



## Review article

## Biomarkers of adverse childhood experiences: A scoping review

Stephanie Deighton<sup>a,\*</sup>, Alexandra Neville<sup>a</sup>, Dennis Pusch<sup>b</sup>, Keith Dobson<sup>a</sup><sup>a</sup> University of Calgary, Department of Psychology, Alberta, Canada<sup>b</sup> Southport Psychological Services, Alberta, Calgary, Canada

## ARTICLE INFO

## Keywords:

Adverse childhood experiences  
ACEs  
Biomarkers  
Adults  
Scoping review

## ABSTRACT

Adverse Childhood Experiences (ACEs) are stressful and/or traumatic experiences that occur during childhood. Research has demonstrated a link between ACEs and risk of physical and mental health disorders, where early life adversity may become “biologically embedded” and have wide-ranging effects on various physiological systems. The aim of this study was to identify the extent and breadth of recent research activity relating to biological measures of ACEs in adulthood. We undertook a scoping review including published research articles. Medline and PsycINFO were searched for articles from 2007 to July 2017. Articles were eligible if they included adult participants, were written in English, and reported on a biomarker of childhood adversity in adulthood. Forty articles met our inclusion criteria. Studies investigated a range of ACEs that were often measured retrospectively. The studies identified biomarkers related to inflammation (e.g., CRP), cardio/metabolic systems (e.g., BMI), genetics (e.g., telomere length), and endocrine systems (e.g., cortisol), as well as composites of multiple physiological systems. However, not every study identified found significant associations. Health behaviours, emotional distress, social relationships, and socioeconomic factors may help explain some of these associations. Further research is needed to better understand biomarkers of ACEs in adulthood and their relationship to health conditions.

## 1. Introduction

Adverse childhood experiences (ACEs) are typically defined as stressful and/or traumatic experiences that occur during childhood. Emotional, physical, and sexual abuse, emotional and physical neglect, and household dysfunction (i.e., household substance abuse, mental illness, and criminal behaviour; domestic violence; parental divorce or separation) are all considered ACEs if they were experienced before the age of 18 years (Dube et al., 2001). Estimates suggest a high proportion of individuals have experienced ACEs (Dong et al., 2004a; Felitti et al., 1998). It has been projected that approximately two in every three Americans have experienced at least one ACE, and 12% have indicated experiencing at least 4 types of ACEs (Dong et al., 2004a). In a study of 8629 adults, Dong and Colleagues (2004a) found that 67.3% of participants reported experiencing at least one ACE, with the most common ACEs being substance abuse in the household (28.2%), physical abuse (26.4%), domestic violence (24.1%), sexual abuse (21.0%), and mental illness in the household (20.3%). Additionally, studies have found that exposure to one ACE significantly increases the incidence of having additional ACEs (Dong et al., 2004a; Felitti et al., 1998). These

prevalence estimates are specific to American populations. How they extend to other countries and cultures is an important area for further research.

ACEs can have a lasting impact on health and quality of life throughout the lifespan (Anda et al., 2006) and are associated with a wide range of long-term poor health outcomes, including increased risk of heart, lung, and liver disease, cancer, HIV, type 2 diabetes, obesity, and poorer overall self-rated health (Caspi et al., 2006; Danese et al., 2009; Felitti et al., 1998; Middlebrooks and Audage, 2008). Mental health issues such as addiction, suicide risk, depression, post-traumatic stress disorder (PTSD), and anxiety disorders have also been found to be associated with a history of ACEs (Anda et al., 2006; Hovens et al., 2010; Weber et al., 2008). There appears to be a strong graded or dose-response relationship between exposure to ACEs and poor health outcomes, where individuals who experience a higher number of ACEs may be at a greater risk of poor health (Felitti et al., 1998). Anda and Colleagues (2006) identified a graded relationship of the ACE score (i.e. the sum of the categories of ACEs endorsed) to 18 different outcomes which can be divided into the following categories: mental health disturbances, somatic disturbances, substance abuse, sexuality (i.e., early

*Abbreviations:* ACEs, adverse childhood experiences; HPA, hypothalamic-pituitary-adrenal; PTSD, post-traumatic stress disorder; IL-6, interleukin-6; TNF- $\alpha$ , tissue necrosis factor- $\alpha$ ; CRP, c-reactive protein; WC, waist circumference; BMI, Body mass index

\* Corresponding author at: Department of Psychology, University of Calgary, 2500 University Drive NW, Calgary, AB, T2N 1N4, Canada.

E-mail address: [smdeight@ucalgary.ca](mailto:smdeight@ucalgary.ca) (S. Deighton).

<https://doi.org/10.1016/j.psychres.2018.08.097>

Received 9 January 2018; Received in revised form 24 August 2018; Accepted 24 August 2018

Available online 25 August 2018

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**Table 1**  
Research strategy.

Research component	Research terms
#1 Adverse childhood events	(Adverse childhood event) OR (Adverse childhood experience) OR (Childhood advers*) OR (Adverse experience*) OR (ACE) OR (Stress) OR (Life event) OR (Interpersonal relations) OR (Conflict) OR (Aggression) OR (Abuse) OR (Violence) OR (Victim*) OR (Family dysfunction) OR (Emotional trauma) OR (Neglect) OR (Maltreat*) OR (Parent* psychopathology) OR (Social deprivation) OR (Social environment)
#2 Biomarkers	(biomarker*) OR (Biologic* marker*) 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 (Blood) OR (Hair) OR (Saliva) OR (Urine) OR (Body Mass Index) OR (Heart rate) OR (Cardiovascular reactivity) OR (Physiological correlates) OR (Metabolic) OR (Endocrine) OR (Molecular) OR (Proteomics) OR (Metabolomic*) OR (Acute-phase proteins) OR (Dehydroepiandrosterone) OR (Fatty Acids) OR (Thyroid hormones) OR (adiponectin) OR (triglycerides) OR (DNA methylation) OR (high density lipoprotein) OR (Progesterone)
#3	#1 AND #2

intercourse, promiscuity, sexual dissatisfaction), and perceived stress and anger control. They found that for people with greater than four ACEs, their risk for anxiety, depressed affect, severe obesity, and alcoholism increased by 2.4-, 3.6-, 1.9-, and 7.2-fold, respectively. A graded relationship between an individual's ACE score also exists for self-reported liver disease and ischemic heart disease (Dong et al., 2003, 2004b).

Research has begun to investigate the molecular mechanisms through which early life adversity influences body physiology and becomes “biologically embedded” (Berens et al., 2017). Biological embedding occurs when experiences alter human biological and developmental processes, and these experiences have the potential to influence health, wellbeing, learning, or behaviour over the life course via their impact on biological and developmental states (Hertzman, 2012). Early life adversity has been found to have wide-ranging effects on neural, endocrine, immune, and metabolic physiology. These effects likely stem from alterations within the hypothalamic-pituitary-adrenal (HPA) and autonomic axes, which are involved in response to stress (Berens et al., 2017). Excess early activation results in dysregulation of the stress system, abnormal levels of peripheral and central cortisol levels, reduced immune function, and increased inflammatory markers (Berens et al., 2017; Middlebrooks and Audage, 2008). These neurobiological changes are thought to increase the risk for health problems in adults both directly and indirectly (Korotana et al., 2016).

