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The maltreated eco-phenotype of eating disorders: a new diagnostic specifier? A systematic review of the evidence and comprehensive description

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Abstract

This systematic review aimed to summarize the evidence on the existence of a distinct phenotypic expression of Eating Disorders (EDs) associated with childhood maltreatment (CM), the so-called maltreated eco-phenotype of EDs. PRISMA standards were followed. Articles providing data about the characteristics of individuals with an ED reporting CM were included. Relevant results were extracted and summarized. A quality assessment was performed. A total of 1207 records were identified and screened, and 97 articles published between 1994 and 2023 were included. Findings revealed distinct biological and clinical features in patients with EDs reporting CM, including neuroanatomical changes, altered stress responses, ghrelin levels, inflammation markers, and gut microbiota composition. Clinically, CM correlated with severer eating behaviors, higher psychiatric comorbidity, impulsivity, emotional dysregulation, and risky behaviors. Additionally, CM was associated with poorer treatment outcomes, especially in general psychopathology and psychiatric comorbidities. This review highlighted the need to move towards an etiologically informed nosography, recognizing CM not merely as a risk factor, but also as an etiologic agent shaping different eco-phenotypic variants of EDs.

Keywords

Eating disorders, anorexia nervosa, bulimia nervosa, binge-eating disorder, childhood maltreatment, early

trauma, childhood abuse, maltreated eco-phenotype, systematic review, diagnostic specifier

1. Introduction

The concept of disease eco-phenotype encompasses the manifestation of pathologies beyond the immediate physical level to incorporate a constellation of factors, including socio-cultural dynamics, personal experiences, and traumatic events such as childhood maltreatment (CM) [1]. This theoretical framework facilitates a deepened understanding of the interplay between genetic predisposition and the unique set of experiences of the individual in the development and course of disorders. Thus, it allows the differentiation of clinical manifestations of diseases based on developmental trajectories, with implications in terms of personalized and targeted treatments. In the field of psychiatry, a particular focus has been posed on the role of CM in modifying the phenotypic presentation of mental illnesses [2,3].

CM is remarkably widespread, with a prevalence around 15% within the general population and exceeding 50% among patients with psychiatric disorders [4]. Historically, research predominantly emphasized sexual and physical abuse as risk factors for psychopathology. However, literature has progressively broadened its perspective on CM, with a growing emphasis on the profound impact of emotional abuse and neglect [2]. Accordingly, the World Health Organization (WHO) provided a comprehensive definition of CM, emphasizing the betrayal of a child by an individual in a position of responsibility, trust, or power as a core aspect of CM: *"Child maltreatment comprises abuse and neglect that occurs to children under 18 years of age. It includes all types of physical and/or emotional ill-treatment, sexual abuse, neglect, negligence as well as commercial or other forms of exploitation, all of which result in actual or potential harm to the child's health, development or dignity within the context of relationships of responsibility, trust, or power."* [5]. Extensive research over the years elucidated the role of all forms of CM as transdiagnostic risk factors for psychopathology given their influence on the developmental trajectory of individuals, encompassing biological, emotional processing, and self-concept dimensions [6–9]. Moving from the observation that CM not only increases the likelihood of developing psychopathology, but also activates molecular, neuroanatomical, and psychological modifications that distinguish maltreated and non-maltreated individuals, numerous studies provided descriptions of the distinct characteristics exhibited by patients with various mental disorders when a history of childhood trauma is present [2,3]. Notably, Teicher et al. (2013) extensively described the maltreated eco-phenotypes of mood, anxiety, and substance abuse disorders, highlighting key features such as earlier age at onset, heightened symptom severity, more pernicious disease course, increased risk of suicide, compromised quality of life, and higher prevalence of psychiatric comorbidities compared to individuals with the same diagnoses but no history of CM [3]. Moreover, neurobiological findings revealed specific alterations associated with CM, including reduced hippocampal volume, heightened amygdala reactivity, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, and changes in inflammatory markers [3]. An increasing number of studies showed similar findings within the scope of other psychiatric disorders, including personality disorders and psychoses [2,10,11]. This led to a proposed necessity to modify the current diagnostic nosology, preferably incorporating specifiers to refer to the CM-associated eco-phenotype of mental illnesses [2].

