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Inflammatory mediation of the relationship between early adversity and major depressive disorder: A systematic review

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ABSTRACT

Early adverse experience is related to psychiatric illness that occurs decades later. The mechanisms underlying this phenomenon have not been fully identified. There is a translational and clinical literature linking early adversity with Major Depressive Disorder (MDD) and inflammation. We reviewed articles that examine whether inflammation mediates this relationship.

Methods: Literature review of PUB MED, CINAHL and APA Psycinfo articles that explicitly examine inflammation as a mediator between early adversity and depression using ((((((((((adversity) OR (trauma)) OR (maltreatment)) OR (child abuse)) AND (inflammation)) OR (inflammatory cytokines)) OR (crp)) OR (il-6)) OR (tnf)) AND (mediates)) AND (depression)))))))) as key words.

Results: 2842 articles were initially identified. 1338 non-human studies were excluded and 512 more were filtered out as reviews. The remaining 992 titles and, when necessary, abstracts and manuscripts were reviewed and 956 were removed as being of other non-related phenomena. Four additional studies were added by hand searching the references of remaining studies. Out of these 40, 15 explicitly examined inflammation as a mediator of the relationship between early adversity and later depression. Approximately half (8/15) showed evidence that inflammation mediated the relationship between early adversity and depression. Sensitivity analyses showed that studies taking place in clinical populations, in youth and those that used the Adverse Childhood Events Scale to measure adversity, and IL-6 and TNF-α (as opposed to CRP) to measure inflammation were most likely to show mediation.

Conclusions: There is evidence to support the model of inflammation mediating the relationship between early adversity and depression. Certain measures in clinical populations appear more likely to support this model. Further study with more standardized, robust methods will help to answer this question more definitively and may elucidate a subtype of depression related to early adversity by alterations in immune function.

1. Introduction

While mood disorders rarely emerge until the second decade of life, earlier environmental factors contribute to their incidence and severity (Campbell et al., 2016; Dube S. , et al., 2003). These include exposure to violence, poor nutrition and caretaking (Felitti, et al., 1998), neglect and physical and sexual abuse (McCrory and Mayes, 2015). The biological mechanisms linking the incidence of childhood adversity with behavioral change decades later have not yet been identified. This gap in understanding developmental pathophysiology limits our ability to treat and prevent many debilitating disorders that emerge in adolescence and adulthood. Epigenetic, humoral and neural findings suggest a plausible model whereby inflammation mediates the relationship between adversity and later behavioral illness. In the following we will review the literature examining this model (see Fig. 1).

1.1. Early adversity and MDD

There are several studies that suggest a relationship between early adversity and later anxiety (Young et al., 1997), psychosis (Varese, et al., 2012), borderline personality (Porter, et al., 2020) and major depressive disorders. The Adverse Childhood Events (ACE) study demonstrated a cumulative effect of adverse experience whereby a greater number of exposures yielded a higher likelihood of mental and physical health

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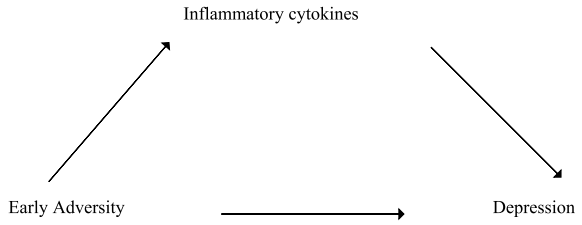


Fig. 1. Mediational Model illustrated.

outcomes associated with a shortened lifespan including substance use disorder, depression, obesity, suicidal behavior, cardiovascular disease and cancer (Felitti, et al., 1998). Specifically, they utilized a scale assessing seven types of adversity occurring prior to age 18 including physical, psychological or sexual abuse, violence against one's mother or having a parent who used drugs, was incarcerated, mentally ill or suicidal. These effects of childhood adversity can last into late life. Looking at retrospective ACE data in individuals over 60 showed that those who report multiple episodes of adverse events including witnessing domestic violence, being physically hurt or cursed at by parents, being sexual touched or forced to touch someone else sexually or being forced into intercourse prior to 18 were more likely to have depressive symptoms measured by Patient Health Questionnaire (PHQ)-8 (Kroenke et al., 2001) in their 60s. Repeated physical abuse and one or more episode of forced sexual intercourse had the greatest impact when placed in a statistical model with other adverse events (Ege et al., 2015). A Meta-analysis conducted in 2012 showed that individuals who had experienced childhood adversity were twice as likely to have recurrent and protracted (treatment resistant) depression as those that did not have early adversity (Nanni et al., 2012).

1.2. Adversity, epigenetics, inflammatory milieu and depression

Translational research on early experience suggests mechanisms whereby adversity may promulgate lasting biological change. In their landmark 1957 paper Levine and colleagues recognized that the routine handling of mice in early life wrought enduring structural and functional modifications to the hypothalamic-pituitary-adrenal (HPA) axis (Levine S. , 1957). Further research determined that these alterations were related to increases in hypothalamic corticotropin releasing hormone (CRH) mRNA and decreases in glucocorticoid receptor (GR) mRNA (Liu, et al., 1997). These adversity-related changes in the translation of GR mRNA, driven by altered thyroid, serotonin and nerve growth factor inducible protein-A (NGFI-A) function (Smythe et al., 1994; Meaney et al., 2000; Hellstrom et al., 2012; Hall and Perona, 2012), appear to be related to an increase in the number of methyl groups attached to the promotor region of the GR gene, Nr3c1 (Weaver, et al., 2004; Sapozhnikov and Szyf, 2021). Human postmortem suicide research has identified an analogous epigenetic alteration in those abused and neglected in youth, affecting the function, but not the sequence of hippocampal Nr3c1 (McGowan, et al., 2009). These series of observations, taking place over half a century, demonstrate the link between developmental experience, epigenetic change, brain morphology and inflammatory processes.

1.3. Early adversity and inflammation

Numerous epidemiologic and clinical studies using a variety of methodologies have shown a link between childhood adversity and adult levels of inflammatory markers regardless of related physical or environmental phenomena. The British National Child Development Study showed that early adversity, measured by prospective findings of outplacement, physical neglect or parental separation, mental illness, drug use, domestic conflict or legal dispute, correlated with levels of C-reactive protein (CRP), an acute phase reactant often used as a general marker of inflammation, during adulthood. Socioeconomic and health behavior factors tended to mediate this relationship suggesting a model where behaviors secondary to early adversity may increase the likelihood of inflammation (Chen and Lacey, 2018). Likewise in The Midlife in the US (MIDUS) adiposity was an intermediary in the relationship between adversity, measured by Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994 and CRP (Pinto Pereira, Stein Merkin, Seeman and Power, 2019). The Dunedin Multidisciplinary Health and Development Study showed that early adversity, measured by a combination of observations of parenting, discipline and changes in caregiver prior to age 11 and physical and sexual abuse recalled retrospectively at age 26, was a risk factor for adult increases in CRP independent of other adult or childhood factors (Danese et al., 2007). Other inflammatory markers play an important role as demonstrated in a meta-analysis of 25 studies showing early adversity to correlate with adult levels of tumor necrosis factor-α (TNF-α), interleukin-6 I (L-6) as well as CRP (Baumeister et al., 2016).

1.4. Inflammatory processes and depression

The relationship between inflammation and depression is based on decades of research showing correlations with internal and externally induced alterations in immune function. Research utilizing the dexamethasone suppression test paradigm, where subjects are given a bolus of exogenous cortisol, has shown a different response between healthy controls and individuals with MDD (Heim et al., 2008; Dowlati et al., 2010). Other extrinsic modulators of immune function like interferon α (IFN-α), a treatment for Hepatitis C (Chiu et al., 2017), show depressive effects which last long after administration. Trials of anti-cytokine agents, conducted primarily in inflammatory illnesses, found decreased depressive symptoms when compared with placebo (Kappelmann et al., 2018) demonstrating the ability of inflammatory cytokines to modify mood.

Looking at internal modulators in immune function, 24 pro and anti-inflammatory cytokines are correlated with depression (Syed, et al., 2018). This milieu is so powerful, that even when healthy (Eisenberger, et al., 2010) peripheral blood mononuclear cells (PBMC) were introduced into the plasma of those with MDD there was a non-normative and less vigorous inflammatory response (Syed, et al., 2018) suggesting a possible bidirectional relationship between humoral environment and immune function.

