Clustering of Depression and Inflammation in Adolescents Previously Exposed to Childhood Adversity

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Background: There is mounting interest in the hypothesis that inflammation contributes to the pathogenesis of depression and underlies depressed patients' vulnerability to comorbid medical conditions. However, research on depression and inflammation has yielded conflicting findings, fostering speculation that these conditions associate only in certain subgroups, such as patients exposed to childhood adversity.

Methods: We studied 147 female adolescents. All were in good health at baseline but at high risk for depression because of family history or cognitive vulnerability. Subjects were assessed every 6 months for 2.5 years, undergoing diagnostic interviews and venipuncture for measurement of two inflammatory biomarkers, C-reactive protein (CRP) and interleukin-6 (IL-6). Childhood adversity was indexed by parental separation, low socioeconomic status, and familial psychopathology.

Results: Multilevel models indicated that childhood adversity promotes clustering of depression and inflammation. Among subjects exposed to high childhood adversity, the transition to depression was accompanied by increases in both CRP and IL-6. Higher CRP remained evident 6 months later, even after depressive symptoms had abated. These lingering effects were bidirectional, such that among subjects with childhood adversity, high IL-6 forecasted depression 6 months later, even after concurrent inflammation was considered. This coupling of depression and inflammation was not apparent in subjects without childhood adversity.

Conclusions: These findings suggest that childhood adversity promotes the formation of a neuroimmune pipeline in which inflammatory signaling between the brain and periphery is amplified. Once established, this pipeline leads to a coupling of depression and inflammation, which may contribute to later affective difficulties and biomedical complications.

Key Words: Adolescence, childhood adversity, cytokines, depression, inflammation, socioeconomic status

Depression is a common psychiatric disorder with significant personal, social, and economic consequences, for both patients and society (1). Additionally, depression heightens risks for morbidity and mortality from chronic diseases associated with aging, including autoimmune, metabolic, and cardiovascular conditions (2). In an effort to understand the pathogenesis of depression and the mechanisms through which it confers vulnerability to other conditions, researchers have increasingly begun studying low-grade inflammation. Various scenarios have been proposed. Most center around the notion that stress triggers the release of pro-inflammatory cytokines, which access the central nervous system, eliciting neurobehavioral adjustments that manifest as depressive symptoms (3–5). These symptoms are thought to further exacerbate inflammation and, in doing so, contribute to the pathogenesis of various diseases of aging (6–8), many of which involve excessive cytokine activity (9,10).

Research has documented associations between syndromal depression and inflammatory biomarkers, as well as a graded, linear relation of the latter with dysphoric symptoms (11). However, the strength of these connections varies substantially across studies, with some articles reporting sizeable depression-related increases in biomarkers of inflammation, such as C-reactive protein (CRP) and interleukin-6 (IL-6), and others failing to detect such patterns (12). The state of the field is accurately summed up by the title of a recent editorial: "Where there is depression, there is inflammation ... sometimes" (13). To account for the inconsistencies in this literature, some researchers speculate that depression and inflammation co-occur only in certain subgroups of patients, such as those exposed to childhood adversity (14). This hypothesis grows out of mounting evidence that severe childhood stressors promote the formation of a neural-immune pipeline (15), wherein inflammatory cytokine signaling between the brain and the periphery is markedly amplified (16). Once established, a pipeline such as this could lead depression and inflammation to couple more tightly than otherwise expected.

Consistent with this possibility, recent studies have found that depression and inflammation cluster in persons who experienced childhood adversity. Danese and colleagues (14) stratified the Dunedin cohort into four subgroups based on history of childhood maltreatment and past-year major depression. Low-grade inflammation was indexed by a composite of CRP, fibrinogen, and leukocyte counts. Composite scores were higher among subjects with a maltreatment history and recent depression, relative to controls with neither. Greater inflammation was also seen among subjects exposed to maltreatment alone. However, depressed subjects who were negative for maltreatment were statistically indistinguishable from controls. Conceptually similar patterns emerged in a study of immune responses to acute mental stress (17). In this work, adults who were currently depressed and had been maltreated in childhood, exhibited showed larger stress-related increases in plasma IL-6 than healthy control subjects, as well as enhanced DNA binding of the proinflammatory transcription factor nuclear factor-kappa B.

