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A Systematic Review of the Biological Correlates and Consequences of Childhood Maltreatment and Adverse Childhood Experiences

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Abstract

Childhood maltreatment (CM) and adverse childhood experiences (ACEs) are two primary forms of interpersonal victimization that have been associated with a host of deleterious health outcomes. Studies over the past decade have begun to use a range of biologically informed methods to better understand the role biology plays in the relationship between CM, ACEs, and later life outcomes. This line of research has shown that both forms of victimization occur at sensitive periods of development, which can increase the likelihood of "getting under the skin" and influence health and behavior across the life course. This review examines the current state of knowledge on this hypothesis. One hundred and ninety-nine studies are included in this systematic review based on criteria that they be written in English, use a biologically informed method, and be conducted on samples of humans. Results reveal that latent additive genetic influences, biological system functioning captured by biomarkers, polygenic risk scores, and neurobiological factors are commonly associated with exposure and response to CM and ACEs. The implication of these findings for the existing body of research on early life victimization and recommendations for future research and policy are discussed.

Keywords

child abuse, family issues and mediators, etiology, criminology

Biopsychosocial research on the correlates and consequences of victimization has grown at a rapid rate over the past two decades (Fazel et al., 2018). Multiple methodological techniques from the biopsychosocial perspective, including twin and sibling designs, biomarker assessments, candidate gene approaches, genome wide association studies (GWAS), epigenetics, and neurobiological analyses have been used to study victimization (Cassiers et al., 2018; Cecil et al., 2020; Deighton et al., 2018). These biologically informed methods have expanded our understanding of individual-, family-, and neighborhood-level correlates and consequences of various forms of interpersonal victimization (Barnes & Beaver, 2012; Blanco et al., 2015). Within this body of research, two forms of interpersonal victimization have received considerable empirical attention: childhood maltreatment (CM) and adverse childhood experiences (ACEs; Deighton et al., 2018). Taken together, contemporary research on CM and ACEs suggests that these experiences may have long-lasting effects because they occur during sensitive developmental time periods where they are more likely to "get under the skin," thus resulting in a range of negative health and behavioral outcomes throughout the life course (Dunn et al., 2020; Taylor et al., 1997). These potential consequences include depression (Dennison et al., 2016), anxiety (Fonzo et al., 2010), post-traumatic stress disorder (Herzog et al., 2020), substance abuse (Van Dam et al., 2014), delinquency (Connolly & Kavish, 2019), criminal behavior (Vaske et al., 2012), and future victimization (Tanksley et al., 2020).

Several reviews have examined the relationship between biological factors, CM, and ACEs including the effect of latent additive genetic and environmental influences (Koenen et al., 2008), biological systems captured through measured biomarker activity (Deighton et al., 2018), single-nucleotide polymorphisms (SNPs; Maglione et al., 2018), polygenic scores (Anand et al., 2015; Gerritsen et al., 2017), DNA methylation (Cecil et al., 2020), and neurobiological structures (Cassiers et al., 2018; Herzog & Schmahl, 2018). For example, Cecil

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et al. (2020) systematically reviewed 72 studies assessing the effects of CM on DNA methylation. Results showed that CM experiences were associated with small, albeit statistically significant, alterations in DNA methylation. Maglione et al. (2018) conducted a similar review of 31 studies evaluating the relationship between CM and several negative psychopathological outcomes within the context of genetic risk measured through candidate genes. Their findings showed that CM is positively associated with antisocial misconduct, depression, internalizing symptoms, borderline personality disorder, and neuroticism in the presence of specific candidate genes (i.e., monoamine oxidase A [MAOA], serotonin-transporter-linked promoter region [5-HTTLPR], corticotropin-releasing hormone [CRH], FK506 binding protein 51 [FKBP5], oxytocin receptor [OXTR], tryptophan hydroxylase 1 [TPh1], neuroendocrine tumor [NET], dopamine transporter 1 [DAT1], nuclear receptor subfamily 3 group c 1 [NR3C1], C-reactive protein [CRP], and interleukin 1β [IL-1β]). While these reviews are informative, none have systematically assessed the current state of knowledge over the last decade on CM and ACEs across multiple levels of biological functioning. In addition, few reviews (Cecil et al., 2020) have discussed the implications of biologically informed research for future social science research on CM and ACEs.

The limitations of current reviews highlight the need to systematically evaluate the role genetics/biology play in contributing to individual differences in exposure to CM and ACEs and the consequences from such experiences. As such, the current study systematically reviews the existing body of research on CM, ACEs, and a number of biological influences including (1) latent sources of genetic variation; (2) objective measures of biological system functioning (i.e., nervous system, endocrine system, inflammatory system, cardiovascular system, metabolic system, or multiple system functioning); (3) polygenic risk scores; and (4) neurobiological structures in limbic, cortical, and other regions of the brain. In line with previous research (Sedlak et al., 2010), CM is conceptualized as sexual, physical, or emotional abuse as well as physical and emotional neglect perpetrated by a family member or caregiver onto a child before the age of 18. ACEs are conceptualized as stressful/traumatic life experiences that occur during childhood and/or adolescence. ACEs include witnessing violence, parental separation, family member mental illness, parental incarceration, abuse or neglect, and parent/caregiver substance abuse (Deighton et al., 2018). ACEs, while inclusive of CM, also characterize another dimension of trauma experienced during formative years of life-course development.

Current Study

This study systematically evaluates the current state of empirical knowledge on the biological correlates and consequences of CM and ACEs. The current study proceeds in a series of three interrelated steps. First, a systematic review of literature published between 2010 and 2020 was conducted.[1] This step focused on examining the link between latent genetic influences, biological system functioning, polygenic risk scores, and neurobiological structures with CM and ACEs. The second step of the analysis focused on synthesizing the gathered information to provide a comprehensive overview of the findings. This discussion briefly summarizes common biological mechanisms shown to operate as sources of vulnerability and resilience to CM and ACEs. More detail information can be found in Online Supplementary Table 1. The third step focused on discussing the theoretical, methodological, and practical implications of the results for future research directed at further understanding of the underlying mechanisms involved in examining individual differences in susceptibility and resilience to the residual effects of CM and ACEs.

Table 1. Study Characteristics by Victimization Type.

Study Characteristics	Childhood Maltreatment ($n = 176$)		Adverse Childhood Experiences ($n = 26$)	
	n	%	*n*	%
Study design				
Cross-sectional	140	79.1	17	65.4
Longitudinal	37	20.9	9	34.6
Comparison group				
Yes	121	68.4	13	50.0
No	56	31.6	13	50.0

Note. $N = 199$.

Method

Search Strategy

Searches for relevant literature were conducted between March 6, 2020, and March 17, 2020.[2] Seven online search engines were used to retrieve literature for the systematic review: PsychInfo, PsycArticles, Criminal Justice Abstracts, Psychology and Behavioral Sciences Collection, PubMed, Social Sciences Full Text, and SocINDEX. Search terms included "behavioral genetic*," OR "gene*," OR "GWAS," OR "biomarker*," OR "neuro*," AND "maltreatment*," OR "child* abuse," OR "adolesc* abuse," OR "adverse childhood experience*." A visual representation for the process of article selection is shown in Figure 1.[3]

Inclusion Criteria

Studies were included for further evaluation if they met the following criteria: (1) used a biologically informed method (i.e., behavioral genetic, biomarker, genome wide platform, neurobiological structure), (2) were published between 2010 and 2020, (3) were written in English, and (4) were conducted on the samples of humans.