In clinical populations (Heim et al., 2008; Dowlati et al., 2010) this relationship is evinced where elevations in inflammation are associated with early adversity (Danese, et al., 2011), presage the onset of depression (Miller and Cole, 2012; Khandaker et al., 2014) and may define a subtype characterized by anhedonia (Eisenberger, et al., 2010), treatment resistance (Strawbridge et al., 2015) and heightened risk of suicide (Ganança, et al., 2016; Felger and Lotrich, 2013). This inflammation often occurs in the context of immune system activation, being evident in assays from stimulated lymphocytes (Miller and Chen, 2010) and in circulating levels of cytokines (Carpenter, et al., 2010) and is also manifest in increasing transcription of mRNA associated with immune function both in experimentally controlled maternal separation in primates (Cole, et al., 2012) as well as adults who have experienced low socio-economic status (Miller G. E. et al., 2009) and trauma in childhood (Levine et al., 2015).

The above translational and human findings illustrate the complex relationship between adversity, inflammatory change and neuropsychiatric findings. Demonstrating that inflammation mediates the relationship between early adversity and later depression has been more difficult. We reviewed the extant literature for evidence supporting this mediational model.

In order to cast a broad net, we utilized multiple definitions of adversity, inflammation and combined findings of depressive symptoms with those of categorical diagnosis. Raising our sensitivity in this way

will provide a broader array of studies to examine.

2. Methods

A Pub Med and EBSCO host CINAHL and APA Psycinfo search for manuscripts using Boolean arguments as follows:

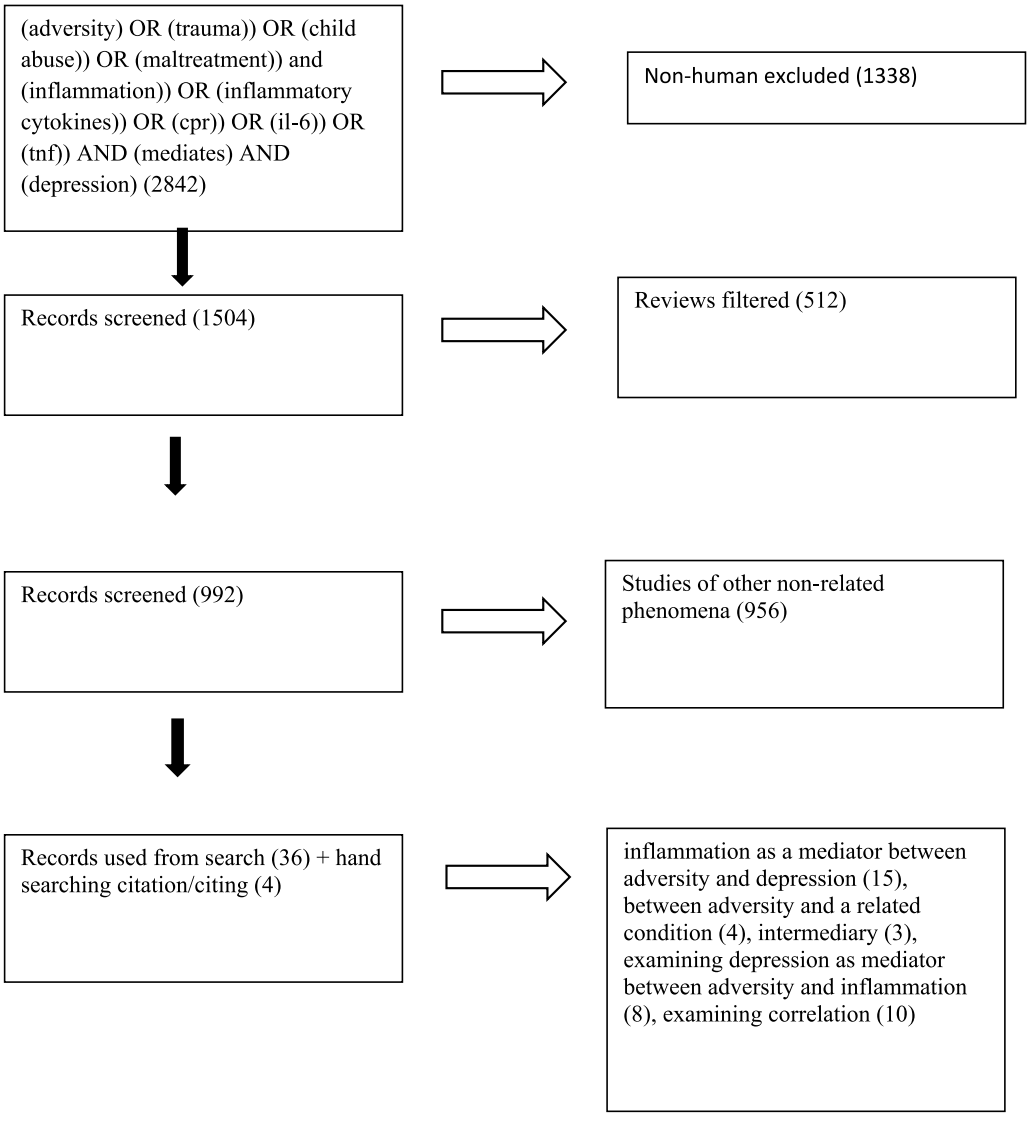
Search: ((((((((((adversity) OR (trauma)) OR (maltreatment)) OR (child abuse)) AND (inflammation)) OR (inflammatory cytokines)) OR (crp)) OR (il-6)) OR (tnf)) AND (mediates)) AND (depression).

((("adversities" [All Fields] OR "adversity" [All Fields] OR ("injuries" [MeSH Subheading] OR "injuries" [All Fields] OR "trauma" [All Fields] OR "wounds and injuries" [MeSH Terms] OR ("wounds" [All Fields] AND "injuries" [All Fields]) OR "wounds and injuries" [All Fields] OR "trauma s" [All Fields] OR "traumas" [All Fields]) OR ("maltreat" [All Fields] OR "maltreated" [All Fields] OR "maltreating" [All Fields] OR "maltreatment" [All Fields] OR "maltreatment s" [All Fields] OR "maltreatments" [All Fields]) OR ("child abuse" [MeSH Terms] OR ("child" [All Fields] AND "abuse" [All Fields]) OR "child abuse" [All Fields])) AND ("inflammation" [MeSH Terms] OR "inflammation" [All Fields] OR "inflammations" [All Fields] OR "inflammation s" [All Fields])) OR (("inflammatories" [All Fields] OR "inflammatory" [All Fields]) AND ("cytokin" [All Fields] OR "cytokine s" [All Fields] OR "cytokines" [Supplementary Concept] OR "cytokines" [All Fields] OR "cytokine" [All Fields] OR "cytokines" [MeSH Terms] OR "cytokinic" [All Fields] OR "cytokins" [All Fields])) OR ("curr res psychol" [Journal] OR "crp" [All Fields]) OR ("interleukin 6" [Supplementary Concept] OR "interleukin 6" [All Fields] OR "il 6" [All Fields] OR "il6 protein human" [Supplementary Concept] OR "il6 protein human" [All Fields] OR "interleukin 6" [MeSH Terms]) OR "tnf" [All Fields]) AND ("mediated" [All Fields] OR "mediational" [All Fields] OR "mediator" [All Fields] OR "mediator s" [All Fields] OR "mediators" [All Fields] OR "negotiating" [MeSH Terms] OR "negotiating" [All Fields] OR "mediate" [All Fields] OR "mediates" [All Fields] OR "mediating" [All Fields] OR "mediation" [All Fields] OR "mediations" [All Fields]) AND ("depressed" [All Fields] OR "depression" [MeSH Terms] OR "depression" [All Fields] OR "depressions" [All Fields] OR "depression s" [All Fields] OR "depressive disorder" [MeSH Terms] OR ("depressive" [All Fields] AND "disorder" [All Fields]) OR "depressive disorder" [All Fields] OR "depressivity" [All Fields] OR "depressive" [All Fields] OR "depressively" [All Fields] OR "depressiveness" [All Fields] OR "depressives" [All Fields])

Translations

Adversity: "adversities" [All Fields] OR "adversity" [All Fields].

Table 1
Prisma diagram of search process and results.



Trauma: “injuries" [Subheading] OR “injuries" [All Fields] OR “trauma" [All Fields] OR “wounds and injuries" [MeSH Terms] OR (“wounds" [All Fields] AND “injuries" [All Fields]) OR “wounds and injuries" [All Fields] OR "trauma’s" [All Fields] OR “traumas" [All Fields].

Maltreatment: “maltreat" [All Fields] OR “maltreated" [All Fields] OR “maltreating" [All Fields] OR “maltreatment" [All Fields] OR "maltreatment’s" [All Fields] OR “maltreatments" [All Fields].

