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Inflammation and early life stress: An updated review of childhood trauma and inflammatory markers in adulthood

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ABSTRACT

Inflammation, as a neurobiological consequence of childhood trauma, has frequently been reported across research, however, recent investigations suggest this relationship may be dependent on specificities such as type of trauma, type of inflammatory marker, and additional mediatory variables - such as body mass index (BMI), age, and sex. As an updated version of a previous review by Baumeister et al., the current review comprised a search of PubMed, which identified 37 articles that collectively assessed 4 inflammatory markers (CRP, IL-6, TNFα and IL-1β). A review of the studies revealed predominantly non-significant associations between childhood trauma and elevated levels of all inflammatory markers in adulthood. However, in line with previous research, discrepancies in significance arose when considering type of trauma, type of inflammatory marker, and additional variables. Compared to neglect, abuse showed greater significant associations with elevated inflammatory markers in adulthood, though this was dependent on the individual subtypes (emotional, physical or sexual). Mediation analyses reported BMI as a significant mediator, though, when controlled for, no significant differences were found. Sex differences were reported but investigations were sparse. Future research should investigate the mediatory role of sex differences in the inflammatory effects of childhood trauma. Many studies in the review were restricted by use of the same trauma measure – the Childhood Trauma Questionnaire. To assess greater variety of trauma types, future studies should utilize other standardized measures to explore these avenues.

1. Introduction

Traumatic events during childhood have longstanding associations with risk of developing both physical and mental illness in adulthood. Research predominantly focuses on child abuse and neglect which encompass emotional, sexual, and physical abuse and emotional and physical neglect (Beilharz et al., 2020; Sweeney et al., 2015; Clemens et al., 2018; Agorastos et al., 2014; Noteboom et al., 2021; Ballard et al., 2015). Recent statistics suggest 20.7% of adults in England and Wales have experienced childhood abuse under the age of 16, with greater prevalence in women (25%) compared to men (16%) (Elkin, 2020, January 14).

Associations between childhood trauma and physical health outcomes in adulthood suggest greater presentation of health problems in individuals with history of trauma. Evidenced problems include cardiovascular complications (respiratory disorder, cardiovascular disease, and asthma) (Sweeney et al., 2015; Noteboom et al., 2021), musculoskeletal disorders (Noteboom et al., 2021), digestive disorders (Noteboom et al., 2021), migraines (Sweeney et al., 2015; Noteboom et al., 2021), arthritis (Sweeney et al., 2015), low energy, and poorer sleep quality (Beilharz et al., 2020).

Similar associations are evident for psychological health outcomes. Individuals with history of trauma show increased psychological distress and lower emotional wellbeing (Beilharz et al., 2020), anhedonia and depressive mood (Sweeney et al., 2015), and higher rates of lifetime suicide ideation and attempt (Sweeney et al., 2015; Ballard et al., 2015). Extending this, research suggests increased vulnerability to several psychiatric disorders following trauma; examples include association with clinical characteristics of bipolar disorder (Aas et al., 2016), diagnosis of post-traumatic stress disorder (PTSD) and PTSD symptom clusters, and antisocial personality disorder (Ballard et al., 2015).

Associated health outcomes are further shown to be mediated by sex; males are more likely to suffer from physical health problems while females are more likely to experience poorer psychiatric and emotional outcomes (Sweeney et al., 2015). Type of trauma (Clemens et al., 2018; Ballard et al., 2015) and the number of traumatic experiences (Clemens

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et al., 2018; Agorastos et al., 2014) are also shown to differentially impact health outcomes.

Many of the health outcomes seen in individuals with a history of childhood trauma resemble sickness behaviors experienced during the course of infection. For example, low energy and poor sleep quality (Beilharz et al., 2020). Sickness behavior describes a drastic change in experience and behavior occurring with physical illness (Dantzer et al., 2008). When exposed to virus and bacteria, the innate immune system provides an initial line of defence against pathogens via inflammation (Baumeister et al., 2016; Xiao, 2017; Chen et al., 2017). Within this process immune cells produce inflammatory mediators, such as pro-inflammatory cytokines, that induce sickness behaviours (Dantzer et al., 2008). Given overlaps in sickness behavior and health outcomes evidenced in those with a history of childhood trauma, the immune system and relative inflammatory processes are under investigation as mediatory mechanisms in the above associations.

Trends in research support this theory, showing elevated levels of pro-inflammatory cytokines and C-reactive protein (CRP) in those with a history of childhood trauma. A review by Nemeroff (2016) outlined evidence for increased CRP in adulthood and adolescence following childhood trauma. Such associations have also been identified for pro-inflammatory cytokines. A recent meta-analysis by Baumeister et al. (2016) found consistent elevation of CRP, Interleukin-6 (IL-6) and Tumour Necrosis Factor (TNF-α) in participants with history of childhood trauma. When addressed independently, individual types of trauma differentially impacted inflammatory markers; CRP was not significantly associated with sexual or physical abuse, however it was primarily related to parental absence. These differential effects could be expected given the mediating effects of trauma type on health outcomes experienced.

In this review, we provide an updated scope for inflammation as a neurobiological consequence of childhood trauma, addressing IL-6, TNFα, CRP and Interleukin 1-beta (IL-1β) as markers of inflammation. As an updated version of Baumeister et al. (2016) review we followed the same exclusion and inclusion criteria. We report on 37 articles all of which were not included in the original review.

2. Methods

2.1. Search strategy and selection

A review of the literature was performed via PubMed, using the following search terms: ("Childhood Maltreatment" OR "Childhood Trauma" OR "Childhood Adversity" OR "Early Life Stress" OR "Child Abuse" OR "Child Neglect") AND ("C-reactive Protein" OR "CRP" OR "Tumour Necrosis Factor" OR "TNF-α" OR "Cytokine" OR "Interleukin" OR "IL-6" OR "Inflammatory" OR "Inflammation" OR "Interleukin 6"). The review was performed between 31 March and 11 July 2021. Filters were applied for restriction to human participants and publications in English language. A timeline of 16/02/2015 to 11/07/2021 was applied to provide an update of the original search, from Baumeister et al. (2016). The initial search produced 236 results. Titles and abstracts were scrutinised for appropriateness to the present objective and relevant criteria. Details on exclusion and inclusion criteria can be seen in Table 1. In line with the original review (Baumeister et al., 2016), articles were excluded if they investigated inflammatory levels stimulated by stress tasks- such as the Trier Social Stress Test (TSST)- to focus on naturally occurring inflammatory levels potentially associated with trauma. Upon assessment of titles and abstracts, two additional reasons were added to the original exclusion criteria: restriction to gene expression and no access to full version. As an area requiring extensive investigation, articles addressing gene expression were excluded from the review to facilitate an in depth exploration of the association between childhood trauma and inflammatory marker levels in adulthood. Forty-five articles were eligible for full text screening. Eight articles were then removed due to insufficient assessment of associations between childhood trauma and inflammation. Thirty-seven studies were included in the review (see Fig. 1 for a procedural flowchart). Though not included in Baumeister et al. (2016) review, upon assessment, IL-1β also showed consistent reporting across studies thus is discussed as an additional marker of interest in the results.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Any type of traumatic experience before 18	No assessment of relevant inflammatory markers
Assesses CRP, IL-6, TNF-α, or IL-1β in participants aged 18 or older	No assessment of inflammation in adulthood
General or clinical population	No assessment of childhood trauma
	Inflammatory markers assessed following stimulation (for example with lab stress tasks)
	Assessment of gene expression for relevant inflammatory markers
	Previously reported on sample (reviews)
	No access to full version
	Focus on adverse socioeconomic status

For study characteristics see supplementary material 1. For a summary of the types of inflammatory markers, types of childhood traumas, severity of childhood trauma, and number of traumatic experiences assessed in each article, see Table 2. For reports on significance see Table 3.

2.2. Grouping for results

Results were grouped by inflammatory markers and sub-grouped based on the methodological assessments of childhood trauma, with the predominant method being the Childhood Trauma Questionnaire (CTQ). For all inflammatory markers (except combined measures of inflammation) subgroups included '*CTQ total score*', '*CTQ individual subscale assessments*' and '*other measures and childhood trauma types*'. Investigation using a combined measure of inflammation was sparse, therefore results were insufficient for the same categorical groupings. For CRP and IL-6 an additional subgrouping for '*CTQ abuse versus neglect*' was included. Additional groupings for *'number of trauma types'*, '*abuse severity*', '*sex differences'*, '*BMI as a mediator'*, '*additional mediators'* and '*association with clinical characteristics*' were then addressed.

