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SYSTEMATIC REVIEW

Inflammation and depression in young people: a systematic review and proposed inflammatory pathways

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Depression onset peaks during adolescence and young adulthood. Current treatments are only moderately effective, driving the search for novel pathophysiological mechanisms underlying youth depression. Inflammatory dysregulation has been shown in adults with depression, however, less is known about inflammation in youth depression. This systematic review identified 109 studies examining the association between inflammation and youth depression and showed subtle evidence for inflammatory dysregulation in youth depression. Longitudinal studies support the bidirectional association between inflammation and depression in youth. We hypothesise multiple inflammatory pathways contributing to depression. More research is needed on anti-inflammatory treatments, potentially tailored to individual symptom profiles.

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BACKGROUND

Major Depressive Disorder (MDD) has its peak period of onset in young adulthood, with many reporting first onset by 18 years [1, 2]. Early onset of MDD is associated with greater risk for recurrence of depressive episodes, and negative consequences for educational and occupational capacity [3–5]. MDD is the largest mental health contributor to disease burden in adolescents globally [6]. Unfortunately, response rates to treatment are only modest for psychotherapy and pharmacotherapy in adolescents [7–9]. A better understanding of the underlying pathophysiological mechanisms associated with MDD, and depressive symptoms more generally, in youth is critical to improve efficacy of available treatments, develop novel treatments, and select patients that will most likely benefit from treatments targeting these biological pathways.

Studies investigating major biological mechanisms in the aetiology of youth depression have primarily focused on the serotonin and hypothalamic–pituitary–adrenal (HPA) axis dysregulation hypotheses [10, 11]. However, in the last few decades, it has been proposed that inflammation may play an important role in depression, given that depression shows high comorbidity with inflammatory conditions, such as asthma, cardiovascular disease, obesity and inflammatory bowel disease [12–16]. The immune system protects the body from pathogens, this response is called inflammation. Inflammation is affected by stress via numerous pathways (Supplementary Note 1), therefore low mood could potentially affect inflammation. Studies have also shown that people receiving immunotherapy for HIV or cancer often develop depressive symptoms [17–19]. Moreover, meta-analyses have demonstrated that adults with depression show higher levels of peripheral cytokines, such as interleukin (IL)-6, C-reactive protein (CRP), and tumour necrosis factor alpha (TNF-α), likely due to the effect of psychological or physiological stress on the immune system (Supplementary Note 1) [20–22]. Cytokines are proteins released by immune cells that facilitate cell communication, including communication with the central nervous system. However, the role of inflammation in the pathophysiology of depression in youth is less studied, despite the fact that adolescence and young adulthood represent a period in which the immune system undergoes major developments, including reduction in lymphatic tissue size and changes in sex hormones that affect cytokine release (Supplementary Note 1 and Fig. 1).

Therefore, in the current report, we: (1) present a systematic review of the literature on the association between inflammation and depression (capturing both MDD and dimensional depressive symptoms) in youth, (2) characterise potential sources that could lead to heterogeneity in the association between inflammation and depression in youth, such as age, sex, body mass index and medication use [23–28], and (3) propose potential biological pathways explaining this link between inflammation and depressive symptoms. We hypothesise that there will be an association between higher inflammation and depression in youth, although not as pronounced as in adults due to shorter disease duration.

Search strategy and selection criteria for systematic review

The systematic review was conducted following the PRISMA guidelines [29]. PubMed/MEDLINE and PsycInfo databases were

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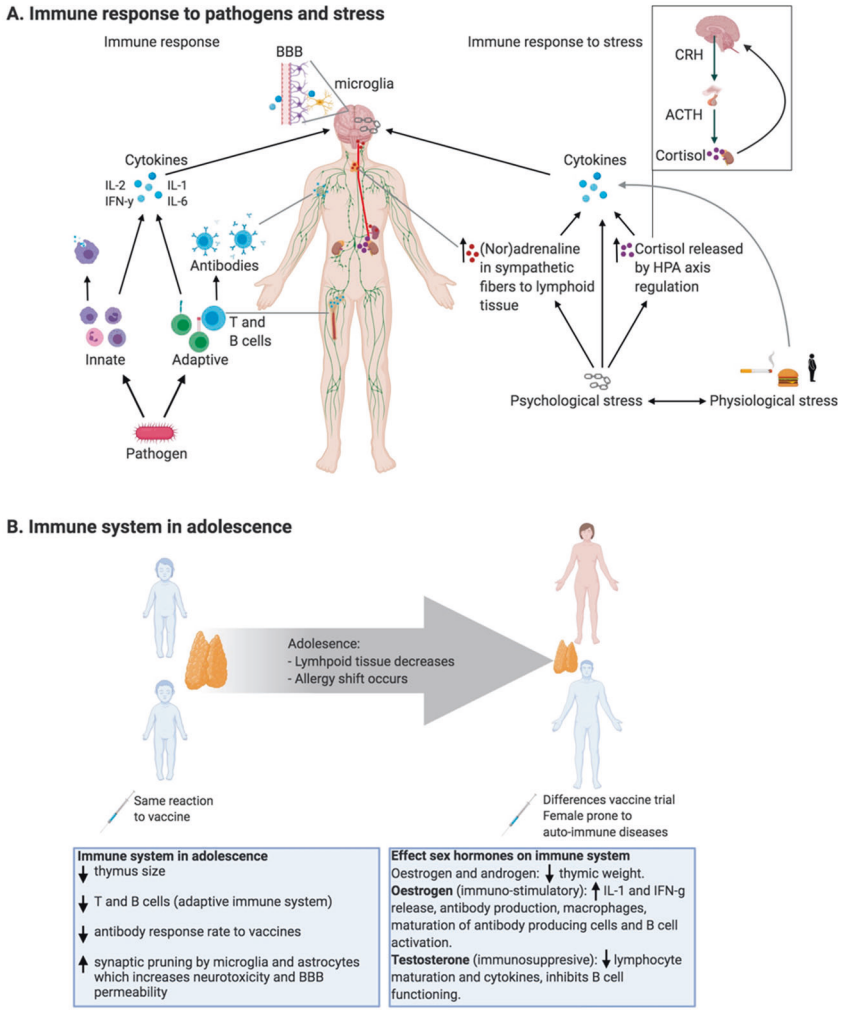


