Review
Childhood maltreatment and inflammatory markers: a systematic review

Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R.
Childhood maltreatment and inflammatory markers: a systematic review.

Objective: Childhood maltreatment (CM) has been associated with several diseases in adult life, including diabetes, obesity and mental disorders. Inflammatory conditions have been postulated as possible mediators of this relationship. The aim was to conduct a systematic review regarding the association between CM and inflammatory markers in adulthood.

Method: A literature search of the PubMed, ISI, EMBASE and PsychINFO databases was conducted. The key terms used were as follows: ‘Child Maltreatment’, ‘Childhood Trauma’, ‘Early Life Stress’, ‘Psychological Stress’, ‘Emotional Stress’, ‘Child Abuse’ and ‘Child Neglect’. They were cross-referenced separately with the terms: ‘C-reactive Protein (CRP)’, ‘Tumor Necrosis Factor’, ‘Cytokine’, ‘Interleukin’, ‘Inflammatory’ and ‘Inflammation’.

Results: Twenty articles remained in the review after exclusion criteria were applied. Studies showed that a history of CM was associated with increased levels of CRP, fibrinogen and proinflammatory cytokines. Increased levels of circulating CRP in individuals with a history of CM were the most robust finding among the studies. Data about anti-inflammatory mediators are still few and inconsistent.

Conclusion: Childhood maltreatment is associated with a chronic inflammatory state independent of clinical comorbidities. However, studies are heterogeneous regarding CM assessment and definition. Important methodological improvements are needed to better understand the potential impact of CM on inflammatory response.

Summations
- Childhood maltreatment is associated with increased levels of C-reactive protein.
- Childhood maltreatment is related to with increased proinflammatory cytokines.

Considerations
- Non significant effects could be related to the heterogeneity of methods.
- Chronic inflammatory state is independent of clinical comorbidities.

Introduction
Childhood maltreatment (CM) has been defined as acts of commission or omission by parents or caregivers that result in potential harm to the child’s health, and include experiences such as physical, sexual and psychological abuse, as well as physical or emotional neglect (1). Accumulating evidence shows that individuals that suffered CM present higher rates of morbidity and mortality from
chronic diseases (2) and are more vulnerable to the development of mental disorders (3–5), diabetes, asthma, obesity, atherosclerosis, neurodegeneration and coronary heart disease (6–8).

Adults who experienced abuse or neglect as children appear to have alterations in hypothalamic–pituitary–adrenal (HPA) axis functioning (9). These alterations have been investigated by several studies that focused on how early adverse experiences can become important risk factors for poor adult health and clinical impairment (10–12). It was shown that CM survivors present neuroendocrine stress response desensitization, including enhanced cortisol resistance, as well as increased central corticotropin-releasing factor (CRF) activity (13, 14). Furthermore, researchers have explored the interactive pathways between the central nervous system, the endocrine system and the immune system to understand the physiological sequelae of childhood adversities (15). The HPA axis and the autonomic nervous system provide immune system regulation in a bidirectional association (16). Examples of these relationships are that several immune cells have receptors for one or more of the stress hormones released by the HPA axis, and that lymphocytes can synthesize hormones such as adrenocorticotropic hormone (ACTH) (17).

Based on this, recent studies have investigated the overall effect of early-life stress on the production of acute-phase proteins that modulate inflammation (18–20). The inflammatory response is part of the complex immune system response of the organism to harmful stimuli, such as pathogens, damaged cells or environmental demands (i.e. ‘stresors’), with both local and systemic effects. Research has demonstrated evidence for long-term alterations in human inflammatory response associated with CM, including the increase in the production of C-reactive protein (CRP) (21) and proinflammatory cytokines, such as Interleukin (IL)-6 (22) and Tumour necrosis factor (TNF)-\(\alpha\) (23). In addition, data from animal models supports this idea, since the first evidence of certain immune responses being compromised following removal from the mother was reported in young monkeys (24). Thereby, there has been an increasing volume of studies exploring the relationship between CM and immune system (8, 10, 25). Alterations in inflammatory markers are now a candidate biomarkers for mediating the health consequences associated with childhood adversities (10). A recent systematic review sought to investigate similar questions about childhood adversities and poor health but was limited to the research on inflammatory biomarkers associated with cardiovascular risk in young adults only (8).

Aims of the study

This article presents a systematic review of the literature regarding CM and inflammatory mediators, focusing entirely on human studies. In addition, it discusses methodological issues that might explain inconsistencies among studies, which might be enhanced in future research.