Eating disorders (EDs) - encompassing Anorexia Nervosa (AN), Bulimia Nervosa (BN), Binge Eating Disorder (BED), and Other Specified Feeding or Eating Disorders (OSFED) - are among the psychiatric illnesses most strongly associated with the presence of childhood trauma, with prevalence rates reaching up to 59% [12]. The current nosology describes these disorders as having a common psychopathological core characterized by an overemphasis on the importance of body shape and weight in determining one's self-esteem, and by pathological eating behaviors ranging from fasting, to binge eating, or purging [13,14]. Although the Diagnostic and Statistical Manual (DSM) of mental disorders acknowledges CM as a potential risk factor

for the development of EDs, neither the DSM nor the International Classification of Diseases currently recognize its potential influence on the phenotypic presentation of these disorders through specific codes or diagnostic specifiers [13,14]. Despite this, in recent years, the study of trauma as a possible phenotypic modifier of EDs gained increasing interest and a great number of studies have been published on this subject.

The main systematic reviews or meta-analysis of recent literature in this field have each focused on some specific aspects of the topic. In particular, the meta-analysis by Molendijk et al. (2017) elucidated to what extent CM affects some of the defining clinical features of EDs, including age at onset, prevalence of psychiatric comorbidities, suicidal behaviors, binge-purge behaviors, and disease severity [12]. Various reviews, on the other hand, focused on the possible psychopathological and/or biological mechanisms involved in the link between childhood trauma and the development/maintenance of EDs [15–19]. For what concerns the impact of CM on treatment outcome, Day et al. (2023) offered an in-depth analysis of how CM and the presence of Post-Traumatic Stress Disorder (PTSD) can alter responses to standard treatments [20], while Brewerton et al. (2019) and Mitchell et al. (2021) provided an overview of the importance of a trauma-informed care and practice for patients with EDs [21,22]. However, a systematic review of the literature is missing that provides a comprehensive description of the current knowledge about the specific characteristics of patients with EDs and a history of CM from an integrated psychopathological, clinical, biological, and treatment-informed perspective. Furthermore, in recent years, alongside the exponential growth of interest in this area, the development of statistical methodologies such as network analysis and structural equation modeling (SEM) allowed deepening the knowledge of the complex interactions between psychopathological variables involved in shaping disease phenotypes both cross-sectionally and longitudinally. However, there is currently no systematic review that is recent enough to provide an overview of studies that have adopted these innovative approaches.

Therefore, the objective of this study was to conduct an updated systematic review of the literature about the role of CM in modifying the phenotypic presentation of EDs from the multi-faceted perspective of biological, clinical, psychological, and pshycopathological correlates, longitudinal characteristics, and treatment outcomes to provide a summary of the evidence of the existence of a maltreated eco-phenotype of EDs and a comprehensive description of its defining features.

2. Methods

The present systematic review was conducted and reported following the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

2.1 Search strategy and selection criteria

Both the PubMed and ClinicalTrials.gov databases were searched for peer-reviewed articles on the topics of both EDs and CM. Additional field tags were embedded in the search string in order to exclude articles that were not written in English and reviews or meta-analyses. However, an initial search was performed without filtering out non-English language articles, in order to take note of the number of excluded articles based on language. For the ClinicalTrials.gov database, the search was limited to studies marked as "Completed" or "Terminated". The full search string is provided below.

(eating disorder OR anorexia nervosa OR bulimia nervosa OR binge eating disorder OR disordered eating) AND (childhood trauma OR childhood abuse OR childhood maltreatment OR early trauma OR early abuse OR early maltreatment OR maltreated ecophenotype OR traumatic ecophenotype OR maltreated subtype OR traumatic subtype OR complex ptsd OR complex post-traumatic stress disorder OR adverse childhood experiences OR maltreated OR adolescent trauma OR adolescent maltreatment OR adolescent sexual abuse OR adolescent emotional abuse OR adolescent physical abuse OR childhood neglect OR early neglect OR neglect) AND eng[la] NOT review[pt] NOT systematic review[pt] NOT meta-analysis[pt]