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These findings provide initial evidence that childhood adversity contributes to a phenotype marked by clustering of depression and inflammation. However, before definitive conclusions about the existence of this phenotype can be made, several questions must be answered. The first has to do with directionality. The Dunedin findings are based on a single timepoint analysis of inflammation, making it difficult to ascertain the temporal ordering of this phenomenon. Longitudinal studies with repeated assessments of depression and inflammation are needed to clarify the direction of these observations. Multiwave studies would also provide a longer-term perspective on these dynamics, revealing whether childhood adversity confers risks for lingering effects of depression in which signs of low-grade inflammation persist even once mood symptoms have resolved (or vice versa). If present, these lingering effects might explain why depression forecasts vulnerability to conditions, such as heart disease, that often manifest several decades into the future. The second open question concerns the specificity of childhood adversity. Previous research in this area has focused on maltreatment, but other kinds of childhood adversity, such as low socioeconomic status (SES), have been linked to low-grade inflammation in adulthood (18–20), as well as mental and physical health problems across the life span (21). If these other forms of childhood adversity, which are more prevalent than maltreatment, also promote clustering of depression and inflammation, it would have implications for public health and etiological theories.

To address these questions, we analyzed data from a 6-wave study of adolescents, all of whom were healthy at baseline but at high-risk for an episode of depression. We predicted that depression and inflammation would co-occur among these subjects but that the magnitude of this association would vary depending on previous exposure to childhood adversity.

Methods and Materials

Subjects

Subjects were recruited from Vancouver, Canada, through advertisements in local media. Eligibility criteria included being 1) female, aged 15 to 19 years, and fluent in English; 2) free of acute illness in the past 2 weeks, as evidenced by self-report, absence of fever, and normal complete blood count; 3) without a history of major psychiatric disorders or chronic medical illnesses, as reported during structured interviews; and 4) without standing medications other than birth control. To enroll, subjects also had to be at high risk for having an episode of depression over the follow-up. High-risk was defined as having a first-degree relative with a history of depression and/or elevated scores on cognitive vulnerability to depression. Family psychiatric history was ascertained during screening interviews with subjects using standardized probes from the National Comorbidity Study (22). Cognitive vulnerability was defined as scoring in the top quartile of the local distribution on the Dysfunctional Attitudes Scale (23) or the Adolescent Cognitive Style Questionnaire (24). These indices reliably identify adolescents who go on to develop episodes of depression (25). Written consent was obtained from all subjects. For those younger than 18 years, consent was also obtained from a parent or guardian. The University of British Columbia's Research Ethics Board approved the protocol.

Procedures

Subjects were assessed every 6 months over a 2.5-year period. At each of six visits they completed a psychiatric assessment, gave blood for measurement of inflammatory biomarkers, and responded to questionnaires.

Depressive Episodes. Psychiatric assessments were conducted with the Structured Clinical Interview for DSM-IV-TR (SCID) Axis I Disorders—Non-Patient Edition (26). The baseline interview covered lifetime history. At follow-up visits, the interview covered the 6-month interval since the previous assessment. Reliability was estimated by having assessors independently rate 10% of the SCIDs blind to the original interviewer's judgments. The median weighted kappa was .69. Whenever an interview suggested a possible disorder, the entire team reviewed the SCID by audiotape and derived a consensus diagnosis. The severity of depressive episodes was indexed with the 24-item Hamilton Rating Scale for Depression (HRSD), using probes from Williams's structured interview guide (27). The intraclass correlation for HRSD ratings was .64.

Inflammatory Outcomes. Blood was obtained via antecubital venipuncture at each visit. To control for circadian and dietary variations, sessions always occurred between 8 and 11 AM, following an overnight fasting period. Blood was drawn into Serum-Separator Tubes (Becton-Dickinson, Oakville, Ontario, Canada). After serum was harvested by centrifugation, it was frozen at −30°C. C-reactive protein was measured by high-sensitivity chemiluminescence on an Immulite 2000 (Diagnostic Products Corporation, Los Angeles, California). This assay has a minimum detection threshold of .20 mg/L and intraassay variability of 2.2%. C-reactive protein was modeled as both a continuous and categorical outcome. For the latter analyses, we dummy-coded CRP as below or above 3 mg/L, the cutoff established by the American Heart Association and Centers for Disease Control as reflecting high-risk for cardiovascular disease (28). Interleukin-6 was measured in duplicate by commercially available high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). These kits have a minimum detection threshold of .039 pg/mL. Intraassay variability was less than 10%.

