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Review

Adverse Childhood Experiences and Adult Obesity: A Systematic Review of Plausible Mechanisms and Meta-Analysis of Cross-Sectional Studies

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ABSTRACT

Adverse childhood experiences (ACEs) can become biologically embedded leaving a lasting signature on multiple body systems. ACE scores have been used to associate childhood adversity to a wide range of adverse health conditions over the life course, most notably substance-related disorders. Multiple studies have shown that the presence of elevated ACE scores predicts obesity in adulthood. However, a gap exists in the literature elucidating the pathways from childhood adversity to increased BMI in adulthood. We systematically reviewed these mechanisms as well as discuss novel plausible pathways. We searched PubMed, PsycInfo, Embase, and Web of Science and after applying exclusion criteria identified 18 articles for qualitative analysis. The most commonly cited mechanisms linking ACEs to obesity are social disruption, health behaviors, and chronic stress response. Ten observational studies (n = 118,691) were quantitatively summarized and demonstrated a positive association between ACE and adult obesity with a pooled odds ratio of 1.46 (CI = 1.28, 1.64) with moderate heterogeneity (I^2 = 70.8%). Our results found a 46% increase in the odds of adult obesity following exposure to multiple ACEs. Based on our qualitative synthesis and review of the most recent relevant literature, we propose biologically plausible explanations for the significant positive relationship between ACEs and adult obesity. Reducing exposure to ACEs, improved screening and detection of trauma, better access to trauma-informed care, and improvements to the food environment are likely to improve downstream health outcomes related to eating behavior.

1. Introduction

Obesity is a major public health concern in the US and worldwide. In recent years there has been increased interest in psychosocial risk factors for various health outcomes, most notably stress [1,2], trauma [3,4], and adverse childhood experiences (ACEs) [5,6] all of which can become "biologically embedded" [7]. Early life experiences can leave a lasting signature on genetic predispositions that affect emerging brain architecture and long-term mental and physical health [8]. Trauma has a measurable and enduring effect on the functional dynamics of the brain-body-mind, even in individuals who experience trauma but do not develop posttraumatic stress disorder (PTSD) [9]. Efforts to explain the relationship between childhood adversity and adult obesity often focus on stress-induced overeating [10]. Known pathways of association between stress and obesity include childhood poverty, impaired sleep, and embedded neurobiological pathways [11]. Other important avenues include interference with self-regulation and more recently changes in the gut microbiome [12]. The relationship between ACEs and adult obesity has been described, however there is little data or consensus on mediating mechanisms that drive this association over the life course. A recent statement from the American Heart Association states that "substantial evidence" links early life adversity to poor cardiometabolic outcomes, but very few studies have tested mechanisms [13]. The goal of this review is to synthesize current knowledge on ACEs and obesity in order to make predictions and point toward future directions.

1.1. Adverse Childhood Experiences

The original ACE measure is a ten-question (17-item) seven-

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category questionnaire introduced in a large managed care population in Southern California [5]. Yes/no questions investigate the presence of childhood maltreatment (emotional, physical, sexual, and neglect) and household dysfunction (violence between parents, parental separation, household substance abuse, mental illness, incarceration) during the first 18 years of life. In the original sample population, individuals who experienced four or more ACEs had a 12-fold increase in risks for substance use disorders (SUDs), depression, and suicide attempts, and a 1.4 to 1.6-fold increase in risk for severe obesity (BMI > 35) [5]. Several variations of the original ACE measure have been adapted and expanded for other surveys in other communities with different sample characteristics [14] but the current study focuses only on individual level ACEs.

1.2. Previous Systematic Reviews and Meta-Analyses

A systematic review published in 2010 summarized eight articles linking adult obesity to a wide range of psychosocial factors in childhood [10]. Two systematic reviews and meta-analysis published in 2014 found significant associations with childhood maltreatment/abuse (not ACE-specific) and adult obesity, with one citing that elevated stress increases cravings for palatable foods [15] and the other suggesting "food addiction" as a potential mechanism [16]. Both meta-analyses reported a 95% confidence interval (CI) within 24-47% increased odds of adult obesity following various forms of childhood adversity. A recent systematic review and meta-analysis examined the relationship between adversity/trauma and overweight (BMI at or above 25) prior to reaching adulthood (during childhood and adolescence) [17]. The authors found a pooled odds ratio (OR) of 1.12 (CI = 1.01, 1.25) with heterogenous results ($I^2 = 52.0\%$) suggesting it may take many years for childhood adversity to manifest into adult obesity. The largest systematic review and random-effects meta-analysis (n = 253,719 for all outcomes) to date combined cross-sectional, case-control, and cohort studies and reported the OR for adult overweight/obesity as 1.39 (CI = 1.13, 1.71) following exposure to childhood adversity, with high heterogeneity across the eight studies ($I^2 = 75.1\%$) [18]. What is lacking from the prior systematic reviews is qualitative information about mediating mechanisms that accumulate and cross-associate over time, which is the primary objective of the current investigation. This meta-analysis is the first to describe adult obesity outcomes from cross-sectional studies using individual-level ACE scores. While cross-sectional studies do not establish causal relationships, we are interested in 1) previous authors efforts to explain this association and 2) population-based and/or weighted samples, in order to generate a stable estimate with external validity. Because of growth in ACE research in recent years, there is a sufficient body of published studies to create a pooled life course association with obesity.