The final search was conducted on the 21st of July, 2023, and included all results from database inception. Studies were included according to the following inclusion criteria (screened in this order): published after January 1st 1994; written in English; provided data on human participants; provided original data; were not case reports or series; provided quantitative data; included patients with current clinical diagnoses of EDs according to DSM-IV (or later editions) or ICD-10 (or later editions) [24,25]; assessed CM using validated instruments or clinical interviews following acceptable definitions of CM; provided data or analyses related to individuals suffering from an ED describing specific characteristics associated with CM. In cases where a study included aggregated samples (e.g., patients with a current ED diagnosis together with recovered patients, or patients with CM together with individuals who reported adverse experiences in adulthood), it was included only if it reported results on the subgroups of interest for the current systematic review, or alternatively, it was excluded. Articles were excluded if they were found to be duplicate reports of previously published studies.

2.2 Study selection, data extraction and quality assessment

Any articles published before 1994 were excluded from the retrieved records. Titles and abstracts were screened independently by CD and GM. After the first screening phase, full reports of included records were retrieved and further assessed for eligibility by CD and GM. Finally, CD, and GM conducted data extraction on eligible reports, retrieving the following information: country where patient recruitment took place, study design, diagnostic criteria used for assessing ED, sample size for each diagnostic subgroup (only for the samples where the analyses of interest were conducted), participants' gender, age range (underage, adults, or mixed sample), instrument used for assessing CM, and results relevant to the topic of the review. A result was considered relevant when it described the characteristics of patients with EDs that were specific to the subgroup of individuals reporting CM, as opposed to those without a history of CM (e.g., comparisons between patients with and without CM, or associations between levels of exposure to CM and another measure). Since the validity of negative results in scientific literature is considered to be quite low in the absence of an appropriate discussion on the achieved statistical power, and given that the latter is rarely reported, especially in observational studies [26], negative results were extracted and reported only if they represented one of the main outcomes, for which the study was powered.

The methodological quality assessment of cross-sectional studies was conducted by CD and GM, using the Newcastle-Ottawa Scale (NOS) adaptation for cross-sectional studies [27]. The same instrument was used for longitudinal studies, with the two additional items from the original NOS related to prospective evaluations (i.e., adequate follow-up duration and presence of attrition bias).

In cases of disagreement among reviewers at any phase of the review process, the full-text report was retrieved and independently assessed by expert reviewers ER and EC, with discussions held until a consensus was reached. A consensus was reached for all studies. Furthermore, a random subset comprising 30% of the full-text reports was independently reviewed by ER and EC to ensure the quality of the process and data.

2.3 Narrative synthesis

Given the inherent heterogeneity of the data, a narrative synthesis approach was chosen to summarize and analyze the findings [28]. The synthesis process involved identifying emerging themes within the included studies, which were grouped according to shared characteristics of the main findings. These groupings allowed for the organization of the narrative synthesis. Overall, three main types of findings related to the maltreated eco-phenotype were searched:

1. Biological correlates: results that describe differences in terms of organ anatomy and function, including endocrinological, neurobiological and immunological features.
2. Clinical, psychological, and psychopathological correlates: findings showing different ED characteristics, in terms of etiopathogenetic, diagnostic, psychopathological and behavioral features.
3. Longitudinal characteristics and treatment outcomes: results from studies that highlight a distinct disease trajectory following the diagnosis of ED, in terms of varying prognosis and response to the different treatments offered.

For each main theme, a coherent and comprehensive account of all key findings from each study was summarized and reported.

3. Results

The complete flow diagram of the study selection process is reported in Figure 1. The initial search identified a total of 1207 records, of which 1053 were screened and 97 were finally included in the review. The characteristics and main findings of the included studies are reported in Supplementary Table 1, 2, and 3. Two reports referred to the same sample, therefore they were summarized together [29,30]. Most of the selected studies were conducted in Europe (n_{Italy} = 38, n_{France} = 4, n_{Spain} = 4, $n_{Germany}$ = 3, $n_{Belgium}$ = 1, $n_{Denmark}$ = 1, n_{Norway} = 1, n_{Poland} = 1, $n_{Portugal}$ = 1), while the remaining were conducted in the United States (n = 14), Canada (n = 12), the United Kingdom (n = 12), Israel (n = 3), Japan (n = 1) and South Korea (n = 1) (Supplementary Table 1, 2, and 3). Regarding the study design, the vast majority of included reports were cross-sectional in nature (n = 81, including one with a retrospective chart review methodology), whereas 15 were longitudinal (of which 2 were retrospective) and 1 was a randomized controlled trial (RCT) (Supplementary Table 1, 2 and 3). More than half of the included studies used the DSM-IV criteria for diagnosing EDs (n = 54), while 38 studies used the DSM-5 criteria, and 5 studies used the ICD-10 criteria (Supplementary Table 1, 2, and 3).