Fig. 1 Immune system. In **A** the adaptive and innate immune response is shown, as well as the immune response during stress. **B** Displays the changes the immune system undergoes during adolescence.

searched and articles published up to 1 May 2021 were included. The search terms were: (1) 'adolescence' [Mesh] OR 'child' [Mesh] OR 'young adult' [Mesh] OR 'youth', AND (2) 'depression' [Mesh] OR 'Major Depressive Disorder' [Mesh] OR 'MDD', AND (3) "inflammation' [Mesh] OR 'cytokines' [Mesh] OR 'interleukin' OR 'immunoprotein' OR 'inflammat*'. Articles were included if they were written in English, peer reviewed, conducted in human participants, and if the mean age of the sample was within the 14 to 25 range (when both males and females have started puberty). In addition, the direct association between depression or depressive symptoms with inflammation had to be explored. Studies were excluded if participants had a medical or inflammatory condition, schizophrenia or bipolar disorder. Reference lists of selected studies were screened for any additional articles of interest. All abstracts were screened by LL and YT, disagreements were discussed with LS and consensus was reached. LL and YT extracted all information in duplicate from the full-text articles (Fig. 2). The quality of all studies was rated. As there is no 'gold standard' tool to evaluate quality for observational study designs, we developed study quality assessment criteria based on the Cochrane Consumers and Communication Review Group Study Quality Guide (2013) and the Critical Appraisal Skills Programme [30]. This is the first systematic review on inflammation in young people that includes different study designs.

In addition, an exploratory meta-analysis was performed for case–control studies, as other study designs did not have

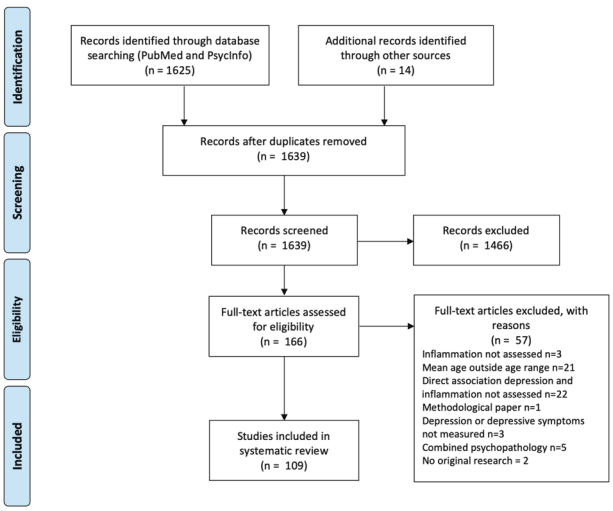


Fig. 2 Flowchart of study selection for systematic review. In the screening stage records were screened based on the following inclusion criteria: the study (1) was not a review, (2) assessed inflammation and depression, (3) was conducted in people (as opposed to animals), (4) included young people and (5) did not include participants with comorbid inflammatory conditions. Additional records were identified by screening reference lists of selected studies.

enough comparable independent studies. The cytokines IFN-γ, IL-1β, IL-2, IL-6 and TNF-α were included in the meta-analysis as they were reported in 5 or more studies. Since few studies could be included due to limited response to our request to authors to share the relevant information, detailed methods and results of the meta-analysis are presented in the Supplementary Note 2.

RESULTS

In total, 109 studies on inflammation in youth depression were identified by our systematic literature search, including case (MDD) versus control studies, studies investigating associations between dimensional measures of depression and inflammation, and longitudinal studies (naturalistic, intervention, and biological induction studies) (Supplementary Table 2). The quality of most studies included was rated moderate to high (Supplementary Tables 3, 4).

Case–control differences

Thirty studies examined differences between youth with MDD and healthy controls, and five studies examining the effect of treatment also examined case–control differences at baseline, resulting in a total of thirty-five studies. Groups were often matched for age and gender, with many also controlling for BMI. Studies examined inflammatory, anti-inflammatory, and kynurenine pathway markers, as well as blood cell count and cell activation (Supplementary Table 2). Sample sizes were small to moderate (62% of the studies included ≤50 participants) and, in most studies, MDD was diagnosed based on clinical interview. Cytokines showing significant differences between young people with MDD and healthy controls in most studies were IL-2 ($k = 6$/9 studies) and interferon gamma (IFN-γ; $k = 7$/11). However, the direction of effects for IL-2 and IFN-γ were inconsistent, with three [31–33] studies showing increased and three [34–36] showing decreased levels of IL-2; and four [31, 33, 37, 38] studies showing increased and three [35, 39] decreased levels of IFN-γ. Very few studies showed significant differences between cases and controls for other markers including IL-1β ($k = 2$ [31, 33]/13 [32, 34, 35, 37–44]), IL-4 ($k = 2$ [33, 42]/8 [34, 35, 37–39, 45]), IL-6 ($k = 4$ [32, 33, 40, 44]/19 [31, 34, 37–39, 41–43, 45–50]), CRP ($k = 2$ [51, 52]/9 [40, 42, 45, 48, 50, 53, 54]), and TNF-α ($k = 4$ [33, 35, 44, 48]/16 [32, 34, 37–39, 41–43, 45, 46, 50, 54]). No differences were found for IL-8 ($k = 0$/5 [34, 39, 42, 43, 45]). Very few (<5) studies examined other cytokines including IL-1α, IL-1Ra, IL-5, IL-7, IL-9, IL-12, IL-13, IL-16, IL-17, chemokines (e.g. CCL2–CCL17), salivary antibodies, kynurenine pathway metabolites, and lymphocytes, often with mixed results. Altogether, results from the case–control studies show limited evidence, with very few studies showing differences for commonly studied cytokines such as IL-1β, IL-6, TNF-α, and CRP. Studies did show differences in IL-2 and IFN-γ, but in opposite directions across studies, which is in line with the high level of heterogeneity found in our exploratory meta-analysis among studies examining IFN-γ, IL-2 and TNF-α (see Supplementary Note 2, Supplementary Tables 5, 6 and Supplementary Fig. 1). Overall, our exploratory meta-analysis revealed a statistically significant higher level of IL-1β in depression, but no differences in the levels of the other cytokines in adolescents with depression versus healthy controls. These results are in keeping with a recent meta-analysis of cytokines in case–control studies of children and adolescents, which contrast sharply with adult depression studies and could also be attributed to small sample sizes, limited number of available studies in adolescents or the heterogeneity of depression resulting in associations between depressive symptoms and inflammatory levels of specific markers (also see section 'Potential inflammatory pathways associated with depressive symptoms' below) [55].