3. Results

3.1. Inflammatory markers

3.1.1. C-reactive protein (CRP)

Twenty-two studies assessed the association between Childhood trauma and CRP levels in adulthood. Eleven of these addressed trauma as an overall total score (Takizawa et al., 2015; Li et al., 2015b; Boeck et al., 2016; Plant et al., 2016; Baldwin et al., 2018; Imai et al., 2018; Counotte et al., 2019; John-Henderson et al., 2020; Gouin et al., 2020; Tannous et al., 2020; Lacey et al., 2020), 11 assessed trauma as individual subtypes (Fanning et al., 2015; Powers et al., 2016; Mitchell et al., 2018; Finy and Christian, 2018; Chamberlain et al., 2019; Quidé et al., 2019; Pinto Pereira et al., 2019; Kim et al., 2019; Powers et al., 2019; Kraynak et al., 2019; Lacey et al., 2020), and 4 assessed effects by number of traumas experienced (Lin et al., 2016; Aas et al., 2017; Baldwin et al., 2018; Lacey et al., 2020). The predominant finding across studies was a non-significant association between childhood trauma and CRP levels in adulthood, though significant reports were still consistently presented. Significant positive associations between childhood trauma and adult CRP levels were mainly attributed to specific types of trauma, measures assessing greater variation in trauma type, and mediation by other variables.

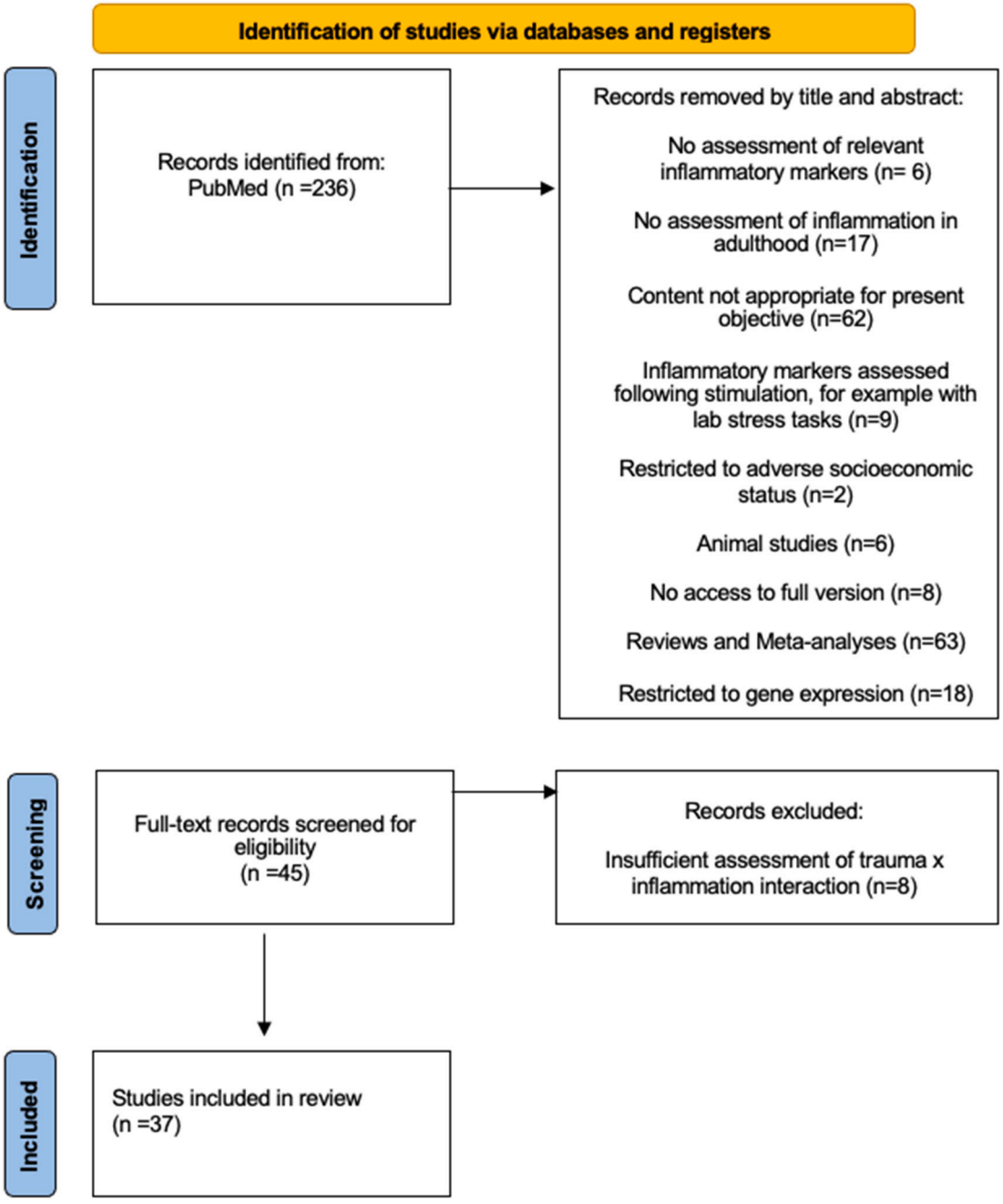

Fig. 1. PRISMA flowchart for selection processes.

3.1.1.1. CTQ total score. Seven studies assessed childhood trauma using an overall total score on the Childhood Trauma Questionnaire (Bernstein et al., 1994) (CTQ) (Boeck et al., 2016; Plant et al., 2016; Baldwin et al., 2018; Imai et al., 2018; Counotte et al., 2019; Gouin et al., 2020; Tannous et al., 2020), 6 of which found no association between childhood trauma and CRP levels in adulthood in both correlational and regression analyses. Though Baldwin et al. (2018) found total CTQ score to positively correlate with elevated CRP levels in adulthood ($p < 0.05$), this was only applicable to female participants. Collectively, results suggest no significant effect of childhood trauma on CRP levels in later life.

3.1.1.2. Total abuse vs total neglect. When grouping CTQ into two subscales, abuse (emotional, sexual and physical) and neglect (emotional and physical), Fanning et al. (2015) found a significant positive correlation for abuse ($p < 0.001$), where participants with higher childhood abuse scores had higher levels of CRP in adulthood. However, the same result was not found for neglect. Regression analyses further presented childhood abuse as a significant predictor of CRP levels in adulthood. Though using an alternate measure of abuse and neglect, the Adverse Childhood Events Questionnaire (Felitti et al., 1998) (ACE), Kim et al. (2019) reinforced non-significant associations for childhood neglect and CRP levels in adulthood, suggesting childhood neglect does not affect future CRP levels. They also found the ACE abuse subscale to be non-significantly associated with CRP levels. Comparative to the CTQ, the ACE is a 10 item self-report measure assessing a broader range of traumatic events in childhood. Alongside assessment of physical, sexual and emotional abuse, and physical and emotional neglect, the ACE incorporates items of household dysfunction – including domestic violence, incarceration, mental health conditions, chronic health

Table 2
Summary of the types of inflammatory markers types of childhood traumas, severity of traumas, and number of traumas assessed across 37 studies included in the current review.

Study	Inflammatory markers	Type of trauma	Severity of trauma	Number of traumas
Takizawa et al. (2015)	CRP	Bullying victimization	0 = never bullied ('never' at both 7 and 11 years) 1 = occasionally bullied ('sometimes' at either 7 or 11 years) 2 = frequently bullied ('frequently' at either 7 or 11 years, or 'sometimes' at both ages).	N/A
Hostinar et al. (2015)	Combined (CRP, IL-6, fibrinogen, *E*-Selectin, and Intercellular Adhesion Molecule-1)	Physical abuse Emotional abuse Sexual abuse Emotional neglect Physical neglect Parental divorce Parental substance abuse Parental depression	N/A	0 1 2 3 4+
Li et al. (2015a)	IL-6 IL-1β TNFα	Physical abuse Emotional abuse Sexual abuse Emotional neglect Physical neglect	N/A	N/A
Li et al. (2015b)	CRP	Parental substance abuse Witnessing physical violence in the family Physical abuse	N/A	N/A
Fanning et al. (2015)	CRP IL-6	Physical abuse Emotional abuse Sexual abuse Emotional neglect Physical neglect	N/A	N/A
Lin et al. (2016)	CRP	Doing a year of school over again Parental substance abuse Physical abuse	N/A	0 1 2
Petrov et al. (2016)	Combined (IL-6, CRP and Fibrinogen)	Physical abuse Emotional abuse Sexual abuse	N/A	N/A
Grosse et al. (2016)	IL-6 TNFα	Physical abuse Emotional abuse Sexual abuse Emotional neglect Physical neglect	N/A	N/A
Powers et al. (2016)	CRP	Physical abuse Emotional abuse Sexual abuse	0 = none or mild abuse 1 = the presence of moderate or severe abuse scores for at least one of the three types of abuse	N/A
Boeck et al. (2016)	CRP IL-1β IL-6 TNFα	Physical abuse Emotional abuse Sexual abuse Emotional neglect Physical neglect	None Low/moderate Severe	N/A
Plant et al. (2016)	CRP	Physical abuse Emotional abuse Sexual abuse Emotional neglect	N/A	N/A
Hostinar et al. (2017)	Combine (CRP, IL-6, Fibrinogen)	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Aas et al. (2017)	CRP	Physical abuse Sexual abuse Emotional abuse	N/A	0 1 2 3
Baldwin et al. (2018)	CRP	Exposure to domestic violence frequent bullying by peers Physical maltreatment by an adult Sexual abuse Emotional abuse Emotional neglect physical neglect	Not exposed to victimization Exposed to one type of victimization Multiple types of victimization	0 1 2+
Mitchell et al. (2018)	TNFα IL-6 CRP	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A