Material and methods

The research question that directed this review was as follows: Is CM history associated with changes in inflammatory mediators? To conduct this review, the following search engines were consulted: PubMed, ISI, EMBASE and PsychInfo, at or around January 2013. The keywords used were ‘Child Maltreatment’, ‘Childhood Trauma’, ‘Early Life Stress’, ‘Psychological Stress’, ‘Emotional Stress’, ‘Child Abuse’ and ‘Child Neglect’. They were cross-referenced separately with the terms: ‘C-Reactive Protein’, ‘Tumor Necrosis Factor’, ‘Cytokine’, ‘Interleukin’, ‘Inflammatory’ and ‘Inflammation’. The search criteria were presence of at least one selected term in any field of article. In addition, the reference lists of selected studies were consulted searching for relevant articles. Well-conducted observational studies, randomized controlled trials (RCT), cross-sectional, and case-control studies were considered. Articles from 2002 to 2013 were included from peer-reviewed publications only. We included articles published in English. The selected articles were systematically and independently examined by two investigators (RC and TV) according to the inclusion and exclusion criteria. We excluded the following: (i) reviews and theoretical articles, (ii) letter to editors, case reports, animal studies, (iii) articles without inflammatory mediators as dependent variable, (iv) articles without CM as independent variable and (v) republished data. Any discordance between the reviewers was discussed to reach a shared conclusion.

In addition, we measured the methodological weight of studies (0–6) using a quality score described by Fisher and Hosang (26), attributing one point to each one of the following characteristics: standardized CM assessment measure; controlling for body mass index (BMI); assessment of inflammatory mediators using more than one technique; longitudinal design; samples composed by more than 100 subjects, with at least 25% of the sample referencing a history of CM.
Results

The search identified 760 papers. This list was screened by hand, and exclusion criteria were applied. The flow chart is shown in Fig. 1. The final search resulted in 20 studies analysing the association between CM and inflammatory mediators. Most of final studies were retrospective, except for four studies. A summary of these studies, including their methodological characteristics is shown in Table 1.

Childhood maltreatment assessment

Most articles used the concept of childhood abuse (physical, sexual or emotional) and neglect (emotional or physical) as an independent variable, but others used trauma, early life stress, maltreatment or adverse childhood experiences to define this kind of event. Ten studies (50%) (19, 20, 22, 23, 27-32) used the Childhood Trauma Questionnaire (CTQ) (33), which investigates the frequency of CM-related experiences. The CTQ is a 28-item self-report instrument consisting of five subscales: emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse. The psychometric properties of CTQ is Cronbach’s alpha = 0.79–0.94; and reliability coefficients = 0.80–0.83 (34). The scores from CTQ were based on 4-point likert-scale, ranging from 1 absence to 4 severe evaluating level of CM. The CTQ yields a total score and subscale scores for each type of CM. Dennison et al. (30) used a short CTQ version with eight questions to identify presence or absence of childhood traumatic events.

Three prospective longitudinal studies from birth accessed CM and adverse childhood experiences using behavioural observations, parent reports and retrospective reports once they reached adulthood (21, 35, 36). Although it was not a standardized CM measurement, those authors demonstrated careful methodological investigation of CM experiences, including several indicators related to it. Two studies (37, 38) used The Risky Families questionnaire (39), which assesses the relation of family stress to mental and physical health outcomes in adulthood. The Risky Families questionnaire Cronbach’s alpha is = 0.77–0.85 (40). They evaluated whether individuals felt love and were cared for, were verbally and/or physically abused, lived with a substance abuser, and were shown physical affection. Participants responded on a scale ranging from 1 (rarely or none of the time) to 4 (most or all of the time).

Two studies (19, 41) used the Early Trauma Inventory (ETI) (42) that investigates childhood trauma experiences. The ETI provides separate scores in four domains: physical, sexual, and emotional abuse, and general trauma (i.e. natural disaster, family mental illness). The values from ETI can be analysed using each trauma domain or an index of total early trauma exposure through the sum of the domains. The ETI Cronbach’s alpha is = 0.75–0.95 (34). Pace et al. (19) used only the scores of physical and sexual abuse of the ETI. Tietjen et al. (43) investigated adverse childhood experiences using a 10-item self-report questionnaire, and the questions were related to experiences including abuse, neglect and exposure to household dysfunction (violence against mother/stepmother, parental substance abuse, mental illness, criminal behaviour and parental separation or divorce).

Lehto et al. (44) examined the history of CM in a subsample from a part of the clinical arm of general population study, using the initial background questionnaire required in 1998, with questions “Did you experience maltreatment at home?” and then, subdivided the sample in two groups (absence or presence of CM. However, this investigation method of CM was not standardized. Heggul et al. (45) used a modified version of the