Dimensional measures of depressive symptoms

Twenty-one studies examined cross-sectional associations between severity of depressive symptoms and inflammation in a single group at a single timepoint, often consisting of healthy individuals from community samples. While most of these studies included males and females, three studies only included females [56–58], and one only included males [59]. Most studies corrected for confounding factors such as age, sex, and BMI or waist circumference. Sample sizes were relatively large, with three studies including <100 participants, while nine included >1000 participants. Higher IL-1β [60] was associated with increased depressive severity in healthy individuals in only one study, while two studies showed no such association [59, 61]. Higher IL-6 (after induced stress) [62–65] was associated with higher depressive symptoms in some studies, but multiple studies showed that IL-6 and CRP were not associated with depressive symptom severity (Supplementary Table 2) [57, 60, 61, 66–70]. Other cytokines were only examined in a few studies each, showing no association between depressive symptoms and IL-2, IL-10, and TNF-α, and a positive association with higher vascular endothelial growth factor (VEGF). Overall, there was little evidence for an association between pro-inflammatory proteins IL-1β, IL-6, and CRP and dimensional measures of depressive severity in healthy youth, while conclusions about other inflammatory markers are constrained by the small number of studies. The lack of association between inflammation and dimensional measures of depression in otherwise healthy young people from community samples may indicate that clinical levels of depression are required for an association with inflammatory dysregulation.

Longitudinal association between inflammation and depression

A longitudinal study design was employed in studies examining: (a) the effect of treatment on the association between inflammation and depression, (b) the naturalistic relationship between youth depression and inflammation over time, or (c) the effect of induced inflammation on youth depressive symptoms, discussed separately below.

Changes in inflammatory markers in response to treatment. Sixteen studies examined the effect of treatment on inflammation and depression using either antidepressants ($k = 6$), cognitive behavioural therapy (CBT, $k = 5$), anti-inflammatory medication ($k = 2$), exercise/movement ($k = 2$), or meditation ($k = 1$). Most were conducted in youth with MDD (80%) and time to follow-up was between 4- and 12 weeks. The antidepressant studies included only small to moderate sample sizes (22–43 participants). While all studies showed that SSRI's reduced depressive symptoms for some participants, and influenced the levels of at least one cytokine, both increases [71] and decreases [72] in cytokine levels were observed [33, 35, 39, 71–73]. Notably, these results did not always align with the pro- or anti-inflammatory nature of each cytokine, as studies showed that pro-inflammatory cytokines such as TNF-α decreased [33, 73], while increases in some pro-inflammatory cytokines were observed post-treatment (e.g. IL-2) (Supplementary Table 2) [35, 71]. These observations of both increases and decreases in different cytokines following antidepressant treatment could be caused by a shift in the balance between Th1 (IFN-γ and IL-2) and Th2 (IL-4, IL-5, IL-13) cytokines. For example, one study showed that the antidepressant escitalopram shifted the Th1/Th2 balance of cytokines towards Th2 cytokines involved in repair and regulation of the inflammatory response [39]. Similar approaches investigating these interacting components of the cytokine system, rather than individual cytokine levels, are required to better understand the anti-inflammatory effects of antidepressants. Furthermore, inconsistent findings may also be due to variability in the type, dose, and duration of use of each antidepressant.

Decreased IL-6 and TNF-α levels, but not CRP, were found after CBT treatment, exercise and meditation; even though the reduction in these cytokines were inconsistently associated with reduced depressive symptoms [74–81]. Finally, two studies examined the effects of anti-inflammatory agents in relatively small samples; one examining rosuvastatin and aspirin, and another studying omega-3 fatty acids. Both studies showed no efficacy of these agents in lowering depression or cytokine levels, although preliminary evidence suggested a beneficial effect of rosuvastatin in a subgroup of patients younger than 18 and a subgroup with more severe depression at baseline [82, 83]. In summary, evidence suggests that antidepressants have pleiotropic effects on inflammation in young people with depression, likely dependent on the type of SSRI and cytokine measured. More research in larger samples expanding beyond the examination of individual cytokine levels is required to determine potential beneficial effects of antidepressants, as well as anti-inflammatory agents, CBT, exercise and mindfulness.

Naturalistic prospective association between depression and inflammation

Twenty-five studies investigated the naturalistic prospective association between baseline inflammatory levels and depression at follow-up or changes in depressive symptoms over time, or between depression at baseline and changes in inflammation over time. Two longitudinal studies examined the link between genes and depression.

Inflammation preceding depression. Nine of seventeen studies examining the association between inflammation at baseline and depression at follow-up originated from two large non-clinical community cohorts: ALSPAC (Avon Longitudinal Study of Parents and Children Birth Cohort) and ACE (Adolescent Cognition and Emotion study). In the ALSPAC cohort, comprising ~9000 children from birth, IL-6 and CRP were measured at 9 years and depressive symptoms at age 18. The ACE study comprised 307 adolescents aged 16 at baseline and included multiple follow-up assessments within 1–5 years. Studies based on these cohorts showed that higher baseline IL-6 and change in TNF-α were predictive of higher depressive symptoms at follow-up, or mediated the association of anxiety or stressful life events at baseline and depressive symptoms at follow-up [84–91]. Except for one study from the ALSPAC cohort where CRP changes over time preceded depression [92], higher CRP levels were not associated with subsequent onset or changes in depression, which was confirmed in studies independent from these two large cohorts (follow-up from 20 weeks to 10 years) [93–98].