(*continued on next page*)

Table 2 (*continued*)

Study	Inflammatory markers	Type of trauma	Severity of trauma	Number of traumas
Pedrotti Moreira et al. (2018)	TNFα IL-6	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Munjiza et al. (2018)	IL-6	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Toft et al. (2018)	IL-1β TNFα	Sexual assault Physical abuse Other traumatic events which have led to serious problems later in life.	N/A	N/A
Imai et al. (2018)	CRP IL-1β IL-6 TNFα	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Finy and Christian (2018)	CRP IL-6	Physical abuse Sexual abuse Emotional abuse	N/A	N/A
Chamberlain et al. (2019)	CRP	Not having enough to eat Not feeling loves in childhood Wanting to change one's childhood Sexual touching in childhood Sexual acts in childhood.	N/A	N/A
Davis et al. (2019)	IL-6	Physical abuse Sexual abuse Emotional abuse	N/A	N/A
Quidé et al. (2019)	CRP IL-6 TNFα	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Pinto Pereira et al. (2019)	CRP	Physical abuse Emotional abuse Sexual abuse Physical neglect Emotional neglect	N/A	N/A
Müller et al. (2019)	IL-6	Physical abuse Emotional abuse Sexual abuse Physical neglect Emotional neglect	N/A	N/A
Kim et al. (2019)	CRP	Physical abuse Sexual abuse Emotional abuse Neglect Lack of protection Parental divorce Marital violence Family substance Misuse Familial mental health difficulties Familial imprisonment	N/A	Abuse (0–3) Neglect (0–2) Family dysfunction (0–5)
Counotte et al. (2019)	CRP IL-6 TNFα	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Powers et al. (2019)	CRP	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Kraynak et al. (2019)	IL-6	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
John-Henderson et al. (2020)	CRP IL-6	Physical abuse Verbal abuse Sexual abuse Physical neglect Emotional neglect	N/A	N/A

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Table 2 (*continued*)

Study	Inflammatory markers	Type of trauma	Severity of trauma	Number of traumas
		Parent alcohol abuse Domestic violence Parental incarceration Family mental illness Absence of parent through divorce, death or abandonment.		
Gouin et al. (2020)	CRP IL-6 TNFα	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Tannous et al. (2020)	CRP	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Lacey et al. (2020)	CRP	Parental death Parental offending Parental separation Parental substance misuse Parental mental illness Family conflict Sexual abuse Physical abuse Emotional abuse Emotional neglect Physical neglect Witnessed abuse	N/A	0 1 2 3 4+
Ng et al. (2020)	IL-6 IL-1β	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Bock et al. (2020)	IL-1β	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	No trauma Mild/moderate Severe	N/A
McCormack et al. (2021)	IL-6	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A
Renna et al. (2021)	Combined (IL-6, IL-1β & TNFα)	Physical abuse Sexual abuse Emotional abuse Emotional neglect Physical neglect	N/A	N/A

Abbreviations: CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-1β = Interleukin 1 beta; TNFα = Tumour Necrosis Factor alpha.

conditions, and substance abuse – and further utilises a combination of dichotomous (yes or no) and continuous (never, once, twice, sometimes, often and very often) scoring (Felitti et al., 1998).

Discrepancies could therefore be partially attributed to the use of different trauma measures. Other studies using the CTQ support a significant positive correlation between total abuse and CRP levels ($p < 0.01$ tp $p < 0.05$) (Finy and Christian, 2018; Powers et al., 2019). Though Finy and Christian (2018) reported further evidence for childhood abuse as a significant predictor of CRP levels in adulthood ($p < 0.05$), Powers et al. (2019) did not support these findings. Non-significant findings may be attributable to their smaller sample sizes. Collectively, distinction between significance of abuse and non-significance of neglect reinforces the importance of distinguishing between trauma type in measurement.

3.1.1.3. Individual subscale assessment. When assessed in isolation, CTQ subscales for different types of trauma presented different associations with CRP levels in adulthood. Mitchell et al. (2018) found emotional neglect, emotional abuse, and physical abuse to significantly predict elevated CRP levels in adulthood ($p < 0.05$) while physical neglect and sexual abuse were non-significant. However, significance for emotional and physical abuse did not uphold when adjusting for body mass index (BMI). Significance for emotional neglect remained, suggesting this was the only type of abuse to have an effect on CRP in this sample, independent of other variables. Further research found physical abuse to have no significant association with CRP levels (Quidé et al., 2019; Kraynak et al., 2019). On the contrary, Quidé et al. (2019) found sexual abuse to be the only trauma type to significantly predict elevated CRP levels in adulthood ($p < 0.05$), though this was restricted to patients with schizophrenia. Chamberlain et al. (2019) also reported on contributions of clinical status to the effects of childhood trauma on CRP levels. Overall, the partial least squares (PLS) regression - including specific CTQ items, BMI, Hamilton Depression Rating Scale items, Beck's Depression Inventory items, and State Trait Anxiety Inventory items-accounted for 26.7% of variance in CRP levels in adulthood, and PLS scores were highest in treatment-resistant depression, followed by untreated and treatment-responsive depression. However, due to the independent contribution of BMI, depressive symptoms, and childhood trauma in this regression, caution is needed when interpreting these results.

Pinto Pereira et al. (2019) found those with experience of childhood sexual abuse had 57.9% higher CRP levels in adulthood, however this was only relevant to non-white participants; white participants presented a mean increase of 16.7%. Differences were also evident for other types of trauma, with the greatest contrast reported for emotional neglect −2.3% in the British Birth Cohort versus 15.6% in the Midlife in the United States (MIDUS) study. Physical neglect was associated with a 23.8% increase in CRP levels in adulthood for the British Birth Cohort only - the second largest difference. Results suggest effect of childhood trauma on CRP levels in adulthood is dependent on the type of trauma experienced, clinical status, and sample characteristics.

3.1.1.4. Other childhood trauma measures and types. Plant et al. (2016) explored total scores on the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) and Child Attachment and Play Assessment (CAPA), and also found a non-significant association between childhood trauma and adulthood CRP levels. Those exposed to childhood trauma showed no significant difference in CRP levels in adulthood and, in a regression analysis, childhood trauma was not a significant predictor of CRP levels in later life. The CECA.Q is a 16 item questionnaire based on the Childhood Experience of Care and Abuse interview, covering parental loss, neglect, hostile parenting, support, and physical and sexual abuse before the age of 17. Comparative to the CTQ, scoring for each item is dichotomous (yes or no) and additional trauma types are assessed; less attention is given to specific types of neglect and abuse in contrast (Smith et al., 2002). The CAPA is a doll-play procedure assessing attachment and complex trauma in children aged 3–11 years. While the CTQ is a strong measure of trauma occurrence, the CAPA is a clinical tool focused on assessing young children's mental representations of attachment and relationships (About the CAPA: CAPARetrieved 9 October, n.d.).

Similar to Plant et al. (2016), John-Henderson et al. (2020) reinforced no significant difference in CRP levels relative to trauma experience using the ACE questionnaire, encompassing physical, verbal, and sexual abuse, physical and emotional neglect, parental alcohol abuse, domestic violence, parental incarceration, family mental illness, and absence of a parent through divorce, death, or abandonment. Studied in the Blackfeet tribal community, significance was relative to sense of belonging to the tribal community; childhood trauma was only a significant predictor of elevated CRP levels in those with low levels of community belonging ($p < 0.001$.) Similar findings were also present for interaction with sex; Kim et al. (2019) found family dysfunction to be significantly correlated with elevated CRP levels ($p < 0.05$), however this was only reported in females. Interestingly, although Plant et al. (2016) found no significant association for childhood trauma, they did find exposure to prenatal maternal depression to predict significant elevation for CRP levels in adulthood ($p < 0.05$). Results may suggest that predisposition to chronic inflammation could exist with stress occurring before birth.

Where abuse and neglect were measured in conjunction with parental substance abuse and exposure to domestic violence, childhood trauma showed a significant positive correlation with CRP ($p < 0.05$) (Li et al., 2015b; Baldwin et al., 2018). Baldwin et al. (2018) also included peer bullying in their measure of childhood trauma. Measured in isolation, peer victimization has shown significant association with elevated CRP levels in adulthood; those exposed to peer victimization had significantly higher CRP ($p < 0.001$) and clinically relevant CRP (>3 mg/L) levels ($p < 0.01$) in adulthood (Takizawa et al., 2015). Li et al. (2015b) found significant correlations to be restricted to participants living in Canadian cities; those in Latin American cities showed no significant associations. In their regression analysis, the authors found social adversity (encompassing parental substance abuse, witnessing physical violence in the family, and physical abuse) to be a significant predictor of elevated CRP levels in adulthood, though again restricted to the Canadian sample. This was after adjusting for age, sex, current marital status, and financial strain. In this sample, prevalence ratios further showed a 40% increase in CRP levels >3 mg/dL in participants with a history of social adversity. Where social adversity was a collective measure of parental substance abuse, witnessing physical violence in the family, and physical abuse, the contribution of each individual trauma type to this percentage increase is unknown. However, Lacey et al. (2020) reported on these trauma types independently, finding physical abuse to be associated with greater elevation of CRP levels (17.57%) in adulthood than witnessing abuse (13.75%), family conflict (9.05%), and parental substance misuse (4.22%). This was relative to retrospective reports of childhood trauma; in prospective reports, parental substance misuse was in fact associated with a decrease (−24.26%) in CRP levels in adulthood. In their paper, Lacey et al. (2020) stress the importance of considering report type in trauma research.

