal self-injury [NSSI]), is among the most reliable predictors of suicide deaths and suicide attempts in adolescents and is more common than suicide deaths.[3,4] National surveys of US high school students indicate 1 year point prevalence rates of 10.2% for suicide attempts and 22.2% for clinically significant suicidal ideation.[5] NSSI is more common than suicide attempts in adolescents and is estimated at 22.1%,[6] with data indicating increasing rates,[7] and NSSI is a strong predictor of later suicide attempts.[4] Despite extensive research on suicide risk and protective factors, the suicide rate has not declined significantly over the past 60 years,[2] underscoring the critical need for research on mechanisms contributing to suicide and self-harm risk that could be targeted through treatment.[8] Understanding the role of inflammatory mechanisms could help to define the biological profile of those at highest risk and inform the development of targeted and integrated preventive interventions.[9]

Pro-inflammatory cytokines are signalling proteins in the body that typically trigger inflammation to help fight threats. They can also alter the metabolism of key monoamines that are involved in the pathogenesis of mood disorders.[10] At high levels, pro-inflammatory cytokines such as C-reactive protein (CRP) and interleukin-6 (IL-6) contribute to the onset of depressive symptoms and possibly to the incidence of major depressive disorder, especially in at-risk populations, including adolescents.[11] Indeed, meta-analytic research has shown that CRP and IL-6 are concurrently and prospectively associated with depression symptoms in adolescents.[11] Multiple psychosocial factors can drive the upregulation of inflammation, including chronic stress, trauma and sleep disturbances.[12,13] Depression, stress and sleep disturbances are well-established risk factors for self-harm,[14,15] with depressive disorders being the most prevalent mental health disorder among adolescent suicide victims, at rates ranging from 49% to 64%.[16,17]

Research on the links between inflammation and self-harm in adolescence is nascent and, thus far, inconclusive. Individuals who attempted suicide as adolescents and young adults (through age 24) have been found to have significantly elevated systemic inflammation, measured at age 35.[18] Whether these elevations in inflammation had an earlier adolescent onset which persisted into adulthood is unknown. One study comparing adolescents with at least five episodes of NSSI during the past 12 months and healthy controls did not detect differences in levels of IL-6 or CRP.[19] Another population-based cohort study of youth in the UK failed to detect a significant association between levels of IL-6 and CRP at age 9.5 years and self-harm at age 16 years.[20] By contrast, Melhem et al[21] found that youth aged 15–30 years old admitted for suicide attempts had higher levels of CRP than healthy controls. However, no difference in CRP was detected when comparing youth admitted for suicidal ideation with healthy controls. Given variability in the frequency and chronicity of self-harm during adolescence, clarifying prospective associations among indicators of inflammation and self-harm, particularly over a short timespan, has potential for illuminating risk pathways for self-harm that could be targeted using new treatment strategies.

Current study

The current study focuses on self-harm as the primary outcome variable, with the aim of evaluating whether markers of inflammation (IL-6 and CRP) predict self-harm over a relatively brief 3-month time frame within a sample selected for elevated suicide/self-harm

risk at project entry. We hypothesised that higher levels of inflammation would predict greater levels of self-harm, with secondary analyses evaluating the separate self-harm subcomponents of NSSI and suicide attempts. We also examined the prospective associations between inflammation levels and three suicide risk indicators that have been implicated in inflammatory pathways: prior suicidal ideation,[22,23] depression[11,24] and sleep disturbances.[25,26] Consistent with past studies, we hypothesised that higher levels of inflammation would predict higher levels of suicidal ideation, depression symptoms and poorer sleep. To our knowledge, this is the first study to examine whether inflammatory markers predict short-term (i.e. 3 month) self-harm levels in a sample of youth identified as having elevated suicide and self-harm risk.

Method

Participants

Fifty-one youth (86.3% female, M_{age} = 16.1 years) were recruited from an out-patient programme for youth suicide and self-harm risk (18 of whom had participated in programme randomised clinical trials[27,32]). Inclusion criteria were: age 12–19 years; a history of suicidal events (i.e. suicide attempts, interrupted suicide attempts, aborted suicide attempts or severe suicidal ideation); and prior self-harm (suicide attempts or NSSI). Exclusion criteria were no contact information (address, telephone number) needed for follow-up; living situation, functioning or other characteristics that would interfere with participation/assessments (immediate risk of out-of-state placement, severe cognitive disability, acute psychosis); youth who did not speak English; and primary caregiver who did not speak English or Spanish. Our sample was demographically diverse and had a high risk for self-harm. During the 12 months preceding the baseline assessment, 86% of the sample had gone to a mental health clinic or a professional counsellor (e.g. psychologist, therapist, mental health clinic), 49% had seen a psychiatrist, 33% had been in an in-patient or residential setting for psychiatric problems, and 28% had been in a partial hospital admission programme. Over half the sample reported current use of selective serotonin reuptake inhibitors (SSRIs) at baseline.