1.3. Potential Mechanisms

A recent systematic review examined proposed mediators in the relationship between early life adversity (not exclusively ACE) and cooccurring binge eating disorder (BED) and obesity [19]. The authors identified depression, self-criticism, dissociation, PTSD symptoms, specific interpersonal factors, such as attachment quality, eating disorder (ED) symptoms, and neurobiological factors. Recent reports have suggested that food addiction (FA) may be involved in the pathway from trauma to obesity [20–22], but this is only beginning to be elucidated. A recent study of active US military (n = 179) found that the association between traumatic experiences and higher BMI was mediated by disordered eating [23]. Positron emission tomography (PET) data has shown that long-term exposure to psychosocial adversity is associated with reduced striatal dopamine (DA) synthesis capacity [24] which may be one explanation for the strong relationship between ACEs and SUDs. Furthermore, a recent functional resting state magnetic resonance imaging (fMRI) study of 186 adults (ages 18-50) without a history of SUD, ED, metabolic complications, or bariatric surgery determined that early life adversity may alter connectivity of brain regions in the extended reward network, which can be both a cause and consequence of FA [25].

These studies suggest insufficient data regarding mechanisms that link ACEs to adult obesity. One aim of the current systematic review is to extract mediators either tested or proposed/hypothesized by authors which link ACEs to health outcomes. Identifying novel pathways may be useful to inform future intervention strategies at the individual (treatment) and public health (food environment policy) levels.

1.4. Current Investigation

To date, none of the published meta-analyses have focused specifically on population-based associations between ACE scores and adult obesity. We hypothesize that a meta-analysis of studies using only the ACE measure will have less heterogeneity than previous reports using a wider range of adversity/trauma measures, and less than reports combining multiple study designs. The aim of the current study is to identify all cross-sectional studies of adults that describe the association between ACE scores and obesity (BMI at or above 30), and to systematically review proposed mediators and/or mechanisms offered by the authors (from the discussion section and beyond).

2. Methods

The systematic review and meta-analysis follow the guidelines and criteria set by the Preferred Reporting Items for Systematic Reviews (PRISMA) [26]. We have included a copy of the PRISMA checklist as supporting information. An ethics statement was not required.

2.1. Search Strategy

The literature search for this study included only English peer-reviewed articles published before June 9, 2019. The articles were identified using the following databases: PubMed, PsycInfo, Embase, and Web of Science using basic search terms: adverse childhood experience* AND obesity (see Figure 1). The literature review was conducted in duplicate by two investigators (DAW and TDB) and any discrepancies were resolved through discussion until consensus was reached. Additionally, to ensure that no studies were missed a more extensive search was conducted by one of the investigators (DAW) using a wider range of Medical Subject Heading (Mesh) terms and text words from each database: adverse childhood experience*, child abuse, adverse childhood event, childhood adversit*, childhood trauma AND obesity, body mass index, BMI, overweight, weight gain, adiposity. Reference lists were also manually scanned during full-text review. A list of search terms, strategies, and results from each database in the extensive search can be found in Supplement A.

2.2. Exclusion

Initial screening by title and abstract of English articles led to full-text article assessment for eligibility. Exclusions were based on 1) not using cross-sectional study design (e.g. cohort, case-control) to avoid potential for reverse association between ACE and weight 2) not using the ACE measure or close modification (e.g. Childhood Trauma Questionnaire) 3) not using BMI as the outcome measure of obesity (either from medical records or self-report) 4) studies of obesity in children/adolescents and 5) studies on specific clinical populations (e.g. bariatric, psychiatric). Quantitative synthesis for meta-analysis included only articles reporting both ORs and CIs (or standard errors) using logistic regression models using ACE as a predictor and obesity (defined by BMI) as the outcome. When obesity was not clearly defined, authors were contacted to ensure that study participants reported obesity based on BMI.

