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The association of child maltreatment and systemic inflammation in adulthood: A systematic review

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Abstract

Introduction: Child maltreatment (CM) is associated with mental and physical health disorders in adulthood. Some studies have identified elevated markers of systemic inflammation in adult survivors of CM, and inflammation may mediate the association between CM with later health problems. However, there are methodological inconsistencies in studies of the association between CM and systemic inflammation and findings are conflicting. We performed a systemic review to examine the association of CM with systemic inflammation in adults.

Methods: A systematic review was performed following PRISMA . Medline, Embase, Scopus and PsychInfo were searched for studies of the association of CM with blood markers of inflammation in adults. Quality was assessed using the Crowe Critical Appraisal Tool. We had intended to perform a meta-analysis but this was not possible due to variation in study design and reporting.

Results: Forty-six articles met criteria for inclusion in the review. The most widely reported biomarkers were C-Reactive Protein (CRP) (n=29), interleukin-6 (n=25) and Tumour Necrosis Factor-alpha (TNF-a). Four studies were prospective (all relating to CRP) and the remainder were retrospective. 85% of studies were based in Western settings. In the prospective studies, CM was associated with elevated CRP in adulthood. Results of retrospective studies were conflicting. Methodological issues relating to the construct of CM, methods of analysis, and accounting for confounding or mediating variables (particularly Body Mass Index) may contribute to the uncertainty in the field.

Conclusions: There is some robust evidence from prospective studies that CM is associated with elevated CRP in adulthood. We have identified significant methodological issues in the literature and have proposed measures that future researchers could employ to improve consistency across studies. Further prospective, longitudinal, research using robust and comparable measures of CM with careful consideration of confounding and mediating variables are required to bring clarity to this field.

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Introduction

Childhood maltreatment (CM) is common worldwide[1, 2]. Studies have consistently shown CM, particularly multiple and cumulative exposures, to be associated with a range of adverse physical, psychological, and social outcomes[1-6]. That this association persists after adjustment for environmental and behavioural factors suggests underlying biological mechanisms which may mediate the relationship between CM and health and social outcomes in later life[2, 7]. Understanding the biological correlates of CM will help to clarify the mechanisms linking CM with adverse outcomes, and offers the prospect of enhanced risk stratification of young people who have been subject to maltreatment and may identify new treatment targets to break the link between childhood experiences and adverse physical and mental health outcomes in adulthood[2].

Low-grade systemic inflammation is generally defined as 2-3 fold elevations in inflammatory markers like C-reactive protein (CRP), Interleukin-6 (Il-6) and tumour necrosis factor alpha (TNF-a)[8]. This represents a chronic low-level activation of the immune system (likely representing excessive sensitivity to inflammatory stimuli and deficiencies of the anti-inflammatory pathways which would normally terminate such responses) and is distinguished from high-grade inflammatory states with markedly elevated inflammatory markers such as occurs in acute infections, severe illnesses, and auto-inflammatory diseases. Low-grade, systemic inflammation has been identified in adult survivors of CM[9].

Inflammation and physical health disorders

Low-grade inflammation has been associated with a range of physical health conditions such as cardiovascular disease and diabetes[10, 11]. Notably, a large body of work has associated low-grade elevations in CRP with cardiovascular events - however subsequent work has questioned the direction of causality in this relationship[12]. Other inflammatory markers have been associated with cardiovascular disease, particularly Interleukin-6[10]. A large international study using Mendelian randomisation techniques has supported a causal relationship between elevated levels of Il-6 and cardiac disease[10]. Further supporting evidence for the role of low-grade inflammation in cardiovascular disease is provided by the recent CANTO trial of the specific Il-1b antagonist Canakinumab which was shown to reduce rates of myocardial infarction, stroke and death in patients

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treated following an MI with elevated CRP[13].

Inflammation and mental health disorders

Low-grade inflammation is also associated with a range mental health disorders. A wide body of work has associated major depressive disorder with low-grade elevations in inflammatory markers like CRP, Il-6, and TNF-a[14, 15]. The neurobiological effects of peripheral cytokines may mediate the relationship between external stressors and depression[14]. Low-grade inflammation is also associated with conditions like post-traumatic stress disorder (PTSD), schizophrenia, and bipolar affective disorder[8, 16]. A recent Mendelian randomisation analysis has suggested a causal relationship between CRP and both schizophrenia and bipolar affective disorder[16].

Inflammation and child maltreatment

An emerging body of evidence, therefore, has shown that low-grade systemic inflammation is associated with physical and mental health disorders and that this relationship is at least partially causal. Although it is known that CM is associated with low-grade, systemic inflammation [9], previous reviews have identified significant heterogeneity in the literature particularly in relation to the definition and ascertainment of CM [17, 18]. Studies have offered varying definitions of CM ranging from narrowly focused childhood physical or sexual abuse, to more broadly defined Adverse Childhood Experience (ACEs)[17, 18]. These differing patterns of CM will likely have different effects on development, contributing to the heterogeneity in the literature. Furthermore, research in this area has highlighted the role of potential mediators between CM and inflammation (particularly body mass index (BMI)) and raise questions about the causality of this relationship that were not fully addressed in previous reviews[19, 20]. In this light, this current review aimed to examine the association between CM and systemic inflammation in adulthood, with particular consideration of the causality of this relationship.

Methods

We performed a systematic review of the association between CM and low-grade inflammation. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were

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90 followed[21]. The search and synthesis plan were pre-specified in a protocol registered with
91 PROSPERO (CRD42020187027).

92 Research questions

93 Our primary research question was: “Is CM associated with elevated markers of systemic
94 inflammation adulthood?”. We also prespecified secondary questions: “Are differences in later life
95 inflammation associated with specific sub-types, timings, or durations of abuse?” and “What mediates
96 any association between CM and inflammation?”

97 Inclusion criteria

98 We included non-randomised observational studies. Our study population was human adults (>18
99 years of age). Participants could be drawn from healthy samples or clinical (mental or physical health
100 disorder) samples, however we excluded studies of participants with pro-inflammatory physical health
101 conditions (in particular autoimmune disease and cancer). Participants could be drawn from
102 community or hospital-based samples.
103 Our exposure was CM (defined as physical abuse, sexual abuse, emotional abuse, physical neglect
104 and/or emotional neglect occurring at least once before the age of 18). We did not place any
105 restrictions on how CM was recorded. Studies could use retrospective or prospective ascertainment;
106 and could record CM using validated scales, or specific measures developed for their study if this was
107 described. CM could be reported as an overall construct or broken down into sub-types of abuse and
108 neglect. Studies could compare between a CM exposed group and a control group or utilise a
109 continuous measure of CM in a sample.
110 Our outcome was blood levels of inflammatory markers. Any marker of the inflammatory response
111 measured in the blood was eligible for inclusion. We excluded studies which reported on stimulated
112 responses (e.g. to stress testing or biological stimulation), studies reporting exclusively on gene
113 expression, *in vitro* production of inflammatory mediators, and studies exclusively measuring
114 inflammation in the central nervous system (e.g. CSF).

115 Search strategy

116 We searched MedLine, Embase, PsychInfo, and Scopus. Our first search term aimed to capture CM.
117 This included MeSH terms “child abuse”, “child abuse, sexual”, “adult survivors of child abuse”,

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"physical abuse", "child, abandoned", "adolescent, institutionalized", "adult survivors of child adverse events" and "adverse childhood experiences", supplemented by title and abstract searches for related terms. The second term sought to identify broadly defined inflammatory dysfunction. This included MeSH terms "inflammation", "C-reactive protein", "acute phase proteins", "tumour necrosis factor alpha", "interleukins", "cytokines", "immune system", "fibrinogen", "leukocytes", and "lymphocytes". This was supplemented by title and abstract searches for related terms.

These terms were combined using the Boolian operator "AND", and duplicates were removed.

The search was adapted to utilise relevant keywords in the other databases used and full information is available in S1 file.

This search was supplemented by manual checking of reference lists of retrieved articles and checking the reference lists of previous reviews in this area.

Methods of review

Records were initially screened against inclusion criteria by 1 reviewer, and a 2nd reviewer independently reviewed a sub-sample of 25% of titles. All included articles were then reviewed by a 2nd reviewer to confirm that they met inclusion criteria. Disagreements were resolved through conference with a 3rd author.

Risk of bias assessment was performed at study level using the Crowe Critical Appraisal Tool v1.4 (https://conchra.com.au/wp-content/uploads/2015/12/CCAT-form-v1.4.pdf). This is a tool for assessment of risk of bias in non-randomised studies. Key components of risk of bias assessment include sampling, ascertainment of exposure, measurement of outcome, and statistical analysis including adjustment for relevant confounding variables. The CCAT assigns a total score from 0-40. According to the tools guidelines studies can be categorised as low quality (<20), moderate quality (20-29), and high quality (30+). All papers were rated by 1 reviewer, and the 2nd reviewer independently quality rated a sub-sample of 25% of papers. Again, disagreements were resolved through conference with a 3rd author.