Overall, significant findings suggest type of trauma may be an important moderator in the effects of childhood trauma on elevated CRP levels in adulthood, though this may be relative to presence of other mediatory variables.

3.1.2. Interleukin 6 (IL-6)

Twenty-three studies assessed the association between childhood trauma and IL-6 levels in adulthood, 11 of which addressed trauma as a total score (Li et al., 2015a; Grosse et al., 2016; Boeck et al., 2016; Pedrotti Moreira et al., 2018; Munjiza et al., 2018; Imai et al., 2018; Counotte et al., 2019; Kraynak et al., 2019; John-Henderson et al., 2020; Gouin et al., 2020; Ng et al., 2020) and 12 assessed individual subtypes (Fanning et al., 2015; Grosse et al., 2016; Mitchell et al., 2018; Pedrotti Moreira et al., 2018; Munjiza et al., 2018; Finy and Christian, 2018; Davis et al., 2019; Quidé et al., 2019; Müller et al., 2019; Kraynak et al., 2019; Ng et al., 2020; McCormack et al., 2021). The predominant finding across studies was a non-significant association between childhood trauma and IL-6 levels in adulthood, though discrepancies arose when considering type of trauma and mediation by other variables.

3.1.2.1. CTQ total score. Correlational analyses presented equal weighting to non-significant and significant results. Imai et al. (2018), Ng et al. (2020) and McCormack et al. (2021) found childhood trauma to be non-significantly correlated with IL-6 levels, while Munjiza et al. (2018), Kraynak et al. (2019) and Gouin et al. (2020) found total trauma scores to be significantly correlated with increased IL-6 levels in adulthood ($p < 0.01$ and $p < 0.05$.) Using regression analyses, studies predominantly supported a non-significant association between childhood trauma and IL-6 levels in adulthood. Grosse et al. (2016), Boeck et al. (2016), Counotte et al. (2019) and Kraynak et al. (2019) found CTQ total scores did not significantly predict IL-6 levels in adulthood. The potential for depressive symptoms as a confounding factor was evidenced in the differential levels of IL-6 in patients with depression when compared with healthy controls (Pedrotti Moreira et al., 2018). In patients with depression, but not in healthy controls, participants with childhood trauma had significantly higher levels of IL-6 than those without a history of trauma ($p < 0.05$). Li et al. (2015a) further found a significant elevation in IL-6 levels in participants exposed to childhood trauma when compared to those not exposed ($p < 0.05$).

3.1.2.2. Abuse versus neglect. When exploring CTQ subscales for abuse and neglect, Fanning et al. (2015) showed no association with IL-6 for abuse or neglect. Finy and Christian (2018), however found abuse to be significantly positively correlated with IL-6 ($p < 0.01$), although this did not translate to predictive value in a regression analysis. Davis et al.

(2019) further found this to be significant ($p < 0.001$) in a larger sample ($n = 214$ and $n = 770$ respectively). Sample sizes for both studies showing significance were larger than Fanning et al. (2015)sample, which may suggest greater power to detect effect in these studies.

3.1.2.3. Individual subscale assessment. Assessment of individual CTQ subscales presented contradictory findings for all trauma types except for emotional neglect. All studies reported non-significant associations between emotional neglect in childhood and IL-6 levels in adulthood (Grosse et al., 2016; Mitchell et al., 2018; Pedrotti Moreira et al., 2018; Munjiza et al., 2018; Quidé et al., 2019; Müller et al., 2019; Kraynak et al., 2019; Ng et al., 2020; McCormack et al., 2021). For physical and emotional abuse, and physical neglect, studies have reported some associations with elevated levels of IL-6 in adulthood at $p < 0.05$ and $p < 0.01$ significance thresholds, though the general consensus was a non-significant association for these individual trauma types (see Table 3*)*. Associations for sexual abuse showed greater distribution; results predominantly showed non-significant associations between sexual abuse and IL-6 levels, however two studies showed sexual abuse to be significantly associated with elevated IL-6 levels at $p < 0.05$ (Grosse et al., 2016; Müller et al., 2019). Where significance was reported at $p < 0.01$, the association was negative (Ng et al., 2020), suggesting that sexual abuse was conversely associated with lower IL-6 levels in adulthood. However, once the factor of trust in one's partner was added to the model this negative association lost significance.

3.1.2.4. Other childhood trauma measures and types. Assessing childhood trauma as a total score on the ACE scale, John-Henderson et al. (2020) found no significant correlation between ACE score and IL-6, and further reported childhood trauma as a non-significant predictor of IL-6 in adulthood. Results support previous non-significant findings in studies utilizing the CTQ.

3.1.3. TNFα

Twelve studies assessed the association between childhood trauma and TNFα levels in adulthood, 8 of which addressed trauma as a total score (Li et al., 2015a; Grosse et al., 2016; Boeck et al., 2016; Pedrotti Moreira et al., 2018; Toft et al., 2018; Imai et al., 2018; Counotte et al., 2019; Gouin et al., 2020) and 4 assessed trauma as individual subtypes (Grosse et al., 2016; Mitchell et al., 2018; Pedrotti Moreira et al., 2018; Quidé et al., 2019). Studies predominantly found a non-significant association between childhood trauma and levels of TNFα in adulthood. Significant positive associations were mainly attributed to use of alternate measures ofchildhood trauma and specific types of trauma experienced.

3.1.3.1. CTQ total score. Five studies found childhood trauma to be non-significantly associated with TNFα levels in adulthood (Grosse et al., 2016; Boeck et al., 2016; Pedrotti Moreira et al., 2018; Imai et al., 2018; Gouin et al., 2020). Correlation analyses revealed no significant correlation between childhood trauma and TNFα levels suggesting experience of trauma does not significantly increase TNFα levels in adulthood (Imai et al., 2018; Gouin et al., 2020). Regression analyses suggest childhood trauma does not predict TNFα levels in adulthood (Grosse et al., 2016; Boeck et al., 2016; Gouin et al., 2020). After comparing those with a history of childhood trauma to those without trauma, Pedrotti Moreira et al. (2018) found no significant differences in adult TNFα levels between those with a history of trauma and those without. Li et al. (2015a), however, reported significantly higher levels of TNFα in those with a history of trauma. Notably, Pedrotti Moreira et al. (2018) used a larger sample size ($n = 166$ versus $n = 75$), which may suggest greater statistical power and thus ability to detect an association.

3.1.3.2. Individual subscale assessment. All studies assessing the association between individual trauma types and TNFα levels in adulthood found associations to be non-significant (Grosse et al., 2016; Mitchell et al., 2018; Pedrotti Moreira et al., 2018; Quidé et al., 2019). Upon a separate regression analysis on participants with at least low trauma, Grosse et al. (2016) found sexual abuse and emotional neglect to significantly predict TNFα levels in adulthood ($p < 0.01$ and $p < 0.05$), however results were group specific. Sexual abuse only significantly predicted TNFα levels in patients with major depressive disorder and emotional abuse only significantly predicted TNFα levels in healthy controls. Significance for emotional neglect was lost when adjusting for other variables, while the significance for sexual abuse remained.

3.1.3.3. Other trauma measures and types. Using an alternate measure of childhood trauma (3 unstandardized questions addressing sexual assault, physical abuse, and any other traumatic event) Toft et al. (2018) found TNFα levels to be significantly higher in those with a history of trauma than those without ($p < 0.05$.). This supports Li et al. (2015a) findings using the CTQ scale. There is concern in the scope for events classified under 'any other traumatic event' and the subsequent lack of standardization. Caution may also be needed relative to lack of adjustment for BMI.

3.1.4. IL-1β

Six studies assessed the association between childhood trauma and IL-1β levels in adulthood, all of which measured trauma using a total score (Li et al., 2015a; Boeck et al., 2016; Toft et al., 2018; Imai et al., 2018; Ng et al., 2020; Bock et al., 2020). Collectively, studies predominantly reported non-significant associations between childhood trauma and IL-1β levels in adulthood. Bock et al. (2020) was the only study to find a significant difference in IL-1β levels between groups when assessed as no trauma, mild/moderate trauma, and severe trauma ($p < 0.05$). The positive relationship suggests those with childhood trauma have higher levels of IL-1β in adulthood compared to those without trauma, and greater severity of trauma can further associate with greater elevation of IL-1β.

3.1.4.1. CTQ total score. Four studies reported non-significant associations between total childhood trauma and IL-1β levels in adulthood (Boeck et al., 2016; Toft et al., 2018; Imai et al., 2018; Ng et al., 2020). Correlational analyses revealed no significant correlation between childhood trauma and IL-1β in adulthood (Imai et al., 2018; Ng et al., 2020). Regression analyses showed childhood trauma did not significantly predict IL-1β levels (Boeck et al., 2016). Group comparison found those with a history of childhood trauma had significantly elevated levels of IL-1β in adulthood ($P < 0.05$) (Li et al., 2015a).