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**Fig. 1.** Flow chart of method.
Table 1. Methodological characteristics of selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample (mean age/mean BMI)</th>
<th>Trauma assessment</th>
<th>Design</th>
<th>Assay</th>
<th>Mediators</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levandowski et al. (32)</td>
<td>67 women with crack cocaine dependence (26/26) 37 women with crack cocaine dependence (26/26) 18 women healthy controls (45.5/26)</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>Plasma ELISA</td>
<td>Adiponectin, Resistin and Leptin</td>
<td>4</td>
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<tr>
<td>Lu et al. (20)</td>
<td>22 patients with MDD and with CM (30.2/21.1) 21 patients with MDD without CM (30.1/21.8) 22 healthy controls (27.7/21.8)</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>Plasma Protein antibody array</td>
<td>IL-6, TNF-α, AgRP, b-FF, BTC, GTR-L, I-TAC, IL-1β, IL-1 R1, MEC, TECK, TGF-β, TRAIL-R4 and VEGF</td>
<td>3</td>
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<tr>
<td>Pace et al. (19)</td>
<td>12 women with PTSD and with childhood physical or sexual abuse (33.75/22.44) 24 women healthy controls (33.88/22.42)</td>
<td>ETI</td>
<td>Cross-sectional</td>
<td>PBM ELISA</td>
<td>NFKB</td>
<td>3</td>
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<tr>
<td>Lopes et al. (23)</td>
<td>16 women with MDD and PTSD symptoms with CM (41.06/26.18) 22 women with MDD without CM (39.73/26.65) 15 women healthy controls (37.03/25.17)</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>PBM CBA</td>
<td>IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α</td>
<td>3</td>
</tr>
<tr>
<td>Carpenter et al. (31)</td>
<td>92 healthy subjects (30.5/26.1) 23% endorsed criteria for moderate CM 25 patients with MDD (47.8/26.3) 32% endorsed criteria for severe childhood emotional abuse 32% endorsed criteria for severe childhood emotional neglect</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>Plasma GRN</td>
<td>CRP</td>
<td>2</td>
</tr>
<tr>
<td>Zeugmann et al. (29)</td>
<td>147 healthy controls (29.4/26.3) 30% experienced 1 indicator of CM 866 participants who completed the age 32 assessment from Dunedin birth cohort 14 healthy controls (29.4/24.3)</td>
<td>CECAQ (modified version)</td>
<td>Cross-sectional</td>
<td>Plasma Comay hsCRP assay</td>
<td>CRP</td>
<td>2</td>
</tr>
<tr>
<td>Lehto et al. (44)</td>
<td>30 subjects with adverse mental symptoms with CM (54/28.85) 117 subjects with adverse mental symptoms without CM (56/27.1)</td>
<td>Questionnaire created by authors</td>
<td>Cross-sectional</td>
<td>Serum MultiPlex Kit</td>
<td>Adiponectin and Resistin</td>
<td>2</td>
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<tr>
<td>Tietjen et al. (43)</td>
<td>100 women with migraine and 41 healthy women 90 of them with early adversity (36.24/30.49) 51 of them without early adversity (38.27/25.53)</td>
<td>Adverse childhood experiences</td>
<td>Cross-sectional</td>
<td>Plasma Nephelometry; AssayGate; Multiplex Kit</td>
<td>CRP, IL-6, TNF-α, TGF-β, Adiponectin</td>
<td>4</td>
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<tr>
<td>Dennison et al. (30)</td>
<td>40 schizophrenia patients (24 with psychological trauma and 16 without) (38.33/27.94) 40 healthy controls (36.2/23.89)</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>Plasma ELISA</td>
<td>IL-1β, IL-6, IL-8 and TNF-α</td>
<td>3</td>
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<tr>
<td>Heggl et al. (45)</td>
<td>10 first-episode psychotic patients with CM (30.25) 18 first-episode psychotic patients without CM (27.9/24.7) 45 healthy controls (26.5/23.4)</td>
<td>CECAQ (modified version)</td>
<td>Cross-sectional</td>
<td>Plasma Comay hsCRP assay</td>
<td>CRP</td>
<td>2</td>
</tr>
<tr>
<td>Rooks et al. (41)</td>
<td>245 male middle-aged twins with early trauma (55/30) 237 male middle-aged twins without early trauma (55/30)</td>
<td>ETI</td>
<td>Cross-sectional</td>
<td>Plasma hs Beckman Coulter Assay</td>
<td>Adiponectin and IL-6</td>
<td>4</td>
</tr>
<tr>
<td>Miller and Chan (38)</td>
<td>135 adolescents (females) at high risk to develop initial episode of depression (17/21.6)</td>
<td>Risky Families questionnaire</td>
<td>Longitudinal</td>
<td>Serum and in vitro ELISA</td>
<td>IL-6</td>
<td>5</td>
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<tr>
<td>Carpenter et al. (22)</td>
<td>19 healthy subjects with moderate-severe CM (32.84/28.11) 50 healthy subjects without CM (24.5/24.61)</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>Plasma ELISA</td>
<td>IL-6</td>
<td>3</td>
</tr>
<tr>
<td>Grassi-Oliveira et al. (27)</td>
<td>853 participants who completed the age 32 assessment from Dunedin birth cohort 26.7% experienced 1 indicator of CM</td>
<td>Behavioural observation and parental reports</td>
<td>Longitudinal</td>
<td>Immunoturbidimetric assay</td>
<td>TNF-α, sTNFR1 and sTNFR2</td>
<td>2</td>
</tr>
<tr>
<td>Danese et al. (36)</td>
<td>865 (673 control group; 109 depressed group; 56 CM group; 27 depressed with CM group) participants who completed the age 32 assessment from Dunedin birth cohort</td>
<td>Behavioural observation and parental reports</td>
<td>Longitudinal</td>
<td>Immunoturbidimetric assay and Coagulation analyser</td>
<td>CRP</td>
<td>5</td>
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<tr>
<td>Danese et al. (21)</td>
<td>866 (561 without CM; 232 probable CM; 83 definite CM history) participants who completed the age 32 assessment from Dunedin birth cohort</td>
<td>Behavioural observation and parental reports</td>
<td>Longitudinal</td>
<td>Immunoturbidimetric assay and Coagulation analyser</td>
<td>CRP, Fibrinogen</td>
<td>5</td>
</tr>
<tr>
<td>Pace et al. (28)</td>
<td>14 male subject with current MDD (25.9/27.8) 14 healthy controls (29.4/24.3)</td>
<td>CTQ</td>
<td>Cross-sectional</td>
<td>Plasma PBMC ELISA</td>
<td>IL-6 and nuclear NFKB DNA binding</td>
<td>3</td>
</tr>
</tbody>
</table>
Childhood maltreatment and inflammation

