Neuroscience and Biobehavioral Reviews 171 (2025) 106062

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Five hypothesized biological mechanisms linking adverse childhood experiences with anxiety, depression, and PTSD: A scoping review

Laura H. Dosanjh [a,1,*], Samantha Lauby [b,2], Jaime Fuentes [c,3], Yessenia Castro [c,4], Fiona N. Conway [c,5], Frances A. Champagne [b,6], Cynthia Franklin [c,7], Bridget Goosby [a,d,8]

[a] Population Research Center, The University of Texas at Austin, USA
[b] Department of Psychology, The University of Texas at Austin, USA
[c] The Steve Hicks School of Social Work, The University of Texas at Austin, USA
[d] Department of Sociology, The University of Texas at Austin, USA

ARTICLE INFO

Keywords:
Adverse childhood experiences
Anxiety
Depression
Post-traumatic stress disorder
Cortisol
Inflammation
Allostatic load
DNA methylation
Aging clocks
Telomere
Mediation
Pathways
Mechanism

ABSTRACT

Adults with symptoms of anxiety, depression, or PTSD and a history of adverse childhood experiences (ACEs) may experience more severe symptoms than those without ACEs. The identification of mechanisms linking ACEs to later mental health problems may provide salient treatment targets to improve outcomes. Several biological markers (cortisol, inflammation, allostatic load, DNA methylation, and telomere length) that are indicative of functional variation in stress response systems, have been hypothesized as potential mechanisms linking ACEs to later mental health outcomes. Much of the evidence supporting this hypothesis examines isolated pairwise associations between variables and it is unclear whether statistical tests of mediation support these conclusions. It is also unclear how much of the extant research has used theory to guide mediation analyses, which may be a salient factor in the recognition of a mechanism. This scoping review surveyed research conducting mediation analysis examining the indirect effect of any of these five biological markers on the relationship between ACEs and anxiety, depression, or PTSD. It further surveyed the use of theory in these analyses. Pubmed and seven electronic databases were searched: (1) APA PsychInfo (2) CINAHL Plus (3) Health Source: Nursing/Academic Edition (4) MEDLINE (5) Psychology and Behavioral Sciences Collection (6) Science and Technology Collection, and (7) SocINDEX. A total of 16 articles were identified. The majority of studies examined depression as an outcome and the statistical significance of indirect effects were mixed across mediators. Common theoretical models and frameworks were consistent with life course theory and evolutionary or developmental perspectives.

There is extensive evidence that adverse childhood experiences (ACEs) have significant negative effects on many major life outcomes in adulthood and are associated with anxiety, depression, and post-traumatic stress disorder (PTSD) (Chapman et al., 2004; Cloitre et al., 2011; Lippard and Nemeroff, 2020; McCutchen et al., 2022; Merrick et al., 2017; Whitaker et al., 2021). Individuals experiencing depression, anxiety, or PTSD after exposure to ACEs often experience a more severe pathophysiology, marked by earlier onset, more severe symptoms, and diminished treatment response compared to those without ACEs (Lippard and Nemeroff, 2020, 2022). Identifying mechanisms linking ACEs to mental health outcomes may offer critical targets for treatment and prevention (Lippard and Nemeroff, 2022). The processes linking ACEs with mental health symptoms are thought to involve changes in stress response regulation, particularly the hypothalamic-pituitary-adrenal

* Corresponding author.
E-mail address: laurados@utexas.edu (L.H. Dosanjh).
[1] https://orcid.org/0000-0002-9184-2961
[2] https://orcid.org/0000-0001-5676-1333
[3] https://orcid.org/0000-0002-8225-0294
[4] https://orcid.org/0000-0003-0994-908X
[5] https://orcid.org/0000-0003-2626-4752
[6] https://orcid.org/0000-0002-3922-084X
[7] https://orcid.org/0000-0003-3777-3077
[8] https://orcid.org/0000-0003-1762-2888

https://doi.org/10.1016/j.neubiorev.2025.106062
Received 5 December 2024; Received in revised form 3 February 2025; Accepted 8 February 2025
Available online 12 February 2025

(HPA) axis, during sensitive developmental periods (Shonkoff et al., 2012). Potential biological markers associated with HPA axis dysregulation or its downstream effects include cortisol, inflammation, allostatic load, DNA methylation, and telomere length (Cooke et al., 2023; Finlay et al., 2022; Krause et al., 2020; Ridout, Levandowski, et al., 2018; Shonkoff et al., 2012). For the purposes of this research, the term stress related biological marker (SBM) specifically refers to any of these five biomarkers. The science supporting these SBMs as mechanisms is still in early stages. Limited research examining relationships between ACEs, mental health, and these five SBMs have employed statistical mediation, which is a critical form of evidence required to support the recognition of a mechanism (Kazdin, 2007; Tryon, 2018). Furthermore, it has been asserted that the formal recognition of a mechanism also requires robust theory to explain causal relationships between variables (Tryon, 2018). This scoping review surveys existing research that tests statistical mediation models in which cortisol, inflammation, allostatic load, DNA methylation, or telomere length are hypothesized to indirectly affect the relationship between ACEs and mental health outcomes. It also clarifies whether these studies were situated within theoretical frameworks. In doing so, this review helps to advance a more cohesive, theory-based understanding of the state of evidence supporting these SBMs as hypothesized mechanisms connecting ACEs to mental health outcomes. Further clarification in this area is crucial in order to identify and improve avenues for assessment, treatment, and prevention of the serious course of mental health symptomatology that can follow in the aftermath of ACEs (Lippard and Nemeroff, 2022).

1. ACEs and anxiety, depression, and PTSD

ACEs are stressful or traumatic events that occur before the age of 18 (Felitti et al., 1998). ACE events include abuse (physical, emotional, sexual), neglect (physical and emotional), and household dysfunction (divorce, domestic violence in the home, substance use disorder or mental illness experienced by a parent, and incarceration of a family member) (Felitti et al., 1998). Other sources of adversity include the death of a parent, separation from a parent, being in foster care, bullying, peer rejection, community violence, or neighborhood instability (Choi et al., 2020; Cronholm et al., 2015; Finkelhor et al., 2013). The original ACE study conceptualized these events within a cumulative dose model, which acknowledges the additive and possibly interactive effect of multiple types of ACEs, and the number of ACE exposures have been associated with increasing risk for multiple deleterious health outcomes (Felitti et al., 1998; McLaughlin, 2020). These outcomes include some of the leading causes of mortality and common mental health diagnoses in adulthood (Felitti et al., 1998; Kessler et al., 2010).

ACEs have been consistently linked to increased risks for anxiety, depression, PTSD, and complex post-traumatic stress disorder (CPTSD) in adulthood (Chapman et al., 2004; Lippard and Nemeroff, 2020; McCutchen et al., 2022; Merrick et al., 2017; Whitaker et al., 2021). CPTSD is a form of PTSD that is often associated with ongoing or chronic exposures that begin in childhood and includes additional symptoms related to disturbances of self-organization, beyond those found in PTSD (Cloitre et al., 2011). The original ACEs study (Felitti et al., 1998) examined associations between the cumulative number of ACEs and long-term health outcomes in 17,337 adult members of the Kaiser Permanente health organization. Investigators discovered that individuals with an ACE score of ≥ 4 had more than 4.5 time the odds of being depressed and more than 12 times the odds of reporting a lifetime suicide attempt than individuals with no ACEs (Felitti, 2002). Later work on population representative datasets corroborated the associations between ACEs and depression in adults (Desch et al., 2023; Ege et al., 2015; Gupta, 2022; Remigio-Baker et al., 2014) and these findings have been replicated through longitudinal prospective cohort studies (Iob et al., 2022; Wang et al., 2021). Similarly, research has demonstrated associations between the number of ACEs and anxiety (Anda et al., 2006; Poole et al., 2017; Racine et al., 2021; Whitaker et al., 2021) and PTSD (Brewin et al., 2000; Cloitre et al., 2019; Frewen et al., 2019; Tabb et al., 2022) in adults. In a sample of adults from the Midlife in the United States study (a nationally representative dataset), individuals with three or more ACEs were 3.05 times (95 % CI: 2.06–4.51) more likely to report an anxiety disorder in the preceding 12 month period compared to those with no ACEs (Whitaker et al., 2021). In a study using nationally representative datasets from both the U.S. and Ireland, ACE exposures were significantly associated with CPTSD including one (AOR = 2.70, $p = .011$), two (AOR = 3.11, $p = .007$), three (AOR = 7.97, $p < .001$), and $\geq$ four (AOR = 15.70 $p < .001$) events (McCutchen et al., 2022). Meta-analytic studies have further supported this evidence and have reported significant relationships between ACEs and depression, anxiety, and PTSD (Crede et al., 2023; Gardner et al., 2019; Racine et al., 2021; Sahle et al., 2022; Tan and Mao, 2023).

ACEs have been linked to a number of mental health disorders beyond anxiety, depression, and PTSD, including conditions such as bipolar, schizotypal, borderline, and narcissistic personality disorders (Afifi et al., 2011; Nemeroff and Binder, 2014; Lippard and Nemeroff, 2020). Anxiety, depression, and PTSD, however, are comparatively more prevalent mental health conditions in the United States and globally (Nochaiwong et al., 2021; Steel et al., 2014), making them particularly relevant for focused investigation. For example, the World Health Organization (WHO) (n.d.) ranked anxiety and depression as the most common mental health disorders globally in 2019 with estimates suggesting that 301 million were living with anxiety and 280 million with depression. By comparison, 40 million people were estimated to be living with bipolar disorder and 24 million with schizophrenia the same year. A recent meta-analysis (Nochaiwong et al., 2021) examining the global prevalence of mental health disorders in 2020 estimated that 28 % of the population experienced symptoms of depression at some point during the year, while 26.9 % experienced symptoms of anxiety, and 24.1 % reported PTSD symptoms. Given the widespread prevalence of anxiety, depression, and PTSD, focused investigations into the role of ACEs in their etiology and pathophysiology - including and the biological pathways between ACEs and these outcomes - have the potential to yield significant public health impact.

1.1. Symptom severity and outcomes

Adults and youth with anxiety, depression, or PTSD and a history of ACEs often experience earlier age of onset, more severe symptoms, and diminished response to treatment compared those without ACEs (Lippard and Nemeroff, 2022). In a sample of 1196 children that were followed longitudinally into adulthood, participants were matched for ACEs, age, race, gender, and socioeconomic status (Widom et al., 2007). Investigators found that children with ACEs were more likely to develop depression and experience symptom onset at an earlier age compared to controls. Other studies have demonstrated that those with ACEs often experience a more severe course of illness. For example, in a sample of 454 adults seeking treatment for depression, those with higher numbers of ACEs reported more lifetime suicide attempts, psychiatric related inpatient admissions, and greater symptom severity (Giampetruzzi et al., 2023). Other studies on anxiety (Lähdepuro et al., 2019) and PTSD (Schalinski et al., 2016) have found greater symptom severity in those with higher ACEs compared to those with lower levels or no ACE exposures. Poor response to treatment in the form of lack of remission, a longer time to remission, or early drop-out have been documented in those with depression anxiety and/or PTSD with a history of ACEs (Bruce et al., 2011; Lippard and Nemeroff, 2020, 2022). A clinical trial with 318 adolescents with major depressive disorder randomized participants to cognitive behavioral therapy, fluoxetine, or combined treatment for 36 weeks, and participants without ACEs made more rapid improvements than those with previous ACE exposures (Waldron et al., 2019). These findings are congruent with a meta-analysis that surveyed 16 epidemiological studies and found that ACEs were associated with a lack of response and lack of remission during treatment for depression

(Nanni et al., 2012). CPTSD, which often develops as a result of prolonged or repeated trauma during childhood, includes a broader spectrum of symptoms and impact on dimensions of functioning than PTSD (Cloitre et al., 2011; Giourou et al., 2018) and meta-analytic work has demonstrated generally poorer treatment outcomes for these individuals (Karatzias et al., 2019). The evidence demonstrating the pernicious course of illness for those with anxiety, depression, or PTSD and a history of ACEs suggests that these complex cases require specifically tailored treatments (Lippard and Nemeroff, 2020, 2022). However, more knowledge is required to build an evidence base for the most effective treatment options for these types of cases.

1.2. Processes linking ACEs and mental health

Understanding how ACEs and mental health outcomes are linked may provide clues to guide future interventions for adults with symptoms of anxiety, depression, or PTSD and a history of ACEs. While research on the associations between ACEs and later mental health outcomes has proliferated, adjacent work has examined the pathways linking these variables. Multiple streams of investigation from within diverse disciplines (such as neuroscience, molecular biology, genomics, developmental psychology, epidemiology, and sociology) have illustrated how early adverse and traumatic experiences can leave a lasting signature on the development and architecture of the brain, immune system, and epigenetic profiles, ultimately setting the stage for later deleterious health outcomes (Shonkoff et al., 2012). At a biological level, exposures to ACEs and other forms of early life stress are thought to influence HPA function, which is involved in the endocrine response to stressors (Smith and Vale, 2006; Straub and Cutolo, 2016). Activation of the HPA axis initiates a cascade of hormones such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (e.g., cortisol), which initially dampens immune activity, suppressing inflammatory cytokines (Shonkoff et al., 2012; Straub and Cutolo, 2016). While short activations of the HPA axis are adaptive, chronic activations and concomitant repeated exposure to elevated glucocorticoid levels lead to wear-and-tear, chronically elevated inflammation, and dysregulation of multiple systems in the body (Bobba-Alves et al., 2022; Finlay et al., 2022; McEwen, 2017). Furthermore, epigenetic studies on the impact of ACEs have found altered DNA methylation patterns of genes that are associated with glucocorticoid signaling and regulation such as *NR3C1* and *FKBP5* (Alexander et al., 2018; Kim et al., 2023) in addition to other stress associated genes such as *SCL6A3*, *SKA2*, and *BDNF* (Kim et al., 2023). Other work has demonstrated that ACEs have been associated with shorter telomeres, which are protein structures that protect the end of chromosomes - with shorter telomere lengths indicating accelerated cellular aging (Ridout, Levandowski, et al., 2018). The biological wear-and-tear associated with ACEs, and alterations in DNA methylation of stress related genes may result in inflammatory, neuroendocrine and metabolic dysregulation, and over time may lead to compromised physical and mental health outcomes (Finlay et al., 2022; McEwen and Stellar, 1993).

1.3. What is a mechanism and state of evidence

Mechanisms are commonly understood to explain how specific phenomenon (and the components thereof) dynamically produce change (Illari and Williamson, 2012). The current research is concerned with identifying the specific components involved in the biological processes linking ACEs to mental health outcomes. Several SBMs including cortisol, inflammation, allostatic load, DNA methylation, and telomere length have been implicated in the stress processes linking ACEs to later mental health outcomes (Cooke et al., 2023; Finlay et al., 2022; Krause et al., 2020; Ridout et al., 2018; Shonkoff et al., 2012) and have consequently been hypothesized as mechanisms (Lippard and Nemeroff, 2020, 2022; Ridout et al., 2018). Work from within intervention science and psychology has suggested that the formal identification of a mechanism requires: 1) statistical evidence of mediation; 2) experimental evidence of causation; and 3) robust theory to explain causal relationships between variables (Kazdin, 2007, 2008, 2009; Tryon, 2018). These criteria work together to establish an evidence-base. The inclusion of theory to explain potentially causal relationships between variables is crucial in examinations of statistical mediation. Statistical mediation can demonstrate relationships between variables, but cannot support the identification of plausibly causal pathways (Fiedler et al., 2011; Tryon, 2018; VanderWeele, 2009). Theoretically driven hypotheses help establish the temporal ordering of variables by explaining potentially causal pathways, allowing statistical outcomes to either support existing theories or point to new avenues to refine theoretical models (MacKinnon and Luecken, 2011; Pirlott and MacKinnon, 2016). While ethics prohibit experimental designs examining the impact of ACEs with human participants, observational human studies can generate theoretical explanations of causation that can be tested through statistical mediation. However, it is currently unclear how many studies have conducted tests of statistical mediation examining the indirect effects of these SBMs on the relationship between ACEs and depression, anxiety, or PTSD, or what patterns exist in this literature related to the statistical significance of indirect effects. Furthermore, it is unknown if the mediation analyses that do exist have been driven by robust theory to explain the potentially causal relationships between variables.