Child abuse: “child abuse" [MeSH Terms] OR (“child" [All Fields] AND “abuse" [All Fields]) OR “child abuse" [All Fields].

Inflammation: “inflammation" [MeSH Terms] OR “inflammation" [All Fields] OR “inflammations" [All Fields] OR "inflammation’s" [All Fields].

Inflammatory: “inflammatories" [All Fields] OR “inflammatory" [All Fields].

Cytokines: “cytokin" [All Fields] OR "cytokine’s" [All Fields] OR “cytokines" [Supplementary Concept] OR “cytokines" [All Fields] OR “cytokine" [All Fields] OR “cytokines" [MeSH Terms] OR “cytokinic" [All Fields] OR “cytokins" [All Fields].

Crp: “Curr Res Psychol" [Journal:_jid101697883] OR “crp" [All Fields].

Il-6: “interleukin-6" [Supplementary Concept] OR “interleukin-6" [All Fields] OR “il 6" [All Fields] OR “il6 protein, human" [Supplementary Concept] OR “il6 protein, human" [All Fields] OR “interleukin-6" [MeSH Terms].

Mediates: “mediated" [All Fields] OR “mediational" [All Fields] OR “mediator" [All Fields] OR "mediator’s" [All Fields] OR “mediators" [All Fields] OR “negotiating" [MeSH Terms] OR “negotiating" [All Fields] OR “mediate" [All Fields] OR “mediates" [All Fields] OR “mediating" [All Fields] OR “mediation" [All Fields] OR “mediations" [All Fields].

Depression: “depressed" [All Fields] OR “depression" [MeSH Terms] OR “depression" [All Fields] OR “depressions" [All Fields] OR "depression’s" [All Fields] OR “depressive disorder" [MeSH Terms] OR (“depressive" [All Fields] AND “disorder" [All Fields]) OR “depressive disorder" [All Fields] OR “depressivity" [All Fields] OR “depressive" [All Fields] OR “depressively" [All Fields] OR “depressiveness" [All Fields] OR “depressives" [All Fields].

Non-human and non-English studies were excluded. Reference lists of relevant articles were hand searched for relevant additional articles. Yielding four additional articles.

Articles were parsed into those that explicitly examined (any) inflammatory measure as a mediator of the relationship between early life adversity and depression – either the score on a scale or absolute presence or absence of Major Depressive Disorder, those that examined inflammatory measures as a moderator, or as an explanatory variable in a multiple regression model. Because we are interested in identifying a depressive subtype, linked to early adversity and inflammation, we also comment on studies that examined inflammation as a mediator between early adversity and another depression related diagnosis, those that looked at depression as a mediator between early adversity and inflammation and those that examined correlations between the variables, but no explicit mediation (see Table 1).

While assessing study quality is difficult in such a heterogeneous group of studies, we apply sensitivity analyses of age of subjects, types of measure of adversity, inflammation and depression as well as study size and clinical (versus non-clinical) population. We report on this only in the studies describing mediation to focus our findings but leave the other data available in the table for studies describing other relationships between adversity, inflammation and depression.

The search yielded 2842 articles. 1338 were excluded as translational and 512 were filtered out as review articles. 956 covered a variety of topics but none directly related to the relationship between early adversity, inflammation and depression. In addition to the 36 remaining manuscripts we added four more articles looking at the relationship between early adversity inflammation and MDD or closely related conditions after hand searching citations and articles cited by our articles. To better understand the role of inflammation as a mediator we parsed them as follows.

3. Results

3.1. Studies describing inflammation as a mediator between early adversity and depressive illness

There were 15 studies that explicitly examined inflammatory measures as mediators of the relationship between early adversity and later depression. Eight of these did show mediation (see Table 2).

Table 2
List of studies that examine inflammation as a mediator between early life adversity and Depression including measures used, size, population, adversity types and age if specified. (studies finding evidence of inflammatory mediation are in bold)

Articles Examining inflammation as a mediator between early adversity and later depressive illness						
STUDY	INFLAM-MATORY MEASURE	PARTICIPANTS	MEASURES	FINDINGS	Adversities identified with inflammatory correlates	Current versus childhood adversity
Cho et al. (2012)	CRP, IL-6	Coronary Artery Risk Development in young Adults (CARDIA).2716 young adult controls	Risky Families Questionnaire, CES-D, sf-12 fatigue,	RFQ score related to later fatigue and CES-D score but not mediated by CRP nor IL6	Not assessed	Not assessed
Iob et al. (2020)	**CRP**	**English Longitudinal Study of Ageing (ELSA).4382 adult controls**	**ACE, CES-D**	**CRP Mediates 7% of relationship between ACE and CES-D score at baseline and 5% of rate of change in CES-D**	**Low parental bonding was most strongly correlated with CRP, followed by loss experiences and household dysfunction. Threat measures were not correlated with CRP.**	**Not assessed**
Iob et al. (2021)	**Cortisol**	**Twins Early Development Study. 290 child, adolescent and young adult controls**	**ACE, CES-D**	**Low cortisol at 11yo mediates 10–20% of the relationship between ACE score and CES-D score at age 21.**	**Cortisol mediated 11% of the relationship for individuals with 3+ ACEs, 20% of the relationship for those who had experienced**	**Not assessed**

(continued on next page)

Table 2 (*continued*)

Articles Examining inflammation as a mediator between early adversity and later depressive illness						
STUDY	INFLAM-MATORY MEASURE	PARTICIPANTS	MEASURES	FINDINGS	Adversities identified with inflammatory correlates	Current versus childhood adversity
					bullying, and 18% of dysfunctional parenting/emotional abuse.	
(Iob et al., 2022)	CRP	Avon Longitudinal Study of Parents and Children (ALSPAC). 3931 child controls	Retrospective and prospective questionnaire of adversity (Houtepen LC, 2018), SMFQ	ACE score correlated with MFQ depression at ages 18–23. CRP did not.	Not assessed	ACE measured prenatally 0–3, 3–7, 7–11, 12–17 or 0–18 was not related to crp levels, 0–18 showed the strongest relationship to depression Bullying 7–12 showed a stronger relationship with CRP. Sexual abuse and physical abuse from 12 to 18 had the strongest association with depressive symptoms.
Flouri et al. (2020)	**CRP, IL-6**	**Avon Longitudinal Study of Parents and 4263 Children (ALSPAC) during adolescence**	**43 item proprietary questionnaire of adverse lifetime events from prenatal to 9.5 years in 3 year tranches (ALE), depressive symptoms on MFQ**	**Only IL-6 mediates relationship between early adversity and MFQ depressive score in 3802 at age 10.5**	**Not assessed**	**ALE at all stages, all correlated with MFQ depression scores at 17.5, Highest correlation was in older tranches. IL-6 correlated with adverse events measured at 61, 73 and 110 months, CRP only at 61 and 73 months. No younger ALE measures correlated with inflam.**
Li and Xiang (2023)	**hs.CRP**	**6518 Chinese adults over 60**	**ACE 7 items from original plus 5 additional related items, CES-D**	**Hs-CRP mediates relationship between ACE and CES-D**	**CRP increases with the number of ACEs (from 0 to > 4)**	**Age of exposure not identified**
Maes, et al. (2018)	**hs-CRP**	**118 adult Brazilian psychiatry clinic anxiety and depressive d/o patients and 54 controls**	**CTQ. SCID, HDRS**	**Early Lifetime Trauma associated with MDD and with DRP through BMI, CRP associated with HDRS score**	**Number or type of early life trauma events did not alter crp levels**	**Age of exposure not identified**
Maes, et al. (2022)	**PHA and LPS stimulated and unstimulated panel of 27 cytokines including IL-6, TNF α but not including CRP**	**30 Adult Thai Psychiatric clinic patients with MDD and 20 matched controls**	**ACE, MINI, HDRS**	**Inflam. response to LPS or pHA stimulation mediated relationship between ACE and HDRS ratings**	**Mental and physical trauma as well as mental neglect are significantly associated with inflammatory change across a panel of 27 cytokines including IL-6 and TNF-α but not CRP.**	**Not assessed**
Mitchell et al. (2018)	Hs-CRP, IL-6, TNF-α	77 adult pregnant women	CES-D, CTQ, BMI	CTQ correlated with CRP but mediated by BMI, no relationship to depression	Physical and emotional abuse as well as emotional neglect predicted elevated CRP, BMI mediated the relationship between physical abuse and serum crp and il6 in pregnant women	Not assessed
(O'Shields et al., 2022)	**CRP, IL-6, fibrinogen, sICAM-1, sE-selectin, TNF-α measured individually and as a composite**	**Midlife in US (MIDUS) 2118 adults**	**CTQ, CES-D**	**Inflammation composite score mediated relationship between adversity and depression measures showing significant regression coefficients**	**Physical abuse correlates with CRP and SE-selectin, sexual abuse with fibrinogen and CRP, physical neglect with CRP, IL-6 and fibrinogen, emotional abuse with CRP.**	**Childhood maltreatment was related to inflammation and later depression, however, recent, adult stressors, while also related to depression, were not related to inflammation.**
Palmos, et al. (2022)	CRP	UK Biobank, 500,000 adult controls	Proprietary assessments of Depression, childhood adversity and BMI	Trauma was associated with CRP and MDD, but CRP and MDD were not associated, once trauma	BMI predicts crp beta = .07 (.06-.08), childhood trauma (b = .02 (.01-.03) and adult trauma b = .03	Childhood and adult trauma were associated with CRP but not physical trauma