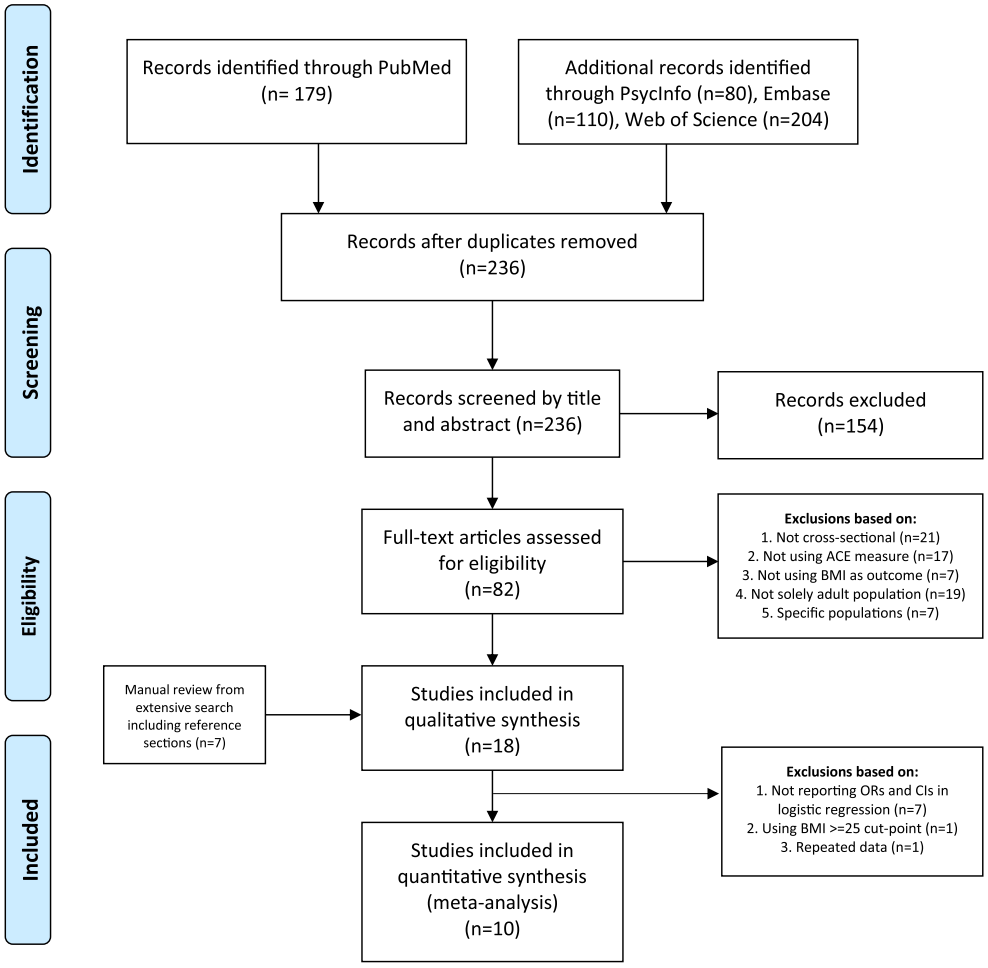

Figure 1. Flow Diagram of Search Strategy: Adverse Childhood Experience* and Obesity.

2.3. Data Synthesis and Analysis

Both authors independently summarized the data from the included studies and resolved any discrepancies through consensus. The following information was extracted from each study: year of publication, first author's name, data source (if not original research), sample size, country, sample population, noteworthy demographic characteristics, number of ACE questions used, number of ACE categories identified, ACE cut-point for analysis, BMI measurement (medical records or self-report), BMI cut-point for statistical analysis, statistical model, adjusted OR, and the 95% CI. When studies reported BMIs above 30 in their statistical models, authors were contacted to see if the BMI = 30 cut-point was available. Qualitative analysis conducted separately by both authors investigated mediating mechanisms mentioned in the discussion section and beyond, across four domains: 1) Attitudinal/Behavioral (health attitudes/beliefs, health behaviors, coping mechanisms) 2) Brain/Mind (neurological changes, chronic stress response, cognitive functioning, mental health) 3) Body Systems (nervous, immune, endocrine, cardiovascular) and 4) Social Factors (socioeconomic status, perceived discrimination, social support/disruption). These domains were chosen prior to the analysis based on authors prior knowledge of this topic.

The Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies was used to assess study quality (up to 10 points, with 9-10 being very good, 7-8 good, 5-6 satisfactory, and 0-4 unsatisfactory) despite being somewhat controversial in use with cross-sectional studies [27,28]. The original adaptation of the NOS for cross-sectional studies [29] was not a good fit for our data so we used the adaptation created by Modesti and colleagues (2016) [30]. While cross-sectional data is generally recognized as low quality compared to other study designs (e.g. cohort, case-control, longitudinal, randomized controlled trials) it remains the most feasible approach to assess relationships between harmful childhood exposures and adult health outcomes. The NOS quality assessment was conducted independently by both authors for all studies meeting inclusion criteria for meta-analysis.

2.4. Statistical Analysis

The adjusted OR and corresponding 95% CIs were extracted from each study and pooled to assess a life course association between ACE exposure and adult obesity. A restricted maximum likelihood (REML) random effects model was used due to variations in study populations, inconsistency in assessment of ACE exposure, and the use of different covariates for adjustment across studies. The I-squared (I^2) statistic was used to assess heterogeneity across the included studies. Heterogeneity was assumed to be present if the I^2 statistic was greater than 50% and considered high above 75% [31]. Subgroup analysis was conducted for the studies using 1) a BMI cut-point greater than 30 to assess obesity and 2) ACE cut-point lower than four. Further sensitivity analysis 1) removing the lowest OR 2) removing the highest OR and 3) removing the highest weighted study were conducted, in order to assess the impact of individual studies on the overall effect size. A final sensitivity analysis removed studies with NOS score below five to assess the impact of low-quality studies on the overall estimate. Visual inspection of the funnel plot was used to assess publication bias, and a trim-and-fill technique was used for publication bias assessment. An Egger test

evaluated the impact of small study effects. All analysis was performed using Stata 16 (Stata Corp, College Station, TX) [32].

3. Results

3.1. Literature Search and Study Characteristics

Figure 1 summarizes the number of records identified in each database after duplicates and non-English articles were removed (n = 236). Initial screening by title and abstract led to 154 exclusions, leaving 82 articles for full-text eligibility assessment. Eleven articles met full inclusion criteria from the basic search [5,33–42]. One study was a conference abstract [41] and was included because the subsequent publication used obesity status as an adjustment for cardiovascular risk factors, rather than as a reported outcome [43]. The extensive search (conducted to ensure that no studies were missed and to scan reference lists for articles that may have been in other databases) yielded 2,561 articles from all four databases, and after duplicates were removed, 1,663 titles and abstracts were scanned to find additional studies that met inclusion criteria. Combined with a manual review of reference lists, seven additional articles were added to the qualitative analysis [44–50].

