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Review article

Inflammation as a mediator between adverse childhood experiences and adult depression: A meta-analytic structural equation model

Andrea Zagaria [a], Valeria Fiori [a], Mariacarolina Vacca [a], Caterina Lombardo [a], Carmine M. Pariante [b], Andrea Ballesio [a,*]

[a] Department of Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy
[b] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

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ABSTRACT

Exposure to adverse childhood experiences (ACEs) confers a higher risk of developing depression in adulthood, yet the mediation of inflammation remains under debate. To test this model, we conducted a systematic review and two-stage structural equation modelling meta-analysis of studies reporting correlations between ACEs before age 18, inflammatory markers and depression severity in adulthood. Scopus, Pubmed, Medline, PsycInfo, and CINAHL were searched up to 2 October 2023. Twenty-two studies reporting data on C-reactive protein (CRP, n = 12,935), interleukin-6 (IL-6, n = 4108), tumour necrosis factor-α (TNF-α, n = 2256) and composite measures of inflammation (n = 1674) were included. Unadjusted models revealed that CRP (β = 0.003, 95 % LBCI 0.0002 to 0.0068), IL-6 (β = 0.003, 95 % LBCI 0.001 to 0.006), and composite inflammation (β = 0.009, 95 % LBCI 0.004 to 0.018) significantly mediated the association between ACEs and adult depression. The mediation effects no longer survived after adjusting for BMI; however, a serial mediation model revealed that BMI and IL-6 sequentially mediated the association between ACEs and depression (β = 0.002, 95 % LBCI 0.0005 to 0.0046), accounting for 14.59 % and 9.94 % of the variance of IL-6 and depressive symptoms, respectively. Due to the cross-sectional nature of assessment of inflammation and depression findings should be approached with caution; however, results suggest that complex interactions of psychoneuroimmunological and metabolic factors underlie the association between ACEs and adulthood depression.

1. Introduction

Prevalence of adverse childhood experiences (ACEs) is remarkably high. Estimates showed that 47 % to 64 % of Western adults reported at least one ACE, while 9 % to 17 % reported four or more ACEs (Bellis et al., 2014; Swedo et al., 2023). ACEs may include exposure to several types of abuse and neglect in childhood, including physical, emotional, and sexual abuse and physical and emotional neglect (Bernstein et al., 1998). Strong evidence demonstrated that exposure to ACEs is associated with higher risk of negative psychosocial/behavioural and medical outcomes (Petruccelli et al., 2019). ACEs have been particularly associated with a higher risk of adulthood depression, with ORs ranging from 1.34 to 3.17 in meta-analysis (e.g., Tan and Mao, 2023). The underlying psychobiological factors linking ACEs to depressive symptomatology, however, are still elusive, with inflammatory response being a putative mechanism (Iob et al., 2020; Maayan and Maayan, 2023).

Inflammation is considered a primary defence of the body against physical damage, pathogen exposure, and psychosocial threats (e.g., Hänsel et al., 2010) which is orchestrated by innate immune system. According to the social signal transduction theory of depression (Slavich and Irwin, 2014; Shields et al., 2024), experiences of social threat and adversity upregulate components of immune system involved in inflammation that may drive the pathogenesis of depression. Consistently, a previous meta-analysis showed that peripheral levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) and acute phase inflammatory proteins such as C-reactive protein (CRP) were higher in individuals exposed to ACEs than in non-exposed controls (Baumeister et al., 2016), although more recent evidence found predominantly non-significant associations between ACEs and elevated levels of all inflammatory markers in adulthood (Brown et al., 2021). Traditional mechanisms proposed to be involved in ACEs-related inflammation include sympathetic nervous system activation following exposure to early life stress which may determine a shift in the profile of innate immune cells with an increase

* Corresponding author at: Department of Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Via dei Marsi 78, 00185 Rome, Italy.
E-mail address: andrea.ballesio@uniroma1.it (A. Ballesio).

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long-term upregulation of proinflammatory gene transcription in monocytes (e.g., Cole et al., 2012; Mondelli and Vernon, 2019); greater methylation of the glucocorticoid receptors (Klengel et al., 2013); increased nuclear factor-kappa B activity, a key transcriptional control pathway in the inflammatory response (Pace et al., 2012); and glucocorticoids resistance, i.e., the inability of cortisol to exert its anti-inflammatory action (Miller et al., 2002).

Notably, while normal, temporally restricted activation of inflammatory response is not harmful *per sè*, chronically or disproportionally activated inflammation may become a pathogenetic factor for physical illness (Furman et al., 2019) and could be associated with the onset of depressive symptoms in a subgroup of individuals (Milaneschi et al., 2021). Indeed, strong evidence supports the presence of higher levels of CRP, IL-6, and TNF-α in patients with depression compared to healthy controls (Dowlati et al., 2010; Osimo et al., 2020), although this is not fully explained by the increased presence of ACEs in this population (Pitharouli et al., 2021). Levels of inflammatory markers may also prospectively predict the severity of depression (Mac Giollabhui et al., 2021; Ballesio et al., 2024). In healthy samples, experimental endotoxemia, a translational model of systemic inflammation has been associated with depressogenic effects (e.g., Lasselin et al., 2021). Finally, recent studies using Mendelian randomization, an analytic procedure using genetic variants which is not susceptible to confounding and reverse causality bias (Ballesio, 2023), suggested that genetically determined inflammation was associated with depression (Kappelmann et al., 2021; Galan et al., 2022).

From this perspective, it is plausible that the association between ACEs and adult depression may be, at least partially, mediated by inflammation. This hypothesis, despite being widely accepted (Slavich and Irwin, 2014; Baumeister et al., 2016; Maayan and Maayan, 2023), is still lacking meta-analytic investigation, which is considered fundamental in evidence-based healthcare (Gopalakrishnan and Ganeshkumar, 2013). Meta-analytic structural equation modelling is an advanced statistical technique which enables to test mediation hypotheses in systematic reviews, increasing statistical power and precision of estimate compared to bivariate meta-analysis, ultimately enriching the robustness of the findings (Zagaria et al., 2023). Also, meta-analytic structural equation modelling allows to account for potential confounders and test sequential mediation (i.e., with two or more mediators). This represents an advancement compared to traditional pairwise meta-analysis, where confounders are predominantly examined as moderators through meta-regressions in an attempt to explain between-study heterogeneity. On the other hand, meta-analytic structural equation modelling permits disentangling the unique contribution of each predictor after controlling for potential confounding factors (Cheung and Hong, 2017). An accurate control of confounders appears of utmost importance in this field, as the associations between ACEs, inflammation, and depression may be remarkably influenced by several factors including body mass index (BMI, e.g., Danese and Tan, 2014; Mitchell et al., 2018; Brown et al., 2021) and age (Maayan and Maayan, 2023). To advance the field, we therefore conducted a systematic review and structural equation modelling meta-analysis testing the association between ACEs and depression and the mediating role of inflammation.