Childhood Adversity. Using data from baseline interviews, we formed a childhood adversity index. One point was assigned for each of the following risks: 1) birth to a teenage mother, who was younger than 20 years old at delivery, 2) familial disruption before age 15, caused by the death of a parent or divorce or separation from a parent that lasted more than 1 year; 3) a history of affective illness in parents/guardians; 4) low household education, wherein parents/guardians had a high school diploma or less; and 5) limited economic resources, as reflected by leasing (rather than owning) the family's primary residence from birth through school entry. Scores on the childhood adversity index could range from 0 to 5.

Alternative Explanations. We examined alternative explanations by statistically controlling for plausible demographic and biobehavioral confounders (29). The demographic confounders were age at baseline and racial/ethnic group. The biobehavioral confounders were central adiposity, indexed by waist-to-hip ratio (WHR), weekly alcohol use, and contraceptive medication. Preliminary analyses revealed that alcohol and contraceptive use were stable over follow-up (intraclass correlations = .72, .65, respectively). Thus, we simplified models by treating these covariates as between-subjects factors. For alcohol, we used the average number of weekly drinks across the study; for birth control, subjects were coded positive if they reported using oral, implantable, or injectable contraceptives during the study. In contrast, analyses showed that WHR increased over time (B = .024, SE = .013, p = .06), so we modeled it as a time-varying covariate. We also considered including cigarette smoking as a covariate, given its links with depression and inflammation (29). However, only three subjects were regular

Table 1. Characteristics of Sample at Study Entry ($N = 147$)

Characteristic	Mean ± SD or *n* (%)
Age	17.01 ± 1.33
Caucasian	71 (48.30)
East or South Asian	63 (42.86)
Parental Education (years)	15.92 ± 1.37
Family History of Depression	46 (31.29)
Cognitive Vulnerability to Depression	130 (88.43)
Waist-to-Hip Ratio	.75 (.05)
Alcohol Use (drinks/week)	1.57 ± 5.90
Contraceptive Use	33 (22.45)
Hamilton Rating Scale for Depression	4.16 ± 4.12
C-Reactive Protein (mg/L)	.70 ± 1.16
C-Reactive Protein in High-Risk Range (≥3 mg/L)	8 (3.40)
Interleukin-6 (pg/mL)	.67 ± .66
Childhood Adversities	
None	55 (37.41)
One	55 (37.41)
Two or more	37 (25.18)

smokers at any point in the study, so there was too little variance to justify modeling its effects.

Statistical Approach

On six occasions subjects had CRP greater than 10 mg/L. Values in this range are usually indicative of trauma, infection, or pathology. Thus, we followed published guidelines that recommend excluding such observations from analyses (30). For similar reasons, we excluded five IL-6 values greater than 10 pg/mL. After the outliers were removed, both CRP and IL-6 showed roughly normal distributions. Reanalysis of the data including outliers yielded identical findings.

To examine links between depression and inflammation, we estimated a series of multilevel models using HLM 6.08 (31). For analyses that treated CRP and IL-6 as continuous outcomes, standard two-level linear models were used. In analyses in which CRP was treated as binary, the models assumed an underlying Bernoulli distribution. The general structure of the models was as follows. At level 1, inflammatory outcomes were estimated as a function of time, WHR, depression, and a residual. Time was coded in months from study entry, and depression was coded as presence/absence of a clinical episode over the past six months. The depression variable was person-centered in all analyses. This allowed us to examine within-person covariation of depression and inflammation. In other words, we could ask, how do subjects' inflammation levels differ at visits when they have versus have not experienced a recent depressive episode?