Exclusion Criteria

Studies were excluded from consideration if they met one or more of the following criteria: (1) had measures of SNPs or DNA methylation with no other measures of latent additive genetic influences, biological system functioning, polygenic

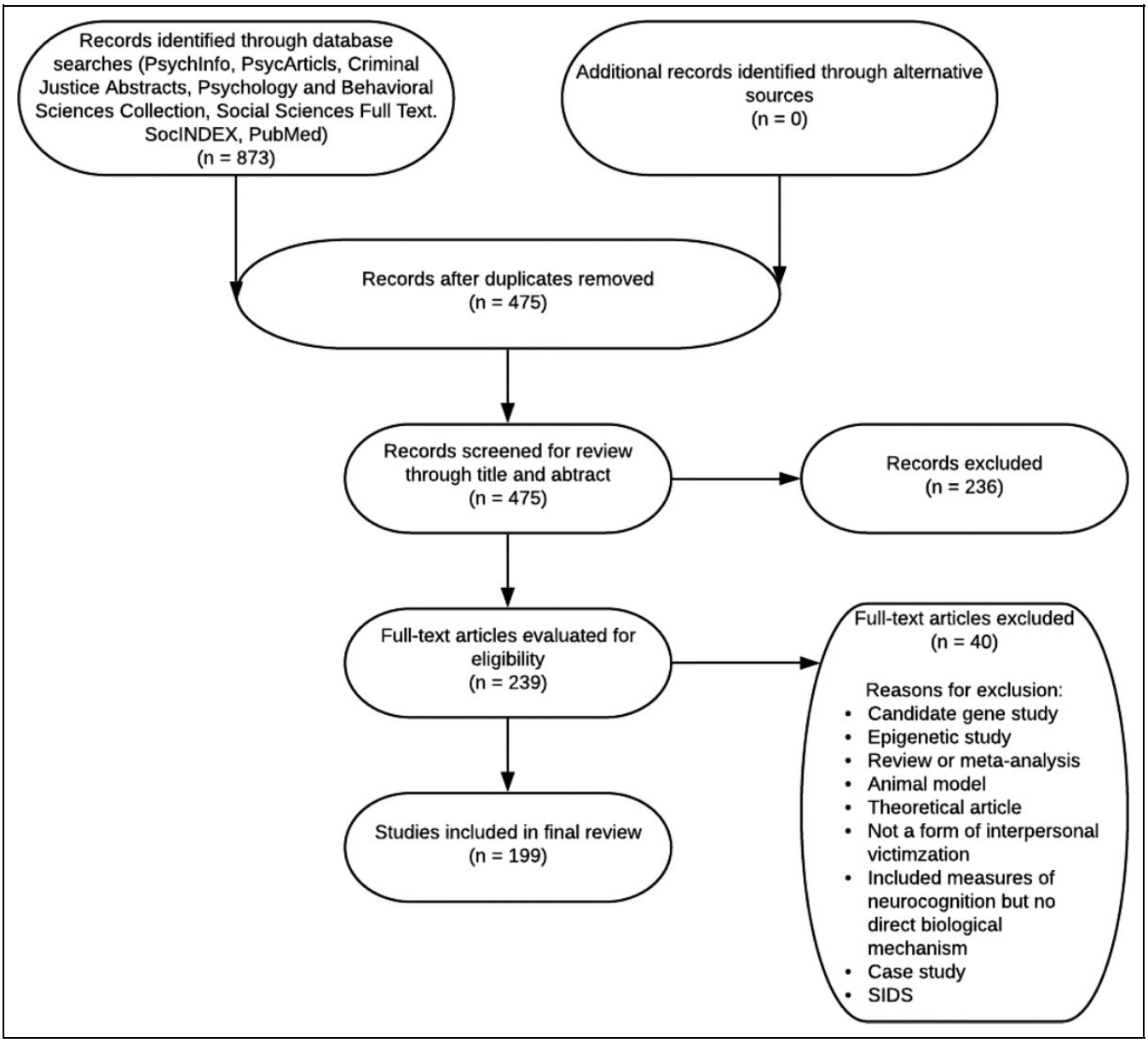

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines flow diagram.

scores, limbic, cortical, or other structure functioning;[4] (2) were a review, systematic review, or meta-analysis; (3) included models with animals; (4) provided no empirical tests (i.e., theoretical articles); (5) included measures of neurocognition, but no direct measurement of a neurobiological system; (6) included cases of sudden infant death syndrome; and (7) were based on case studies.

Results

Study Characteristics

In total, 199 studies included methods focused on examining latent genetic influences, biomarkers, polygenic scores, and neurobiological system structures in relation to CM and ACEs (see Online Supplementary Table 1). As can be seen in Table 1, most of the studies focused on CM ($n = 176$). A small subset focused on ACEs ($n = 26$). In total, three studies examined CM and ACEs concurrently. Studies on CM included both cross-sectional ($n = 140$) and longitudinal ($n = 37$) research designs. Of the 176 studies on CM, 121 included some form of a comparison group (i.e., control, twins, siblings, adoptee, or family members).[5] Studies on ACEs were mostly cross-sectional ($n = 17$) and were split evenly between the use of comparison groups ($n = 13$) and no comparison group ($n = 13$).

Latent Genetic Influences

Table 2 presents the number of studies using behavioral genetic methods to estimate the magnitude of latent additive genetic

Table 2. The Number of Studies Using Behavior Genetic Designs by Victimization Type.

Behavior Genetic Design	Childhood Maltreatment ($n = 176$)		Adverse Childhood Experiences ($n = 26$)	
	n	%	*n*	%
Twin sample	18	85.7	3	60.0
Sibling sample	2	9.5	1	20.0
Adoptee sample	1	4.8	1	20.0

Note. $N = 199$.

effects on CM and ACEs as well as their association with deleterious outcomes. Of the 176 CM studies, twin-based designs ($n = 18$), sibling designs ($n = 2$), and adoptee designs ($n = 1$) were used. As shown in the Online Supplementary Table, many of these twin-based studies ($n = 10$) relied on twin samples from the Environmental Risk Longitudinal Twin Study, which is a spin-off of the Twins Early Development Study (Trouton et al., 2002), and assess a birth cohort of 2,232 British children from England and Wales starting in 1994–1995.[6] Results from these studies showed that a combination of additive genetic (i.e., the summative effect of genetic material that contributes to the observed variation in phenotypic expression), shared environmental (i.e., environmental factors experienced similarly across twins, siblings, and family members that create phenotypic similarities), and nonshared environmental influences (i.e., environmental factors that are unique to twins, siblings, and family members who create phenotypic differences) accounted for the variance in CM. Studies reported that genetic factors accounted for between 13% and 70% of individual differences in CM, the shared environment accounted for between 0% and 60%, and the nonshared environment accounted for 14% and 50% (Bowes et al., 2013; Fisher et al., 2015; Pezzoli et al., 2019; Pittner et al., 2019).