Procedures

Assessments were scheduled at this study's baseline and at 3- and 6-month follow-ups. Participants provided blood samples and height and weight measurements at the baseline and at the 3-month assessment. At every assessment, trained assessors evaluated self-harm via structured clinical interviews, and participants self-reported their suicidal ideation, depression and sleep disturbances using a Qualtrics survey. Assessors were trained for the administration and scoring of each measure. For interview measures (Suicide Attempt and Self-Injury Interview; SASII), after initial training, assessors were observed, and interviews were co-rated by a designated 'gold-standard' interviewer until they demonstrated 0.80 interrater reliability. Thereafter, co-ratings were completed for about one of every 15 randomly selected interviews, with co-ratings indicating strong interrater reliability for self-harm classification (suicide attempt versus NSSI: 98.3% agreement; kappa = 0.96, $P < 0.001$). Parents and youth ≥18 years old provided written informed consent, and youth <18 years provided written assent. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by the University of California Los Angeles Institutional Review Board (#13-001704).

Inflammation

Circulating levels of inflammation were assessed by assays of plasma inflammatory biomarkers IL-6 and CRP. These markers were selected because of our theoretical focus on inflammation and evidence that both IL-6 and CRP are robustly associated with depression.[11] IL-6 and CRP were measured in collected plasma. Whole blood was collected into EDTA tubes via venepuncture by a licensed phlebotomist. Within 2 h of collection, whole blood was centrifuged at 4 °C, separated into plasma aliquots and stored at −80 °C.

Plasma levels of IL-6 were assayed in duplicate in a single batch using the Meso Scale Discovery (MSD) MULTI-SPOT Assay System (Rockville, MD) with a custom 5-plex from the Proinflammatory Panel 1 Human Kit as previously described.[29] In addition to IL-6, MSD assays were used to evaluate plasma levels of TNF-α, IL-6, IL-8 and IL-10. Given the *a priori* hypothesis and specific focus on IL-6, these other analytes are not reported. Assays were performed according to the manufacturer's protocol. ECL signals were measured on the MESO QuickPlex SQ 120 instrument (Rockville, MD), and the DISCOVERY WORKBENCH software (Rockville, MD) was used to generate a four-parameter logistic fit curve. The mean intra-assay coefficient of variation (CV) for IL-6 was 2.4%, and the mean inter-assay CV was 7.0%. The lower limit of detection for IL-6 was 0.2 pg/mL, which occurred in less than 2% of the sample; values lower than the lower limit of detection were imputed as 0.2 pg/mL.

CRP levels were assayed in duplicate using Human CRP Quantikine ELISA (R&D Systems) according to the manufacturer's protocol as previously described.[30] The intra-assay CV for CRP was 3.3%, and the mean inter-assay CV was 4.5%. For CRP, the lower limit of detection was 0.2 mg/L, which occurred in about 20% of the sample; values lower than the lower limit of detection were imputed as 0.2 mg/L. The upper limit of detection was 25 mg/L, which occurred in one sample or 1%; this value was truncated to 3 s.d. above the mean.

Measures

Self-harm episodes

Self-harm episodes were measured using the SASII, a clinician-administered, semi-structured measure used in prior studies of self-harm in adolescents and adults and showing strong interrater reliability and external validity.[31] For this study, we used a briefer SASII, which provided dates of all self-harm episodes (suicide attempts and NSSI), associated suicidal intent and medical severity/potential lethality within a specified time period.[15] We asked about all self-harm episodes during the past 6 months at baseline and all self-harm episodes since the last assessment at follow-ups. Self-harm was defined to include all NSSI and suicide attempts. As in prior research,[27] suicide attempts were defined to include interrupted and actual suicide attempts. We used pre-specified cut-off points for classifying self-harm episodes based on prior studies[28] as follows: self-harm 0, 1–3, 4–9 and ≥10; NSSI 0, 1–3, 4–6 and ≥7. Suicide attempts were categorised as absent (0) versus present (1) owing to low frequency. Use of the brief SASII reduced assessment burden, and it demonstrated good convergence with the Columbia-Suicide Severity Rating Scale (modified slightly[27]) for identifying/classifying self-harm (kappa = 1.00, $P < 0.001$), suicide attempts (kappa = 0.80, $P < 0.001$) and NSSI (kappa = 0.91, $P < 0.001$).

Past-month suicidal ideation

Past-month suicidal ideation was assessed using the Suicidal Ideation Questionnaire – Junior (SIQ-JR), a 15-item self-report questionnaire with demonstrated psychometric adequacy.[32] Item

scores (range: 0 to 6) were summed, with higher scores indicating greater ideation. A total score ≥24 indicates severe suicidal ideation. Cronbach's α ranged from 0.95 to 0.97.

Past-week depressive symptoms

Past-week depressive symptoms were self-reported using the well-established 20-item Center for Epidemiological Studies-Depression Scale (CES-D).[33] Item scores (range: 0 to 3) were summed to yield a total score (range 0–60). Total score ≥24 is generally used as an indicator of severe depression in adolescents.[34] Cronbach's α ranged from 0.92 to 0.93.