3.2. Qualitative Analysis

The 18 articles included in the qualitative analysis can be found in Table 1. Thirteen (72%) of the articles are from the US, and the majority of those are from national datasets designed to be representative of the US population. While the generalizability of the original ACE study [5] has been questioned because the Kaiser sample was predominately white and middle-to-upper class insured patients, national datasets typically use weighting techniques to offset these issues. Age distribution was heterogeneous across the studies, but age is routinely adjusted for in models. It is important to acknowledge that not all studies used the exact same tool. Some researchers have added or removed/collapsed questions for optimal relevance with their target population, as many authors have argued in favor of extending the conventional ACE measure [14]. For example, the ACE International Questionnaire has 24 questions; however, none of these differences impacted our quantitative analysis.

Supplement B identifies the potential mechanisms and mediators mentioned by each study. Five [37,40,42,44,47] out of 18 studies gave mention to pathways from ACE to specifically obesity, whereas others discussed pathways from ACE to negative health outcomes in general. These five studies are reviewed in more detail below (section 4.1). Table 2 summarizes the prevalence of identified categories of mechanisms from most to least common.

3.3. Quantitative Analysis

Ten articles met criteria for meta-analysis (Figure 2) which shows an overall OR = 1.46 (CI = 1.28, 1.64) across all studies (n = 118,691) and moderate heterogeneity (I^2 = 70.8%). Supplement C summarizes the Newcastle-Ottawa Scale scores for all ten articles. One article with unsatisfactory quality [33] was removed for sensitivity analysis but had no effect on our estimate (OR = 1.45 CI = 1.27, 1.64) so we included it. Subgroup analysis using REML separating the BMI cut-points did not reveal a directional trend, but the test of group differences was significant ($p < 0.01$). One study that used BMI at or above 35 to define obesity reported an OR = 1.90 (CI = 1.60, 2.20) [47] while one study that used BMI at or above 40 reported an OR = 1.35 (CI = 1.15, 1.55) [35] leaving an OR = 1.32 (CI = 1.24, 1.40) across the other eight studies (Supplement D). Further subgroup analysis separated ACE exposure (by number of ACEs) showed an increasing gradient where the two studies [36,41] using ACE at or above one as the cut-point generated a pooled OR = 1.29 (CI = 1.20, 1.38) and the one study [48] using the ACE at or above two cut-point revealed an OR = 1.30 (CI = 1.05, 1.55) while the other seven studies using the ACE at or above four revealed OR = 1.62 (CI = 1.35, 1.90). However, differences were not significant ($p = 0.08$) (Supplement E). A final subgroup analysis removed the study with smallest effect size [36] (resulting OR = 1.50, CI = 1.30, 1.71), the largest effect size [45] (resulting OR = 1.45, CI = 1.27, 1.63) and the largest weight [41] (resulting OR = 1.50, C = 1.29, 1.72). In summary, no single study significantly changed the overall estimated effect size.

A funnel plot used to assess publication bias revealed visual asymmetry on each side of the overall estimate (Figure 3). The trim-and-fill technique was used to impute two studies to create funnel plot symmetry, leading to a slight reduction in the overall effect size after adding the two imputed studies (OR = 1.41, CI = 1.22, 1.61) indicating slight publication bias in favor of positive results. An Egger test was conducted for the presence of small study effects and was significant ($p = 0.02$); however, this test has limited power due to our small sample size (n = 10) and moderate-to-high levels of heterogeneity present.

4. Discussion

4.1. Qualitative Analysis

Only five of the eighteen studies mentioned potential pathways linking ACEs to obesity. The original ACE investigators proposed a direct biological pathway: repeated stress impact glucocorticoids leading to increased intra-abdominal and other fat deposits [47]. Investigators using data from Iowa suggest a behavioral pathway referencing links between trauma and disordered eating [44]. Authors from a study of multiple colleges in Georgia discuss changes in health behaviors: lower fruit and vegetable consumption and less sleep, as well as modified biological systems: stress response altering hormonal and immune factors [37]. A study from Tunisia conducted formal mediation analysis and found that risk of overweight/obesity due to violence is partially mediated by poor mental health [42]. These authors concluded that among people with EDs, treatment is likely to be more effective if tailored to individuals with a history of childhood exposure to violence. Finally, a recent study highlights the possible role of psychosocial stressors in predicting BMI outcomes, suggesting that ACEs in conjunction with perceived discrimination may impart an enduring biological imprint [40].

From all studies included in our qualitative synthesis, the most commonly cited explanations for the relationship between ACE and negative health outcomes included: social disruption, changes in health behaviors, chronic stress response (e.g. hypothalamic-pituitary-adrenal [HPA] axis), and mental health (e.g. depression). This pattern was the same in the subgroup that discussed obesity-specific mechanisms. With respect to social factors, a recent cohort study from Ireland identified a significant interaction between ACEs and income in predicting overweight/obesity, suggesting that the joint effects contribute to a toxic stress state that lead to increased weight gain over time [51]. It has recently been proposed that the maltreatment-obesity association is spurious and driven by confounding through the home food environment. However, after testing, researchers have found limited confounding influence [52]. Results suggest that there is a measurable effect of ACEs on BMI net of social factors, consistent with the biological embedding of adversity theory (section 4.3).