There is a foundation of evidence supporting the possibility that each of these five SBMs could mediate the relationship between ACEs and depression, anxiety, or PTSD in adults. The majority of this evidence, however, has relied on examinations of isolated pairwise associations between variables such as between ACEs and cortisol (from blood, urine, saliva, or hair) (Brindle et al., 2022; Demakakos and Steptoe, 2022), various inflammatory markers (Baumeister et al., 2016; Coelho et al., 2014), allostatic load (Finlay et al., 2022), DNA methylation (Cicchetti et al., 2016; Non et al., 2016; Parade et al., 2021; Tozzi et al., 2018), and telomere length (Bürgin et al., 2019). Each of these SBMs, in turn, have been associated with depression, anxiety, or PTSD symptoms or diagnosis. Highlights of this work demonstrate these mental health issues as outcomes associated with cortisol (Dedovic and Ngiam, 2015; Herbert, 2013; Pan et al., 2018; Sa et al., 2010; Zajkowska et al., 2022), inflammation (Danese and Baldwin, 2017; Miller and Raison, 2016; Passos et al., 2015; Salim et al., 2012), allostatic load (Guidi et al., 2021; Kobrosly et al., 2014), DNA methylation (Argentieri et al., 2017; Humphreys et al., 2019; Panek et al., 2014), and telomere length (Kuehl et al., 2022; Malouff and Schutte, 2017; Simon et al., 2006). Notably, a recent review (Zagaria et al., 2024) synthesized some of this foundational evidence supporting statistical mediation. Investigators surveyed studies assessing associations between any ACE and inflammation, or between inflammation and depression, and conducted meta-analytic structural equation modelling analysis to assess statistical mediation. Investigators found that three inflammatory markers (CRP, IL-6, and composite variables) significantly mediated associations between ACEs and adult depression.

Fewer studies have examined the indirect effects of cortisol, inflammation, allostatic load, DNA methylation, or telomere length on the relationship between ACEs and depression, anxiety, or PTSD. A recent systematic review (Maayan and Maayan, 2024) examined the relationships between childhood and/or adult adversity, inflammation, and depression. The inclusion criteria allowed varied statistical analyses (ie. regression, correlation, moderation, and mediation), mediating variables (ie. markers other than inflammatory or latent variables comprised of inflammation plus psychological measures), outcome variables (ie. depression, associated physical health outcomes, or latent

variables comprised of depressive symptoms plus other psychosocial measures), sample populations (ie. both child and adult), and forms of adversity (ie. both child and adult adversity). Therefore, the review by Maayan and Maayan (2024) was not able to provide a focused analysis on the state of the science related to the mediation effects of inflammation on the relationship between ACEs before the age of 18 and symptoms of depression in adult populations. The authors of the current scoping review are furthermore unaware of other reviews outlining the mediating role of cortisol, inflammation, allostatic load, DNA methylation, or telomere length on the relationship between ACEs and depression, anxiety, or PTSD. While there is a robust repository of preliminary evidence to support the possibility that each of these five SBMs may function as mechanisms linking ACEs to depression, anxiety, or PTSD, the body of research employing statistical mediation with the variables appears to be in a nascent stage of development. This body of research may require further development; however, a critical first step is to synthesize and consolidate the existing literature in order to identify future directions in the iterative process of identifying mechanisms linking ACEs to later mental health outcomes.

1.4. Current work

As suggested by Arksey and O'Malley (2005), scoping reviews are particularly suited for identifying gaps in the literature by broadly surveying existing research without being constrained by study quality or heterogeneity in design. They are also well suited for consolidating and synthesizing research across emerging or complex fields where knowledge is often spread across various disciplines (Mak and Thomas, 2022; Munn et al., 2018). The study of SBMs such as cortisol, inflammation, allostatic load, DNA methylation, and telomere length as potential mediators of the relationship between adverse childhood experiences (ACEs) and later mental health issues is still in a nascent-stage and involves work from within multiple disciplines. Given the limited comprehensive reviews and expected diversity in study designs, a scoping review was deemed the most appropriate method.

This review aimed to map the extent of research investigating the potential mediating roles of five key SBMs—cortisol, inflammation, allostatic load, DNA methylation, and telomere length—in the relationship between ACEs and mental health outcomes such as depression, anxiety, or PTSD. Specifically, the review sought to identify how many studies have conducted statistical mediation analyses, and whether these studies were framed by robust theoretical frameworks to explain the causal relationships between variables. By mapping this research landscape, the study aims to clarify the current state of evidence and highlight areas in need of further investigation. Ultimately, this scoping review contributes to advancing a more integrated, theory-driven understanding of the state of science examining whether these SBMs may function as mechanisms linking ACEs to mental health outcomes. This research is guided by the following research questions:

1. How many studies exist that conduct statistical mediation analyses to examine either cortisol, inflammation, allostatic load, DNA methylation, or telomere length as hypothesized mediators of the relationship between ACEs (within a cumulative dose framework) and symptoms or diagnosis of anxiety, depression, or PTSD in adults?
2. How many of these studies have found statistically significant, versus non-significant indirect effects and what are the patterns of significance across mediators and outcomes?
3. What type of ACEs have been included in statistical mediation models examining the effects of the identified SBMs on the associations between ACEs (analyzed within a cumulative dose framework) and anxiety, depression, and PTSD?
4. What theories and models have been used to frame research examining the statistical mediating effect of these SBMs on the relationship between ACEs and anxiety, depression, or PTSD?

2. Methods

2.1. Protocol and registration

Design of this scoping review was supported by methodological frameworks described by Arksey and O'Malley (2005) and Colquhoun and colleagues (2014). The steps outlined by these authors include: identifying a research question, identifying relevant literature, selecting studies, charting the data, and collating, summarizing, and reporting results (Arksey and O'Malley, 2005; Colquhoun et al., 2014; Levac et al., 2010). The scoping review protocol was developed with the Preferred Reporting Items for Systematic Reviews and Meta Analyses extension for Scoping Reviews (PRISMA ScR) checklist and the results were reported according to PRISMA ScR guidelines (Tricco et al., 2018). A protocol was registered with Open Science Framework (OSF) (https://osf.io/vf5mg/?view_only=218260963bd64541807b46bf80398493). While stakeholder consultation is often incorporated into scoping reviews to provide additional insights and identify gaps (Mak and Thomas, 2022), it was not conducted in this review as the research team possessed the necessary expertise to comprehensively address the study objectives.

2.2. Eligibility criteria

Studies were eligible for inclusion if they were written in English, published in peer-reviewed journals, and included statistical mediation analyses examining the indirect effects of at least one of five identified SBMs, including cortisol, inflammation, allostatic load, DNA methylation, or telomere length on the relationship between ACEs and symptoms or diagnosis of either anxiety, depression, or PTSD. There were no limitations regarding the years of publication. Sample participants were adults (18 + years), and symptoms or diagnosis of depression, anxiety, or PTSD were measured, with or without comorbid symptoms or diagnosis. ACEs were conceptualized within the cumulative dose model (ACEs were summed) and included at least three types of ACEs in recognition of the role of dosing effects as conceptualized by the original ACEs study investigators (Felitti et al., 1998).

The exclusion criteria included: studies not in English, not peer reviewed, or with non-human animal subjects. Studies were excluded that did not plan or conduct tests of statistical mediation where the indirect effect of either cortisol, inflammation, allostatic load, DNA methylation, or telomere length on the relationship between ACEs and either depression, anxiety, or PTSD was assessed. Studies were excluded that did not measure or examine symptoms or diagnosis of either depression, anxiety, or PTSD. Studies that captured less than three ACEs or ACEs were scored in a binary fashion (ie. exposed versus not exposed) were excluded. Studies conducted with participants younger than 18 years old were excluded. For more information on the inclusion and exclusion criteria, please see the protocol registered with Open Science Framework.

2.3. Information sources and search strategy

PubMed and seven additional electronic databases were systematically searched to identify and retrieve all relevant published studies. The electronic databases included: (1) APA PsychInfo (2) CINAHL Plus (3) Health Source: Nursing/Academic Edition (4) MEDLINE (5) Psychology and Behavioral Sciences Collection (6) Science and Technology Collection, and (7) SocINDEX. Search terms were developed and refined in consultation with an academic librarian and the final terms were grouped into four categories with Boolean operators (AND OR) and wildcard symbols: (1) "adverse childhood experiences" OR "ACE* " OR "abuse" or "neglect" or "childhood trauma" or "child maltreatment" or "early life stress" or "household dysfunction" OR "adverse child* " OR (child* n3 abuse*) OR "child*neglect" OR (child* n3 trauma*) OR "child* maltreatment" OR "child* adversity"; AND (2) "biomarker* " OR "Biologic* marker* " OR "allostatic" OR "Immun* " OR "Inflammat* "

OR "c-reactive protein" OR "interleukin-6" OR "tissue necrosis factor alpha" OR "fibrinogen" OR "Leukocyte" OR "Cytokine" OR "Glucocorticoid receptor" OR "Insulin" OR "glucose" OR "Epigenetic" OR "Telomere" OR "Cortisol" OR "Saliva" OR "Body Mass Index" OR "Heart rate variability" OR "Cardiovascular reactivity" OR "Physiological correlates" OR "Metabolic" OR "Endocrine" OR "Metabolomic* " OR "Dehydroepiandrosterone" OR "Thyroid hormones" OR "adiponectin" OR "triglycerides" OR "DNA methylation" OR "methylation" OR "epigenetic age" OR "clock" OR "accelerated age* " OR "high density lipoprotein"; AND (3) "mental health" or "depress* " or "anxiety" or "post-traumatic-stress disorder" or "posttraumatic" OR "PTSD"; AND (4) "mediation" or "mediator" or "mediating" or "mediat* ". Hand searching was also conducted to identify relevant articles and sources included Google Scholar and review articles identified during title and abstract screening. The last search was conducted on September 5, 2024.

2.4. Selection of sources of evidence and data charting

Zotero (Trinoskey et al., 2009) was used for the deduplication of records yielded by the search of electronic databases and title and abstract screening was conducted in Rayyan (Ouzzani et al., 2016). Three reviewers participated in a pilot of the search strategy based on 20 records randomly selected by the librarian and the eligibility criteria was tested and confirmed with 95 % inter-rater agreement. A two-level

PRISMA Diagram

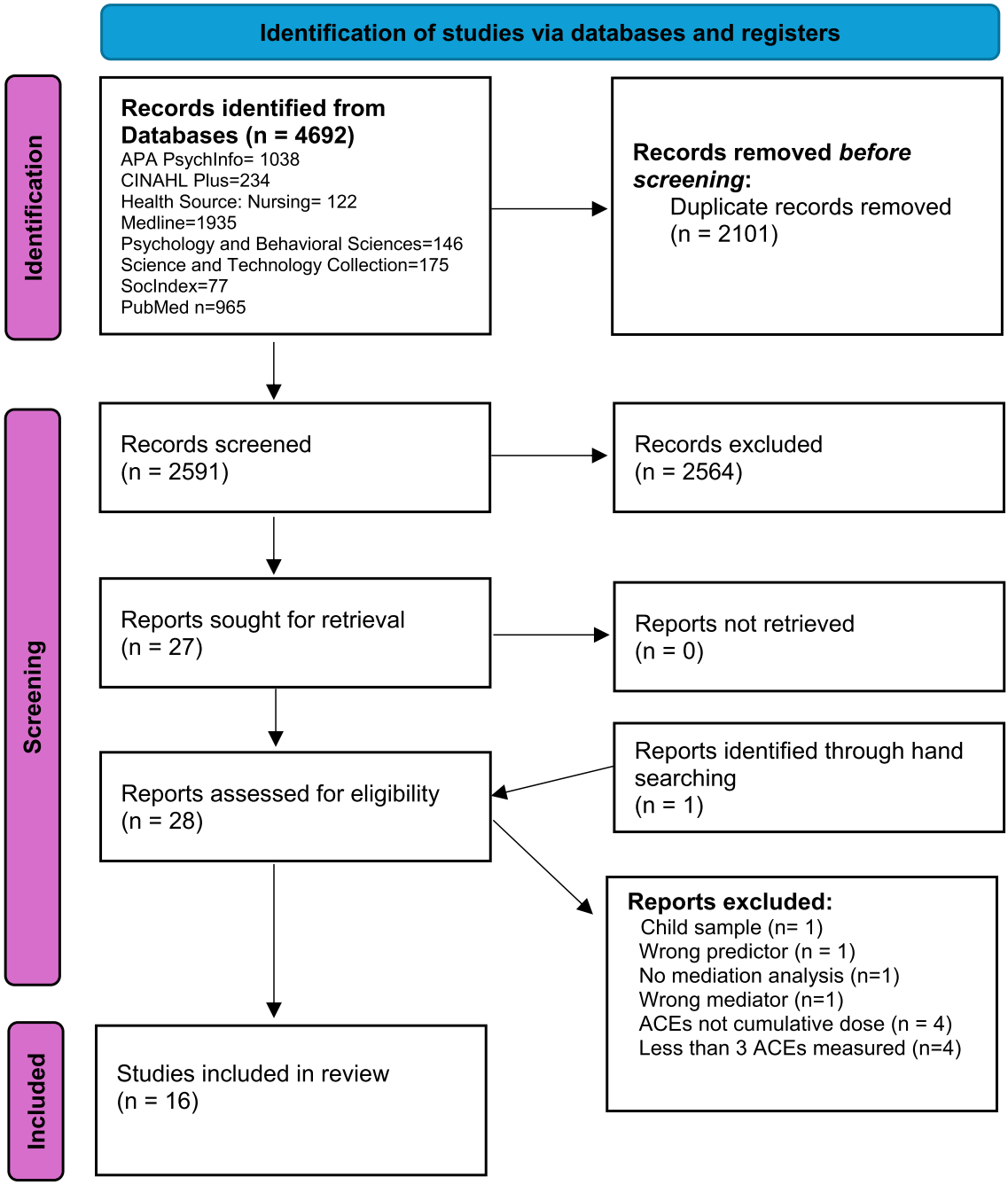


Fig. 1. PRISMA Diagram.

screening process was then conducted, with the first level including titles and abstracts and the second level involving full text review. Two reviewers independently and in duplicate screened all records at both levels of review. Agreement was calculated as the percentage of records where both reviewers made the same inclusion or exclusion decision (McHugh, 2012). Title and abstract screening yielded 99 % inter-rater agreement and full text screening resulted in 93 % inter-rater agreement. Disagreements at both levels were resolved by consensus discussion between all three reviewers. Two reviewers independently and in duplicate collected the specified data items from each record included in the final sample. Discrepancies were resolved by consensus discussion between all three reviewers. Highlights of data items extracted from the final sample of studies included: study title and author, publication year, discipline of first author, sample size, sample demographics (age, gender, race, income), study design, survey tools for ACEs, depression, anxiety, and PTSD, type of SBMs used, type of mediation analysis, number of mediation models assessed, results of mediation analyses, and theoretical framework or models used to drive analysis (if any).