Past-month sleep disturbance

Past-month sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI).[35] This established subjective measure assesses seven domains of sleep on a 0–3 scale: sleep quality, trouble falling asleep, amount of sleep, sleep efficiency, sleep troubles, sleep medication and the impact of sleep problems on daytime functioning. A global summary score (range: 0–21) indicates overall sleep disturbance, and scores >5 suggest poor sleep. The PSQI global score has been demonstrated to have adequate reliability and validity in adolescent samples.[36]

Data analytic approach

The primary outcome was total self-harm, assessed at 3 months and again at 6 months. The primary predictor variables were IL-6 and CRP at baseline and at 3 months. For IL-6 and CRP, we replaced outliers greater than 3 s.d. from the pooled mean with the next highest value. This pertained to two data points for CRP and two data points for IL-6. Then, values were natural-log transformed.

Because we had repeated measures of the predictor and outcome variables, such that inflammation level at baseline predicted self-harm at 3 months and inflammation at 3 months predicted self-harm at 6 months, we used generalised linear mixed models in SAS 9.4 (i.e. PROC GLIMMIX). We accommodated the ordinal outcome variable by specifying a multinomial distribution and a cumulative logit link function and used Laplace approximation methods. Suicide attempts, a binary outcome variable, was estimated using the binomial distribution and a logit link function in PROC GLIMMIX. Models included random intercepts and the control of past-6-month self-harm, NSSI, or suicide attempt measured at baseline. Continuous secondary outcomes, including SIQ-JR, CES-D and PSQI, were estimated with full maximum likelihood using mixed linear models in SAS 9.4 (i.e. PROC MIXED). Models included random intercepts and the control of the outcome variable at the time of the inflammation measurement. For example, we simultaneously examined whether baseline levels of inflammation and baseline levels of CES-D predicted 3-month CES-D, and whether 3-month levels of inflammation and 3-month levels of CES-D predicted 6-month CES-D. Adjusted models controlled for depression symptoms at the time of the inflammation measurement (if not already included in the model), self-report of current SSRI use (0 = none), baseline age in months and self-report of past-month smoking (0 = none).

Results

Participants

Table 1 presents the characteristics of the sample at baseline (N = 51). The sample was predominantly female (86.3%), with a mean age of 16.1 years (s.d. = 1.8, range: 12.8 to 19.6). Youth were diverse in ethnic and racial composition: 11 of 51 (21.57%) endorsed Hispanic/Latino ethnicity; 21 (41.18%) self-reported race other than White; and 16 (31.37%) described themselves as multiracial. At the baseline assessment, 38 youths (74.5%) reported self-harm in the previous 6 months: suicide attempts, n = 15/51 (29.4%); NSSI, n = 33/51 (64.7%). Depressive symptoms were common, with 31 of 51 youths (60.78%) reporting clinically elevated depressive symptoms on the CES-D and 19 (37.25%) meeting Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version criteria for current major depressive disorder. Sleep disturbance was also frequent: 81.6% of youth had elevated PSQI scores. The mean CRP level of 2.2 mg/L was above the 'normal' range for adults (i.e. 1 mg/L).

Most youths (40 of 51, 78.4%) participated in the two follow-up assessments. Six (11.8%) participated in two of the three assessments,

Table 1 Participant characteristics at baseline

	Baseline, Max. N = 51				
	Total N	Mean/N	s.d./%	Min.	Max.
Demographic characteristics					
Age, years (mean)	51	16.09	1.77	12.83	19.58
Sex	51	–	–	–	–
Female	–	44	86.27%	–	–
Male	–	6	11.76%	–	–
Unreported	–	1	1.96%	–	–
Hispanic (versus not Hispanic)	51	11	21.57%	–	–
Race	51	–	–	–	–
White	–	30	58.82%	–	–
Black	–	1	1.96%	–	–
Asian	–	3	5.88%	–	–
Other	–	1	1.96%	–	–
Multiracial	–	16	31.37%	–	–
Insurance[a]	42	–	–	–	–
Public	–	2	4.76%	–	–
Private	–	40	95.24%	–	–
Inflammation[b]					
CRP mg/L	51	2.18	4.27	0.20	25.00
IL-6 pg/ml	51	0.9	1.4	0.2	8.8
Youth clinical variables					
SASII self-harm, past 6 months	51				
0	–	13	25.49	–	–
1–3	–	18	35.29	–	–
4–9	–	6	11.76	–	–
≥10	–	14	27.45	–	–
SASII suicidal attempts, past 6 months	51				
0	–	36	70.59%	–	–
≥1	–	15	29.41%	–	–
SASII NSSI, past 6 months	51				
0	–	18	35.29%	–	–
1–3	–	13	25.49%	–	–
4–6	–	3	5.88%	–	–
≥7	–	17	33.33%	–	–
SIQ-JR suicidal ideation, mean	51	36.49	22.44	0	86
SIQ-JR ≥ 24		31	60.78		
CES-D total score, mean	51	27.8	12.92	0	54
CES-D ≥ 24	–	31	60.78%	–	–
PSQI, mean	49	8.84	3.71	0	16
PSQI, ≥5	–	40	81.63%	–	–
Any counselling, past 12 months	51	44	86.27%		
SSRI use, current	51	28	54.90%	–	–
Cigarette smoking	50	14	28.00%	–	–