Data extraction was performed using a pre-specified form. Data extraction was performed by 1 reviewer, with a 2nd reviewer independently performing data extraction for a sample of 25% of included papers.

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Synthesis

We had intended to perform a meta-analysis of the most widely reported inflammatory markers as specified in the protocol. A more detailed review of included articles showed that this was not feasible due to differences in the construct of CM being utilised, incommensurable methods of analysis and inconsistent accounting for covariates. This is discussed further below. These challenges led us to conclude that a meta-analysis would be of questionable validity. We have instead presented our findings in a narrative format with focus on the most widely reported inflammatory markers, and methodological factors.

Results

The PRISMA flow chart is shown in figure 1. Details of reasons for exclusion of articles are shown in S1 table. A total of 46 papers were included in this review. All papers were rated as moderate to high quality (CCAT scores ranged from 23-38, median- 32). 30 papers reported on multiple biomarkers. The frequency with which biomarkers were reported is shown in table 1. The most widely reported biomarkers were CRP (n=29), interleukin-6 (n=25), and TNF-a (n= 16). Details of these are discussed below. Details of other biomarkers reported are shown in S2 table.

Figure 1- PRISMA Flow Diagram

Table 1- Frequency with which biomarkers are reported in included studies

Biomarker	Number of studies
C-reactive protein (CRP)	29
Interleukin 6 (Il-6)	25
Tumour necrosis factor alpha (TNF-a)	16
Interleukin 1b (Il-1b)	8
Interleukin 10 (Il-10)	6
Fibrinogen	5
Soluble tumour necrosis factor receptor 1 (sTNFR1)	3
Soluble tumour necrosis factor receptor 2 (sTNFR2)	2
Adiponectin	2
Brain derived neurotrophic factor (BDNF)	2
Interferon gamma (IFN-y)	2
Interleukin-4 (Il-4)	2
Resistin	2
Transforming growth factor beta (TGFB)	2
White cell count (WCC)	2
Interleukin 2 (Il-2)	1
Interleukin 8 (Il-8)	1
Interleukin 12 (Il-12)	1
Interleukin 1 receptor antagonist (Il-1RA)	2
Soluble interleukin 6 receptor (sIl-6R)	1
Agouiti related protein (AgRP)	1
Basic fibroblast growth factor (bFGF)	1

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Betacellulin (BTC)	1
Cell-mediated immunity (EBV titre)	1
Chemokine Ligand-2 (CL-2)	1
D-Dimer	1
E-Selectin	2
Glucocorticoid induced tumour necrosis factor ligand (GITR-L)	1
Glycoprotein 130	1
Insulin-like growth factor-binding protein 2 (IGFBP2)	1
Interferon induced T-cell alpha chemoattractant (I-TAC)	1
Monocyte chemoattractant protein 1 (MCP-1)	1
Mucosae-associated epithelial chemokine (MEC)	1
Neurotrophin-4	1
Platelet derived growth factor (PDGF)	1
Salivary alpha amylase (sAA)	1
Stem cell factor (SCF)	1
Soluble intracellular adhesion molecule 2 (sICAM2)	1
Soluble immunoglobulin A (sIgA)	1
Thymus expressed chemokine (TECK)	1
Tumour necrosis factor related apoptosis inducing ligand-receptor 4 (TRAIL-R4)	1
Vascular endothelial growth factor (VEGF)	1
Von Wilebrand Factor (vWF)	1

Methodological features

Over 90% (n= 42) of the 46 included studies recorded CM exposure retrospectively, with the Childhood Trauma Questionnaire (CTQ) being the most widely reported scale (n=29). CTQ is a 28-item self-report measure of childhood trauma, which can be considered as a total score, or as subscales representing physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse[22]. Of papers utilising the CTQ, 13 reported only on the total score, 8 reported on subscales only, and 8 reported on both. 13 papers reported on the CTQ as a dichotomous variable (using a recognised cut-off point to define high versus low scores) and 16 analysed CTQ as a continuous variable. The remaining studies utilised their own measures of CM based on their dataset (n=9) or other standardised scales (n=8). After CTQ the most widely used standardised scale was the Early Trauma Inventory (ETI)[23]. This is a 56-item self-report scale which generates 5 variables- total number of traumas, physical trauma, emotional trauma, sexual trauma, and general traumas. General trauma includes a range of adverse exposures including parental separation, bereavement, natural disaster, and political violence. Most studies did not specify the timing or duration of CM in their analysis.

There was significant variation in statistical techniques used and where multivariate analysis was performed there was inconsistency as to which covariates were included. Eighty-five percent (n=39) of the studies were conducted in Western settings (North America, Europe, Australasia), with the

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183 remainder taking place in Brazil (n=4), China (n=2), and Japan (n=1). Ten studies were restricted to

184 female participants, and one was restricted to males.

185 C-reactive protein

186 The association between CM and CRP was reported in 29 papers (full details in table 1a and 1b).

187 Nine reported on clinical samples and 20 on non-clinical samples.

188

Table 1a: Papers reporting CRP: Clinical populations

Author	Sample details	Sample Size	Sample demographics	Abuse measure	CCAT score	Main findings
Aas 2017 [29]	Participants in TOPS study of psychotic disorders in Oslo Norway. Consecutively recruited outpatients with schizophrenia and bipolar disorder and matching controls	483	Schizophrenia: Age= 28.6 (9.3) Female= 55 (41.0%) Bipolar Disorder Age= 32.2 (11.7) Female= 73 (59%) Control: Age= 30.9 (7.5) Female= 86 (41%)	CTQ- analysed as number of types of abuse/neglect.	36	Abuse severity was associated with CRP and BMI. On ANCOVA significant effect of abuse severity for elevated but this was non-significant after BMI was added to the model.
Counotte 2019 [24]	Participants in a study of participants with psychotic disorders, ultra-high risk for psychosis (UHR), unaffected siblings, and controls, in the Netherlands.	117	Psychosis Age= 25.5 (23-30) Male= 6 (15.8%) UHR Age= 24.0 (20-29) Female= 6 (54.5%) Siblings Age= 25.5 (21.3- 30.0) Female= 12 (41.4%) Controls: Age= 24.0 (21.0-26.0) Female= 21 (53.8%)	CTQ- dichotomised; total and sub-components	38	No significant association of CTQ with CRP in models which adjust for age, sex, BMI, smoking, drug use, and education.
Fanning 2015 [30]	Community recruited participants with and without personality disorder in a larger study about the correlates of impulsive aggression in Chicago USA	134	Personality Disorder Age= 36.0 (7.7) Female= 38 (48.1%) Control: Age- 31.9 (9.2) Female= 30 (54.5%)	CTQ- separated to abuse and neglect sub-components; continuous analysis.	30	Abuse but not neglect was correlated with CRP in an unadjusted analysis.
Hepgul 2012 [31]	Inpatients with first episode psychosis (FEP) and healthy controls in the UK. Participants had no significant physical illnesses.	195	FEP Age= 27.0 (0.6) Female= 60 (57.5%) Controls: Age= 26.3 (0.6) Female= 67 (32.3%)	CTQ- dichotomous; total and subcomponents	33	In an unadjusted comparison of patients with and without CM, and controls there was a non-significant trend towards higher CRP in patients with a history of CM. There were significant difference in CRP when grouped by sexual abuse with the highest CRP level in the group of patients exposed to sexual abuse.
Imai 2008 [25]	Female outpatients with PTSD and matching controls in Japan.	40 (participants with PTSD)	Age= 38.3 (10.1) Female= 100%	CTQ- total; continuous	37	No correlation of CTQ (total or subscales) with CRP in an unadjusted analysis

	Participants had no significant physical illnesses. Analysis of inflammation and abuse only included the PTSD group.					
Palmos 2019 [26]	Participants retrieved from 2 studies. Controls recruited from SeLCoH study of mental and physical health in the general population in London. MDD participants recruited from the control arm of the ADD trial of metyrapone in depression. Participants had no other mental or physical illnesses.	465	MDD: Age= 48.50 (16.14) Female= 79 (48.1%) Control Age= 48.50 (16.14) Female= 158 (52.5%)	CTQ total score; dichotomised	37	No significant association of CM with CRP in model adjusted for age, gender, ethnicity, smoking and BMI.
De Punder 2018 [28]	Patients with depression were recruited from an affective disorders clinic and controls from public advertisements. Participants did not have other mental or physical illnesses. Neither patients or controls taking psychotropic medications. Study in Berlin Germany	86	MDD and CM Age= 38.09 (11.36) Female= 14 MDD no CM Age= 32.61 (11.74) Female= 18 Control and CM Age= 38.09 (11.36) Female= 14 Control no CM Age= 33.9 (9.77) Female= 13	ETI- Dichotomised	31	Significant difference in CRP between groups which attenuated to non-significance after adjusting for BMI and smoking.
Quide 2019 [32]	Participants were outpatients with schizophrenia/ schizoaffective disorder, bipolar disorder, and healthy controls from Austrailia. All aged 18-65 with no significant physical illnesses	209	Schizophrenia: Age= 41.78 (11.33) Female= 29 Bipolar Disorder: Age= 38.11 (12.31) Female= 46 Control: Age= 36.17 (11.57) Female= 34 BMI not noted.	CTQ- Sub-components; continuous	35	No association of maltreatment with CRP in control or bipolar group. In schizophrenia group significant association of sexual abuse and CRP in a model also significant for sex and anti-psychotic dose. No other significant associations of abuse sub-types in schizophrenia group. All analyses were unadjusted..
Zeugmann 2013 [27]	Inpatients with MDD in Germany.	25	Age= 47.8 (15.02) Female= 17 (68%)	CTQ- subcomponents; continuous	31	No association of CTQ with CRP in an unadjusted analysis.