The level 1 models yielded a series of intercepts that reflected each subject's CRP and IL-6 values at study entry (β_{0i} coefficients). They also yielded a series of slopes that reflected, for each subject, how strongly the outcome being considered related to the various level 1 predictors: time (β_{1i}), WHR (β_{2i}), and depression (β_{2i}). In level 2 models, each of these person-specific coefficients was estimated as a function of age, racial/ethnic group, alcohol, contraception, childhood adversity, and a random error term. The key parameter in these models was the cross-level interaction term, γ_{21}. When this coefficient was significantly different from zero, it suggested a cross-level interaction in which the nature of the depression–inflammation link varied for persons low versus high in childhood adversity. All of the analyses were random-slope models, using full maximum likelihood estimation and robust standard errors.

Results

Preliminary Analyses

The study involved 147 female adolescents who mirrored the broader Vancouver population in terms of racial/ethnic background (Table 1). Although the mean years of parental education was high, the sample had a good deal of socioeconomic variability. Fifteen percent of subjects came from households in which the maximum parental education was high school. The rest came from families in which parents had up to an associate's degree (36%) or a bachelor's degree or higher (49%). Because of the strict inclusion criteria, subjects were medically healthy and without standing prescriptions other than birth control. At study entry, CRP and IL-6 values were well within normal limits, except eight subjects with CRP greater than 3 mg/L. On the whole, the sample began the study with modest levels of depressive symptoms, as reflected in HRSD scores. There were no consistent associations between depressive symptoms and inflammatory biomarkers ($ps > .35$), likely because of the fairly restricted range of HRSD scores in the sample.

Over the course of the project, 40 subjects had a depressive episode (27.2%). In most instances, these episodes resolved quickly (mean = 1.56 months, SD = 1.62, range = .5–7.20). That said, six subjects had episodes that stretched across multiple study visits, and five subjects recovered, only to experience a recurrence later in the study. Of the 53 total episodes catalogued, 25 met criteria for major depression and 28 for minor depression. Risks of depression varied by study entry criteria ($\chi^2 = 6.76$, $p = .02$). Among subjects who qualified based on cognitive vulnerability, 20.8% had a depressive episode. Rates were higher among those who qualified based on family history (29.4%) or who had both cognitive vulnerability and family history (44.8%).

Childhood adversity was marginally associated with depression risk ($\chi^2 = 6.70$, $p = .06$); 20.0% of subjects without adversities experienced a depressive episode. The figures were 25.5% and 37.8% for subjects with 1 and 2 or more childhood adversities, respectively. Neither the duration ($p = .65$) nor severity of episodes

Table 2. Childhood Adversity as a Moderator of Depression's Association with Inflammatory Proteins—Concurrent Analyses

Predictor	Serum CRP Coefficient	SE	*p*	Serum CRP > 3 OR	95% CI	*p*	Serum IL-6 Coefficient	SE	*p*
Constant	−.86	.33	.01	.51	.30–.88	.02	–.47	.36	.31
Age	.04	.12	.73	1.13	.99–1.30	.08	.00	.13	.98
Caucasian	−.18	.26	.49	1.10	.68–1.82	.69	.29	.37	.44
Contraception	.63	.38	.10	1.08	.63–1.83	.79	.26	.40	.52
Alcohol Use	.01	.15	.95	.94	.73–1.23	.66	−.21	.25	.41
Early Adversity	.57	.23	.01	2.14	1.53–2.98	.001	.43	.22	.05

In level 1 models, the outcomes were predicted from time, coded in months from study entry, waist-to-hip ratio, and depression in the 6 months before assessment (0 = absent; 1 = present). In level 2 models, age is centered at the sample mean. Caucasian is coded as 0 = no and 1 = yes. Contraception is coded as 0 = nonuser and 1 = user. Alcohol is drinks per week.

CI, confidence interval; CRP; C-reactive protein; IL-6, interleukin 6; OR, odds ratio.

($p = .49$) varied by childhood adversity. Indeed, average HRSD episode ratings were virtually identical across adversity categories (20.1, 19.7, 17.1). Few subjects received antidepressant medication for their symptoms (12.5%), and childhood adversity was unrelated to the likelihood of doing so ($p = .70$). Childhood adversity was not directly related to the inflammatory biomarkers, either at baseline ($ps > .84$) or over follow-up ($ps > .15$).