Depression preceding inflammation. Thirteen studies examined the association between depression at baseline or changes in depression over time and inflammation at follow-up (1 week to 10 years). Overall, these studies suggest that depressive symptoms predict higher CRP and IL-6 levels at follow-up (9 [74, 87, 88, 95, 97–101]/13 [102–105] studies), and some studies showed that this relationship may be influenced by smoking, metabolic factors, and childhood adversity. Cumulative depressive episodes were specifically associated with higher CRP at 10-year follow-up, while higher IL-6 was observed within a week following the emergence of depressive symptoms [93, 95].

In summary, there is longitudinal evidence that elevated levels of IL-6 and TNF-α precede and follow depression in young people. This is in line with a recent meta-analysis of longitudinal adult studies, which showed that higher TNF-α and IL-6 both precede and follow higher depressive symptoms [106]. Notably, early life stress, BMI, and smoking may mediate these associations. Though there are 18 longitudinal studies, half were part of two large non-clinical cohorts. Given that most of these studies were in the general population, these results are not directly comparable to clinical settings, and conclusions about the relationship between inflammation and the course of depression in youth remains to be elucidated. Additionally, only few cytokines were studied in these naturalistic prospective studies.

Changes in depression after biological induction of inflammation

Biological induction of inflammation can be used to study the causal relationship between inflammation and depression. We identified fifteen studies that used a biological intervention in the form of endotoxin, lipopolysaccharide (LPS), influenza or typhoid vaccine, to induce a transient immune response in healthy young adults with no previous diagnosis of psychiatric illness. Most studies comprised university students, and employed a randomised placebo-controlled design ($N = 30–115$). All fifteen studies elicited a robust inflammatory response, evidenced by increases in IL-6 and TNF-α. Notably, across all studies there was evidence that the administration of an inflammatory agent, regardless of type, induced increased self-reported and observer-rated depressed mood over time. Additionally, other depression-related measures including reward motivation ($k = 4$ [107–110]/4), social disconnection ($k = 4$ [111–114]/6), confusion [115, 116], and global memory deficits [117] were significantly impacted by biologically induced inflammation, while changes in sleep were not observed [116, 118]. Increased levels of both cytokines and depressed mood generally normalised 8 h post biological induction. These biological induction studies provide a mechanistic proof of principle for the causal effect of inflammation on inducing a classical depressive phenotype. However, given the transient nature of the inflammatory response and associated changes in mood, and the levels of IL-6 recorded after biological induction (100–1000 pg/ml) far exceeding the basal cytokine levels (~0.5–4 pg/ml) observed in case–control studies, the mechanisms and inflammatory pathways involved in clinical youth populations with MDD may differ to some extent.

Sources of heterogeneity

The studies reviewed show inconsistent and heterogeneous findings regarding inflammation and youth depression (Table 1, Supplementary Table 7). This may be partly explained by differences in study designs, inflammatory markers assessed, methodological approaches including correction for confounding effects of medication and lifestyle factors, and the heterogeneity of depression itself (Supplementary Table 2).

Study design and sample selection. As with many individual biological mechanisms underlying psychiatric disorders [119, 120], the true association between inflammation and depression is likely to have a small to moderate effect size, meaning that large sample sizes are required for detection. Indeed, most consistent findings were observed in large cohorts (ACE, ALSPAC). Additionally, inflammation may be associated with severity of depressive symptoms, as evidenced by findings of no relationship between inflammation and depression severity in non-clinical healthy community samples. While all biological induction studies in healthy individuals showed a strong association with the development of depressive symptoms, it is important to note that chemically-induced elevation of cytokine IL-6 levels far exceeded the range of systemic inflammation observed in clinical samples. Thus, stronger associations between depressive symptoms and inflammation recorded in those with either more severe depression of clinical entity (case–control studies) or higher levels of inflammatory cytokines (biological induction studies), suggests that depressive symptoms or inflammatory stimuli must be particularly potent to show an association with each other.

A recent meta-analysis showed an association between higher inflammation and lower socio-economic status (SES) in adults [121], and since most of the cross-sectional and dimensional youth studies

Table 1. Key findings of the systematic review by study design.

Study design	Key findings
Cross-sectional and dimensional	Based on the reviewed studies there is some evidence for inflammatory dysregulation in youth with MDD in clinical samples, whereas generally no associations between inflammatory cytokines and dimensional measures of depression were found in healthy individuals from community samples.
Cross-sectional	Differences in inflammatory cytokines were inconsistent across studies. For example, IL-2 and IFN-γ showed significant differences in most clinical studies, but both increases and decreases in cytokine levels were observed.
Cross-sectional	Most cross-sectional clinical studies found no differences in cytokines IL-6, CRP, and TNF-α in youth with MDD, which have been most consistently implicated in adult MDD.
Longitudinal	Longitudinal studies did suggest some evidence for a role of IL-6, CRP, and TNF-α in youth depression, but mostly in those with a higher number of depressive episodes, higher depressive symptom severity and in the presence of pre-existing risk factors such as early life stress, prior anxiety, smoking, or metabolic dysregulations.
Longitudinal-naturalistic	Longitudinal studies confirmed a bidirectional relationship between inflammation and depression: increases in inflammatory cytokines were predictive of subsequent depression and depression was also shown to precede increased levels of inflammatory cytokines.
Longitudinal-intervention	Most of the intervention studies focused on the effects of antidepressants on inflammation, showing inconsistent findings. These inconsistencies may be due to differences in type of antidepressant, duration of use, or differences in baseline cytokine levels, which remains to be investigated.
Females seem particularly vulnerable to inflammation-associated depression in adolescence and young adulthood, which was consistent across longitudinal, case–control and biological induction studies.	
Early life or chronic stress was highlighted as a key factor mediating the relationship between inflammation and depressive symptoms.	
Inflammatory dysregulation seems to be particularly related to neurovegetative symptoms of depression, including appetite disturbances, sleep disturbances, fatigue, and psychomotor retardation, as well as social disconnection and anhedonia.	

reviewed here did not match participants on SES, this might have contributed to the heterogeneity of the results. Lastly, while studies including participants with a diagnosis of bipolar disorder and schizophrenia were not included (e.g. studies that examined associations between dimensional measures of depression in a sample with bipolar disorder), some studies included participants with comorbid anxiety disorders. The presence or absence of comorbid disorders may have further contributed to the heterogeneity of the findings between studies as comorbidity between depression and anxiety has previously been shown to moderate associations with inflammatory cytokines [122]. However, the majority of studies reviewed here did not examine or adjusted for this effect of comorbidity.