3.1.4.2. Individual subscale assessment. As the only study using individual subscales to investigate association between IL-1β and childhood trauma, Ng et al. (2020) found no significant correlations between individual CTQ subscales and IL-1β levels in adulthood. Results suggest type of trauma does not affect IL-1β levels in adulthood.

3.1.4.3. Other trauma measures and types. Asking participants three binary coded questions related to sexual assault, physical abuse, and any other traumatic event leading to a serious problem later in life, Toft et al. (2018) reported no difference in IL-1β levels in participants with experience of childhood trauma and those without. This does not support Li et al. (2015a) findings with comparitive use of the CTQ. Discrepancies may be partially attributed to the differential measures of childhood trauma and included trauma types.

3.1.4.4. Aggregated measure of inflammation (including IL-6, CRP, TNF-α and IL-1β). Four studies assessed inflammation as an aggregated measure including IL-6 and CRP (Hostinar et al., 2015; Petrov et al., 2016; Hostinar et al., 2017; Renna et al., 2021), and TNF-α and IL-1β (Renna

Table 3
Significance for correlational and regression analyses, group comparisons, and prevalence ratios across 37 studies included in the current review.

Study	Correlations, regressions, prevalence ratios and group comparisons	Significance
Takizawa et al. (2015)	*Group comparisons*	
	Bully victimization *vs* no victimisation x CRP	$P < 0.001$ (*Continuous CRP*) $p < 0.01$ (*Clinically relevant CRP >3 mg/l*)
Hostinar et al. (2015)	*Correlation*	
	Total trauma x Inflammation	$P < 0.01$
	Regression	
	Total trauma x inflammation	$P < 0.01$* **Addition of other variables reduced significance to $p < 0.05$*
Li et al. (2015a)	*Group comparisons*	
	CTQ trauma *vs* no trauma x IL-1β	$P < 0.05$
	CTQ trauma *vs* no trauma x TNFα	$P < 0.05$
	CTQ trauma *vs* no trauma x IL-6	No difference
Li et al. (2015b)	*Correlation*	
	Total social adversity x CRP	$P < 0.05$ (*Canadian cities*) Non-significant (*Latin American cities*)
	Regression	
	Total social adversity x CRP	$P < 0.05$ (*Canadian cities*) Non-significant (*Latin American cities*) 40% increase (*Canadian sample only*)
	Prevalence ratios	
	Total social adversity x CRP >3 mg/dL	
Fanning et al. (2015)	*Correlations*	
	CTQ abuse x CRP	$P < 0.001$
	CTQ neglect x CRP	Non-significant
	CTQ abuse x IL-6	Non-significant
	CTQ neglect x IL-6	Non-significant
	Regression	
	CTQ abuse x CRP	$P < 0.01$
Lin et al. (2016)	*Regression*	
	Total number of adverse events x CRP	$P = 0.001$*
	One or more childhood adversities x CRP	$P = 0.001$* **After adjusting for race, age, and sex ($p = 0.01$.) After adjusting for BMI and smoking ($P = 0.003$.)*
Petrov et al. (2016)	*Correlations*	
	CTQ Abuse x Inflammation	$P < 0.05$
Grosse et al. (2016)	*Regression* (*total sample*)	
	CTQ total score x IL-6	Non-significant
	CTQ total score x TNFα	Non-significant
	CTQ subscales x IL-6	Non-significant for all
	CTQ subscales x TNFα	Non-significant for all
	Regression (*using at least low trauma*)	
	CTQ Sexual abuse x IL-6	$P < 0.05$ (*MDD group only*)
	CTQ Emotional abuse x IL-6	$P < 0.05$ (*HC group only*)
	CTQ Other subscales x IL-6	Non-significant
	CTQ Sexual abuse x TNFα	$P < 0.01$ (*MDD group only*)
	CTQ Emotional neglect x TNFα	$P < 0.05$ (*HC group only*) *
	CTQ Other subscales x TNFα	Non-significant **Significance lost when adjusting for variables.*
Powers et al. (2016)	*Correlations*	
	CTQ Abuse severity x CRP	Non-significant
	Regression	
	CTQ Abuse severity x CRP	Non-significant * **Significant when adding current MDD and emotion dysregulation into the model.*
Boeck et al. (2016)	*ANCOVA and Regression*	
	CTQ severity classification x CRP	Non-significant
	CTQ severity classification x IL-1β	Non-significant
	CTQ severity classification x IL-6	Non-significant
	CTQ severity classification x TNFα	Non-significant
	CTQ total score x CRP	Non-significant
	CTQ total score x IL-1β	Non-significant
	CTQ total score x IL-6	Non-significant
	CTQ total score x TNFα	Non-significant
Plant et al. (2016)	*Regression*	
	Childhood maltreatment x CRP	Non-significant
	Childhood maltreatment x dichotomized CRP	Non-significant
Hostinar et al. (2017)	*Correlation*	
	CTQ total score x inflammation	Non-significant
	Regression	
	CTQ total score x inflammation	Non-significant
	(Maltreatment * frontal asymmetry) x inflammation	$P < 0.05$

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Table 3 (*continued*)

Study	Correlations, regressions, prevalence ratios and group comparisons	Significance
Aas et al. (2017)	*Group comparison*	
	CTQ number of types of abuse x CRP	$P < 0.05$*
		**No longer significant when adjusting for BMI.*
Baldwin et al. (2018)	*Correlation*	
	Childhood victimization x CRP	$P < 0.05$ (*females only*)
	Group comparison	
	No Victimization vs one victimization x CRP	$P < 0.05$ (*females only*)
	No victimization vs ploy-victimization x CRP	Non-significant
Mitchell et al. (2018)	*Linear mixed model*	
	CTQ Physical abuse x CRP	$P < 0.05$ *
	CTQ Sexual abuse x CRP	Non-significant
	CTQ Emotional abuse x CRP	$P < 0.05$ *
	CTQ Emotional neglect x CRP	$P < 0.05$
	CTQ Physical neglect x CRP	Non-significant
	All CTQ subscales x IL-6	Non-significant
	All CTQ subscales and TNFα	Non-significant
		**Significance lost when adjusting for BMI.*
Pedrotti Moreira et al. (2018)	*Group comparison*	
	CTQ trauma vs no trauma x IL-6	$P < 0.05$ (*MDD patients only*)
	CTQ trauma vs no trauma x TNFa	Non-significant
	CTQ Physical abuse x IL-6	$P < 0.05$ (*MDD patients only*)
	CTQ Emotional abuse x IL-6	$P < 0.001$ (*MDD patients only*)
	Other CTQ subscales x IL-6	Non-significant
	All CTQ subscales x TNFa	Non-significant for all
Munjiza et al. (2018)	*Correlations*	
	CTQ total score x IL-6	$P < 0.01$
	CTQ Physical abuse x IL-6	$P < 0.01$ (*MDD patients only*)
	CTQ Emotional abuse x IL-6	$P < 0.01$ (*MDD patients only*)
	CTQ Physical neglect x IL-6	$P < 0.01$ (*MDD patients only*)
	CTQ Emotional neglect x IL-6	Non-significant
	CTQ Sexual abuse x IL-6	Not prevalent enough in the sample for statistical analysis.
Toft et al. (2018)	*Group comparison*	
	Trauma vs no trauma x TNFα	$P < 0.05$ (*only severe depression*)
	Trauma vs no trauma x IL-1β	Non-significant
Imai et al. (2018)	*Correlations*	
	CTQ total score x IL-6	Non-significant
	CTQ total score x CRP	Non-significant
	CTQ total score x TNFα	Non-significant
	CTQ total score x IL-1β	Non-significant
Finy and Christian (2018)	*Correlations*	
	CTQ Abuse x CRP	$P < 0.01$
	CTQ Abuse x IL-6	$P < 0.01$
	Regression	
	CTQ abuse x CRP	$P < 0.05$
	CTQ abuse x IL-6	Non-significant
Chamberlain et al. (2019)	*Partial least squares regression*	
	PLS1 x CRP	Account for 26.7% of variance in CRP.
		Significantly weighted items:
		CTQ (*7*) & (*10*), *BMI*, *HAM-D* (*5*) & (*8*), *BDI* (*15*.)
Davis et al. (2019)	*Correlation*	
	CTQ abuse x IL-6	$P \leq 0.001$
Quidé et al. (2019)	*Regression*	
	Overall model x TNFa	$P < 0.01$(*BD group only*)
		$P < 0.05$ (*BD/SZ group only*)
	Overall model x IL-6	Non-significant
	Overall model x CRP	$P < 0.05$ (*SZ group only*.)
	All CTQ subscales x TNFα	Non-significant
	CTQ Sexual abuse x IL-6	$P < 0.05$ (*SZ group only*)
	All other CTQ subscales x IL-6	Non-significant
	All CTQ subscales x CRP	Non-significant
Pinto Pereira et al. (2019)	*Mean percentage difference*	
	Physical abuse x CRP	20% BBC
		23.2% MIDUS
	Sexual abuse x CRP	57.9% non-white MIDUS
		16.7% White MIDUS
	Emotional abuse x CRP	11.6% BBC
		7.26% MIDUS
	Emotional neglect	2.28% BBC
		17.6% MIDUS
	Physical neglect x CRP	23.8% BCC
Muller et al. (2019)	*Correlation* (*total sample*)	
	CTQ Sexual abuse x IL-6	$P < 0.05$
	CTQ Physical neglect x IL-6	$P < 0.01$
	Other CTQ subscales x IL-6	Non-significant