Concurrent Analyses

The first series of analyses addressed these questions: does inflammation differ at visits when subjects have versus have not experienced a recent depressive episode? Does the nature of this association depend on earlier childhood adversities? As Table 2 indicates, significant cross-level interactions were observed for CRP, both as a continuous and categorical outcome, and for IL-6 (*ps* from .001 to .05). Importantly, these interactions were independent of the covariates in the models: age, racial/ethnic group, central adiposity, alcohol use, and contraceptives.

To interpret these findings, we plotted estimated values of inflammatory outcomes as a function of recent depression and childhood adversity, following standard algorithms (32). As the upper panel of Figure 1 shows, at visits when subjects had recently experienced a depressive episode, they showed higher circulating IL-6, relative to visits when they were euthymic. The magnitude of these changes varied in proportion to childhood adversity. To the extent they had been exposed to earlier adversity, subjects displayed progressively larger IL-6 increases upon transitioning from healthy to depressed states. Also notable is that under euthymic conditions, childhood adversity was unrelated to IL-6 concentrations.

Generally similar patterns were observed for CRP. Among subjects exposed to higher levels of childhood adversity, the transition to depression was accompanied by a relative increase in CRP (middle panel), and a greater likelihood of having CRP ≥3 mg/L (lower panel), placing them in the elevated risk category by American Heart Association/Centers for Disease Control and Prevention guidelines. In contrast, the transition to depression was accompanied by declining CRP in subjects without childhood adversity. A similar trend, although less strong, was apparent for subjects exposed to one form of childhood adversity.

Lagged Analyses

Because they focus on concurrent associations, the foregoing analyses cannot elucidate the temporal ordering of depression and inflammation or evaluate whether these states have lingering influences. To address these questions, we next estimated a series of time-lagged models. In the first set, inflammatory outcomes at Visit *N* were predicted from the depression assessment performed at Visit *N-1*. Also in the model were time, values of the inflammatory outcome itself at Visit *N-1*, childhood adversity, and demographic and biobehavioral covariates. As Table 3 shows, there was a significant cross-level interaction for CRP status ($p = .02$). Follow-up analyses suggested that depression had a lingering influence on CRP status, but this was apparent only among subjects exposed higher levels of childhood adversity (2+ forms). In other words, 6 months after visits when a depressive episode had been recorded, these individuals were more likely than other subjects to still have CRP ≥3 mg/L. In fact, 10.7% of the depressed subjects in the high childhood adversity category showed this pattern, whereas none of the other subjects did. We considered the possibility that these subjects had unusually severe or lengthy depressions but, as reported earlier, these episode characteristics were unrelated to childhood adversity. These findings also held up when we included current depression (as recorded at Visit *N*, simultaneous with CRP)

