Inflammatory Markers and the Pathogenesis of Pediatric Depression and Suicide: A Systematic Review of the Literature

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ABSTRACT

Objective: To evaluate the relationship and identify support for pathways linking inflammatory processes with depression and suicide in children and adolescents.

Data Sources: We designed and implemented comprehensive literature searches in MEDLINE, PsycINFO, and EMBASE. We searched the databases with database-specific controlled vocabulary in conjunction with keywords (eg, *inflammation, interleukin, cytokine, C-reactive protein, depression, suicide*) in various combinations for reports published in English through May 2013.

Study Selection: The searches identified a total of 1,543 citations, of which 55 were selected for further review and ultimately 27 were identified for inclusion. Studies were selected using 2 criteria. The first criterion required that studies include a biological measure of inflammatory markers in childhood or adolescence. The second criterion required that the studies include a measure of depression or suicide in childhood or adolescence. Articles selected for the review were based on the use of standardized experimental procedures and validated assessment measures.

Data Extraction: All articles were assessed by 2 authors, which ensured that the inclusion criteria were met. Studies were reviewed for association of inflammatory markers with depression and/or suicide. Extracted data included authors, year of publication, study design, population characteristics, inflammatory markers, and depression/suicide measures. Significant and nonsignificant findings were tabulated.

Results: The majority of studies were on depression; 2 studies were on suicide, and 7 studies were on inflammatory medical conditions. Most of the participants were adolescents. Interleukin (IL)-1α, IL-1β, IL-1 receptor antagonist, IL-2, soluble IL-2 receptors, IL-4, IL-6, IL-10, interferon-γ, tumor necrosis factor-α, C-reactive protein, erythrocyte sedimentation rate, and inflammatory cells were assayed across the studies. There was extensive variation in depression measures. Five of the 9 cross-sectional and 3 of the 7 longitudinal studies on depression found a positive association between inflammation and depression. In 3 studies evaluating depression and early adversity, inflammation was more significantly related to adversity than depression was. Results from studies of medical conditions involving inflammation and depression were mixed.

Conclusions: The extant literature provides sufficient data to support a link between inflammatory processes and pediatric depression. However, the directionality of the associations and pathways between the 2 conditions remains to be elucidated. At present, there is insufficient evidence to support the relationship between inflammation and suicidality in youth. Studies on inflammatory medical conditions are warranted in order to understand biological pathways linking inflammation and depression.

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There has been a growing recognition of the relationship between inflammatory processes and depression in adults, to the extent that some researchers have posited that depression is an "inflammatory illness."[1] Consistent associations between adult depression and elevated levels of interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were found in 2 recent meta-analyses.[2,3] There are a few individual studies that failed to find an association between inflammation and depression in adults.[4,5] With respect to the relationship between inflammation and suicide, elevated IL-6 and TNF-α have been reported to be associated with suicide attempts or suicidal ideation in depressed adults, even after controlling for depression.[6,7] In adults, postmortem changes in depressed suicide victims show increased mRNA of IL-1β, IL-6, and TNF-α in the prefrontal cortex.[8] In children and adolescents, there are fewer studies, but the weight of the evidence also supports a relationship between inflammatory markers and depression and is suggestive of an association with suicidal ideation and behavior as well.[8]

Of note, critical reviews of the extant literature in adults observe that most of the findings are cross-sectional, so that it is impossible to determine whether inflammation precedes depression/suicide or vice versa. Moreover, even in prospective studies of adults, participants studied have already had long-standing processes of depression and inflammation, and, additionally, these relationships between depression and inflammatory biomarkers are confounded by obesity, smoking, and other lifestyle factors that can have a strong effect on both depressive presentation and inflammatory response.

The purpose of this systematic review is to identify, in the extant literature, the extent to which there is support for pathways linking inflammatory processes and depression and suicidality (meaning suicidal ideation and/or attempt) in children and adolescents. To do so, we first review studies using several different designs: cross-sectional, longitudinal, and naturalistic

Clinical Points

- Current evidence supports the role of inflammation in children and adolescent depression.
- Prospective studies identifying clinical utility of inflammatory markers for predicting treatment response and suicidal events in depressed adolescents are warranted.
- Clinicians should be aware of a link between inflammatory processes and depression and understand that inflammatory biomarkers could be clinically applied for the management of depression in the future.

experimental (eg, depression related to exogenous agents [vaccines]) studies in youth examining the relationship between inflammatory responses and depression and/or suicidality. We then review pediatric studies of inflammatory medical conditions and the relationships between these diseases and depressive and suicidal outcomes. We conclude with recommendations for future research and clinical care to address gaps in the field with respect to understanding the relationship of the possible pathways linking inflammatory processes and the pathogenesis of early-onset depression and suicidality. To our knowledge, this review is the first to discuss the relationships of inflammatory medical conditions with depression in children and adolescents. We also note that our review is more explicitly focused on inflammation and suicidality, while others have looked at suicidality in the context of the relationship between inflammation and depression.

METHOD

We conducted systematic searches in MEDLINE and PsycINFO on Ovid and EMBASE through May 2013 (see Figure 1). MEDLINE, PsycINFO, and EMBASE are bibliographic databases developed, maintained, and updated, respectively, by the US National Library of Medicine, American Psychological Association, and Elsevier for Life Sciences. Collectively, they index millions of studies published in peer-reviewed journals in the biological and behavioral sciences.

We developed systematic literature search strategies for each database utilizing a combination of preferred subject terms from the database-specific thesauri as well as keywords, searched mainly in titles and abstracts of articles. Advanced search features in each database (eg, expanding/narrowing subject terms along the hierarchical structures within the database thesaurus, requiring that a subject term be of major emphasis in the article, and using wild cards to retrieve variances in word forms and spelling) allowed for focusing/expanding/limiting the search strategy and thus broadening or focusing the search results as deemed appropriate.