Table 1b Papers reporting CRP: Non-clinical populations

Author	Sample details	Sample Size	Sample demographics	Abuse measure	CCAT score	Main findings
Anderson 2018 [36]	Mothers of participants in the ALSPAC longitudinal cohort in Bristol, UK. Mothers were invited to participate an average of 18 years after enrolment in the study.	3612	Age= 48.13 (4.35) Female= 100%	Childhood adversity variables were extracted from questionnaire items administered earlier in course of cohort, and combined using factor analysis. The paper includes wider measures of childhood adversity, of relevance to this review are data on sexual abuse and non-sexual abuse (physical, abuse, and emotional abuse and neglect).	33	No association of sexual or non-sexual abuse with CRP in model which adjusted for age at assessment, socioeconomic status, ethnicity, and BMI. No association of cumulative adversity with CRP.
Baldwin 2018 [33]	E-Risk twin study, a longitudinal birth cohort of twins born in England and Wales in 1994-1995. Outcomes assessed at age 18.	1789..	Age= 18.4 (0.36) Female= 912 (51%)	Childhood Victimisation- Prospectively collected data on physical abuse and neglect, emotional abuse and neglect and exposure to domestic violence.	36	Greater exposure to childhood victimisation associated with higher CRP in total sample. This was driven by female participants. On gender stratified analysis effect was significant in females only. Remained significant after adjusting for SES, waist-hip ratio, and latent genetic risk score.
Bertone-Johnstone 2012 [47]	Participants in Nurses Health Study II. A cohort of female nurses in USA recruited in 1989. A sub-sample was invited to provide blood samples between 1996-1999.	702.	Age= 48.9 (SD not reported) Female= 100%	Physical abuse- Adapted Revised Conflict Tactics Scale. Sexual abuse- Adapted Sexual Experiences Survey	33	Elevated CRP was associated with adolescent SA only in models adjusted for age, ethnicity, and SES. Association non-significant after adjustment for BMI. There was no association with PA.
Boeck 2016 [43]	Cohort study of new mothers recruited in Ulm Germany. Participant had no mental or physical health problems. Bloods collected 3 months post-partum	30	Age= 31.6 (6.0) Female= 100%	CTQ- total and subcomponents; dichotomised	35	CM not associated with CRP on adjusted or unadjusted analyses.
Carpenter 2012 [37]	Sub-sample of a larger cohort study of stress and biomarkers based in Providence USA. Participants were community based with no history of mental or physical health problems.	92	Age= 30.5 (9.2) Female= 47 (51.1%)	CTQ- total and subcomponents; continuous.	35	No correlation between CTQ (total or sub-components) and CRP.
Danese 2007 [9]	Participants in longitudinal cohort study in Dunedin New Zealand. Bloods collected at visit at age 32.	892.	Age= 32 Female= 435 (48.8%)	Prospectively recorded childhood maltreatment including parental rejection and harsh discipline, and retrospective report of physical and sexual abuse.	35	CM associated with elevated CRP, in unadjusted analyses and models adjusting for childhood confounders, and adult health and behaviour, including overweight.

Finy 2018 [19]	Pregnant woman recruited in Ohio USA. Participants were physically healthy.	214	Age= 29.38 (4.93) Female= 100%	CTQ- subscales of physical abuse, sexual abuse, and emotional abuse; continuous	35	CTQ score was positively correlated with CRP. In structural equation models childhood abuse had a significant indirect effect on CRP, which was mediated by BMI.
Gong 2019 [38]	Study of Chinese University students exploring association of schizotypal personality traits, childhood abuse, and CRP. Participants had no physical or mental illnesses or family history of mental illness.	224	Age= 18.86 (0.86) Female= 74 (33%)	CTQ- total and subcomponents; continuous	31	Analyses were stratified by gender. No correlation between total CTQ or subscales with CRP in males or females in an unadjusted analysis.
Gouin 2012 [39]	Participants in a study of stress in older adult dementia caregivers in Canada. Participants excluded if had illnesses which affect immune system, or BMI >40.	130	Abused Age= 62.47 (12.07) Female= 46 (80.7%) Non-Abused Age= 67.2 (13.74) Sex= 61 (83.5%)	CTQ- total (excluding physical neglect); dichotomised	35	No association of abuse with CRP in a model adjusting for age, sex, ethnicity, education, BMI, marital status, sleep disturbance, and caregiving status.
Hartwell 2013 [40]	Control group in a larger study on gender differences in stress responses in cocaine dependency in South Carolina USA. Participants were non-cocaine using controls with no mental or physical illnesses.	39	Age= 35.69 (12.0) Female= 20 (51.3%)	ETI- Number of traumas	36	There was no association of ETI with CRP in a model adjusted for gender and smoking status.
Kim 2019 [41]	Healthy students at a university in Texas USA.	85	Age=21.0 (no SD) Female= 61 (71.7%)	ACEs questionnaire- specific analyses based on items on abuse and neglect	29	No significant association of abuse or neglect with CRP in unadjusted analysis and analysis adjusted for age, gender, ethnicity, parental education, depressive symptoms and perceived stress.
Matthews 2014 [20]	Participants in the Pittsburgh site of the SWAN cohort study of menopause and aging.	326	Age= 45.7 (2.5) Female= 100%	CTQ- total and subcomponents; dichotomised	37	SA, EA, EN, PN, and total number of abuse types were associated with higher CRP over 7 years adjusting for age, race, education, smoking status, medications, cardiovascular disease, hormone therapy and depressive symptoms. Generalised estimating equations showed that emotional and sexual abuse, physical neglect, and total numbers of types of abuse related to CRP through BMI. Emotional abuse and neglect related to CRP independent of BMI.
Nikulina 2014 [35]	Prospective cohort study of court substantiated cases of child neglect and matching controls from a midwestern city in the USA. Cases were recruited between 1967-1971.	528	Age= 41 (no SD) Female= 269 (51%)	Court substantiated cases of child neglect	29	Overall no significant association of childhood neglect with CRP in a model that adjusted for BMI. Significant interaction by race with increased CRP associated with neglect in white ethnicity only.
Osborn 2019 [34]	Offspring of participants of a longitudinal cohort of abuse/neglect in Midwestern USA. The primary aim of this study was to assess the	443	Age= 23.4 (5.23) Female= 215 (48.5%) BMI not reported	Prospective- CPS documentation. Retrospective- LONGSCAN and Conflict Tactics Scale.	30	Prospective maltreatment was significantly associated with elevated CRP. When analysed by abuse type this was only significant for physical abuse. No retrospective measure was associated with CRP.

	agreement between prospective and retrospective measures of maltreatment, and how these predict CRP.					
Pinto Pereira 2019 [45]	1) 1958 British Birth Cohort (BBC): A longitudinal cohort of all born in one week in 1958. Bloods collected at visit age 45. 2) Midlife in United States (MIDUS): Cohort of adults 25-75 in USA recruited in 1994-1995. 2nd wave of data collection (MIDUS-II) followed up original sample 10 years later.	British Birth Cohort= 7661 MIDUS= 1255	British Birth Cohort: Age= 45.2 (44.3-46.0) (mean and range) Female= 3828 (50%) MIDUS Age - Male= 57.9 (36-86) - Female= 56.9 (35-86) Female= 713 (56.8%)	Physical, emotional and sexual abuse; emotional neglect and physical neglect (British Birth Cohort only). Derived from study questions. All measures retrospective except from prospective record of neglect in British Birth Cohort.	25	In linear regression adjusted for age, race, gender, and other types of abuse; physical abuse was associated with increased CRP in BBC but not MIDUS. The association of physical abuse and CRP in BBC attenuated to non-significance after adjusting for BMI. Other forms of maltreatment were not associated with CRP in either sample.
Powers 2016 [42]	Participants were a subgroup with type 2 diabetes drawn from a larger study of risk factors for PTSD in low socioeconomic status urban African-American women in Atlanta Georgia.	40	Age= 51.88 (7.57) Female= 100%	CTQ- total; continuous	30	CM was not correlated with CRP in an unadjusted analysis.
Rooks 2012 [48]	Male middle aged twins born between 1946-1956 from the Vietnam Era Twin Registry in USA.	482	Age= 55(3) Female= 0	ETI- total; continuous	32	Trauma exposure was associated with increased CRP. When adjusted for obesity relationship attenuated to non-significance.
Schrepf 2014 [49]	Participants in MIDUS-2 biomarker project in USA.	687	Age= 52.2 (10.9) Female=56% BMI not stated	CTQ- subcomponents; continuous	31	CRP was correlated with emotional abuse, physical abuse, and physical neglect. No significant correlation with sexual abuse or emotional neglect. Analysis was unadjusted.
Slopen 2010 [46]	Participants in MIDUS cohort in USA	999	White Participants (n=822): Age= 58.66 (11.65) Female= 52.8% BMI= 29.14 (5.95) African-American Participants (n=177): Age= 54.15 (10.71) Female= 67.23% BMI= 33.35 (8.89)	Early life adversity questionnaire	33	No association of early life adversity with CRP in analysis adjusted for age, gender, ethnicity, cardiovascular disease, and BMI.
Thurston 2017 [44]	Participants in the MsHeart study of peri- and post-menopausal women aged 40-60 in Pitsburgh USA. Excluded if history of signficiant physical illness	286	Abuse/Neglect Age= 53.68 (4.11) Female= 100%) No abuse/neglect Age= 54.28 (3.90) Female= 100%	CTQ- total and subcomponents; dichotomised	29	No association of CM with CRP in unadjusted analysis.