CES-D, Center for Epidemiologic Studies-Depression Scale; CRP, C-reactive protein; IL-6, interleukin-6; NSSI, non-suicidal self-injury; PSQI, Pittsburgh Sleep Quality Index; SASII, Suicide Attempt Self-Injury Interview; SIQ-JR, Suicidal Ideation Questionnaire – Junior (total score); SSRI, selective serotonin reuptake inhibitor.
a. Nine participants had missing information about insurance.
b. Descriptive statistics were based on raw values, wherein values below the lower limit of detection were replaced with the lower limit of detection. Correlations were computed using truncated and natural-log-transformed values.

Table 2 Prospective associations of IL-6 and CRP[a] with self-harm 3 months later

	Outcome: self-harm						Outcome: NSSI					
	Unadjusted models			Adjusted models			Unadjusted models			Adjusted models		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
IL-6	3.3	1.1, 10.0	0.032	3.3	1.1, 9.9	0.035	3.5	1.1, 11.8	0.041	3.7	1.0, 13.5	0.045
Baseline level of outcome	2.7	1.2, 6.1	0.018	2.9	1.2, 6.9	0.020	2.5	1.1, 5.6	0.024	3.2	1.2, 8.1	0.020
CES-D	–	–	–	1.0	1.0, 1.1	0.666	–	–	–	1.0	0.9, 1.1	0.974
CRP	1.61	0.93, 2.80	0.089	1.59	0.92, 2.76	0.094	1.75	0.99, 3.10	0.054	1.61	0.88, 2.97	0.118
Baseline level of outcome	2.72	1.17, 6.32	0.021	2.36	1.08, 5.15	0.033	2.60	1.19, 5.66	0.018	2.71	1.15, 6.38	0.025
CES-D	–	–	–	1.01	0.96, 1.06	0.620	–	–	–	1.00	0.95, 1.06	0.979

CES-D, Center for Epidemiologic Studies-Depression Scale; CRP, C-reactive protein; IL-6, interleukin-6; NSSI, non-suicidal self-injury; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.
a. IL-6 and CRP were truncated to 3 s.d. above the mean and natural-log transformed. Adjusted models control for depression symptoms, SSRI use, age and past-month smoking.

and five (9.8%) participated in one of the three assessments. Missingness was not associated with baseline inflammation levels, SASII variables, SIQ-JR, CES-D, PSQI, SSRI use, substance use (cigarette smoking, alcohol use, marijuana use), age, sex, Hispanic ethnicity or race. Participation was weaker for online surveys assessing the secondary outcome variables: 27 of 51 (52.9%) participated in all three assessments; 18 (35.3%) participated in two of the three assessments and six (11.8%) participated in one assessment. Pattern-mixture models assessed whether estimates in the mixed models were informatively dependent on missing data patterns;[37] analyses were not sensitive to missing data patterns.

Primary outcomes: self-harm episodes, suicide attempts and NSSI

As shown in Table 2, mixed models were used to examine the associations between inflammation markers at baseline and 3 months and clinical outcomes at 3 and 6 months, respectively, over and above the control of the baseline level of the outcome variable. That is, the associations between baseline levels of inflammation and 3-month self-harm outcomes and between 3-month levels of inflammation and 6-month self-harm outcomes were estimated simultaneously. IL-6 predicted a higher frequency of self-harm episodes 3 months later; one unit increase in log-transformed IL-6 was associated with a 3.3-fold increase in the odds of the youth reporting self-harm episodes in a higher stratum. Probes for effects for each self-harm component (NSSI, suicide attempts) revealed that IL-6 specifically predicted NSSI episodes 3 months later (odds ratio [OR] = 3.5, 95% CI: 1.1, 11.8). The effect for suicide attempts was not statistically significant ($B = -3.6$, s.e. = 3.7, $P = 0.331$; OR = 0.03, 95% CI: <0.01, 45.2). The associations between IL-6 and self-harm and between IL-6 and NSSI specifically remained statistically significant with the additional control of depression symptoms, SSRI use, age and past-month smoking.

We also found a positive association between CRP and self-harm, but this relationship did not reach statistical significance (self-harm, $B = 0.48$, s.e. = 0.27, $P = 0.089$; NSSI, $B = 0.56$, s.e. = 0.28, $P = 0.054$); see Table 2. As the model predicting suicide attempts did not converge, we approximated suicide attempts with suicidal behaviours, inclusive of actual, interrupted and aborted attempts (0 = none, 1 = any). As expected, CRP was not significantly associated with suicidal behaviours ($B = 0.03$, s.e. = 0.66, $P = 0.966$, OR = 1.03, 95% CI: 0.27, 3.91).