2.5. Synthesis of results

The results of this study were examined according to the framework established by Levac and colleagues (2010). Descriptive numerical summaries and thematic analyses were used to answer the research questions put forth by this study. Descriptive statistics were summarized for sample demographics, ACE prevalence, mental health symptomatology, and SBMs. Effect sizes related to the mediation outcomes were examined based on indirect effect coefficients, mediation proportion, and R^2 values, where reported, in each study.

3. Results

As presented in Fig. 1, the search strategy described in the methods section resulted in 4692 records comprised of 1935 from Medline, 1038 from APA Psychinfo, 965 from Pubmed, and 754 from other electronic databases. After duplicates were removed a pool of 2591 records were identified for review. A total of 2564 records were excluded during the process of title and abstract screening, and an additional single article was identified through hand searching, resulting in 28 records for full text-review. An additional 12 articles were excluded after full-text review, resulting in a final sample of 16 studies.

The studies in the final sample were published between 2020 and 2024 (Bakouni et al., 2023; Comtois-Cabana et al., 2023; Gardhouse, 2021; Iob et al., 2020; Ju et al., 2020; Klopack et al., 2022; Li and Xiang, 2023; Maes et al., 2022; Martinez et al., 2024; O'Shields et al., 2024; O'Shields, Mowbray, et al., 2022; O'Shields, Patel, et al., 2022; O'Shields and Gibbs, 2021; Wiegand et al., 2021; Willemen et al., 2022), except for one study published in 2012 (Cho et al., 2012). As presented in Table 1, the first authors of these 16 studies were from various disciplines including psychiatry (n = 4), social work (n = 4), medicine (n = 3), epidemiology (n = 2), psychology (n = 2), and gerontology (n = 1). These publications represent research from seven different countries including the United States of America (n = 7), Canada (n = 3), China (n = 2), Germany (n = 1), the United Kingdom (n = 1), the Netherlands (n = 1), and Thailand (n = 1). The sample sizes in these studies ranged from 60 to 6518 with a total of 29,796 participants across all studies. There were ten studies where the gender of participants was more than 51 % female and six with samples more than 51 % male, while no studies reported participants with transgender, non-binary, or other gender identities. Ten studies reported the race and ethnicity of their participants. Of those, eight reported that the majority of the participant sample was White (=<54 %), while one study reported a participant sample that was predominantly Black (85 %), and the remaining study reported a generally even distribution of multiple racial/ethnic groups. The age of the participants in these samples was generally older. Nine studies contained participant samples where the mean age was above 50 years old: of those studies, four contained participant samples with a mean age above 60. Two studies contained participant samples with mean ages of 40 and 44, and the remaining five studies had a sample of participants with mean ages between 24 and 35 years. Markers of socioeconomic status also trended towards the higher end. Two studies did not report either educational attainment or income of participants. Of the eleven studies that reported on educational attainment, seven studies reported that the largest proportion of the participant sample had some college education, and four studies reported high school or less. Eight studies reported monetary assets, which were captured through wealth, income, or yearly expenditures. The studies that reported average yearly income were distributed as follows: $75,000 or above (n = 3) and $25,000-$50,000 (n = 2). One study reported median wealth as being $232,000 and another reported that 50 % of participants were in the two highest wealth quintiles. The last study reported that the mean yearly household expenditure was 62,000 yuan.

3.1. Predictors

ACEs were the predictor variable examined in all studies. The measurement, number, and type of ACEs in this sample of studies varied considerably. Nine studies used established screeners. Of those, seven studies used the Childhood Trauma Questionnaire (Bernstein et al., 1997), which contains items related to emotional, physical, and sexual abuse in addition to emotional and physical neglect. One study used the Risky Families Questionnaire (Taylor et al., 2006) and contained items related to abuse, neglect, and household dysfunction. Another study used four items from the original ACEs study screener (Felitti et al., 1998) including physical and emotional abuse, emotional neglect, and witnessing domestic violence. Of the remaining studies, one study did not report the number or type of ACEs but indicated that items were comprised of stressful life experiences before the age of 12. Six studies used scales constructed for the purposes of the specific study and the number of ACEs ranged from 3 to 12. The type of ACEs reported in these studies fall into three categories: 1) those that match the items from Felitti's (1998) original ten ACEs; 2) those that match expanded scale items related to other family and community sources of adversity; 3) and those that have not been commonly included in ACE frameworks. The ACEs items that align with the original ACEs study were distributed across studies as follows: physical abuse (n = 6), sexual abuse (n = 4), parental separation or divorce (n = 3), substance use in the household (n = 3), emotional neglect (n = 2), witnessing domestic violence (n = 2), household or parental mental illness (n = 2), emotional abuse (n = 2), and incarceration of a household member (n = 1). Expanded scale ACEs items were distributed across studies as follows: death of a parent (n = 3), separation from a parent (n = 2), foster care (n = 2), child poverty (n = 1), sibling death (n = 1), bullying (n = 1), unsafe neighborhood (n = 1), and physical assault (not from parents) (n = 1). The least traditional ACEs items were distributed across studies as follows: parental education less than high school (n = 1), parental arguments (n = 1), child welfare visits (n = 1), parental disability (n = 1), low maternal bonding (n = 1), low paternal bonding (n = 1), and 24 h-institutionalization (n = 1).

3.2. Outcomes

While the outcomes of interest of this scoping review included anxiety, depression, and PTSD, 13 studies in the final sample examined depression, two studies examined anxiety, one study examined both depression and anxiety, and no studies examined PTSD. Most of the studies used well established instruments to measure depression or anxiety. Among the 13 studies examining depression, seven studies used the Center for Epidemiologic Studies of Depression (CESD) (Radloff, 1977), two used the Beck Depression Inventory (BDI) (Beck et al., 1996), two used the Patient Health Questionnaire (PHQ) (Kroenke et al., 2001),

Table 1
Characteristics of Studies Conducting Mediation Analyses.

Author, Year, Discipline & Country	Sample & Size	Sample Demographics	Number and type of ACES	Mental health outcome	Mediator(s) and models	Mediation Analysis and Control	Design	Mediation Results*
Cho et al., (2012); Psychiatry; USA	Participants from CARDIA study n = 2716	Mean age= 40; 55 % female; Race: 57 % White, 43 % Black; Mean years of education: 12	7 items: Risky Families Questionnaire: felt loved; shown physical affection; verbally abused; physically abused; family member aware of child's whereabouts; lived with a substance user; lived in well-organized household	Depressive symptoms: CES-D (minus fatigue and sleep disturbance items)	CRP and IL−6: Simple mediation: 4 models: 1 and 2) CRP as mediator with and without controls; 2 and 3) IL−6 as mediator with and without controls	Baron and Kenny and Sobel In control models 2 and 4: age, gender, ethnicity, education	Longitudinal ACEs and CRP at baseline, depression and IL−6 at follow up (5 years later)	CRP not significant. IL−6 significant in model without covariates: (b=0.249, p = 0.001), 2 % mediated by IL−6 (p = 0.009)
Iob et al., (2020); Epidemiology; United Kingdom	Participants from the English Longitudinal Study of Aging n = 4382	Mean age = 70; 56 % female; 50 % in two highest wealth quintiles	12 items: sexual abuse, physical assault, physical abuse from parents, parent arguments, parent mental illness or substance abuse, parent separation or divorce, maternal bonding, paternal bonding, separation from mother for more than six months, parent death, foster care or adoption, and 24-institutionalization	Depressive symptoms: Centre for Epidemiological Studies Depression scale (CESD−8). Two variables: baseline depression and slope of depression symptoms.	CRP Two parallel mediation models: Model 1: two variables representing CRP (one at baseline and slope of CRP) with additional mediators (adult socioeconomic position, lifestyle factors and use of anti-inflammatory/anti-hypertensive drugs) and control variables. Model 2: CRP baseline and slope with control variables.	Parallel process latent growth curve modelling; 5000 bootstraps in Mplus Controls: Sex, age, and childhood SES position	Longitudinal ACEs at wave 3, CRP at waves 2, 4, 6, Depressive symptoms at waves 6, 7, 8.	Significant for baseline CRP but not slope of CRP in both models. In model 1, baseline CRP levels mediated 7 % and 5 % of the association of total ACEs with the intercept and slope of depressive symptoms independently of possible confounders and additional mediators.
Li and Xiang, (2023); Medicine; China	Participants from the China Health and Retirement Longitudinal Study, n = 6518	Mean age= 68; 51 % female; 84 % middle school or below; mean annual household expenditure: $62 K (in yuan).	12 items: domestic violence, physical abuse, household substance abuse, emotional neglect, incarcerated household members, household mental illness, and parental separation or divorce, sibling death, parental death, parental disability, bullying and unsafe neighborhood	Depressive symptoms Centre for Epidemiological Studies Depression Scale (CES-D)	high sensitivity C-reactive protein (HsCRP) and white blood cells Simple mediation. Models 1–4 Indirect effects of CRP on either total ACEs or 7 conventional ACEs with depression as binary or continuous variable. Models 5–8 Indirect effects of white blood cells on either total ACEs or 7 conventional ACEs with depression as binary or continuous variable. All models adjusted for control variables.	Baron and Kenny approach using the mediation package in R; 1000 bootstraps Controls: age, sex, marital status, educational level, hukou status (region of residence), and childhood economic hardship	Cross-sectional	hsCRP significant in all models. In model with total ACEs and depression as binary outcome, high sensitivity C-reactive protein explained 1.17 % of the association between ACEs and depressive symptoms. Indirect effect (B=0.0004, 95 % CI=0.00008–0.0005). White blood cell count did not have a significant mediating effect in any model.
Maes et al., (2022); Medicine; Thailand	Participants recruited from the outpatient clinic of the Department of Psychiatry at King Chulalongkorn Memorial Hospital in Bangkok, Thailand and surrounding community. Depressed patients	Mean age: Controls: 33.6 Depressed: 28; 66 % female; Mean years of education: 16	4 items from ACEs questionnaire; (1) mental trauma, (2) physical trauma, (3) mental neglect, (4) witnessing mother being abused (domestic violence).	Latent variable with symptoms of depression (Hamilton Depression Rating Scale), anxiety (Thai State Trait Anxiety Assessment), recent suicidal behavior (Columbia Suicide Severity Rating Scale), severity of diagnosis (ie.	Inflammatory latent variable comprised of: T cell growth, growth factors, neuro-immunotoxicity Parallel mediation model with one mediator of interest. Second mediator latent variable comprised of immune markers and return of illness.	Partial Least Squares path analysis (SmartPLS); 5000 bootstraps, SPSS Controls: sexual abuse, age	Cross-sectional	There were significant specific indirect effects of ACE-on the mental health outcome that were mediated by the inflammatory variable (t = −2.22, p = 0.026)

(*continued on next page*)

Table 1 (*continued*)

Author, Year, Discipline & Country	Sample & Size	Sample Demographics	Number and type of ACES	Mental health outcome	Mediator(s) and models	Mediation Analysis and Control	Design	Mediation Results*
	n = 20; Healthy controls n = 30			with or without psychotic features).				
O'Shields et al., (2022); Social Work; USA	Participants from Midlife Development in the United States study, n = 2118	Mean age= 53; 54.9 % male; Race: 71.3 % White; Mean income= $76 K	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect.	Depression as a latent variable from 4 subscales of Center for Epidemiological Studies Depression Scale (CES-D). Subscales: depressed affect, somatic activity, anhedonia, and interpersonal challenge.	Inflammation (as latent variable) including: C-reactive protein, fibrinogen, IL−6, sICAM−1, sE-selectin, and TNF- α. Parallel mediation with recent stress as second mediator. Model 1) without control variables Model 2) with control variables.	Structural Equation Modeling in R with Lavaan package. Controls: BMI, Age, tobacco use, anti-depressant medications, NSAIDS, race, sex/ gender, income	Cross-sectional	The indirect paths were significant in both models. In model 2, ACEs were associated with inflammation (B=0.064, $p < 0.01$) and inflammation was associated with depression (B=0.139, $p < 0.01$).
O'Shields et al., (2024); Social Work; USA	Participants from Midlife Development in the United States study, n = 1914	Mean age: 53; 54 % female; Race: 77 % White; Mean income: $77 K	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect. Scored as latent variable.	Depressive symptoms; Centre for Epidemiological Studies Depression Scale (CES-D). As latent variable.	C-reactive protein Indirect effects: 1) parallel mediation with two mediators: CRP and Social support; 2) serial mediation (ACEs–>social support–> CRP–>depression) Model 1) with covariates, Model 2) Sensitivity analysis including participants with high CRP levels.	Structural equation modelling (SEM) in R, indirect effects with Sobel test. Controls: age, income, education, race/ ethnicity, sex, BMI, NSAID, antidepressant use, smoking	Cross-sectional	Null finding
Willemen et al., (2022); Psychiatry; Netherlands	Participants from multi-ethnic cohort study (HELIUS) n = 5998	Mean age= 44 57.8 % female; Race: 21 % Dutch, 19 % African-Surinamese; 18 % Moroccan; 16.7 % Turkish; 29 % medium-high education	4 domains of ACEs: physical abuse, emotional abuse, sexual abuse, emotional neglect.	Depressed mood using Patient Health Questionnaire−9 (PHQ−9)	High sensitivity C-reactive protein	Mediation planned but not conducted as pre-testing revealed no significant association between ACEs and CRP.	Cross-sectional	Null finding
Gardhouse et al., (2021); Psychology; Canada	Females with either no diagnosis, or depression, and borderline personality disorder, and/or PTSD, n = 64	Mean age= 29; 100 % female; Race: 53.9 % White; 12.6 % mixed race; 62 % college education; 23.8 % earned $35-$50 K;	Specific items not reported. Authors state that items related to childhood adversity (12 years and under) from the The Stress and Adversity Inventory for Adults (STRAIN) were used.	Depressive symptoms: Beck Depression Inventory-II (BDI-II)	Parallel mediation: free cortisol and inflammation (IL−6) from plasma.	Structural equation modelling; Lavaan in R; 10,000 bootstraps. No controls in mediation	Cross-sectional	When both mediators were added to the model, the total effect was reduced by 42.3 %
Bakouni et al., (2023); Medicine; Canada	French speaking community living older adults n = 724	69.2 % of sample 65–70 years; 55 % male; 44.8 % grade 8–12 education.	7 items: witnessing domestic violence, physical abuse (3 items), sexual abuse (2 items), child welfare visits.	Anxiety symptoms from the Generalized Anxiety Disorder Questionnaire. Variables as 1) persistence (ie. presence of anxiety symptoms at both T1 and T2), and 2) Anxiety	Salivary cortisol: two variables (at baseline, and during an interview). Parallel mediation with traumatic life events, daily hassles, and psychological resilience. Model 1) outcome as anxiety	Hayes Process (20,000 bootstrap) Control: Sex, recent family violence, cognitive functioning and chronic physical disorders	Cross-sectional	Null finding: neither cortisol variable was significant in the models.