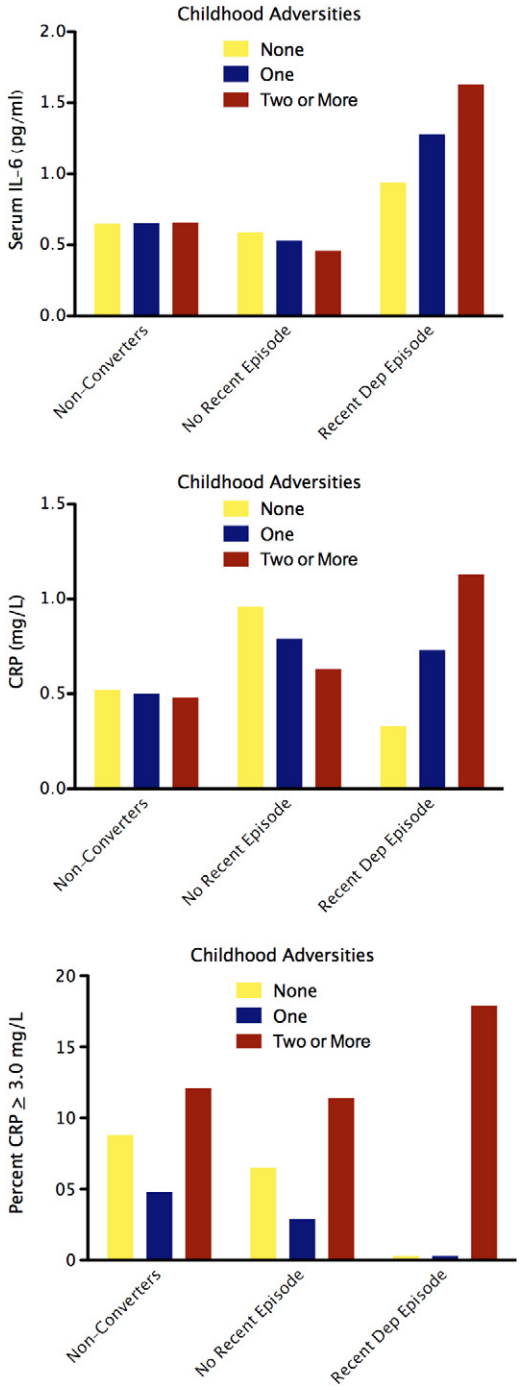

Figure 1. Estimated values of inflammatory outcomes as a function of recent depression and childhood adversity. At visits when subjects had recently experienced depression, they showed higher levels of inflammatory biomarkers, relative to visits when they were euthymic. However, the magnitude of these changes varied in proportion to childhood adversity. To the extent they had been exposed to earlier adversity, subjects displayed progressively larger interleukin-6 (IL-6; upper panel) and C-reactive protein (CRP; middle panel) increases upon transitioning from healthy to depressed states. With recent depression, these subjects also displayed a greater likelihood of having CRP ≥3 mg/L, placing them in the elevated risk category for cardiovascular disease as outlined in American Heart Association/Centers for Disease Control and Prevention guidelines (lower panel). These associations persisted following adjustment for demographic and biobehavioral confounders. The label "Non-Converters" refers to subjects who did not experience a depressive episode during the study.

Table 3. Childhood Adversity as a Moderator of Depression's Prospective Association with Inflammatory Proteins

Predictor	Serum CRP Coefficient	SE	*p*	Serum CRP ≥ 3 OR	95% CI	*p*	Serum IL-6 Coefficient	SE	*p*
Constant	.34	.47	.48	.33	.10–1.10	.07	.18	.11	.12
Age	.02	.12	.85	1.22	.99–1.52	.07	.07	.05	.13
Caucasian	−.17	.32	.60	1.18	.52–2.66	.69	.06	.12	.63
Contraception	−.61	.33	.07	.74	.23–2.45	.62	−.34	.15	.03
Alcohol Use	.37	.17	.03	.88	.45–1.72	.71	.06	.10	.55
Early Adversity	−.29	.24	.22	3.09	1.23–7.75	.02	−.11	.07	.14

In level 1 models, outcomes measured at Visit *N* were predicted from time, coded in months from study entry, and waist-to-hip ratio. Also in the level 1, equations were depression in the 6 months before Visit *N-1*, scored as 0 = absent; 1 = present, and levels of the outcome itself at Visit *N-1*. In level 2 models, age is centered at the sample mean. Caucasian is coded as 0 = no and 1 = yes. Contraception is coded as 0 = nonuser and 1 = user. Alcohol is drinks per week.

CI, confidence interval; CRP; C-reactive protein; IL-6, interleukin 6; OR, odds ratio.

to the model. Nonetheless, these findings emerged in only a small group of subjects and were not paralleled by effects for IL-6 or continuous CRP (Table 3; *p*s = .14 and .22, respectively.)

The second series of lagged analyses explored inflammation as a predictor of subsequent depression. Using multilevel models that assumed an underlying Bernoulli distribution of the outcome, depression status at Visit *N* was predicted from inflammatory markers assessed at Visit *N-1*. Also in the models were time, depression status at Visit *N-1*, childhood adversity, and demographic and biobehavioral covariates. As Table 4 shows, there was a significant cross-level interaction for IL-6, $p = .01$. This finding is plotted in Figure 2, again using standard algorithms (32). The pattern suggests that elevated IL-6 forecasts risks for depression 6 months later, above and beyond standard covariates and concurrent depression. But the direction of this association varies by childhood adversity. When adversity-exposed subjects display high IL-6 levels, relative to their average over the project, they have increased depression rates six months forward. This patterning is not evident among subjects exposed to a single childhood adversity. And it runs in the opposite direction for those with no history of childhood adversity. When these patients show high IL-6 levels, relative to their project average, they have lower depression risk six months forward.