In terms of methodological quality, the median score for cross-sectional studies was 7, with an interquartile range of 7 to 8, out of a possible maximum of 10. For longitudinal studies, the median score was 10, with an interquartile range of 9 to 11, out of a maximum of 12. These scores suggest that, despite the inherent limitations of observational studies, the overall quality was commendable. Most studies demonstrated acceptable sample sizes and response rates, utilized validated instruments for the assessment of CM, and, in the case of longitudinal studies, ensured adequate follow-up durations and minimized the risk of attrition bias.

3.1 The maltreated eco-phenotype of EDs: biological correlates

3.1.1 Neuroanatomy

Neuroimaging studies performed in patients with AN and BN showed preliminary evidence of specific modifications induced by CM at a neuroanatomical level [31–34]. Maltreated patients exhibited reduced ***gray matter*** volume in the right paracentral lobule and left inferior temporal gyrus, reduced ***white matter*** integrity in corpus callosum, internal capsule, posterior thalamic radiation, longitudinal fasciculus, and corona radiata as compared to non-maltreated counterparts [34]. A negative correlation between gray and white matter changes and the levels of emotional and physical neglect was observed [34]. Furthermore, maltreated patients showed lower ***cortical thickness*** values in the left superior frontal, right caudal middle frontal, and right superior parietal gyri [31] and significantly lower local ***gyrification index*** in the left middle temporal gyrus [32]. Finally, Molina-Ruiz et al. (2023) showed that volumes of the putamen (both hemispheres) were negatively correlated with self-reported early traumatization scores in combined analysis of ED and control subjects, although the result did not reach statistical significance in each diagnostic subgroup [33].

3.1.2 Endogenous stress response system

Several studies showed that early trauma impacts the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system activity in patients with AN and/or BN [35–43]. Patients with CM had lower ***24-h urinary free cortisol levels*** [38], lower morning ***plasmatic cortisol levels*** [37] and lower ***saliva cortisol awakening response (CAR)*** [39,40,42] than non-maltreated patients, with a significant negative correlation between the number of traumas and CAR [42]. As a further demonstration of dampened basal activity of the endogenous stress response system in patients with EDs reporting early trauma, Monteleone et al. 2020 showed that maltreated patients had decreased morning secretion of ***salivary alpha-amylase*** [40], a marker of the sympathetic nervous system activity. Furthermore, Diaz-Marsa et al. (2007) showed that in patients with AN-bp and BN cortisol suppression after the administration of 0.25 mg dexamethasone was significantly correlated with the presence of childhood traumatic events [36], suggesting the presence of an increased sensitization of the hypothalamic-pituitary glucocorticoid receptors in this group. In contrast with these results, the study

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performed by Castellini et al. (2012) did not show a direct effect of childhood abuse (sexual or physical) on plasmatic cortisol levels [35]. However, it underlined a positive association between plasmatic cortisol levels and sexual desire in physically or sexually abused patients, suggesting that these women would experience an automatic fear response determining significant increase in cortisol levels when perceiving sexual desire. For what concerns the effect of psychotherapy in terms of modifying cortisol levels, Lelli et al. (2019) showed that hypocortisolism persisted after CBT-E in patients with AN and BN reporting CM [37].

Two studies evaluated the biological and emotional response to psychosocial stress exposure (Trier Social Stress Test – TSST) of maltreated patients with EDs as compared to those without CM [41,43]. Contrasting results were found in patients with AN. Indeed, one study showed that maltreated women exhibited a blunted cortisol response and reduced anxiety increase after TSST as compared to non-maltreated patients [43], whereas another one did not confirm this result [41]. In particular, the latter study showed that both maltreated patients with AN and BN had heightened emotional reactivity, lower levels of hunger and more severe body dissatisfaction after TSST. Furthermore, higher cortisol production was observed in patients with AN, regardless of the presence of CM, and in patients with BN and emotional CM. Emotional and not physical CM was the most significant determinant of the experimental differences observed in this study.