The concept of allostatic load (McEwen and Stellar, 1993) is one perspective used to understand the processes that link early life adversity and poor health outcomes in adulthood directly (Friedman et al., 2015). This idea is that regulatory systems constantly adjust to the demands of everyday life to maintain stability through these changes, which is known as allostasis (Sterling and Eyer, 1988). When physiological systems, such as the nervous, endocrine, and the immune system, face chronic and repeated exposure to ACEs they have to make repeated adjustments to maintain stability, and may eventually lose their ability to function properly. These systems are also highly integrated, and so activation of one system commonly results in responses in the other systems, resulting in changes in physiology that lead to poor health outcomes (Danese and McEwen, 2012).

Indirect risk for poor health outcomes from ACEs may occur through impairments in cognitive, social, and emotional functioning, and increased engagement in health risk behaviours, all of which may act as mediators between the association of ACEs and poor health outcomes (Korotana et al., 2016). For example, children who grew up with an abusive or neglectful parent often have less stable and supportive social relationships in adulthood (Savla et al., 2013), which may then affect adult health (Repetti et al., 2002). ACEs may also affect emotion regulation, where individuals avoid experiencing adverse emotions, and avoidance in turn can predict psychological distress (Marx and Sloan, 2002). Emotion dysregulation has been linked to disorders such as post-traumatic stress disorder (PTSD), anxiety, and depression (Danese et al., 2009; Ehring and Quack, 2010; Schilling et al., 2007).

Additionally, ACEs are associated with health-risk behaviours such as smoking, drug and alcohol abuse, physical inactivity and risky sexual behaviour, which may in turn contribute to poor health outcomes (Dong et al., 2004a, 2003; Felitti et al., 1998).

Given that research has demonstrated a link between ACEs and risk of both physical and mental health disorders, there is growing interest in the direct and indirect effects of ACEs on neural, endocrine, immune, and metabolic physiology. Although studies have highlighted the relationship between early life adversity and immune dysregulation related to cardiovascular disease (Slopen et al., 2012), the biological mechanisms through which ACEs impact physical and mental health remains a relatively new area of research. The aim of this scoping review was to identify the extent and breadth of research activity relating to biological measures reflecting the potential effect of ACEs in adulthood. Research activity relating to nervous system, endocrine, inflammatory, cardio/metabolic, genetic and multisystem biomarkers of ACEs in adulthood will be identified.

## 2. Method

### 2.1. Identifying the research question and relevant studies

This scoping review was guided by a defined methodological framework (Arksey and O'Malley, 2005). Medline and PsycINFO were searched for published articles from 2007 to July 2017. The research strategy included key words related to adverse childhood experiences and biomarkers combined with Boolean operators AND and OR (Table 1). Articles were eligible for inclusion in this review if they included adult, human participants, were written in English, were original research articles published in peer reviewed journals, and reported on a biological measure of childhood adversity in adults. Meta-analyses, review articles, and neuro-imaging studies were excluded.

### 2.2. Study selection and charting the data

The initial research identified 3034 articles (see Fig. 1). Electronic research results were downloaded into EndNote bibliographic software. Duplicates were deleted. Two reviewers (first and second authors) independently screened the titles and abstracts against the inclusion and exclusion criteria. Full texts were reviewed for all articles that were potentially relevant to the research question. Articles were excluded from the full text review if they investigated adult trauma, PTSD or stressful life events that were not specific to childhood. Authors met regularly to discuss challenges related to the review process and to refine the research strategy. Any disagreements about the eligibility of an article were resolved through discussion. Forty articles met the eligibility criteria and were included in the review. Ten additional articles were identified and retained during the full text review. Information from the primary research reports were recorded as follows (Arksey and O'Malley, 2005):

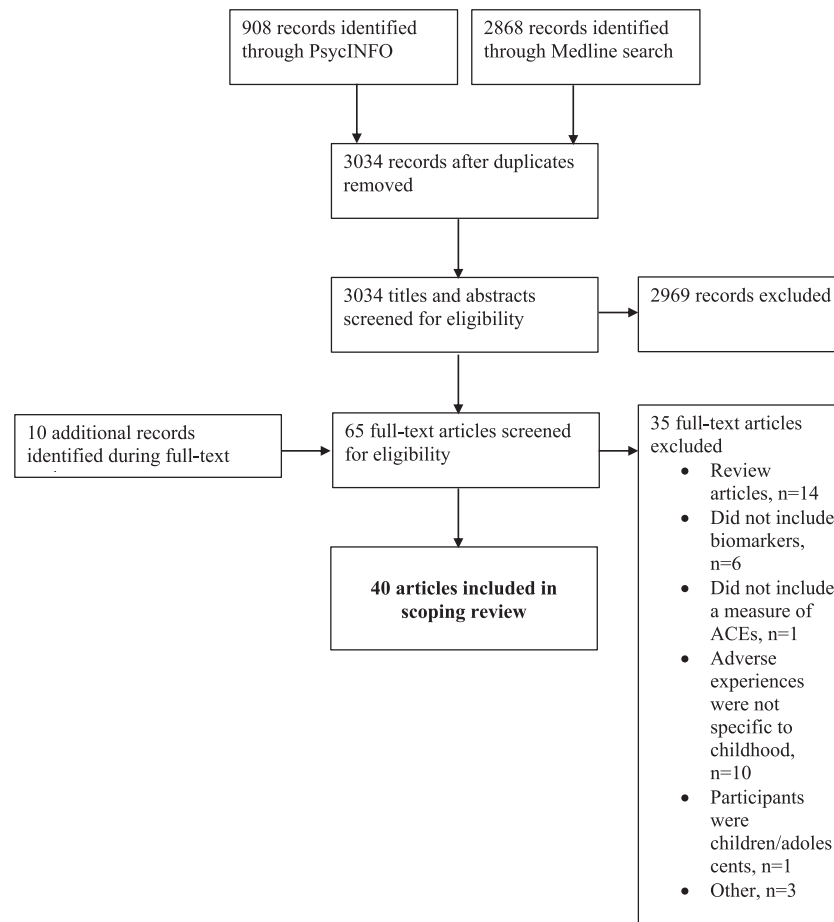


Fig. 1. Summary of research and selection of articles for scoping review.

- Author(s), year of publication.
- Study population.
- ACEs.
- Biomarker(s) organized thematically into 5 different biomarker categories: Nervous system/endocrine markers, Inflammatory biomarkers, Cardio/Metabolic biomarkers, Genetic biomarkers, and Multisystem composite scores.
- Methodology.
- Primary outcomes.

### 3. Results

#### 3.1. Description of studies

Characteristics of the 40 studies are shown in Table 2. The majority of studies were cross-sectional in design ( $n = 26$ ). Participants varied widely across studies such as individuals with mental health disorders ( $n = 6$ ), individuals with physical health conditions ( $n = 2$ ), caregivers of an individual with dementia ( $n = 1$ ), prison inmates ( $n = 1$ ), college students ( $n = 1$ ), female registered nurses ( $n = 1$ ) and police cadets ( $n = 1$ ). Twenty-three studies included subsamples from larger studies (e.g. population-based cohort studies). Studies often measured ACEs retrospectively. Most ACEs were investigated using parent or self-report questionnaires ( $n = 37$ ), while a few used semi-structured interviews ( $n = 3$ ). Some studies focused on exposure to a specific ACE, such as sexual abuse ( $n = 6$ ). Others investigated childhood abuse more broadly (e.g. physical, emotional and sexual abuse and neglect) ( $n = 16$ ). Many studies examined multiple types of ACEs under terms such as childhood life events, early life adversity, or childhood trauma ( $n = 14$ ). For example, [Elsenberg et al. \(2017\)](#) measured “adverse

events” such as parental divorce, being a victim of sexual intimidation or violence and breaking up with a boyfriend/girlfriend using a semi-structured interview. An adverse event score was then calculated by summing the number of events reported. Several studies used multiple measures (e.g., different questionnaires) of ACEs and combined them into a composite score used in analyses.