(*continued on next page*)

Table 2 (*continued*)

Articles Examining inflammation as a mediator between early adversity and later depressive illness						
STUDY	INFLAM-MATORY MEASURE	PARTICIPANTS	MEASURES	FINDINGS	Adversities identified with inflammatory correlates	Current versus childhood adversity
				and BMI were controlled for	(.02-.04) but not physical trauma	
Spindola, et al. (2017)	**NR3C1, TNF, TNFR1 and IL1B mRNA expression**	**20 children with MDD 49 with depressive symptoms and 61 controls from a Brazilian epidemiologic study**	**DAWBA to assess MDD diagnosis, CBCL for depressive symptoms, 4-part proprietary scale to assess history of maltreatment**	**The aggregate 4 gene expression mediated he relationship between maltreatment and MDD diagnosis**	**Not assessed**	**Not assessed**
Walker, et al. (2022)	IL-6	201 public university undergraduates with mean age 20	Childhood Maltreatment (CMIS), CES-D	CMIS did not correlate with IL-6, but did with depression	No differentiation based on subtype	Not assessed
Willemen, et al. (2022)	Hs-CRP	Healthy Life in an Urban Setting (HELIUS) study of 5998 adult controls in Amsterdam	PHQ-9, Nemesis trauma questionnaire ((De Graaf, Ten Have and van Dorsselaer, 2010)-2 (retrospective report of 4 types of adversity	Maltreatment associated with PHQ-9 depression score, but not with CRP	Subtype of childhood maltreatment between emotional neglect, emotional abuse, physical neglect and sexual abuse did not differentiate based on CRP level	Not assessed
Zeugmann, et al. (2013)	CRP, fibrinogen, resistin Serum Amyloid A, tnf α, e -selectin	25 of 58 adult psychiatric clinic patients	CTQ, HDRS	Of all inflammatory markers only fibrinogen associated with physical neglect, no marker associated with HDRS	Physical neglect predicted fibrinogen scores more so than emotional abuse or neglect	Not assessed

3.1.1. *Studies showing mediation*

In the English Longitudinal Study of Ageing (ELSA) surveying 4328 subjects CRP mediated the relationship between Adverse Childhood Events (ACE) score and Center for Epidemiologic Studies (CES-D) (Radloff, 1977) depression score explaining 7% of the correlation at baseline and 5% of the effect of adversity on rate of change (Iob et al., 2020). Mediation effects of CRP were larger for loss items on the ACE questionnaire.

While not explicitly an inflammatory cytokine, low cortisol measured at age 11 by the same lab in 290 youth from the Twins Early Development Study (TEDS) mediated 11% of the relationship between ACE score and depressive symptoms measured at age 21 by the Short Mood and Feelings Questionnaire (SMFQ) (Angold et al., 1995). Those that experienced Bullying or dysfunctional parenting/emotional abuse had an even higher level (20% and 18% respectively) of mediation by cortisol level (Iob et al., 2021).

A US study on 2118 adults (Midlife in US – MIDUS) showed that participants who experienced CTQ measured trauma were more likely to have higher CES-D score and that this relationship was mediated by a composite inflammation score based on levels of fibrinogen, CRP, IL-6, sICAM-1, sE-selectin and TNF-α (O'Shields et al., 2022).

An elderly Chinese epidemiologic sample of 6518 adults over 60 found that hs-CRP mediated the relationship between depression as rated by CES-D and several versions of the ACE inventory: the 7-item original battery, a 9-item expanded battery covering neighborhood safety and bullying and a 12-item version covering sibling death parental death or disability (Li and Xiang, 2023).

Two studies in clinical populations with the same lead author showed inflammatory mediation. One of 118 adults in Brazil, showing that high sensitivity (hs) CRP mediated the relationship between CTQ and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) scores (Maes, et al., 2018). A Thai study of 30 MDD clinic patients and 20 matched controls showed that inflammatory response to lipopolysaccharide stimulation mediated the relationship between ACE score and HDRS rating (Maes, et al., 2022).

Another Brazilian study separated 130 children, aged 6–12, into cohorts of 20 with MDD diagnosed by the Development and Well Being Assessment Scale (DAWBA) (Goodman et al., 2000) 49 with depressive symptoms assessed with the Child Behavior Checklist (CBCL) (Achenbach, 1991) but no diagnosis and 61 controls. They found that children with maltreatment defined by a four-part scale assessing physical neglect, abuse, emotional maltreatment and sexual abuse (Cicchetti, 1993) had a correlation with MDD mediated by a composite consisting of mRNA levels of inflammation related genes NR3C1, TNF, TNFR1 and IL1B (Spindola, et al., 2017).

An epidemiologic study in 4263 youth utilizing the Avon Longitudinal Study of Parents and Children (ALSPAC), (Flouri et al., 2020) showed that IL-6 (but not CRP) mediates the relationship between early life adversity, measured between age 1–9 by maternal report on a 43 item scale, and assessments of internalizing symptoms measured by report on the mood and feelings questionnaire (MFQ) from age 9–11. The level of inflammatory markers did not explain the opposite relationship; that between early internalizing symptoms and later life events, nor did it explain the relationship between depression and later adverse events.

3.1.2. *Studies failing to show mediation*

Utilizing the same ALSPAC sample, but only examining CRP in young adulthood (ages 18–23) a different research group found a lack of mediation of MFQ depression score (Iob et al., 2022).

Another cohort of 2716 youth measuring both CRP and IL-6 in the Coronary Artery Risk Development in young Adults (CARDIA) study found no mediation between scores on the Risky Families Questionnaire (Taylor et al., 2006; Felitti et al., 1998) and CES-D depression score assessed 10–15 years later when sociodemographic factors (age, gender, ethnicity and education) were taken into account (Cho et al., 2012). In pregnant women (Mitchell et al., 2018) the relationship between CTQ score and hs-CRP was mediated by BMI, however there was no independent relationship between CRP and CES-D depression score, nor between CTQ and inflammatory measures il-6 and TNF-α.

In the UK Biobank, an epidemiological study of over 500,000 adults, adversity, defined by a proprietary assessment that took into account

early trauma including familial abuse, sexual molestation and feeling loved or hated as a child as well as being taken to a doctor when needed, correlated with both CRP levels and MDD assessed by The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) (Kessler and Ustün, 2004). CRP, however, did not correlate with MDD once Trauma and BMI were accounted for (Palmos, et al., 2022).

In the Dutch Healthy Life in an Urban Setting (HELIUS) study of 5998 adults, CRP did not mediate the relationship between maltreatment, measured with the 4 item Nemesis (De Graaf, Ten Have and van Dorsselaer, 2010) retrospective scale assessing history of emotional, physical and sexual abuse as well as emotional neglect, and depressive symptoms measured by PHQ-9 (Kroenke et al., 2001; Willemen et al., 2022).

A smaller clinical study of 25 adult clinic patients found fibrinogen to be the only marker associated with physical trauma, but no association between these findings and HDRS rated depression (Zeugmann, et al., 2013).

A study of 201 U.S. undergraduates found no correlation between child maltreatment, measured by the Child Maltreatment Interview Schedule-Short Form (CMIS-SF) and Il-6 level but did between CMIS and depression as well as suicidal ideation as well as between IL-6 and suicidal ideation (Walker, et al., 2022).

3.1.3. Sensitivity analyses

While systematic reviews of clinical trials will assign study quality based upon size and/or methodology, this is rare in studies of mediation (Vo and Vansteelandt, 2022). In the following we examine several aspects of study methodology in order to perform sensitivity analyses amongst dimensions that, in a more homogeneous group of studies, might be used to delineate quality.