Additionally, as shown in Online Supplementary Table 1, many of the genetically informed CM studies examined the effect of CM on mental and physical health outcomes including psychotic symptoms ($n = 1$), suicidal ideation ($n = 1$), personality disorders ($n = 1$), bipolar disorder ($n = 1$), attention deficit hyperactivity disorder (ADHD; $n = 2$), conduct problems ($n = 1$), chronic health conditions ($n = 1$), criminal behavior ($n = 1$), cognitive functioning ($n = 1$), and neurodevelopmental disorders ($n = 2$). One of the benefits of genetically informed studies is their ability to examine the association between CM and later life outcomes while using a participant's co-twin or co-sibling as a counterfactual. Doing so controls for the confounding effects of genetic and shared environmental influences. After controlling for these influences, several studies found that the effect of CM on negative health outcomes became statistically nonsignificant (Berenz et al., 2013; Danese et al., 2017; Dinkler et al., 2017), suggesting that factors attributable to genetics and/or the shared environment account for a large part of the correlation between CM and deleterious health and physical outcomes. However, one study reported a significant effect of CM on psychotic symptoms at age 12 even after controlling for the effects of familial confounding associated with the genetic susceptibility to developing psychosis (Arseneault et al., 2011).[7]

Four studies examined the association between CM and biological system functioning of the inflammatory system via biomarker measurement while controlling for latent genetic and shared environmental influences. Using a twin-based design, Baldwin et al. (2018) reported a significant association between CM and levels of CRP at age 18 net of latent genetic influences. York et al. (2013) examined the effect of CM on micronuclei (i.e., extranuclear bodies formed by cellular damage) and found that twins with more experiences of CM had higher levels of micronuclei compared to their co-twins with less experiences of CM. Conversely, Rooks et al. (2012) examined the relationship between CM, CRP, and interleukin-6 (IL-6) levels in a sample of monozygotic and dizygotic twin pairs and found that between-pair differences explained more of the relationship than within-twin differences, suggesting that the association between CM and inflammation is largely influenced by factors that cluster within families.

The number of behavior genetic designs used to study the magnitude of latent genetic and environmental influences on individual differences in ACEs are also shown in Table 2. The designs examining ACEs included twin designs ($n = 3$), a sibling comparison design ($n = 1$), and an adoptee design ($n = 1$). These studies examined criminal offending ($n = 1$), delinquency ($n = 1$), and memory functions ($n = 1$). For example, Beckley et al. (2018) assessed the effect of ACEs on being a victim, offender, or dual victim–offender in a sample of 2,232 British twins. Their results showed that additive genetic, shared environmental, and nonshared environmental effects accounted for the variance in being a victim, offender, or victim–offender. Additionally, ACEs were used to model environmental effects on being a victim, offender, or victim–offender. Results showed that each additional ACE a twin experienced significantly increased the likelihood of being a victim, offender, and victim–offender, thus providing support for ACEs as both shared and nonshared environmental influencers. Connolly and Kavish (2019) examined sibling differences in childhood adversity and provide additional evidence for ACEs as a significant environmental contributor to delinquency during middle adolescence. However, additional analyses revealed that siblings with higher levels of childhood adversity were no more likely to demonstrate slower declines in delinquent behavior from middle adolescence to young adulthood compared to their co-sibling, suggesting that familial factors accounted for variation in developmental patterns of offending. Eaves et al. (2010) reported that ACEs accounted for roughly 30% of shared environmental variation in antisocial behavior in a family cohort of participants. Additionally, socioeconomic status influenced the relationship between CM and adult memory whereby experiences of CM were inversely associated with memory net of family confounds among individuals living in high socioeconomic areas (Goldberg et al., 2013). Tanksley and colleagues (2020) examined the effects of anxiety, conduct disorder

symptomatology, and self-control on exposure to multiple ACEs using a sample of British twins. After controlling for genetic confounding, only self-control was associated with multiple ACEs (conceptualized as polyvictimization), suggesting that exposure to ACEs is for the most part not a random event. Indeed, vulnerability in exposure to ACEs, and the association between ACEs and deleterious outcomes, is influenced by a litany of factors that co-occur within families (Connolly, 2020; Schwartz et al., 2019).

Biomarkers

The count and percentage of the total number of studies using biomarkers to measure individual differences in nervous, endocrine, inflammatory, cardiovascular, metabolic, and multisystem functionality are presented in Table 3. This table also shows the number of studies that reported significant relationships between CM, ACEs, and biomarkers. CM was associated with biomarker assessments of nervous and endocrine system functioning. Biomarkers used to measure nervous system functionality included cortisol ($n_{\text{Total}} = 29$; $n_{\text{Significant}} = 28$), dehydroepiandrosterone (DHEA; $n_{\text{Total}} = 5$; $n_{\text{Significant}} = 4$), oxytocin ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 3$), brain-derived neurotrophic factor (BDNF; $n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), norepinephrine ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), dopamine ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and endocannabinoids ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). Studies measuring endocrine system functionality used biomarker measurements including cortisol ($n_{\text{Total}} = 29$; $n_{\text{Significant}} = 28$), DHEA ($n_{\text{Total}} = 5$; $n_{\text{Significant}} = 4$), oxytocin ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 3$), adiponectin ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 1$), alpha-amylase ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 1$), leptin ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 0$), lymphocytes ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), orexin ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), prolactin response ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and soluble intercellular adhesion molecule-1 (SICAM-1; $n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). Several studies reported increased levels of biomarker activity (i.e., BDNF, cortisol, DHEA, dopamine, adiponectin, and oxytocin) associated with nervous and endocrine systems in participants reporting CM compared to matched controls (Aas et al., 2017; Bücker et al., 2015; Cicchetti et al., 2015). In contrast, other studies reported decreases in biomarkers (i.e., DHEA, cortisol, and oxytocin) capturing biological system functionality (Dahmen et al., 2018; Kaess et al., 2018). Collectively, these studies inform research on the connection between CM, nervous system, and endocrine system functioning by showing that CM is associated with *alterations* in levels of biomarkers capturing nervous and endocrine system functionality in comparison to nonmaltreated matched comparisons.

The connection between CM and inflammatory system functioning was examined using several different measures. Biomarkers including CRP ($n_{\text{Total}} = 12$; $n_{\text{Significant}} = 10$), interleukin-10 ($n_{\text{Total}} = 10$; $n_{\text{Significant}} = 1$), IL-6 ($n_{\text{Total}} = 8$; $n_{\text{Significant}} = 5$), cytokine tumor necrosis factor-alpha (CTNFα; $n_{\text{Total}} = 3$; $n_{\text{Significant}} = 1$), resistin ($n_{\text{Total}} = 3$; $n_{\text{Significant}} = 1$), cytokines ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), E-selectin ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 1$), fibrinogen ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), soluble tumor necrosis factor receptor type 1 ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 0$), 8-isoprostane ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), CD40-ligand (CD40L; $n_{\text{Total}} = 1$; $n_{\text{Significant}} = 0$), glycoprotein 130 ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), IL-1β ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), serum-amyloid-a ($n = 1$; $n_{\text{Significant}} = 0$), and transforming growth factor-beta ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$) were used to capture inflammation in response to childhood trauma. Collectively, these studies conveyed that more reports of CM were associated with higher levels of inflammation (Lee et al., 2017; Rooks et al., 2012), suggesting that inflammatory systems are more likely to experience dysregulation among participants with a history of CM compared to nonbiologically related controls. The effect of CM on the cardiovascular system was also captured through different biomarker measures such as heart rate reactivity (HR; $n_{\text{Total}} = 9$; $n_{\text{Significant}} = 8$), respiratory sinus arrhythmia (RSA; $n_{\text{Total}} = 6$; $n_{\text{Significant}} = 6$), and blood pressure ($n_{\text{Total}} = 3$; $n_{\text{Significant}} = 2$). Results from these studies were similar to those examining the relationship between CM and functionality of the nervous and endocrine system—CM was linked to both higher and lower levels of mean HR, HR reactivity, RSA, and blood pressure (Dale et al., 2018). Johnson et al. (2017), for example, found that participants who reported CM compared to matched controls had increased cardiometabolic risk (i.e., CRP, diastolic, and systolic blood pressure). Several other studies included measures of various biomarkers associated with the metabolic system, multiple systems (i.e., allostatic load),[8] and other biological functions (i.e., telomeres). Results from these studies showed that CM was associated with dysregulated activity across biological systems compared to nonmaltreated matched controls.