#### 3.2. Nervous system/endocrine markers

Ten studies related directly to neuroendocrine system biomarkers. Studies included a variety of populations including women with chronic pain ([Nicolson et al., 2010](#)), PTSD ([Friedman et al., 2007](#); [Van Voorhees et al., 2014](#)), female prison inmates ([Brewer-Smyth and Burgess, 2008](#)), college students ([Hanson and Chen, 2010](#)), police cadets ([Pole et al., 2007](#)), depressed adults ([Wielgaard et al., 2017](#)) and healthy adults ([Carpenter et al., 2007, 2011](#); [Wielgaard et al., 2017](#)). One of the 10 studies found evidence of alterations in emotional and physiological reactivity (i.e. less positive emotion, greater skin conductance, and eyeblink electromyogram) in response to threat ([Pole et al., 2007](#)). Several studies investigated the link between childhood sexual abuse and cortisol levels ([Brewer-Smyth and Burgess, 2008](#); [Friedman et al., 2007](#); [Nicolson et al., 2010](#)). For example, one study found that female prison inmates who were sexually abused by a family member had significantly decreased diurnal cortisol variation ([Brewer-Smyth and Burgess, 2008](#)). In another study, women with PTSD who had experienced sexual abuse in both childhood and adulthood were found to have significantly higher levels of urinary cortisol, norepinephrine, and dopamine compared to women who had experienced only childhood sexual abuse ([Friedman et al., 2007](#)). Unfortunately, this study did not include a control group of women without PTSD or childhood sexual

**Table 2**  
Overview of studies included in the scoping review.

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary outcomes
Beach et al. (2011)	A subset of participants from the Iowa Adoptee Study, N = 155 females	Childhood sexual abuse	Deoxyribonucleic acid methylation at the 5HTT promoter	Cross-sectional	There was a significant effect of childhood sexual abuse on methylation of the 5HTT promoter region. Degree of methylation mediated the impact of childhood sexual abuse on symptoms of antisocial personality disorder in adulthood. Childhood sexual abuse was associated with epigenetic change. There was a significant interaction between biological parent psychopathology and childhood sexual abuse in the prediction of methylation. Methylation partially mediated the effect of childhood sexual abuse on antisocial characteristics.
Beach et al. (2013)	A subset of participants from the Iowa Adoptee Study, N = 155 females	Childhood sexual abuse	Epigenetic change (DNA methylation)		Persons heterozygous for the Bcl1 variant to were less vulnerable for recurrent depressive symptoms in conjunction with childhood adversity and had lower cortisol binding globulin serum levels. In persons with childhood adversity the 22/23EK variant (glucocorticoid receptor gene polymorphism) was associated with a trend to lower cortisol and higher cortisol binding globulin levels.
Bet et al. (2009)	A subset of participants from the Longitudinal Aging Study Amsterdam (LASA), N = 906 males and females, 65 years and older	Childhood adversity (war experiences, impaired physical health, death or separation of parents and sexual abuse)	HPA-axis markers (cortisol and cortisol binding globulin)	Longitudinal	Plasma levels of CRP and IL-6 were higher in women who reported sexual abuse during adolescence (ages 11–17 years) compared to women who did no report abuse. Adult BMI and alcohol consumption partly mediated this relationship. Sexual abuse during childhood (before 11 years) and physical abuse during childhood and/or adolescence was not associated with inflammatory marker levels.
Bertone-Johnson et al. (2012)	A subset of participants from The Nurses Health Study II (NHS2), N = 702 female registered nurses, 24–42 years	Childhood physical and sexual abuse	C-reactive protein (CRP), Interleukin (IL)-6, and Tumor necrosis factor alpha receptor 2 (sTNFR2)	Cross-sectional	Childhood maltreatment was associated with significantly lower cortisol and ACTH baseline-to-peak deltas, in response to a psychosocial stressor. Childhood maltreatment was associated with greater overall peripheral release of IL-6 during a psychosocial stressor, and significantly elevated IL-6 concentrations
Brewer-Smyth and Burgess (2008)	Female inmates from minimum and maximum-security units of a women's prison (n = 137) and noncriminal females (n = 12, mean age 34.59 for no childhood abuse and 34.16 for history of childhood abuse	Childhood sexual abuse by a family member	Salivary cortisol	Modified case-control design	Childhood maltreatment was associated with significantly lower cortisol and ACTH baseline-to-peak deltas, in response to a psychosocial stressor. Childhood maltreatment was associated with greater overall peripheral release of IL-6 during a psychosocial stressor, and significantly elevated IL-6 concentrations
Carpenter et al. (2007)	Healthy adults recruited from the community (N = 50), aged 20–59 years	Childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect)	Plasma adrenocorticotropin hormone (ACTH)/Cortisol reactivity	Cross-sectional	Childhood maltreatment was associated with significantly lower cortisol and ACTH baseline-to-peak deltas, in response to a psychosocial stressor. Childhood maltreatment was associated with greater overall peripheral release of IL-6 during a psychosocial stressor, and significantly elevated IL-6 concentrations
Carpenter et al. (2010)	Healthy adults recruited from the community (N = 69), aged 18–64 years	Childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect)	Plasma IL-6	Cross-sectional	Childhood maltreatment was associated with significantly lower cortisol and ACTH baseline-to-peak deltas, in response to a psychosocial stressor. Childhood maltreatment was associated with greater overall peripheral release of IL-6 during a psychosocial stressor, and significantly elevated IL-6 concentrations

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Table 2 (continued)