(*continued on next page*)

Table 1 (*continued*)

Author, Year, Discipline & Country	Sample & Size	Sample Demographics	Number and type of ACES	Mental health outcome	Mediator(s) and models	Mediation Analysis and Control	Design	Mediation Results*
				incidence (anxiety absent at T1 and present at T2).	persistence; Model 2) outcome as anxiety incidence. Both models adjusted for control variables.			
Ju et al., (2020); Psychiatry; China	Inpatient and outpatient psychiatric patients and healthy controls from community; n = 251	Mean age = 34; 52 % male; average years of education = 10.7;	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect.	Depressive symptoms with Zung Self-Reporting Depression Scale (SDS)	Plasma cortisol Parallel mediation with dysfunctional attitudes. Adjusted for control variables. Model tested in participants with major depressive disorder.	Hayes Process Macro in SPSS; 5000 bootstraps Controls: age, gender, BMI and education	Cross-sectional	Mediation model explained 27.8 % of variance in depression severity; when cortisol and dysfunctional attitudes in the model, the direct effect between ACEs and depression were no longer significant. Total effect: $R^2 = 0.234$
Comptois-Cabana et al., 2023; Psychology; Canada	Men recruited from general population ages 18–35, n = 160	Mean age = 24; 100 % male; other demographics not reported.	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect.	Depressive symptoms using Beck Depression Inventory-II.	DNA methylation levels within two CPG cites: NR3C1_2_CpG_49to52 and SLC6A3_1_CpG_16 Simple mediation: 6 Models tested with and without control variables. Mediators as follows: Models 1–2) NR3C1_2_CpG_49to52; Models 3–4) SLC6A3_1_CpG_16; Models 5–6) The methylation levels of both CpG sites summed to derive a cumulative index of methylation.	Mediation package in R, confidence intervals estimated using 1000 Monte Carlo simulations. Control: Age, drug consumption	Cross-sectional	In separate models, each CPG site did not have a significant mediating effect. The cumulative DNAm variable with both CPG cites had a significant effect in both models. When tested with controls it explained 16 % of the association between maltreatment experiences and depressive symptoms (B = 0.16, 95 % CI = 0.03–0.41, p = 0.02).
Klopack et al. (2022); Gerontology; USA	Participants from Health and Retirement Study (nationally representative sample of older adults) n = 2672	Median age 67; 56.6 % female; Race: 83.4 % non-Hispanic White; 31.6 % had 16 + years of education; Median wealth: $232 K	8 items: physical abuse, parental substance use, separation from parent, death of parent, foster care, child poverty, separation or divorce, parental education less than high school.	Depressive symptoms Centre for Epidemiological Studies Depression Scale (CES-D)	DNAm aging clocks Simple mediation 3 models with mediators: 1) GrimAge 2)DunedinPoAm38 3) Phenoage Models adjusted for control variables.	Structural equation modelling in Mplus. Bias corrected boot strap, 1000 draws Controls: race, gender, chronological age	Cross-sectional	GrimAge and Dunedin significant, PhenoAge not significant. GrimAge explained 9–14 % of association between ACEs and adult depressive symptoms; DunedinPoAm38 explained 2–7 % of association between ACEs and adult depressive symptoms
Martinez et al., (2024); Epidemiology; USA	Participants from Detroit Neighborhood Health Study, n = 515	Mean age= 51; 58 % female; Race: 85 % Black; 55 % some college or more; 48 % under $25 K	3 items: emotional, physical, and sexual abuse. Items from Childhood Trauma Questionnaire, Revised Conflict Tactics Scales, and Nurse's Health Study	Depressive symptoms: Patient Health Questionnaire−9 (PHQ−9)	Aging clocks and inflammation: 3 models with parallel mediation. Mediators in model 1) Latent variable comprised of GrimAge and PhenoAge (called Systemic Biological Aging), and latent variable comprised of Horvath and Skin&Blood clocks (called epigenetic age). Mediators in model 2) CRP and IL−6 as observed variables, in	Structural equation modelling in R Controls: gender, age, and parental education. Race added to model 2 only.	Longitudinal Depression variable from the time point after collection of biological data.	Null findings: no statistically significant indirect effects.

(*continued on next page*)

Table 1 (*continued*)

Author, Year, Discipline & Country	Sample & Size	Sample Demographics	Number and type of ACES	Mental health outcome	Mediator(s) and models	Mediation Analysis and Control	Design	Mediation Results*
					addition to cytomegalovirus and herpes simplex virus antibodies. Mediators in model 3) GrimAge, PhenoAge, Horvath, and Skin&Blood as observed variables. All models adjusted for control variables.			
Wiegand et al., (2021); Psychiatry; Germany	Participants between ages of 18–50 years old; n = 143	Mean age= 26; 65.7 % male; Race: 100 % White;	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect.	Social anxiety: Liebowitz Social Anxiety Scale (LSAS).	DNA methylation: Simple mediation: Mediator constructed from 13 CPG sites upstream of either *ADAMTS16* or *GALR1* that were associated with both total CTQ and LSAS. Model adjusted for control variables.	Hayes Process Macro, model 4; 5000 bootstraps in SPSS Control: age and sex	Cross-sectional	Null finding.
O'Shields and Gibbs, (2021); Social Work; USA	Participants from Midlife in the United States Refresher Biomarker study, n = 691	Mean age: 53 (m), 51 (f); 50.1 % male; Race: 81 % White; 40.6 % had college degree; mean household income: $101 K (m), $82 K (f)	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect.	Depressive symptoms Centre for Epidemiological Studies Depression Scale (CES-D)	Allostatic Load index (0−16) with 16 biomarkers Simple and moderated mediation. Simple mediation models: 1) tested in males; 2) tested in females. Moderated mediation models with age moderating path between ACEs and allostatic load: 1) tested in males; 2) tested in females. Models adjusted for control variables.	Baron-Kenney method used in SPSS; Sobel test identified significance Controls: age, socioeconomic status, racial/ethnic identity. recent stress, prior medical condition, current prescription medication, education level	Cross-sectional	Null finding
O'Shields et al., (2022); Social Work; USA	Participants from Midlife Development in the United States study, n = 880	Mean age= 54; 55.7 % female; Race: 92.6 % White; Average education: some college; Mean income= $79 K	5 domains: Childhood Trauma Questionnaire: emotional, physical, and sexual abuse, emotional and physical neglect.	Depressive symptoms using World Health Organization's Composite International Diagnostic Interview-Short Form (CIDI-SF)	Allostatic load (AL) with scores ranging 0–7 representing 7 systems. Systems included: sympathetic nervous system, peripheral nervous system, hypothalamic pituitary adrenal axis, immune, cardiovascular, metabolic, and lipids. Simple mediation: Model 1) using general cut-off scores for allostatic load. Model 2) using sex specific cut-off scores of allostatic load. Both models adjusted for control variables.	Mediation package in R: Quasi-Bayesian Monte Carlo method; 10,000 simulations. Control: recent stress, age, education, non-White racial/ethnic identity, income, female sex, prescription medication use.	Longitudinal ACEs and allostatic load at Wave 2, depressive symptoms at Wave 3.	Significant mediation effect: AL explained between 9 % and 10 % of association between ACEs and depressive symptoms (9 % for sex specific AL mediator; 10 % for general AL mediator).

and one used the World Health Organization's Composite International Diagnostic Interview Short Form (CIDI-SF) (Kessler et al., 1998). One additional study on depression used the Zung Self Rated Depression Scale (Zung, 1965). The study examining both anxiety and depression constructed a latent variable comprised of items from the Hamilton Depression Rating Scale (Hamilton, 1960), the Thai State Trait Anxiety Scale (Spielberger et al., 1983), and the Columbia Suicide Severity Rating Scale (Posner et al., 2011). Of the two studies that examined anxiety, one used the Generalized Anxiety Disorder Questionnaire (GAD) (Spitzer et al., 2006), and one used the Lebowitz Social Anxiety Scale (LSAS) (Stangier and Heidenreich, 2005).

3.3. Mediators

All studies in the final sample conducted or planned a mediation analysis where ACEs were the predictor variable, the outcome variable was either depression or anxiety, and the mediator was one of the identified SBMs related to the effects of stress reactivity and/or HPA axis function including inflammation, cortisol, allostatic load, or DNA methylation. No studies in the final sample examined telomere length as a mediator. The biological mediators in the final sample of studies, including those that contained more than one marker, included: markers of inflammation (n = 9), cortisol (n = 3), allostatic load (n = 2), DNA methylation of specific CpG sites (n = 2), and aging clocks based on DNA methylation (n = 2). The studies that examined inflammatory markers included: c-reactive protein, high sensitivity c-reactive protein, IL-6, white blood cells, and two studies used various immune markers to construct latent variables. Cortisol was captured through saliva, plasma, or urine. The two studies that used allostatic load used markers to capture several physiological systems including: the sympathetic nervous system, peripheral nervous system, HPA axis, immune system, neuroendocrine, cardiovascular and metabolic systems, including lipids. The studies that examined DNA methylation in specific regions focused on candidate genes included *NR3C1*, *SLC6A3*, *ADAMTS16,* and *GALR1*. The two studies that examined epigenetic aging clocks used the HorvathAge, which is a first-generation clock and four second generation clocks including the GrimAge, DunedinPoAm38, Phenoage and Skin&Blood.

3.4. Mediation

The design and methodological approaches to mediation analysis varied across studies. Of the 16 studies in the final sample, 12 used a cross-sectional design and four employed a longitudinal design. Mediation approaches included path analysis (n = 6), structural equation modeling (n = 4), the causal steps approach (n = 3), latent growth curve analysis (n = 1), partial least squares path analysis (n = 1), and one study included mediation in the plan of analysis but did not conduct the analysis due to the results of pretests. Six studies conducted simple mediation analysis, and one study conducted both simple mediation and moderated mediation. Eight studies conducted parallel mediation, and one study examined both parallel and serial mediation models. In the studies that employed parallel mediation, including those that tested more than one model, the combinations of mediators were as follows: 1) inflammation and recent stress; 2) C-reactive protein and adult socioeconomic status, lifestyle factors, and use of anti-inflammatory drugs; 3) C-reactive protein and social support; 4) a latent variable for inflammation with another latent variable comprised of inflammatory markers and frequency of returning mental health symptoms; 5) C-reactive protein and IL-6, cytomegalovirus, and herpes simplex virus antibodies; 6) salivary cortisol and traumatic life events, daily hassles, and psychological resilience; 7) plasma cortisol and dysfunctional attitudes; 8) free cortisol and inflammation (IL-6); and 9) two latent variables comprised of aging clocks (GrimAge with PhenoAge and Horvath with Skin&Blood).

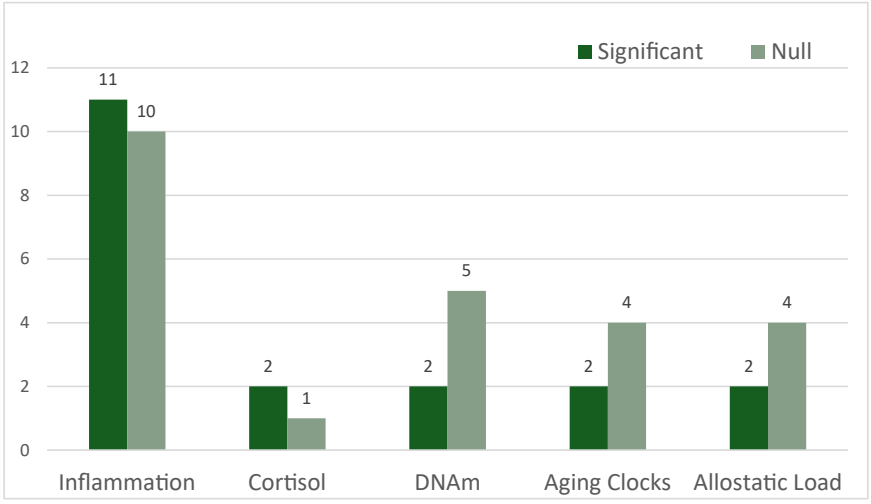
A total of 62.5 % (10/16) of the studies in the final sample found a significant mediating effect of the biological variable on the relationship between ACEs and depression; none of the mediation models examining anxiety were statistically significant. Six of the ten studies with significant findings reported the proportion of the mediated effect as follows: 1) DNAm of CpG sites on both *NR3C1* and *SLC6A3* together (16 %); 2) GrimAge clock (9–14 %) and DunedinPoAm38 clock (2–7 %); 3) allostatic load (9–10 %); 4) baseline C-reactive protein (5–7 %); 5) IL-6 (2 %); and 6) C-reactive protein (1.17 %). Three of the four additional studies with statistically significant findings used structural equation modelling or path analysis. One study reported that the indirect paths were significant as the ACEs variable was associated with inflammation (a latent variable comprised of six inflammatory markers) (B=0.06, $p < 0.01$) and inflammation was associated with depression (B=0.14, $p < 0.01$). A second study reported that there were significant indirect effects of ACE on mental health that were mediated by inflammation ($t = -2.22$, $p = 0.03$). The third study reported that the total effect of the model was reduced by 42.3 % when both mediators (free cortisol and IL-6) were examined together. The last study examining cortisol and dysfunctional attitudes as mediators in parallel mediation reported that the model accounted for 27.8 % of the variation in depression.

Among the 16 studies in the final sample that tested the hypothesized mediating effects of the SBMs on the relationship between ACEs and depression or anxiety, most studies tested more than one model. Within the final sample, there were a total of 43 models were tested. Fig. 2 presents patterns of statistical significance by mediator type. Studies examining inflammation tested 21 models, of which 11 were statistically significant (52 %). Studies examining cortisol tested three models, of which two were statistically (67 %). DNA methylation studies tested seven models, of which two were statistically significant (28.5 %). Studies with aging clocks tested six models and two were statistically significant (33 %). Studies examining allostatic load tested six models and two were statistically significant (33 %).

As presented in Table 2, nine studies (56.25 %) in the final sample integrated theories, models, or conceptual frameworks to inform hypotheses related to statistical mediation of the SBMs on the relationships between ACEs and anxiety or depression. Three models/theories implemented by these studies acknowledge the role of early and cumulative stress in altering developmental and biological processes (through immune, neuroendocrine, epigenetic, and metabolic pathways) leading to health and disease across the life course. These frameworks include the biological embedding of stress framework (Hertzman, 2012; Shonkoff, 2012), allostatic load and wear and tear (McEwen, 1998; Sterling, 2012), and accelerated aging (Belsky et al., 2015; Crimmins, 2015; McEwen, 2002). One study employed the biopsychosocial model (Engel, 1977), which generally acknowledges the intersecting influences of multiple systems (including psychological, social, and biological) in health and disease. Another study employed the Social Signal Transduction Theory of Depression (Slavich and Irwin, 2014) which has been described as a multi-level framework that identifies the neural, molecular, and genomic processes that link social-environmental adversity with depression pathogenesis, maintenance, and recurrence. Two other studies employed models/theories including the Strength and Vulnerability Integration Model (SAVI) (Charles, 2010b) and Social Safety Theory (SST) (Slavich, 2020). The SAVI is particularly focused on biological and psychological influences on emotion regulation in the context of aging, while the SST provides evolutionary and biological perspectives on threat response, adaptation, and health.

4. Discussion

This scoping review sought to survey existing research that conducted statistical mediation analysis examining the indirect effects of either cortisol, inflammation, allostatic load, DNA methylation, or telomere length on the relationship between ACEs and anxiety, depression, or PTSD in adult samples. A central objective of this review



Note. One study tested both inflammation and cortisol and was counted in both categories.

Fig. 2. Number of Mediator Models by Mediator: Significant versus Null Findings.

Table 2
Theories, Models, or Conceptual Frameworks used in Nine of Sixteen Studies.