The role of sex. Female sex influenced the association between depression and inflammation. Longitudinal, case–control, and biological induction studies identified females as particularly vulnerable to inflammation-associated depression [31–33, 41, 51, 88, 113, 123]. As discussed in Supplementary Note 1, during puberty, sex hormones rise, sex differences in MDD prevalence emerge, and females become more susceptive to allergies or autoimmune diseases, probably in part because of the immuno-stimulatory role of oestrogen.

Medication use, lifestyle, stress and genetic factors. The use of antidepressants and lifestyle factors such as smoking, higher dietary inflammatory index [124] and increased fat mass, as well as higher levels of stress and genetic factors may influence or underlie the association between inflammation and depression in youth. The relationship between lifestyle factors and depression is bidirectional (Supplementary Note 1), and linked to inflammation.

Some studies showed that BMI mediated the association between inflammation and depression or early life adversity [65, 103, 104]. These associations between BMI and inflammation are likely due to the pro-inflammatory effect of adipose tissue, which releases circulating inflammatory markers, such as cytokines and adipokines, resulting in immune activation [125]. However, many case–control studies matched participants on BMI, making it unlikely that this would solely drive the observed heterogeneity. Studies showed no strong association between depression and other metabolic factors in young people, such as circulating fat and appetite-related hormones and cytokines. In particular, the studies found no association with adiponectin [48, 50, 71, 126, 127] and ghrelin [128] and minimal association with leptin [101, 126], and there was mixed evidence regarding another metabolic marker, insulin sensitivity in the pathophysiology of youth depression [50, 71].

Moreover, young people with depression were more likely to display inflammation if they had disturbed sleep [69, 85], in keeping with the pro-inflammatory effect of poor sleep [129]. Poor sleep over time has been shown to elevate cytokine levels and bias tryptophan metabolism away from the serotonin production pathway [130], potentially explaining how poor sleep might contribute to increased inflammation and depression. Altogether, these studies show that factors such as obesity (or high BMI), smoking, and sleep influence the relationship between inflammation and depression, and that interventions improving these factors may have positive effects on inflammatory levels and depression [130].

Many of the differences in cytokines IFN-γ, IL-2, IL-4, IL-6 in youth with depression were unaffected by medication commencement or treatment, and both positive and negative findings were recorded in both medicated and drug free/naive participants [32, 34, 37, 41–43, 48–50]. Adult studies have shown more consistent effects of antidepressants on the relationship between inflammation and depression [131]. Thus, the influence of antidepressants on inflammatory dysregulations in youth depression remains to be further explored.

Our review revealed an important role for stress influencing the relationship between inflammation and depression in youth. For example, the longitudinal ACE cohort study found that pro-inflammatory proteins CRP and IL-6 moderated the association between prior stressful events and depression at follow-up [90]. Early life adversity may also interact with inflammation, with 6 [66, 97, 103–105, 132] of 7 studies showing that early life adversity is strongly associated with inflammation in young people, particularly CRP; however, this association was often independent of depressive symptoms. These findings are consistent with a meta-analysis in adults on the effect of early life trauma on inflammation, in which higher CRP, IL-6 and TNF-α was found, suggesting long-lasting effects [133].

Finally, genetic studies have suggested that NFKβ expression, IL-6 and IL-18, but not TNF-α or IL-1β, haplotype were associated with depression [134–138]. However, given the well-known issues with small candidate-gene studies, and the fact that these results have not been replicated in large (GWAS) studies, the results should be interpreted with caution.

Heterogeneity of depression. Depression is a complex heterogeneous disorder. Since some neurovegetative symptoms among the MDD diagnostic criteria encompass features of opposite polarity (e.g. appetite/weight loss vs. gain; insomnia vs. hypersomnia), there are many different symptom combinations that all qualify for the same DSM-5 diagnosis of MDD [139]. Additionally, in childhood and adolescence, depression may be characterised by irritability rather than depressed mood, further increasing heterogeneity. Distinct pathophysiological mechanisms may underlie (at least a proportion of) the different symptom profiles. Consequently, inflammation may only be present in a subset of young people with depression. This may explain the inconsistency in the presence and direction of associations between depression and specific inflammatory cytokines.

In adults, initial studies have found support for differential relationships between elevated inflammatory cytokines and specific depressive symptoms. For example, inflammatory dysregulation (e.g. elevated basal levels of CRP, IL-6, and TNF-α) combined with metabolic alterations (e.g. metabolic syndrome, obesity, leptin and insulin resistance, dyslipidaemia) has been specifically linked to symptoms characterised by an altered energy intake/expenditure balance, including excessive sleepiness, hyperphagia, weight gain, and fatigue (see section 'Potential inflammatory pathways associated with depressive symptoms' below) [140–143]. Given the co-occurrence of immune dysregulations with metabolic dysregulations in patients with atypical depressive symptoms, the term 'immuno-metabolic depression' (IMD) was recently proposed to describe this inflammatory phenotype [144]. Alterations in these immuno-metabolic pathways are shared between depression and cardiometabolic conditions and thus, this inflammatory phenotype may explain the bidirectional connection between depression and conditions such as obesity, metabolic syndrome, cardiovascular disease, and diabetes [145, 146].

Nonetheless, higher levels of pro-inflammatory cytokines have also been associated with opposing neurovegetative symptoms including fragmented sleep, decreased appetite, and weight loss [147, 148]. Additionally, higher cytokine levels have been linked to other symptoms of depression, including reward abnormalities and social withdrawal [110, 113]. This suggests the existence of multiple inflammatory depressive phenotypes, each characterised by unique inflammatory pathways involving the interaction of inflammation with a host of other biological dysregulations (i.e. metabolism and diurnal rhythm) giving rise to distinct depressive symptoms.