Secondary outcomes: suicidal ideation, depression, self-reported sleep problems

Table 3 shows results of analyses examining associations between IL-6 or CRP and secondary clinical characteristics 3 months later. IL-6 predicted greater scores on the CES-D 3 months later ($B = 4.1$, s.e. = 1.7, $P = 0.027$, $d = 0.2$, 95% CI: 0.0, 0.4)[a] but not on the SIQ-JR ($B = -2.1$, s.e. = 4.0, $P = 0.602$, $d = -0.1$, 95% CI: −0.3, 0.2) or the PSQI ($B = 0.3$, s.e. = 0.5, $P = 0.607$, $d = 0.1$, 95% CI: −0.2, 0.3). The association between IL-6 and CES-D was not statistically significant when controlling for SSRI use, age and smoking ($B = 3.4$, s.e. = 1.7, $P = 0.061$). The associations between CRP and these secondary outcomes 3 months later were weaker and not statistically significant: SIQ-JR, $B = -2.06$, s.e. = 2.51, $P = 0.419$, $d = -0.12$, 95% CI: −0.41, 0.18; CES-D, $B = 2.08$, s.e. = 1.09, $P = 0.067$, $d = 0.21$, 95% CI: −0.02, 0.43; PSQI, $B = 0.65$, s.e. = 0.34, $P = 0.069$, $d = 0.27$, 95% CI: −0.02, 0.56. Controlling for SSRI use, smoking and youth age yielded similar parameter estimates and statistical significance levels, with no change in conclusions.

Discussion

We examined prospective associations between inflammation levels and self-harm 3 months later in 51 youths selected for elevated suicide/self-harm risk. This study found that IL-6 predicted a three-fold increase in the odds of youth endorsing a higher stratum of self-harm episodes over the subsequent 3 months, over and above baseline levels of self-harm and concurrent depression symptoms. CRP showed a weaker trend-level association with self-harm that did not reach statistical significance. Additional investigation showed that the association between IL-6 and self-harm was driven by NSSI, and not suicide attempts.

These results suggest that there may be a direct risk pathway between inflammation and recurring self-harm – specifically, NSSI. IL-6 is an index of high levels of circulating inflammation, which acts on the central nervous system and gives rise to symptoms of sickness, including fevers, aching joints and fatigue,[38] as well as neural sensitivity to negative social experiences such as rejection and negative feedback.[39] Given that a common function of NSSI is to reduce unpleasant feelings,[40] youths with high levels of inflammation may engage in NSSI as a way to seek relief from these sensations.

The current study is one of only a few that have found a significant prospective association between inflammation levels and self-harm in youth. Our unique methodological approach helps to explain our finding that IL-6 predicts self-harm. First, youth in the current study were at very high risk of engaging in self-harm, given that 75% of our sample had recent self-harm within 6 months, and all had a lifetime history of self-harm and a suicidal event at the time of enrollment. These inclusionary criteria allowed us to detect more self-harm episodes and specifically study the role of inflammation in predicting recurrence of self-harm. Second, we

[a] Cohen's *d* was approximated by dividing the difference in estimated CES-D score associated with 1 s.d. change in ln(IL-6) by the s.d. of CES-D score at 3 months and 6 months.

Table 3 Prospective associations of IL-6 and CRP[a] with suicidality, depression and sleep disturbances

	Outcome: post 3-month SIQ-JR			Outcome: post 3-month CES-D			Outcome: post 3-month PSQI		
	B (s.e.)	*P*	95% CI	*B* (s.e.)	*P*	95% CI	*B* (s.e.)	*P*	95% CI
IL-6	−2.1 (4.0)	0.602	−10.3, 6.1	4.1 (1.7)	0.027	0.5, 7.6	0.3 (0.5)	0.607	−0.8, 1.4
Current level of outcome	0.4 (0.1)	0.002	0.2, 0.7	0.6 (0.1)	<0.001	0.4, 0.8	0.4 (0.1)	<0.001	0.2, 0.6
CRP	−2.06 (2.51)	0.419	−7.23, 3.10	2.08 (1.09)	0.067	−0.16, 4.32	0.65 (0.34)	0.069	−0.06, 1.36
Current level of outcome	0.42 (0.12)	0.002	0.18, 0.66	0.61 (0.1)	<0.001	0.41, 0.81	0.48 (0.10)	<0.001	0.26, 0.69

CES-D, Center for Epidemiologic Studies-Depression Scale; CRP, C-reactive protein; IL-6, interleukin-6; PSQI, Pittsburgh Sleep Quality Index; SIQ-JR, Suicidal Ideation Questionnaire – Junior (total score).
a. IL-6 and CRP were truncated to 3 s.d. above the mean and natural-log transformed. Adjusted models controlling for SSRI use, smoking and youth age showed comparable results.

uniquely examined whether inflammation levels predicted self-harm over the subsequent 3 months and demonstrated that inflammation is a proximal predictor of self-harm. Psychobiological risk factors such as elevated levels of inflammation may increase vulnerability to self-harm in the near term, but not over several years.