2. Materials and methods

The study followed the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) and was registered to the PROSPERO International database of the University of York Centre for Reviews (ID number CRD42023471274).

2.1. Search strategy and selection

A systematic literature search of published studies was conducted using Pubmed, Scopus, Medline, Psycinfo, and CINAHL. Additional records were searched by consulting a previous meta-analysis on ACEs and inflammation (Baumeister et al., 2016). The search string included the following keywords: Childhood Maltreatment OR Childhood Trauma OR Childhood Adversity OR Early Life Stress OR Child Abuse OR Child Neglect OR Adverse Childhood Experiences AND C-reactive Protein OR CRP OR Tumour Necrosis Factor OR TNF-α OR Cytokine OR Interleukin OR IL-6 OR Inflammatory OR Inflammation AND depressi*. Database search was conducted by the first and the second authors under the supervision of the last author on 2 October 2023. Articles were included if they provided original data about the association (e.g., correlation coefficients, effect sizes of group differences) of any ACE before age 18 with peripheral markers of inflammation and depressive symptoms/diagnosis in adult humans (individuals aged 18 or older). Several biomarkers of inflammation were eligible, including cytokines (e.g., IL-6, IL-1β, IL-8, TNF-α, interferon-γ), chemokines, CRP, fibrinogen, and white blood cell count. The first and the second authors independently screened titles and abstracts as well as full-text articles against eligibility criteria. Disagreements between the reviewers were resolved by discussion with the last author. Detailed search strategy for each database is reported in the Supplementary Material.

2.2. Data extraction and quality appraisal

Data from included studies were extracted by the second author using a standardized datasheet form built to extract the following study characteristics: number of participants, % of females, mean age, type of sample (i.e., healthy individuals, patients with depression), type of inflammatory marker, depression measure, ACE measure. Also, correlation coefficients between ACEs, inflammatory markers, and depression were extracted to proceed with meta-analytic calculations. If correlation coefficients were not available in original studies, they were derived from other effect size metrics (e.g., Cohen's d, Odds Ratio) following Lipsey and Wilson (2001) and Borenstein et al. (2009). Alternatively, *t*-value and or *F*-ratio statistics were transformed into Cohen's d and then converted into correlation coefficients (Lipsey and Wilson, 2001). Extracted data were cross-checked by the first and the last author.

The quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies (Moola et al., 2017). The checklist included eight statements (e.g., "Were the study subjects and the setting described in detail?", "Were the outcomes measured in a valid and reliable way?"), with four possible response options: yes, no, unclear, not applicable. The total number of "yes" answers is considered an indicator of higher study quality (Moola et al., 2017).

2.3. Data analysis

Data were analysed via *R* version 4.2.2 using the *metaSEM* (Cheung, 2015) and *OpenMx* (Boker et al., 2011) packages.

Meta-analytic structural equation modelling was applied through a two-stage structural equation modelling (TSSEM) approach (Cheung and Chan, 2005). In Stage 1 of the TSSEM, the correlation matrices extracted from primary studies were combined using either fixed or random effects models via maximum likelihood estimation. Specifically, the homogeneity of the correlation matrices was primarily examined within a fixed effects model. Data were considered homogeneous when the following goodness-of-fit indices met their respective cut-offs (Browne and Cudeck, 1993; Wang and Wang, 2019): the root mean square error of approximation (RMSEA; reasonable when <0.08), the comparative fit index and the Tucker-Lewis index (CFI and TLI, respectively; acceptable when >0.90), and the standardized root mean squared residual (SRMR; acceptable when <0.08). If the assumption of homogeneity proved untenable, random effects models were carried out and the heterogeneity of the correlation coefficients was quantified using the I^2 statistics (Higgins and Thompson, 2002). I^2 values of 0.25, 0.50 and 0.75 indicate low, medium, and high levels of heterogeneity,

respectively (Higgins et al., 2003). In Stage 2 of the TSSEM, the hypothesised path model was fitted on the pooled correlation matrix estimated from Stage 1 by minimising the weighted least squares fit function (Browne, 1984). Three distinct partial mediation models were examined, each exploring the role of a different inflammation marker as a mediator in the relationship between ACEs and depressive symptoms: CRP as a mediator (Model 1); IL-6 as a mediator (Model 2); TNF-α as a mediator (Model 3); composite inflammation as a mediator (Model 4). For significance testing of the indirect effects, 95 % likelihood-based confidence intervals were computed (95 % LBCI; Neale and Miller, 1997; Cheung, 2009). Furthermore, two control analyses were carried out examining the role of age and BMI as potential confounders in the mediation models.

Methods for assessing publication bias within the meta-analytic structural equation modelling framework are still in the early stages of development (Scherer et al., 2019; Jak and Cheung, 2020). Nonetheless, exploratory analyses for assessing publication bias were conducted at the level of individual correlations, rather than on correlation matrices (e.g., Scherer et al., 2019). First, the correlations were transformed into Fisher's z and combined using random effects models via restricted maximum likelihood estimation (Borenstein et al., 2009). Thereafter, the evidence of publication bias for single correlations was examined by visually inspecting the funnel plot and by conducting Egger's regression test to detect its asymmetry (Egger et al., 1997). In the absence of any missing studies, the funnel plot's shape should resemble an inverted funnel, symmetrical in nature, with a wide base containing smaller studies exhibiting significant variability, and a narrow apex (Tehrani and Yamini, 2020).