We tested and refined our search strategy in MEDLINE by various preferred terminology/keywords combinations first by using the Boolean operator OR for each of the components of the research question as follows:

1. Inflammatory markers and conditions: inflammation/ cytokine/ interleukin/ interferon/ tumor necrosis factor/ C-reactive protein/ inflammatory/ irritable bowel syndrome/ IBD/ diabetes mellitus/ arthritis/ asthma/ neuroinflammation
2. Depression/suicide: depressive disorder/ depressive disorder, major/ depressive disorder, treatment-resistant/ dysthymic disorder/ seasonal affective disorder/ major depression/ suicide/ suicidality/ suicidal ideation/ suicidal attempt

The 2 search clusters were then combined by the Boolean operator AND. Finally, the results were limited to those that were in children and adolescents (birth to age 18 years), published in peer-reviewed journals, and in English. The search strategy tested in MEDLINE was then translated into the database-specific search language and conventions in PsycINFO and EMBASE. The searches retrieved 672 results in MEDLINE, 207 results in PsycINFO, and 664 results in EMBASE. Across the 3 databases, we identified a total of 1,543 citations.

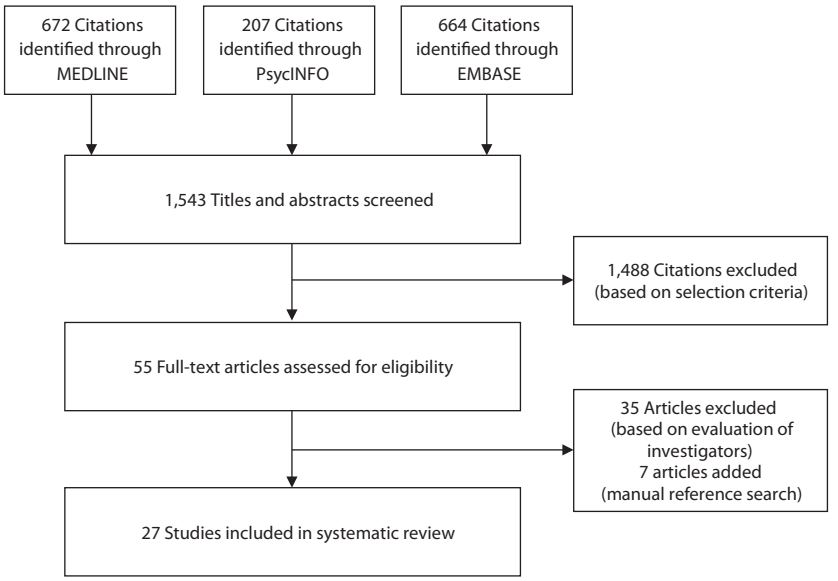
We read all of the abstracts, and we selected articles using 2 criteria. The first criterion was that the studies had to include a biological measure of inflammatory markers in childhood or adolescence (birth to age 18 years). The second criterion required that the studies included a measure of depression or suicide in childhood or adolescence. Articles selected for the review were based on the use of standardized experimental procedures and validated assessment measures regardless of sample size. Fifty-five studies were selected on the basis of the above criteria.

For the selected studies, we identified citing articles through the Web of Science and Scopus databases and searched the reference sections for additional relevant publications. Seven articles were identified and added through the manual reference search. We then reviewed the full manuscripts of the selected articles for key information: study design, source of participants, sample size, age, measurement of inflammation and depression, covariates, and findings. Two investigators (J.-W.K. and D.A.B.) evaluated and rated the articles based on a Likert scale of 1 (least relevant) to 5 (most relevant). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for the review.

RESULTS

We identified 27 studies for inclusion in this review. Sample sizes for studies ranged from 23 participants[9] to 4,655 participants,[10] with a total number of youth included in the review of 18,621. The majority of studies in the current review were cross-sectional. There were 7 longitudinal studies on depression (see Table 1). Among the 27 studies, only 2 studies used samples in which all participants were children, and 11 studies included both child and adolescent participants; the remaining 14 studies used samples in which all participants were adolescents. There were 2 studies of

Figure 1. Study Selection Flowchart



suicide and 7 studies of inflammatory medical conditions (see Tables 2 and 3, respectively).

With respect to the inflammatory markers, IL-1α, IL-1β, IL-1 receptor antagonist, IL-2, soluble IL-2 receptors, IL-4, IL-6, IL-10, interferon (IFN)-γ, TNF-α, erythrocyte sedimentation rate (ESR), and inflammatory cells (eosinophils, T lymphocytes, and mast cells) were assayed. The majority of studies measured plasma levels of inflammatory markers; the remaining studies measured saliva levels (1 study), genetic polymorphisms (3 studies), protein and mRNA in prefrontal cortex (1 study), and cells in the mucosa of stomach and duodenum (1 study). The majority of studies assessed 2 or more markers; only 8 studies measured 1 marker in each study.

There was extensive variation in the measures of depression among the selected studies. The Children's Depression Inventory (CDI)[11] and the Beck Depression Inventory (BDI)[12] were the most commonly used dimensional measures (6 studies and 5 studies, respectively). Many studies measured depression using subscales of general behavioral questionnaires. Ten studies used a total of 4 different types of standard psychiatric interviews for diagnosing depression. In 3 studies, depression was used only as a mediator, not as a predictor and/or an outcome measure.

The central findings from these studies are summarized in Tables 1–3. In the following paragraphs, we present the results of our review organized by consistent themes in these findings.

Inflammatory Processes and Depression in Youth

Cross-sectional studies. In one of the first studies to examine inflammatory cytokines in depressed adolescents, Brambilla and colleagues[13] observed no differences in plasma levels of IL-1β and TNF-α in a group of children and adolescents with major depressive disorder (MDD) or dysthymia (n = 22) compared to healthy controls (n = 11), although a negative finding could be attributable to the small sample size (Table 1). On the other hand, recent findings are in support of a relationship between inflammatory markers and pediatric depression. Keller and colleagues[14] examined the relationship between salivary IL-6 and children's internalizing and externalizing symptoms (N = 329). Higher levels of IL-6 were related to greater self-reported depressive symptoms, as measured with the CDI, in girls (n = 177) but not in boys (n = 152). Henje Blom and colleagues[15] measured IL-1β, IL-2, IL-6, IL-10, IFN-γ, and TNF-α in a sample of female adolescents with MDD (n = 42) and healthy controls (n = 60). The patient group showed higher levels of IL-1β, IL-2, and IL-10 relative to the control group ($P < .05$). The nonmedicated patients (n = 26) showed elevated levels of IL-1β, IL-2, and IL-6 relative to the controls; only IL-2 was *elevated* in the medicated patients (n = 16) compared to controls. In the adolescents with MDD, IL-6 and IFN-γ levels positively correlated with internalizing symptoms including depression, as measured with the emotional subscale of the Strengths and Difficulties Questionnaire (SDQ).[16] Gabbay and colleagues[17] measured the plasma levels of IFN-γ, TNF-α, IL-6, IL-1β, and IL-4 in adolescents with depression, and while there were no group differences with respect to most of those cytokines, depressed adolescents (n = 30) were found to have significantly higher levels of IFN-γ ($P < .003$) compared to healthy controls (n = 15). Similar results were obtained when medicated subjects (n = 17) were excluded. Also, depressed adolescents had a higher ratio of IFN-γ/IL-4, which may be suggestive of an imbalance between a proinflammatory (ie, IFN-γ) and anti-inflammatory (ie, IL-4) response.