Table 1 Legend: BMI- Body mass index, CM- Child Maltreatment, CRP- C-reactive protein, CTQ- Childhood Trauma Questionnaire, EA- Emotional abuse, EN- Emotional neglect, ETI- Early Trauma Inventory, FEP- First Episode Psychosis, MDD- Major Depressive Disorder, PA- Physical abuse, PN- Physical abuse, SA- Sexual abuse, UHR- Ultra-high risk

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All papers reporting clinical samples were retrospective and all but one used CTQ to record CM. Four studies did not find any association between CM and CRP[24-27]. A further two studies found initially significant associations between CM measures and CRP, which attenuated to non-significance on adjustment for BMI[28, 29]. Significant associations between CM with CRP were reported in three studies. In a study comparing 79 participants with personality disorder and 55 healthy controls Fanning et al demonstrated a significant association between abuse and CRP, as measured retrospectively using the CTQ, but not neglect, in a bivariate correlation which did not adjust for covariates[30]. In a sample of 96 participants with first episode psychosis and 99 healthy controls, Hepgul *et al* found a trend towards elevated CRP in patients who had experienced CM, but this only reached statistical significance when participants were grouped by exposure to sexual abuse and, again, did not adjust for covariates[31]. In a study of 209 participants with schizophrenia/schizoaffective disorder, bipolar affective disorder and healthy controls, Quide et al demonstrated a significant association between sexual abuse and elevated CRP in schizophrenia patients only[32]. No other associations of CRP with other abuse sub-types or in different clinical groups was demonstrated. The analysis adjusted for age, gender, disease severity, and medication use, but did not adjust for BMI.

Of 20 studies examining the association between CM and CRP in non-clinical samples, 16 were retrospective and four prospective. The four prospective studies found significant associations between CM and elevated CRP. In a prospective twin study, Baldwin et al reported an association between CM and elevated CRP at age 18[33]. On stratified analysis this effect was significant in females only and remained significant after adjusting for covariates including waist-hip ratio. Osborn et al reported on the association between retrospective and prospective measures of CM with CRP[34]. They found that CRP was associated with prospective measures of abuse only. Of note their analysis adjusted for age, sex, ethnicity, parental occupation, heavy drinking, smoking, and depression but did not adjust for BMI. Danese et al reported on a large prospective cohort in New Zealand that measured CM using a combination of prospective and retrospective reports[9]. They demonstrated a significant association between CM and CRP which remained significant in extensively adjusted models, including adjustments for adult health behaviours and obesity. They estimated that 10% of low-grade inflammation as measured by CRP may be independently attributable to CM. Nikulina et al report a US cohort exposed to court substantiated neglect and

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controls matched for age, sex, ethnicity, and socioeconomic status. In a model adjusting for BMI there was no significant association between neglect and CRP in the total sample, however the study did identify a significant interaction with race (authors' terminology)- wherein neglect was associated with elevated CRP in white participants only[35]. Their analysis considered family poverty as a covariate in this analysis, but it did not reach significance threshold for inclusion in the final model.

Of the 16 retrospective studies in non-clinical samples, nine studies found no significant association between child maltreatment and CRP[36-44]. A further 4 found initially significant associations which attenuated to non-significance on adjustment for BMI[45-48]. Finy et al report a study of 214 pregnant women (of whom 51.4% were overweight or obese) in which they reported small but statistically significant associations of CTQ score with CRP[19]. Through structural equation modelling, this association was found to be indirect and mediated by elevated BMI. Similarly, Matthews et al in a middle-aged female sample, found that sexual abuse, physical neglect and total number of abuse types were associated with elevated CRP in a relationship mediated by elevated BMI. They also found that emotional abuse and neglect were independently associated with elevated CRP[20]. Schrepf and colleagues, in a study of 687 participants in the MIDUS-II biomarker project found that CM was significantly associated with elevated CRP in adulthood in a relationship that was mediated by elevated BMI. They found that this relationship was mediated by a latent distress measure which was associated with using food as a coping mechanism. The association between BMI and CRP was stronger in females than males[49].

To summarise an association between CM and later elevation of CRP was demonstrated in four prospective studies in non-clinical samples, which adjusted for relevant covariates (however one did not adjust for BMI). Most retrospective studies (13/16) found either no association of CRP with BMI or an association which attenuated to non-significance on adjustment for BMI or other obesity measures. Three studies found a significant association of CM with CRP, all of which found that this to be mediated by elevated BMI.

Interleukin-6

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245 The association between CM and Il-6 was reported in 25 papers, 15 of which were based on clinical
246 samples. Details of included papers are shown in tables 2a and 2b. All papers utilised retrospective
247 measures of CM. Nineteen papers used CTQ to measure CM.

248

Table 2a- Studies reporting interleukin-6: Clinical populations

Author	Sample Characteristics	Sample Size	Sample Demographics	Maltreatment Measure	CCAT Score	Main Findings
Corsi-Zuelli 2020 [50]	Participants in the STREAM Cohort of patients with first episode psychosis, unaffected siblings, and healthy controls in Sao Paulo Brazil.	422	FEP: Age= 30.8 (12.5) Female= 37% Siblings: Age= 30.7 (10.5) Female= 68.4% Controls: Age= 31.3 (11) Female= 48.6%	CTQ- subcomponents; dichotomised	35	In analyses adjusted for age, gender, BMI, smoking, substance use, education, and relationship status, no significant association of interleukin-6 with any subcomponent of abuse or neglect.
Counotte 2019 [24]	Participants in a study of participants with psychotic disorders, ultra-high risk for psychosis, unaffected siblings, and controls, in the Netherlands.	117	Psychosis Age= 25.5 (23-30) Male= 6 (15.8%) UHR Age= 24.0 (20-29) Female= 6 (54.5%) Siblings Age= 25.5 (21.3- 30.0) Female= 12 (41.4%) Controls: Age= 24.0 (21.0-26.0) Female= 21 (53.8%)	CTQ- total; dichotomised	38	No significant effect on CTQ on any inflammatory marker in models which adjust for age, sex, BMI, smoking, drug use, and education.
Dennison 2012 [54]	Patients with schizophrenia in Cork Ireland recruited from outpatient and inpatient settings. Controls recruited from local university.	80	Schizophrenia Age= 38.33 (1.7) Female= 16 (40%) Controls: Age= 36.2 (1.76) Female= 27 (67.5%)	CTQ- total; dichotomised	31	Higher levels of Il-6 in patients with schizophrenia who reported exposure to CM compared to patients with schizophrenia who did not report maltreatment and healthy controls, in an analysis that did not adjust for covariates
Fanning 2015 [30]	Community recruited participants with and without personality disorderin a larger study about the correlates of impulsive aggression in Chicago USA	134	Personality Disorder Age= 36.0 (7.7) Female= 38 (48.1%) Control: Age- 31.9 (9.2) Female= 30 (54.5%)	CTQ- separated to abuse and neglect sub-components; continuous analysis.	30	No association of abuse or neglect with Il-6 in an unadjusted analysis.