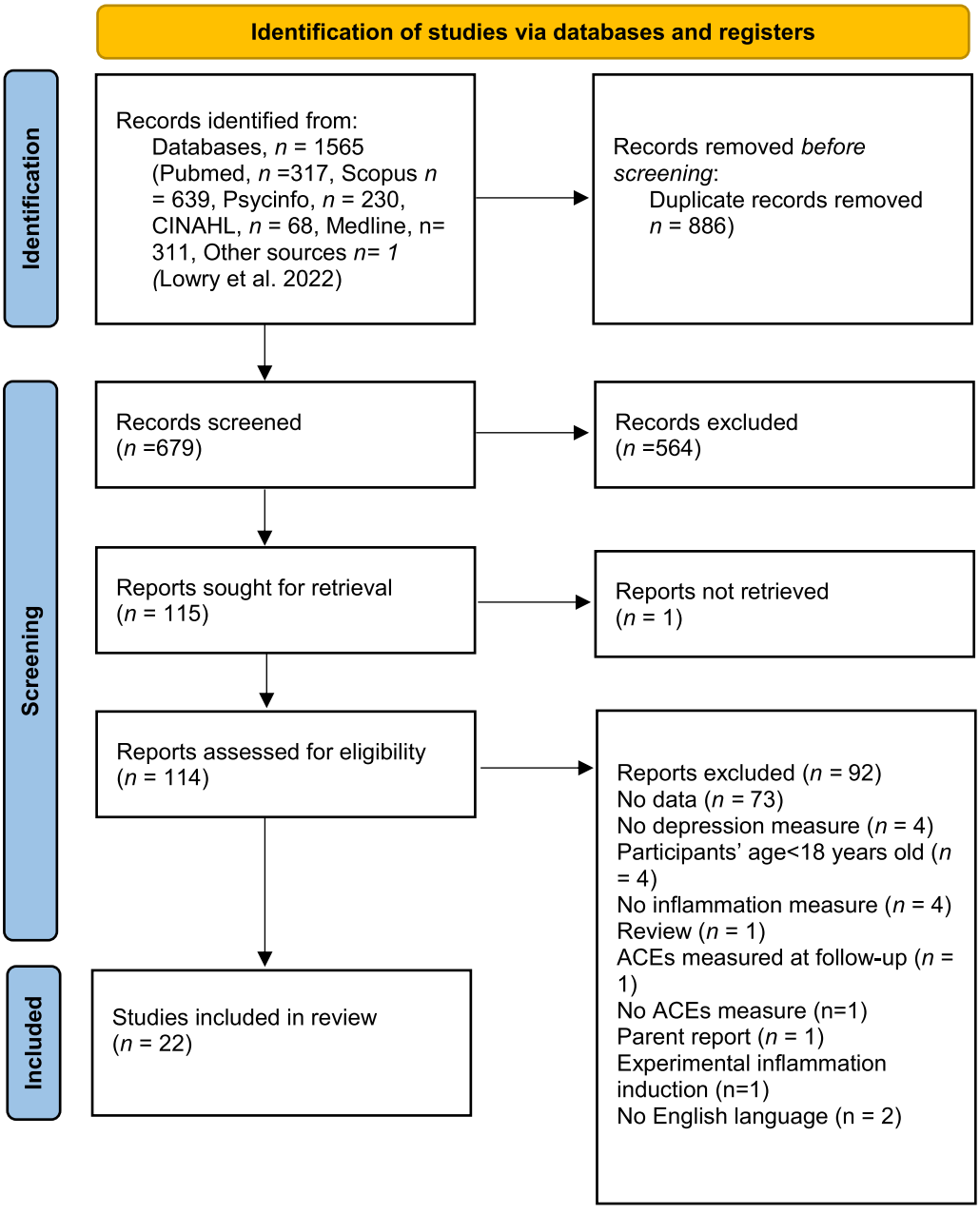

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
For more information, visit: http://www.prisma-statement.org/.

3. Results

3.1. Search process

Detailed search flow is reported in Fig. 1. Database search identified 1565 records (Pubmed, $n = 317$, Scopus $n = 639$, Psycinfo, $n = 230$, CINAHL, $n = 68$, Medline, $n = 311$). One additional record (Lowry et al., 2022) was detected by consulting the meta-analysis of Baumeister et al. (2016). After duplicates removal, 679 titles and abstracts were screened against eligibility criteria. Thereafter, 114 full texts were screened, and 22 met the eligibility criteria and were included in the review.

3.2. Study characteristics

Detailed information of included studies are reported in Table 1. The mean age of the participants was 38.56 ± 8.1 years. The overall percentage of females was 67.99 %. Almost all the studies used standardized measures to investigate adverse childhood experiences (ACEs). Specifically, eight studies (Congio et al., 2022; Hostinar et al., 2017; Jones et al., 2023; Kleih et al., 2022; McCormack et al., 2021; Mehta et al., 2022; O'Shields et al., 2022; Rengasamy et al., 2022) used the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) and one (Davis et al., 2019) used the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Bernstein et al., 2003), three studies (Chiang et al., 2017; Runsten et al., 2014; Taylor et al., 2006) used the Risky Families questionnaire (RFQ) (Taylor et al., 2004), two studies (De Punder et al., 2018; Kuhlman et al., 2020) used the Early Trauma Inventory (ETI) (Bremner et al., 2000), one (Gardhouse et al., 2021) used the Stress and Adversity Inventory for Adults (STRAIN) (Slavich and Shields, 2018), one (John-Henderson et al., 2020) the Adverse Childhood Experiences Study Questionnaire (Felitti et al., 1998), one (Lowry et al., 2022) used the Life History Interview (LHI) and another one (Walker et al., 2022) the Childhood Maltreatment Interview Schedule-Short Form (CMIS-SF; Briere, 1992). Among the twenty-one studies, four used ad hoc questionnaires on ACEs. In particular, one study (Batsika et al., 2021) used 29 questions, one study (Hostinar et al., 2015) used a summary measure of adverse events experienced before age 18, one study (Nakamura et al., 2022) used a measure of the occurrence of three adverse events linked to health disparities and one study (Watt et al., 2020) used ten questions from the original ACE study (Felitti et al., 1998).

With respect to inflammatory markers, twelve studies examined IL-6 (Chiang et al., 2017; Davis et al., 2019; De Punder et al., 2018;

Table 1
Study characteristics.