Table 3 also provides a count of studies examining the relationship between ACEs and biomarker activity. Cortisol ($n_{\text{Total}} = 5$; $n_{\text{Significant}} = 2$), BDNF ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 0$), SICAM-1 $n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and insulin ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$) were biomarkers used to measure nervous and endocrine system functionality when examining ACEs. Findings revealed that ACEs were associated with dysfunctional activity in these biomarkers (Carroll et al., 2013; Drury et al., 2014; Fuller-Rowell et al., 2019). Specifically, experiencing more ACEs was associated with reductions in cortisol reactivity (Peckins et al., 2012), BDNF (S. Kim et al., 2019), and SICAM-1 (Slopen et al., 2010) as well as a resistance to insulin in diabetic participants (Fuller-Rowell et al., 2019). ACEs were also associated with increased levels of inflammatory markers including CRP ($n_{\text{Total}} = 7$; $n_{\text{Significant}} = 4$), E-selectin ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), IL-6 ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), CTNFα ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and fibrinogen ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). Evidence from the metabolic and multisystem studies indicated that ACEs were associated with increased allostatic load ($n_{\text{Total}} = 3$; $n_{\text{Significant}} = 3$), which is a cumulative measure of multiple biomarkers. ACEs were also linked to higher blood pressure ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), body mass index (BMI; $n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), and metabolites ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). Moreover, Drury et al. (2014) found that increases in ACEs were related to decreased telomere length (i.e., a measure of early aging).

Table 3. Biomarker by Victimization Type.

	Childhood Maltreatment ($n = 176$)				Adverse Childhood Experiences ($n = 26$)			
Biomarker	*n* (Total)	% (Total)	*n* (Significant)	% (Significant)	*n* (Total)	% (Total)	*n* (Significant)	% (Significant)
Nervous system								
BDNF	2	1.1	2	1.1	1	3.3	0	0
Cortisol	29	16.5	28	15.9	5	16.7	2	7.7
DHEA	5	2.8	4	2.3				
Dopamine	1	0.6	1	0.6				
Endocannabinoids	1	0.6	1	0.6				
Norepinephrine	2	1.1	2	1.1				
Oxytocin	4	2.3	3	1.7				
Endocrine system								
Adiponectin	2	1.1	1	0.6				
Alpha-amylase	2	1.1	1	0.6				
Cortisol	29	16.5	28	15.9	5	16.7	2	7.7
DHEA	5	2.8	4	2.3				
Insulin					1	3.3	1	3.8
Leptin	1	0.6	0	0.0				
Lymphocytes	1	0.6	1	0.6				
Orexin	1	0.6	1	0.6				
Oxytocin	4	2.3	3	1.7				
PRL response	1	0.6	1	0.6				
SICAM-1	1	0.6	1	0.6	1	3.3	1	3.8
Inflammatory system								
8-ISO	1	0.6	1	0.6				
CD40L	1	0.6	0	0.0				
CRP	12	6.8	10	5.7	7	23.3	4	15.4
CTNFα	3	1.7	1	0.6	1	3.3	1	3.8
Cytokines	2	1.1	2	1.1				
E-selectin	2	1.1	1	0.6	2	6.7	2	7.7
Fibrinogen	2	1.1	2	1.1	1	3.3	1	3.8
gp130	1	0.6	1	0.6				
IL-1β	1	0.6	1	0.6				
IL-10	1	0.6	1	0.6				
IL-6	8	4.5	5	2.8	2	6.7	2	7.7
Resistin	3	1.7	1	0.6				
SAA	1	0.6	0	0.0				
TNFR-R1	2	1.1	0	0.0				
TGFβ	1	0.6	1	0.6				
Cardiovascular system								
Blood pressure	3	1.7	2	1.1	2	6.7	2	7.7
HR	9	5.1	8	4.5				
RSA	6	3.4	6	3.4				
Allostatic load	1	0.6	1	0.6	3	10.0	3	11.5
Antioxidants	1	0.6	1	0.6				
BMI	6	3.4	5	2.8	2	6.7	2	7.7
Dietary fat intake	1	0.6	1	0.6				
HbA1c	1	0.6	1	0.6				
Lipids	2	1.1	2	1.1				
Metabolites	2	1.1	2	1.1	1	3.3	1	3.8
Micronuclei	1	0.6	1	0.6				
Mitochondrial activity	2	1.1	2	1.1				
Telomeres	3	1.7	3	1.7	1	3.3	1	3.8
Triglycerides	1	0.6	0	0.0				

Note. $N = 199$. 8-ISO = 8-isoprostane; BMI = body mass index; BDNF = brain-derived neurotrophic factor; CD40L = CD40-ligand; CRP = C-reactive protein; CTNFα = cytokine tumor necrosis factors-alpha; DHEA = dehydroepiandrosterone; HbA1c = glycated hemoglobin; gp130 = glycoprotein 130; HR = heart rate; IL-1β = interleukin 1β; IL-10 = interleukin-10; IL-6 = interleukin-6; PRL response = prolactin response; RSA = respiratory sinus arrhythmia; SAA = serum-amyloid-a; SICAM-1 = soluble intercellular adhesion molecule-1; TNFR-R1 = soluble tumor necrosis factor receptor type 1; TGFβ = transforming growth factor-beta.

Polygenic Scores

GWAS are a novel way to examine the extent to which multiple genes explain variation in traits and environments.[9] Few studies ($n = 4$) have examined CM and ACEs using polygenic scores (see Table 4). One study found that the TRCP5 gene located on the X chromosome was associated with the age of onset of bipolar disorder among participants reporting CM

Table 4. The Number and Percentage of Studies Measuring Polygenic Scores by Victimization Type.

	Childhood Maltreatment ($n = 176$)		Adverse Childhood Experiences ($n = 26$)	
Polygenic Scores	*n*	%	*n*	%
ADHD	1	12.5	1	100.0
BDNF Val66Met	1	12.5		
Bipolar disorder	1	12.5		
CRH	1	12.5		
CYP11A1	1	12.5		
CYP17A1	1	12.5		
FKBP5	1	12.5		
NR3C2	1	12.5		

Note. $N = 199$. BDNF Val66Met = brain-derived neurotrophic factor; CRH = corticotropin-releasing hormone; CYP11A1 = Cytochrome P450 Family 11 Subfamily A Member 1; CYP17A1 = Cytochrome P450 Family 17 Subfamily A Member 1; FKBP5 = FK506 binding protein 51; NR3C2 = Nuclear Receptor Subfamily 3 Group C Member 2.