Theory, Model, or Conceptual Framework	Mediators	Number of Studies (of 16)
Biopsychosocial	Cortisol	1
Biological embedding	Aging clocks, DNA methylation, inflammation	3
Aging	Aging clocks, inflammation	2
Allostatic load and wear and tear	Allostatic load	3
Social Signal Transduction Theory of Depression	Inflammation	1
Social Safety Theory	Inflammation	1
Strength and Vulnerability Integration Conceptual Model	Cortisol	1

Note. 9/16 studies used a theory, model, or conceptual framework. Of those, three used more than one.

was to assess the size of the existing evidence base and to identify patterns of statistical significance of indirect effects across mediators and outcomes. Further aims of this review were to describe the number and types of ACEs included in the cumulative dose frameworks used in these studies and to evaluate the theoretical frameworks used to support the mediation tests conducted in this body of research. This review was designed to assess the state of the science supporting the formal identification of biological mechanisms underlying the relationship between ACEs and depression, anxiety, and PTSD. The identification of mechanisms in this area could provide critical progress in the process of improving treatment for adults with mental health symptoms and a history of ACEs – a population that has often presented with complex symptoms and challenges that are often harder to treat (Liu, 2017).

Our first research question aimed to assess the size of the existing evidence base of studies that met the inclusion criteria. The inclusion criteria required implementation of statistical mediation examining the indirect effects of one of the identified SBMs on the relationship between ACEs and either anxiety, depression, or PTSD in adult participant samples. ACEs were meant to be sum scored in alignment with the cumulative dose framework which acknowledges dosing effects (McLaughlin, 2020). Sixteen studies were identified from an initial pool of 2591 records, suggesting that the evidence base in this area is presently underdeveloped. However, given that all but one of these studies were published between 2020 and 2024, it is likely that this area of inquiry is in a nascent period of development and may be gaining momentum. Furthermore, this small body of research may signal increasing interest and recognition across disciplines regarding the importance of understanding the biological processes linking adverse childhood experiences (ACEs) to mental health outcomes. The authors of these studies come from diverse fields including social work, medicine, psychology, psychiatry, psychology, epidemiology, and gerontology, suggesting that this emerging area of inquiry is attracting attention and being examined from a wide range of scholarly perspectives. While the integration of biology into social science research and vice versa poses methodological and practical challenges (Renwick, 2016), the call to bridge these disciplines in examinations of human behavior, health, and development from both social and biological scientists is decades old (Bateson et al., 2017; Crimmins and Seeman, 2001; Fletcher and Boardman, 2013; Maynard et al., 2018). This movement towards integrative, multilevel, interdisciplinary approaches signals an epistemological shift that is related to the emergence of biosocial research as a specific domain that acknowledges the biological and social as mutually constituting forces that must be evaluated together in order to understand complex health and developmental outcomes (Harris and McDade, 2018). The diverse academic backgrounds of the authors in this emerging literature highlights growing transdisciplinary efforts to examine complex interactions between social and biological phenomenon. Biosocial frameworks may provide key insights in future advances in our understanding of the biological mechanisms linking ACEs to anxiety, depression, and PTSD.

Our second research question sought to identify patterns of statistical significance across mediator types and mental health outcomes. Most studies focused on depression (81.25 %), while two studies (12.5 %) examined anxiety, and none examined PTSD. Accounting for the fact that neither study on anxiety found statistically significant mediating effects, findings suggest that the indirect effects of SBMs on the relationship between ACEs and mental health are more established for depression, with notable gaps for anxiety and PTSD. Inflammation was the most frequently examined mediator (56.25 %), followed by DNA methylation (25 %), cortisol (18.75 %), and allostatic load (12.5 %). Telomere length was not studied. Emerging evidence has suggested that changes in telomere length can result in both positive and negative consequences (Bevelacqua et al., 2021), therefore the lack of focus on telomere length as a hypothesized mediator may suggest reduced confidence or interest in this marker as a reliable predictor of health and disease. Each of the other four mediators (inflammation, cortisol, DNA methylation, allostatic load) showed statistically significant effects on the ACEs-depression link in at least one model. However, results were

mixed, with cortisol showing the highest proportion of significant findings (67 % of the 3 models tested), while inflammation was most frequently studied but yielded a lower proportion of significant results (52 % of the 21 models tested). The mixed findings across all mediators may reflect the small sample of studies, methodological differences (e.g., specific markers such as CRP versus IL-6, or salivary cortisol versus free cortisol), and differences in population samples. Notably, among the studies that reported the proportion of the total effect attributable to the mediation effect, DNA methylation (CpG sites on both *NR3C1* and *SLC6A3* together: 16 %; GrimAge clock: 9–14 %) showed the largest effects on the ACEs-depression link. These findings underscore the potential of inflammation, cortisol, and DNA methylation as mediators, but further research is needed to clarify patterns and explore moderating factors.

While concrete conclusions regarding patterns of statistical significance of the identified mediators cannot be drawn due to the small sample of studies in this review, the mixed findings may indicate the presence of moderating variables. Examinations that include moderators can detect the conditions (ie. for whom and when) under which variables are associated (Wu and Zumbo, 2008). It is possible that the mixed outcomes across studies and models indicate that further examinations are required to understand the limits on the mediating effect of SBMs on associations between ACEs and depression. Notably, the demographics in the final sample of studies were predominantly White, higher income, and there was no documentation regarding gender identity (apart from binary male/female categories) or sexual orientation, which prevented examination of the effects of many recognized elements that comprise the social determinants of health. The higher incidences of ACEs in minoritized communities (Mersky et al., 2021), life course perspectives that emphasize the cumulative impacts of lifetime stressors (Jones et al., 2019), and previous work linking racial and other forms of discrimination to inflammation, cortisol, DNA methylation, and allostatic load might suggest that experiences of stressors such as discrimination and poverty are important to consider (Chen et al., 2022; Diamond et al., 2021; Goosby et al., 2018; Mendoza et al., 2017; Santos et al., 2018). Life course perspectives would suggest that the accumulation of stressors including ACEs and repeated experiences of discrimination related to minority identity or the experience of poverty over time could interact and influence the possibility of dysregulated stress systems during the adult years. In the current sample of studies, the effects of minority identity, discrimination, or poverty on the relationship between ACEs and SBMs were not examined.

An additional perspective that may provide insight on the mixed findings could be related to current conceptualizations of mechanisms linking ACEs to anxiety, depression, or PTSD that assume linearity and independence between and within the biological systems involved with stress. Goosby and Cheadle (2024) outline how the immune system is a complex, cross-scale system that interacts within itself and the other bodily systems it protects. They suggest that analyzing immune components (such as single or clusters of cytokines) independently overlooks these dynamic interactions and assumes linear relationships within and between biological and social systems. This perspective provides a new lens with which to evaluate the studies identified by this review. Most of the mediation analyses in this sample of studies examined a single biological mediator, which assumes independent and linear contributions to anxiety or depression after earlier ACE exposures. If the stress processes (that include glucocorticoids, inflammation, allostatic load, and DNA methylation) are also assumed to be complex, dynamic, and connected via cross-system feedback loops, it stands that examinations of one hypothesized mediator at a time might lead to inaccurate results. Investigations that do not account for the dynamic and complex interplay between systems may only capture a simplified or partial version of the complex reality and thus complicate replication in future research. This perspective may provide an additional explanation for the mixed findings in the significance of indirect effects in this sample of studies. Future work seeking to identify mechanisms or salient leverage points in the processes linking ACEs to later mental health outcomes would benefit from research designs that account for non-linear and complex relationships between and within biological systems.

To clarify patterns of statistical significance and test moderators of interest, future work might include parallel mediation tests or other complex models with all identified SBMs on large and diverse samples. Inflammation, cortisol, allostatic load, and DNA methylation could be compared for relative effect sizes and proportion of influence on total effects within the same sample. The inclusion of variables such as discrimination and poverty, and sub-group analysis based on demographic details such as age, race, sexual orientation and gender identity could also reveal differential effects related to important social determinants of health. This knowledge could greatly contribute to elucidating whether there are specific SBMs that best represent the biological processes linking ACEs to later mental health issues or whether their contributions are additive due to the interacting biological systems that they operate within.

Our third research question aimed to identify the type of ACEs included in the mediation analyses. Results indicated that the number and types of ACEs employed by the studies in this review were limited, which has significant implications. The majority of the studies (62.5 %) examined five or fewer types of ACEs and most often included physical, emotional, and sexual abuse, and emotional and physical neglect, while excluding household dysfunction and community sources of adversity. The cumulative dose model of adversity espoused by Felitti and colleagues (1998) acknowledges that different forms of childhood adversity often co-occur and research that fails to measure several types may be limited by unmeasured and confounding adversities (McLaughlin, 2020). The lack of comprehensive engagement with household dysfunction and expanded scale items has implications regarding limited representation of adversities across populations. The expanded scale items are meant to capture adversities that occur in community environments such as neighborhood violence, bullying, or peer rejection (Finkelhor et al., 2013). These items are thought to be more common among low-income, urban, and racialized communities (Liu et al., 2018; Wade et al., 2014), therefore these types of adversities are important in order to capture experiences that are representative of diverse populations. The mediation models in these studies may have been hindered by unmeasured and confounding forms of adversities. This limitation may have also hidden the full dosage effect of ACEs on the hypothesized biological mediators, thus affecting the outcome of entire mediation models. Future studies should include a comprehensive list of ACE items to capture the full impact of early life stress, while avoiding any confounding effects, and accurately representing adversities that are common across various populations.

Our fourth research question of this research agenda was to identify current theories or models being used to explain the hypothesized mediating influence of SBMs on the relationship between ACEs and depression, anxiety, or PTSD. Slightly over half (56.25 %) of the studies engaged with theoretical frameworks. Given the diversity of fields represented in the final sample of studies, this finding may reflect the often observed fundamental differences between disciplines regarding methodology and approaches to research (Renwick, 2016). For example, it has been noted that epidemiology is a quantitative discipline that relies on methodological principles and rarely emphasizes theoretical frameworks (Kelly-Irving and Delpierre, 2019). Similar observations regarding lack of theory have been made in connection to health behavior and medical education research (Bolander Laksov et al., 2017; Painter et al., 2008). By contrast, theoretical frameworks are often heavily emphasized in social work, sociology, and in many areas of biology (Parton, 2000; Shou et al., 2015; Swingewood, 1999).

The theories or models used in this sample of studies included the biological embedding of stress framework (Hertzman, 2012; Shonkoff, 2012), allostatic load and wear and tear (McEwen, 1998; Sterling, 2012), accelerated aging (Belsky et al., 2015; Crimmins, 2015; McEwen, 2002), the biopsychosocial model (Engel, 1977), the Social Signal

Transduction Theory of Depression (Slavich and Irwin, 2014), the Strength and Vulnerability Integration Model (SAVI) (Charles, 2010b), and Social Safety Theory (SST) (Slavich, 2020). All of these frameworks acknowledge the complex interplay between social and biological systems, which is consistent with the fundamental definition of a biosocial framework as put forth by Harris and McDade (2019). While it is commonly understood that biosocial approaches draw on models and methods from multiple disciplines, the theories and models in the final sample of studies share links with life course theory, developmental, and/or evolutionary perspectives (Ashe et al., 2021; Berens et al., 2017; Bobba-Alves et al., 2022; Charles, 2010a; Hertzman, 2012; Hunt et al., 2022; McEwen, 2002; Nist, 2016; Seeman et al., 2001; Simons et al., 2021; Slavich, 2020; Slavich and Irwin, 2014; Zahodne et al., 2019). The use of theories that share these commonalities may indicate that the biosocial researchers in this sample are coalescing around a shared set of assumptions and guiding principles in examinations of ACEs, biological systems, and mental health. Biosocial researchers in this area may further benefit from engaging with emerging theoretical work that has built on theories of allostasis, biological embedding, and aging models, which also align with life course, developmental, and evolutionary perspectives. For example, active inference theories of interoception recognize the brain as a predictive organ, one that continually anticipates environmental demands based on previous experiences (Barrett et al., 2016). Active inference perspectives emphasize the brain's role in making predictions within the complex, non-linear systems of both the body and social environment; these predictions govern physiological stress processes including metabolism and energy regulation, and ultimately function to ensure survival (Barrett et al., 2016; Goosby and Cheadle, 2024). The current evidence base would benefit from an increased volume of theory driven analysis and future researchers in this area should continue to engage with, test, modify, and build theoretical frameworks explaining the relationships and potential causal phenomenon linking ACEs, SBMs (inflammation, cortisol, DNA methylation, allostatic load), and anxiety, depression, and PTSD.

4.1. Limitations

This review consolidates the existing science examining five SBMs as hypothesized mediators of the relationship between ACEs and anxiety, depression and/or PTSD. However, there are some limitations in the scope of this endeavor. This study was limited by the scarcity of studies available for review that met the inclusion criteria. The inclusion criteria required that all studies use at least three ACEs that were scored continuously, and eight studies were excluded accordingly. This decision was made to acknowledge the role of dosing effects, in alignment with Felitti's (1998) cumulative dose model of ACEs. However, these eight studies may have influenced the overall outcomes of this review. The design of this scoping review did not include risk of bias assessment, therefore the studies in the final sample may have contained biases that would influence the interpretation of results. This review also excluded publications not written in English therefore these results may have missed important research on the topic that has been published in journals where English is not used in scientific discourse.

4.2. Future directions and conclusion

This scoping review contributes important knowledge regarding the state of evidence on statistical mediation and theory in the extant work examining either cortisol, inflammation, DNA methylation, allostatic load, or telomere length as variables linking ACEs and mental health outcomes. This work helps to advance an understanding of the current evidence base supporting the possibility that any of these SBMs might be recognized as mechanisms that could, in the future, be targeted for interventions in adults with symptoms of anxiety, depression, or PTSD and a history of ACEs. The findings of this review reveal that this area of study requires a great deal more data to facilitate identification of patterns across mediators and outcomes. While no studies examined telomere length as a mediator, PTSD as an outcome, and anxiety was scarcely studied, studies on other mediators yielded mixed results when depression was the outcome. In order to evaluate potential moderators, future research should include more diverse participant samples, including those with racial, sexual, and gender minority identity and those with varying levels of socio-economic status. Future studies should consider methodological approaches that recognize the complex and interacting nature of the multiple bodily systems involved in stress processes in order to clarify whether these markers influence mental health symptoms independently or have additive effects in the years subsequent to ACEs. Investigators should report not just direct and indirect effects from mediation models, but also the proportion of variance in the outcome that is attributed the mediator in order to facilitate comparisons of effects across studies. Furthermore, future studies should continue to work towards building theory to support causal explanations and hypotheses involved in the mediation models. Future work in this area is crucial to identify mechanisms linking ACEs to anxiety, depression, and PTSD. This knowledge could provide new directions for assessment, treatment, and prevention of the serious course of mental health symptomatology that can follow in the aftermath of ACEs (Lippard and Nemeroff, 2022).

Funding

This study was supported by the National Institute of Child Health and Human Development under award numbers T32HD007081 and P2CHD042849. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgements

The authors of this work would like to thank Dr. Jacob Cheadle for the valuable insight and feedback provided during the development of this manuscript. The authors dedicate this work to U.S. Army Major, Dr. Jose "Joey" E. Velasquez Jr. (1984-2025), a dear friend and colleague whose camaraderie and intellectual acumen greatly influenced the first author's PhD journey and approach to scoping review methodology.

References

Afifi, T.O., Mather, A., Boman, J., Fleisher, W., Enns, M.W., Macmillan, H., Sareen, J., 2011. Childhood adversity and personality disorders: results from a nationally representative population-based study. J. Psychiatr. Res. 45 (6), 814–822. https://doi.org/10.1016/j.jpsychires.2010.11.008.