3.1.3.1. Age. In the small sample of studies youth were slightly more likely to show mediation with 3/5 child studies as opposed to 5/10 adult studies showing mediation.

3.1.3.2. Inflammatory marker. IL-6 and TNF-α performed best, each showing mediation in three of the five studies in which they were measured. Fibrinogen showed mediation in one of the two studies in which it was part of a panel as did cortisol in the only study in which it was assessed. CRP, the more non-specific measure of inflammation, was assessed in the majority of mediational studies, we identified 11, but showed mediation in only four, failing in at least one study in which IL-6 had succeeded.

3.1.3.3. Depression measure. Four of the seven studies that utilized the CES-D demonstrated inflammatory mediation, as did two of the three using the HDRS, one out of two that used MFQ or SMFQ showed mediation as did the one study that used the DAWBA and CBCL. Neither the study that used the PHQ-9 nor the one that used a proprietary depression scale show mediation.

3.1.3.4. Adversity measures. Studies utilizing the ACE questionnaire were most likely to demonstrate mediation with all four doing so. Neither the CTQ nor other proprietary scales performed as well with two of the four studies that used each showing mediation. None of the other measures, the RFQ, Nemesis or CMIS assessments showed mediation in the respective studies that utilized each of them.

3.1.3.5. Study size. Four out of the seven smaller (<1000 subjects) studies demonstrated inflammatory mediation of the relationship between adversity and depression as did four of the eight larger studies.

3.1.3.6. Psychiatrically ill versus control populations. Clinical populations were more likely to show inflammatory mediation of the relationship between adversity and depression. Three out of four did so, whereas only five out of 11 control studies showed mediation.

3.2. Studies examining inflammation as an intermediary, but not a mediator between adversity and depression

Three other studies examine inflammation as an intermediary, but not explicitly a mediator, between adversity and depression. One in adolescents and two in cancer patients. In the adolescent study (Kautz, et al., 2020) CRP and Il-6 moderated the relationship between adverse experience as measured by the Life Events Inventory (LEI) (Safford et al., 2007) 3 months before a blood draw reporting on fights between family, unpleasant household chores, insufficient leisure time and being unsatisfied with appearance and depression 1 year later. Because of the short time course and the difference in scope of looking at adversity at one time point rather than during the totality of childhood, this study measures a different aspect of adverse experience.

In a study of patients with head and neck and with colon cancer, relationships between inflammation (TNF-α across the sample and CRP in colon cancer only) and depressive symptoms measured by the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) disappeared when CTQ was controlled for suggesting that inflammation was not a mediator (Archer et al., 2012). Likewise, in patients with lung cancer, scores on the Risky Families Questionnaire assessment of early childhood adversity were associated with depression scores on the PHQ-9 independently of CRP (McFarland et al., 2020).

3.3. Studies examining inflammation as a mediator between early adverse experience and another diagnosis

Two other studies examined inflammation as a mediator between adverse experience and another diagnosis related to depression. The relationship between early life adversity and self-harm was not mediated by IL-6 (Russell, et al., 2019). However, CRP (but not IL-6) did mediate the relationship between CTQ measured adversity and aggression in personality disorder patients, and this effect showed an indirect mediation through Beck Depression Inventory II (Beck, 1996) and SCID (First et al., 1997, 2002) major depressive disorder (Fanning et al., 2017).

3.4. Studies examining depression as a mediator between adversity and inflammation

Similarly, some studies examine depression as a mediator between early adversity and inflammation. Research using the Avon Longitudinal Study found that depression did not mediate the relationship between early adversity measured by 5 dimensions including 1) being put in foster care, 2) physically hurt by someone, 3) sexually abused, 4) separated from mother or 5) father and il-6 or CRP levels at ages 10 and 15, however BMI did mediate this relationship (Slopen et al., 2013). 20-year-old subjects in a different protocol who experienced adverse events measured by parental interview assessing maternal psychopathology, harsh discipline, low income, or parental discord or criminality between ages 5 and 15 were more likely to have elevated levels of CRP at age 20 as well as depressive symptoms measured by BDI. BDI did appear to mediate the relationship between adversity and inflammation, but not independently as its contribution to inflammation was completely accounted for by increases in BMI and smoking (Raposa et al., 2014). Another study showed depression measured by CES-D to mediate (and BMI to moderate) the relationship between early adversity measured by the Risky Families Questionnaire and inflammation measured by IL-6 reactivity to a Trier Social Stress Task, but not at pre-test baseline (Chiang et al., 2017). A study in pregnant adults found that early adversity, measured by CTQ, was correlated with IL-6 and CRP levels during pregnancy, and that this relationship was mediated by pre-pregnancy BMI but not by CES-D depression score (Finy and Christian, 2018). Hostinar (Hostinar et al., 2015) examined the relationship

between current and prior adversity (measured by Recent life events and ACE questionnaires respectively) and the occurrence of inflammation in the form of increased CRP, IL-6, fibrinogen, e-selectin ICAM-1, finding that CES-D does not mediate the relationship between early or recent adversity and inflammation. A study of Black women with type 2 diabetes showed that CTQ measured child abuse trended towards correlation with hs-CRP ($p = 0.67$) and that MINI International Neuropsychiatric Interview (MINI) (Sheehan, et al., 1997) measured MDD predicted 13% of the variance in hs-CRP above that of child abuse alone.

In a Brazilian study of 58 women with PTSD and 41 controls change in IL-1 β over the course of a year was related to BDI score at that time and TNF-α was related to CTQ and BMI (Davis, et al., 2019). A Chilean study of 622 youth using a proprietary measure of adversity based on the Social Readjustment Rating Scale (Holmes and Rahe, 1967) capturing serious interpersonal conflict stress, serious financial stress, and maternal depressive symptoms at 4 points between infancy and adolescence showed that depression in childhood or adolescence was not related to hs-CRP measured in adolescence (Reid, et al., 2020).

3.5. Studies examining correlation but not mediation between adversity, inflammation and depression

The last group of related studies do look at the correlation between adverse childhood events and later inflammation as well as depression, but they do not explicitly evaluate the question of whether inflammation is a mediator of the relationship. In the Environmental Risk Longitudinal Twin Study, 41 children from homes where physical and/or sexual abuse was identified by parent interview were compared with 46 children from homes absent from abuse by the same measure and assessed with the Childhood Depression Inventory at age 12. Those who both scored high for depressive symptoms and were maltreated had elevated hs-CRP (Danese, et al., 2011). Research looking at 147 teens age15–19 in Vancouver showed that those with childhood adversity (defined on a 5 item scale that assessed for birth to a teen parent, loss of parent for more than a year during childhood, having a parent with less than a high school education, a history of an affective disorder or limited economic resources assessed by parents and renting rather than owning their home) had more likelihood of elevated il-6 and CRP during a depressive episode (but not when euthymic), had CRP levels that outlasted depressive episodes and il-6 levels that predicted further episodes. Using this they propose that those patients with childhood adversity are a separate subtype, particularly with respect to the relationship with MDD and inflammation (Miller and Cole, 2012).

An assessment of 41 inflammatory markers in a depressed and non-depressed British sample found evidence for a correlation between CTQ score and only one marker, serum amyloid A. This was rendered insignificant, however, by correction for multiple comparisons. They cite their earlier work to suggest that BMI may be a more proximal cause of inflammation in those with MDD (Palmos, et al., 2019). Another group examined single nucleotide polymorphisms (SNPs) in genes for inflammatory cytokines finding that an IL-6 SNP mediated the relationship between CTQ and MDD (Cohen-Woods, et al., 2018). In a study of pregnant adolescents, only those with both high RFQ adversity scores and high PHQ-9 depressive ratings had elevated CRP (Walsh, et al., 2016).

In a study where early adversity (measured by CTQ), HPA axis modification (measured by hair levels of cortisol and cortisone), levels of depression and structural neural change were measured, researchers found that hair levels of cortisone were related to early adversity and depressive symptoms and that hair cortisol corelated with structural neural change in frontal and striatal regions (Green, et al., 2021), but not hippocampus. They note that while the relative stability of hair cortisol as a marker may help elucidate relationships between HPA axis function and neural and mood outcomes obscured by diurnal variation in cortisol levels, the relationship with hippocampal structure may be more directly related to blood levels. In the same sample this group looked at effects of CRP and a methylation signature that, in other research, had correlated with levels of CRP (Green, et al., 2021). They found that CRP and, to a greater extent, its methylation signature correlated with neural findings, that CRP alone correlated with increased depression score and that neither correlated with being diagnosed with MDD by SCID. This work suggests the potential utility of identifying an epigenetic analog of humoral findings and that the variability in the relationship between depression and inflammation may depend on population and measures utilized.