Compared with IL-6, CRP had a weaker, non-significant association with self-harm. One possible reason for this difference may be that IL-6 is produced immediately following environmental stressors and injuries, whereas CRP is produced in response to ongoing (i.e. weeks to months) elevation of IL-6 or chronic low-grade systemic inflammation.[41,42] Thus, IL-6 may reflect stressful events that precipitate self-harm (e.g. rejection, conflict) more potently and closer in time to the event than CRP. A future study could examine whether IL-6 mediates the short-term associations between stressful events and self-harm; this would further increase our understanding of this possible target of intervention.

With respect to secondary outcomes, IL-6 predicted depression symptoms on the CES-D 3 months later, consistent with past epidemiological studies supporting small prospective associations between inflammation and depression.[11,38,43] A non-significant trend-level association was also found between CRP and depression 3 months later, as well as CRP and sleep disturbance 3 months later. In the context of the literature supporting links between depression, sleep disturbance and self-harm, these results support the value of future studies to elucidate pathways by which self-harm risk may be exacerbated through inflammatory processes, depression and sleep disturbance.

The study must be interpreted in the context of its limitations. First, even in this high-risk sample, rates of suicide attempts and suicidal behaviour were low, resulting in low statistical power for the analyses. Second, this exploratory study had a relatively small sample, limiting our ability to examine moderators such as gender and increasing the possibility of type II errors. Participants' clinical characteristics were heterogenous, raising challenges in ascertaining exactly how these potential covariates may be involved in the association between circulating inflammation levels and self-harm, and the results may not generalise to samples with lower self-harm risk. Furthermore, although we addressed missing data using full maximum likelihood estimation in our model, and pattern mixture modelling revealed no evidence of an informative attrition mechanism with respect to the results, it is still possible that missing observations could have contributed to potentially unaccounted bias. We recommend that these short-term associations between inflammation and self-harm be replicated in a larger fully powered sample in future studies.

These limitations are offset by the study's numerous strengths, including a prospective study design, a racially and ethnically diverse sample, and the use of gold standard assessments (e.g. inflammation via blood sample, self-harm via clinical interview). We found that IL-6 predicted self-harm – specifically, NSSI – over 3 months, even when controlling for baseline self-harm and depression, thereby increasing our understanding of whether and how inflammation may be implicated in risk of self-harm. The findings suggest that inflammation – specifically, IL-6 – may be a viable biological marker of short-term risk of self-harm, and that it may reflect precipitating stressors that likewise increase risk of self-harm. Although more replication is necessary, the study's findings signal a future possibility of identifying youth in periods of risk based on this biological marker. Moreover, future research may explore the potential for personalised, biologically informed treatment approaches and consider whether strategies that reduce elevated levels of IL-6 might mitigate suicide risk. Thus, inflammation could be a novel target for interventions that aim to reduce recurrence of self-harm in high-risk youth.

Sunhye Bai, Prevention Research Center, The Pennsylvania State University, USA; and The Ballmer Institute for Children's Behavioral Health, University of Oregon, USA†; **Joan R. Asarnow**, Department of Psychiatry and Behavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, USA; **Kalina N. Babeva**, Child Psychiatry and Behavioral Medicine, Seattle Children's Hospital, USA; **Michael R. Irwin**, Department of Psychiatry and Behavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, USA; and Cousins Center for Psychoneuroimmunology, David Geffen School of Medicine, University of California Los Angeles, USA

Correspondence: Sunhye Bai. Email: sunnybai@uoregon.edu

First received 4 Oct 2023, final revision 4 Dec 2023, accepted 29 Dec 2023

Data availability

The data that support the findings of this study are available from J.R.A. upon reasonable request; data that could compromise the privacy of research participants are not available. The analytic code associated with the manuscript is available from the corresponding author, S.B., upon reasonable request. Plasma samples are not available owing to their containing information that could compromise the privacy of research participants. Measures that were used in the study are available publicly or through referenced sources.

Acknowledgements

We thank the research participants and the many staff and colleagues who made this project possible.

Author contributions

S.B. developed the research question, carried out data collection, analysed the data and wrote the article; J.R.A. developed the research question, designed the study, carried out data collection, analysed the data and wrote the article; K.N.B. developed the research question, designed the study, carried out data collection and wrote the article; and M.R.I. developed the research question, designed the study, carried out data collection and wrote the article.

Funding

This work was funded by the Cousins Center for Psychoneuroimmunology, David Geffen School of Medicine, University of California Los Angeles (J.R.A. and M.R.I.). Additional support was provided by the National Institute of Mental Health (J.R.A., supplement to NIMH R01MH093898), the American Foundation for Suicide Prevention (J.R.A., LSRG-0-008-13) and the National Center for Advancing Translational Sciences (S.B., KL2TR002015). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health or other funding organisations.