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample (mean age/mean BMI)</th>
<th>Trauma assessment</th>
<th>Design</th>
<th>Assay</th>
<th>Mediators</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al. (37)</td>
<td>3248 participants without symptoms of long-term disease or disability [40.1/28.48]</td>
<td>Risky Families questionnaire</td>
<td>Cross-sectional</td>
<td>Plasma Immuno nephelometric assay</td>
<td>CRP</td>
<td>3</td>
</tr>
<tr>
<td>Chen et al. (48)</td>
<td>37 children with asthma [13.2/ns]</td>
<td>SES, UCLA Life Stress Interview</td>
<td>Cross-sectional</td>
<td>PBMC ELISA</td>
<td>IL-4/IL-5, IL-13 and</td>
<td>2</td>
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</tbody>
</table>

* Differences in BMI between groups, but the authors adjusted the analysis for it.
PTSD, Post-Traumatic Stress Disorder; CTQ, Childhood Trauma Questionnaire; ETI, Early Trauma Inventory; PBI, Parental Bonding Instrument; PBMC, peripheral blood mononuclear cells; BCA, Bicinchoninic acid assay; CBA, Cytometric Bead Array; ELISA, Enzyme-linked immunosorbent assay; TSST, Trier Social Stress Test; SES: socioeconomic status; BMI, body mass index; BO, behavioural observation; CECAG, Childhood Experience of Care and Abuse Questionnaire; IL, Interleukin; CRP, C-reactive protein; IFN, interferon; NFkB, nuclear factor kappa beta; TNF, tumour necrosis factor; sTNFR, Soluble TNF receptor; TGF, transforming growth factor; AgRP, agouti-related protein; b-FGF, basic fibroblast growth factor; GITR-L, glucocorticoid-induced tumour necrosis factor-ligand; I-TAC, interferon induced T cell α chemoattractant; MEC, mucosa-associated epithelial chemokine; TECK, thymus expressed chemokine; TRAIL-RA, tumour necrosis factor related apoptosis inducing ligand-receptor 4; VEGF, vascular endothelial growth factor; BTC, betacellulin; CM, childhood maltreatment; MDD, Major Depression Disorder.

Childhood Experience of Care and Abuse Questionnaire (46) with questions about loss of parents, separation from parents for more than 6 months, and physical and sexual abuse before the age of 17. The Childhood Experience of Care and Abuse Cronbach’s alpha is 0.86 to 0.91 (47). The physical and sexual abuse dichotomized with a score of 0 for absence of any CM and a score of 1 for presence of one or more CM variables (physical or sexual or both). Chen et al. (48) assessed psychological stress with University of California Los Angeles Life Stress Interview (49), focusing on family relationships, friendships, school and home life (parental work stress, family member health, and neighbourhood quality). In this study, an interviewer rated the extent of chronic stress on a 1–5 scale.

In general, we found there is great heterogeneity in the methods used for CM assessment. Most of the studies \([n = 16 (80\%)]\) used a general CM score and did not analyse the effect of different types of CM experiences on inflammatory measurements. Moreover, in agreement with a review (34) which focused on comparing the existing instruments of retrospective interpersonal assessment of CM, the CTQ and the ETI stand out for having more favourable characteristics, such as assessing multiple types of trauma, and reporting better psychiatric properties.

Inflammatory mediators

Cytokines. Cytokines are a heterogeneous group of messenger proteins produced by immune cells as well as non-immune cells. The primary role of these proteins/molecules is the communication between cells to regulate immune responses; however, they exert effects beyond the inflammatory response (50). Cytokines have specific biological activities that vary according to the interplay between pro- and anti-inflammatory mediators. Thus, some cytokines are directly or indirectly involved in inflammatory processes, while others are known to dampen the immune response, by counteracting cellular activation, as well as the production of proinflammatory cytokines. The proinflammatory cytokines investigated in the studies included were TNF-α, soluble TNF receptor 1 (sTNFR1), sTNFR2, IL-1β, IL-1 receptor 1 (IL-1 R1), IL-2, IL-6, IL-8, interferon (IFN)-γ, agouti-related protein (AgRP), basic fibroblast growth factor (b-FGF), glucocorticoid-induced tumour necrosis factor-ligand (GITR-L), interferon induced T cell α chemoattractant (I-TAC), mucosa-associated epithelial chemokine (MEC), thymus expressed chemokine (TECK), tumour necrosis factor related apoptosis inducing ligand-receptor 4 (TRAIL-RA), vascular endothelial growth factor (VEGF), leptin and resistin. The anti-inflammatory cytokines investigated were IL-4, transforming growth factor (TGF)-β1, IL-5, IL-10, IL-13, adiponectin and betacellulin (BTC).