Studies that examined the relationship between C-reactive protein (CRP) and early-onset depression have been contradictory, with 1 study supporting an association and

1 finding no association with depression.[18,19] Chaiton and colleagues[18] studied the data obtained from a province-wide survey of a representative sample of youth in Quebec, Canada, and found no association between serum concentrations of CRP and depressive symptoms after adjustment for potential confounding variables such as body mass index (BMI), smoking, cholesterol concentration, and blood pressure. Danese and colleagues[19] studied a sample of 12-year-old children (N = 174) to examine whether maltreated children who also experience depression at the time of inflammation assessment would show elevated CRP levels. They found that children who were both depressed and maltreated (n = 13) showed elevated CRP levels relative to control children (n = 84). However, depressed-only (n = 8) and maltreated-only (n = 69) children showed CRP levels similar to those of control children.

In adults, there is a growing consensus that antidepressant treatment results in a decline in inflammatory cytokines, specifically, IL-6 and IL-1β.[20,21] While changes in cytokines with antidepressant treatment have not been studied in depressed adolescents, one study found that nonmedicated, depressed adolescents have higher IL-6 levels than medicated adolescents,[15] and antidepressant treatment explained 26% of the variance related to IL-6 after controlling for BMI and symptom severity, as measured with the emotional subscale of SDQ.

In studies of adults, several functional allelic variants and single-nucleotide polymorphisms (SNPs) of the IL-1β, IL-6, and TNF-α genes have been identified in association with depression.[22] In pediatric populations, we found 3 studies that examined the relationship between genetic variation in inflammatory genes and depression. Misener and colleagues[23] investigated the genes of 4 proinflammatory (IL-1α, IL-1β, IL-6, and TNF-α) and 2 anti-inflammatory (IL-10 and IL-1 receptor antagonist) cytokines in children and their parents from 384 families, each ascertained through a child with depression diagnosed before the age of 15 years. Tests for genetic association were conducted using the transmission disequilibrium test (TDT), a family-based association method that tests for biased transmission of alleles from heterozygous parents to their affected children. No significant evidence was found for an association between childhood-onset mood disorders and any of the genetic polymorphisms investigated, either individual variants or as haplotypes. In a follow-up study by Misener and colleagues,[24] a sample of 646 families (with 782 affected children) was used to test for association between a set of 5 tagging SNPs of the IL-1β gene and childhood-onset depression. None of the SNPs showed evidence for association in the TDT analyses. Gaysina and colleagues[25] investigated whether 2 *CRP* gene polymorphisms (rs1205 and rs3093068) that have been found to influence plasma CRP concentration were associated with adolescent emotional problems (depression/anxiety) and metabolic syndrome. There was a significant interaction between the *CRP* rs1205 genotype and emotional status in adolescence ($P = .05$): the association between adolescent emotional problems and metabolic syndrome was stronger in subjects who were homozygous for the C allele of rs1205 (OR = 1.83; 95% CI, 1.17–2.86) than in carriers of the T allele. A stronger interaction was found when using adolescent emotional problems as a continuous variable ($P = .003$).

Longitudinal studies. Miller and Wrosch[26] followed 90 female adolescents who were at high risk for depression over the course of 1 year and tracked changes in levels of CRP in order to examine the relationship between goal disengagement and inflammation. *High-risk* was defined as having a first-degree relative with a history of affective disorder and/or scoring in the top quartile of the population distribution on 1 of 2 indices of cognitive vulnerability to depression, the Dysfunctional Attitudes Scale[27] and the Adolescent Cognitive Style Questionnaire.[28] Goal disengagement was measured through a questionnaire inquiring how subjects usually reacted when they had to stop pursuing an important goal. To the extent that subjects had difficulties disengaging from unattainable goals, they showed increasing levels of CRP over the follow-up period. This association was independent of potential confounders including BMI, smoking, and depression, as measured with the BDI. Depression was used only as a mediator, not as a predictor and/or an outcome measure in the study.

One prospective study[29] examined the course of depressive symptoms and levels of CRP over time, using data from the prospective population-based Great Smoky Mountains Study. In this study, depression variables were assessed using the Child and Adolescent Psychiatric Assessment (CAPA).[30] Depression status was measured by 2 variables: any current depressive disorder (binary) and the number of total current nonoverlapping depressive symptoms (range, 0–10). CRP levels did not predict depressive symptoms at follow-up. On the other hand, depressive symptoms predicted later higher CRP levels ($P = .03$). Of note is that cumulative depressive episodes exerted the greatest effect on later CRP levels, even after adjusting for potential confounders such as BMI and smoking ($P = .02$). In another prospective, longitudinal analysis by Copeland and colleagues[31] that looked at the association between CRP and generalized anxiety disorder (GAD), GAD was found to be associated with elevated levels of CRP in bivariate associations over time. However, these associations did not remain significant after adjusting for health-related covariates (eg, BMI, medication use). Although depression was not a predictor or an outcome measure in this latter study, it is important to note that 40% of the GAD subjects also met criteria for depressive disorder, and similar high overlap between symptoms and cumulative episodes of GAD and depression was observed (r values, 0.55–0.72, $P < .0001$).