Study name	N total	Female %	Mean age ± SD	Type of sample	Inflammatory marker	Depression measure	ACEs measure
Bitsika et al., 2021	221	58.8 %	44.06 ± 17.83	Healthy subjects	CRP	SDS	Ad hoc questionnaire
Chiang et al., 2017	91	57.14 %	18.37 ± 0.51	Healthy subjects	IL-6	CES-D	RFQ
Congio et al., 2022	67	nr	nr	Clinical (MDD)	hs-CRP	HDRS17	CTQ
Davis et al., 2019	770	55 %	53.50 ± 7.24	Healthy subjects	IL-6	MHI	CTQ-SF
De Punder et al., 2018	88	nr	nr	Clinical (MDD)	IL-6, WBC	MADRS	ETI
Gardhouse et al., 2021	64	100 %	28.7 ± 9.1	Clinical (MDD; BPD)	IL-6; TNF-α; CRP	BDI-II	STRAIN
Hostinar et al., 2015	1180	56 %	57.3 ± 11.5	Healthy subjects	Composite inflammation (IL-6; CRP; fibrinogen; E-Selectin; ICAM-1)	CES-D	Ad hoc questionnaire
Hostinar et al., 2017	314	55.7 %	55.3 ± 11.2	Healthy subjects	Composite inflammation (CRP; IL-6; fibrinogen)	CES-D	CTQ
John-Henderson et al., 2020	90	50 %	37.55 ± 15.74	Healthy subjects	IL-6; CRP	PHQ-9	ACESQ
Jones et al., 2023	331	50.5 %	40.24 ± 6.24	Healthy subjects	IL-6; CRP	BDI-II	CTQ
Kleih et al., 2022	180	100 %	27.6 ± 5.2	Pregnant women	Composite inflammation (TNF-α; IL-6)	CES-D	CTQ
Kuhlman et al., 2020	41	73.2 %	18.49 ± 0.75	Healthy subjects	IL-6	POMS-15	ETI
Lowry et al., 2022	3029	54.8 %	nr	Healthy subjects	hs-CRP	CES-D	LHI
Mehta et al., 2022	54	100 %	39.8 ± 11.90	Healthy subjects	IL-6, CRP	BDI-II	CTQ
McCormack et al., 2021	187	100 %	29.64 ± 6.25	Pregnant women	IL-6	HAM-D	CTQ
Nakamura et al., 2022	3416	58.28 %	68.41 ± 10.24	Healthy subjects	hs-CRP	CES-D	Ad hoc questionnaire
O'Shields et al., 2022	2118	54.91 %	53.02 ± 12.55	Healthy subjects	IL-6; TNF-α; CRP, fibrinogen	CES-D	CTQ
Rengasamy et al., 2022	74	65 %	36.24 ± 10.83	Clinical (TRD)	IL-6; TNF-α	MADRS	CTQ
Runsten et al., 2014	116	nr	42.89 ± 8.09	Healthy subjects	hs-CRP	MINI	RFQ
Taylor et al., 2006	3248	nr	40.1 ± 3.6	Healthy subjects	CRP	CES-D	RFQ
Walker et al., 2022	200	61.5 %	20.49 ± 3.28	Healthy subjects	IL-6	CES-D	CMIS-SF
Watt et al., 2020	93	73 %	21.04 ± 2.05	Healthy subjects	CRP	PHQ-9	Ad hoc questionnaire

Abbreviations: ACESQ = Adverse Childhood Experiences Study Questionnaire, BDI-II = Beck Depression Inventory-II, BPD = borderline personality disorder, CES-D = Center for Epidemiologic Studies-Depression Scale, CMIS-SF = Childhood Maltreatment Interview Schedule-Short Form, CRP = C-reactive protein, CTQ = Childhood Trauma Questionnaire, CTQ-SF = Childhood Trauma Questionnaire-Short Form, ETI = Early Trauma Inventory, HAM-D = Hamilton Depression Rating Scale, HDRS17 = 17-item Hamilton Depression Rating Scale, hs-CRP = High-sensitivity C-reactive protein, ICAM-1 = Intercellular Adhesion Molecule-1, IL-6 = Interleukin 6, LHI = Life History Interview, MADRS = Montgomery–Åsberg Depression Rating Scale, MDD = major depressive disorder, MHI = Mental Health Inventory, MINI = Mini-International Neuropsychiatric Interview, NR = not reported, PHQ-9 = Patient Health Questionnaire-9, POMS-15 = Profile of Mood States, RFQ = Risky Families questionnaire, SDS = 20-item Zung Self-rating Depression Scale, STRAIN = Stress and Adversity Inventory for Adults, TNF-α = Tumour Necrosis Factor α, TRD = treatment-resistant depression, WBC = white blood cell count.

Gardhouse et al., 2021; John-Henderson et al., 2020; Jones et al., 2023; Kuhlman et al., 2020; McCormack et al., 2021; Mehta et al., 2022; O'Shields et al., 2022; Rengasamy et al., 2022; Walker et al., 2022), thirteen CRP (Bitsika et al., 2021; Congio et al., 2022; De Punder et al., 2018; Gardhouse et al., 2021; John-Henderson et al., 2020; Jones et al., 2023; Lowry et al., 2022; Mehta et al., 2022; Nakamura et al., 2022; O'Shields et al., 2022; Runsten et al., 2014; Taylor et al., 2006; Watt et al., 2020), three TNF-α (Gardhouse et al., 2021; O'Shields et al., 2022; Rengasamy et al., 2022), one white blood cell count (De Punder et al., 2018) and one fibrinogen (O'Shields et al., 2022). Although included in the systematic review, studies regarding fibrinogen and white blood cell count were not meta-analysed due to the limited amount of data. Furthermore, three studies employed measures of composite inflammation, consisting of IL-6, CRP, fibrinogen, *E*-Selectin and Intercellular Adhesion Molecule-1 (ICAM-1) (Hostinar et al., 2015), CRP, IL-6 and fibrinogen (Hostinar et al., 2017), and TNF-α and IL-6 (Kleih et al., 2022).

With respect to depression assessment, nine studies (Chiang et al., 2017; Hostinar et al., 2015; Hostinar et al., 2017; Kleih et al., 2022; Lowry et al., 2022; Nakamura et al., 2022; O'Shields et al., 2022; Taylor et al., 2006; Walker et al., 2022) used the Center for Epidemiologic Studies-Depression Scale (CES-D) (Radloff, 1977), while two (De Punder et al., 2018; Rengasamy et al., 2022) administered the Montgomery–Åsberg Depression Rating Scale (MADRS) (Davidson et al., 1986), two other studies (John-Henderson et al., 2020; Watt et al., 2020) used the Patient Health Questionnaire-9 (PHQ-9) (Spitzer et al., 2000), three (Gardhouse et al., 2021; Jones et al., 2023; Mehta et al., 2022) the Beck Depression Inventory-II (Beck et al., 1996), one study (Bitsika et al., 2021) used the 20-item Zung Self-rating Depression Scale (SDS) (Zung, 1965), another one (Congio et al., 2022) the 17-item Hamilton Depression Rating Scale (HDRS17) (Hamilton, 1960), one study (Davis et al., 2019) the Mental Health Inventory (MHI) (Veit and Ware, 1983), one (Kuhlman et al., 2020) used three items of the Profile of Mood States (POMS-15) (McNair et al., 1992), one (McCormack et al., 2021) the Hamilton Depression Rating Scale 21-item version (HAM-D) (Hamilton, 1960) and one (Runsten et al., 2014) the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

3.3. Study quality

According to the JBI Checklist for Analytical Cross-Sectional Studies (Moola et al., 2017), the maximum achievable score for each study was eight. Only three studies obtained the maximum score (De Punder et al., 2018; Gardhouse et al., 2021; Rengasamy et al., 2022). However, in eighteen studies, Item 4 was not applicable. Thirteen studies received a score of seven, three studies scored a six, two studies scored a five and one study scored a four. No studies received a score below four. Summarising qualitative strengths, most of the included studies showed a clear definition of inclusion criteria in the sample, along with a detailed description of study subjects and settings. Additionally, all the studies employed a valid and reliable measure for the outcome, along with the use of appropriate statistical analyses. In terms of weakness, the main critical points were the identification of potential confounding factors and the implementation of strategies to deal with these confounders.