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary outcomes
Carpenter et al. (2011)	Women recruited from the community (N = 100) ages 18–61 years	Childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect)	Salivary Cortisol	Cross-sectional	throughout the stress challenge compared to controls. Childhood physical abuse was associated with lower cortisol response to a psychosocial stressor.
Crosswell et al. (2014)	Female participants (N = 137), aged 21 to 65 years, diagnosed with breast cancer and completed treatment	Childhood abuse (physical and emotional), neglect, and chaotic home environment	Inflammatory markers: Pro-inflammatory cytokines (IL6, IL-1ra, (TNF-RII) and C-reactive protein (CRP)	Cross-sectional	Combined measure of childhood adversity was associated with elevations in plasma levels of IL-6. Positive associations between abuse and IL-6, chaotic home environment and IL-6, and chaotic home environment and TNF-RII.
Danese et al. (2007)	972 members of the Dunedin Multidisciplinary Health and Development Study; age 32 years	Childhood maltreatment	C-reactive protein Fibrinogen White blood cells	Longitudinal	Maltreated children were at greater risk of elevated c-reactive protein in adulthood compared to nonmaltreated children after controlling for early life risks, stress in adulthood, adult health and health behavior. The association between maltreatment and adult inflammation generalized to fibrinogen, white blood cell count, and a composite factor score of inflammation.
Danese et al. (2008)	972 members of the Dunedin Multidisciplinary Health and Development Study; age 32 years	Childhood maltreatment	C-reactive protein Fibrinogen White blood cells	Longitudinal	The association between depression and inflammation was attenuated and no longer significant after adjustment for history of childhood maltreatment.
Danese et al. (2009)	972 members of the Dunedin Multidisciplinary Health and Development Study; age 32 years	Childhood maltreatment	C-reactive protein	Longitudinal	Children who were maltreated were at a greater risk of elevated inflammation (i.e., elevated c-reactive protein) at age 32 years.
Dedert et al. (2010)	Female participants (N = 148) with current PTSD (n = 72), MDD (64), or neither (n = 32); mean age 39.9 years	Childhood abuse (physical and sexual) and witnessing family violence	Waist to hip ratio and BMI	Cross-sectional	After controlling for established developmental risk factors (e.g., family history of heart disease and high childhood BMI) low childhood SES and high childhood social isolation, but not childhood maltreatment was related to greater metabolic risk at age 32 years.
Edmonds et al. (2016)	699 men and women, mean age 51 years; data used from larger personality study	Childhood trauma; High betrayal trauma (e.g., witnessing someone you were very close to deliberately attack a family member) and low betrayal trauma (e.g., witnessing someone who you were not close to attack a family member)	Leukocyte telomere length (LTL)	Cross-sectional	Little evidence of a direct effect of childhood trauma on weight problems. Only childhood physical abuse and BMI resulted in a significant direct effect of trauma on weight outcomes. Results support indirect effects of psychiatric symptoms in the association of childhood traumatic stress and weight problems. Having more high betrayal trauma in childhood was associated with shorter adult LTL, while low betrayal traumas showed no association with LTL.
Elsenburg et al. (2017)	2188 children in the Tracking Adolescents' Individual Lives Survey (TRAILS) cohort study	Adverse events (e.g. physical or mental illness of father or mother, parental divorce, being a victim of bullying,	Body mass index	Longitudinal	There was a positive relation between adverse events before T1 (10–12 years old) and BMI at T5 (21–23 years old). There was a negative relation between

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Table 2 (continued)

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary putcomes
Friedman et al. (2007)	Community sample of 73 women with PTSD, 18–65 years	gossiping, sexual intimidation or violence) Childhood Sexual Abuse	Urinary cortisol Epinephrine Norepinephrine Dopamine	Cross-sectional	adverse events between T3 (14–18 years old) and T5 (21–23 years old) and BMI at T5. Mean daily levels of urinary cortisol, norepinephrine, and dopamine were significantly higher in women with PTSD who had experienced both childhood and adulthood sexual abuse compared to those who experienced childhood sexual abuse only.
Friedman et al. (2015)	1180 men and women, aged 25 to 74 years; MIDUS biomarker project	Early life adversity based on socioeconomic disadvantage (e.g., on welfare) and other stressors (e.g., parental divorce, physical abuse, parental death)	Cumulative allostatic load (AL) (i.e., biomarkers reflecting seven physiological systems). Included: blood pressure, urinary epinephrine and norepinephrine, heart rate variability, urinary cortisol and serum DHEA-S, HDL, cholesterol, triglycerides, BMI, waist-hip-ratio, CRP, IL-6, ICAM-1, fibrinogen, fasting glucose etc.	Cross-sectional	Significant association between childhood physical abuse and AL and remained significant after adjusting for adult educational attainment, social relationships, and health behaviours.  Associations most pronounced for secondary stress systems, including inflammation, cardiovascular function, and lipid metabolism. Neither childhood family risk nor parental warmth significantly predicted cortisol output.
Hanson and Chen (2010)	87 healthy college undergraduate students, 19–25 years	Childhood family psychosocial environment (family conflict/risk and parental warmth)	Salivary Cortisol	Longitudinal	Childhood parental warmth significantly moderated the relation between the severity of stress experienced during the day and daily cortisol output, such that the less warm one's childhood environment, the more cortisol individuals secreted on days in which they also experienced more severe stress. Family risk did not significantly moderate the relation between the daily number of stressors or stress severity and cortisol output.
Hostinar et al. (2015)	(N = 1180) Participants, both men and women, mean age 57.3 years; MIDUS biomarker project	Childhood abuse (physical, emotional and sexual abuse); neglect (physical and emotional); parental divorce; parental substance abuse; and parental depression	Composite measure of low grade inflammation from 5 serum markers (CRP, IL-6, fibrinogen, E-Selectin, and Interleukin Adhesion Molecule-1 (ICAM-1)); Mediators investigated: cortisol output; 12-h urinary epinephrine and norepinephrine output; WC	Cross-sectional	ACEs were associated with higher levels of inflammation, and results were identical when all participants who had a medical history of heart disease or diabetes excluded, or when medication was treated as a covariate. ACEs were associated with greater inflammation via greater sympathetic nervous system output (12-h urinary epinephrine output) and unhealthy lifestyle (greater WC, cigarette smoking, and physical inactivity) Childhood adversity was associated with both shorter telomeres and heightened serum IL-6 levels after controlling for age, caregiving status, gender, BMI, exercise, and sleep. Childhood abuse was associated with heightened IL-6 and TNF-α levels. Abused caregivers had significantly higher
Kiecolt-Glaser et al. (2011)	Community sample of 132 healthy older adults including 58 dementia family caregivers and 74 non-caregivers	Childhood abuse Childhood adversity (death of a parent; severe parental marital problems, an immediate family member suffering from a mental illness; an immediate family member abusing alcohol or lack of at least one close relationship with an adult)	Interleukin (IL)–6 Tumor necrosis factor (TNF)-α Telomere length	Cross-sectional	Abused caregivers had significantly higher

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Table 2 (continued)

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary putcomes
Lehman et al. (2009)	2739 men and women, aged 33 to 45 years; Coronary Artery Risk Development in Young Adults (CARDIA) Study	Family environment (physical and verbal abuse, lived with a substance abuser, felt loved and cared for, was shown physical affection, lived in a well-managed household)	Systolic and diastolic blood pressure change	Longitudinal	TNF- $\alpha$ levels than nonabused caregivers and controls. Family environment was related to negative emotions, which in turn predicted baseline SBP and DBP and change in SBP. However, the association with negative emotions dropped below significance when low childhood SES was included in the model.
Li et al. (2015)	1340 men and women, aged 65 to 74; International Mobility in Aging Study conducted in Canada, Columbia and Brazil	Social and economic adversity indexes (abuse of drugs by parents, witness to domestic violence, physical abuse, low SES, experience of hunger)	C-reactive protein	Cross-sectional	For Canadian sites, but not Latin American sites, social adversity was significantly associated with CRP (more people lower levels in the low or no social adversity group compared to the high social adversity group). After extensive adjustment for health risk behaviours, obesity and chronic conditions this association was attenuated, which may suggest that they help explain the effects of social adversity on inflammation.
Matthews et al. (2014)	326 women aged 42 to 52 years; Women's Health Across the Nation (SWAN) study	Childhood abuse (emotional, physical and sexual) and neglect (emotional and physical)	C-reactive protein	Longitudinal	Sexual and emotional abuse, physical and emotional neglect, and the total number of types of abuse were associated with higher CRP levels over the 7 annual follow-up visits; adjusting for race, age, education, smoking status, use of hormone therapy, depressive symptoms, occurrence of heart attack or stroke, and medications for hypertension. However, when BMI was added to the model this effect was no longer significant, but there were indirect effects of abuse and neglect on CRP through BMI for sexual abuse, physical neglect and total number of types of abuse.
Midei et al. (2010)	311 women aged 42 to 52 years; data from the Women's Health Across the Nation (SWAN) study	Childhood abuse (emotional, physical and sexual) and neglect (emotional and physical)	Body mass index (BMI), waste circumference (WC), and sex-hormone binding globulin (SHBG)	Cross-sectional	Women with history of any abuse/neglect, and specifically physical and sexual abuse had higher WC and BMI at baseline compared to no abuse. Lower levels of baseline SHBG mediated the relationship between any abuse/neglect and baseline WC and BMI. Trait Anger mediated the relationships between any abuse/neglect and baseline WC and BMI.
Midei et al. (2013)	342 women aged 42 to 52 years; Women's Health Across the Nation (SWAN) study	Childhood abuse (emotional, physical and sexual)	Incidence of metabolic syndrome if met 3/5 criteria for: WC, triglycerides, high-density lipoprotein cholesterol (HDL), systolic blood pressure, diastolic blood pressure, and fasting glucose levels	Longitudinal	At baseline, childhood abuse did not predict the presence of metabolic syndrome at baseline. Physical abuse was associated with incident metabolic syndrome over the course of 7 years follow-up in those without the syndrome at the baseline visit. Physical abuse was associated with incidence of elevated WC and high fasting glucose, but not high BP, triglycerides or low LDL. Sexual and emotional abuse were unrelated to metabolic syndrome.