In a study of 194 Hong Kong adults who had prior participated in a study of disordered sleep meant to examine trust as a mediator between childhood sexual abuse and inflammation in adults, the participants who were depressed on the HADS showed a paradoxical negative correlation between the sexual abuse subscale of the CTQ and IL-6 (Ng, et al., 2020).

A Serbian study on a clinical population of 64 inpatients and 53 matched controls showed a correlation between IL-6 and CTQ score in the depressed group only (Munjiza, et al., 2018).

Similarly a study of 52 adolescents with Children's Depression Rating Scale (CDRS-R) (Mayes et al., 2010) assessed MDD and 20 matched controls showed that TNF α and IL-6 correlated with CTQ score in the depressed group only (Rengasamy, et al., 2021) (see Table 3).

Table 3
Listing studies assessing relationship between adversity inflammation and depression (studies finding relationship with inflammation are in bold).

ARTICLES DESCRIBING INFLAMMATION AS AN INTERMEDIARY BETWEEN EARLY ADVERSITY AND DEPRESSION				
Archer et al. (2012)	CRP, TNF-α	Adolescents recruited at 12.5 and measured at 16.5 and 17.5	Life Events Inventory (LEI), ALEQ, CDI	LEI score predicts increased CDI (at 17.5) in those with higher crp and il6 at age 16.5
McFarland et al. (2020)	**CRP**	**Adult Lung Cancer patients**	**Risky Families Questionnaire, PHQ-9**	**RFQ and CRP independently related to PHQ-9 depression score but no mediation by CRP**
(Minelli et al., 2018)	**Genes for inf α, β and γ signaling**	**Adults with depression**	**Proprietary childhood trauma scale**	**Inflammatory genes related to emotional abuse and neglect in mdd**
ARTICLES DESCRIBING INFLAMMATION AS A MEDIATOR BETWEEN EARLY ADVERSITY AND DEPRESSION RELATED CONDITION				
Davis, et al. (2019)	**IL-6**	**770 middle aged adults (age 40–65)**	**CTQ-Short Form, Telephone interview for Cognitive Status, 4 items from Mental Health inventory (Veit and Ware, 1983),**	**IL-6 and depression score mediate relationship between CTQ and Cognitive performance**
Fanning et al. (2017)	**CRP**	**Adults with personality disorders**	**CTQ, CRP, Lifetime History of Aggression (LHA), BDI**	**CRP has an indirect effect on the relationship between CTQ score and BDI depression and both have indirect effects on relationship between CTQ**

(*continued on next page*)

Table 3 (*continued*)

ARTICLES DESCRIBING INFLAMMATION AS AN INTERMEDIARY BETWEEN EARLY ADVERSITY AND DEPRESSION				
				and LHA suggesting mediation in both cases.
Flouri et al. (2019)	**IL-6 (not CRP)**	**Avon Longitudinal Study of Parents and 4583 Children (ALSPAC)**	**43 item proprietary questionnaire, internalizing symptoms on Strengths and difficulties questionnaire**	**IL-6 mediates relationship between early adversity and internalizing symptoms**
Russell, et al. *(2019)*	IL-6, CRP	Avon Longitudinal Study of Parents and 4583 Children (ALSPAC)	ACE, self-harm report	CRP drawn at 9.5 does not mediate relationship between ACE score from age 0–9 and self-harm measured at 16
ARTICLES EXAMINING DEPRESSION AS A MEDIATOR BETWEEN ADVERSITY AND INFLAMMATION				
Chiang et al. (2017)	IL-6 at baseline and in response to Trier Social Stress Test (TSST)	Adolescent 18–20 years old	RFQ, CES-D, BMI, Waist Circumference (WC)	Baseline IL-6 did not mediate relationship between RF score and CES-D. However higher WC moderated the ability of BDI score to mediate the relationship between RFQ score and IL-6 response to TSST.
Finy and Christian (2018)	CRP, IL-6	Pregnant Adults	CTQ, CES-D	CTQ adversity related with pregnancy CRP and IL-6, but not mediated by CES-D
Raposa et al. (2014)	CRP, TNF R–II (marker of TNF activity,	Subjects selected from Mater-University of Queensland Study of Pregnancy	Interview measuring Parental discord, Harsh discipline, Low income, Parental criminality, Maternal psychopathology, Beck Depression Inventory (BDI)	BDI does mediate the relationship between adversity and inflammation however this is mediated and accounted for by the effects of BMI and smoking.
Reid, et al. (2020)	Hs-CRP	622 Chilean children in longitudinal study	Proprietary concomitant measure of adversity, CES-D	No relationship between adolescent CES-D and inflammation or early adversity
Slopen et al. (2013)	CRP, IL-6	Avon Longitudinal Study of Parents and 4583 Children (ALSPAC)	Interview of mothers prior to child age 8 for 1) foster placement,2) physically hurt by other, 3) sexually abused 0r 4) separated from mother or 5)father. SMFQ at age 14, BMI	SMFQ Depression score does not mediate relationship between early adversity and il-6 or CRP at age 15 but BMI does
Hostinar et al. (2015)	CRP, IL-6, fibrinogen, E-Selectin, ICAM-1	Midlife in US (MIDUS) 2118 adults	ACE questionnaire, Recent Life Events (RLE), CES-D score, WC	CES-D does not mediate relationship between ACE and inflammation when adjusted for medical and demographic factors (WC, smoking, exercise)
Powers, et al. (2016)	Hs-CRP	Black Women with T2DM	MINI MDD diagnosis, CTQ	Child abuse CTQ and hs-CRP trended p = 0.067, MDD associated with hs-CRP, emotion dysregulation most correlated with hs-CRP
(D'Elia et al., 2022)	**CRP, coritsol, TNF-α, IL-1β, monocyte chemoattractant protein 1**	**58 women with PTSD and 41 controls**	**MINI,BDI,CTQ**	**Increase in il-1β influenced by BDI score at 1 year, TNF-α score at 1 year influenced by BMI and CTQ score**
ARTICLES EXAMINING CORRELATION BUT NOT MEDIATION BETWEEN ADVERSITY, INFLAMMATION AND DEPRESSION				
Miller and Cole (2012)	**IL-6, CRP**	**Adolescent**	**5 category questionnaire, SCID MDD diagnosis, Hamilton Rating Scale for Depression (HDRS)**	**In those with childhood adversity exposure, depressive episodes moderates relationship with longer elevations in CRP and il-6 predicted later depressive episodes.**
Ng, et al. (2020)	**IL-6, IL-1β**	**194 adults in Hong Kong recruited from prior study of sleep disorder**	**CTQ, HADS**	**CTQ sexual abuse subscale was inversely related to IL-6 in subjects with MDD**
Cohen-Woods, et al. (2018)	**Snp IL-6, CRP**	**Adult MDD**	**CTQ, SCID or Schedule Clinical Assessments Neuropsychiatry (SCAN) interview**	**Il6 snp (rs1818879) as well as marginally CRP snp (rs3093077) mediates relationship between CTQ and MDD**
Poletti, et al. (2022)	IL-1-10, IL-12,13,17, TNF-α, IFN-γ,	Adults ,100 consecutive admissions with either Bipolar or MDD to hospital in Milan, Italy	CTQ, WM change, clinical diagnosis	CTQ not correlated with inflammation in MDD and not mediating relationship with WM change
Danese, et al. (2011)	**hsCRP**	**Child/adolescent TEDS/ Environmental risk (E-risk) cohort**	**Evidence of physical maltreatment on interview, CDI**	**Maltreatment plus depressed had highest CRP levels compared to maltreated only, depressed only or controls**
Walsh, et al. (2016)	**CRP**	**Pregnant adolescents**	**RFQ, PHQ-9**	**Only subjects with high abuse and high depression scores had elevated CRP**
Green, et al. (2021)	**Hair cortisol**	**Adult generation Scotland study**	**SCID mdd, Quick inventory of Depressive Symptomatology (QIDS), CTQ, List of Threatening Experiences (LTE) for recent trauma**	**Cortisol correlates with early (not late) life adversity and with MDD**
Palmos, et al. *(2019)*	41 inflammatory markers	British adults recruited from 2 separate trials (SE London Community Health Study (SELCoH) and the ADD depression trial	CTQ, HDRS, SCID	No correlation between CTQ and inflammation suggesting no mediation
Munjiza, et al. (2018)	**IL-6**	**64 adult Serbian patients and 53 matched controls**	**CTQ, BDI, HDRS**	**CTQ and IL-6 were correlated in depressed patients only**
Rengasamy, et al. (2021)	**IL-6, TNF-α**	**52 adolescents with MDD 20 matched controls**	**CTQ, CDRS-R**	**TNF-α and IL-6 correlated with CTQ in depressed adolescents only**

4. Discussion

Approximately half of the 15 studies assessing 14 separate cohorts showed evidence of inflammation mediating the relationship between adversity and depression. Sensitivity analyses showed that younger, clinical populations and those measuring adversity with the ACE questionnaire and using inflammatory cytokines IL-6 or TNF-α were more likely to show mediation than older samples, epidemiological samples or those using other measures of adversity or CRP. Some of these findings were demonstrated most clearly in the two included studies assessing the ALSPAC cohort. One utilized IL-6 assessed with depressive symptoms assessed at age 10.5 to show that inflammation mediated the relationship between adversity and depression (Flouri et al., 2020). The second assessed depression in the same cohort at age 23 utilizing only CRP as an inflammatory measure to find no evidence of mediation (Iob et al., 2022). While assessments of quality are complicated by the diversity of measures assessments and populations and the challenge of doing so in a review of mediational studies (Vo and Vansteelandt, 2022) it can be concluded that these findings are robust to differences in age, assessment measure and clinical status.