3.4. Structural equation modelling meta-analysis

3.4.1. CRP as a mediator between ACEs and depressive symptoms

Stage 1 analysis based on a fixed effects TSSEM approach rejected the hypothesis of homogeneity of the correlation coefficients: $\chi^2 = 143.874$ (36), $p < .001$, CFI = 0.699; TLI = 0.674; RMSEA = 0.054 (90 % CI 0.045 to 0.064), SRMR = 0.048. Accordingly, heterogeneity was assumed and a random effects TSSEM was carried out. Table 2 shows the pooled correlation matrix along with heterogeneity statistics (k = 13, n = 12,935). The three weighted correlations were significant and in the expected direction, with I^2 statistics ranging between 0.397 and 0.898.

Table 2
Pooled correlations between study variables and heterogeneity statistics from the first stage of two-stage structural equation modelling.

	Estimate	SE	*p*-Value	I^2
Model 1. CRP as a mediator				
ACEs ⇔ CRP	0.046	0.022	.039	0.661
ACEs ⇔ Depressive symptoms	0.203	0.037	<.001	0.898
CRP ⇔ Depressive symptoms	0.077	0.016	<.001	0.397
Model 2. IL-6 as a mediator				
ACEs ⇔ IL-6	0.060	0.023	.009	0.270
ACEs ⇔ Depressive symptoms	0.310	0.032	<.001	0.632
IL-6 ⇔ Depressive symptoms	0.067	0.015	.001	0[b]
Model 3. TNF-α as a mediator				
ACEs ⇔ TNF-α	0.138	0.020	<.001	0[b]
ACEs ⇔ Depressive symptoms	0.188	0.020	<.001	0[b]
TNF-α ⇔ Depressive symptoms	0.082	0.109	.451	0.781
Model 4. Composite inflammation as a mediator[a]				
ACEs ⇔ Composite inflammation	0.081	0.024	<.001	
ACEs ⇔ Depressive symptoms	0.308	0.022	<.001	
Composite inflammation ⇔ Depressive symptoms	0.143	0.023	<.001	

Abbreviations. ACEs: adverse childhood experiences, CRP: C-reactive protein, IL-6: interleukin-6, SE: standard error, TNF: tumour necrosis factor.
[a] Heterogeneity statistics not applicable for fixed effects models.
[b] The between-study variance was fixed to foster optimization and convergence.

In Stage 2, the pooled correlation matrix based on the random-effects approach was employed to fit the partial mediation model. Specifically, ACEs were significantly associated with CRP (β = 0.046, p = .039), which in turn was positively related to depressive symptoms (β = 0.068, $p < .001$). ACEs also exerted a direct effect on depressive symptoms (β = 0.200, p < .001). Moreover, CRP partially mediated the relationship between ACEs and depressive symptoms (β = 0.003, 95 % LBCI 0.0002 to 0.0068). The model accounted for 0.22 % and 4.6 % of the variance of CRP and depressive symptoms, respectively.

3.4.2. IL-6 as a mediator between ACEs and depressive symptoms

Stage 1 analysis based on a fixed effects TSSEM approach rejected the hypothesis of homogeneity of the correlation coefficients: $\chi^2 = 91.592$ (33), p < .001, CFI = 0.834; TLI = 0.819; RMSEA = 0.072 (90 % CI 0.054 to 0.089), SRMR = 0.070. Consistently, heterogeneity was assumed and a random effects TSSEM was conducted. Table 2 reports the pooled correlation matrix along with heterogeneity statistics (k = 12, n = 4108). All the correlation coefficients were statistically significant, with I^2 statistics ranging from 0.270 to 0.632.

In Stage 2 of the TSSEM, the pooled correlation matrix based on the random effects approach was used as the input matrix for the partial mediation model. Findings revealed that ACEs were significantly associated with IL-6 (β = 0.060, p = .009), which in turn was positively related to depressive symptoms (β = 0.048, p = .002). The direct effect of ACEs on depressive symptoms was statistically significant (β = 0.307, p < .001). Moreover, IL-6 partially mediated the relationship between ACEs and depressive symptoms (β = 0.003, 95 % LBCI 0.001 to 0.006). The model accounted for 0.36 % and 9.85 % of the variance of IL-6 and depressive symptoms, respectively.

3.4.3. TNF-α as a mediator between ACEs and depressive symptoms

In Stage 1, the fixed effects TSSEM did not support the homogeneity assumption: $\chi^2 = 23.911$ (6), p = .005, CFI = 0.872; TLI = 0.809; RMSEA = 0.063 (90 % CI 0.037 to 0.090), SRMR = 0.021. Table 2 reports the pooled correlation matrix (k = 3, n = 2256) along with I^2 statistics. ACE exhibited a significant correlation with both TNF-α and

depressive symptoms, but there was no significant correlation between TNF-α and depressive symptoms.

In Stage 2, the pooled correlation matrix based on the random effects approach was employed to fit the partial mediation model. Findings showed that ACEs were positively associated with TNF-α (β = 0.138, p < .001). In contrast, TNF-α showed no significant association with depressive symptoms (β = 0.057, p = .606). The direct path between ACEs and depressive symptoms was significant (β = 0.180, p < .001). Lastly, TNF-α did not mediate the relationship between ACEs and depressive symptoms (β = 0.008, 95 % LBCI −0.023 to 0.040). The model accounted for 1.91 % and 3.88 % of the variance of TNF-α and depressive symptoms, respectively.

3.4.4. Composite inflammation measure as a mediator between ACEs and depressive symptoms

In Stage 1, the fixed effects TSSEM supported the homogeneity assumption: χ^2 = 4.263 (6), p = .658, CFI = 1.000; TLI = 1.013 RMSEA = 0.000 (90 % CI 0.000 to 0.045), SRMR = 0.018. Table 2 reports the pooled correlation matrix (k = 3, n = 1674), in which all the estimates were statistically significant and in the expected direction.

In Stage 2, a fixed effects TSSEM was specified on the pooled correlation matrix to estimate the path model. Specifically, ACEs were significantly associated with composite inflammation (β = 0.081, p < .001), which in turn was positively related to depressive symptoms (β = 0.119, p < .001). ACEs also exerted a direct effect on depressive symptoms (β = 0.298, p < .001). Furthermore, composite inflammation partially mediated the relationship between ACEs and depressive symptoms (β = 0.009, 95 % LBCI 0.004 to 0.018). The model accounted for 0.67 % and 10.89 % of the variance of composite inflammation and depressive symptoms, respectively.

3.4.5. Control analyses

Two control analyses were carried out considering age and BMI as covariates in the mediation models. Although covariates were not reported in all included studies, the TSSEM approach handles missing correlation coefficients through maximum likelihood estimation, which is unbiased and efficient under ignorable missing data conditions (see Cheung and Cheung, 2016).