† Research was conducted while S.B. was employed and funded by the Penn State University, and thus Penn State is the primary institution. S.B. moved to the University of Oregon in September 2023.

Declaration of interest

J.R.A. has received grant, research or other support from the National Institute of Mental Health, the Patient Centered Outcome Research Institute, the American Foundation for Suicide Prevention, the Substance Abuse and Mental Health Services Administration, the American Psychological Foundation, the Society of Clinical Child and Adolescent Psychology (Division 53 of the APA) and the Association for Child and Adolescent Mental Health. She has served as a consultant on quality improvement for depression and suicide/self-harm prevention and serves on the Scientific Council of the American Foundation for Suicide Prevention, the Scientific Advisory Board of the Klingenstein Third Generation Foundation and the Editorial Committee for the Annual Review of Clinical Psychology.

References

1 U.S. Department of Health and Human Services (HHS) Office of the Surgeon General and National Action Alliance for Suicide Prevention. *National Strategy for Suicide Prevention: Goals and Objectives for Action*. HHS, 2012.

2 Centers for Disease Control and Prevention, National Centers for Injury Prevention and Control. *Web-based Injury Statistics Query and Reporting System (WISQARS)*. 2005 (www.cdc.gov/injury/wisqars [cited 19 Sep 2023]).

3 Hawton K, Houston K, Shepperd R. Suicide in young people. Study of 174 cases, aged under 25 years, based on coroners' and medical records. *Br J Psychiatry* 1999; **175**: 271–6.

4 Asarnow JR, Porta G, Spirito A, Emslie G, Clarke G, Wagner KD, et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA trial. *J Am Acad Child Adolesc Psychiatry* 2011; **50**(8): 772–81.

5 Centers for Disease Control and Prevention. *High School Youth Risk Behavior Survey Data*. CDC, 2021 (http://yrbs-explorer.services.cdc.gov/ [cited 19 Sep 2023]).

6 Lim KS, Wong CH, McIntyre RS, Wang J, Zhang Z, Tran BX, et al. Global lifetime and 12-month prevalence of suicidal behavior, deliberate self-harm and non-suicidal self-injury in children and adolescents between 1989 and 2018: a meta-analysis. *Int J Environ Res Public Health* 2019; **16**(22): 4581.

7 Mayor S. Major rise in non-suicidal self harm in England, study shows. *BMJ* 2019; **365**: l4058.

8 Brent DA, McMakin DL, Kennard BD, Goldstein TR, Mayes TL, Douaihy AB. Protecting adolescents from self-harm: a critical review of intervention studies. *J Am Acad Child Adolesc Psychiatry* 2013; **52**(12): 1260–71.

9 Donegan JJ, Nemeroff CB. Suicide and inflammation. In *Neuroinflammation, Gut-Brain Axis and Immunity in Neuropsychiatric Disorders* (ed YK Kim): 379–404. Springer Nature, 2023.

10 Dantzer R, Wollman E, Vitkovic L, Yirmiya R. Cytokines and depression: fortuitous or causative association? *Mol Psychiatry* 1999; **4**(4): 328–32.

11 Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: a meta-analysis. *J Affect Disord* 2020; **277**: 940–8.

12 Kuhlman KR, Horn SR, Chiang JJ, Bower JE. Early life adversity exposure and circulating markers of inflammation in children and adolescents: a systematic review and meta-analysis. *Brain Behav Immun* 2020; **86**: 30–42.

13 Irwin MR. Sleep and inflammation: partners in sickness and in health. *Nat Rev Immunol* 2019; **19**(11): 702–15.

14 Hankin BL, Abela JRZ. Nonsuicidal self-injury in adolescence: prospective rates and risk factors in a 2½ year longitudinal study. *Psychiatry Res* 2011; **186**(1): 65–70.

15 Asarnow JR, Bai S, Babeva KN, Adrian M, Berk MS, Asarnow LD, et al. Sleep in youth with repeated self-harm and high suicidality: does sleep predict self-harm risk? *Suicide Life Threat Behav* 2020; **50**(6): 1189–97.

16 Brent DA, Perper JA, Moritz G, Allman C, Friend A, Roth C, et al. Psychiatric risk factors for adolescent suicide: a case-control study. *J Am Acad Child Adolesc Psychiatry* 1993; **32**(3): 521–9.

17 Shaffer D, Gould MS, Fisher P, Trautman P, Moreau D, Kleinman M, et al. Psychiatric diagnosis in child and adolescent suicide. *Arch Gen Psychiatry* 1996; **53**(4): 339–48.

18 Goldman-Mellor SJ, Caspi A, Harrington H, Hogan S, Nada-Raja S, Poulton R, et al. Suicide attempt in young people: a signal for long-term health care and social needs. *JAMA Psychiatry* 2014; **71**(2): 127.