(Anand et al., 2015). Frodl and colleagues (2014) conducted a genome wide assessment of genes associated with hippocampal volumes and found an interaction between CM and the Val66-Met gene, which encodes for BDNF, on hippocampal volumes. Specifically, participants who were carriers of the Val66Met polymorphism and showed reductions in hippocampal volumes were more likely to report CM. Similar results were found in participants who experienced CM and carried the minor allele of the nuclear receptor subfamily 3 group C member 2 (NR3C2) gene. Compared to participants with no experiences of CM, those who reported experiencing CM and carried the NR3C2 gene showed increased levels of cortisol and reductions in brain volume of the amygdala and hippocampus. Studies on ACEs using a GWA approach have reported that polygenic scores associated with ADHD ($n = 1$) increased vulnerability to experiencing ACEs (Zwicker et al., 2020).

Neurobiological Structures

Table 5 presents the count and percentage of the total number of studies examining neurobiological structures including limbic, cortical, and other systems. Additionally, Table 5 shows the number of studies reporting significant associations between CM, ACEs, and neurobiological structures. There was a considerable amount of research focused on areas of the limbic system as it relates to CM. Limbic structures such as the amygdala ($n_{\text{Total}} = 19$; $n_{\text{Significant}} = 17$), hippocampus ($n_{\text{Total}} = 19$; $n_{\text{Significant}} = 19$), thalamus ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 3$), corpus callosum ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), parahippocampal gyrus ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), olfactory bulb ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and cingulate gyrus ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$) were examined within the context of CM. Results from studies on limbic connectivity showed that individuals who experienced CM, compared to matched controls, demonstrated heightened activity in limbic structures of the brain (Demers et al., 2018; Fonzo et al., 2013; M. J. Kim et al., 2019; Van Dam et al., 2014). Other experimental studies with CM and control groups that manipulated facial expressions presented to participants found that those who experienced CM demonstrated increased activity in limbic regions (Fonzo et al., 2013; Neukel et al., 2019; van Harmelen et al., 2013). Several cortical structures were also implicated in studies on CM. Structures included the prefrontal cortex ($n_{\text{Total}} = 25$; $n_{\text{Significant}} = 23$), anterior cingulate cortex ($n_{\text{Total}} = 15$; $n_{\text{Significant}} = 13$), frontal lobe ($n_{\text{Total}} = 8$; $n_{\text{Significant}} = 7$), orbitofrontal cortex ($n_{\text{Total}} = 6$; $n_{\text{Significant}} = 6$), parietal lobe ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 3$), visual cortex ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), dorsolateral prefrontal cortex ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), dorsomedial prefrontal cortex ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and the ventromedial prefrontal cortex ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). Results from these studies revealed that reductions in volume of white matter tracts associated with cortical functioning were more common in participants reporting CM compared to those with no CM experiences (Bomyea et al., 2020; Busso et al., 2017; Puetz et al., 2019). Additionally, several studies reported increases in gray matter within these cortical areas in maltreated subjects (Ahn et al., 2016; Mielke et al., 2016). Furthermore, three studies examining communication between cortical structures and the limbic system of the brain found that tracts of communication between these two systems were down regulated in participants with a history of CM compared to matched controls (Herzog et al., 2020; Paquola et al., 2017; Peverill et al., 2019). Additional neurobiological structures investigated included the supplementary motor area ($n_{\text{Total}} = 5$; $n_{\text{Significant}} = 5$), inferior frontal gyrus ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 3$), whole brain ($n_{\text{Total}} = 12$; $n_{\text{Significant}} = 12$), insula ($n_{\text{Total}} = 11$; $n_{\text{Significant}} = 11$), putamen ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 3$), temporal gyrus ($n_{\text{Total}} = 4$; $n_{\text{Significant}} = 4$), cerebellum ($n_{\text{Total}} = 3$; $n_{\text{Significant}} = 3$), nucleus accumbens ($n_{\text{Total}} = 3$; $n_{\text{Significant}} = 2$), dentate gyrus ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 1$), precuneus ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 2$), Brodmann area ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), fasciculus ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), inferior parietal lobule ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), lingual gyrus ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), pituitary gland ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), striatum ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), subiculum ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and the supermarginal gyrus ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). Accumulated evidence from these studies demonstrated that CM was associated with abnormal neurobiological functioning within these structures.

Table 5 also presents a count and percentage of studies on ACEs and neurobiological structures. This line of research focused on examining the amygdala ($n_{\text{Total}} = 3$; $n_{\text{Significant}} = 3$) and hippocampus ($n_{\text{Total}} = 2$; $n_{\text{Significant}} = 1$). Additional studies examined the anterior cingulate cortex ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 0$), dentate gyrus ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 0$), orbitofrontal cortex ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), prefrontal cortex ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$), and subiculum ($n_{\text{Total}} = 1$; $n_{\text{Significant}} = 1$). For example, Teicher et al. (2012) reported reductions in connectivity between the hippocampus, dentate gyrus, and subiculum in participants exposed to more ACEs. Reduced connectivity between the prefrontal cortex and amygdala was also reported among individuals with more ACEs during an emotional stimulus task

Table 5. Neurobiological Structure by Victimization Type.

	Childhood Maltreatment ($n = 176$)				Adverse Childhood Experiences ($n = 26$)			
Neurobiological Structure	*n* (Total)	% (Total)	*n* (Significant)	% (Significant)	*n* (Total)	% (Total)	*n* (Significant)	% (Significant)
Limbic regions								
Amygdala	19	10.8	17	9.7	3	11.5	3	11.5
Cingulate gyrus	2	1.1	2	1.1				
Hippocampus	19	10.8	19	10.8	2	7.7	1	3.8
Olfactory bulb	1	0.6	1	0.6				
Parahippocampal gyrus	2	1.1	2	1.1				
Thalamus	4	2.3	3	1.7				
Cortical structures								
Anterior cingulate cortex	15	8.5	13	7.4	1	3.8	0	0.0
Dorsolateral prefrontal cortex	1	0.6	1	0.6				
Dorsomedial prefrontal cortex	1	0.6	1	0.6				
Frontal lobe	8	4.5	7	4.0				
Orbitofrontal cortex	6	3.4	6	3.4	1	3.8	1	3.8
Parietal lobe	4	2.3	3	1.7				
Prefrontal cortex	25	14.2	23	13.1	1	3.8	1	3.8
Ventromedial prefrontal cortex	1	0.6	1	0.6				
Visual cortex	2	1.1	2	1.1				
Other								
Brodmann area	1	0.6	1	0.6				
Cerebellum	3	1.7	3	1.7				
Dentate gyrus	2	1.1	1	0.6	1	3.8	0	0.0
EEG	7	4.0	6	3.4	1	3.8	1	3.8
Fasciculus	1	0.6	1	0.6				
Fusiform gyrus	1	0.6	1	0.6				
Inferior frontal gyrus	4	2.3	3	1.7				
Inferior parietal lobule	1	0.6	1	0.6				
Insula	11	6.3	11	6.3				
Lingual gyrus	1	0.6	1	0.6				
Nucleus accumbens	3	1.7	2	1.1				
Pituitary gland	1	0.6	1	0.6				
Precuneus	2	1.1	2	1.1				
Putamen	4	2.3	3	1.7				
Striatum	1	0.6	1	0.6				
Subiculum	1	0.6	1	0.6	1	3.8	1	3.8
Supermarginal gyrus	1	0.6	1	0.6				
Supplementary motor area	5	2.8	5	2.8				
Temporal gyrus	4	2.3	4	2.3				
Whole brain	12	6.8	12	6.8				

Note. $N = 199$. EEG = electroencephalogram.