3.4.5.1. Age as a covariate. Eight studies measuring CRP reported zero-order correlations between age and the investigated variables (Bitsika et al., 2021; De Punder et al., 2018; John-Henderson et al., 2020; Jones et al., 2023; Mehta et al., 2022; Nakamura et al., 2022; O'Shields et al., 2022; Runsten et al., 2014). When controlling for age, the mediation role of CRP in the relationship between ACEs and depressive symptoms remained statistically significant (β = 0.003, 95 % LBCI 0.0001 to 0.0069). Age did not exert any significant effect on CRP and depressive symptoms (p > .05).

Moreover, ten studies measuring IL-6 reported zero-order correlations between age and the investigated variables (Chiang et al., 2017; De Punder et al., 2018; John-Henderson et al., 2020; Jones et al., 2023; Kuhlman et al., 2020; McCormack et al., 2021; Mehta et al., 2022; O'Shields et al., 2022; Rengasamy et al., 2022; Walker et al., 2022). When controlling for age, the indirect effect of ACEs on depressive symptoms through IL-6 vanished (β = 0.003, 95 % LBCI −0.0007 to 0.0094). More specifically, age was significantly associated with IL-6 (β = 0.064, p = .038) but not with depressive symptoms (p > .05).

Unfortunately, we were unable to run sensitivity analyses on composite inflammation (k = 2) and TNF-α (k = 2) due to the limited data.

3.4.5.2. BMI as a covariate. Seven studies measuring CRP reported zero-order correlations between BMI and the investigated variables (De Punder et al., 2018; John-Henderson et al., 2020; Jones et al., 2023; Mehta et al., 2022; Nakamura et al., 2022; O'Shields et al., 2022; Taylor et al., 2006). When controlling for BMI, the indirect effect between ACEs and depressive symptoms via CRP vanished (β = 0.002, 95 % LBCI −0.001 to 0.005). More specifically, BMI was marginally associated with ACEs (β = 0.048, p = .053), as well as significantly associated with CRP (β = 0.350, p < .001). This resulted in a non-significant relationship between ACEs and CRP (β = 0.029, p = .208).

Moreover, nine studies measuring IL-6 reported zero-order correlations between BMI and the investigated variables (Chiang et al., 2017; De Punder et al., 2018; John-Henderson et al., 2020; Jones et al., 2023; Kuhlman et al., 2020; McCormack et al., 2021; Mehta et al., 2022; O'Shields et al., 2022; Rengasamy et al., 2022). When controlling for BMI, IL-6 did not mediate the relationship between ACEs and depressive symptoms (β = 0.001, 95 % LBCI −0.002 to 0.004). More specifically, BMI was positively associated with ACEs (β = 0.107, p < .001) and IL-6 (β = 0.379, p < .001). This resulted in a non-significant relationship between ACEs and IL-6 (β = 0.019, p = .429).

Unfortunately, we were unable to run sensitivity analyses on composite inflammation (k = 1) and TNF-α (k = 2) due to the limited data.

3.4.5.3. Sequential mediation model. On the basis of such results and from a data-driven perspective, we tested a sequential mediation of BMI and IL-6 in the path between ACEs and depressive symptoms (Fig. 2). Findings revealed a significant relationship between ACEs and BMI (β = 0.107, p < .001), as well as between BMI and IL-6 (β = 0.379, p < .001) and between IL-6 and depressive symptoms (β = 0.050, p = .009). Moreover, ACEs exerted a direct effect on depressive symptoms (β = 0.308, p < .001). Most importantly, the indirect effect linking ACEs to IL-6 via BMI was significant (β = 0.041, 95 % LBCI 0.024 to 0.063), as well as the sequential mediating effect of BMI and IL-6 in the relationship between ACEs and depressive symptoms (β = 0.002, 95 % LBCI 0.0005 to 0.0046). Overall, the model accounted for 14.59 % and 9.94 % of the variance of IL-6 and depressive symptoms, respectively.

As a further step, a subgroup analysis was conducted by excluding a single sample of pregnant women (McCormack et al., 2021). Findings supported the sequential mediation of BMI and IL-6 in the relationship between ACEs and depressive symptoms (β = 0.002, 95 % LBCI 0.0002 to 0.0039). Additionally, we conducted a further subgroup analysis by considering only healthy samples. More specifically, three studies (Rengasamy et al., 2022; De Punder et al., 2018; Gardhouse et al., 2021) conducted on clinical samples with mood disorders were excluded from the analysis. Although the effect remained consistent in size, the sequential mediation linking ACEs to depressive symptoms via BMI and IL-6 was no longer significant, possibly due to lower power (β = 0.002, 95 % LBCI −0.001 to 0.004). Furthermore, we performed a leave-one-out sensitivity analysis, wherein multiple meta-analyses were conducted on each subset of the studies obtained by excluding one study at a time. Findings revealed that the sequential mediation effect did not demonstrate robustness under a null hypothesis significance testing approach (see Supplementary Document). Specifically, while the sequential mediation effect remained significant when excluding 7 out of the 12 studies included in the meta-analysis, it lost significance when excluding 5 out of the 12 studies. This may be partially attributed to lower statistical power, as the effect sizes remained consistent throughout each step of the analysis.

Finally, considering that both the assessment of the mediator and the outcome occurred relatively at the same time, we proceeded to investigate the feasibility of an alternative mediation pathway. In fact, previous research has highlighted that depressive symptoms may predict obesity and higher BMI (e.g., Franko et al., 2005), also underscoring the bidirectional relationship between inflammation and depressive episodes (e.g., Messay et al., 2012; Mac Giollabhui et al., 2021). As detailed in the Supplementary Document, the alternative sequential mediation model linking ACEs to IL-6 through depression symptoms and BMI was not supported by the data (β = 0.001, 95 % LBCI −0.004 to 0.006).

ACEs → BMI → IL-6 (β = 0.041, 95% LBCI 0.024 to 0.063)

ACEs → BMI → IL-6 → Depressive symptoms (β = 0.002, 95% LBCI 0.0005 to 0.0046)

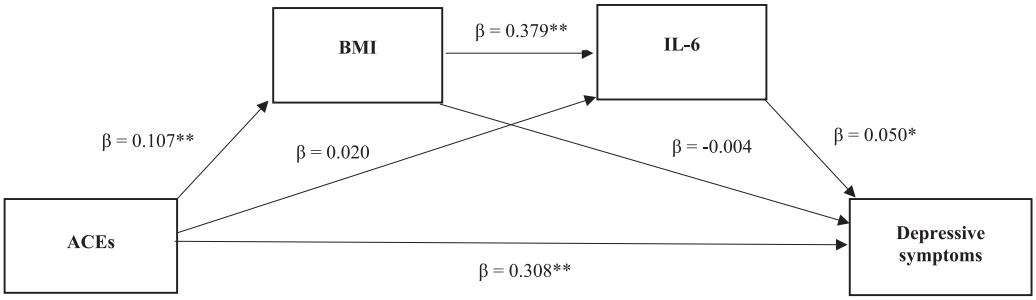

Fig. 2. Sequential mediation model. *$p < .01$, **$p < .001$. Abbreviations: ACEs, adverse childhood experiences; BMI, body mass index; IL-6, interleukin-6.