Alternative Explanations

Family depression history was one component of our childhood adversity index. As such we considered the possibility that it, rather than childhood adversity, causes depression and inflammation to cluster in certain individuals. To evaluate this scenario, we re-estimated the models above while entering family history as a covariate alongside childhood adversity. In all cases, the observed cross-level interactions with childhood adversity remained significant, with *p*s < .03. By contrast, no significant cross-level interactions were apparent for family history, *p*s > .10.

Discussion

Interest in the hypothesis that inflammation contributes to the pathogenesis of depression and its comorbidities is growing rapidly. Despite the mounting interest, research on depression and inflammation has yielded inconsistent findings, leading to speculation that these conditions may cluster only in certain subgroups of patients, like those exposed to childhood adversity. In six waves of data from a study of individuals at high risk for depression, we found strong evidence to support this view. Indeed, among subjects exposed to higher levels of childhood adversity, the transition to depression was accompanied by relative increases in both CRP and IL-6. The higher CRP levels remained evident in these subjects 6 months later, suggesting that childhood adversity potentiates a lingering inflammatory response that is detectable even after the depressive episode has abated. These lingering effects appear to be bidirectional. Among subjects with a history of childhood adversity, high levels of IL-6 forecasted risk of depression 6 months later, even after concurrent inflammation was considered. This coupling of depression and inflammation was not apparent in subjects without childhood adversity.

These findings have several implications for our understanding and management of depression. First, they identify a subgroup of patients, those with childhood adversity, in whom depression and inflammation co-occur. From observational data such as these, inferences about causality cannot be made. However, if the clustering we observed reflects a causal influence of inflammation, these patients may be promising candidates for anti-inflammatory therapies (33). Our findings suggest that such treatments would be ineffective for patients without childhood adversity because depression and inflammation tend to dissociate in them. Second, the lingering effects seen here suggest that childhood adversity may predispose individuals to a scarring phenomenon in which even brief encounters with depression leave a persisting inflamma-

Table 4. Childhood Adversity as a Moderator of Inflammatory Proteins' Prospective Association with Incident Depression

Predictor	Serum CRP OR	95% CI	*p*	Serum CRP ≥ 3 OR	95% CI	*p*	Serum IL-6 OR	95% CI	*p*
Constant	1.51	.97–2.37	.06	.64	.14–2.80	.55	.43	.27–.70	<.01
Age	.93	.82–1.06	.26	1.10	.62–1.97	.74	1.30	1.07–1.59	<.01
Caucasian	.94	.59–1.49	.77	1.55	.30–8.00	.60	.87	.48–1.59	.65
Contraception	1.14	.77–1.71	.51	.56	.13–2.38	.43	.83	.40–1.74	.62
Alcohol Use	.56	.37–.85	.01	.60	.20–1.86	.38	1.55	1.01–2.36	.04
Early Adversity	.83	.67–1.04	.11	.76	.29–1.96	.57	1.50	1.10–2.06	.01

In level 1 models, depression status at Visit *N* was predicted from time, coded in months from study entry, plus the relevant inflammatory parameter and depression status at Visit *N-1*. In all cases, depression was coded as 0 = absent; 1 = present. In level 2 models, age is centered at the sample mean. Caucasian is coded as 0 = no and 1 = yes. Contraception is coded as 0 = nonuser and 1 = user. Alcohol is drinks per week.

CI, confidence interval; CRP; C-reactive protein; IL-6, interleukin 6; OR, odds ratio.