In a study that looked at both IL-6 and CRP, Rohleder and Miller[32] investigated whether state or trait components of depression are associated with inflammatory markers in female adolescents (N = 65). Depressive symptoms were assessed weekly over a period of 20 weeks using a web-based version of the Center for Epidemiologic Studies Depression Scale (CES-D),[33] and inflammatory markers IL-6 and CRP were measured at the beginning and the end of this period.

State levels of depression were defined as the CES-D score the week before the final blood draw, and trait levels were determined through computing a series of average within-person CES-D scores over 20 weeks. Linear regressions controlling for baseline inflammation, age, and BMI demonstrated that trait levels of depressive symptoms were not associated with IL-6 or CRP levels after the observation period. In contrast, state levels of depressive symptoms were associated with changes in IL-6 levels ($P = .03$), suggesting that short-term changes in depressed mood stimulates inflammatory mediators such as IL-6 in female adolescents. In another study, Miller and colleagues[34] examined whether chronic interpersonal stress predicts activation of IL-6 and CRP 6 months forward in female adolescents (N = 103). Interpersonal difficulties were assessed at baseline, and inflammatory markers were measured at that time and 6 months later. The BDI was administered to subjects to measure the depressive symptoms at the 6-month visit. Chronic interpersonal stress at baseline was associated with greater increases in lipopolysaccharide (LPS)-stimulated production of IL-6 over the 6-month follow-up. This association was independent of depressive symptoms. In addition, no consistent pattern of cross-sectional or prospective associations was found between inflammatory markers and depressive symptoms (r values < 0.14, $P > .17$).

Several recent studies investigated the relationships between early adversity, inflammation, and depression. In one longitudinal prospective study, Slopen and colleagues[10] examined whether adverse events in early childhood would have effects on inflammatory markers later and if these effects were sustained over time. They found that the presence and cumulative severity of early childhood adversity from birth to 8 years was associated with higher levels of IL-6 and CRP at age 10 ($P \leq .03$). Adverse events reported in early childhood (1.5 years of age) or middle childhood (between ages 6 to 8 years), and cumulative adverse experiences from birth through 8 years of age predicted increased CRP levels at age 15 ($P \leq .04$). Some of these associations between adverse events and inflammation were mediated by BMI, but no evidence was found that depression mediated these associations. In another prospective study of adolescent girls who were at high risk for depression (N = 147), Miller and Cole[35] found that those youth exposed to higher levels of childhood adversity showed higher levels of IL-6, which in turn predicted depressive symptoms. The participants were assessed every 6 months over a 2.5-year period and underwent diagnostic interviews for depressive episodes and measurements of IL-6 and CRP levels. Among the participants exposed to higher levels of childhood adversity, the transition to depression was accompanied by increases in both IL-6 and CRP levels. Higher CRP levels remained after depressive symptoms abated. The participants with a history of childhood adversity and high levels of IL-6 had increased depression rates 6 months forward, suggesting that childhood adversity promotes coupling of depression and inflammation and potentiates a phenotype in which depression and inflammation occur together. This study supports the possible role of early adversity as a link between inflammation and depression.

Naturalistic experimental studies. We found 2 naturalistic experimental studies that measured inflammatory markers and depressive symptoms in children and adolescents. In one study, to examine possible mechanisms that mediate between viral infection and psychiatric symptoms, Morag and colleagues[36] measured serum levels of IL-1β, IFN-γ, and soluble IL-2 receptors 10 weeks following rubella vaccination in female adolescents (N = 240). An experimental group (n = 60) included subjects who were initially not immune to rubella and were infected following vaccination, and a control group (n = 180) included subjects who were already immune to rubella before vaccination. Compared to the control group and to their own baseline, subjects with low socioeconomic status within the experimental group showed increased depressive symptoms, as measured with the CDI, following vaccination ($P < .05$). However, this study did not find any association between the inflammatory cytokines and depressive symptoms.

In other study, Munitz-Shenkar and colleagues[9] investigated the relationship between changes in serum cytokines (IL-1β, IL-2, and IL-6) and depression/anxiety symptoms in children and adolescents (N = 23) undergoing hematopoietic stem cell transplantation. It was hypothesized that the transplantation process induces alterations in cytokine levels and would contribute to the emergence of depressive and anxiety symptoms. The serum cytokine levels and psychiatric symptoms were measured at 4 timepoints: at conditioning time when treatment is initiated (time 1 = T1), on the day of hematopoietic transplantation (T2), on the day of engraftment (T3), and a week after the engraftment (T4). Up to the time of engraftment (T3), depressive symptoms, as measured by CDI, were relatively high and resolved subsequently. In contrast, serum cytokines (IL-1β and IL-6) increased significantly only after the engraftment (T4). In other words, elevated depressive symptoms preceded the elevation in cytokine levels. No significant correlation was found between the cytokine levels and depressive scores at T1, T2, and T3. However, at T4, negative correlation was found between serum IL-1β and IL-2 levels and depression scores (r values, −0.43 to −0.50; $P < .05$) (Table 1).

Inflammatory Processes and Suicidality in Youth

In depressed adults, elevated IL-6 and TNF-α levels and decreased IL-2 levels have been reported to be associated with suicidal attempts or suicidal ideation, even controlling for depression.[6,7] In children and adolescents, we identified 2 studies that examined the relationship between inflammatory markers and suicidality (Table 2). Gabbay and colleagues[37] measured the plasma levels of proinflammatory and anti-inflammatory cytokines (IFN-γ, TNF-α, IL-6, IL-1β, and IL-4) in suicidal depressed adolescents (n = 12), nonsuicidal depressed adolescents (n = 18), and healthy controls (n = 15). Suicidality was defined as expressing a lethal plan for committing suicide that was perceived by the clinician as presenting an imminent risk to self. The authors found that