Eight studies (40\%) tested association between IL-6 and history of CM with controversial results. Tietjan et al. (43) showed that women with migraine reported adversity more commonly than controls, and demonstrated that those who reported adversity had higher IL-6 plasma levels. Dennison et al. (30) compared subjects with schizophrenia diagnoses with positive and negative history of trauma and a healthy control group and found increased IL-6 levels only in schizophrenia patients with positive history of childhood trauma. Moreover, Miller and Chen (38) assessed adolescent females with repeated measures of psychological stress, harsh family climate in early life and inflammatory markers. They found a significant interaction between harsh family climate and early
life stress in predicting IL-6 production in cultured white blood cells with lipopolysaccharide (LPS) stimulation, but no IL-6 systemic effect. Carpenter et al. (22) investigated plasma IL-6 response to the Trier Social Stress Test (TSST) (a procedure designed to induce psychosocial stress) in healthy adults in comparison with individuals with moderate–severe CM history. This study found that greater stress-induced increase in IL-6 plasma levels was associated with a history of CM. On the other hand, Lopes et al. (23) and Lu et al. (20) found no differences in IL-6 levels between women with Major Depression Disorder (MDD) without history of CM, women with MDD and CM, and healthy controls. Furthermore, Pace et al. (28) found no association between CTQ scores and IL-6 levels after the TSST in MDD patients. In the same way, Rooks et al. (41) found no association between early trauma and IL-6 levels in middle-aged twins. However, those with early trauma had 13% higher levels of IL-6 compared with those without.

Tumour necrosis factor-α levels were analysed in five studies. Dennison et al. (30) compared patients with schizophrenia with and without history of CM and healthy controls. They found a significant positive association between TNF-α levels and the number of traumatic events during childhood in individuals with schizophrenia. In line with this observation, Tietjen (43) compared women migraineurs with history of adversity and women without migraine and without history of early life adversity and demonstrate that those reporting adversity have a higher risk of biomarker levels indicating coagulation. In addition, a positive association between childhood adversity and TNF-α levels was found to be independent of age, oral contraceptive use, BMI, smoking, hypertension, hyperlipidemia and migraine. On the other hand, Lopes et al. (23), Grassi-Oliveira et al. (27) and Lu et al. (20) found no significant difference in TNF-α levels comparing woman with current MDD without history of CM, woman with MDD and CM history, and healthy controls.

Two studies analysed IFN-γ levels. Lopes et al. (23) did not find any group differences in IFN-γ levels between women with MDD with or without history of CM and with healthy controls. In the same way, Chen et al. (48) found no associations regarding chronic family stress with IFN-γ levels in children with or without asthma.

In addition, two studies analysed the association between CM and IL-4 production. Chen et al. (48) found no associations regarding chronic family stress with IL-4 levels in healthy children or children with asthma. Lopes et al. (23) found that women with history of CM and MDD had lower IL-4 levels compared with healthy subjects. However, they found no differences in IL-4 levels regarding women with MDD without CM history.

Other proinflammatory cytokines were analysed regarding the association with CM. Lu et al. (20) demonstrated that peripheral levels of AgRP, b-FGF, GITR-L, I-TAC, IL-1β, IL-1 R1, MEC, TECK, TRAIL-R4 and VEGF were higher in MDD patients with CM compared with MDD patients without CM and normal controls. Lopes et al. (23) found that women with history of CM and MDD had lower IL-2 levels compared with healthy subjects, but no differences regarding women with MDD without CM history. Furthermore, Dennison et al. (2012) analysed IL-1β and IL-8 levels and found no significant differences between schizophrenia patients with or without CM history and healthy subjects. Lu et al. (20) found higher levels of TGF-beta1 and BTC in MDD patients with CM compared to two others groups. In addition, Tietjen et al. (43) found a positive association between CM and TGF-beta1 levels in women with migraine. However, Lopes et al. (23) found no differences in IL-10 levels between women with MDD with or without CM history and healthy subjects. Chen et al. (48) found that higher levels of home stress were associated with higher IL-13 and IL-5 levels among children with asthma. Conversely, among healthy children, higher stress was associated with lower IL-13 and IL-5 levels.

Some studies investigated adipocyte-related cytokines, including adiponectin, leptin and resistin. Adiponectin exerts an anti-inflammatory effect. The impact of CM on adiponectin levels was investigated in three studies, with heterogeneous results. Lehto et al. (44) compared a group of individuals with psychiatric symptoms with and without history of CM, and reported reduced levels of adiponectin in those reporting history of CM. In the same way, Levandowski et al. (32) found reduced levels of plasma Adiponectin in women with crack cocaine-dependence and history of CM. On the other hand, in female patients with migraine, adverse childhood experiences were associated with lower levels of adiponectin, although statistical significance was lost when results were adjusted for age, education levels and stroke risk factors. Tietjen et al. (43), Lehto et al. (44) and Levandowski et al. (32) also found no association between CM and resistin or leptin levels.