Grosse 2016 [55]	Participants in the MOODINFLAME study of inflammatory biomarkers in MDD. Participants were inpatients with MDD in hosptials in Munster Germany. Participants were free from other mental illness or significant physical illnesses. Controls were recruited from the community.	394	MDD: Age= 41 (12) Female= 120 (56%) Control: Age= 36 (12) Female= 114 (63%)	CTQ- total and subcomponents; dichotomised	30	No association of CM with Il-6 in a model adjusting for age, gender, waist hip ratio, and smoking.
Imai 2008 [25]	Female outpatients with PTSD and matching controls in Japan. Participants had no significant physical illnesses. Analysis of inflammation and abuse only included the PTSD group.	40 (participants with PTSD)	Age= 38.3 (10.1) Female= 100%	CTQ- total; continuous	37	No correlation of CTQ (total or subscales) with any inflammatory marker in unadjusted analysis.
Lu 2013 [53]	Study of outpatients with MDD (with and without and history of childhood maltreatment) and controls recruited from Changsha China. Participants had no other mental or physical illnesses.	65	MDD and CM: Age= 30.2 (8.53) Female= 14 (63.6%) MDD no CM: Age= 30.1 (6.81) Female= 11 (52.3%) Control: Age= 27.7 (4.78) Female= 11 (50%)	CTQ- total; dichotomised	. 24	No correlation of CTQ with any cytokine in MDD and CM group in an unadjusted analysis.
Pedrotti Moreira 2018 [56]	Cross-sectional study of participants with MDD in Pelotas Brazil. Participants had no other mental or physical illness.	166	Age= 25.87 (5.25) Female= 124 (74.7%)	CTQ- total; continuous	34	In depressed participants CM was associated with elevated Il-6. This remained significant on linear regression adjusting for schooling and smoking status.
Muller 2019 [57]	Inpatient and outpatients with MDD and matching controls (from local university) recruited in Munich Germany. No other mental or physical illnesses.	88	MDD Age= 39.2 (12) Female= 17 (39%) Control Age= 38.9 (11.8) Female= 17 (39%)	CTQ- subcomponents; continuous	35	In total sample Il-6 was positively correlated with Sexual abuse and physical neglect sub-components only. In the control group no sub-components correlated with Il-6.. In MDD group physical neglect correlated with Il-6 only. Analyses were not adjusted for covariates.
Munjiza 2018 [58]	Inpatients with depression and matching controls in Belgrade Serbia.	117	MDD Age= 45.98 (10.31) Female= 51 (80.0%) Control Age= 46.04 (10.15) Female= 43 (81.1%)	CTQ- total and subcomponents; continuous	30	In the patient group only, Il-6 was positively correlated with total CTQ and PN, EA, and PA sub-components. Il-6 was not correlated with any CTQ component in controls. Analyses were not adjusted for covariates.
Palmos 2019 [26]	Participants retrieved from 2 studies. Controls recruited from SeLCoH study of mental and physical health in the general population in London. MDD participants recruited from the control arm of the ADD	465	MDD: Age= 48.50 (16.14) Female= 79 (48.1%) Control	CTQ- total; dichotomised	37	No significant association of CM with Il-6 in models adjusted for age, gender, ethnicity, smoking and BMI.

	trial of metyrapone in depression. Participants had no other mental or physical illnesses.		Age= 48.50 (16.14) Female= 158 (52.5%)			
Porcu 2018 [51]	Women aged 18-65 in Londrina Brazil. Participants were patient with unipolar or bipolar depression recruited from outpatient clinics, non-depressed smokers were recruited from smoking cessation clinics and non-smoking controls from hospital staff. Participants excluded if had other mental or physical illness	159	Depressed Smokers: Age= 46.07(10.58) Female= 100% Depressed Never-Smokers: Age= 41.08 (13.61) Female= 100% Control Smokers: Age= 43.54 (11.85) Female=100% Control never-smokers: Age= 39.21 (13.19) Female=100%	CTQ- subcomponents; continuous	23	No association of CM with Il-6 in unadjusted analysis.
De Punder 2018 [28]	Patients with depression were recruited from an affective disorders clinic and controls from public advertisements. Participants did not have other mental or physical illnesses. Neither patients or controls taking psychotropic medications. Study in Berlin Germany	86	MDD and MT Age= 38.09 (11.36) Female= 14 (60.1%) MDD no MT Age= 32.61 (11.74) Female= 18 (85.7%) Control and MT Age= 38.09 (11.36) Female= 14 (66.7%) Control no MT: Age= 33.9 (9.77) Female= 13 (61.2%)	ETI- Dichotomised	31	Significant difference in Il-6 between groups which remained significant after adjusting for BMI and smoking. On post-hoc testing significant difference between MDD + ACE vs HC no ACE only. Analyses were unadjusted for covariates.
Quide 2019 [32]	Participants were outpatients with schizophrenia/ schizoaffective disorder, bipolar disorder, and healthy controls from Austrailia. All aged 18-65 with no significant physical illnesses	209	Schizophrenia: Age= 41.78 (11.33) Female= 29 (42.6%) Bipolar Disorder: Age= 38.11 (12.31) Female= 46 (66.7%) Control: Age= 36.17 (11.57) Female= 34 (47.2%)	CTQ- Subcomponents; continuous	35	No association of CM with Il-6 in model adjusted for in a model adjusted for age, gender, symptom severity, and medication usage.
Smith 2011 [52]	Participants in a larger study of influence of genetics and environmental responses to stress in African Americans in Atlanta	110	Sample demographics not reported. States that groups were matched for age and gender.	CTQ- Total; dichotomised	27	Maltreatment was not associated with Il-6 in an unadjusted analysis.

	Georgia. Participants grouped by presence of PTSD and early maltreatment Also describe “extended sample” of 177- unclear origin					

Table 2b Samples reporting interleukin-6: Non-clinical populations

Author	Sample Characteristics	Sample Size	Sample Demographics	Maltreatment Measure	CCAT Score	Main Findings
Bertone-Johnstone 2012 [47]	Participants in Nurses Health Study II. A cohort of female nurses in USA recruited in 1989. A sub-sample was invited to provide blood samples between 1996-1999.	702.	Age= 48.9 (SD not reported) Female= 100%	Physical abuse- Adapted Revised Conflict Tactics Scale. Sexual abuse- Adapted Sexual Experiences Survey	33	Il-6 was associated with adolescent PA and SA but both because non-significant in models adjusting for BMI.
Davis 2019 [59]	Participants in a study of healthy aging in Arizona USA.	770.	Age= 53.5 (7.24) Female= 423 (55%)	CTQ- 10 item short version excluding neglect items; continuous	34	CM was associated with elevated Il-6 in a model adjusted for age, gender, ethnicity, education, smoking, alcohol use, sleep disturbance, and physical activity levels but not BMI.
Finy 2018 [19]	Pregnant woman recruited in Ohio USA. Participants were physically healthy.	214	Age= 29.38 (4.93) Female= 100%	CTQ- subscales of physical abuse, sexual abuse, and emotional abuse; continuous	35	CTQ score was positively correlated Il-6 in an unadjusted analysis.. In structural equation models CM had no effect on Il-6.
Gouin 2012 [39]	Participants in a study of stress in older adult dementia caregivers in Canada. Participants excluded if had illnesses which affect immune system, or BMI >40.	130	Abused Age= 62.47 (12.07) Female= 46 (80.7%) Non-Abused Age= 67.2 (13.74) Sex= 61 (83.5%)	CTQ- total (excluding physical neglect); dichotomised	35	Abuse was associated with elevated Il-6 in a model adjusting for age, sex, ethnicity, education, BMI, marital status, sleep disturbance, and caregiving status.
Hartwell 2013 [40]	Control group in a larger study on gender differences in stress responses in cocaine dependency in South Carolina USA. Participants were non-cocaine using controls with no mental or physical illnesses.	39	Age= 35.69 (12.0) Female= 20 (51.3%)	ETI- Number of traumas	36	Number of traumas was significantly associated with elevated Il-6, in models adjusted for age, sex, and smoking status but not BMI. In analysis of subscales general trauma only was associated with elevated Il-6.
Kiecolt-Glaser 2011 [60]	Participants in a study of caregiving stress in older adults including caregivers for a spouse or parent with dementia and matching controls, in Ohio USA. Participants had no immune-related health problems.	132	Age= 69.7 (10.14) Female= 95 (72%)	CTQ total (excluding physical neglect); dichotomised	36	Abuse was associated with increased Il-6 in a model adjusted for age, sex, BMI, marital status, and caregiver status.
Pinto Pereira 2019 [45]	1) 1958 British Birth Cohort: A longitudinal cohort of all born in one	British Birth	British Birth Cohort: Age= 45.2 (44.3-46.0) (mean and range)	Physical, emotional and sexual abuse; emotional neglect and physical	25	No form of maltreatment was associated with differences in Il-6 in models adjusted for age, gender, ethnicity, socioeconomic status, and BMI or waist hip ratio.