4. Publication bias

Publication bias was assessed for each single correlation reported by at least ten studies (Higgins and Green, 2011). The visual inspection of the funnel plot indicated a reasonable degree of symmetry (see Supplementary Document). Moreover, Egger's tests were not significant for all the examined correlations: ACEs with CRP (1.829, $p = .067$), CRP with depressive symptoms (−1.571, $p = .116$); ACE with IL-6 (0.077, $p = .938$); IL-6 with depressive symptoms (0.091, $p = .927$). The only exception was the association between ACEs and depressive symptoms, which showed a significant degree of asymmetry (3.013, $p = .003$; see Supplementary Fig. 5). Overall, these findings suggested a minimal impact of publication bias on the examined correlations.

5. Discussion

The present meta-analysis indicates that the inflammatory markers, CRP, IL-6, TNF-α and a composite inflammation measure, exert mediation effects in the relationship between ACEs and adult depressive symptoms which are explained by the strong association between BMI and inflammation. Thus, meta-analytic results provide evidence for a complex model, with ACEs predicting adult depression via the sequential mediation of BMI and IL-6. Precisely, the model showed that ACEs predict higher BMI, which in turn predicts higher IL-6, which eventually predicts depressive symptoms severity.

A slight yet significant increase in the risk of overweight and obesity for individuals exposed to ≥2 ACEs has been reported in previous meta-analyses of children and adult samples (Elsenburg et al., 2017; Wiss and Brewerton, 2020; Hughes et al., 2017), with several putative underlying mechanisms (Wiss and Brewerton, 2020). Experiencing physical or sexual abuse in childhood and/or adolescence can predict the development of food addiction in adulthood (Mason et al., 2016), which is a well-known determinant of obesity (Pedram et al., 2013). Moreover, it has been suggested that the high inflammatory response to stress associated with child abuse may reinforce overeating and craving for palatable foods (Hemmingsson, 2018), which might serve as self-medication/compensation mechanisms against trauma (Mason et al., 2016). Interestingly, previous research has indicated that exposure to ACEs has long-term effects on low fruit and vegetable consumption, resulting in unhealthy dietary choices, through its detrimental impact on self-regulation skills (Horino and Yang, 2021; Miller et al., 2011). In this regard, ACEs have demonstrated a significant role in predicting adults' emotional dysregulation (Rudenstine et al., 2019), which is crucial in predisposing risk for overweight and obesity (Leehr et al., 2015; Shriver et al., 2019). The current study, in combination with prior research, highlighted the need for future analyses to explore these mechanisms and their potential interactions in explaining the association between ACEs and BMI.

The mediatory role of BMI between ACEs and inflammation is consistent with previous evidence. Petrov et al. (2016) reported that BMI significantly mediated the association between childhood emotion, physical and sexual abuse and CRP, IL-6, and fibrinogen; Mitchell et al. (2018) showed that BMI mediated the relationship between physical abuse and both serum CRP and IL-6, but not TNF-α. Maes et al. (2018) found that the significant effects of early life trauma on CRP levels were completely mediated by BMI. Summarising previous evidence, however, an updated narrative review recently concluded that evidence on the mediation of BMI between childhood trauma and inflammation was substantially inconclusive (Brown et al., 2021). As a major progression from Brown et al. (2021) review, our meta-analysis, albeit limited by the cross-sectional nature of the data, suggests that the mediation of BMI between ACEs and inflammation is indeed plausible, and can be further, sequentially linked to depression. Of note, this path was detected for IL-6 but not for CRP, likely due to the smaller association between BMI and ACEs in the studies testing the CRP mediation model. Supporting our findings, the alternative pathway linking ACEs to inflammation through depression symptoms and BMI was not significant in our cross-sectional analysis.

Possible immune-to-brain pathways leading to depression have been previously extensively reviewed (e.g., Zunszain et al., 2013; Osimo et al., 2020; Nettis and Pariante, 2020; Ballesio, 2023). These include cytokine production in the brain following microglial activation through humoral (i.e., cytokines diffusion across intact or leaky regions of the blood-brain-barrier, i.e., circumventricular organs), neuronal (e.g., binding of peripheral cytokines to afferent vagus nerve fibres), or cellular pathways (Bower and Kuhlman, 2023), exacerbating changes in monoaminergic neurotransmission, neurotrophic activity, and oxidative stress processes with the following onset of cognitive, affective and motivational symptoms of depression (e.g., Bakunina et al., 2015; Dantzer, 2018; Nettis and Pariante, 2020; Turkheimer et al., 2023; Ballesio, 2023; Ballesio et al., 2023). Consistent with such hypotheses, case-control studies detected the presence of higher corticospinal fluid concentrations of inflammatory markers including IL-6 in patients with depression compared to controls (Enache et al., 2019), and experimental intravenous endotoxin injection in healthy humans induces upregulation of serum and cerebrospinal fluid concentrations of proinflammatory cytokines as well as depressive symptoms (e.g., Lasselin et al., 2021). Alternatively, it has been proposed that peripheral inflammation may reduce blood-brain-barrier permeability which in the long term may disrupt brain homeostasis and trigger depressive symptoms (Turkheimer et al., 2021).

Refining aforementioned immune-to-brain pathways, results of the present study suggest that several neuroimmunometabolic factors leading to depression could be involved in individuals with ACEs. Dietary patterns characterised by high fat intake can lead to increased amount of lipids in adipocytes (Ferreira et al., 2014), which may

increase the release of monocyte chemoattractant protein-1 (MCP-1), a chemokine that increases the infiltration of macrophages and T cells into white adipose tissue and stimulates peripheral release of proinflammatory cytokines including IL-6 (Shelton and Miller, 2010), finally exacerbating a state of low-grade chronic inflammation (Capuron et al., 2017). Alterations of gut microbiota, intestinal dysbiosis, and increased gut permeability may also lead to the production of peripheral inflammatory factors (Torres-Fuentes et al., 2017; Furman et al., 2019). Such immunometabolic alterations may not be restricted to periphery but rather reach the brain. The impact of diet-related inflammation in the brain has been mostly investigated at the level of hypothalamus. For instance, Lopes et al. (2024) recently showed that high fat diet for four weeks resulted in body weight gain and adiposity as well as increased gene expression of pro-inflammatory cytokines such as IL-6 and dysregulation in the nuclear factor kappa B pathway in the hypothalamus of male mice. Notably, such processes have been hypothesised to be involved in hypothalamic circuity remodelling (Miller and Spencer, 2014), dysregulate HPA axis activity and induce subsequent production of glucocorticoids (Burfeind et al., 2016), and eventually determine depressive symptoms (Cernackova et al., 2020). Moreover, another recent mice model suggested that alternation of microbiota may be associated with microglial activation by modulating RAS-NF-κB signal pathway (Liu et al., 2024). It was beyond the aim of the current meta-analysis to clarify the precise biological processes linking ACEs, BMI, IL-6, and depressive symptoms, that should be further elucidated in future mechanistic research.