Table 1. Studies of Inflammatory Markers in Depression in Youth

Study	Subjects	Inflammatory Markers	Depression Measures	Covariates	Findings
Cross-sectional					
Brambilla et al (2004)[13]	N = 33 (11 MDD, 11 dysthymia, 11 healthy controls) Age 6–14 y	Plasma IL-1β, TNF-α	K-SADS (diagnosis)	None	No differences in IL-1β and TNF-α between patients and controls
Keller et al (2010)[14]	N = 329 (normally developing children) Age 8–12 y	Salivary IL-6	CDI	Puberty	Higher IL-6 levels were related to greater depressive symptoms in girls, but not in boys
Henje Blom et al (2012)[15]	N = 102 (42 MDD [16 medicated, 26 unmedicated], 60 healthy controls; all girls) Age 14–18 y	Plasma IL-1β, IL-2, IL-6, IL-10, IFN-γ, TNF-α	Development and Well-Being Assessment (diagnosis) Emotional subscale of SDQ	BMI	MDD showed higher IL-1β, IL-2, and IL-10 than controls; in MDD, IL-6 and IFN-γ levels correlated with depressive symptoms; nonmedicated MDD had higher IL-6 than medicated MDD
Gabbay et al (2009)[17]	N = 45 (30 MDD, 15 healthy controls) Age 12–19 y	Plasma IFN-γ, TNF-α, IL-6, IL-1β, IL-4	K-SADS (diagnosis) CDRS BDI-II	None	MDD had higher IFN-γ and IFN-γ/IL-4 ratio than controls
Chaiton et al (2010)[18]	N = 1,535 (population-based) Age 13 y (n = 721), 16 y (n = 814)	Plasma CRP	Depression subscale of Psychological Distress Scale	BMI, smoking, medication use, cholesterol, blood pressure	No association between CRP and depression after adjustment
Danese et al (2011)[19]	N = 174 (90 depression, 84 controls) Age 12 y	Plasma CRP	CDI	Waist-hip ratio, body temperature	Depressed + maltreated children showed elevated CRP relative to controls
Misener et al (2008)[23]	N = 460 Age 7–14 y (at diagnosis)	IL-1α, IL-1β, IL-6, TNF-α, IL-10, IL-1 receptor antagonist genes	Interview Schedule for Children and Adolescents (diagnosis)	None	No association between genetic polymorphisms and depression
Misener et al (2009)[24]	N = 782 Age 7–14 y (at diagnosis)	IL-1β gene (a set of 5 single-nucleotide polymorphisms)	Interview Schedule for Children and Adolescents (diagnosis)	None	No association between genetic polymorphisms and depression
Gaysina et al (2011)[25]	N = 2,658 (population-based) Age 13–15 y (at assessment of emotional problems)	CRP genes (rs1205 and rs3093068)	Children's Behavior Questionnaire (teacher-rated)	None (gender)	The association between emotional problems and metabolic syndrome was stronger in subjects who were CC homozygotes of rs1205 than in T allele carriers
Longitudinal					
Slopen et al (2013)[10]	n = 4,655 (age 10 y) n = 3,286 (age 15 y) Age 9–15 y	Plasma IL-6, CRP	Development and Well-being Assessment, Emotional subscale of SDQ (age 10 y) Short Mood and Feelings Questionnaire (age 15 y) (mediator)	BMI, smoking, maternal education, household income, depression	Early childhood adversity was associated with higher IL-6 and CRP; depression did not mediate these associations
Miller and Wrosch (2007)[26]	N = 90 (girls at high risk for depression) Mean ± SD age = 17.2 ± 1.4 y (15–19 y at study entry)	Plasma CRP	BDI (mediator)	BMI, smoking, depression	CRP was associated with goal disengagement, independent of confounders
Copeland et al (2012)[29]	N = 1,420 (population-based) Age 9–16, 19, and 21 y (9, 11, and 13 y at intake)	Plasma CRP	CAPA	BMI, smoking, alcohol use, medication use, low SES, recent physical ailments	CRP did not predict depressive symptoms at follow-up, depressive symptoms were associated with later CRP
Copeland et al (2012)[31]	N = 1,420 (population-based) Age 9–16, 19, and 21 y (9, 11, and 13 y at intake)	Plasma CRP	CAPA	BMI, smoking, alcohol use, medication use, low SES, recent physical ailments	No association between CRP and GAD after adjustment; high overlap between GAD and depression
Rohleder and Miller (2008)[32]	N = 65 (girls at high risk for depression) Age 16–21 y	Plasma IL-6, CRP	CES-D	BMI	Trait levels of depression were not associated with IL-6 or CRP; state levels of depression were associated with IL-6

(continued)

Table 1 (continued). Studies of Inflammatory Markers in Depression in Youth

Study	Subjects	Inflammatory Markers	Depression Measures	Covariates	Findings
Longitudinal					
Miller et al (2009)[34]	N = 103 (girls at high risk for depression) Mean ± SD age = 17.2 ± 1.4 y (15–19 y at study entry)	Plasma IL-6, CRP	BDI (mediator)	Oral contraceptive use, SES, smoking, waist-hip ratio, physical activity, depression	Chronic interpersonal stress at baseline was associated with greater increases in lipopolysaccharide-stimulated production of IL-6 over the 6-mo follow-up; no cross-sectional or prospective associations were found between inflammatory markers and depression
Miller and Cole (2012)[35]	N = 147 (girls at high risk for depression) Mean ± SD age = 17.0 ± 1.3 y (15–19 y at study entry)	Plasma IL-6, CRP	SCID (diagnosis) Hamilton Depression Rating Scale	Waist-hip ratio, smoking, alcohol use, contraceptive medication	Subjects with a history of childhood adversity and high levels of IL-6 had increased depression rates 6 mo later
Naturalistic experimental					
Munitz-Shenkar et al (2007)[9]	N = 23 (undergoing hematopoietic stem cell transplantation) Age 6–18 y	Plasma IL-1β, IL-2, IL-6	CDI	None	Elevated depressive symptoms preceded the elevation in IL-1β and IL-6; negative correlation was found between IL-1β and IL-2 and depression after the engraftment
Morag et al (1998)[36]	N = 240 (60 experimental initially not immune to rubella, 180 controls already immune to rubella; all girls) Mean ± SD age = 12.4 ± 0.2 y (range not reported)	Plasma IL-1β, IFN-γ, soluble IL-2 receptors (sIL-2r)	CDI	None	Did not find association between inflammatory markers and depression

Abbreviations: BDI = Beck Depression Inventory, BMI = body mass index, CAPA = Child and Adolescent Psychiatric Assessment, CDI = Children's Depression Inventory, CDRS = Children's Depression Rating Scale, CES-D = Center for Epidemiologic Studies Depression Scale, CRP = C-reactive protein, GAD = generalized anxiety disorder, IFN = interferon, IL = interleukin, K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia, MDD = major depressive disorder, SCID = Structured Clinical Interview for *DSM-IV-TR*, SDQ = Strength and Difficulties Questionnaire, SES = socioeconomic status, TNF-α = tumor necrosis factor-α.