(Peverill et al., 2019). This finding is consistent with evidence of general reductions in amygdalar volume in participants reporting ACEs (Herzog & Schmahl, 2018). Reductions were also found in the orbitofrontal cortex among participants reporting ACEs over a 25-year longitudinal study (Holz et al., 2015).

Discussion

Results from the systematic review show that a range of genetic, physiological, and neurological factors are involved in exposure and response to CM and ACEs. Several factors across different biological systems, including biomarkers capturing nervous, endocrine, inflammatory, cardiovascular, metabolic, and multisystem functioning, polygenic risk scores, and neurobiological structures derivative of the limbic, cortical, and other areas were found to be consistently associated with individual differences in early life victimization and later life consequences of early trauma. The reported findings have three key implications for future research on CM and ACEs.

First, accumulated evidence indicates that CM and ACEs are associated with physiological changes in nervous, endocrine, inflammatory, cardiovascular, and metabolic functioning as well as neurological changes in limbic and cortical structures (Moog et al., 2018; Slopen et al., 2010). Broadly, biomarkers capturing nervous and endocrine system functionality were altered in individuals who reported more experiences of CM and a higher number of ACEs (Aas et al., 2019; Drury et al., 2014). These findings were replicated across multiple studies using cross-sectional (Aas et al., 2017) and longitudinal (Baldwin et al., 2018) designs as well as comparison and control

groups (England-Mason et al., 2018). The reported results are consistent with several other reviews focused on risk factors for experiencing interpersonal violence (Fazel et al., 2018), which converge to suggest that interpersonal victimization alters healthy regulation and functionality of the nervous and endocrine systems (Cassiers et al., 2018; Ioannidis et al., 2020). These alterations may create a dysfunctional loop in functioning, which may result in impaired biological regulation later in life. The timing and severity of changes in biological functionality connected to CM and/or ACEs need to be explored with future biologically informed longitudinal research.

Along these lines, one of the most robust findings from the reviewed literature, which is consistent with previous reviews on maltreatment, stress, and depression (Nusslock & Miller, 2016), is the association between childhood trauma and inflammatory conditions. Inflammatory conditions are often the result of genetic predisposition, environmental insult(s), and stress over the life course. Evidence of inflammation is considered to be an indicator of an individual's immune system being compromised and/or overworked. Biomarkers assessing levels of inflammation have been found to be higher in participants with histories of CM (Fanning et al., 2015) and ACEs (Johnson et al., 2017) across multiple studies, settings, and time periods (Nusslock & Miller, 2016). Taken together, this indicates that CM and ACEs increase the likelihood of demonstrating symptoms of a compromised immune system. CM and ACEs were also found to influence cardiovascular system (Lee et al., 2017), metabolic system (Scheuer et al., 2018), and multisystem functionality (Carroll et al., 2013). Indicators of cardiovascular system function including HR, RSA, and blood pressure were compromised in individuals reporting CM (Dale et al., 2018) and ACEs (Scheuer et al., 2018). Studies reported that ACEs were associated with increases in allostatic load. Experiences of CM were also associated with higher BMI, irregular mitochondrial activity, and accelerated aging (Ridout et al., 2019).

With respect to neurobiological structures, CM and a higher number of ACEs were associated with elevated levels of functional activity and structural changes in several neurological structures of the limbic system (Rodman et al., 2019). Studies also reported functional reductions in cortical structures involved in the regulation of emotions and cognition (van den Berg et al., 2018). Findings indicated decreased connectivity between limbic and cortical regions of the brain (Fonzo et al., 2013), showing that cortical areas of the brain, which regulate emotional response in limbic areas, were downregulated in individuals who experienced CM and ACEs. Based on this evidence, victims of CM and ACEs may not be able to appropriately regulate neurobiological systems related to fear, emotions, and higher order biobehavioral cognitive processes. Longitudinal studies are needed to better understand the temporal pathways between trauma and both physiological and neurobiological change over time.

Second, there exists considerable variation in biological and neurobiological system response to CM and ACEs. Not everyone who experienced these forms of trauma displayed a dysregulation in biological/neurobiological systems (van der Werff et al., 2013). Observed variance in the relationship between experiences of victimization and changes in biological/neurobiological systems offers evidence of biological resilience (Lecei & van Winkel, 2020; Moreno-Lopez et al., 2019). Biological resilience is conceptualized as a multisystematic and time-dependent biological process that results in better functioning in health and behavior when exposed to environmental insults (Moreno-López et al., 2019). To date, biological resilience in response to trauma appears to be influenced by within-individual differences in the ability to activate several neurobiological systems (Lecei & van Winkel, 2020). For example, van der Werff and colleagues (2013) found that resilient participants showed increased connection between the left anterior cingulate cortex, the bilateral lingual gyrus, and the occipital fusiform gyrus (i.e., structures associated with memory and processing of emotional impulses) compared to those who were not categorized as resilient to CM. In the context of the current study, these findings demonstrate that individuals who show higher volume and functionality in cortical areas may not report negative emotional consequences associated with CM and ACEs. This aligns with studies showing decreased connectivity between cortical and limbic structures in individuals who have experienced CM and ACEs (van Rooij et al., 2020). Biological resilience likely occurs as the result of multiple biological/neurobiological systems operating in conjunction in a time-dependent manner. These biological systems likely work in concert with one another, which results in increased biological resilience to childhood adversity. Dahmen and colleagues (2018) demonstrated this "biological cascade" (see Lecei & van Winkel, 2020, for definition of biological cascade) effect in their study of hippocampal volumes and cortisol levels in participants with histories of CM. Results from their study showed that individuals who experienced CM, compared to a control group, had volume reductions in the hippocampus (i.e., a region of brain associated with long-term memory) and lower levels of cortisol reactivity. Taking van der Werff et al.'s (2013) findings into consideration, a pattern emerges suggesting that some participants may be more resilient to the negative effects of CM when they have stronger connectivity between the cortices and hippocampus. This, in turn, may then lead to downstream effects on lower levels of cortisol secretion. Similar results have been reported between cortisol, the pituitary gland (Kaess et al., 2018), and the whole brain (Puetz et al., 2017). Extending these findings into the context of GWAS, Gerritsen and colleagues (2017) showed that carriers of a copy of the NR3C2 gene who were exposed to CM displayed reduced volume in the amygdala and hippocampus as well as higher cortisol levels. Together, these studies indicate that several biological/neurobiological processes work in conjunction to influence biological resilience to CM. Yet, more research on the concept of biological resilience, especially in relation to the type, timing, and frequency of CM and ACEs is needed.

The third way in which biologically informed methods can deepen our understanding of CM and ACEs is through the

acknowledgment that individual-level propensities can increase vulnerability to these types of victimization. Researchers have long recognized that victimization—including CM and ACEs—is not a random occurrence. Genetic influences that cluster within families can conflate findings of the direct effect of childhood adversity on later life outcomes. Dinkler et al. (2017) provide an example of this in their examination of a cohort of twins by demonstrating how familial confounding can conflate the observed significant associations between CM and neurodevelopmental disorders. Specifically, Dinkler et al. (2017) showed that the bivariate association between CM and neurodevelopmental disorders became nonsignificant after controlling for latent genetic and nonshared environmental influences. These findings suggest that unobserved familial influences associated with CM contributed to explaining the correlation with neurodevelopmental disorders. Similar results of familial confounding have been reported for ADHD (Stern et al., 2018), cognitive functioning (Danese et al., 2017), bipolar disorder (Bornovalov et al., 2013), general personality disorders (Berenz et al., 2013), delinquency (Connolly, 2020), and deleterious mental health outcomes (Schwartz et al., 2019).