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Table 3 (*continued*)

Study	Correlations, regressions, prevalence ratios and group comparisons	Significance
	Correlation (*HC vs MDD*)	
	CTQ Physical neglect x IL-6	$P < 0.01$ (*MDD patients only*)
Kim et al. (2019)	*Regression*	
	ACE abuse x CRP	Non-significant
	ACE neglect x CRP	Non-significant
	ACE dysfunction x CRP	Non-significant
	(Female * dysfunction) x CRP	$P < 0.05$
Counotte et al. (2019)	*Regression*	
	CTQ total score x CRP	Non-significant
	CTQ total score x IL-6	Non-significant
	CTQ total score x TNFa	Non-significant
Powers et al. (2019)	*Correlation*	
	CTQ abuse x CRP	$P < 0.05$
	Regression	
	CTQ abuse x CRP	Non-significant
Kraynak et al. (2019)	*Mediation model*	
	CTQ Physical abuse x IL-6	$P < 0.01$
	CTQ Physical neglect x IL-6	$P < 0.05$ *
	CTQ sum score x IL-6	$P < 0.05$ *
	Other CTQ subscales x IL-6	Non-significant
	CTQ Physical abuse x CRP	Non-significant
		**Significance did not hold in regression model.*
John-Henderson et al. (2020)	*Correlation*	
	ACE total score x CRP	Non-significant
	ACE total score x IL-6	Non-significant
	Regression	
	ACE total score x IL-6	Non-significant
	ACE total score x CRP	Non-significant
	(ACE * community belonging) x IL-6	$P < 0.01$(*negative*)
	(ACE * community belonging) x CRP	$P < 0.001$
Gouin et al. (2020)	*Correlations*	
	CTQ total score x CRP	Non-significant
	CTQ total score x TNFα	Non-significant
	CTQ total score x IL-6	$P < 0.05$
	Regressions	
	CTQ total score x CRP	Non-significant
	CTQ total score x TNFα	Non-significant
	CTQ total score x IL-6	$P < 0.05$
	(Martial quality * early life stress) x TNFα	$P < 0.05$
	(Martial quality * early life stress) x IL-6	$P < 0.001$
	(caregiving * early life stress) x IL-6	$P < 0.001$
Tannous et al. (2020)	*Correlation*	
	CTQ total score x CRP	Non-significant
Lacey et al. (2020)	*Mean percentage difference* (*Retrospective data*)	
	ACE total score (1) x CRP	−5.83%
	ACE total score (2) x CRP	3.45%
	ACE total score (3) x CRP	3.23%
	ACE total score (4+) x CRP	7.66%
	Parental separation x CRP	8.57%
	Parental substance misuse x CRP	4.22%
	Parental mental illness x CRP	−4.29%
	Family conflict x CRP	9.05%
	Emotional neglect x CRP	4.10%
	Psychological abuse x CRP	9.51%
	Physical abuse x CRP	17.57%
	Sexual abuse x CRP	−9.32%
	Witnessed abuse x CRP	13.75%
	LCA-derived cluster (parental illness & substance misuse) x CRP	1.81%
	LCA-derived cluster (maltreatment & conflict) x CRP	15.30%
	LCA-derived cluster (polyadversity) x CRP	7.71%
	Mean percentage difference (*Prospective data*)	
	ACE total score (1) x CRP	
	ACE total score (2+) x CRP	13.72%
	Parental separation x CRP	15.89%
	Parental substance misuse x CRP	7.43%
	Parental death x CRP	−24.26%
	Parental mental illness x CRP	8.97%
	Parental offending x CRP	4.16%
	Family conflict x CRP	26.67%
	Physical neglect x CRP	11.95%
	LCA-derived cluster (parental loss) x CRP	10.51%
	LCA-derived cluster (household dysfunction) x CRP	

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Table 3 (*continued*)

Study	Correlations, regressions, prevalence ratios and group comparisons	Significance
		−4.52%
		15.61%
Ng et al. (2020)	*Bivariate Correlations*	
	CTQ total score x IL-6	Non-significant
	CTQ total score x IL-1β	Non-significant
	CTQ Sexual abuse x IL-6	P < 0.01 (*negative -MDD only*)
	All other CTQ subscales x IL-6	Non-significant
	ALL CTQ subscales x IL -1β	Non-significant
	Regression (*predicted*)	
	CTQ sexual abuse x IL-6	P < 0.05 *
		**Significance lost when trust in partner was added into the model.*
Bock et al. (2020)	*Group differences*	
	CTQ no trauma vs mild/moderate trauma vs severe trauma x IL -1β	P < 0.05
McCormack et al. (2021)	*Correlations*	
	Total CTQ score x IL-6	Non-significant
	Individual CTQ subscales x IL-6	Non-significant
Renna et al. (2021)	*Correlation*	
	CTQ Physical abuse x inflammation	P < 0.05
	CTQ Emotional abuse x inflammation	Non-significant
	CTQ Sexual abuse x inflammation	Non-significant
	CTQ Any abuse x inflammation	P < 0.05
	Change over time (*group comparison*)	
	CTQ Emotional abuse x inflammation	P < 0.05
	CTQ Physical abuse x inflammation	P < 0.05
	CTQ Sexual abuse x inflammation	Non-significant
	CTQ Any abuse x inflammation	P < 0.05

Abbreviations: CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-1β = Interleukin 1 beta; TNFα = Tumour Necrosis Factor alpha; CTQ = Childhood Trauma Questionnaire; ACE = Adverse Childhood Events; BMI = Body Mass Index; MDD = Major Depressive Disorder; HC = Healthy Controls; SCZ = Schizophrenia; BD = Bipolar Disorder; BBC = British Birth Cohort; MIDUS = Midlife in the United States; ANCOVA = Analysis of Covariance; LCA = Latent Class Analysis; PLS = Partial Least Squares; HAM-D = Hamilton Depression Rating Scale

et al., 2021). Both studies by Hostinar et al. (2015, 2017) further included fibrinogen, e-selection and ICAM-1 in this combined inflammatory measure. Though Hostinar et al. (2015) and Petrov et al. (2016) found childhood trauma to have a significant positive correlation with inflammation ($p < 0.01$; $p < 0.05$), Hostinar et al. (2017) and Renna et al. (2021) found significance to be relative to mediating factors, notably frontal brain asymmetry and type of trauma experienced. Childhood trauma was only significantly associated with inflammation in participants with high frontal asymmetry ($p < 0.05$) (Hostinar et al., 2017) and participants with a history of physical abuse ($p < 0.05$), but not sexual or emotional abuse (Renna et al., 2021). Considering the combined measure of inflammation used in these studies, knowledge for specific association with IL-6, CRP, TNF-α and IL-1β is restricted.

3.2. Number of trauma types

Six studies reported on the differential contribution of the number of trauma types experienced to the association between childhood trauma and inflammation in adulthood. When compared to participants with no history of trauma, Baldwin et al. (2018) found participants with one type of trauma to have significantly elevated CRP levels in adulthood ($p < 0.05$.) However, when participants with a history of multiple traumas were compared to those without trauma, no significant differences in CRP levels were found. Conversely, Aas et al. (2017) found participants with three types of traumatic experience to have significantly higher CRP than those with no history of trauma ($p < 0.01$.) However, this was only applicable to hypertension patients who, in the absence of trauma, already demonstrated significantly higher CRP levels in comparison to healthy controls. Further to this, Renna et al. (2021) found poly-adversity to minimally increase CRP levels in adulthood (7.71%) and Kim et al. (2019) found total number of ACEs to have no significant effect on CRP. Though addressing inflammation as a composite score of several inflammatory markers, including CRP, Hostinar et al. (2015) further supported linear inflammatory elevation with increase in number of traumatic experiences; those with 3 or 4 types of adversity had higher mean inflammatory levels (≥0.10 mg/L) than those with no trauma, one trauma, or two traumas (<0.10 mg/L). Lin et al. (2016) additionally supported this, reporting higher CRP levels in those with experience of two adversities when compared to those with one adversity. Overall, further research is needed for a better understanding of the differential and additive effects of the number of trauma types experienced.

3.3. Trauma severity

Three studies assessed the role of trauma severity in the association between childhood trauma and inflammation in adulthood (Powers et al., 2016; Boeck et al., 2016). In a regression analysis, classification of trauma severity (categorised as low, moderate, and severe) was not a significant predictor of CRP, IL-1β, TNFα or IL-6 however there was evidence of increased CRP levels in groups with low-moderate experience of childhood trauma (Boeck et al., 2016). This was not transferred to those with severe classification. Powers et al. (2016) also reported non-significant findings, though their investigations were limited to the CTQ abuse subscales. Powers et al. (2016) also utilised a different categorization system of non or mild abuse, and moderate to severe abuse. Both studies had relatively small sample sizes. Comparatively, conducted in a large sample size ($n = 7102$), Takizawa et al. (2015) reported significantly high CRP in those with frequent bullying victimization compared to those without a history of bullying ($p < 0.01$). This however was not translated to those with experience of occasional bullying.