	week in 1958. Bloods collected at visit age 45. 2) Midlife in United States (MIDUS): Cohort of adults 25-75 in USA recruited in 1994-1995. 2nd wave of data collection (MIDUS-II) followed up original sample 10 years later.	Cohort= 7661 MIDUS= 1255	Female= 3828 (50%) <u>MIDUS</u> Age - Male= 57.9 (36-86) - Female= 56.9 (35-86) Female= 713 (56.8%)	neglect (British Birth Cohort only). Derived from study questions. All measures retrospective except from prospective record of neglect in British Birth Cohort		
Rooks 2012 [48]	Male middle aged twins born between 1946-1956 from the Vietnam Era Twin Registry in USA.	482	Age= 55(3) Female= 0	ETI- total; comntinuous	32	CM was not associated with Il-6 in unadjusted analysis or model adjusted for age, income, education, behavioural factors, cardiovascular risk factors (including BMI), and psychiatric diagnoses.
Slopen 2010 [46]	Participants in MIDUS cohort in USA	999	<u>White Participants (n=822)</u>: Age= 58.66 (11.65) Female= 52.8% <u>African-American Participants (n=177)</u>: Age= 54.15 (10.71) Female= 67.23%	No formal tool. Physical, emotional and sexual abuse derived from study questions. All measures retrospective.	33	CM was not associated with Il-6 in model adjusted for age, gender, ethnicity, cardiovascular disease, and BMI..
Thurston 2017 [44]	Participants in the MsHeart study of peri- and post-menopausal women aged 40-60 in Pitsburgh USA. Excluded if history of signficiant physical illness	286	<u>Abuse/Neglect</u> (n=132) Age= 53.68 (4.11) Female= 100% <u>No abuse/neglect (n=163)</u>: Age= 54.28 (3.90) Female= 100%	CTQ- total and subcomponents; dichotomised	29	No difference in Il-6 between CM group and controls in unadjusted analysis.

<u>Table 2 Legend</u>: BMI- Body mass index, CM- Child Maltreatment, CTQ- Childhood Trauma Questionnaire, EA- Emotional abuse, EN- Emotional neglect, ETI- Early Trauma Inventory, Il-6- Interleukin-6, MDD- Major depressive disorder, PA- Physical abuse, PN- Physical abuse, SA- Sexual abuse.

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Of the clinical samples, nine papers did not identify a significant association between CM and Il-6[24-26, 30, 32, 50-53]. Dennison et al reported higher levels of Il-6 in patients with schizophrenia who reported exposure to CM compared to patients with schizophrenia who did not report maltreatment and healthy controls, in an analysis that did not adjust for covariates[54]. Grosse et al reported on 394 patients and controls in the MOODINFLAME study of inflammatory markers in Major Depressive Disorder (MDD)[55]. There was no association between CM and Il-6 in the total sample, nor in the MDD or control groups. In an analysis limited to MDD patients exposed to CM, sexual abuse was associated with elevated Il-6 in an analysis that adjusted for age, gender, smoking, and waist-hip ratio. Pedrotti Moreira et al reported on a cross-sectional study of MDD and healthy control participants in Brazil[56]. They identified a significant association between CM and higher Il-6 in participants with MDD only, in an analysis which adjusted for education and smoking status but not BMI. Muller et al examined the correlation between CTQ scores and inflammatory markers in a sample consisting of patients with MDD and healthy controls[57]. They found a small but significant correlation between sexual abuse and physical neglect with Il-6 in an unadjusted analysis. Munjiza reported that Il-6 was positively correlated with total CTQ, physical neglect, emotional abuse, and physical abuse in an unadjusted analysis limited to participants with MDD only[58]. De Punder et al reported on a sample of patients with MDD and healthy controls[28]. They grouped participants by presence of MDD and exposure to CM and identified a significant between group difference in an analysis which adjusted for BMI and smoking. On post-hoc testing the only significant difference was between the MDD and CM group vs healthy control and no CM, thus this analysis does not clearly distinguish the effects of MDD from CM.

Ten studies reported on non-clinical samples. Three of these found no association between CM and Il-6[45, 48]; a further three studies found associations of CM with elevated Il-6 which attenuated to non-significance after adjustment for BMI[19, 44, 46, 47]. Davis et al, in a study of healthy middle aged adults in the USA, found that CM was significantly associated with elevated Il-6 in a model that adjusted for age, gender, ethnicity, and health behaviours, but not BMI[59]. Gouin et al, in a study of care-giver stress in older adults found a significant association between CM and Il-6 in a model which adjusted for age, sex, ethnicity, education, BMI and social factors[39]. Hartwell *et al* reported a significant association between the number of traumas as measured by the ETI and elevated Il-6 in a model which adjusted for age, sex, and smoking status but not BMI[40]. In another study of care-giver

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279 stress in older adults, Kiecolt-Glaser identified a significant association between CM and elevated Il-6
280 in a model adjusted for age, sex, BMI and social factors[60].

281 In summary most studies did not find a significant association between CM and elevated Il-6. Studies
282 reporting positive findings tended not to adjust for BMI and in some papers positive associations were
283 limited to sub-groups. Notably, two studies that adjusted appropriately for covariates found significant
284 associations between CM and elevated Il-6 in older adults.

285 Tumour necrosis factor-alpha

286 The association between CM with TNF-a was reported in 16 papers, 13 of which were in clinical
287 samples. All studies were retrospective and 14 used the CTQ to measure CM. Details of included
288 papers are shown in tables 3a and 3b.

289

Table 3a- Studies reporting TNF-a: Clinical populations

Author	Sample Characteristics	Sample Size	Sample Demographics	Maltreatment Measure	CCAT Score	Main Findings
Corsi-Zuelli 2020 [50]	Participants in the STREAM Cohort of patients with first episode psychosis, unaffected siblings, and healthy controls in Sao Paulo Brazil.	422	FEP: Age= 30.8 (12.5) Female= 37% Siblings: Age= 30.7 (10.5) Female= 68.4% Controls: Age= 31.3 (11) Female= 48.6%	CTQ- subcomponents; dichotomised	35	In analyses adjusted for age, gender, BMI, smoking, substance use, education, and relationship status no significant association of TNF-a with any subcomponent of abuse or neglect.
Counotte 2019 [24]	Participants in a study of participants with psychotic disorders, ultra-high risk for psychosis, unaffected siblings, and controls, in the Netherlands.	117	Psychosis Age= 25.5 (23-30) Male= 6 (15.8%) UHR Age= 24.0 (20-29) Female= 6 (54.5%) BMI= 23.1 (18.5- 26.2) Siblings Age= 25.5 (21.3- 30.0) Female= 12 (41.4%) Controls: Age= 24.0 (21.0-26.0) Female= 21 (53.8%)	CTQ- dichotomised; total and subcomponents	38	No significant effect on CTQ on any inflammatory marker in models which adjust for age, sex, BMI, smoking, drug use, and education.
Dennison 2012 [54]	Patients with schizophrenia in Cork Ireland recruited from outpatient and inpatient settings. Controls recruited from local university.	80	Schizophrenia Age= 38.33 (1.7) Female= 16 (40%) Controls: Age= 36.2 (1.76) Female= 27 (67.5%)	CTQ- total; dichotomised	31	Compared differences in cytokines across groups (schizophrenia with abuse, schizophrenia without abuse, and control) using ANOVA. Significant between group difference for TNF-a. Post-hoc testing showed significant differences between schizophrenia with and without abuse. Did not adjust for covariates.
Grosse 2016 [55]	Participants in the MOODINFLAME study of inflammatory biomarkers in MDD. Participants were inpatients with MDD in hosptials in Munster Germany. Participants were free from other mental illness or significant physical illnesses. Controls were recruited from the community.	394	MDD: Age= 41 (12) Female= 120 (56%) Control: Age= 36 (12) Female= 114 (63%)	CTQ- total and subcomponents; dichotomised	30	No association of abuse with TNF-a in total sample or MDD or control groups. In a subsample of MDD patient with a history of abuse there was a significant association of sexual abuse only with TNF-a which remained significant after adjusting for age, gender, waist hip ratio, and smoking.