Alexander, N., Kirschbaum, C., Wankerl, M., Stauch, B.J., Stalder, T., Steudte-Schmiedgen, S., Muehlhan, M., Miller, R., 2018. Glucocorticoid receptor gene methylation moderates the association of childhood trauma and cortisol stress reactivity. Psychoneuroendocrinology 90, 68–75. https://doi.org/10.1016/j.psyneuen.2018.01.020.

Anda, R.F., Felitti, V.J., Bremner, J.D., Walker, J.D., Whitfield, C., Perry, B.D., Dube, S. R., Giles, W.H., 2006. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur. Arch. Psychiatry Clin. Neurosci. 256 (3), 174–186. https://doi.org/10.1007/s00406-005-0624-4.

Argentieri, M.A., Nagarajan, S., Seddighzadeh, B., Baccarelli, A.A., Shields, A.E., 2017. Epigenetic pathways in human disease: the impact of DNA methylation on stress-related pathogenesis and current challenges in biomarker development. EBioMedicine 18, 327–350. https://doi.org/10.1016/j.ebiom.2017.03.044.

Arksey, H., O'Malley, L., 2005. Scoping studies: towards a methodological framework. Int. J. Soc. Res. Methodol. 8 (1), 19–32. https://doi.org/10.1080/1364557032000119616.

Ashe, A., Colot, V., Oldroyd, B.P., 2021. How does epigenetics influence the course of evolution? Philos. Trans. R. Soc. B: Biol. Sci. 376 (1826), 20200111. https://doi.org/10.1098/rstb.2020.0111.

Bakouni, H., Ouimet, M.C., Desjardins, S., Forget, H., Vasiliadis, H.-M., 2023. Childhood abuse/neglect and temporal patterns in late-life anxiety. Aging Ment. Health 27 (5), 973–982.

Barrett, L.F., Quigley, K.S., Hamilton, P., 2016. An active inference theory of allostasis and interoception in depression. Philos. Trans. R. Soc. B: Biol. Sci. 371 (1708), 20160011. https://doi.org/10.1098/rstb.2016.0011.

Bateson, P., Cartwright, N., Dupré, J., Laland, K., Noble, D., 2017. New trends in evolutionary biology: biological, philosophical and social science perspectives. Interface Focus 7 (5), 20170051. https://doi.org/10.1098/rsfs.2017.0051.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α (cmedm). Mol. Psychiatry 21 (5), 642–649. https://doi.org/10.1038/mp.2015.67.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX.

Belsky, D.W., Caspi, A., Houts, R., Cohen, H.J., Corcoran, D.L., Danese, A., Harrington, H., Israel, S., Levine, M.E., Schaefer, J.D., Sugden, K., Williams, B., Yashin, A.I., Poulton, R., Moffitt, T.E., 2015. Quantification of biological aging in young adults. Proc. Natl. Acad. Sci. 112 (30), E4104–E4110. https://doi.org/10.1073/pnas.1506264112.

Berens, A.E., Jensen, S.K.G., Nelson, C.A., 2017. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Med. 15 (1), 135. https://doi.org/10.1186/s12916-017-0895-4.

Bernstein, D.P., Ahluvalia, T., Pogge, D., Handelsman, L., 1997. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J. Am. Acad. Child Adolesc. Psychiatry 36 (3), 340–348. https://doi.org/10.1097/00004583-199703000-00012.

Bevelacqua, J.J., Welsh, J., Mortazavi, S. a R., Keshavarz, M., Mortazavi, S.M.J., 2021. Space medicine: why do recently published papers about telomere length alterations increase our uncertainty rather than reduce it? J. Biomed. Phys. Eng. 11 (1), 103–108. https://doi.org/10.31661/jbpe.v0i0.2005-1115.

Bobba-Alves, N., Juster, R.-P., Picard, M., 2022. The energetic cost of allostasis and allostatic load. Psychoneuroendocrinology 146, 105951. https://doi.org/10.1016/j.psyneuen.2022.105951.

Bolander Laksov, K., Dornan, T., Teunissen, P.W., 2017. Making theory explicit—An analysis of how medical education research(ers) describe how they connect to theory. BMC Med. Educ. 17 (1), 18. https://doi.org/10.1186/s12909-016-0848-1.

Brewin, C.R., Andrews, B., Valentine, J.D., 2000. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J. Consult. Clin. Psychol. 68 (5), 748–766. https://doi.org/10.1037//0022-006x.68.5.748.

Brindle, R.C., Pearson, A., Ginty, A.T., 2022. Adverse childhood experiences (ACEs) relate to blunted cardiovascular and cortisol reactivity to acute laboratory stress: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 134, 104530. https://doi.org/10.1016/j.neubiorev.2022.104530.

Bruce, L.C., Heimberg, R.G., Blanco, C., Schneier, F.R., Liebowitz, M.R., 2011. Childhood maltreatment and social anxiety disorder: implications for symptom severity and response to pharmacotherapy. Depress Anxiety 29 (2), 132. https://doi.org/10.1002/da.20909.

Bürgin, D., O'Donovan, A., d'Huart, D., di Gallo, A., Eckert, A., Fegert, J., Schmeck, K., Schmid, M., Boonmann, C., 2019. Adverse childhood experiences and telomere length a look into the heterogeneity of findings-a narrative review. Front. Neurosci. 13, 490. https://doi.org/10.3389/fnins.2019.00490.

Chapman, D.P., Whitfield, C.L., Felitti, V.J., Dube, S.R., Edwards, V.J., Anda, R.F., 2004. Adverse childhood experiences and the risk of depressive disorders in adulthood. J. Affect. Disord. 82 (2), 217–225. https://doi.org/10.1016/j.jad.2003.12.013.

Charles, S.T., 2010a. Strength and vulnerability integration: a model of emotional well-being across adulthood. Psychol. Bull. 136 (6), 1068–1091. https://doi.org/10.1037/a0021232.

Charles, S.T., 2010b. Strength and Vulnerability Integration (SAVI): a model of emotional well-being across adulthood. Psychol. Bull. 136 (6), 1068. https://doi.org/10.1037/a0021232.

Chen, E., Yu, T., Brody, G.H., Lam, P.H., Goosby, B.J., Miller, G.E., 2022. Discrimination and inflammation in adolescents of color. Biol. Psychiatry Glob. Open Sci. 3 (2), 204. https://doi.org/10.1016/j.bpsgos.2022.02.008.

Cho, H.J., Bower, J.E., Kiefe, C.I., Seeman, T.E., Irwin, M.R., 2012. Early life stress and inflammatory mechanisms of fatigue in the coronary artery risk development in young adults (CARDIA) study. Brain, Behav., Immun. 26 (6), 859–865. https://doi.org/10.1016/j.bbi.2012.04.005.

Choi, C., Mersky, J.P., Janczewski, C.E., Plummer Lee, C.-T., Davies, W.H., Lang, A.C., 2020. Validity of an expanded assessment of adverse childhood experiences: A replication study. Child. Youth Serv. Rev. 117, 105216. https://doi.org/10.1016/j.childyouth.2020.105216.

Cicchetti, D., Hetzel, S., Rogosch, F.A., Handley, E.D., Toth, S.L., 2016. An investigation of child maltreatment and epigenetic mechanisms of mental and physical health risk. Dev. Psychopathol. 28 (4pt2), 1305–1317. https://doi.org/10.1017/S0954579416000869.

Cloitre, M., Courtois, C., Charuvastra, A., Carapezza, R., Stolbach, B., Green, B., 2011. Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. J. Trauma. Stress 24, 615–627. https://doi.org/10.1002/jts.20697.

Cloitre, M., Khan, C., Mackintosh, M.-A., Garvert, D.W., Henn-Haase, C.M., Falvey, E.C., Saito, J., 2019. Emotion regulation mediates the relationship between ACES and physical and mental health. Psychol. Trauma.: Theory, Res., Pract., Policy 11 (1), 82–89. https://doi.org/10.1037/tra0000374.

Coelho, R., Viola, T.W., Walss-Bass, C., Brietzke, E., Grassi-Oliveira, R., 2014. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr. Scand. 129 (3), 180–192. https://doi.org/10.1111/acps.12217.

Colquhoun, H.L., Levac, D., O'Brien, K.K., Straus, S., Tricco, A.C., Perrier, L., Kastner, M., Moher, D., 2014. Scoping reviews: time for clarity in definition, methods, and reporting. J. Clin. Epidemiol. 67 (12), 1291–1294. https://doi.org/10.1016/j.jclinepi.2014.03.013.

Comtois-Cabana, M., Barr, E., Provençal, N., Ouellet-Morin, I., 2023. Association between child maltreatment and depressive symptoms in emerging adulthood: The mediating and moderating roles of DNA methylation (cmedm). PloS One 18 (1), e0280203. https://doi.org/10.1371/journal.pone.0280203.

Cooke, E.M., Connolly, E.J., Boisvert, D.L., Hayes, B.E., 2023. A systematic review of the biological correlates and consequences of childhood maltreatment and adverse childhood experiences. Trauma, Violence, Abus. 24 (1), 156–173. https://doi.org/10.1177/15248380211021613.

Crede, M., Tynan, M., Harms, P.D., Lester, P.B., 2023. Clarifying the association between adverse childhood experiences and postdeployment posttraumatic stress disorder symptom severity: a meta-analysis and large-sample investigation. J. Trauma. Stress 36 (4), 700–711. https://doi.org/10.1002/jts.22940.

Crimmins, E.M., 2015. Lifespan and healthspan: past, present, and promise. Gerontologist 55 (6), 901–911. https://doi.org/10.1093/geront/gnv130.

Crimmins, E.M., Seeman, T., 2001. Integrating biology into demographic research on health and aging (with a focus on the MacArthur Study of Successful Aging). Cells and Surveys: Should Biological Measures Be Included in Social Science Research? National Academies Press, US. ⟨https://www.ncbi.nlm.nih.gov/books/NBK110043/⟩.

Cronholm, P.F., Forke, C.M., Wade, R., Bair-Merritt, M.H., Davis, M., Harkins-Schwarz, M., Pachter, L.M., Fein, J.A., 2015. Adverse childhood experiences: expanding the concept of adversity. Am. J. Prev. Med. 49 (3), 354–361. https://doi.org/10.1016/j.amepre.2015.02.001.

Danese, A., Baldwin, J.R., 2017. Hidden wounds? Inflammatory links between childhood trauma and psychopathology. Annu. Rev. Psychol. 68, 517–544. https://doi.org/10.1146/annurev-psych-010416-044208.

Dedovic, K., Ngiam, J., 2015. The cortisol awakening response and major depression: examining the evidence. Neuropsychiatr. Dis. Treat. 11, 1181–1189. https://doi.org/10.2147/NDT.S62289.

Demakakos, P., Steptoe, A., 2022. Adverse childhood experiences and diurnal cortisol patterns in older people in England. Psychoneuroendocrinology 142, 105798. https://doi.org/10.1016/j.psyneuen.2022.105798.

Desch, J., Mansuri, F., Tran, D., Schwartz, S.W., Bakour, C., 2023. The association between adverse childhood experiences and depression trajectories in the Add Health study. Child Abus. Negl. 137, 106034. https://doi.org/10.1016/j.chiabu.2023.106034.

Diamond, L.M., Dehlin, A.J., Alley, J., 2021. Systemic inflammation as a driver of health disparities among sexually-diverse and gender-diverse individuals. Psychoneuroendocrinology 129, 105215. https://doi.org/10.1016/j.psyneuen.2021.105215.

Ege, M.A., Messias, E., Thapa, P.B., Krain, L.P., 2015. Adverse childhood experiences and geriatric depression: results from the 2010 BRFSS. Am. J. Geriatr. Psychiatry 23 (1), 110–114. https://doi.org/10.1016/j.jagp.2014.08.014.

Engel, G.L., 1977. The need for a new medical model: A challenge for biomedicine. Science 196 (4286), 129–136. https://doi.org/10.1126/science.847460.

Felitti, V.J., 2002. The relation between adverse childhood experiences and adult health: turning gold into lead. Perm. J. 6 (1), 44–47.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. Advers. Child. Exp. (ACE) Study *Am. J. Prev. Med.* 14 (4), 245–258. https://doi.org/10.1016/s0749-3797(98)00017-8.

Fiedler, K., Schott, M., Meiser, T., 2011. What mediation analysis can (not) do. J. Exp. Soc. Psychol. 47 (6), 1231–1236. https://doi.org/10.1016/j.jesp.2011.05.007.

Finkelhor, D., Shattuck, A., Turner, H., Hamby, S., 2013. Improving the adverse childhood experiences study scale. JAMA Pediatr. 167 (1), 70–75. https://doi.org/10.1001/jamapediatrics.2013.420.

Finlay, S., Roth, C., Zimsen, T., Bridson, T.L., Sarnyai, Z., McDermott, B., 2022. Adverse childhood experiences and allostatic load: a systematic review. Neurosci. Biobehav. Rev. 136, 104605. https://doi.org/10.1016/j.neubiorev.2022.104605.

Fletcher, J.M., Boardman, J.D., 2013. Integrating work from genetics and the social sciences: an introduction. Biodemography Soc. Biol. 59 (1), 1. https://doi.org/10.1080/19485565.2013.774630.

Frewen, P., Zhu, J., Lanius, R., 2019. Lifetime traumatic stressors and adverse childhood experiences uniquely predict concurrent PTSD, complex PTSD, and dissociative subtype of PTSD symptoms whereas recent adult non-traumatic stressors do not: results from an online survey study. Eur. J. Psychotraumatol. 10 (1), 1606625. https://doi.org/10.1080/20008198.2019.1606625.

Gardhouse, K., Carcone, D., Ruocco, A.C., 2021. Stressed, sick, and sad: neuroendoimmune pathways between subjective lifetime stress and depression. Brain, Behav., Immun. - Health 14, 100249. https://doi.org/10.1016/j.bbih.2021.100249.

Gardner, M.J., Thomas, H.J., Erskine, H.E., 2019. The association between five forms of child maltreatment and depressive and anxiety disorders: a systematic review and meta-analysis. Child Abus. Negl. 96, 104082. https://doi.org/10.1016/j.chiabu.2019.104082.

Giampetruzzi, E., Tan, A.C., LoPilato, A., Kitay, B., Riva Posse, P., McDonald, W.M., Hermida, A.P., Crowell, A., Hershenberg, R., 2023. The impact of adverse childhood experiences on adult depression severity and treatment outcomes. J. Affect. Disord. 333, 233–239. https://doi.org/10.1016/j.jad.2023.04.071.

Giourou, E., Skokou, M., Andrew, S.P., Alexopoulou, K., Gourzis, P., Jelastopulu, E., 2018. Complex posttraumatic stress disorder: The need to consolidate a distinct clinical syndrome or to reevaluate features of psychiatric disorders following interpersonal trauma? World J. Psychiatry 8 (1), 12–19. https://doi.org/10.5498/wjp.v8.i1.12.

Goosby, B.J., Cheadle, J.E., 2024. The immune system is a complex system: Inflammatory morbidity and systemic racism. KZfSS K. ölner Z. F. üR. Soziol. Und Soz. 76 (3), 713–744. https://doi.org/10.1007/s11577-024-00952-4.