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**Table 2** (continued)

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary putcomes
Nicolson et al. (2010)	Women with fibromyalgia (n = 35) or with osteoarthritis only (n = 35)	Childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect)	Salivary cortisol	Longitudinal	More severe childhood maltreatment was associated with higher cortisol throughout the day. Emotional and sexual abuse were most closely linked to cortisol levels. Children with the highest level of social disadvantage were estimated to have 1.69 times the expected CMR in adulthood compared to those with the lowest social disadvantage.
Non et al. (2014)	312 men and women, aged 38 to 48 years; EdHealth Study sample drawn from the larger New England Family Study	Measured childhood social disadvantage (e.g., change in parental marital status etc.) and SES factors (e.g., crowded housing density, more than 1.5 person per room etc.)	Cardio metabolic risk (CMR) score from 8 biomarkers: Systolic and diastolic BP, triglycerides, high- and low-density lipoproteins, hemoglobin A <sub>1c</sub> , CRP, and WC	Longitudinal	Graded relationship found with social disadvantage and CMR score. Cadets who reported childhood trauma reported less positive emotion and showed greater SC responses across all threat levels. Cadets who reported childhood trauma showed larger eyeblink responses and rated themselves as experiencing more negative emotions as threat level of the condition increased.
Pole et al. (2007)	90 psychiatrically healthy, urban police cadets	Childhood trauma (Disaster, physical assault, serious illness, serious accident, serious abuse, serious neglect, and sexual assault)	Eyeblink electromyogram (EMG)  Skin conductance (SC)	Cross-sectional	Trauma in early life is associated with increased inflammation as measured by CRP, but this was not found with IL-6, when twins are treated as individuals. After separating between and within effects (to control for familial factors) significant effects were observed for only the between pair association of early trauma and inflammatory markers. Levels of inflammation were highest when both twins were exposed to trauma. Tests of direct and indirect effects showed that childhood trauma was associated with elevated CRP, via elevated BMI. This relationship was mediated by a broad measure of distress, which was associated with using food as a coping mechanism
Rooks et al. (2012)	482 male middle-aged twins (241 pairs), mean age 55; Twins  Heart Study (THS) and the Stress and Vascular Evaluation in Twins (SAVEIT)	Childhood abuse (physical, sexual and emotional), and general trauma	Heart rate responses CRP and IL-6	Cross-sectional	Early life adversity predicted higher levels of log interleukin-6, fibrinogen, endothelial leukocyte adhesion molecule-1, and soluble intercellular adhesion molecule-1 among African Americans, but not among whites. The associations of early life adversity and several inflammatory biomarkers were attenuated after adjustment for health behaviours and body mass index, adult stressors, and depressive symptoms.
Schrepf et al. (2014)	687 healthy men and women, aged 25 to 74 years; Midlife in the United States (MIDUS) biomarker project	Childhood abuse (emotional, physical and sexual) and neglect (emotional and physical)	CRP and BMI	Cross-sectional	Childhood adversity was associated with elevated cumulative biological risk among
Slopen et al. (2010)	Subsamples from the Midlife in the United States (MIDUS) biomarker study: One from participants who were enrolled in the original MIDUS longitudinal sample, and one from a city specific sample of African Americans	Early life adversity (a composite score reflecting three domains of stress: Stressful events during childhood, relationship with parents during childhood, frequency of verbal and physical assault by parents)	C-reactive protein (CRP)  Interleukin-6 (IL-6)	Cross-sectional	Childhood adversity was associated with elevated cumulative biological risk among
Slopen et al. (2014)	550 adults from the Chicago Community	Childhood adversity	Fibrinogen Endothelial leukocyte adhesion molecule-1 Soluble intercellular adhesion molecule-1 Index of cumulative biological risk (including systolic and diastolic blood pressure, resting heart	Cross-sectional	Childhood adversity was associated with elevated cumulative biological risk among

(continued on next page)



Table 2 (continued)

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary putcomes
Smith et al. (2010)	Adult Health Study 329 heterosexual and 475 lesbian women with no history of heart attack or stroke, aged 34 to 64; Epidemiologic Study of Health Risk in Women (ESTHER) Project	Childhood sexual abuse (CSA)-intrafamilial CSA, extrafamilial CSA	rate, C-reactive protein, waist circumference, hemoglobin A1c, and total and high density lipoprotein cholesterol)  BMI	Cross-sectional	Individuals who resided in low affluence neighborhoods.  Intrafamilial CSA and extrafamilial CSA were associated with being obese (BMI > 30).  Intrafamilial CSA remained significant after adjusting for demographic and mental health variables.  No change in global methylation with a history of childhood trauma, although there was global methylation in subjects with PTSD compared to controls.
Smith et al. (2011)	110 African American subjects both men and women. PTSD history with (n = 25) and without (n = 25) a history of childhood trauma, and controls with (n = 26) and without (n = 34) a history of childhood trauma; Plasma cytokine levels were evaluated in an additional 126 subjects	Childhood trauma (sexual, physical, and emotional abuse)	DNA methylation; Inflammatory markers: Pro-inflammatory (IL6, IFN $\alpha$ , IL1b, IL2, and TNF- $\alpha$ ) and anti-inflammatory  (IL4 and IL10) cytokines	Cross-sectional	Plasma IL-2 and TNF $\alpha$ were increased in subjects with a history of child abuse in a smaller sample.  In a larger sample (51 with a history of child abuse with 126 independent sample added) a history of child abuse was associated with higher levels of TNF $\alpha$ , but not IL-2.
Su et al. (2014)	221 healthy adolescents and young adults, ages 13–29 years	Adverse childhood experience (childhood abuse, neglect, and growing up with household dysfunction)	Plasma endothelin-1 levels Total peripheral resistance (TPR) index Cardiac output (CO) index Pulse wave velocity (PWV) Blood pressure	Cross-sectional	Exposure to ACEs was associated with increased plasma endothelin-1 levels, DBP, TPR index, and PWV.  Young adults who exposed to multiple traumatic adverse childhood experiences showed a faster increase in blood pressure levels in young adulthood than those with no ACEs.
Su et al. (2015)	394 participants were recruited by use of family health history questionnaires obtained from a county-wide public school screening of children in grades kindergarten through 8	Adverse childhood experiences (childhood abuse, neglect, and growing up with household dysfunction)	Telomere length	Longitudinal	Participants reporting a history of childhood maltreatment had significantly shorter telomeres than those who did not; there were no differences between groups in age, sex, smoking, BMI, or other demographic factors.
Tyrka et al. (2010)	31 participants (women and men) ages 18 to 64 recruited through advertisements in the community	Childhood maltreatment	Blood serum cortisol Dehydroepiandrosterone (DHEA)	Cross-sectional	After controlling for age, sex and PTSD status, exposure to childhood maltreatment was significantly associated with cortisol secretion (inversely) and cortisol/DHEA ratio.  Associations remained significant for cortisol, but fell just below significant for cortisol/DHEA ratio when MDD diagnosis was accounted for in the model.
Van Voorhees et al. (2014)	100 subjects were smokers with (n = 43) and without (n = 57) PTSD, aged 18 to 65 years; part of larger smoking cessation study	Childhood abuse (physical and sexual), and witness to family violence	Telomere length	Cross-sectional	Childhood life events and childhood trauma were not related to shorter telomere length.
Verhoeven et al. (2015)	620 persons with a remitted depressive or anxiety disorder diagnosis, 1672 persons with a current diagnosis, and 644 controls, 18–65 years	Childhood life events (divorce or parents, parental loss, separation from home) and Childhood trauma (emotional neglect, psychological abuse, physical abuse, sexual abuse)	Telomere length	Cross-sectional	