19 Kindler J, Koenig J, Lerch S, van der Venne P, Resch F, Kaess M. Increased immunological markers in female adolescents with non-suicidal self-injury. *J Affect Disord* 2022; **318**: 191–5.

20 Russell AE, Heron J, Gunnell D, Ford T, Hemani G, Joinson C, et al. Pathways between early-life adversity and adolescent self-harm: the mediating role of inflammation in the Avon Longitudinal study of Parents and Children. *J Child Psychol Psychiatry* 2019; **60**(10): 1094–103.

21 Melhem NM, Munroe S, Marsland A, Gray K, Brent D, Porta G, et al. Blunted HPA axis activity prior to suicide attempt and increased inflammation in attempters. *Psychoneuroendocrinology* 2017; **77**: 284–94.

22 Ribeiro JD, Franklin JC, Fox KR, Bentley KH, Kleiman EM, Chang BP, et al. Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. *Psychol Med* 2016; **46**(2): 225–36.

23 McHugh CM, Corderoy A, Ryan CJ, Hickie IB, Large MM. Association between suicidal ideation and suicide: meta-analyses of odds ratios, sensitivity, specificity and positive predictive value. *BJPsych Open* 2019; **5**(2): e18.

24 Ribeiro JD, Huang X, Fox KR, Franklin JC. Depression and hopelessness as risk factors for suicide ideation, attempts and death: meta-analysis of longitudinal studies. *Br J Psychiatry* 2018; **212**(5): 279–86.

25 Liu RT, Steele SJ, Hamilton JL, Do QBP, Furbish K, Burke TA, et al. Sleep and suicide: a systematic review and meta-analysis of longitudinal studies. *Clin Psychol Rev* 2020; **81**: 101895.

26 Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 2016; **80**(1): 40–52.

27 Asarnow JR, Hughes JL, Babeva KN, Sugar CA. Cognitive-behavioral family treatment for suicide attempt prevention: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 2017; **56**(6): 506–14.

28 Mccauley E, Berk MS, Asarnow JR, Adrian M, Cohen J, Korslund K, et al. Efficacy of dialectical behavior therapy for adolescents at high risk for suicide: a randomized clinical trial. *JAMA Psychiatry* 2018; **75**(8): 777–85.

29 Piber D, Olmstead R, Cho JH, Guzman M, Irwin MR. Interferon-γ moderation of poor sleep maintenance and depressed mood in community-dwelling older adults. *Psychol Med* 2023; **53**(8): 3548–56.

30 Boyle CC, Cho JH, Eisenberger NI, Olmstead RE, Piber D, Sadeghi N, et al. Motivation and sensitivity to monetary reward in late-life insomnia: moderating role of sex and the inflammatory marker CRP. *Neuropsychopharmacology* 2020; **45**(10): 1664–71.

31 Linehan MM, Comtois KA, Brown MZ, Heard HL, Wagner A. Suicide Attempt Self-Injury Interview (SASII): development, reliability, and validity of a scale to assess suicide attempts and intentional self-injury. *Psychol Assess* 2006; **18**(3): 303–12.

32 Reynolds WM. *Suicidal Ideation Questionnaire*. Psychological Assessment Resources, 1987.

33 Radloff LS. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *J Youth Adolesc* 1991; **20**(2): 149–66.

34 Roberts RE, Lewinsohn PM, Seeley JR. Screening for adolescent depression: a comparison of depression scales. *J Am Acad Child Adolesc Psychiatry* 1991; **30**: 58–66.

35 Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**(2): 193–213.

36 de la Vega R, Tomé-Pires C, Solé E, Racine M, Castarlenas E, Jensen MP, et al. The Pittsburgh Sleep Quality Index: validity and factor structure in young people. *Psychol Assess* 2015; **27**(4): e22–7.

37 Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods* 1997; **2**(1): 64–78.

38 Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 2007; **21**(2): 153–60.

39 Eisenberger NI, Moieni M, Inagaki TK, Muscatell KA, Irwin MR. In sickness and in health: the co-regulation of inflammation and social behavior. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 2017; **42**(1): 242–53.

40 Zetterqvist M, Lundh LG, Dahlström Ö, Svedin CG. Prevalence and function of non-suicidal self-injury (NSSI) in a community sample of adolescents, using suggested DSM-5 criteria for a potential NSSI disorder. *J Abnorm Child Psychol* 2013; **41**(5): 759–73.

41 Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014; **6**(10): a016295.

42 Nehring SM, Goyal A, Patel BC. C reactive protein. In *StatPearls*. StatPearls Publishing, 2023 (http://www.ncbi.nlm.nih.gov/books/NBK441843/ [cited 19 Sep 2023]).

43 Khandaker GM, Stochl J, Zammit S, Goodyer I, Lewis G, Jones PB. Childhood inflammatory markers and intelligence as predictors of subsequent persistent depressive symptoms: a longitudinal cohort study. *Psychol Med* 2018; **48**(9): 1514–22.