Results from twin and sibling designs support the idea that negative health outcomes related to CM and ACEs may be partly attributable to separate influences other than the experience of victimization per say. Longitudinal research controlling for latent genetic and shared environmental influence shows just how familial factors influence the association between CM, ACEs, and life outcomes. Behavior genetic research can also help illuminate underlying processes that account for exposure to childhood adversity through two conditions. These conditions are evocative and passive gene-environment correlation (*r*GE). Evocative *r*GE refers to a biologically mediated process whereby heritable behaviors passed down through families are expressed and exert responses from individuals in surrounding environments. Tanksley et al. (2020) provide an example of evocative *r*GE in their study examining the relationship between low self-control and victimization in a cohort of twins. Their study reported that a significant portion of variance in self-control was accounted for by latent genetic effects. Genetic and nonshared environmental effects also explained the covariance between self-control and experiencing victimization later in life. These findings suggest that genetic propensities for self-control may increase the likelihood of individuals putting themselves in situations where victimization is likely.

Passive *r*GE refers to the interaction between child–parent genotypes and rearing environments. Indicators of passive *r*GEs are assessed through shared variance across parenting processes, parenting behavior, and child behavior. Thus, parents pass down traits that influence children's behavior as well as the rearing environment that children and parents interact in. Eaves et al.'s (2010) study on family cohorts found that childhood ACEs were largely explained by parental ACEs and parental antisocial behavior—an example of a passive *r*GE. Parental expression of antisocial behavior and experiences of ACEs were, therefore, passively transmitted to children through shared characteristics at the family level. Similar results were reported by Pittner et al. (2019) in a sample of 413 parent–child dyads regarding emotional abuse, such that shared genetic traits passed down through families significantly contributed to the likelihood of perpetrating emotional abuse.

The finding that biological resilience, evocative *r*GE's, and passive *r*GE's influence response and exposure to CM and ACEs provides theoretical support for the diathesis stress (Gottesman & Shields, 1972) and differential susceptibility (Belsky & Pluess, 2013) models of stress responsivity. Briefly, the diathesis stress perspective posits that individual differences in genetic susceptibility to negative behavioral adaptations will increase in stressful and negative environments. Alternatively, the differential susceptibility model views genes as malleable and outcomes are dependent upon exposure to a continuum of negative and/or positive environments. The major difference between these two models of stress responsivity is that genetic plasticity under differential susceptibility can lead to both positive and negative behavioral adaptations in response to environmental cues while adaptive outcomes in the diathesis stress model can only reach a threshold of functionality, meaning that individuals with genetic susceptibility cannot positively adapt even in positive environments (Belsky & Pluess, 2013; Elbau et al., 2019). Evidence from findings of biological resilience in response to CM and ACEs provides conditional support for the differential susceptibility model; however, more research using robust longitudinal designs is needed before firm conclusions to this effect can be made.

Recommendations for Future Research, Practice, and Policy

This study has implications for integrating biologically informed methods into the study of CM and ACEs. This section provides recommendations on how to advance biopsychosocial research, practice, and policy on early life experiences of victimization.

Use longitudinal family-based research designs. Studies should attempt to include examinations of the relationship between latent genetic influences, biological systems, polygenic scores, and neurobiological structural systems in relation to CM and ACEs. Whether looking at vulnerability or response to victimization, it is apparent that the most robust studies (Baldwin et al., 2018; Beckley et al., 2018) use samples of individuals taken from families observed over time. Samples of twins, siblings, adoptees, and families provide a natural control and quasi-experimental method to examine victimization while accounting for latent genetic and environmental influences. Additionally, more research is needed to understand the dynamic processes that occur within families and familial experiences that influence vulnerability and response to CM and ACEs over the life course.

Use GWAS to identify genetic variants associated with trauma. Association studies examining whole genomes are replete with

information that can guide our understanding of CM and ACEs. These same findings can extend to DNA methylation studies (see Cecil et al., 2020). Several polygenic risk scores (Gerritsen et al., 2017; Zwicker et al., 2020) were found to increase vulnerability to ACEs and negative outcomes associated with CM. Future studies should continue to use GWAS to explore genetic variants associated with CM/ACEs.

Use multisystem models to explain exposure and response to CM. Studies should consider collecting and examining variables within a multilevel setting. Indeed, individuals, families, and neighborhoods are intertwined. In order to capture the entirety of human behavior and biological functioning, we need to consider biological, psychological, and sociological effects on individuals and families (Bronfenbrenner & Morris, 2007). Multisystem models recognize these transactional processes across different levels of analysis and seek to provide information on top-down and bottom-up effects. Mutlilevel models can inform our understanding of exposure and response to trauma by capturing the complexity of physiological and macroenvironmental factors.

Model biological and neurobiological systems as latent traits. Behavioral genetic research has been modeling genetic and environmental effects as latent traits for decades. The current review identified several biomarkers and neurobiological structures that captured functioning of overall biological/neurobiological systems; however, these biomarkers and neurobiological structures were often included as one-shot indicators. Moving forward, studies should consider collecting biological information associated with biological systems and including them in models as latent traits. For example, studies could examine multiple inflammatory markers and include them in a model evaluating latent immune response. Similar processes can be done for structures of the limbic, endocrine, and cardiovascular system. While allostatic load captures this to some degree, systems need to be modeled in accordance with the structures and markers associated within those systems.

Examine the role of biological resilience. Several studies have examined resilience to CM and ACEs from a neurocognitive and behavioral perspective (see Scoglio et al., 2019). Few studies have examined the role of biological resilience in relation to CM and ACEs across the life course (see Lecei & van Winkel, 2020; Moreno-López et al., 2019). Future studies should consider the role that biological resilience has on experiences of CM/ACEs. It may be beneficial for researchers to model biological resilience as a latent trait to examine the mediating and moderating role it has on CM, ACEs, and later life negative health and behavior.

Preventing CM and ACEs. Genetically informed designs indicate that maltreatment and maltreatment-oriented behaviors often cluster within families (Arseneault et al., 2011). This is consistent with a large body of work documenting the inter- and trans-generational nature of exposure to CM (Moog et al., 2018). Practitioners and policy makers may be able to leverage these findings to develop preventative techniques aimed at identifying families and parents who may be more susceptible to engaging in CM in order to intervene upon and prevent potential maltreatment.

Treatment programs for exposure to CM and ACEs. The reviewed studies find that biological systems and structures are altered in response to CM and ACEs. Individual differences in biological functionality in response to CM and ACEs may influence individual variation in expression or personality traits and psychopathological disorders as well as interactions between children, families, and their broader contextual environment (Ioannidis et al., 2020). Treatment providers and practitioners could use the identified research regarding biological change in response to CM and ACEs to guide the development of biologically informed treatment programs aimed at reducing the negative effects of CM and ACEs throughout the life course. Scientists have already started to do this through various techniques such as neurophysiological psychotherapy (McCullough & Mathura, 2019) and neuroimaging biofeedback systems (Carrion et al., 2013; Roos et al., 2018). However, the area of biologically informed treatment for CM and ACEs is relatively new and requires more attention and focus on practical implications (Boparai et al., 2018; Heim et al., 2019).