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**Table 2** (continued)

Author(s), year of publication	Study population	ACE(s)	Biomarker(s)	Methodology	Primary putcomes
Wielgaard et al. (2017)	418 depressed and healthy participants from the Netherlands Study of Depression in Older Persons (NESDO), mean age 70.8 years	Childhood abuse (e.g., physical, sexual and psychological abuse, and emotional neglect)	Diurnal salivary cortisol levels	Cross-sectional	Physical and psychological abuse were associated with lower morning cortisol even after adjusting for MDD, age, hours of sleep, awakening time, smoking, anti-depressant medication and negative life events in the past 5 years. Sexual abuse was associated with more dynamic changes in cortisol in the hour after awakening and lower morning cortisol after adjusting for confounders.

abuse, and thus is limited to comparisons between women with childhood sexual abuse who did and did not also experience sexual abuse in adulthood. Furthermore, [Wielgaard et al. \(2017\)](#) found that sexual abuse was associated with lower morning cortisol at awakening and more dynamic changes in salivary cortisol levels in the hours after awakening. In healthy participants this effect remained significant, whereas in depressed participants this effect was not significant ([Wielgaard et al., 2017](#)).

[Nicolson et al. \(2010\)](#) found a link between severity of childhood maltreatment and cortisol, such that more severe childhood maltreatment was associated with higher salivary cortisol levels throughout the day, particularly emotional and sexual abuse. This relationship was found across participants with fibromyalgia and osteoarthritis, regardless of depressive or PTSD symptomatology ([Nicolson et al., 2010](#)). Conversely, three studies found a negative association between childhood abuse and cortisol levels. [Van Voorhees et al. \(2014\)](#) found a significant inverse association between cortisol secretion and childhood maltreatment. [Carpenter et al. \(2011\)](#) also found that childhood maltreatment was associated with lower salivary cortisol response to a standardized laboratory stressor. Similarly, [Wielgaard et al. \(2017\)](#) found that physical and psychological abuse were associated with lower morning salivary cortisol levels.

In addition, [Bet et al. \(2009\)](#) found that, in individuals carrying the glucocorticoid receptor polymorphism 22/23EK, there was an effect of childhood adversity on cortisol and cortisol binding globulin levels resulting in a decrease of Free Cortisol Index ([Bet et al., 2009](#)). In another study, neither childhood family risk or parental warmth predicted cortisol output, but more severe daily stress was associated with greater cortisol secretion for individuals who experienced more difficult childhood environments ([Hanson and Chen, 2010](#)).

Overall, studies that have investigated nervous system/endocrine markers were conducted with a variety of populations, affecting generalizability between the studies. One study found evidence of less positive emotion, greater skin conductance and greater eyeblink response in those who experienced childhood trauma. There were mixed findings for the direction of cortisol change associated with ACEs, however studies investigated different indicators of cortisol (e.g., salivary, urinary, blood etc.). While, five studies found a decrease in salivary cortisol associated with ACEs, one study found an increase in salivary cortisol throughout the day. Two additional studies found increased cortisol output when measuring urinary cortisol and cortisol secretion in response to stress.

### 3.3. Inflammatory biomarkers

Fourteen studies investigated inflammatory biomarkers related to ACEs. All 14 studies showed a link between ACEs and greater inflammation ([Bertone-Johnson et al., 2012](#); [Carpenter et al., 2010](#); [Crosswell et al., 2014](#); [Danese et al., 2008, 2007](#); [Hostinar et al., 2015](#); [Kiecolt-Glaser et al., 2011](#); [Li et al., 2015](#); [Matthews et al., 2014](#); [Rooks et al., 2012](#); [Schrepf et al., 2014](#); [Slopen et al., 2010](#); [Smith et al., 2011](#)). There is evidence that childhood abuse is associated with elevated Interleukin (IL)-6 ([Carpenter et al., 2010](#); [Crosswell et al., 2014](#)) and tumor necrosis factor (TNF- $\alpha$ ) levels ([Kiecolt-Glaser et al., 2011](#); [Smith et al., 2011](#)). In addition, [Kiecolt-Glaser et al. \(2011\)](#) showed that individuals who had experienced child abuse and were caregivers of an individual with progressive dementia, had higher TNF- $\alpha$  levels than non-abused caregivers and controls. In this study, childhood adversities (e.g. death of a parent, an immediate family member suffering from a mental illness etc.) were associated with greater inflammation even after controlling for age and caregiving status, demonstrating the importance of ACEs in this relationship ([Kiecolt-Glaser et al., 2011](#)). In another study, the association between early life adversity and inflammatory markers was found among African Americans, but not among European Americans. Further analyses demonstrated that the influence of early life adversity on health behaviours may partially

account for this association ([Slopen et al., 2010](#)). [Bertone-Johnson et al. \(2012\)](#) found that sexual abuse during adolescence, but not physical abuse was associated with elevated plasma C-reactive protein (CRP) and IL-6 ([Bertone-Johnson et al., 2012](#)). Social adversity ([Li et al., 2015](#)) and trauma early in life ([Rooks et al., 2012](#); [Schrepf et al., 2014](#)) and childhood maltreatment ([Danese et al., 2007, 2008, 2009](#)) have been associated with elevated CRP. However, health risk behaviours, obesity, and chronic conditions may partly explain the effects of social adversity on inflammation ([Li et al., 2015](#)). Similarly, adult BMI and alcohol consumption was found to partly explain the effects of adolescent sexual abuse and elevated CRP and IL-6 levels in adulthood ([Bertone-Johnson et al., 2012](#)). Furthermore, [Matthews and colleagues \(2014\)](#) found that when BMI was added to a model already adjusting for multiple factors (e.g., race, age, education, smoking status) it explained the relationship between childhood abuse and neglect, and elevated CRP over a 7-year follow-up. Indirect effects of abuse and neglect on CRP through BMI were found for sexual abuse, physical neglect and total number of types of abuse ([Matthews et al., 2014](#)).