Table 2. Studies of Inflammatory Markers in Suicide in Youth

Study	Subjects, Design	Inflammatory Markers	Suicide Measures	Covariates	Findings
Gabbay et al (2009)[37]	N = 45 (12 suicidal MDD, 18 nonsuicidal MDD, 15 healthy controls) Age 12–19 y Cross-sectional	Plasma IFN-γ, TNF-α, IL-6, IL-1β, IL-4	K-SADS (diagnosis) Beck Scale for Suicidal Ideation	None (age, gender)	IFN-γ was increased in both suicidal and nonsuicidal MDD compared to controls; TNF-α was decreased in suicidal MDD compared to nonsuicidal MDD
Pandey et al (2012)[38]	N = 48 (24 suicide victims, 24 controls) Age 12–20 y Cross-sectional	Protein and mRNA of IL-1β, IL-6, and TNF-α in prefrontal cortex	SCID (diagnosis)	Postmortem interval, pH of the brain	Increased mRNA and protein expression of IL-1β, IL-6, and TNF-α in BA 10 of suicide victims relative to controls

Abbreviations: BA = Brodmann area, IFN = interferon, IL = interleukin, K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia, MDD = major depressive disorder, SCID = Structured Clinical Interview for *DSM-IV* Disorders, TNF-α = tumor necrosis factor-α.

IFN-γ level was increased in both suicidal and nonsuicidal depressed individuals compared to controls ($P < .02$) and that TNF-α level was *decreased* in suicidal depressed adolescents compared to nonsuicidal adolescents with depression ($P = .03$). The authors suggested that immune system dysregulation, specifically the changes in TNF-α, is associated with suicidal symptomatology in the context of adolescents with depression. In the other study, Pandey and colleagues[38] studied the gene and protein expression levels of proinflammatory cytokines in the prefrontal cortex of 24 adolescent suicide victims and 24 controls and reported increased mRNA and protein expression levels of IL-1β, IL-6, and TNF-α in Brodmann area 10 of suicide victims relative to controls. Of note, only one third (n = 8) of the suicide victims had a diagnosis of major depression, suggesting an independent association between inflammatory cytokines and suicidality in youth (Table 2).

Inflammatory Conditions and Depression in Youth

Inflammatory conditions can be defined as immune-mediated processes in the body that have been associated with brain dysfunction, such as depression. In these studies, inflammatory markers can be measured directly or can be part of disease severity measures used to document current

disease activity. Physical conditions that have growing support for linkage to immune system dysregulation include diabetes, asthma, and inflammatory bowel disease (IBD). In type 1 diabetes, proinflammatory cytokines such as IFN-γ, TNF-α, and IL-1 have been implicated in pathogenesis,[39] while in type 2 diabetes, immune system changes, including elevated cytokines and chemokines, are thought to be linked to increased adipose tissue.[40]

Hood and colleagues[41] investigated the relationship between metabolic and inflammatory (IL-6, CRP) markers and depression (CES-D) in 2,359 youth with either type 1 or type 2 diabetes and found a significant association between CRP and depressive severity in the type 1 group (Table 3). However, this association did not remain significant after adjustment for demographic and clinical covariates and stratification by diabetes type in the regression model. In a study with a large cohort (N = 1,420) of children (aged 10–16 years) that evaluated the relationship between inflammation (CRP) and co-occurring asthma and depression (evaluated via the CAPA), the co-occurrence of depression and asthma predicted elevated CRP ($P \leq .04$).[42] This finding is consistent with findings in adult asthmatics showing significant correlations between depressive severity and proinflammatory cytokines.[43] Interestingly, the co-occurrence of CRP and asthma did not predict depression over time, and the co-occurrence of CRP and depression did not predict asthma over time, thus ruling out alternative directions of effects. Finally, in children with IBD, an autoimmune-mediated gastrointestinal disease associated with high rates of depression, depressive severity (measured with the CDI) has been significantly associated with increased IBD activity ($P = .02$) using a disease activity instrument that incorporated ESR, a nonspecific inflammatory marker.[44] A more recent study has shown that depressed youth with IBD who have high levels of somatic depressive symptoms (eg, fatigue, sleep disturbance, decreased concentration) on the Children's Depression Rating Scale-Revised[45] have significantly higher ESR levels ($P < .01$), consistent with inflammation, than controls.[46]

There is increased evidence of an association between depression and inflammation in another set of disorders, chronic fatigue syndrome and functional abdominal disorders (eg, functional dyspepsia, IBD), both previously considered to be without clear organic causes and thus diagnoses of exclusion. Chronic fatigue syndrome, characterized by fatigue and other neuropsychological disturbances such as headaches, myalgias, decreased concentration, and depression, has been associated with elevation of proinflammatory cytokines (eg, IFN-γ, TNF-α) and decreased natural killer cells in adults.[47]

In a longitudinal study on a sample of severely fatigued (n = 67) and nonfatigued (n = 61) adolescent girls, ter Wolbeek and colleagues[48] examined pro- and anti-inflammatory cytokine production (ie, LPS-induced IL-6, TNF-α, and IL-10 and CD2CD28-induced IFN-γ, IL-4, and IL-10) at 3 timepoints: T1 (spring), T2 after 6 months (autumn), and T3 after 12 months (spring). Depressive symptoms were measured using the BDI. In the fatigued group, participants with high scores of depression showed elevated IL-10 production compared to those with a low level of depression ($P < .01$). The IFN-γ/IL-10 ratio was decreased in the depressed fatigued subgroup as well ($P < .01$). Within the nonfatigued group, there was no effect of depression on the inflammatory function. Another study by ter Wolbeek and colleagues[49] evaluated the role of cytokines in fatigue development in a sample of healthy females (n = 64) and found that higher IFN-γ and IFN-γ/IL-4 ratio and lower TNF-α and IL-10 at baseline were related to fatigue severity 4½ years later ($P < .05$). Increase as well as decrease in fatigue severity was accompanied by respective increases and decreases in depressive symptoms and anxiety ($P < .001$).