3.4. Sex differences

In a stratified analysis, Baldwin et al. (2018) found a sex-specific effect of childhood trauma on CRP levels in adulthood. Compared to participants not exposed to childhood trauma, participants exposed to

one type of childhood trauma had significantly higher levels of CRP in adulthood, though this was only evident in females. This was further reinforced by Kim et al. (2019). Reporting on abuse, neglect, and family dysfunction (from the ACE questionnaire) as non-significant predictors of CRP in adulthood, this study found that the addition of the interaction term female*dysfunction produced a significant association between family dysfunction and CRP levels in female participants only. Interestingly, studies using female participants only (Powers et al., 2016; Boeck et al., 2016; Mitchell et al., 2018; Imai et al., 2018; Finy and Christian, 2018; Powers et al., 2019; Gouin et al., 2020; McCormack et al., 2021) most often presented non-significant associations between childhood trauma and inflammation, particularly dependent on the type of inflammatory marker and type of trauma. In addition, several other studies found no effect of participant sex on significance outcome; results remained the same even after adjusting for sex (Hostinar et al., 2015; Lin et al., 2016; Davis et al., 2019; Quidé et al., 2019; Pinto Pereira et al., 2019). Further research is needed to better understand potential sex differences in the impact of childhood trauma on inflammation in adulthood.

3.5. BMI as a mediator

In mediation analyses, Petrov et al. (2016) and Mitchell et al. (2018) found BMI to be a significant mediator for the relationship between childhood trauma and inflammation. Using a combined total score for the CTQ abuse subscales and an aggregated measure of inflammation, Petrov et al. (2016) reported a standardized indirect effect for BMI at $p < 0.01$. Comparing the different types of abuse and neglect from the CTQ subscales, Mitchell et al. (2018) found a significant indirect effect ($p < 0.05$) of BMI on associations between physical abuse and both CRP and IL-6 ($p < 0.05$). BMI also showed a significant total effect for emotional abuse and neglect ($p < 0.05$). Mediatory effects of BMI were not evident for physical neglect or sexual abuse. When adjusting for BMI in their analyses, Aas et al. (2017) and Powers et al. (2019) reported loss of previously significant associations between childhood trauma and inflammation. Results for Powers et al. (2019), however, should be approached with caution. Significance was lost after the simultaneous inclusion of several factors, including depressive symptom severity -a factor by which associations have also significantly differed. As such, we cannot assume loss of significance was attributed in isolation to the addition of BMI. Most studies accounting for BMI in their analyses contrarily found significance to remain for association between childhood trauma and inflammation in adulthood (Takizawa et al., 2015; Lin et al., 2016; Plant et al., 2016; Kraynak et al., 2019; Gouin et al., 2020).

3.6. Additional mediators

Studies outlined further potential mediators in the relationship between childhood trauma and inflammation in adulthood, however these were study-specific and thus no trends can be reported on. Additional factors shown to effect association are martial quality (Gouin et al., 2020), trust in a relationship (Grosse et al., 2016), frontal brain asymmetry (Hostinar et al., 2017), community belonging (John-Henderson et al., 2020), and geographical location (Li et al., 2015b).

3.7. Clinical characteristics

Trends were evident across studies, and types of inflammatory markers, for the role of clinical characteristics in the association between childhood trauma and inflammation in adulthood. Most frequently, studies reported difference in association between participants with major depressive disorder (MDD) and healthy controls (Grosse et al., 2016; Pedrotti Moreira et al., 2018; Munjiza et al., 2018; Müller et al., 2019; Ng et al., 2020). Where associations between childhood trauma and elevated levels of inflammatory markers were reported in these studies, significance was restricted to patients in the MDD group only. Toft et al. (2018) further found associations to be relative to the severity of depression; significant increase in TNFα in those with childhood trauma (compared to those without trauma) were only significant in participants with severe depression. Quidé et al. (2019) extended findings to other psychiatric disorders- schizophrenia and bipolar disorder – though effect of childhood trauma on inflammatory profiles in patients were dependent on type of inflammatory marker and type of childhood trauma.

With the predominant use of the CTQ as a measure of childhood trauma, studies consistently assessed trauma as '*any time before the age of 18*'; investigation of the potential differential effects of the age of trauma on inflammatory levels, and poor psychological and physical health outcomes, is therefore absent in these studies. Research has shown differential association with psychiatric health outcomes relative to timing of trauma; symptoms of emotional dysregulation, post-traumatic stress disorder and depression are shown to be higher in those exposed to trauma in earlier developmental stages (Dunn et al., 2017, 2018). However, investigation is sparse, particularly with regard to inflammatory associations. Considering the importance of biological and social developmental stages in childhood, age of abuse could mediate the association between childhood trauma, inflammation, and poor health outcomes. Investigation of the effect of age of trauma on inflammatory levels, and subsequent health outcomes in adulthood, could be a valuable addition to scientific research.

4. Discussion

Thirty-seven studies were assessed in this review, all of which were not included in the original review (Baumeister et al., 2016). The predominant finding was a non-significant association between childhood trauma and inflammation, with variation dependent on the different types of trauma and inflammatory markers assessed. Greatest consistencies in non-significant findings were predominantly evident in the relationship between childhood trauma and two specific inflammatory markers (TNFα and *IL*-1β). Greatest variations in significance status were predominantly reported for CRP and IL-6, where a larger number of significant findings emerged relative to individual trauma types and addition of mediatory variables. However, CRP and IL-6 were assessed in a larger number of studies ($n = 18$ and $n = 17$) than TNFα ($n = 10$) and *IL*-1β ($n = 5$), which could account for some of the variance. Number of articles assessing CRP, IL-6 and TNFα were near matches for those in the review we aimed to update (CRP, $n = 18$; IL-6, $n = 15$; TNFα, $n = 10$) (Baumeister et al., 2016). Contrasting with the predominant trends identified in the current review, Baumeister et al. (2016) additional meta-analysis concluded consistent significant elevation in levels of CRP, IL-6 and TNFα.

Both reviews found evidence for the differential effects of trauma types on inflammatory profiles in adulthood. Baumeister et al. (2016) found sexual and physical abuse to be significantly associated with TNFα and IL-6, but not CRP. In the current review, significant associations for sexual abuse were more often evident with IL-6 than TNFα and CRP, however significance was frequently dependent on clinical characteristics (only in MDD and SCZ patients.) This was also evident for the significant association between sexual abuse and TNFα, though this was not translated to CRP. Irrespective of this, Baumeister et al. (2016) found the proportion of patients with any psychiatric disorder did not moderate the associations between childhood trauma and CRP, or childhood trauma and TNFα. Contrasting with Baumeister et al. (2016) results, physical abuse was not significantly associated with TNFα, however, was significantly associated with CRP. Though some reports showed physical abuse to be associated with IL-6, findings were more often non-significant. Further discrepancies between the two reviews exist for the relationship between emotional abuse and CRP levels; Baumeister et al. (2016) found no significant associations, while some studies in the current review evidenced significant association between these variables. The sparsity of this finding, however, should be noted. In unison

with the previous review, we did find emotional abuse to be non-significantly associated with TNFα.

Though type of traumatic event has a frequent significant effect on inflammatory levels, this is less apparent for the additive effects of number of trauma types experienced. Where research investigating the effect of number of trauma types is sparse, the additive effects of traumatic events are inconclusive. Research does, however, indicate a linear elevation in inflammatory levels with an increasing number of traumatic experiences (Hostinar et al., 2015), and greatest effect with experience of three or more types of adversities when compared to one type of trauma (Hostinar et al., 2015; Aas et al., 2017). Interestingly discrepancies arise for effect of two types of trauma; Lin et al. (2016) found higher CRP in participants with two adversities when compared to those with one adversity, while Hostinar et al. (2015) found mean composite inflammatory levels (including CRP) to be lower in participants with two types of adversity comparative to one. Disparities could suggest the additive effect of traumatic events is dependent on the specific types of trauma experienced. Investigations, however, are predominantly restricted to CRP; future research should investigate the additive effect of traumatic events on additional inflammatory markers including IL-6, IL-1β and TNFα.

Regarding severity, the effects of trauma severity on inflammatory levels in adulthood are also inconclusive. In the current review, investigations of association for abuse severity are restricted to three studies (Takizawa et al., 2015; Powers et al., 2016; Boeck et al., 2016) highlighting the need for additional research in this area. Those studies assessing effect of severity presented inconsistent findings that may be attributed to the different types of trauma assessed. For investigation of bullying victimization, Takizawa et al. (2015) found victimization to associate with significant elevation in CRP when frequent but not occasional. Comparatively Boeck et al. (2016) found increase in CRP levels to be restricted to low-moderate trauma when assessing childhood abuse (emotional, physical and sexual) and neglect (emotional and physical). Isolated investigation of abuse, however, showed no translation for significant association (Powers et al., 2016). Caution is needed in drawing inference about the potential contribution of trauma type to the effect of abuse severity on inflammatory levels in adulthood; studies do not utilize a standardized categorization system for abuse severity – partially due to different measures of childhood trauma – limiting validity. Two studies also used small samples sizes (n = 30 and n = 40) (Powers et al., 2016; Boeck et al., 2016) with limited statistical power to detect association. Further research attending to these methodological limitations is needed for better conclusions to be drawn.