In the mediational studies that separated adversity assessments into components, CRP was related to most facets of adversity, but did not appear consistently more sensitive to one type of adversity. Cortisol showed more mediation in subjects who had experienced bullying, dysfunctional parenting and/or emotional abuse. Fibrinogen correlated with sexual abuse and physical neglect and IL-6 with physical neglect in one study and then with general childhood adversity in several others.

Likewise, adversity occurring in childhood was more likely to lead to depression mediated by inflammation (O'Shields et al., 2022). The studies that assessed adversity by age during childhood did not show consistent patterns for discrete epochs. One study (Iob et al., 2022) was not able to differentiate between ages. The other (Flouri et al., 2020) showed that adversity assessed at age 5 and 6 was more likely associated with IL-6 whereas that at 5, 6 and 10 was more likely associated with CRP. Assessments in this study under age 5 were not associated with inflammation. While this begins to describe a critical period, more work would need to be done to define exact ages and mechanisms, furthermore, inflammatory cytokines which tend to increase during aging, may not be the most sensitive indicator of the effects of earliest adversity.

14 of the 25 additional depression-related or non-mediational studies included showed a similar overall trend of inflammation as a component of the relationship between early adversity and a later depression related phenomenon. While they are not directly relevant to the question of inflammation mediating the association between adversity and later depression, they do clarify several issues. Studies like (Green, et al., 2021) show that concomitantly assessed stress is less related to depression than early life adversity reaffirming the import of sensitive developmental periods in the progression towards later inflammation and depression. Their study also was one of those reviewed showing that early life trauma is related to inflammation in a manner that alters brain grey matter volume in frontal, temporal and cingulate cortices. This dovetails with evidence supporting neural changes related to inflammation in both MDD and Bipolar disorder in white matter tracts (Poletti, et al., 2022) and in functional connectivity in corticostriatal circuits which appear decreased in relationship to CRP levels and levels of anhedonia, a specific depressive symptom (Felger, et al., 2016).

Many of the studies find BMI to be a moderator of the relationship between adversity and inflammation (Mitchell et al., 2018; Palmos et al., 2019; Chiang et al., 2017; Hostinar et al., 2015). Findings in depression, where elevated levels of inflammation correlate with specific changes in connectivity (Felger et al., 2016) are particularly suggestive of a mechanism whereby the inflammation that accompanies obesity may predispose to depressive neural change. Questions remain, however, about temporal relationship and pathophysiology, with the possibility emerging that the depression following obesity may differ from the increased eating associated with atypical depression or even that inflammation may have independent bidirectional neural relationships with both obesity and psychopathology. Further longitudinal information on neural underpinnings in these areas, such as examinations of structural differences as well as humoral measures and other indicators of behavior would help answer these questions.

4.1. Future directions

The studies done are markedly heterogeneous and there appears to be complexity in the relationship beyond a simple mediational model. This complexity likely comes from 3 sources.

4.1.1. Definitions of adversity and its developmental time of occurrence

Part of the challenge of studying adverse events is their pleiomorphic, non-specific definition. Concepts of allostatic load (McEwen) in human and translational research and the epidemiologic findings of the Adverse Childhood Events (ACE) study are based on a cumulative notion of stress. The ACE data is based on a questionnaire containing 10 items referring to a diverse array of putatively stressful events including neglect, physical and sexual abuse, parental separation and illness. All events that present challenge but markedly diverse and non-specific in their phenomenology and impact. Nonetheless, like in many other areas of taxonomy there has emerged a contrast between lumping and splitting whereby the concept of an ACE score combines and tabulates adverse events to predict those who may suffer later pathology. In this their approach works, albeit yielding a broad array of outcomes ranging from mood to behavioral and substance addictions to dementia. Other researchers have tried to look at the individual adverse experiences to determine whether specific types of experience may better match up with specific outcomes or, in the project of identifying pathophysiology, an endophenotype that may begin to explain the mechanistic link between early adverse experience and later outcome.

Life history theory posits that early adversity will alter the trajectory of development toward earlier reproduction, ostensibly in the service of compensating for a foreshortened lifespan, allowing the most opportunity for successful procreation (Roff, 1993). While some scientists have examined cumulative exposure, (Edwards et al., 2003) citing additive effects of adverse childhood events and their correlation to mental health measures (Edwards et al., 2003) and rates of illicit drug use (Dube S. , et al., 2003; Felitti et al., 1998). Still others have looked at dimensions of threat and deprivation (McLaughlin et al., 2021) finding a dimensional measure more accurate in predicting relationships between exposures such as poverty and violence and deficits in cognitive control and emotional regulation (Lambert et al., 2017) and hypothesizing that threats would advance maturational processes, while deprivation may retard development.

Along these lines there appears to be a general trend of early adverse experience being preparative in some way with threatening experiences in particular (like sexual abuse) (Magnus, et al., 2018) causing increased likelihood of early puberty (Chisholm et al., 2005) and advanced cellular aging when measured by (Horvath, 2013) DNA methylation aging clock (Sumner et al., 2019), and by telomere length (Hanssen et al., 2017; Ridout et al., 2018) as well as neural signs of adolescent cortical thinning in ventromedial prefrontal cortex (Colich et al., 2020). Research utilizing more precise definitions of adversity collected in a standardized manner would help determine relationships between early adverse experience, inflammation and later depression. In this way immune change may tell us about experiences that have occurred that created the epigenetic change seen in translational research.

4.1.2. Measurement of Inflammation

Indeed, the propensity of an individual to have an immune response with classic symptoms is related to multiple humoral mediators. Some of these have been defined. The ones most commonly (and easily) examined in connection with adverse experience are Interleukin 6 and TNF α,

cytokines produced by WBC and C-reactive protein, an acute phase reactant produced by the liver often in response to elevations in cytokines like IL-6. Both have their utility in research, mainly driven by ease of collection, but also their limitations as non-specific (Del Giudice and Gangestad, 2018). There are many chemical signals that accompany an enhanced inflammatory state and, to this point, in the published literature these are not as broadly utilized. Because of this the chemical markers of inflammation are limited and the markers most utilized apparently may not be robust enough markers nor effectors of depressive risk to reliably be mediators.

In our sample of 15 mediational studies IL-6 and TNF-α, the measures explicitly produced by WBC outperformed CRP as a mediator of the relationship between adversity and depression. The HPA axis, glucocorticoid receptors and white blood cells are facets of the stress response system that work together to regulate inflammation (Sapolsky et al., 2000). While cortisol can acutely decrease global immune response (Sapolsky et al., 2000), chronic elevations in cortisol, such as those associated with early neglect and abuse (Heim et al., 2008) are associated with glucocorticoid resistance (Wilkinson et al., 2018), likely modulated by decreased availability of glucocorticoid receptor (McGowan, et al., 2009) This glucocorticoid resistance may prime the body for constitutive and acute stress-related increases in inflammatory cytokines (Cohen, et al., 2012; Sorrells and Sapolsky, 2010).