In terms of functional gastrointestinal disorders, Schurman and colleagues[50] studied 59 patients with functional dyspepsia who underwent upper endoscopy with biopsy, with the aim of exploring the relationship between mucosal inflammation and psychological functioning. Inflammatory cells (eosinophils, T lymphocytes, and mast cells) in the mucosa of stomach and duodenum were enumerated, and depressive symptoms were measured using the Behavior Assessment System for Children.[51] Peak stomach mast cell density and mean stomach mast cell density correlated with parent report of child depressive symptoms (r values, 0.28–0.31; $P < .05$), suggesting a possible association between histologic inflammation and depression in pediatric functional dyspepsia (Table 3).

DISCUSSION

Summary of Main Findings and Review of Study Designs

The articles reviewed here provide preliminary evidence for the role of inflammation in child and adolescent depression. Five of the 9 cross-sectional studies of inflammatory markers in depression found a positive association between inflammation and depression.[14,15,17,19,25] Of 7 longitudinal studies, 1 study[35] found that inflammation is followed by depression, 2 studies[29,32] found inflammation as a sequela of depression, and the remaining studies found no relationship. Three studies showed a link between early or current stressors, inflammation, and depression.[10,19,35] Other studies that support a link between inflammation and depression include experimental exposure to virus, immunologic response, and subsequent depressive symptomatology[9,36] and 1 study showing an association between a genetic polymorphism for CRP and depression.[25] For depression linked to medical conditions, positive associations were reported between inflammation and depression for asthma, IBD, chronic fatigue syndrome, and functional bowel syndromes but not diabetes.

There are several reasons for the inconsistency across studies, including methodology, heterogeneity of depression, and different pathways mediating the relationship between inflammation and depression under different conditions (eg, vaccine, trauma, medical conditions). We first review the significant methodological gaps in the literature and then make recommendations for future research.

Table 3. Studies of Inflammatory Conditions and Depression in Youth

Study	Subjects, Design	Inflammatory Markers	Depression Measures	Covariates	Findings
Hood et al (2012)[41]	N = 2,359 (with diabetes; population-based) Mean ± SD age = 15.2 ± 3.1 y (range not reported) Cross-sectional	Plasma IL-6, CRP	CES-D	BMI, highest parental education, health insurance coverage, number of caregivers in the home	No association between CRP and depression after adjustment
Shanahan et al (2013)[42]	N = 1,420 (population-based) Age 10–16 y Longitudinal	Plasma CRP	CAPA	BMI, smoking, alcohol use, medication use, low SES, recent physical ailments	The co-occurrence of asthma and depression predicted heightened CRP
Szigethy et al (2004)[44]	N = 102 (with IBD) Mean ± SD age = 14.8 ± 1.9 y (11–18 y) Cross-sectional	Plasma ESR	K-SADS-PL (diagnosis) CDI	None	Depression severity was significantly associated with increased IBD activity using a disease activity instrument that incorporated ESR
Benhayon et al (2013)[46]	N = 115 (96 patients with Crohn disease and depression, 19 healthy controls) Mean ± SD age = 14.4 ± 2.3 y (patients), 14.8 ± 2.0 y (controls); 9–17 y (recruitment ages for Crohn disease) Cross-sectional	Plasma ESR, CRP	K-SADS-PL (diagnosis) CDI CDRS-R	None	Patients showed higher ESR levels than controls
Ter Wolbeek et al (2007)[48]	N = 128 (67 fatigued, 61 nonfatigued; all girls) Mean ± SD age = 15.2 ± 1.4 y (fatigued), 14.7 ± 1.6 y (nonfatigued); range not reported Longitudinal	Plasma IL-6, TNF-α, IL-10, IFN-γ, IL-4	BDI	Puberty, smoking	Fatigued subjects with high depression showed more elevated IL-10 than those with low depression; IFN-γ/IL-10 ratio was decreased in the depressed fatigued subjects
Ter Wolbeek et al (2011)[49]	N = 64 (healthy females with baseline cytokine data) Mean ± SD age = 14.6 ± 1.4 y (baseline), 19.0 ± 1.6 y (follow-up) Longitudinal	Plasma TNF-α, IL-10, IFN-γ, IL-4	BDI	Smoking, alcohol and drug use	Higher IFN-γ and IFN-γ/IL-4 ratio, and lower TNF-α and IL-10 at baseline were related to fatigue severity 4½ y later; Increase/decrease in fatigue severity was accompanied by increase/decrease in depressive symptoms
Schurman et al (2010)[50]	N = 59 (with functional dyspepsia who underwent upper endoscopy with biopsy) Age 8–17 y (recruitment criteria) Cross-sectional	Inflammatory cells (eosinophils, T lymphocytes, and mast cells) in the mucosa of stomach and duodenum	BASC	None	Peak and mean stomach mast cell densities correlated with depressive symptoms

Abbreviations: BASC = Behavior Assessment System for Children, BDI = Beck Depression Inventory, BMI = body mass index, CAPA = Child and Adolescent Psychiatric Assessment, CDI = Children's Depression Inventory, CDRS-R = Children's Depression Rating Scale-Revised, CES-D = Center for Epidemiologic Studies Depression Scale, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IBD = inflammatory bowel disease, IFN = interferon, IL = interleukin, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version, SES = socioeconomic status, TNF-α = tumor necrosis factor-α.