The sTNFR1 and sTNFR2 peripheral levels were analysed in MDD patients and controls by Grassi-Oliveira et al. (27). The authors found that levels of sTNFR2, but not sTNFR1, were.
Fibrinogen is a protein that is essential for the coagulation of blood and it is produced by the liver and synthesized by hepatocytes. As a non-specific phase-reactant, it is a down-stream component of the inflammatory cascade. Three studies investigated this factor. Zeugmann et al. (29) showed that CM and metabolic syndrome both independently influenced fibrinogen levels in depressed patients. Danese et al. (21) analysed fibrinogen levels in participants divided into four groups: depressed group, CM group, depressed with CM history group and a control group, who completed the age 32 assessment from the Dunedin birth-cohort. The association between CM and elevated adult fibrinogen levels was significant. Furthermore, in 2007, Danese et al. (35) analysed participants without CM, participants with probable CM history and participants with definite CM experiences, who completed the age 32 assessments from Dunedin birth cohort. There was a significant dose–response association between CM and the composite factor score of inflammation generalized (logged CRP, fibrinogen and white blood cells) by continuous measures.

**Methodological quality.** Three studies (15%) were scored as having higher methodological quality (5 points) but none achieved all six possible methodological points. In addition, three studies (15%) scored 4 points; eight studies (40%) scored 3 points and five studies (25%) scored 2 points. A summary of the CM effects on each inflammatory mediator described above, taking into account the methodological quality weight of the evidences, is shown in Table 2. In addition, a summary of the most studied inflammatory mediators is shown in Fig. 2.

**Discussion**

In this study, we conducted a systematic literature review focused on the impact of CM on inflammatory mediators. Although at present the evidence is strong in supporting an association of increased inflammatory response with CM, there were a considerable number of studies that did not find a significant effect of CM on immune markers. This is not surprising due to the heterogeneity of the methodological characteristics of the selected studies. For instance, a considerable number of studies cited were compromised by sample heterogeneity and low number of subjects with history of CM (19, 29, 44, 45) – issues that might have inhibited the detection of differences between groups or the relationship between CM and inflammatory mediators. Nevertheless, the present review corroborates the literature on the association between CM
and inflammatory response, and highlights the potential long-term consequences of stressful experiences during early life development on increasing risk for manifestation of psychopathology later in life.

**Proinflammatory cytokines.** Independent of the sample clinical comorbidity, particularly depression, most of the findings demonstrated an increase in the peripheral plasma/serum levels of several proinflammatory cytokines with presence of CM. Therefore, it is possible that those who experienced major stressors early in life may be more vulnerable to immune dysregulation in adulthood regardless of their subsequent physical or mental health sequelae. The strongest results that showed systemic elevated baseline inflammation levels associated with CM experiences were in studies supported by longitudinal data and investigations with larger samples. In addition, relevant to the specific effects of CM on lymphocytes, one study (38) investigated *in vitro* IL-6 production and found a significant interaction between harsh family environment and early life stress in predicting IL-6 production over time in cultured white blood cells. Moreover, regarding IL-6, recent studies have shown that IL-6 is a cytokine not only involved in inflammation and infection responses but also in the regulation of metabolic, regenerative and neural processes. The IL-6 regenerative effect is an anti-inflammatory activity mediated by classic signalling, whereas proinflammatory responses of IL-6 are mediated by transsignalling (52). Whereas only few cells express the IL-6 receptor that responds to IL-6 (classic signalling), all cells can be stimulated via a soluble IL-6 protein receptor (trans-signalling) since this protein – gp130 – is ubiquitously expressed. This is important since IL-6 was the most investigated cytokine by the selected studies, but some studies found no association between CM and higher levels of IL-6.

In addition, adult individuals with a history of CM showed not only elevated baseline

<table>
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<th>Table 2. Pondered results of selected studies</th>
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<td>Childhood maltreatment influence on inflammatory mediators</td>
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<td>Higher levels</td>
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<td>Proinflammatory cytokines</td>
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<tr>
<td>IL-1β</td>
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<tr>
<td>IL-1 R1</td>
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<td>IL-2</td>
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<td>IL-6</td>
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<td>IL-8</td>
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<tr>
<td>TNF-α</td>
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<td>IFN-γ</td>
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<td>sTNFR1</td>
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<td>AgRP</td>
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<td>b-FGF</td>
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<td>GITR-L</td>
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<td>I-TAC</td>
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<td>MEC</td>
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<td>TRAIL-RA</td>
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<td>VEGF</td>
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<td>Leptin</td>
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<td>Anti-inflammatory cytokines</td>
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<td>IL-4</td>
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<td>IL-5</td>
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<td>IL-13</td>
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<td>TGF-beta1</td>
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<tr>
<td>BTC</td>
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<tr>
<td>Adiponectin</td>
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<td>Others mediators</td>
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<tr>
<td>CRP</td>
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<tr>
<td>NRP</td>
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<td>Fibrinogen</td>
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Dot size was proportional to the methodological score of the study.