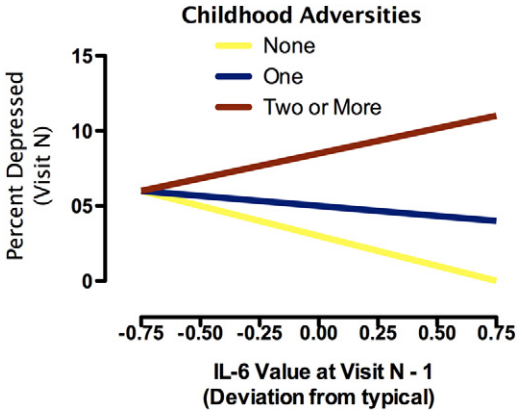

Figure 2. Estimated prevalence of depression as a function of interleukin-6 (IL-6) and childhood adversity. Lagged models revealed that when adversity-exposed subjects displayed high IL-6 levels, relative to their average over the project, they had increased depression rates 6 months forward. These associations persisted following adjustment for standard covariates and concurrent depression, that is, at time of IL-6 measurement.

tory residue (and vice versa). These findings converge with and extend studies of remitted depressed patients, in some of whom CRP remains elevated after symptom remission (34). As a consequence of these lingering effects, childhood adversity may predispose individuals to complicated depressions, characterized by treatment nonresponse, residual mood symptoms, or frequent relapse (3,35). The increased exposure to inflammatory mediators may also heighten these patients' vulnerability to comorbid medical conditions, such as diabetes, autoimmune disorders, and cardiovascular disease. As such, additional monitoring of adversity-exposed patients for psychiatric difficulties and medical comorbidities may be advantageous. Third, these findings suggest that even "mundane" forms of childhood adversity (36), involving parental separation and socioeconomic difficulties, can promote clustering of depression and inflammation. The fact that such clustering arises without exposure to more severe adversity, such as maltreatment, suggests that even normative childhood stressors may exert lasting influences on neural-immune crosstalk. This findings take on special relevance at present, when rates of childhood poverty and familial instability are increasing.

How might childhood adversity promote the clustering of depression and inflammation? We considered a number of explanations via statistical analysis, including adversity-related differences in the severity or duration of depressive episodes, and the contribution of putative demographic and biobehavioral confounds. None of these variables accounted for the consistent pattern of cross-level interactions. Instead, we speculate that childhood adversity fosters the emergence of a vigorous neural-immune pipeline, which amplifies cytokine signaling between the central nervous system and peripheral lymphoid structures (15). Such a pipeline could become embedded through any of several mechanisms, including post-translational modification of proteins involved with cytokine signaling (37), or densification of sympathetic connections that enable crosstalk between neural stress-response centers and peripheral immune compartments (38). Also potentially relevant are epigenetic alterations to genes involved with the propagation or transduction of inflammatory signals (39,40). Alternatively, the clustering could arise as a consequence of disparities in central serotonergic activity (41,42), imparted through previous adversity (43) or relevant allelic variation (44).

Several limitations of this study must be considered. We observed a relatively small number of depressive episodes, and they were generally of brief duration and mild severity. Considering these clinical features and the sample's characteristics—otherwise healthy teenagers from mostly middle-class families—the clustering we observed is even more striking. That said, to ascertain the clinical significance of these observations, research is needed on patients with severe, persistent depression. Such work could reveal whether clustering presages vulnerability to more complicated affective disorders and subsequent comorbid disease. Another weakness of the study was its failure to assess maltreatment. In the absence of such data, it remains uncertain whether the observed clustering arises from the "mundane" adversity captured by our index, versus unmeasured but co-occuring experiences with maltreatment. We view this scenario as somewhat unlikely, given prospective data showing that both impoverished and maltreated children go on to have more adult inflammation, and these effects are statistically independent (45). A final limitation is that our adversity index was constructed in a manner that treated all exposures as equally powerful. Follow-up analyses were supportive of this approach, suggesting that each type of adversity was associated with later clustering. However, because rates of exposure to some adversities were low, we lacked the power to formally test for distinct influences. Future research with larger, more vulnerable samples is needed to address this question. Because our study was limited to female adolescents, follow-ups with broader demographic representation would also be desirable.

To summarize, these results suggest that childhood adversity potentiates a phenotype in which depression and inflammation co-occur. This clustering has implications for our understanding of depression's pathogenesis, the mechanisms by which it confers susceptibility to comorbidities, and possibly for targeted application of anti-inflammatory therapy. More broadly, the findings contribute to an emerging consensus that childhood social conditions are important in establishing life course trajectories that eventuate in differential vulnerability to disease and disability (15,36).

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