Goosby, B.J., Cheadle, J.E., Mitchell, C., 2018. Stress-related biosocial mechanisms of discrimination and African American health inequities. Annu. Rev. Sociol. 44 (1), 319–340. https://doi.org/10.1146/annurev-soc-060116-053403.
Guidi, J., Lucente, M., Sonino, N., Fava, G.A., 2021. Allostatic load and its impact on health: a systematic review. Psychother. Psychosom. 90 (1), 11–27. https://doi.org/10.1159/000510696.
Gupta, S., 2022. First-time exploration of adverse childhood experiences among adults in Delaware using BRFSS data: a cross-sectional study. Public Health Pract. 3, 100233. https://doi.org/10.1016/j.puhip.2022.100233.
Hamilton, M., 1960. A rating scale for depression. J. Neurol., Neurosurg., Psychiatry 23 (1), 56. https://doi.org/10.1136/jnnp.23.1.56.
Harris, K.M., McDade, T.W., 2018. The biosocial approach to human development, behavior, and health across the life course. Russell Sage Found. J. Soc. Sci.: RSF 4 (4), 2–26. https://doi.org/10.7758/RSF.2018.4.4.01.
Herbert, J., 2013. Cortisol and depression: three questions for psychiatry. Psychol. Med. 43 (3), 449–469. https://doi.org/10.1017/S0033291712000955.
Hertzman, C., 2012. Putting the concept of biological embedding in historical perspective. Suppl 2 Proc. Natl. Acad. Sci. USA 109 (2), 17160–17167. https://doi.org/10.1073/pnas.1202203109.
Humphreys, K.L., Moore, S.R., Davis, E.G., MacIsaac, J.L., Lin, D.T.S., Kobor, M.S., Gotlib, I.H., 2019. DNA methylation of HPA-axis genes and the onset of major depressive disorder in adolescent girls: A prospective analysis. Transl. Psychiatry 9, 245. https://doi.org/10.1038/s41398-019-0582-7.
Hunt, A., St John-Smith, P., Abed, R., 2022. The biopsychosocial model advanced by evolutionary theory. In: St John-Smith, P., Abed, R. (Eds.), Evolutionary Psychiatry: Current Perspectives on Evolution and Mental Health. Cambridge University Press, pp. 19–34. https://doi.org/10.1017/9781009030564.004.
Illari, P.M., Williamson, J., 2012. What is a mechanism? Thinking about mechanisms across the sciences. Eur. J. Philos. Sci. 2 (1), 119–135. https://doi.org/10.1007/s13194-011-0038-2.
Iob, E., Lacey, R., Steptoe, A., 2020. The long-term association of adverse childhood experiences with C-reactive protein and hair cortisol: cumulative risk versus dimensions of adversity. Brain, Behav., Immun. 87, 318–328. https://doi.org/10.1016/j.bbi.2019.12.019.
Iob, E., Lacey, R., Giunchiglia, V., Steptoe, A., 2022. Adverse childhood experiences and severity levels of inflammation and depression from childhood to young adulthood: A longitudinal cohort study. Mol. Psychiatry 1–9. https://doi.org/10.1038/s41380-022-01478-x.
Jones, N.L., Gilman, S.E., Cheng, T.L., Drury, S.S., Hill, C.V., Geronimus, A.T., 2019. Life course approaches to the causes of health disparities. Am. J. Public Health 109 (1), S48–S55. https://doi.org/10.2105/AJPH.2018.304738.
Ju, Y., Wang, M., Lu, X., Sun, J., Dong, Q., Zhang, L., Liu, B., Liu, J., Yan, D., Guo, H., Zhao, F., Liao, M., Zhang, X., Zhang, Y., Li, L., 2020. The effects of childhood trauma on the onset, severity and improvement of depression: the role of dysfunctional attitudes and cortisol levels (rzh). J. Affect. Disord. 276, 402–410. https://doi.org/10.1016/j.jad.2020.07.023.
Karatzias, T., Murphy, P., Cloitre, M., Bisson, J., Roberts, N., Shevlin, M., Hyland, P., Maercker, A., Ben-Ezra, M., Coventry, P., Mason-Roberts, S., Bradley, A., Hutton, P., 2019. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol. Med. 49 (11), 1761–1775. https://doi.org/10.1017/S0033291719000436.
Kazdin, A.E., 2007. Mediators and mechanisms of change in psychotherapy research. Annu. Rev. Clin. Psychol. 3 (1), 1–27. https://doi.org/10.1146/annurev.clinpsy.3.022806.091432.
Kazdin, A.E., 2008. Evidence-based treatment and practice: New opportunities to bridge clinical research and practice, enhance the knowledge base, and improve patient care. Am. Psychol. 63 (3), 146–159. https://doi.org/10.1037/0003-066X.63.3.146.
Kazdin, A.E., 2009. Understanding how and why psychotherapy leads to change. Psychother. Res. 19 (4–5), 418–428. https://doi.org/10.1080/10503300802448899.
Kelly-Irving, M., Delpierre, C., 2019. A critique of the adverse childhood experiences framework in epidemiology and public health: uses and misuses. Soc. Policy Soc. 18, 1–12. https://doi.org/10.1017/S1474746419000101.
Kessler, R.C., Andrews, G., Mroczek, D., Ustun, B., Wittchen, H.-U., 1998. The world health organization composite international diagnostic interview short-form (CIDI-SF). Int. J. Methods Psychiatr. Res. 7 (4), 171–185. https://doi.org/10.1002/mpr.47.
Kessler, R.C., McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A. M., Aguilar-Gaxiola, S., Alhamzawi, A.O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O., Williams, D.R., 2010. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br. J. Psychiatry.: J. Ment. Sci. 197 (5), 378–385. https://doi.org/10.1192/bjp.bp.110.080499.
Kim, K., Yaffe, K., Rehkopf, D.H., Zheng, Y., Nannini, D.R., Perak, A.M., Nagata, J.M., Miller, G.E., Zhang, K., Lloyd-Jones, D.M., Joyce, B.T., Hou, L., 2023. Association of adverse childhood experiences with accelerated epigenetic aging in midlife. JAMA Netw. Open 6 (6), e2317987. https://doi.org/10.1001/jamanetworkopen.2023.17987.
Klopack, E.T., Crimmins, E.M., Cole, S.W., Seeman, T.E., Carroll, J.E., 2022. Accelerated epigenetic aging mediates link between adverse childhood experiences and depressive symptoms in older adults: results from the Health and Retirement Study. SSM - Popul. Health 17, 101071. https://doi.org/10.1016/j.ssmph.2022.101071.
Kobrosly, R.W., van Wijngaarden, E., Seplaki, C.L., Cory-Slechta, D.A., Moynihan, J., 2014. Depressive Symptoms are associated with allostatic load among community-dwelling older adults. Physiol. Behav. 123, 223–230. https://doi.org/10.1016/j.physbeh.2013.10.014.
Krause, B.J., Artigas, R., Sciolla, A.F., Hamilton, J., 2020. Epigenetic mechanisms activated by childhood adversity. Epigenomics 12 (14), 1239–1255. https://doi.org/10.2217/epi-2020-0042.
Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
Kuehl, L.K., de Punder, K., Deuter, C.E., Martens, D.S., Heim, C., Otte, C., Wingenfeld, K., Entringer, S., 2022. Telomere length in individuals with and without major depression and adverse childhood experiences. Psychoneuroendocrinology 142, 105762. https://doi.org/10.1016/j.psyneuen.2022.105762.
Lähdepuro, A., Savolainen, K., Lahti-Pulkkinen, M., Eriksson, J.G., Lahti, J., Tuovinen, S., Kajantie, E., Pesonen, A.-K., Heinonen, K., Räikkönen, K., 2019. The impact of early life stress on anxiety symptoms in late adulthood. Sci. Rep. 9 (1), 4395. https://doi.org/10.1038/s41598-019-40698-0.
Levac, D., Colquhoun, H., O'Brien, K.K., 2010. Scoping studies: advancing the methodology. Implement. Sci. 5 (1), 69. https://doi.org/10.1186/1748-5908-5-69.
Li, C., Xiang, S., 2023. Adverse childhood experiences, inflammation, and depressive symptoms in late life: a population-based study (cmedm). J. Gerontol. Ser. B, Psychol. Sci. Soc. Sci. 78 (2), 220–229. https://doi.org/10.1093/geronb/gbac179.
Lippard, E.T.C., Nemeroff, C.B., 2020. The devastating clinical consequences of child abuse and neglect: increased disease vulnerability and poor treatment response in mood disorders. Am. J. Psychiatry 177 (1), 20–36. https://doi.org/10.1176/appi.ajp.2019.19010020.
Lippard, E.T.C., Nemeroff, C.B., 2022. Going beyond risk factor: childhood maltreatment and associated modifiable targets to improve life-long outcomes in mood disorders. Pharmacol., Biochem. Behav. 215 (N.PAG-N.PAG. syh).
Liu, R.T., 2017. Childhood adversities and depression in adulthood: current findings and future directions. Clin. Psychol.: A Publ. Div. Clin. Psychol. Am. Psychol. Assoc. 24 (2), 140–153. https://doi.org/10.1111/cpsp.12190.
Liu, S.R., Kia-Keating, M., Nylund-Gibson, K., 2018. Patterns of adversity and pathways to health among White, Black, and Latinx youth. Child Abus. Negl. 86, 89–99. https://doi.org/10.1016/j.chiabu.2018.09.007.
Maayan, L., Maayan, M., 2024. Inflammatory mediation of the relationship between early adversity and major depressive disorder: a systematic review. J. Psychiatr. Res. 169, 364–377. https://doi.org/10.1016/j.jpsychires.2023.11.025.
MacKinnon, D.P., Luecken, L.J., 2011. Statistical analysis for identifying mediating variables in public health dentistry interventions. J. Public Health Dent. 71 (1), S37. https://doi.org/10.1111/j.1752-7325.2011.00252.x.
Maes, M., Rachayon, M., Jirakran, K., Sodsai, P., Klinchanhom, S., Debnath, M., Basta-Kaim, A., Kubera, M., Almulla, A.F., Sughondhabirom, A., 2022. Adverse childhood experiences predict the phenome of affective disorders and these effects are mediated by staging, neuroimmunotoxic and growth factor profiles (cmedm). Cells 11 (9). https://doi.org/10.3390/cells11091564.
Mak, S., Thomas, A., 2022. Steps for conducting a scoping review. J. Grad. Med. Educ. 14 (5), 565–567. https://doi.org/10.4300/JGME-D-22-00621.1.
Malouff, J.M., Schutte, N.S., 2017. A meta-analysis of the relationship between anxiety and telomere length. Anxiety, Stress, Coping 30 (3), 264–272. https://doi.org/10.1080/10615806.2016.1261286.
Martinez, R.A.M., Howard, A.G., Fernández-Rhodes, L., Maselko, J., Pence, B.W., Dhingra, R., Galea, S., Uddin, M., Wildman, D.E., Aiello, A.E., 2024. Does biological age mediate the relationship between childhood adversity and depression? Insights from the Detroit Neighborhood Health Study. Soc. Sci. Med. 340 (1982), 116440. https://doi.org/10.1016/j.socscimed.2023.116440.
Maynard, B.R., Boutwell, B.B., Vaughn, M.G., Naeger, S., Dell, N., 2018. Biosocial research in social work journals: a systematic review. Res. Soc. Work Pract. 28 (2), 107–115. https://doi.org/10.1177/1049731515615678.
McCutchen, C., Hyland, P., Shevlin, M., Cloitre, M., 2022. The occurrence and co-occurrence of ACEs and their relationship to mental health in the United States and Ireland. Child Abus. Negl. 129, 105681. https://doi.org/10.1016/j.chiabu.2022.105681.
McEwen, B.S., 1998. Stress, adaptation, and disease. Allostasis and allostatic load. Ann. N. Y. Acad. Sci. 840, 33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x.
McEwen, B.S., 2002. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. Neurobiol. Aging 23 (5), 921–939. https://doi.org/10.1016/S0197-4580(02)00027-1.
McEwen, B.S., 2017. Neurobiological and systemic effects of chronic stress. Chronic Stress (Thousand Oaks Calif.) 1, 2470547017692328. https://doi.org/10.1177/2470547017692328.
McEwen, B.S., Stellar, E., 1993. Stress and the individual: Mechanisms leading to disease. Arch. Intern. Med. 153 (18), 2093–2101. https://doi.org/10.1001/archinte.1993.00410180039004.
McHugh, M.L., 2012. Interrater reliability: the kappa statistic. Biochem. Med. 22 (3), 276–282.
McLaughlin, K., 2020. Early life stress and psychopathology. In: Harkness, K.L., Hayden, E.P. (Eds.), The Oxford Handbook of Stress and Mental Health. Oxford University Press, pp. 44–74. https://doi.org/10.1093/oxfordhb/9780190681777.013.3.
Mendoza, V.B. de, Huang, Y., Crusto, C.A., Sun, Y.V., Taylor, J.Y., 2017. Perceived racial discrimination and DNA methylation among African American women in the InterGEN Study. Biol. Res. Nurs. 20 (2), 145. https://doi.org/10.1177/1099800417748759.
Merrick, M.T., Ports, K.A., Ford, D.C., Afifi, T.O., Gershoff, E.T., Grogan-Kaylor, A., 2017. Unpacking the impact of adverse childhood experiences on adult mental health. Child Abus. Negl. 69, 10–19. https://doi.org/10.1016/j.chiabu.2017.03.016.
Mersky, J.P., Choi, C., Plummer Lee, C., Janczewski, C.E., 2021. Disparities in adverse childhood experiences by race/ethnicity, gender, and economic status: intersectional