In summary, all fourteen studies showed a link between ACEs and increased inflammatory biomarkers including increased: IL-6, TNF- $\alpha$ , and CRP. Furthermore, there was evidence that health risk behaviours, obesity, BMI, and chronic conditions may be potential mediators of these effects.

### 3.4. Cardio/metabolic biomarkers

Eleven studies were included that focused on metabolic systems. Of those, 3 studies showed a link between ACEs and blood pressure ([Lehman et al., 2009](#); [Su et al., 2014, 2015](#)). For example, ACEs were associated with blood pressure trajectories from childhood to young adulthood ([Su et al., 2015](#)). [Su et al. \(2015\)](#) also found that individuals who experienced multiple ACEs showed a faster increase in blood pressure after age 30, compared to those who did not experience ACEs. [Lehman et al. \(2009\)](#) observed that low childhood socioeconomic status predicted increased blood pressure over time indirectly through associations with harsh childhood family environment, negative emotionality and health behaviours ([Lehman et al., 2009](#)).

Five studies found evidence that associated ACEs with body mass index (BMI) ([Dedert et al., 2010](#); [Elsenburg et al., 2017](#); [Midei et al., 2013](#); [Schrepf et al., 2014](#); [Smith et al., 2011, 2010](#)). [Midei et al. \(2013\)](#) found that women with a history of physical and sexual abuse had higher BMI and waist circumference (WC) compared to women with no history of abuse. This effect was mediated by lower levels of sex hormone binding globulin and higher trait anger scores. They also investigated health risk behaviours and depressive symptoms as potential mediators, however these were not significant ([Midei et al., 2010](#)). [Dedert et al. \(2010\)](#) found evidence for a direct effect of childhood physical abuse and increased BMI. They also noted that models supported an indirect effect of childhood trauma on BMI through psychiatric symptoms. Finally, [Smith et al. \(2010\)](#) observed that childhood sexual abuse, in particular intrafamilial abuse, resulted in increased risk for a BMI greater than 30 in women even after adjusting for demographic and mental health variables.

Three studies created composite cardiometabolic and metabolic risk scores using biomarkers such as blood pressure, triglyceride levels, and waste circumference. [Midei et al. \(2013\)](#) found that while childhood abuse did not predict the presence of incident metabolic syndrome at baseline, physical abuse was associated with the development of metabolic syndrome over the 7 years of follow-up, after adjusting for depressive symptoms and health behaviours ([Midei et al., 2013](#)). [Non et al. \(2014\)](#) created a cardiometabolic risk (CMR) score from 8 biomarkers and found that children with the highest level of social disadvantage were estimated to have a greater than expected CMR in adulthood compared to those with the lower social disadvantage. This risk persisted even after adjusting for health behaviours and depressive symptoms ([Non et al., 2014](#)). [Danese and Colleagues \(2009\)](#) created a

metabolic risk score using biomarkers such as weight, blood pressure, total cholesterol, high-density lipoprotein (HDL), glycated hemoglobin, and oxygen consumption. After controlling for developmental risk factors (i.e., family history of heart disease and high childhood BMI) they found that childhood socioeconomic status and childhood social isolation were associated with increased metabolic risk, however, childhood maltreatment was not (Danese et al., 2009).

Overall, three studies found an association between ACEs and increased blood pressure (i.e., increased blood pressure trajectories over time and faster increased blood pressure after the age of 30). One study identified negative emotionality and health behaviours as mediators. Five studies found that ACEs were associated with increased BMI and/WC. Studies identified potential mediators for these relationships including psychiatric symptoms, sex hormone binding globulin and trait anger. Finally, three studies created composite scores involving multiple cardio/metabolic biomarkers (e.g., blood pressure, triglyceride levels, and waste circumference) and found that ACEs were associated with higher cardio/metabolic risk.

### 3.5. Genetic biomarkers

Seven studies were related to genetic biomarkers. Four studies investigated an association between ACEs and telomere length (Edmonds et al., 2016; Kiecolt-Glaser et al., 2011; Tyrka et al., 2010; Verhoeven et al., 2015). While one study showed that childhood life events and trauma were not related to shorter telomere length (Verhoeven et al., 2015), three others demonstrated that childhood trauma, adversity or maltreatment may be related to shorter telomeres (Edmonds et al., 2016; Kiecolt-Glaser et al., 2011; Tyrka et al., 2010). There is evidence that childhood adversity is associated with shorter telomere length even after controlling for age, sex, smoking, caregiving status, BMI, exercise, and sleep (Kiecolt-Glaser et al., 2011; Tyrka et al., 2010). Three studies investigated epigenetic changes by measuring DNA methylation. Two studies looked at DNA methylation of the *5HTT* promoter region, which is a key regulator of serotonergic neurotransmission. Both studies found a strong association of childhood sexual abuse with DNA methylation of the *5HTT* promoter region (Beach et al., 2013, 2011). Beach et al. (2011) found that the degree of methylation mediated the impact of childhood sexual abuse on symptoms of antisocial personality in adulthood. One study investigated global DNA methylation of immune related genes but did not find an association with a history of childhood trauma. Smith et al. (2011) found no change in global DNA methylation in those with a history of childhood trauma compared to controls.

In conclusion, seven studies investigated genetic biomarkers such as telomere length and epigenetic markers (i.e., DNA methylation). Although one study found that ACEs were not related to telomere length, the results from three other studies suggested that ACEs were associated with decreased telomere length. While one study did not find any evidence of global DNA methylation associated with ACEs, two studies found a strong association of childhood sexual abuse with DNA methylation of the *5HTT* promoter region which is a key regulator of serotonergic neurotransmission.

### 3.6. Multisystem composite scores

Two studies used a composite score as a measure of biological risk that spanned multiple biological systems (e.g. cardiovascular, metabolic and immune) (Friedman et al., 2015; Slopen et al., 2014). Friedman et al. (2015) created a cumulative allostatic load score using biomarkers reflecting seven physiological systems (e.g., blood pressure, urinary cortisol, waist-hip-ratio, CRP etc.). Whereas, Slopen et al. (2014) created an index composed of eight different biomarkers, including systolic and diastolic blood pressure, resting heart rate, CRP, WC, hemoglobin A1c, and high-density lipoprotein cholesterol. These studies showed a positive association between cumulative biological risk and childhood adversity. For example, Slopen et al. (2014) found

that the association between cumulative biological risk and childhood adversity was modified by neighbourhood context, such that the relationship was stronger for individuals in low-affluence neighbourhoods and attenuated in individuals in higher affluence neighbourhoods (Slopen et al., 2014). Friedman et al. (2015) investigated both a composite measure of early life adversity as well as different types of early life adversity individually, in relation to biological risk. They found a relationship between socioeconomic adversity and biological risk that was mediated by adult education and social relationships. In addition, childhood physical abuse was significantly related to biological risk even after adjusting for adult education, social relationships and health behaviours (Friedman et al., 2015).

In conclusion, two studies created a composite measure of biological risk spanning multiple biological systems (e.g., cardio, metabolic, immune). Both studies found a positive association between cumulative biological risk and childhood adversity. The studies also identified neighborhood context as a potential moderator, and adult education as well as social relationships as mediators of this relationship.