Measurement of CM and ACEs. CM and ACEs are complex forms of early adversity that influence behavior throughout the life course. Consistent with previous work (Bousman et al., 2017; Cowell et al., 2015), this study found several inconsistencies regarding the measurement of both CM and ACEs. Few studies captured the diversity, severity, and chronicity of CM and ACEs throughout childhood, adolescence, and young adulthood. Further, the traditional ACE screener has been criticized for being limited in scope (Finkelhor et al., 2013). Lack of consistency in cross-sectional and longitudinal measurement of CM and ACEs poses problems when determining causality of the relationship between these forms of adversity and later life adaptation. Future work should attempt to validate robust longitudinal measures of CM and ACEs that accurately assess domain specific, severe, and chronic forms of adversity.

Conduct meta-analytic studies assessing the biological correlates and consequences of CM and ACEs. This review identified 199 works assessing the biological correlates and consequences of CM and ACEs including latent genetics, biological mechanisms, polygenic scores, and neurobiological structures. The sheer magnitude and diversity in methodological designs made it difficult to provide a textual interpretation of design quality and strength of the identified relationships (see Online Supplemental Table 1 for more detailed descriptions of the identified studies). We recognize these limitations and hope that future researchers will see the utility of this review and recognize the importance of developing more focused meta-analyses examining each biological correlate and consequence of CM and ACEs in a subset of studies in order to provide a more robust

analysis of design quality, magnitude, strength, and directionality of the identified relationships. For example, one meta-analysis could examine the relationship between biological mechanisms associated with neuroendocrine functionality and CM/ACEs. This would include a subset of the identified studies and would allow for the needed coding to assess relationship strength and design quality.

Conclusion

This study systematically reviewed 199 articles examining the relationship between genetic, physiological, and neurological sources of influence on CM and ACEs. Results highlight how biologically informed methods can be used to broaden our understanding of the correlates and consequences of CM and ACEs. The studies identified herein are limited in their diversity to those published in English that relied on the samples of participants from largely European ancestries. Because of this, as well as limitations to sample sizes and geographic regions, findings from this review may not be representative of the collective diversity across nations, states, identities, cultures, religions, ages, races, ethnicities, and ancestries. Additionally, these studies relied on technological innovations to capture biomarkers, polygenetic scores, and neurobiological systems. These can be expensive and require an added degree of expertise and analysis. In order to capture the full range of variability in human behavioral adaptations, future research should attempt to use biologically informed methods to assess outcomes associated with CM and ACEs in samples from diverse ancestral domains. Population strata outside of traditional European samples will provide a more robust account of the biological processes associated with vulnerability to CM/ACEs as well as outcomes of these exposures. Taken together, this study provides support for the continued need to explore changes in response to trauma associated with victimization and factors that influence risk of experiencing future victimization from a biologically informed perspective. In this way, biopsychosocial research can deepen our understanding of the etiology and deleterious outcomes of CM and ACEs in an effort to improve theory and intervention/prevention efforts.

Critical Findings

- This is the first review to systematically evaluate the current state of evidence from research using biologically informed methods on CM and ACEs, with a specific focus on correlates and consequences of these two forms of interpersonal victimization.
- Current results suggest that experiencing CM/ACEs are associated with minimal change in neurobiological and biological systems. Although small, these changes are often associated with behavioral and health outcomes over time.
- Results from behavior genetic studies and GWAS indicate that experiencing CM and ACEs are not a random event. Genetic and environmental effects that co-occur within families significantly influence the likelihood of being a victim of CM and/or experiencing ACEs.

Implications for Practice

- Practitioners and treatment providers should be aware of how biological mechanisms (i.e., neural structures and physiological processes) change in response to trauma and how trauma is related to psychopathology and health.

Implications for Policy

- Policymakers should consider the observation that maltreatment and maltreatment-oriented behaviors often cluster within families, in part, due to biological and environmental factors shared between family members.
- Treatment can be framed around developing biological feedback and monitoring systems to examine the "skin deep" effect that CM/ACEs may have on individuals undergoing therapy.

Implications for Research

- Research needs to continue using biologically informed methods to (1) help control for familial confounding, which will help aid in identifying salient childhood experiences associated with behavior problems and poor health, and (2) better understand how biological processes contribute to vulnerability for and resilience to CM/ACEs.
- Studies should continue to use the most rigorous quasi-experimental, multilevel, and biologically informed methods when studying CM/ACEs.

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Supplemental Material

The supplemental material for this article is available online.

Notes

1. We opted to focus only on research published between 2010 and 2020 as several reviews have already expertly documented research on the effects of childhood maltreatment (CM) and adverse childhood experiences (ACEs) from biological perspectives in studies prior to 2010. For a review, please see Cicchetti and Rogosch (2012), Coates (2010), De Bellis et al. (2011), Hart

and Rubia (2012), Heim et al. (2010), McCrory et al. (2011), McCrory et al. (2010), Tomalski and Johnson (2010), and Twardosz & Lutzker (2010).

2. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (see Moher et al., 2009).
3. The inclusion criteria for this study did not specify measurement criteria for CM and ACEs. Measures of CM and ACEs include a broad range of victimization experiences that occur throughout childhood. Accurately measuring the diversity, chronicity, and severity of CM and ACEs is an important aspect of future research; however, the current study did not designate measurement criteria for CM and ACEs. This is a noteworthy limitation and a challenge for future research as noted in the future directions.
4. We omit studies on candidate genes and epigenetics on these forms of interpersonal victimization as several reviews on these topics have been published elsewhere (see Cecil et al., 2020; Maglione et al., 2018). However, we include the implications of these reviews in our discussion to provide a more meaningful understanding of the implications of biopsychosocial research within the context of individuals, families, and neighborhoods.
5. Several references are made throughout this article to control groups and comparison groups involving twins, relatives, and nonrelated participants. Online Supplementary Table 1 provides an overview of which studies included twins, relatives, and nonrelated controls. Most comparison groups, unless otherwise specified as a twin or family member, are unrelated controls.
6. It is important to note the methodological limitations to twin, family, and adoptee designs based on sample size. We recommend Verhulst (2017) to readers interested in discussions about sample size and power analyses for twin designs. We also hope readers take note of the sample sizes and design qualities outlined in Online Supplementary Table 1.
7. Deviation in results from this study, however, are most likely attributable to the measure of genetic risk, which was captured as a difference score (i.e., low, high, and highest levels of risk) between twins rather than modeling variation in latent genetic components between twins.
8. The term allostatic load refers to the process by which multiple physiological systems engage in constant flux and adjustment in response to ever-changing stimuli (Seeman et al., 2010). Thus, allostatic load is operationally conceptualized as a multisystem perspective in which cumulative physiological systems engage in cross talk to influence the bodies physiologic response to perceived demands and stimuli.
9. A polygenic risk score (PRS) is an individual's score of genetic loading for a disease or trait (Lewis & Vassos, 2020). PRSs are derived from the summation of the number of risk alleles an individual carries weighted by each alleles effect size based on recent evidence from a genome wide association studies (GWAS). Studies discussed herein derived polygenic scores of single-nucleotide polymorphisms from significant effect sizes taken from genome wide analyses. See Tam et al. (2019) and Visscher et al. (2017) for a review of GWAS as well as a discussion of their benefits over traditional candidate gene studies and various limitations including issues with sampling.

References

References marked with an asterisk indicate studies included in the systematic review.

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