First, sample sizes were generally small to modest, and samples were not adequately powered. This is especially true in clinical studies, since these samples were heterogeneous, consisting of subjects at risk for depression as well as depressed subjects. Second, depression measures varied from dimensional self-reports to formal, interview-based diagnostic assessments. In future studies, it would be optimal to include both categorical (diagnosis) and dimensional (symptom) measures in order to examine outcomes of known clinical significance and to detect subclinical or early manifestation of symptoms, respectively. Further, different clusters of depressive symptoms (eg, somatic, cognitive) may have different etiologic relationships to inflammation, and studies in youth did not assess depression in this way, as has been done for adults with cardiovascular disease or after interferon treatment.[52,53] Third, many studies did not control for known confounders, such as obesity and smoking, and some of the studies that included these covariates did not find significant association between inflammation and depression after adjustment. The literature suggests other potential confounders as well. Early adversity may also have contributed to variability among and within studies. In 2 studies, depressed subjects were on medication, such as selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, and antipsychotics, which might have had immune-regulatory effects on the subjects.[15,17] Also, early adversity may be related to later inflammatory response. It is important to note that there is a lack of prospective and

experimental studies from which stronger inferences can be drawn. Sleep may also be a confounder that could account for the relationship between depression and inflammation. Therefore, lack of consistent measurement and adjustment for potential confounders (eg, obesity, smoking, adversity, medication use) could have contributed to variability among studies. Finally, it is important to consider differences in how cytokines were measured (eg, plasma versus salivary, consideration of diurnal variation), which could significantly impact findings.

We discuss several additional important themes that have been more completely addressed in studies of adults. As noted, there is preliminary evidence that early adversity leads to an inflammatory response. However, few of these studies have assessed children prospectively, but instead have assessed them as adolescents or adults and correlated current inflammatory response to past adversity. Early adverse experiences in childhood, such as low socioeconomic status, maltreatment, or problems in early family environment, have long-lasting effects on neurobiological functioning and health outcomes across the life span.[54] Increasing evidence also suggests that childhood adversity may contribute to inflammation,[55] and evidence from both preclinical and clinical studies suggests that inflammation might act as a biological mechanism linking between early adversity and various health outcomes including depression.[56] However, it is unclear to what extent the studies are indicative of the prospective relationships between early adversity, inflammation, and depression. Furthermore, most of the studies that measured early adversity were not designed to address the question of the length of the "incubation period"[34] between exposure to early adversity and subsequent alterations in inflammatory processes.

As noted above, clinical studies often did not assess for medication exposure. Meta-analyses show that, in adults, antidepressant treatment results in a reduction in cytokines, most reliably, IL-6 and TNF-α.[21] The only study to address this in adolescents found that depressed youth exposed to SSRIs had lower levels of cytokines than adolescents who were untreated.[15]

There have been reports relating levels of blood, cerebrospinal fluid, and even postmortem cytokines to suicidal behavior in adults.[6–8] In youth, there is a paucity of studies, and those that have examined the issue were small and resulted in contradictory findings.[37,38]

In this review, we found preliminary evidence for the relationship between inflammation and suicidality in children and adolescents. One clinical study[37] and 1 postmortem brain research study[38] reported cross-sectional association between inflammatory markers (IFN-γ, TNF-α, IL-6, IL-1β) and suicidality. Of note, the result of decreased TNF-α in suicidal depressed adolescents compared to nonsuicidal counterparts was in the opposite direction of most adult studies,[2] suggesting a possibility of different underlying pathophysiology of suicidality between adolescents and adults. However, future studies examining associations between inflammation and suicidality in youth should control for depression, as has been done in adult studies.

To date, very few studies measured inflammatory markers and depression in inflammatory medical conditions. It is important to note that research on chronic illnesses with an inflammatory basis and commonly diagnosed in children and adolescents, such as IBD and asthma, may be useful to examine the link and possible biological pathways between inflammation and depression.

This review is constrained by several limitations. First, given the preliminary stage of research in this field, only minimal exclusion criteria were used, and studies were included regardless of sample size. However, all included studies had a good or reasonable design and methodology for what they were intended to measure. Second, between-study heterogeneity did not allow us to cluster any specific study designs or to conduct a meta-analysis for the included studies.

Recommendations for Future Research to Improve Clinical Care

This review points to important methodological and substantive considerations that would strengthen future research and clinical care as described below.

1. Adequately powered, prospective studies of the relationship between inflammatory markers and depression and suicidality onset are needed that assess and control for potential confounders in order to clarify the direction and strength of the relationship between inflammation and these pathological outcomes. One possible design would be to assess inflammatory markers in prospective studies of youth at high risk for depression, such as the offspring of depressed parents.
2. Studies are needed that examine the relationships among antidepressant treatment, levels of inflammatory markers and parallel measures of gene expression, and treatment outcome in adolescents. Studies in adults have identified higher pretreatment levels of inflammatory cytokines with a lower likelihood of treatment response,[57] reduction of inflammatory cytokines as a function of antidepressant treatment,[20] change in gene expression and micro-RNA levels related to inflammatory function as a predictor of treatment response,[58,59] and efficacy of anti-inflammatory agents (eg, a TNF-α antagonist) in depressed patients with high baseline inflammatory markers.[60]
3. Studies that examine the relationship between inflammatory markers, antidepressant treatment, and suicidal events in depressed adolescents are required. While antidepressants appear to be as effective in adolescents as in adults, there is reluctance to prescribe antidepressants in this age group due to concern about suicidal events, and, in fact, the rates of diagnosis of depression and of prescriptions for SSRIs in this age group have declined.[61] The identification of inflammatory

biomarkers that could predict early treatment response and also identify those at risk for suicidal events would help to improve the risk-benefit ratio and match patients to more effective treatments.

4. Studies are needed that examine the relationship of inflammatory markers to disease course and depression in chronic inflammatory disease such as IBD. It is now well known that the rate of depression is increased in inflammatory diseases like IBD. However, it is not yet known how the inflammatory processes of these diseases affect the onset and course of depression or how treatment of depression may influence inflammatory processes and chronic disease course. A better understanding of this interrelationship could be critical for more holistic and optimal management of chronic inflammatory diseases.
5. Studies of the relationship of early adversity to inflammation, depression, and medical comorbidities are warranted. Prospective research that studies the relationship of early adversity to inflammation and adverse outcomes should assess both depression and other medical comorbidities such as obesity and cardiovascular disease for which inflammation is also thought to play a role. Because early adversity is linked to numerous chronic conditions (obesity, smoking, cardiovascular disease, depression, and attempted suicide), such studies could shed light on the relationships among these frequently comorbid disorders, such as depression and cardiovascular disease.[62] These studies might elucidate common roots for 2 of the major causes of disability worldwide: cardiovascular disease and depression.[63]

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