analysis of a nationally representative sample. Child Abus. Negl. 117, 105066. https://doi.org/10.1016/j.chiabu.2021.105066.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: From evolutionary imperative to modern treatment target. Article 1 Nat. Rev. Immunol. 16 (1). https://doi.org/10.1038/nri.2015.5.
Munn, Z., Peters, M.D.J., Stern, C., Tufanaru, C., McArthur, A., Aromataris, E., 2018. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med. Res. Methodol. 18 (1), 143. https://doi.org/10.1186/s12874-018-0611-x.
Nanni, V., Uher, R., Danese, A., 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am. J. Psychiatry 169 (2), 141–151. https://doi.org/10.1176/appi.ajp.2011.11020335.
Nemeroff, C.B., Binder, E., 2014. The preeminent role of childhood abuse and neglect in vulnerability to major psychiatric disorders: toward elucidating the underlying neurobiological mechanisms (psyh). J. Am. Acad. Child Adolesc. Psychiatry 53 (4), 395–397. https://doi.org/10.1016/j.jaac.2014.02.004.
Nist, M.D., 2016. Biological embedding: evaluation and analysis of an emerging concept for nursing scholarship. J. Adv. Nurs. 73 (2), 349. https://doi.org/10.1111/jan.13168.
Nochaiwong, S., Ruengorn, C., Thavorn, K., Hutton, B., Awiphan, R., Phosuya, C., Ruanta, Y., Wongpakaran, N., Wongpakaran, T., 2021. Global prevalence of mental health issues among the general population during the coronavirus disease-2019 pandemic: a systematic review and meta-analysis. Sci. Rep. 11 (1), 10173. https://doi.org/10.1038/s41598-021-89700-8.
Non, A.L., Hollister, B.M., Humphreys, K.L., Childebayeva, A., Esteves, K., Zeanah, C.H., Fox, N.A., Nelson, C.A., Drury, S.S., 2016. DNA methylation at stress-related genes is associated with exposure to early life institutionalization. Am. J. Phys. Anthropol. 161 (1), 84–93. https://doi.org/10.1002/ajpa.23010.
O'Shields, J., Gibbs, J.J., 2021. Depressive symptoms, childhood maltreatment, and allostatic load: The importance of sex differences (cmedm). Psychoneuroendocrinology 126, 105130. https://doi.org/10.1016/j.psyneuen.2021.105130.
O'Shields, J., Mowbray, O., Cooper, Z., 2024. The effects of childhood maltreatment on social support, inflammation, and depressive symptoms in adulthood. Soc. Sci. Med. 340, 116481. https://doi.org/10.1016/j.socscimed.2023.116481.
O'Shields, J., Mowbray, O., Patel, D., 2022. Allostatic load as a mediator of childhood maltreatment and adulthood depressive symptoms: a longitudinal analysis (cmedm). Psychoneuroendocrinology 143, 105839. https://doi.org/10.1016/j.psyneuen.2022.105839.
O'Shields, J., Patel, D., Mowbray, O.P., 2022. Childhood maltreatment and inflammation: Leveraging structural equation modeling to test the social signal transduction theory of depression (cmedm). J. Affect. Disord. 311, 173–180. https://doi.org/10.1016/j.jad.2022.05.077.
Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan—a web and mobile app for systematic reviews. Syst. Rev. 5 (1), 210. https://doi.org/10.1186/s13643-016-0384-4.
Painter, J.E., Borba, C.P.C., Hynes, M., Mays, D., Glanz, K., 2008. The use of theory in health behavior research from 2000 to 2005: a systematic review. Ann. Behav. Med.: A Publ. Soc. Behav. Med. 35 (3), 358–362. https://doi.org/10.1007/s12160-008-9042-y.
Pan, X., Wang, Z., Wu, X., Wen, S.W., Liu, A., 2018. Salivary cortisol in post-traumatic stress disorder: a systematic review and meta-analysis. BMC Psychiatry 18 (1), 324. https://doi.org/10.1186/s12888-018-1910-9.
Panek, M., Pietras, T., Szemraj, J., Kuna, P., 2014. Association analysis of the glucocorticoid receptor gene (NR3C1) haplotypes (ER22/23EK, N363S, BclI) with mood and anxiety disorders in patients with asthma. Experimental and Therapeutic Medicine, 8(2), 662–670. https://doi.org/10.3892/etm.2014.1734.
Parade, S.H., Huffhines, L., Daniels, T.E., Stroud, L.R., Nugent, N.R., Tyrka, A.R., 2021. A systematic review of childhood maltreatment and DNA methylation: candidate gene and epigenome-wide approaches. Article 1 Transl. Psychiatry 11 (1). https://doi.org/10.1038/s41398-021-01207-y.
Parton, N., 2000. Some thoughts on the relationship between theory and practice in and for social work. Br. J. Soc. Work 30 (4), 449–463. https://doi.org/10.1093/bjsw/30.4.449.
Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhães, P.V., Kapczinski, F., Kauer-Sant'Anna, M., 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry 2 (11), 1002–1012. https://doi.org/10.1016/S2215-0366(15)00309-0.
Pirlott, A.G., MacKinnon, D.P., 2016. Design approaches to experimental mediation. J. Exp. Soc. Psychol. 66, 29. https://doi.org/10.1016/j.jesp.2015.09.012.
Poole, J.C., Dobson, K.S., Pusch, D., 2017. Anxiety among adults with a history of childhood adversity: psychological resilience moderates the indirect effect of emotion dysregulation. J. Affect. Disord. 217, 144–152. https://doi.org/10.1016/j.jad.2017.03.047.
Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168 (12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704.
Racine, N., Devereaux, C., Cooke, J.E., Eirich, R., Zhu, J., Madigan, S., 2021. Adverse childhood experiences and maternal anxiety and depression: a meta-analysis. BMC Psychiatry 21 (1), 28. https://doi.org/10.1186/s12888-020-03017-w.
Radloff, L.S., 1977. The CES-D Scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1 (3), 385–401. https://doi.org/10.1177/014662167700100306.
Remigio-Baker, R.A., Hayes, D.K., Reyes-Salvail, F., 2014. Adverse childhood events and current depressive symptoms among women in Hawaii: 2010 BRFSS, Hawaii. Matern. Child Health J. 18 (10), 2300–2308. https://doi.org/10.1007/s10995-013-1374-y.
Renwick, C., 2016. Biology, social science and history: Interdisciplinarity in three directions. Palgrave Commun. 2 (1), 1–5. https://doi.org/10.1057/palcomms.2016.1.
Ridout, K.K., Khan, M., Ridout, S.J., 2018. Adverse childhood experiences run deep: Toxic early life stress, telomeres, and mitochondrial DNA copy number, the biological markers of cumulative stress. Bioessay.: N. Rev. Mol., Cell. Dev. Biol. 40 (9), e1800077. https://doi.org/10.1002/bies.201800077.
Ridout, K.K., Levandowski, M., Ridout, S.J., Gantz, L., Goonan, K., Palermo, D., Price, L. H., Tyrka, A.R., 2018. Early life adversity and telomere length: a meta-analysis. Mol. Psychiatry 23 (4), 858–871. https://doi.org/10.1038/mp.2017.26.
Sa, V., Fg, Z., J, van, P., Rh, D., Jc, V., R., van, D., Wj, H., Jh, S., Bw, P., 2010. Salivary cortisol levels in persons with and without different anxiety disorders. Psychosom. Med. 72 (4). https://doi.org/10.1097/PSY.0b013e3181d2f0c8.
Sahle, B.W., Reavley, N.J., Li, W., Morgan, A.J., Yap, M.B.H., Reupert, A., Jorm, A.F., 2022. The association between adverse childhood experiences and common mental disorders and suicidality: an umbrella review of systematic reviews and meta-analyses. Eur. Child Adolesc. Psychiatry 31 (10), 1489–1499. https://doi.org/10.1007/s00787-021-01745-2.
Salim, S., Chugh, G., Asghar, M., 2012. Inflammation in anxiety. Adv. Protein Chem. Struct. Biol. 88, 1–25. https://doi.org/10.1016/B978-0-12-398314-5.00001-5.
Santos, H.P., Nephew, B.C., Bhattacharya, A., Tan, X., Smith, L., Alyamani, R.A.S., Martin, E.M., Perreira, K., Fry, R.C., Murgatroyd, C., 2018. Discrimination exposure and DNA methylation of stress-related genes in Latina mothers. Psychoneuroendocrinology 98, 131–138. https://doi.org/10.1016/j.psyneuen.2018.08.014.
Schalinski, I., Teicher, M.H., Nischk, D., Hinderer, E., Müller, O., Rockstroh, B., 2016. Type and timing of adverse childhood experiences differentially affect severity of PTSD, dissociative and depressive symptoms in adult inpatients. BMC Psychiatry 16 (1), 295. https://doi.org/10.1186/s12888-016-1004-5.
Seeman, T.E., McEwen, B.S., Rowe, J.W., Singer, B.H., 2001. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc. Natl. Acad. Sci. USA 98 (8), 4770–4775. https://doi.org/10.1073/pnas.081072698.
Shonkoff, J.P., 2012. Leveraging the biology of adversity to address the roots of disparities in health and development. Suppl 2 Proc. Natl. Acad. Sci. USA 109 (2), 17302–17307. https://doi.org/10.1073/pnas.1121259109.
Shonkoff, J.P., Garner, A.S., Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, & Section on Developmental and Behavioral Pediatrics, 2012. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 129 (1), e232–246. https://doi.org/10.1542/peds.2011-2663.
Shou, W., Bergstrom, C.T., Chakraborty, A.K., Skinner, F.K., 2015. Theory, models and biology. eLife 4, e07158. https://doi.org/10.7554/eLife.07158.
Simon, N.M., Smoller, J.W., McNamara, K.L., Maser, R.S., Zalta, A.K., Pollack, M.H., Nierenberg, A.A., Fava, M., Wong, K.-K., 2006. Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. Biol. Psychiatry 60 (5), 432–435. https://doi.org/10.1016/j.biopsych.2006.02.004.
Simons, R.L., Lei, M.-K., Klopach, E., Berg, M., Zhang, Y., Beach, S.S.R., 2021. Re)setting epigenetic clocks: An important avenue whereby social conditions become biologically embedded across the life course. J. Health Soc. Behav. 62 (3), 436–453. https://doi.org/10.1177/00221465211009309.
Slavich, G.M., 2020. Social safety theory: a biologically based evolutionary perspective on life stress, health, and behavior. Annu. Rev. Clin. Psychol. 16, 265–295. https://doi.org/10.1146/annurev-clinpsy-032816-045159.
Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol. Bull. 140 (3), 774–815. https://doi.org/10.1037/a0035302.
Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialog. Clin. Neurosci. 8 (4), 383–395. https://doi.org/10.31887/DCNS.2006.8.4/ssmith.
Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1983. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.
Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166 (10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.
Stangier, U., Heidenreich, T., 2005. Liebowitz social anxiety scale. Hogrefe.
Steel, Z., Marnane, C., Iranpour, C., Chey, T., Jackson, J.W., Patel, V., Silove, D., 2014. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. Int. J. Epidemiol. 43 (2), 476–493. https://doi.org/10.1093/ije/dyu038.
Sterling, P., 2012. Allostasis: a model of predictive regulation. Physiol. Behav. 106 (1), 5–15. https://doi.org/10.1016/j.physbeh.2011.06.004.
Straub, R.H., Cutolo, M., 2016. Glucocorticoids and chronic inflammation. Rheumatology 55 (suppl_2), ii6–ii14. https://doi.org/10.1093/rheumatology/kew348.
Swingewood, A., 1999. Sociological theory. In: Taylor, S. (Ed.), Sociology. Palgrave, London, pp. 50–72. https://doi.org/10.1007/978-1-349-27552-6_3.
Tabb, L.P., Rich, J.A., Waite, D., Alberto, C., Harris, E., Gardner, J., Gentile, N., Corbin, T. J., 2022. Examining associations between adverse childhood experiences and posttraumatic stress disorder symptoms among young survivors of urban violence. J. Urban Health.: Bull. N. Y. Acad. Med. 99 (4), 669–679. https://doi.org/10.1007/s11524-022-00628-4.

Tan, M., Mao, P., 2023. Type and dose-response effect of adverse childhood experiences in predicting depression: a systematic review and meta-analysis. Child Abus. Negl. 139, 106091. https://doi.org/10.1016/j.chiabu.2023.106091.

Taylor, S.E., Lehman, B.J., Kiefe, C.I., Seeman, T.E., 2006. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biol. Psychiatry 60 (8), 819–824. https://doi.org/10.1016/j.biopsych.2006.03.016.

Tozzi, L., Farrell, C., Booij, L., Doolin, K., Nemoda, Z., Szyf, M., Pomares, F.B., Chiarella, J., O'Keane, V., Frodl, T., 2018. Epigenetic changes of FKBP5 as a link connecting genetic and environmental risk factors with structural and functional brain changes in major depression. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 43 (5), 1138–1145. https://doi.org/10.1038/npp.2017.290.

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., Moher, D., Peters, M.D.J., Horsley, T., Weeks, L., Hempel, S., Akl, E.A., Chang, C., McGowan, J., Stewart, L., Hartline, L., Aldcroft, A., Wilson, M.G., Garritty, C., Strauss, S.E., 2018. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann. Intern. Med. 169 (7), 467–473. https://doi.org/10.7326/M18-0850.

Trinoskey, J., Brahmi, F.A., Gall, C., 2009. Zotero: a product review. J. Electron. Resour. Med. Libr. 6 (3), 224–229. https://doi.org/10.1080/15424060903167229.

Tryon, W.W., 2018. Mediators and mechanisms. Clin. Psychol. Sci. 6 (5), 619–628. https://doi.org/10.1177/2167702618765791.

VanderWeele, T.J., 2009. Mediation and mechanism. Eur. J. Epidemiol. 24 (5), 217–224. https://doi.org/10.1007/s10654-009-9331-1.

Wade, R., Shea, J.A., Rubin, D., Wood, J., 2014. Adverse childhood experiences of low-income urban youth. Pediatrics 134 (1), e13–20. https://doi.org/10.1542/peds.2013-2475.

Waldron, E.M., Howard, K.R., Reinecke, M.A., 2019. The long-term effect of trauma history on adolescent depression treatment. Psychol. Trauma.: Theory, Res., Pract. Policy 11 (7), 751–759. https://doi.org/10.1037/tra0000457.

Wang, D., Jiang, Q., Yang, Z., Choi, J.-K., 2021. The longitudinal influences of adverse childhood experiences and positive childhood experiences at family, school, and neighborhood on adolescent depression and anxiety. J. Affect. Disord. 292, 542–551. https://doi.org/10.1016/j.jad.2021.05.108.

Whitaker, R.C., Dearth-Wesley, T., Herman, A.N., Block, A.E., Holderness, M.H., Waring, N.A., Oakes, J.M., 2021. The interaction of adverse childhood experiences and gender as risk factors for depression and anxiety disorders in US adults: a cross-sectional study. BMC Public Health 21 (1), 2078. https://doi.org/10.1186/s12889-021-12058-z.

Widom, C.S., DuMont, K., Czaja, S.J., 2007. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch. Gen. Psychiatry 64 (1), 49–56. https://doi.org/10.1001/archpsyc.64.1.49.

Wiegand, A., Munk, M.H.J., Drohm, S., Fallgatter, A.J., MacIsaac, J.L., Kobor, M.S., Nieratschker, V., Kreifelts, B., 2021. Neural correlates of attentional control in social anxiety disorder: the impact of early-life adversity and DNA methylation (cmedm). J. Psychiatry Neurosci.: JPN 46 (6), E663–E674. https://doi.org/10.1503/jpn.210064.

Willemen, F.E.M., van Zuiden, M., Zantvoord, J.B., de Rooij, S.R., van den Born, B.-J.H., Hak, A.E., Thomaes, K., Segeren, M., Elsenburg, L.K., Lok, A., 2022. Associations between child maltreatment, inflammation, and comorbid metabolic syndrome to depressed mood in a multiethnic urban population: The HELIUS study (cmedm). Front. Psychol. 13, 787029. https://doi.org/10.3389/fpsyg.2022.787029.

World Health Organization. (n.d.). Mental disorders. ⟨https://www.who.int/news-room/fact-sheets/detail/mental-disorders⟩.

Wu, A.D., Zumbo, B.D., 2008. Understanding and using mediators and moderators. Soc. Indic. Res. 87 (3), 367–392. https://doi.org/10.1007/s11205-007-9143-1.

Zagaria, A., Fiori, V., Vacca, M., Lombardo, C., Pariante, C.M., Ballesio, A., 2024. Inflammation as a mediator between adverse childhood experiences and adult depression: a meta-analytic structural equation model. J. Affect. Disord. 357, 85–96. https://doi.org/10.1016/j.jad.2024.04.072.

Zahodne, L.B., Sharifian, N., Manly, J.J., Sumner, J.A., Crowe, M., Wadley, V.G., Howard, V.J., Murchland, A.R., Brenowitz, W.D., Weuve, J., 2019. Life course biopsychosocial effects of retrospective childhood social support and later-life cognition. Psychol. Aging 34 (7), 867–883. https://doi.org/10.1037/pag0000395.

Zajkowska, Z., Gullett, N., Walsh, A., Zonca, V., Pedersen, G.A., Souza, L., Kieling, C., Fisher, H.L., Kohrt, B.A., Mondelli, V., 2022. Cortisol and development of depression in adolescence and young adulthood – a systematic review and meta-analysis. Psychoneuroendocrinology 136, 105625. https://doi.org/10.1016/j.psyneuen.2021.105625.

Zung, W., 1965. A self-rating depression scale. Arch. Gen. Psychiatry 12 (1), 63–70. https://doi.org/10.1001/archpsyc.1965.01720310065008.