The second most suggested category “health behaviors” is extremely broad, including smoking, eating, exercise, sleep, etc. all of which have major implications on human health. Addiction-like eating is likely to be conceptualized as a health behavior but could also be viewed as a coping mechanism or a cause/consequence of neurological changes (see Table 2). With respect to obesity, it has been suggested that the chronic stress response should also consider the role of weight stigma, which can be very stressful and perpetuate a negative cycle [12]. The least commonly cited pathways were changes in cognitive functioning and

Table 1
Qualitative Analysis of Studies Linking ACE Scores to Adult Obesity

Year	First Author	Dataset	N	Country	Population	Demographic Characteristics	#ACE Questions	#ACE Categories	ACE Cut-Point	BMI Measurement	BMI Cut-Point	Model	Adjusted OR	95% CI
1998	Felitti	Kaiser	9,508	U.S.	Hospital San Diego	Mean age 56; 84% white	17	7	4+	Records	>=35	Logistic	1.6	1.2, 2.1
2006	Anda	Kaiser two waves	17,377	U.S.	Hospital San Diego	73-76% white	18	8	4+	Records	>=35	Logistic	1.9	1.6, 2.2
2010	Dube	BRFSS 2002	5,378	U.S.	Texas	46% had atleast 1 ACE	17	7	2+	Self-report	>=30	Logistic	1.3	1.1, 1.6
2014	Almuneef	n/a	931	Saudi Arabia	Diverse SES	90% younger than 45	24 (ACE-IQ)	8	4+	Self-report	>=30	Logistic	1.7	1.0, 2.9
2014	Bellis	n/a	1,567	U.K.	Diverse	Age range 18-70	11	n/a	4+	Self-report	>=40	Logistic	3.02	1.38, 6.62
2014	Kreatsoulas	BRFSS 2009-2011	45,644	U.S.	Representative	Age range 18-99	17	7	1+	Self-report	>=30	Logistic	1.3	1.2, 1.4
2015	Friedman	MIDUS	3,996	U.S.	Representative	92% white	19	7	n/a	Self-report	>=30	Ordinal Logistic	1.14	1.06, 1.22
2016	Mouton	SCCS	22,227	U.S.	12 States	Age range 40-79	10	3	4+	Self-report	>=40	Logistic	1.35	1.16, 1.57
2016	Almuneef	n/a	10,156	Saudi Arabia	13 Regions	Mean age 32 yrs; 41% college	24 (ACE-IQ)	8	4+	Self-report	>=30	Logistic	2.25	1.66, 3.05
2016	Rehkopf	NLSY 2012	7,266	U.S.	Representative	Age range 47-54	3	3	1	Self-report	>=30	Logistic	1.23	1.03, 1.48
2016	Campbell	BRFSS 2011	48,526	U.S.	5 States	85% white; 57% married	11	8	4+	Self-report	>=25	Logistic	1.16	0.98, 1.37
2016	Wade	SEPA HHS	1,784	U.S.	Philadelphia	57% single	14 (Expanded)	14	4+	Self-report	>=30	Logistic	1.29	0.88, 1.88
2017	Downey	BRFSS 2012	6,361	U.S.	Iowa	91% white	11	8	4+	Self-report	>=30	Logistic	1.5	1.2, 1.9
2018	Windle	DECOY	2,969	U.S.	Georgia Colleges	7 universities	10	10	n/a	Self-report	n/a	Linear Regression	n/a	n/a
2018	Mhamdi	n/a	2,120	Tunisia	Hospital	Mean age 36 yrs.	24 (ACE-IQ)	8	n/a	Records	>=25	Linear Regression	n/a	n/a
2018	Hazlehurst	BRFSS 2011	32, 151	U.S.	Washington	502 unique zip codes	11	8	2+	Self-report	>=30	Prevalance Ratio	n/a	n/a
2019	Riem	n/a	951	Netherlands	Representative	Mean age 55 yrs.	6	6	3+	Self-report	>=30	Linear Regression	n/a	n/a
2019	Vasquez	NESARC 2012-2013	10,548	U.S.	55 and older	Mean age 67	33	16	n/a	Self-report	n/a	ANCOVA	n/a	n/a

Legend: BRFSS = Behavioral Risk Factor Surveillance System; MIDUS = Midlife in the United States; SCCS = Southern Community Cohort Study; NLSY = National Longitudinal Surveys; SEPA HHA = Southern Pennsylvania Household Heath Survey;
DECOY = Documenting Experiences with Cigarettes and Tobacco in Youth; NESARC = National Epidemiologic Survey on Alcohol and Related Condition; SES = Socioeconomic Status; IQ = International Questionnaire

Table 2
Frequency of Mediating Mechanism Mentioned

Mediating Mechanism	Mentioned (n = 18)	Freq. (%)
Social Support/Disruption	18	100
Health Behaviors	17	94
Chronic Stress Response	15	83
Mental Health	15	83
Socieconomic Status	13	72
Cardiovascular	10	56
Coping Mechanisms	9	50
Nervous System	9	50
Endocrine System	9	50
Neurological Changes	8	44
Health Attitudes/Beliefs	7	39
Immune System	7	39
Perceived Discrimination	3	17
Cognitive Functioning	2	11

perceived discrimination. However, from the perspective of the four identified domains, Body Systems received the least average amount of mentions, suggesting that the concept of biological embedding is less known, or at least more difficult to research. Psychological factors such as emotion dysregulation and dissociation explaining the association between trauma and eating pathology have been discussed elsewhere [53–56].