5.1. Clinical implications

Present results may implicate that BMI and inflammation could be a potential target for depression prevention in individuals with a history of trauma or ACEs. The finding that the association between ACEs and inflammation could be best described as indirect via BMI may suggest that effective clinical interventions focused on early life exposures to adversities and subsequential inflammation should include the assessment of weight gain trajectories. Parallelly, early trauma-informed screening may be successful in reducing the risk of overweight/obesity (Wiss and Brewerton, 2020), thus indirectly protecting against associated inflammation. Nevertheless, clinicians should also contemplate the evidence that BMI could be indicative of multiple latent health-related conditions (e.g., cardiovascular disease, diabetes, mood disorders) in order to appropriately address its relationships with cumulative childhood stress exposure. In this respect, the identification of pernicious behavioural mechanisms (e.g., overeating) and potential protective factors (e.g., emotion regulation) underlying the ACEs-BMI pathway should be an important public health priority as it would be informative in delineating the best strategies for the prevention and treatment of inflammation in individuals with trauma histories.

Notably, cumulative evidence has indicated the type and the severity of traumatic events as the second most associated determinant of treatment-seeking, after psychopathology itself (Gavrilovic et al., 2005). Previous research suggested that about 37 % of individuals with a history of ACEs seek psychological support (Sheerin et al., 2016), although the type of intervention offered to these patients rarely takes into consideration its impact on biological variables such as inflammation. Research highlighted significant broader deficiencies in psychological support approaches for victims of traumatic events associated with comorbid chronic inflammation (Glynn et al., 2022). This treatment gap emphasized the urge to implement integrated healthcare approaches to address medical and psychological comorbidities accompanying ACEs and the underlying mechanism of inflammation. We recently conducted a comprehensive network meta-analysis on the impact of psychotherapies on immune outcomes suggesting that mindfulness-based cognitive therapy and mindfulness-based stress reduction interventions may consistently be associated with reduced inflammation in randomised controlled trials (Ballesio et al., 2023). However, whether this reduction may drive improvements in depression, especially in individuals with ACEs is still not demonstrated. Further research on how these biological processes, associated with psychological support of individuals with ACEs, could affect depression aetiology is imperative.

5.2. Limitations

Several limitations should be mentioned. First, the assessment of putative mediator (i.e., inflammation) and outcome (i.e., depression) occurred relatively at the same time. With cross-sectional data, we cannot infer that changes in inflammatory levels that are associated with ACEs predict changes in depressive symptoms. To thoroughly investigate a longitudinal mediation hypothesis, the prior levels of a variable must be measured and controlled for (see Little, 2013); therefore, the directionality of these associations remains to be confirmed using multiple assessments (e.g., Zagaria et al., 2023). Related to this, multiple assessment design would allow to fully test an alternative pathway linking ACEs to inflammation through depression symptoms and BMI which, as mentioned above, was not significant in our cross-sectional analysis (see Supplemental Material). Second, several variables that are presumed to play a key role were not considered in the present study due to a lack of data needed for meta-analytic calculations. Namely, ACEs are associated with physical inactivity, smoking, heavy alcohol use, and diabetes (Hughes et al., 2017), which could all be associated also with BMI. Greater childhood trauma has also been significantly associated with poorer sleep (Brindle et al., 2018), which is a strong predictor of depression (Hertenstein et al., 2019) and which may increase inflammatory signalling (e.g., Ballesio et al., 2022; Zagaria et al., 2022) and BMI (Norton et al., 2018; Lombardo et al., 2020). In order to consider these factors in further structural equation modelling meta-analyses, future studies are encouraged to report zero-order correlation coefficients with the main variables (ACEs, inflammation, depression). Third, the composite inflammation score incorporated different inflammatory biomarkers and its interpretation might be biased by the heterogeneity of indicators used for its computation (Strawbridge et al., 2015). To date, which biomarkers best represent a comprehensive index of inflammation is under debate in the literature. The identification of an optimal approach to operationalizing the composite inflammation score requires further investigation. Finally, due to limited data available, we were unable to consider the differential impact of different types of ACEs (e.g., parental absence, sexual abuse, physical abuse; Lacey et al., 2020), nor several potential other moderators such as duration of ACEs exposure, the context of the stressor, and relationship to the perpetrator (Baumeister et al., 2016).

6. Conclusion

Regardless of the aforementioned limitations, the present meta-analysis has the strength to provide at least two novel insights into the study of depressogenic mechanisms associated with ACEs: 1) it explains why the available literature on the role of inflammation as a single mediator between ACEs and depression yielded only weak and spurious effects; 2) it suggests that BMI is not a mere confounder, but rather a plausible process variable in the association between ACEs, inflammation, and depressive symptoms. Putatively, precise biological (e.g., HPA axis activity, neurotrophic factors, oxidative stress processes) and psychological (e.g., affect regulation, health behaviour, eating patterns) mechanisms are likely to play a role and should be integrated into even more complex models. Moreover, different path directions (i.e., ACEs leading to higher BMI through the mediation of depressive symptoms) are also plausible and should be investigated. Finally, we would also point out that ACEs may lead to several other psychopathological outcomes including post-traumatic stress disorders, psychotic disorders, and personality disorders (Hughes et al., 2017; Cerrato et al., 2017) in which depression is often comorbid. An effort should be made to explore potential disease-specific mechanisms linking ACEs to these conditions.

However, our study confirms the crucial role of inflammation in the paths between ACEs and depression, even as one element of complex sequential models.

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CRediT authorship contribution statement

Andrea Zagaria: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Valeria Fiori:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Mariacarolina Vacca:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Caterina Lombardo:** Writing – original draft. **Carmine M. Pariante:** Writing – review & editing, Writing – original draft. **Andrea Ballesio:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

Authors did not use generative AI and AI-assisted technologies in the writing this manuscript.

Declaration of competing interest

Authors have no conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.04.072.

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