In major depressive disorder (Heim et al., 2008; Dowlati et al., 2010) this is most evident where elevations in inflammation are associated with early adversity (Danese, et al., 2011), presage the onset of disease (Miller and Cole, 2012; Khandaker et al., 2014) and may define a subtype characterized by anhedonia (Eisenberger, et al., 2010), treatment resistance (Strawbridge et al., 2015) and heightened risk of suicide (Ganança, et al., 2016; Felger and Lotrich, 2013). Obesity, often comorbid with MDD, also causes, and can be sequel to early adversity associated elevations in CRP and IL6 (Taylor et al., 2006; Slopen et al., 2010; Miller and Chen, 2010; Matthews et al., 2014; Cheng et al., 2016). This inflammation often occurs in the context of immune system activation, being evident in assays from stimulated lymphocytes (Miller and Chen, 2010) and in circulating levels of cytokines (Carpenter, et al., 2010). Is also manifest in increasing transcription of mRNA associated with immune function both in experimentally controlled maternal separation in primates (Cole, et al., 2012) as well as adults who have experienced low socio-economic status (Miller G. E. et al., 2009) and trauma in childhood (Levine et al., 2015).

Studies looking at specific depressive symptoms linked with inflammatory measures, however, have found that CRP is associated with increased levels of depressed mood, altered appetite, sleep disturbance, fatigue and worrying while IL-6 was associated with anhedonia, decreased sleep and increased appetite (Milaneschi, et al., 2021). Some research suggests that late life depression may have a different relationship with inflammation. In the elderly a pattern emerges suggesting that more consistent elevated CRP is correlated with depressive symptoms (at least in women) (Bell et al., 2017). Other longitudinal work found a bidirectional relationship between IL-6 (but not CRP) and depression over a 6-year period where depression predicted concomitant and later elevated IL-6 and IL-6 level predicted a more chronic course of depression, however this was also isolated to women only (Lamers, et al., 2019). Meta-Analytic data suggests a robust relationship between CRP and depression as well as IL-6, but less so for TNF-α, and not at all for IL-β (Haapakoski et al., 2015).

Another study attempting to separate out medical comorbidities from issues of late life depression found, in an elderly, non-medically comorbid sample of 62 on medication (avg age 60.7) versus 26 on placebo (average age 65.2), no difference in inflammatory cytokines or response to escitalopram combined with celecoxib, an anti-inflammatory cox-II inhibitor. The authors note that since much of MDD is comorbid with medical illness that these are likely separate aspects of MDD, with the possibility being that they are separate etiopathological entities (Luning Prak, et al., 2022). Given the link between adversity, depression and multiple medical morbidities, it would be interesting to look at such a cohort for relative lack of exposure to early adversity and note that they may be a distinct depressive subtype without an inflammatory, medical component, and that their findings may suggest a novel way to parse out a subset of depression, rather than speak for the diagnosis.

In any event it is likely that as mechanisms of the relationship between adversity, inflammation and depression are better identified, specific measures will be more accurate and illustrating the link. In our studies we can speculate that the measures most closely linked to white cell function are most robust in part due to the possible epigenetic change wrought by early adversity and its impact on WBC expression of specific inflammatory cytokines.

4.1.3. Nosology of Depression

The third challenge lies in the pleiomorphic definition of depression itself. There are 227 possible combination of symptoms that would meet criteria for MDD (Zimmerman et al., 2015). While the diagnostic category has clear utility in clinical communication and even in selection of treatment, it admittedly is not based on a unified biological principle (First et al., 2002). Therefore, the aspects of altered function that may cohere around a relationship to inflammation, or a particular biologic process may only sometimes be the ones captured in population-based surveys of illness. Indeed, in the studies we identified those that utilized depressed clinical populations were more likely to show mediational effects than ones that used epidemiologic samples where depression is defined by an 8 item rating scale (the CES), most closely modeled on the DSM definition of MDD (Iob et al., 2020; Iob et al., 2021). Or the MFQ, a 13-item scale that captures similar symptoms, but differently defined (Flouri et al., 2019). These variations render the question into one on alterations in items rated by (slightly) differing scales related to depression. Far away from the proverbial carving nature at its "natural joints" (Plato, 1925) that is more akin to a biological relationship. Studies that look at depression linked to pharmacologic modulators of inflammatory function tend to show specific symptoms like fatigue (Smedley et al., 1983) and anhedonia (Felger, et al., 2020) suggesting that these symptoms may have a closer link to inflammation.

The solution to these 3 problems would include a definition of adversity, clear markers for inflammation and accurate biologically coherent and distinct diagnosis of a mood type disorder. All of these beg a series of research endeavors and questions. These include precise and standardized definitions and collection methods of adversity. Some examples of this include collecting accounts from several sources (Grant et al., 2020) including, if possible, prospective assessments (Reuben, et al., 2016) and using specific behavioral definitions and some of the more focused dimensional measures recommended in Berman et al. (Berman, et al., 2022) to more accurately assess the exposure to threat and deprivation that seems most closely linked to developmental outcomes. This type of information may be able to be collected in prospect, but rarely is available in the kind of research base available where it is collected in retrospect. Including such collection in prospective studies, ones which are simple and replicable while also being comprehensive and accurate would help in this regard.

In terms of immune markers, newer studies tend to collect a broader array of cytokines with some including 60 or more markers https://reporter.nih.gov/search/JbRgAtchAUKHOoW2X1vObQ/projects/map/project-details/10395492#description. These may help in the definition of a particular marker or group of markers, but again will need to be easily collectable and would be most useful if they were routinely available from already available samples.

Finally in terms of psychiatric nosology, the project underway to define an alternate, more biologically based, set of criteria, the Research Domain Criteria (R-DOC), launched a decade ago, is still in its early stages. RDOC has identified some symptoms and dimensions that may have more biological coherence and utility for translational usage, but in part it too is limited by instrumentation and the nature of psychiatric

mental health data readily available. Neuroimaging, for example, which has made tremendous strides based on technology of imaging the brain and utilizing advanced software to analyze the results, is still a relatively crude representation of the ground truth of brain function. Likewise other measures of mental phenomena are still based on interview techniques developed in prior centuries.

At this point it does appear that there are changes in inflammation that comes after adversity, and yet, the methods that we are able to use to identify these changes are probably too primitive to specify the phenomenon we are examining. The most important part of this inflammation remains obscured. It appears in this and other research that the inflammatory system, named after the observed medical phenomenon, that accompany its activation, may be better thought of as an early warning system. Sometimes that warning is arrayed against infectious agents, as is well established. But sometimes they come against other environmental signals, allowing the body a post-transcriptional way to modify processes to enable survival and reproduction despite a hostile environment. It is plausible that some of this adaptation, occurring relatively early in life and before reproduction, may influence biological outcomes such as cardiovascular and psychiatric illnesses including depression. The details however of which markers do this, and how they change brain processes sheltered behind the blood brain barrier is still unclear requiring more human and translational work to elucidate.

Just like the long recognized diagnostic signs of glycosuria and fever do not readily reveal underlying pathology of diabetes or infection so too inflammation and mood disturbance do not yet help us understand a fine-grained mechanistic progression from adversity to depression. Furthermore, the few studies that speak to this issue suggest that adversity sets up a vulnerability to later poor outcomes one of which is mood disorders and another of which is changes in HPA function. The question remains if this inflammation is a necessary part of pathophysiology or if it is an epiphenomenon. The studies extant do not yet conclusively answer this, in part because of study design and in part because the techniques and definitions are not readily available to do so.

4.2. Limitations

Because of the small number of studies and the diversity of methods used, a meta-analysis was not done. Likewise, methods were so disparate that an analysis of quality also was not appropriate to these findings. This would have added to the power of our findings but ran the risk of combining disparate measures. Nonetheless, we were able to review the literature, identify that mediation was not dependent on age, inflammatory or depressive measure, but that the ACE may be more sensitive as well as assessments of IL-6 and TNF-α in clinical and youth populations. We also included many studies that did not specifically examine inflammation as a mediator. This broadened the scope of our review to identify a depressive-inflammatory adversity related subtype but departed from our initial goal to identify inflammation as a specific mediator.

4.3. Conclusions

There is some evidence for inflammation as a mediator of the relationship between early adversity and later depressive disorder supporting the conclusion that there likely is a depressive subtype defined by its relationship to early adversity and inflammation. These findings would be more robust with the use of standardized measures of adversity, inflammation and depressive symptoms. Studies utilizing the ACE questionnaire to identify adversity as well as inflammatory cytokines IL-6 and TNF-α rather than CRP in clinically depressed populations appear most likely to show mediation. Future studies using these methods may heighten sensitivity and better elucidate the relationship between early events that alter inflammatory behavior and influence the development of later pathology. A future mechanistic identification of this pathophysiology will facilitate the development of biomarkers and targets for treatment and prevention of illness.

Declaration of competing interest

I have no relevant interests to declare that would affect the findings in this manuscript.

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