Unfortunately, in youth, the majority of studies only examined inflammation in relation to a total score on depressive scales, without examining different symptom dimensions (Supplementary Table 2). Examining the association between inflammation and different symptom dimensions is further hindered by the fact that most rating scales for depression only capture typical (insomnia, loss of appetite) but not atypical (hypersomnia, hyperphagia) neurovegetative symptoms. The few studies that did explore associations between individual depressive symptoms and inflammation (mostly IL-6, CRP, IL-1β, and TNF-α, whereas markers such as IL-2 and IFN-γ have not been studied in this context) found some preliminary evidence for associations between low-grade systemic inflammation with sleep disturbances [69, 85] and other neurovegetative symptoms such as appetite disturbances, fatigue, pain, and psychomotor retardation [41, 85]. In contrast, biological induction studies producing transient inflammation in healthy individuals showed no associations between inflammation and neurovegetative symptoms [115, 116, 118]. Additionally, inconsistent with findings of immuno-metabolic depression in adults, associations between increased pro-inflammatory cytokines and neurovegetative depressive symptoms did not co-occur with detectable changes in metabolic markers such as adiponectin, leptin and ghrelin in adolescents [48, 50, 71, 126, 127]. A further separation between opposite neurovegetative symptoms (e.g. increased versus decreased appetite and weight, hypersomnia versus insomnia) in future studies is required to reveal a potential distinct immuno-metabolic phenotype in youth, similar to the one previously observed in adults. Such studies will need to use rating scales that capture the diversity of neurovegetative depressive symptoms.

Potential inflammatory pathways associated with depressive symptoms

Increases in pro-inflammatory cytokines have been associated with atypical neurovegetative symptoms including hyperphagia, weight gain, fatigue, and hypersomnia (Fig. 3 in green) as well as typical neurovegetative symptoms including insomnia and decreased appetite (Fig. 3 in blue). Different inflammatory pathways may contribute to these different depressive symptom profiles.

For example, atypical neurovegetative symptoms have been specifically linked to metabolic dysregulation in addition to inflammation [144], in which inflammatory cytokines such as IL-6 and TNF-α induce central leptin resistance [149, 150] and can promote insulin resistance peripherally [151]. Central leptin resistance increases appetite and food intake by blunting the anorexigenic effect of CRH via reduced excitation and by disinhibiting the orexigenic (appetite stimulating) neuropeptide Y [152]. Lower CRH (associated with hypocortisolism) also reduces noradrenergic tone, which promotes fatigue, longer sleep duration, and daytime sleeping [153–155]. Reduced noradrenergic signalling leads to increased production of Th1 cytokines (IFN-γ and IL-2) and decreased production of Th2 cytokines (especially IL-4), thus shifting the Th1/Th2 balance towards Th1 polarisation (Th1 shift) [156]. In addition, Th1 and Th2 responses are mutually inhibitory. IL-4 is an anti-somnogenic cytokine (inhibiting sleep) and decreased production in IL-4 may thus further exacerbate hypersomnia. This is in line with decreased levels of IL-4 and increased levels of IL-2 observed in adults with atypical depression [157]. Noteworthy, leptin and insulin resistance can also act directly on depressed mood partly via reduced neurogenesis in the hippocampus [158, 159].

In contrast, depression with typical neurovegetative symptoms is characterised by a hyperactive HPA axis, as reflected by hypercortisolism [154]. Enhanced CRH signalling inhibits neuropeptide Y, resulting in appetite loss. In addition, higher CRH increases noradrenergic tone [153], and increased cortisol downregulates 5-HT1A receptor functioning, resulting in decreased serotonin [160]. Enhanced noradrenergic signalling and decreased serotonin activity may lower the production of Th1 cytokines (IL-2, IFN-γ), causing a Th2 shift [161]. This is consistent with previous observations of higher levels of IL-4 versus lower levels of IL-2 and IFN-γ in melancholic depression (characterised by typical neurovegetative symptoms amongst other symptoms) [162, 163]. A chronic hypernoradrenergic state may also drive the increase in systemic IL-6 levels, since norepinephrine upregulates IL-6 production [156]. Lastly, serotonin is a precursor for melatonin, thus reduced serotonin results in lower levels of melatonin, contributing to disturbed sleep. Diminished melatonin levels also reduce Th1 response by decreasing the production of IL-2 and IFN-γ through melatonin receptors on Th1 cells, further contributing to a shift towards Th2 [164].

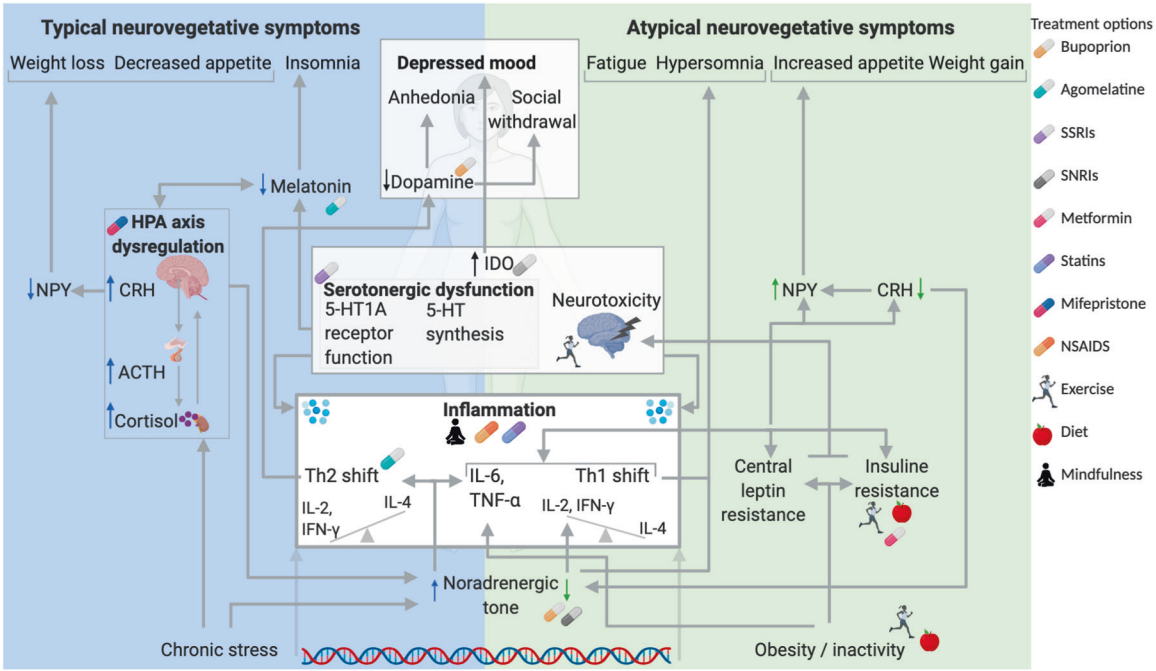


Fig. 3 Proposed pathways between inflammation and individual depressive symptoms. Hypothesised inflammatory pathways associated with specific depressive symptoms and potential interventions targeting these pathways are displayed. In blue hypothesised pathways leading to typical neurovegetative symptoms (e.g. weight loss, decreased appetite, and insomnia) are displayed, and in green, hypothesised pathways leading to atypical neurovegetative symptoms (e.g. fatigue, hypersomnia, increased appetite and weight gain) are shown.