4.2. Quantitative Analysis

To our knowledge, no meta-analysis has investigated the relationship between individual level ACE scores and adult obesity using only cross-sectional data (aiming for a generalizable estimate). Among these studies combined, there is 46% increase in odds of adult obesity following childhood adversity as measured by ACE (41% after adjusting for publication bias using the trim-and-fill technique, see Figure 3). This estimate is slightly higher than previous meta-analysis from 2014 (multiple measures of childhood adversity) that report 34% [15] and 36% [16] increase in odds of adult obesity, as well as the 2017 publication (multiple study designs) that reports a 39% increase (including both overweight and obesity) [18]. We suspect that using only cross-sectional measures of individual-level ACE scores led to a slightly higher estimate (due to unmeasured confounders), and our I^2 (70.8%) was also lower than two of the studies [16,18] as hypothesized. One study had less heterogeneity ($I^2 = 65.8\%$) but only included cohort studies (including prospective) with control groups of non-abused children, which can reduce potential for residual confounding as well as reduce methodological heterogeneity. Meanwhile, it is important to note that with only ten studies, our measure of heterogeneity should be interpreted with caution.

Assessment of publication bias suggests that there is a slight yet detectable bias toward reporting of positive results, although this may be attributable to between-study heterogeneity. Studies finding no relationship between ACE and obesity are less likely to get published. More realistically, many studies that were excluded during initial screening and eligibility assessment reported BMI as an adjustment rather than an outcome, therefore did not always report the OR. It is possible that models with ACE-obesity relationships closer to the null (OR = 1) favored use of BMI as a covariate in the adjustment of other outcomes, such as respiratory disorders [57], diabetes [58], or cardiovascular disease [43]. It is also likely that authors did not report ACE-obesity relationships in their final publications because their research questions were focused elsewhere. In summary, adjustment for publication bias reduces the estimate by 5% to OR = 1.41, which is closer to the three previous meta-analytic reports.

4.3. Biological Embedding of Adversity

In this section, we assume phenotypic overlap between individuals exposed to a high number of ACEs and those diagnosed with PTSD. They have been conceptually merged in an effort to identify similarities in predisposing individuals to behavioral health disorders associated with weight changes. However, there are likely different biological signatures associated with differential exposures and susceptibilities that have not yet been elucidated. From a broad perspective, four characteristics define biological embedding: 1) life experience translates into neurobiological adaptations 2) adaptions vary according to the intensity 3) effects are stable and long-term and 4) effects influence behavioral patterns or mental health outcomes over the lifetime [59]. Observable neural changes following childhood psychosocial adversity include 1) structural variation in gray and white matter 2) functional variation in brain activity and functional connectivity and 3) altered neurotransmitter metabolism [7]. From an obesity-risk perspective,

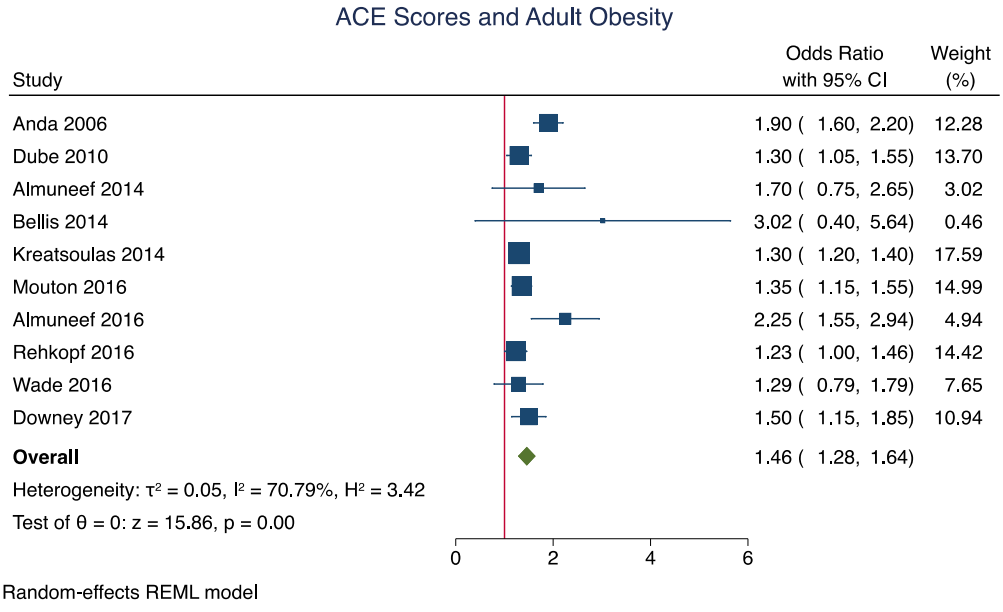

Figure 2. Random Effects Meta-Analysis of ACE Scores and Adult Obesity.