Studies investigating the mediatory role of BMI in the association between childhood trauma and inflammation found BMI to be a significant mediator in this relationship. Research shows higher BMI to be associated with greater exposure to chronic low-grade inflammation (Cooper et al., 2019) and has been known to affect cytokine levels in peripheral blood (Monteiro and Azevedo, 2010; Schmidt et al., 2015; Pitharouli et al., 2021). However, Baumeister et al. (2016) reported no moderating effect for BMI. Frequent adjustment for BMI across studies found no loss of significance, emphasising existence of a relationship between childhood trauma and inflammation irrespective of BMI.

Studies further found a mediatory role of clinical phenotypes in the association between childhood trauma and inflammation (Grosse et al., 2016; Pedrotti Moreira et al., 2018; Munjiza et al., 2018; Quidé et al., 2019; Müller et al., 2019; Ng et al., 2020). Significant associations between childhood trauma and inflammation were predominantly associated with IL-6 (Grosse et al., 2016; Pedrotti Moreira et al., 2018; Munjiza et al., 2018; Quidé et al., 2019; Müller et al., 2019; Ng et al., 2020), though this is partially due to more studies investigating IL-6 in these patients groups, when compared to TNFα, CRP and IL-1β. That being said, significant elevations in TNFα (Toft et al., 2018; Quidé et al., 2019) and CRP (Powers et al., 2016; Quidé et al., 2019) levels in adulthood, in relation to childhood trauma, were also evident. Associations between childhood trauma, CRP levels, and depression have been expanded upon in a recent study by Pitharouli et al. (2021). Assessing CRP levels in patients with lifetime depression compared with controls, this study found patients with depression to have higher CRP levels in adulthood than healthy controls (2.4 mg/L compared with 2.1 mg/L, respectively). Further to this, clinically significant CRP levels (>3 mg/L) were evident in more patients than controls (21.2% compared with 16.8%, respectively). When early life trauma was added as a covariate, association between depression and CRP was attenuated but remained significant. Results suggest early life trauma contributes to elevated CRP levels in adulthood, however pro-inflammatory profiles are evident in patients with psychiatric disorders irrespective of trauma history. Though excluded from the current review scope, another recent review extends association between inflammation and major depression to altered expression of genes belonging to the inflammatory system (Mariani et al., 2021). Though not relating to early life trauma, it is important to note that these inflammatory profiles have shown potential in predicting clinical outcome, though this was specific to psychosis (Kose et al., 2021). Further research also highlights the contribution of childhood trauma – specifically severity of trauma- to lack of antidepressant treatment response (Nikkheslat et al., 2020).

Aligned with previous research (Beilharz et al., 2020; Sweeney et al., 2015; Clemens et al., 2018; Agorastos et al., 2014; Noteboom et al., 2021; Ballard et al., 2015), the studies in this review predominantly focused on child abuse and neglect, using the CTQ as a measure of trauma. Consistent with statistics reporting a greater prevalence of childhood abuse in women (Elkin, 2020, January 14), the majority of the included studies reported gender distributions of 50–100% female. Reports on sex-specific effects of childhood trauma on inflammation in adulthood were inconclusive and predominantly showed no effect on significance when controlling for sex (Hostinar et al., 2015; Lin et al., 2016; Davis et al., 2019; Quidé et al., 2019; Pinto Pereira et al., 2019). Where sex-specific effects were evident, significant association between childhood trauma and inflammation occurred in females but not males (Baldwin et al., 2018; Kim et al., 2019). Where prevalence of childhood trauma may be greater in females, sex differences in the effects of trauma on inflammation are therefore less clear. Though not relating to childhood trauma, a recent systematic review (Lombardo et al., 2021) on sex hormones and the immune system in affective disorders, suggests testosterone in men may have protective factors in bipolar depression through anti-inflammatory effects. These anti-inflammatory effects of testosterone could contribute to the explanation for sex differences in inflammatory levels.

4.1. Strengths and limitations

Consistent use of the standardized CTQ as a measure of childhood trauma across the studies provides good reliability for findings. As a sensitive and valid screening questionnaire, the CTQ is a longstanding reliable and valid assessment tool for childhood trauma (Bernstein et al., 1997). With high internal consistency scores (Bernstein et al., 1997; Liebschutz et al., 2018), discrepancies when assessing individual subscales can more confidently be interpreted as differential effects of trauma type on inflammatory levels in adulthood. Davis et al. (2019) did however comment on their sole use of abuse subscales based on its tendency to present higher reliability than the neglect subscales, which could explain the consistencies in abuse associating with higher inflammation in adulthood more frequently than neglect. Consistent use of the CTQ may also isolate findings to specific types of trauma: abuse and neglect. Other studies utilizing alternate measures opened the investigation to other types of trauma, such as peer victimization (Takizawa et al., 2015; Baldwin et al., 2018), parental substance abuse (Hostinar et al., 2015; Li et al., 2015b; Lin et al., 2016; John-Henderson et al., 2020; Lacey et al., 2020), family mental health difficulties (Hostinar et al., 2015; Kim et al., 2019; John-Henderson et al., 2020; Lacey et al., 2020), and witnessing domestic violence (Li et al., 2015b; Baldwin et al., 2018; Kim et al., 2019; John-Henderson et al., 2020; Lacey et al.,

2020). Relating to this, Takizawa et al. (2015) was the only study to directly assess trauma outside of the family environment. Peer victimization should be more often investigated, given that schools are where children spend the majority of their time. Significant results across a large sample size (n = 7102) representing the general population suggests greater need to assess this trauma type.

To better understand trauma as a broad spectrum, more studies should utilize other standardized measures of childhood trauma, such as the ACE. Caution is needed when using these measures; Lacey et al. (2020) highlighted this in their comparative use of retrospective and prospective reports. Percentage difference in CRP levels in adulthood relative to childhood trauma differed between use of the ACE as a prospective or retrospective report. The most striking difference occured with parental substance misuse, where retrospective reports signified a 4.22% increase in CRP, while prospective reports indicated a 24.26% decrease in CRP. A recent study (Gayer-Anderson et al., 2020) comparing the CTQ and CECA in patients with psychosis and population-based controls found convergent validity to be dependent on type of trauma reported; for sexual and emotional abuse high convergent validity was evident, however for physical abuse reports with the CECA were high compared to reports on the CTQ.

With regard to sample size, studies reporting consistent significant findings tended to have larger sample sizes (n = 770–11,198). Though there are exceptions to this rule (with smaller sample studies reporting on mixed significance), studies with larger samples sparsely reported non-significant associations. The only exception was Li et al. (2015b) who found significance to be dependent on the city participants were sampled from. A collective of studies reporting consistent non-significant findings used sample sizes below 100 (range n = 30–85) (Powers et al., 2016; Boeck et al., 2016; Plant et al., 2016; Kim et al., 2019) and thus likely had limited power to detect significant effects. Generalisability of these non-significant results is therefore also limited. Irrespective of this, the majority of studies addressed in this review have adequate sample sizes that were taken from the general population. Distribution of study populations across different countries and communities strengthens generalisability of findings and addresses potential concern for cultural bias.

5. Conclusion

This review of studies between February 2015 and July 2021 found trend of predominantly non-significant associations between childhood trauma and inflammation in adulthood. Assessment of individual trauma types and the inclusion of mediatory variables found discrepancies in results; discrepancies in significance arose when considering type of trauma, type of inflammatory marker, and additional factors such as BMI, sex, and clinical phenotypes. Findings may suggest the effects of childhood trauma on inflammation may exist through mediation of other variables and may have implications for identification of, and early clinical intervention for, subpopulations at higher risk of chronic inflammation and poor health outcomes following exposure to childhood trauma. Examples include female patients and patients with obesity (Baldwin et al., 2018; Mitchell et al., 2018). As such, some studies have therefore discussed the need for target intervention strategies for these higher risk populations. Suggested strategies include a combination of direct targets of early trauma (such as psychological therapies and community-based interventions in communities vulnerable to family conflict) (Petrov et al., 2016; Baldwin et al., 2018), biobehavioural and lifestyle treatments for indirect target of inflammatory regulation (i.e., physical activity, sleep improvement, and healthy diet) (Petrov et al., 2016; Baldwin et al., 2018), and anti-inflammatory medication for direct treatment of inflammation (Baldwin et al., 2018; Munjiza et al., 2018). In considering clinical implication however, it is important to note that the review has concluded inconsistent associations and thus suggested clinical applications require further research. As an additional concern, many studies in the current review were restricted by use of the CTQ as a measure of childhood trauma. To assess greater variety of trauma types, future studies should utilize other standardized measures to explore these avenues.

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