IL, Interleukin; CRP, C-reactive protein; IFN, interferon; NRP, nuclear factor kappa-light-chain-enhancer of activated B cells; TNF, tumour necrosis factor; sTNFR, soluble TNF receptor; TGF, transforming growth factor; AgRP, agouti-related protein; b-FGF, basic fibroblast growth factor; GITR-L, glucocorticoid-induced tumour necrosis factor-ligand; I-TAC, interferon induced T cell α chemoattractant; MEC, mucosa-associated epithelial chemokine; TECK, thymus expressed chemokine; TRAIL-RA, tumour necrosis factor related apoptosis inducing ligand-receptor 4; VEGF, vascular endothelial growth factor; BTC, betacellulin.
inflammation levels but also greater inflammatory response to psychosocial stress (TSST) (22). Miller et al. (7) proposed a model to explain why those who experienced CM have an enhanced proinflammatory phenotype. The model’s central premise is that the stress that occurs during a sensitive period, when immune function is highly plastic, gets embedded in the functioning of the cells that regulate inflammation. Therefore, the monocytes/macrophages will develop response tendencies that give rise to a chronic proinflammatory state, increasing the levels of circulating cytokines. In addition, how the innate immune cells respond to stimuli has important consequences for the activities of other leukocytes, particularly the T- and B-cells that orchestrate adaptive immune responses. As a result, it is possible that chronic inflammation renders the host vulnerable to infection and tumour growth by also suppressing adaptive immune functions.

Regarding particularly diseases, immune alterations have been previously reported in several psychiatric phenotypes, including mood disorders and schizophrenia (for review see 53, 54), and these immune changes are linked to symptom severity. The mechanisms underlying this association also include an increase in the levels of peripheral proinflammatory cytokines. Cytokines might modify the balance of several neurotransmitters, as well as mitochondrial dysfunction, free radical production and also degeneration in nervous cells (55). This is important since almost all of the included studies were conducted with psychiatric patients.

The neuroinflammation signalling between peripheral and central response involves the activation of resident macrophages on central nervous system, called microglia. Microglial functioning dysregulation is associated with both mental diseases and critical changes in neuronal activity (56). The classical M1 microglial activation results in secretion of innate proinflammatory cytokines TNF-α and IL-1β, which can directly injure specific neurons if overexpressed (57). Furthermore, animals injected with IL-1β or TNF-α in specific brain regions stay in a corner of their home cage in a curved posture and demonstrate reduced interest in their social environment – depressive-like behaviour (58). In this vein, studies with rodents have also showed that early life stress induces premature activation of the immune system that can significantly shift the developmental trajectory of microglia, changing the patterns of activation of these cells regarding subsequent challenges (for review see 59). As a consequence, rats exposed to stress early in life are more vulnerable to exaggerated proinflammatory cytokine production following an LPS challenge in adulthood, suggesting that this proinflammatory state remains throughout the years and increases the risk for subsequent brain disorders.

Finally, it is particularly important that previous reports evidenced that the fold-change in levels of proinflammatory cytokines in blood from psychiatric patients do not seem to behave at the same level of magnitude as those in the blood of inflammatory-related disorders patients such as rheumatoid arthritis (60, 61). Although we have not explored this kind of different patterns, it is possible that distinct psychiatric phenotypes may also induce distinct proinflammatory cytokines levels unbalance, as well as the effects of CM on these markers.

**Anti-inflammatory cytokines.** Few of the reviewed studies investigated anti-inflammatory mediators and the results were very inconsistent. Some of the findings pointed to increased levels of IL-5, IL-13 and TGF-beta1, whereas others found no association or reduced levels of anti-inflammatory mediators. For instance, Lehto et al. (44) and Levandowski et al. (32) report lower serum/plasma adiponectin levels in individuals with a history of CM. In animal studies, adiponectin administration attenuates sympathetic nervous system activity (62, 63). However, as highlighted above, there is a complex network of bidirectional signals between the nervous, endocrine and immune systems. For example, cortisol is a powerful anti-inflammatory regulator of the transcriptional-control pathways that orchestrate immune responses to infection and injuries (16). In a classic negative feedback circuit, cortisol binds to glucocorticoid receptors located within macrophages and other immune cells, and slows down the inflammatory processes. Thus, the dysregulation of the HPA axis in maltreated individuals, because of pituitary hyporesponsiveness to CRH and/or increased glucocorticoid receptor sensitivity to cortisol, has the potential to create a systemic proinflammatory state. In a similar manner, reduced levels of anti-inflammatory cytokines might be because of feedback mechanisms and may have a role in the chronic inflammation state associated with CM.