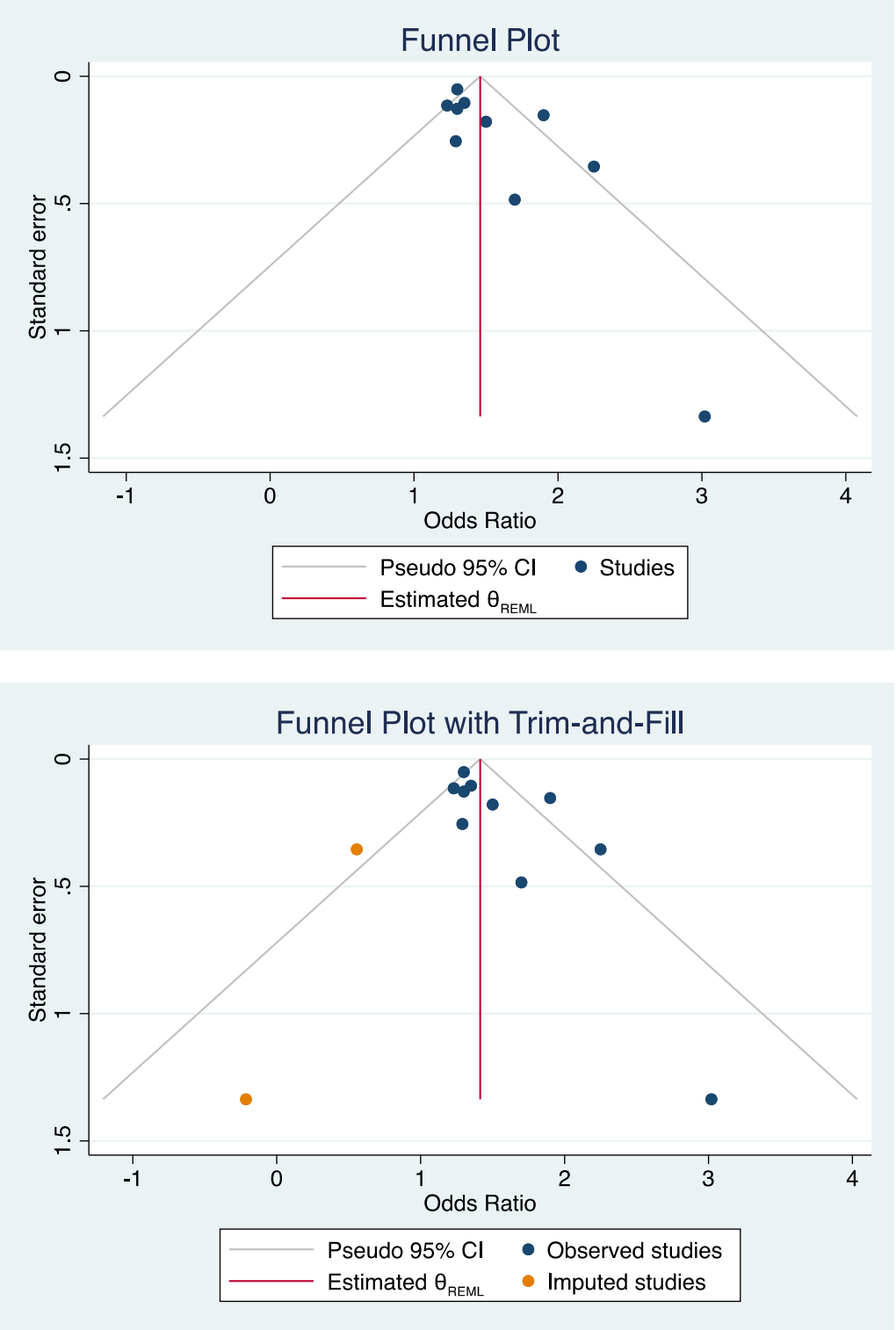

Figure 3. Funnel Plot (Top) and Funnel Plot with Trim-and-Fill (Bottom) of Meta-Analysis of ACE Scores and Adult Obesity.

identified biological manifestations of early life abuse include: 1) increased inflammation 2) increased HPA axis reactivity 3) sleep disturbances and 4) suppression of the immune system [15]. All of these pathways and others have been identified as potential mediators (supplement B), which summarizes the range of mechanisms mentioned in the 18 studies meeting inclusion criteria. We attempt to synthesize this information rather than focus on individual studies, in order to propose directions for future research.

Functional MRI data on adolescents exposed to childhood trauma (n = 64) suggests that altered cortico-limbic circuitry may in part explain the association between trauma, emotional disturbances, and risky health behavior [60]. PTSD manifests in systemic inflammation which is known to increase risk for comorbid obesity [61]. A recent systematic review and meta-analysis found a positive dose-response association between child abuse (not limited to ACE) and adult obesity, suggesting that an elevated inflammatory response to stress increases

craving for palatable foods and decreases executive functioning [62]. Any change in stress neurobiology is likely to influence reward. Based on observed deficits in the ventral striatum, reward responsiveness and processing may be a primary mediator of the effects of early life adversity [63]. Increased density of striatal dopamine active transporter (DAT) has been shown in PTSD, which may reflect higher DA turnover [64]. Anhedonia is an important diagnostic feature of PTSD which may result from deficits in reward functioning [65]. Several DA genes including receptors and transporters have been associated with traumatic stress [66]. Animal models of comorbid PTSD and addiction reveal distinct changes in the hippocampus, mPFC, and amygdala [67]. At the simplest level, PTSD symptoms are likely to increase the risk for obesity through negative impact on health behaviors.

4.4. Eating Disorders and Psychiatric Disorders

Childhood adversities are strongly associated with psychiatric symptoms in US adolescents [68] and throughout their lifespan [69]. A recent study of older adults (ages 65+ n = 5,806) has shown that having experienced any ACEs was associated with higher adjusted odds of having a past-year psychiatric disorder (OR = 2.11 CI:1.74-2.56) [70]. For this reason, a wide range of mental health conditions, including EDs, may mediate ACEs and obesity. The most common EDs are characterized by binge eating, e.g. BED and bulimia nervosa (BN), which have both been linked to FA, childhood maltreatment, weight gain, overweight/obesity, disinhibition-impulsivity, SUDs, attention deficit hyperactivity disorder, PTSD, obsessive-compulsive disorder, mood, and anxiety disorders [71–82]. On the other hand, anorexia nervosa (AN), especially the restricting subtype (AN-R), has typically been associated with underweight as well as histories of child maltreatment [76,79,83]. Loss-of-control eating can lead to dieting behavior, particularly among women, when noticing or fearing weight increases, or possibly as a result of trying to regain a sense of control over their lives [84]. Restrictive EDs or subclinical dieters may maintain normal or low BMIs, which likely confounds the estimate between ACEs and BMI. Future research linking ACEs to obesity should consider pathways to various EDs.