Imai 2008 [25]	Female outpatients with PTSD and matching controls in Japan. Participants had no significant physical illnesses. Analysis of inflammation and abuse only included the PTSD group.	40 (participants with PTSD)	Age= 38.3 (10.1) Female= 100%	CTQ- total; continuous	. 37	No correlation of CTQ (total or subscales) with any inflammatory marker in unadjusted analysis
Kraav 2019 [61]	Sub-sample of the NeuroDep study of MDD in Kuopio Finland. All participants had MDD and had no other mental or physical illnesses.	78	Physical Violence: Age= 41.63 (9.7) Female= 12 (50%) Control: Age= 37.24 (12.5) Female= 30 (55.6)	ACEs questionnaire. Due to low sample size only included physical abuse item.	32	TNF-a did not differ between groups in an unadjusted analysis.
Lu 2013 [53]	Study of outpatients with MDD (with and without and history of childhood maltreatment) and controls recruited from Changsha China. Participants had no other mental or physical illnesses.	65	MDD and CM: Age= 30.2 (8.53) Female= 14 (63.6%) MDD no CM: Age= 30.1 (6.81) Female= 11 (52.3%) Control: Age= 27.7 (4.78) Female= 11 (50%)	CTQ- total; dichotomised	24	No correlation of CTQ with TNF-a in any group, in an unadjusted analysis.
Pedrotti Moreira 2018 [56]	Cross-sectional study of participants with MDD in Pelotas Brazil. Participants had no other mental or physical illness.	166	Age= 25.87 (5.25) Female= 124 (74.7%)	CTQ- total; continuous	34	There was no association of abuse and TNF-a in model adjusting for age, smoking status, and schooling.
Palmos 2019 [26]	Participants retrieved from 2 studies. Controls recruited from SeLCoH study of mental and physical health in the general population in London. MDD participants recruited from the control arm of the ADD trial of metyrapone in depression. Participants had no other mental or physical illnesses.	465	MDD: Age= 48.50 (16.14) Female= 79 (48.1%) Control Age= 48.50 (16.14) Female= 158 (52.5%)	CTQ total score; dichotomised	37	No significant association of CM with TNF-a in models adjusted for age, gender, ethnicity, smoking and BMI.
Quide 2019 [32]	Participants were outpatients with schizophrenia/ schizoaffective disorder, bipolar disorder, and healthy controls from Austrailia. All aged 18-65 with no significant physical illnesses	209	Schizophrenia: Age= 41.78 (11.33) Female= 29 (42.6%) Bipolar Disorder: Age= 38.11 (12.31) Female= 46 (66.7%) Control: Age= 36.17 (11.57) Female= 34 (47.2%)	CTQ- Sub-components; continuous	35	No association of maltreatment with any inflammatory marker in control or bipolar group. In schizophrenia group significant association of sexual abuse and CRP in a model also significant for sex and anti-psychotic dose. No other significant associations in schizophrenia group.
Smith 2011 [52]	Participants in a larger study of influence of genetics and environmental responses to stress in African Americans in Atlanta Georgia. Participants	110	Sample demographics not reported. States that groups were matched for age and gender.	CTQ- Total; dichotomised	27	CM associated with TNF-a but no other inflammatory markers in an analysis adjusted for age, gender, socioeconomic status, mental health outcomes, but not BMI.

	grouped by presence of PTSD and early maltreatment					
Toft 2018 [62]	Patients with MDD admitted to a psychiatric hospital in Norway.	128	Mild: Age= 39.4 (10.8) Female= 20 (71.4%) Moderate Age= 44.2 (12.0) Female= 28 (66.7%) Severe Age= 41.3 (11.7) Female= 44 (75.9%)	No formal measure. Asked about trauma on admission interview and grouped as trauma present or absent.	27	Trauma exposure associated with elevated TNF-a in an unadjusted analysis.
Zeugmann 2013 [27]	Inpatients with MDD in Germany.	25	Age= 47.8 (15.02) Female= 17 (68%)	CTQ- subcomponents; continuous	31	No association of CM with TNF-a in an unadjusted analysis..

Table 3b- Studies reporting TNF-a: Non-clinical populations

Author	Sample Characteristics	Sample Size	Sample Demographics	Maltreatment Measure	CCAT Score	Main Findings
Gouin 2012 [39]	Participants in a study of stress in older adult dementia caregivers in Canada. Participants excluded if had illnesses which affect immune system, or BMI >40.	130 Abused= 57 Non-Abused= 73	Abused Age= 62.47 (12.07) Female= 46 (80.7%) Non-Abused Age= 67.2 (13.74) Sex= 61 (83.5%)	CTQ- total (excluding physical neglect); dichotomised	35	No association of CM with TNF-in a model adjusted for age, sex, ethnicity, education, BMI, marital status, sleep disturbance and caregiving status.
Hartwell 2013 [40]	Control group in a larger study on gender differences in stress responses in cocaine dependency in South Carolina USA. Participants were non-cocaine using controls with no mental or physical illnesses.	39	Age= 35.69 (12.0) Female= 20 (51.3%)	ETI- Number of traumas	36	Number of traumas was significantly associated with elevated TNF-a in models adjusted for age, sex, and smoking status, but not BMI.
Kiecolt-Glaser 2011 [60]	Participants in a study of caregiving stress in older adults including caregivers for a spouse or parent with dementia and matching controls, in Ohio USA. Participants had no immune-related health problems.	132	Age= 69.7 (10.14) Female= 95 (72%)	CTQ Total (excludes physical neglect); dichotomised	36	CM was not associated with TNF-a, in a model adjusted for age, sex, BMI, marital status, and caregiver status.

Table 3 Legend: BMI- Body mass index, CM- Child Maltreatment, CTQ- Childhood Trauma Questionnaire, EA- Emotional abuse, EN- Emotional neglect, ETI- Early Trauma Inventory, MDD- Major depressive disorder, PA- Physical abuse, PN- Physical abuse, TNF-a- Tumour Necrosis Factor Alpha, SA- Sexual abuse.

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Ten papers, all reporting clinical samples, did not identify a significant association between CM and TNF-a[24-27, 32, 50, 53, 55, 56, 61]. Dennision et al reported elevated levels of TNF-a in participants with schizophrenia and a history of CM compared to participants with schizophrenia only, in an analysis which did not adjust for covariates[54]. Smith et al reported that TNF-a was associated with elevated TNF-a in a sample of 110 African-Americans with and without PTSD, in an analysis which adjusted for age, gender, education, substance use, mental health factors, but not BMI. Toft et al, in a sample of 128 inpatients with MDD, found a significant association between CM (which was not measured using a formal tool) and elevated TNF-a in an unadjusted analysis[62].

In non-clinical samples, two studies did not find a significant association between CM and TNF-a[39, 60]. Hartwell et al in a study of 39 healthy adults in the USA, reported a significant association between the number of traumas on the ETI and elevated TNF-a in an analysis which adjusted for age, sex, and smoking status but not BMI[40].

To summarise most studies did not find a significant association between CM and elevated TNF-a, and none of the studies reporting significant associations had adjusted for BMI.

Discussion

This systematic review examining the association between CM and markers of systemic inflammation has identified significant variation in the conduct and statistical analysis of studies in this area to the extent that quantitative synthesis of the findings would be invalid. Of note, there was wide variation in how CM exposure was recorded and analysed; for example as a dichotomous versus a continuous variable; as an overall construct versus its subcomponents. Furthermore, the method of analysis varied widely, including between group comparisons, bivariate correlations, linear regression, and more complex modelling. Of note, in analyses where adjustment for covariates was possible there was no consistency in which variables were included. Unsurprisingly, in this context, the findings of studies in this field are inconsistent: the majority of retrospective studies showed no association between CM and inflammatory markers; a number of unadjusted analyses showed statistically significant associations,, and a smaller number of fully adjusted analyses showed statistically

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317 significant associations but with generally small effect sizes. The variation in conduct and analysis of
318 studies makes it challenging to integrate these disparate findings into a cohesive whole.

319

320 This review highlights several limitations in the existing literature. Only four studies (less than 10%)
321 included prospective measures of CM, and these studies only related to CRP. All four of these studies
322 found a significant association between CM and elevated CRP later in life, and two highlighted
323 significant interactions with ethnicity or gender. Baldwin et al have highlighted that retrospective and
324 prospective measures of CM tend to capture different groups of individuals and are not clearly
325 measuring the same construct[63]. This is further supported by the findings of Osborn and colleagues
326 who found that prospective but not retrospective measures of CM were associated with elevated
327 CRP[34]. Despite this small prospective evidence base, and its narrow focus on CRP, the existence
328 of these appropriately adjusted prospective studies demonstrating an association between CM and
329 later increases in CRP suggests that further examination of the links between CM and inflammation is
330 still warranted, but only if studies have sufficient methodological rigour.

331 In the research base as a whole, studies were inconsistent in their construct of CM: an overall “CM”
332 construct versus sub-types of maltreatment; as a dichotomous variable treating CM as present or
333 absent, or as a continuous measure of the severity of CM. Statistical properties of the way the
334 construct of CM is presented and analysed may contribute to important differences in results (e.g.
335 analyses of continuous measures have more statistical power than dichotomous variables). Studies
336 were also inconsistent in their reporting and analysis of sub-types of abuse. Studies describing results
337 for individual sub-types of CM have reported different effects for different types of maltreatment (most
338 commonly stronger associations of sexual abuse with inflammation)[29, 31, 32, 47, 55]. An approach
339 based on individual sub-types of maltreatment may, however, neglect the inherent complexity and
340 clustering of adversities. For example rather than a specific effect of child sexual abuse as opposed to
341 other maltreatment, the associations found between sexual abuse and inflammation may be more
342 reflective of sexual abuse exposure indexing an overall greater severity of maltreatment exposure and
343 a clustering of multiple adversities[64, 65]. There were limited data on the timing and duration of CM
344 which limits the ability to draw conclusions about sensitive periods in the development of the immune

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system. Overall, the inconsistencies in measurement of CM could be masking potentially important findings, especially regarding mechanisms.