**The role of others mediators.** Elevation in circulating CRP levels in individuals with history of CM was the most robust finding among the reviewed studies. Because cytokines have short half-lives, research usually focuses on CRP as an alternative, especially because it has a long half-life and can be detected at low levels (7). Since CRP is an acute-phase protein released by the liver in response to IL-6 and TNF-α liberation, it is widely used as a
marker of inflammation. In addition, CRP is a component of the humoral innate immune system and facilitates recognition of pathogens and their killing through the activation of complement or the recruitment of macrophages and neutrophils. Therefore, increased CRP levels, as well as fibrinogen, corroborate with the systemic elevated baseline inflammation levels associated with CM experiences.

Only two studies sought to investigate NFkB functioning and just one found a positive association with childhood emotional abuse experiences. However, NFkB is a promising candidate for converting psychosocial stress, including CM experiences, into immune intracellular activation and gene expression (64). Increased NFkB activation has been described in blood lymphocytes of women stressed by the experience of breast biopsy, an extreme life-threatening stressful situation characterized by anxiety and desperation (65). Moreover, a growing body of evidence supports that altered NFkB activation contributes to the pathophysiology of lifestyle-related diseases such as diabetes mellitus, cardiovascular disease and atherosclerosis (66–68). Therefore, the role of NFkB in mediating long-term immune response alterations associated with childhood adversities should be further explored.

**Methodological issues.** Our results must be considered taking into account some methodological limitations of the reviewed studies. In addition, it should be noted that in accordance with our criteria, only three studies were scored with five methodological quality points. First, most of the studies were cross-sectional or report retrospective data. Retrospective CM assessment is susceptible to memory bias, because participants were asked to recall events that happened a long time ago, and the harmful memories can be underestimated. Second, although there were three longitudinal studies reviewed, they were all from the New Zealand birth-cohort (21, 35, 36). Considering that inflammation response can be influenced by ethnicity and ancestry (69), studies in other parts of the world, involving repeated collection of biological data, would be useful. Third, certain associations may have been missed because of small sample sizes, especially regarding anti-inflammatory mediators, which lead to the studies receiving low methodological quality points. The most consistent findings of this review were extracted from studies with larger samples.

Fourth, the modest quantity of studies that have attempted to refine the assessment of inflammatory mediators, including both *ex vivo* and *in vivo* measurements, resulted in a large amount of data on the systemic effects of CM experiences, but few data regarding specific associations with immune cell function. Fifth, most of the studies investigated IL-6, TNF-α and CRP. Hence, there is limited information about other pro-and anti-inflammatory cytokines, as well as intracellular immune pathways. Therefore, stronger conclusions about the effects of CM on inflammatory cytokines may be investigated in future meta-analysis. Finally, the majority of studies considered different types of trauma and abuse as one phenomenon and/or did not distinguish the nature of maltreatment. This may be because of the fact that much of the published literature is based on studies originally designed for other proposes, with CM effects deriving from secondary analyses. However, the nature of adverse childhood experiences can be very different depending, for example, on the number, the duration, the timing, the type, and the method of assessment of adversities. In this sense, the response to even very similar adversities can be very different depending on individual characteristics of resilience and vulnerability, including genetic background and previous experiences. Thus, the impact of different types of childhood adversities on inflammatory mediators definitely should be addressed in further research.

**Future directions.** Exactly how CM generates a proinflammatory phenotype is still unclear and probably is a result of a complex network of biological pathways affected by such experiences. Epigenetic processes hold substantial promise to resolve and explain many of these unsolved mechanisms, since they operate at the interface between genetics and the environment (70, 71). For example, Krukowski et al. (72) showed that at least in part, glucocorticoids dysregulate immune function (natural killer cell activity and cytokine production), by modifying chromatin accessibility at promoter regions proximal to immune effector genes. However, there is scarce evidence that early life stress, psychosocial distress, maladaptive behaviours or emotions result in epigenetic modifications that impact immune function. This evidence will probably emerge from animal studies or in studies with CM survivors (73).

In addition, recent studies have focused on the role of Toll-Like Receptors (TLRs) regarding how the brain monitors and triggers peripheral immune signals (58, 74). The discovery that not only immune cells, but also neurons, astroglia and resident microglia, express a large majority of the 13 already identified TLRs has challenged the way
neuroscience explains neuroimmune interactions. Some findings demonstrated that TLRs is relevant in the activation of NFkB proinflammatory pathways elicited by stress exposure in the brain pre-frontal cortex (75, 76). However, these findings are incipient and derived from studies with adult animals, thus little is known about the impact of early-life stress on TLRs.

In summary, CM experiences may result in physiological responses that endure long after the initial threat has ceased, thus becoming detrimental to immune system functioning, and resulting in a chronic inflammatory state. This is a major issue since several studies have provided convincing evidence linking childhood stress-induced immune dysregulation with morbidity and mortality (77). However, more research is needed to understand the consequences of CM persist across the lifespan, and perhaps with the increase of studies in this field it will be possible to investigate particularly effects of CM regarding inflammatory pathways in specific diseases. Future studies should also offer new insights on the reversibility of the damage associated with CM experiences, including studies testing if interventions focused on the behavioural sequelae of childhood adversities could reduce the abnormalities in immune system function.

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Declaration of interest

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