4.5. Practice Implications

Based on our qualitative synthesis of the available evidence, we propose that FA is a less-known yet biologically plausible explanation for the relationship between ACEs and adult obesity. Currently FA is not recognized in the DSM-5 therefore many individuals with trauma histories and loss-of-control eating patterns are not able to access nutritional support. There is no accepted standard of treatment for FA and considerable controversy remains. Meanwhile, ACE scores and trauma history may help design interventions with respect to nutrition and other recovery-related goals. Efforts to reduce obesity and disordered eating will require integrated biopsychosocial approaches that include mental health professionals (i.e. psychiatrists, therapists), registered dietitian nutritionists, health coaches, and other forms of social support. These professionals and peer specialists must “be on the same page” about underlying drivers of dysfunction and any personalized treatment strategies. Importantly, reducing weight stigma in society is likely to improve health outcomes. Awareness of the FA construct has important implications for society, challenging the common assumption that all eating behavior is simply a “choice” but rather for some individuals a consequence of chronic exposure to highly palatable foods and biologically-based coping mechanism for trauma.

Trauma-informed ED treatment should consider the biological embedding of adversity, susceptibility to reward-based eating, and the associated neural adaptations that stem from chronic exposure to highly palatable foods. Given how difficult it is for people to change their eating habits in the Western food environment, investing public health resources into trauma treatment appears wise. Early trauma-informed screening and care may not only reduce obesity, but may also reduce substance and eating disorders, as well many other psychiatric conditions. Understanding pathways from childhood trauma to adult obesity should be an important public health priority, as it will help identify important vulnerability factors in order to guide prevention and intervention strategies. Ultimately, targeting the food environment through public health interventions may be more effective than individual treatments.

5. Conclusions

5.1. Limitations

The current investigation only examined cross-sectional studies which cannot infer causation. Different adjustments across models was not accounted for, therefore residual confounding by other unmeasured factors is likely. We did not differentiate between forms of mental health (mostly depression) due to the limited number of studies in our review. Our qualitative analysis did not investigate the role of sleep as a mediator but rather included it as a health behavior. Our qualitative analysis did not attempt to investigate gender differences that have emerged in prior ACE research [34,42]. Given that adults are being asked about experiences from their childhood, ACE scores are subject to recall bias [85]. There also appears to be no consensus as to what constitutes an ACE, as several studies have modified the original scale to best fit their sample under study. Other measures of adverse experiences at the community (racism, violence, bullying, and foster care) [86] and family levels (death of a parent and socioeconomic hardship) [87,88] were not included in our analysis. Most of the studies (nine out of ten in meta-analysis) used self-reported obesity based on BMI measures which are often under-reported [89]. Some studies describing a statistical association between ACE and obesity were not included in the meta-analysis due to the use of analytic methods other than logistic regression (e.g. ordinal logistic regression, linear regression). Finally, we did not consider non-English studies due to our emphasis on qualitative assessment.

5.2. Future Research

Our systematic review and meta-analysis have suggested that many unmeasured confounders between ACE and obesity likely exist. We have proposed that FA is a potential mediator, but to date this has only been shown in one study [25] therefore more research is needed. Statistical mediation analyses should control for ED severity. Future research on DNA methylation following unfavorable life experiences may provide additional insight related to obesity outcomes. Changes in gut microbiome is an emerging correlate of early life stress [90] and is a plausible pathway to obesity, as well as cross-associated with epigenetic modification [91]. Future research should investigate specifically which other psychiatric disorders (post-traumatic stress, substance, mood, anxiety) confound the relationship between ACEs and obesity. Additionally, psychiatric medications are frequently associated with weight gain [92,93] therefore should be considered in future efforts to make unbiased estimates of mental health conditions driving BMI changes. Finally, if FA does link ACEs to adult obesity, interventions at the individual (counseling), group (psychoeducation), and community (reducing ACEs) levels should be tested. From a public health standpoint, policy interventions aimed at the food industry to prevent marketing of addictive food to children may be critical to reverse obesity trends and should be implemented [94,95].

5.3. Summary

In ten cross-sectional studies pooled for meta-analysis (n = 118,691) we have identified a 46% increase in odds of adult obesity following exposure to multiple ACEs (95% CI 28-64%) with moderate

heterogeneity present ($I^2 = 70.8\%$). As hypothesized, heterogeneity was less than previous meta-analysis that combined multiple study designs and/or measures of adversity. Odds of obesity increase as the number of ACEs increase. However, the gradient is not significant ($p = 0.08$) (see supplement D). Sensitivity analysis revealed that no single study significantly impacted the overall estimated effect size. These findings are robust and consistent with previous estimates. What this study adds is an in-depth exploration of mediating mechanisms that cross-associate over the lifespan. We have identified that several unmeasured confounders likely exist. Based on the evidence that is currently available, childhood adversity can become biologically embedded in ways that increase susceptibility to substance-related disorders and predispose individuals to overeating. The potential pathway to FA may be an important and modifiable mechanism connecting childhood adversity to obesity over the life course.

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Supplementary materials

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