The conceptualisation and measurement of CM and ACEs more broadly is an area of ongoing debate with relevance to study methodology in this area. Total scores based on the number of forms of CM or ACEs a person has been exposed to is a straight forward way of conceptualising and measuring CM, however it does not reflect the fact that categories of CM or ACE are not equal in their severity or impacts[64]. Analyses based on specific exposures to sub-types of CM or ACE can reflect differential severity and impacts of different types of maltreatment, but fail to reflect the common clustering of maltreatment types (for example intra-familial sexual abuse will almost always be association with physical abuse, emotional abuse, and neglect), and can lose this inherent complexity[64]. Recent work using latent class analysis has identified common clusters of adversity which may represent a better way of conceptualising this area moving forwards[65, 66]. Furthermore it is important to recognise and account for wider forms of adversity which are not fully reflect in traditional conceptions of CM and ACE (which focus more on the immediate family environment), in particular socioeconomic status and wider social adversities such as discrimination[66, 67]. In a similar vein, neurodevelopmental conditions are related to risk of exposure to CM[68] but were not considered as covariates in any of the included studies.

Studies varied greatly in their accounting for potential confounding and mediating variables. Of note, BMI appears to have an important role in the relationship between CM, systemic inflammation and psychopathology. As highlighted previously, most studies finding significant associations between CM and systemic inflammation did not adjust for BMI or related measures (e.g. waist-hip ratio), yet studies employing structural equation modelling suggested that the relationship between CM and inflammation might be mediated by BMI. Based on the current literature it is plausible to speculate that the association between CM and systemic inflammation might be primarily mediated by elevated BMI, but further direct data on this possible association are required.

Most studies were based in Europe or North America and predominantly included participants of white ethnicity. Two studies[35, 46] found significant interactions with ethnicity, contrastingly finding a relationship between neglect and CRP in people of white ethnicity only[35]; and Il-6, fibrinogen, E-Selectin, and sICAM for African-Americans only[46]. Associations between race and health outcomes (particularly in the USA, where there are strong associations between ethnicity and poverty and poor

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375 access to healthcare) are likely to be confounded by a range of social and environmental factors[67],
376 and it would be helpful for these apparent associations to be explored more widely and in other
377 settings.

378 One study[33] found a significant relationship between CM and CRP for females only. Other studies
379 did not directly examine the role of gender, however many studies were conducted exclusively in
380 females or in predominantly female samples which may further affect the overall results. There did not
381 appear to be a consist difference in effects observed in studies limited to participants with psychiatric
382 diagnosis as compared to those limited to community volunteers.

383

384 This systematic review is subject to several limitations. Whilst attempts were made to be exhaustive,
385 practical limitations precluded inclusion of foreign language titles and grey literature. Whilst attempting
386 to focus on studies where CM was predominantly child abuse or neglect, limitations in how abuse was
387 measured has meant that some included studies also include broader domains of childhood trauma
388 such as bullying and parental separation. The original protocol for this study aimed to perform a meta-
389 analysis but this was unfortunately neither practicable nor appropriate due to i. significant variation in
390 the exposure concept (CM as a dichotomous or continuous variable; as an overall construct or as
391 sub-components), ii. the use of measurement tools (in particular, difficulties combining between-
392 group comparisons and linear analyses), and iii. inconsistencies in adjustment for covariates where
393 this was done at all. These problems would have significantly impacted the statistical robustness of
394 any findings and potentially created more confusion or, worse, amplified biases, in this already
395 challenging field.

396

397 Overall this systematic review has identified an association between CM and elevated CRP in
398 prospective studies, however findings of retrospective studies and for other biomarkers are conflicting.
399 Tentatively at least part of the association between CM and systemic inflammation may be mediated
400 by the association of CM and elevated BMI, which itself may be driven by physiological (such as
401 dysregulated stress-reactivity leading to dysregulation of metabolic pathways) or psychological (such
402 as emotional dysregulation or impulsivity leading to dysregulated eating behaviours) factors, or indeed
403 both. Obesity is strongly associated with low-grade inflammation in a mechanism which may be

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404 partially mediated by alterations in the gut microbiome and gut permeability[69], factors which have
405 also been suggested as important drivers of low-grade inflammation and age-related disease[70].
406 Additional previously unmeasured covariates may also mediate the association of CM with elevated
407 BMI and inflammation, for example neurodevelopmental disorders (which previous work by our group
408 has shown to be associated with obesity[71]) and the gut microbiome, which may mediate the
409 relationship between a range of adverse exposure and inflammation[70]. All of this highlights the
410 importance of applying complex systems methodologies to exploring the interaction of variables
411 holistically and longitudinally[72].

412 Achieving the research goal of understanding these potentially complex mechanisms would have
413 practical relevance since, if the main mediator is obesity or the gut microbiome, the most effective
414 interventions would likely involve weight loss, exercise, dietary change and early intervention to
415 prevent obesity; whereas if the association between CM and systemic inflammation were more direct,
416 this may point towards a role for anti-inflammatory medications. Further prospective, longitudinal,
417 research using robust and comparable measures of CM with careful consideration of confounding and
418 mediating variables, particularly BMI, are required to bring clarity to this field.

419

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678 Supporting Information

679 S1 File- Details of search strategy

680 S2 File- PRISMA checklist

681 S3 File- Systematic review protocol

682 S1 Table- Details of excluded articles

683 S2 Table- Results relating to other biomarkers

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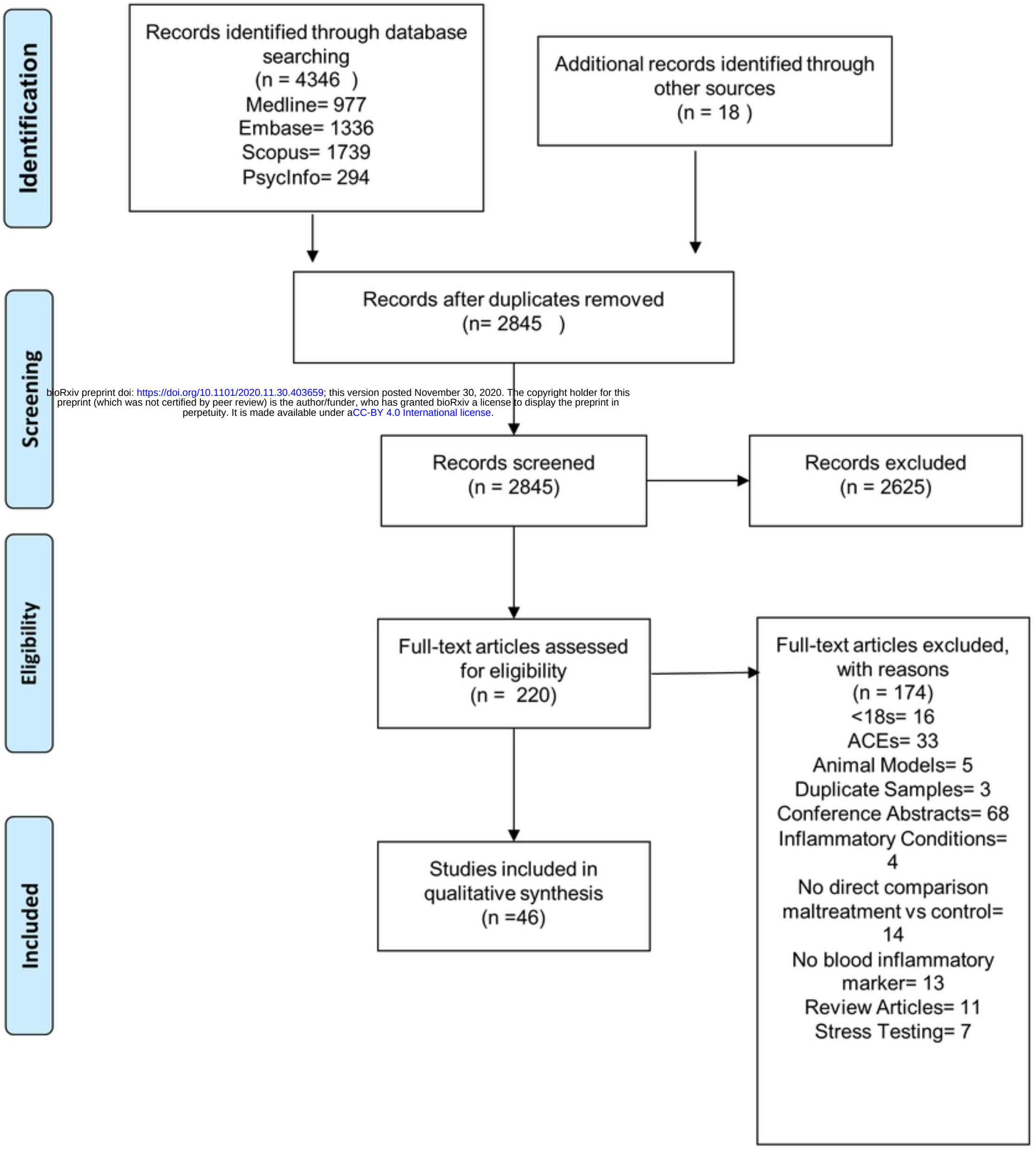

Figure 1