In addition to neurovegetative depressive symptoms, inflammation can induce depressed mood via: (1) lower serotonin synthesis via indoleamine 2,3-dioxygenase (IDO) activation-induced tryptophan depletion and (2) neurotoxicity via IDO-induced activation of the kynurenine pathway [165]. Furthermore, inflammation has been associated with depressive symptoms of anhedonia and social withdrawal, likely through its inhibitory effects on dopamine, especially in the ventral striatum [166].

The distinct inflammatory pathways associated with specific symptoms of depression in youth in Fig. 3 are intended as preliminary, as many of the reported associations have not been specifically tested in MDD and are mostly based on adult literature. Future studies are required to evaluate the hypothesised inflammatory pathways and the suggested interventions targeting specific aspects of these pathways in youth depression.

FUTURE RESEARCH DIRECTIONS

Our systematic review revealed inconsistent findings in many of the cytokines studied for their role in youth depression, likely due to demographic (e.g. stage of development, sex), clinical and methodological heterogeneity. For example, abnormal levels of IL-2 and IFN-γ were found in most studies comparing young people with MDD to healthy controls, but the direction of effects was inconsistent. This could point to unreliable findings due to small sample sizes. Alternatively, these opposite effects could be due to different inflammatory mechanisms in youth with different symptom profiles (see section 'Potential inflammatory pathways associated with depressive symptoms'). IL-2 is produced by Th cells (specifically pro-inflammatory Th1 cells) and cytotoxic T cells, as part of the adaptive immune system. IFN-γ is produced by natural killer and lymphoid cells of the innate immune system and Th1 and cytotoxic T cells of the adaptive immune system. In addition to pro-inflammatory properties, IL-2 and IFN-γ also have anti-inflammatory properties, for example by suppressing Th17 cells and stimulating regulatory T cells. An imbalance between Th1 (producing IL-2 and IFN-γ) and Th2 activity has been suggested in depression [37, 167, 168]. A shift towards either Th1 or Th2 may depend on different symptom profiles (typical versus atypical neurovegetative symptoms, see section 'Potential inflammatory pathways associated with depressive symptoms' for details), potentially explaining the findings of both increased and decreased levels of IL-2 and IFN-γ in the youth MDD studies. If these hypothesised associations between the direction of IL-2 and IFN-γ alterations and specific symptom profiles of depression are confirmed, this may inform the use of anti-inflammatory treatment in youth depression. For example, the antioxidant melatonin has been shown to increase IL-2 and IFN-γ through its action on Th1 cells [169], thereby causing a shift towards Th1. Thus, melatonin may be a promising therapeutic option for those with typical neurovegetative symptoms (including insomnia), associated with IL-2 and IFN-γ downregulation. Alternatively, Serotonin Norepinephrine Reuptake Inhibitors such as duloxetine have been associated with a shift towards Th2 [161], and may be more promising for young people with atypical neurovegetative symptoms, showing IL-2 and IFN-γ upregulation. However, since these different inflammatory pathways associated with typical versus atypical neurovegetative symptoms profiles are speculative at present, future studies are required to investigate the mechanisms by which the adaptive immune system, including the balance between Th1 and Th2 activity, contribute to specific symptom profiles in youth.

Surprisingly, while elevated levels of cytokines IL-6, CRP, and TNF-α in depression is one of the most robust findings in adults with MDD [13, 170], very few studies (including clinical studies and large community studies) found differences in these cytokines in young people with MDD. It is possible that the cumulative stress experienced by adults with depression may be partly driving the elevated levels of these cytokines, compared to young people who may be in earlier stages of a depressive illness. This consistent with studies showing elevated IL-6 in young people with a history of childhood adversity, arguably a form of chronic stress. Additionally, two studies showed associations between CRP and cumulative episodes of depression. Thus, IL-6 and CRP alterations

Table 2. Effect of different treatments on depression and inflammation in youth and adults.

	Youth		Adult	
Treatment	**Depression**	**Inflammation**	**Depression**	**Inflammation**
Antidepressant	✓ [183] ↓	E, review	✓ [184] ↓	✓[185] ↓
CBT	✓ [186] ⬇	E, review	✓ [187] ⬇	E [188]
Exercise	✓ [189] ⬇	R	✓ [190] ↓	R [178]
Diet	R	R	R	R
Mindfulness	✓ [191] ↓	R	✓ [192] ↓	E [188]
Anti-inflammatory agents	R, review	R	✓ [176, 177] ⬇	R [193][a]

Anti-inflammatory agents: there is strong evidence for omega-3, statins, and non-steroidal anti-inflammatory drugs such as celecoxib in adults and limited evidence for the effect of rosuvastatin and aspirin in youth. The cited references refer to meta-analyses.
CBT cognitive behavioural therapy, ✓ Good quality evidence, *E* some evidence, *R* more research needed, review: based on findings in this review. Direction of effect based on meta-analysis effect size (odds ratio, standardised mean difference or Hedges' g): ↓ small effect size (SMD < 0.5, Hedges' g < 0.5, and OR < 3.47) and ⬇ medium–large effect size (SMD > 0.5, Hedges' g > 0.5, and OR > 3.47).
[a]Refers to a systematic review.

may still play a role in young people with depression, but perhaps only in those with prolonged exposure to stress. A potential mechanism underlying this association may be glucocorticoid resistance built up over repeated episodes of stress, which results in an inability of the glucocorticoid receptor to suppress the activation of Nfkβ, resulting in cascading inflammatory pathways culminating in the release of IL-6 and CRP [171]. However, it is important to note that long-term stress or trauma is only one pathway that can explain the relationship between inflammation and depression.