## 4. Discussion

The current scoping review sought to examine the extent, breadth and nature of recent research activity relating to biological measures of ACEs in adulthood. We identified 40 primary studies that investigated biomarkers from a range of physiological systems that included biological measures of cardiac, metabolic, immune, genetic, endocrine and stress response systems. Furthermore, two papers created a composite score of biomarkers that spanned multiple physiological systems to create an index of cumulative biological risk and allostatic load. The studies looked at both direct and indirect relationships of ACEs and biological measures in adulthood. The studies varied by design (i.e., cross-sectional, longitudinal), population (e.g., healthy men and women, women with breast cancer, male twins, participants with PTSD) and how they measured ACEs. The results of this scoping review may be useful for those interested in further investigating biomarkers in adulthood related to ACEs. While studies did identify biomarkers associated with ACEs both directly and indirectly, gaps in the literature suggest a need for further research in this area.

There was considerable variation in how studies conceptualized ACEs and different methods that resulted to compute ACE scores. Rather than creating a composite of early life adversity or ACEs score, some studies looked at specific categories of ACEs. For example, multiple studies looked at childhood sexual abuse only. Other studies created composite scores of ACEs, early life adversity, childhood social disadvantage, or family environment. Creating cumulative indices of early life adversity is often a preferred method as this takes into account the fact that various ACEs are interrelated and often co-occur (Felitti et al., 1998; Taylor et al., 2011). However, work that distinguishes among different types of ACEs allows for a more in-depth comparison of the effects of different types of ACEs in adulthood. For instance, when Friedman and colleagues investigated specific aspects of the effects of early life adversity on allostatic load in adulthood, they discovered that only childhood physical abuse was related to allostatic load and that these effects were more pronounced for biomarkers related to secondary stress systems (Friedman et al., 2015).

The majority of studies investigated biomarkers of specific physiological systems such as immune system biomarkers or genetic biomarkers (i.e., telomere length or epigenetic changes) (Beach et al., 2011; Edmonds et al., 2016). However, these systems are highly integrated, and the activation of one system commonly results in responses in other systems. Further, multiple systems typically respond to chronic stress (Danese and McEwen, 2012). In studies that investigated body mass index as a metabolic biomarker of child abuse, other physiological systems may come into play. For instance, dysregulation of the HPA axis and cortisol may be a mechanism that connects abuse to increased BMI and fasting glucose (Cicchetti and Rogosch, 2001; Heim

et al., 2000). Despite this knowledge, we only identified two studies that created a multi-system composite score using biomarkers of multiple physiological systems. For instance, Slopen et al. (2010) created a biological risk index from eight different biomarkers and found that childhood adversity was associated with this index in adulthood (Slopen et al., 2010). Friedman and colleagues also created a composite score to represent cumulative allostatic load. They included biomarkers reflecting seven physiological systems incorporating immune, cardiovascular, and endocrine functioning, as well as stress response, and found that childhood physical abuse was related to biological risk in adulthood (Friedman et al., 2015).

Consistent with the idea that ACEs may become biologically embedded and increase the risk for health problems in adulthood through both direct and indirect methods, the majority of the identified studies either investigated mediating effects of or adjusted for variables such as health risk behaviours (e.g., smoking, physical inactivity, unhealthy eating, alcohol consumption), family history of heart disease, emotional distress, psychopathology, socioeconomic status and social relationships (Bertone-Johnson et al., 2012; Danese et al., 2009; Lehman et al., 2009; Li et al., 2015; Matthews et al., 2014; Midei et al., 2010, 2013; Schrepf et al., 2014). This methodology is important to note because these other variables may help explain the association of ACEs with certain biomarkers. For instance, an unhealthy diet may contribute to higher BMI, WC and fasting glucose, but such a diet may also be related to using food as a coping strategy or binge eating, as both have been shown to partially explain the relationship between childhood abuse and obesity (Dong et al., 2004b; Greenfield and Marks, 2009; Rohde et al., 2008). Negative emotions such as depression and anger have also been shown to help explain the association of childhood abuse with central adiposity and ischemic heart disease (Dong et al., 2004b; Midei et al., 2010). The study conducted by Schrepf et al. (2014) found that childhood trauma was associated with elevated levels of CRP, via elevated BMI. They further found that this relationship was mediated by a measure of distress related to using food as a coping mechanism (Schrepf et al., 2014). On the other hand, Non et al. (2014) created a cardiometabolic risk score from 8 biomarkers and found that children with the highest level of social disadvantage were estimated to have a greater than expected cardiometabolic risk in adulthood compared to those with lower social disadvantage, even after adjusting for health behaviours and depressive symptoms (Non et al., 2014).

It is important to note that this was a scoping review rather than a systematic review or meta-analysis, as the heterogeneity and the preliminary nature of the current literature would preclude using such methods. Scoping reviews do not include a formal assessment of the quality of the studies. Despite no such assessment, information was extracted about the methodology and sample of each study. The goal of the review was to include a representative, rather than an exhaustive overview of the literature and it is possible that we may have missed relevant studies.

Several areas for further research in regards to biological measures of ACEs in adulthood are made manifest through this review. First, the majority of studies used a cross-sectional design. Further studies using longitudinal methods are needed to more directly assess whether exposure to ACEs actually caused a change in biomarkers. Second, many studies were conducted in specific populations (e.g., middle aged male twins (Rooks et al., 2012), females with breast cancer (Crosswell et al., 2014), African Americans with PTSD (Smith et al., 2011), urban police cadets (Pole et al., 2007), female registered nurses (Bertone-Johnson et al., 2012) etc.), the results of which may not generalize to other populations. More research is needed in larger representative samples. As the research develops, comparisons between different diagnostic groups (e.g., patients with cancer and patients with heart disease) can be investigated in relation to biomarkers of ACEs in adulthood. Third, there are differences in how ACEs are measured and conceptualized among studies, making it difficult to compare studies. Thus, more consistency is needed to define and measure ACEs.

Moreover, a limitation for our scoping review was that we did not include PTSD as a search term. Although the term ‘stress’ was included, studies that report on biomarkers for individuals with PTSD may not have been included in this review. Biological system dysregulation present following the development of PTSD may be similar to the dysregulation observed following exposure to ACEs, thus PTSD should be included in future reviews of biomarkers. Finally, it is noted that this review did not include imaging studies, as it focused on more direct markers of biological processes. Future studies could potentially explore neuroimaging and imagery of other organ systems, as the literature develops.

In conclusion, ACEs may be related to inflammatory (e.g., TNF- $\alpha$ , IL-6, CRP) (Crosswell et al., 2014; Danese et al., 2009; Kiecolt-Glaser et al., 2011; Smith et al., 2011), cardio/ metabolic (e.g., BMI, WC, blood pressure) (Midei et al., 2013; Su et al., 2014), genetic (e.g., 5HTT promoter DNA methylation, telomere length) (Beach et al., 2011; Edmonds et al., 2016; Tyrka et al., 2010), and endocrine (e.g., cortisol) (Carpenter et al., 2007, 2010; Bertone-Johnson et al., 2012) biomarkers, as well as composite indices representing multiple physiological systems (Friedman et al., 2015; Slopen et al., 2014). However, not every study identified found significant associations. Health behaviours, emotional distress, social relationships, psychopathology and socioeconomic factors may help explain some of these associations. Further research is needed to better understand the biological measures of ACEs in adulthood and their relationship to health conditions.

## Acknowledgement

This review was funded by a grant from the Palix Foundation.

## Conflict of Interest

The authors have no conflicts of interest to declare.

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