The immune system is highly complex with pleiotropic effects of each cytokine depending on the target cell, in addition to their ability to influence one another through synergy and antagonism [172]. Furthermore, cytokines contribute to a multitude of pathways relating to immunity, apoptosis, and cell differentiation and development [173]. Therefore, future studies should move beyond examining a selective subset of individual cytokines. Instead, studies could include a broad spectrum of immune measures reflecting the different components of the immune system and investigate how they interact (e.g. using a composite index [148]). A composite index could capture the effect of ratios and interactions of multiple cytokines. Furthermore, the central immune response has not been studied in youth depression, therefore it is currently unknown whether identified peripheral immune dysregulations represent central nervous system dysregulation. The examination of cytokine levels in cerebrospinal fluid, or in the brain using positron-emission tomography studies or post-mortem assessment of microglial cells, could further illuminate these inflammatory pathways. Finally, the dynamic nature of cytokine profiles and their variation throughout development indicates that longitudinal investigations are critical [174].

Implications for treatment

The evidence discussed in this review suggests that inflammation may play a role in youth depression, but the inflammatory dysregulations are subtle, and the direction of effects (increased versus decreased cytokine levels) were inconsistent. Very few treatment studies have been conducted in youth depression investigating the effect of anti-inflammatory treatment or the anti-inflammatory or mood-altering effects of other treatments such as exercise, mindfulness, antidepressants, and meditation (Table 2). Given the scarcity of evidence, conclusions regarding the efficacy of particular treatments in youth are limited. However, evidence from adult studies suggests that particular treatments may be efficacious in reducing inflammation and improving symptoms of depression (Table 2). Given that the presence of inflammation has previously been associated with poorer treatment response to

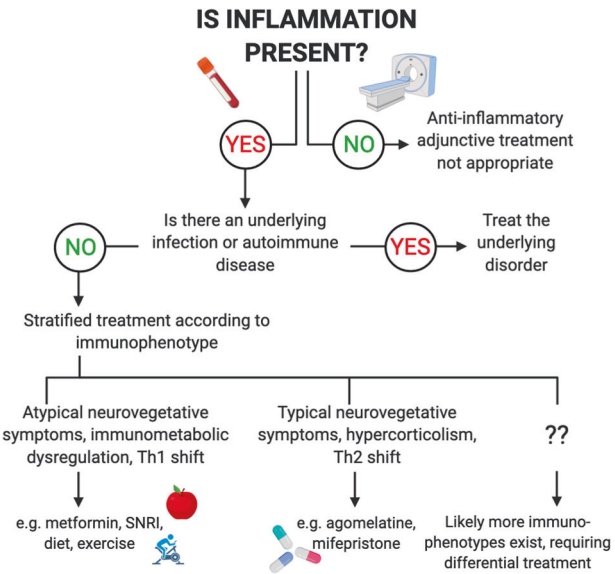


Fig. 4 Proposed decision tree for commencing anti-inflammatory treatment in young people with depression. The decision tree shows the potential anti-inflammatory treatment option for young people with depression based on their specific depressive symptoms.

first-line antidepressant therapies [175], screening young people with depression for increased inflammation (ideally across blood, CSF, and imaging markers of inflammation) and specific symptom profiles may help select a more personalised treatment option for evaluation in future clinical trials (Fig. 4). If there are any signs of inflammation not caused by infections and other underlying diseases such as autoimmune diseases, immunomodulatory treatment as a mono- or adjunct-therapy for depression could be considered. This could involve drugs with known anti-inflammatory properties, such as non-steroidal anti-inflammatory drugs (NSAIDs; particularly celecoxib), glucocorticoids, and statins, which have shown promising effects in reducing depressive symptoms in adult clinical trials [176, 177]. Alternatively, interventions indirectly targeting inflammation, such as exercise, diet and mindfulness, could be considered given some promising (albeit limited) evidence for their beneficial anti-inflammatory and antidepressant effects both in youth and adults (Table 2) [78, 80, 83, 178, 179]. In particular, changes in exercise and diet have been linked to weight reduction, which leads to reduced secretion of pro-inflammatory cytokines and adipokines from fat

cells [180], thus decreasing peripheral inflammation. Exercise has also been shown to decrease efferent vagal nerve activity resulting in decreased immune activation, while acute exercise temporarily activates the HPA axis [181], which also has an anti-inflammatory effect. Additionally, psychotherapy has been shown to lower chronic stress and cortisol levels leading to glucocorticoid sensitisation which has an immunosuppressive effect [180]. Moreover, mindfulness and the introduction of cognitive techniques such as reframing, have been shown to give individuals appropriate tools to distance themselves from maladaptive coping strategies such as smoking and the consumption of high fat food, which also has an anti-inflammatory effect [130, 182]. However, most these studies into the mechanisms have been done in adults.

Future clinical trials are needed to test the anti-inflammatory and clinical effects of these interventions that have previously shown promising results in adults with depression (Table 2), and to elucidate their mechanisms of action in young people with depression. As we propose above, it is plausible that not one but multiple different 'immunophenotypes' exist in youth depression, each characterised by a unique clustering of immune and other biological dysregulations with a specific symptom profile. This is important to consider in future treatment studies, as guiding the choice of anti-inflammatory intervention by a patient's immunophenotype may lead to more favourable outcomes (Fig. 4). Given that the proposed immunophenotypes are mostly based on (indirect) evidence in adults, a critical next step is to further characterise inflammatory pathways and their relationship to specific symptom profiles in young people with depression.

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AUTHOR CONTRIBUTIONS

The literature search was conducted by YJT and LL, and this process was supervised by LS. All authors contributed to writing and reviewing of the paper.

COMPETING INTERESTS

MB is a co-inventor of two provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, while assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialisation event. MB has served as a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay, and Wyeth; and has served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck, and Servier. BP has received (non-related) research funding from Jansen Research and Boehringer Ingelheim. The other authors report no competing interests.

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