3.1.3 Inflammation markers and ghrelin

Early trauma was also demonstrated to impact on inflammation markers [44,45] and ghrelin [46]. In particular, Bou Khalil et al. (2022) showed that maltreated patients with AN had a higher *neutrophil-to-lymphocyte ratio* [44], whereas Rodrìguez-Quiroga et al. (2021) demonstrated that CM was associated with higher levels of *tumor necrosis factor-alpha (TNF-α)* in a mixed sample of patients with EDs [45]. Furthermore, Rossi et al. (2021) showed in a mixed sample of patients with EDs including AN, BN, and BED, that those reporting CM had higher *ghrelin* levels, and early traumatic experiences moderated the association between ghrelin and overeating-related pathological behaviors [46]. The association between childhood sexual abuse and binge eating was mediated by elevated ghrelin, suggesting a possible involvement of this orexigenic molecule in maintaining pathological overeating-related behaviors in traumatized patients.

3.1.4 Microbiota-gut-brain axis

Only one study is available regarding the impact of CM on microbiota-gut-brain axis [47], showing that CM predicted lower *fecal levels of propionic and butyric acid* and higher levels of trait anxiety in a mixed sample of individuals with AN, BN and BED. A serial mediation model showed an indirect effect of CM on higher ED-specific psychopathology through the mediation of impaired levels of butyric acid, which in turn determined increased anxiety. PERMANOVA analysis showed that patients in the cluster characterized by CM, increased anxiety, binge eating behaviors, and reduced butyric acid showed different *microbiome composition*.

3.1.5 Genetics, monoaminergic, and glucocorticoid systems

Several studies evaluated the interactions between CM and genetic factors in determining neurobiological abnormalities and behavioral tendencies in patients with EDs [48–52]. Patients who were carriers of the low-function allele of the dopamine D2 receptor (DRD2) Taq1A polymorphism showed higher rates of sensation seeking, only in the presence of a history of childhood sexual abuse [49]. However, in patients with a bulimia-spectrum disorder, no significant difference was found between those with early trauma (sexual or physical) and those without it in terms of DRD2 gene promoter methylation [48]. On the other side, with a classification based on a biallelic model of serotonin transporter promoter region (5-HTTLPR) polymorphism, multiple regression analyses indicated significant proportions of variance in stimulus seeking and insecure attachment to be explained by abuse × genotype interaction effects, with greater psychopathology always occurring in S-allele carriers who had been abused [50]. Furthermore, patients who were carriers of the S-allele showed higher levels of dissocial behavior, only in the presence of CM [51]. Furthermore, the presence of early sexual abuse

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was associated with reduced serotonin transporter density on platelets [53]. No effects related to childhood abuse were observed regarding methylation of the glucocorticoid receptor gene (NR3C1) promoter [52].

3.2 The maltreated eco-phenotype of EDs: clinical, psychological, and psychopathological correlates

3.2.1 ED-symptoms

Castellini et al. (2018) and Lelli et al. (2019) found that patients with AN or BN and a history of childhood abuse had a lower *age at disease onset* [37,54]. Furthermore, according to Castellini et al. (2018) abused patients had a *history of overweight during childhood* more frequently [54].

Several studies underlined that patients with *bingeing/purging subtypes of EDs*, namely AN-bp or BN, reported CM more frequently than those with AN-r [36,55–62]. Furthermore, among patients with AN-r, a higher rate of sexual abuse was observed when a previous history of BN was reported [63].

An association between CM and greater severity of *pathological eating behaviors* was observed, specifically binge-eating [54,62,64–66], purging [54,60,62,64–67], and restricting behaviors [60]. Furthermore, among patients with BN or BED, night eating syndrome with binge eating was significantly associated with the presence of higher levels of physical neglect [68].

Most of the studies underlined significant associations across the different ED diagnoses between childhood trauma exposure and increased severity of various dimensions of *ED-specific psychopathology* including drive for thinness and/or shape, weight, and eating concerns [38,41,56,62,66,68–75]. In particular, Guillaume et al. (2016) underlined an association between the number of traumas experienced and an increased severity of ED symptoms [70], whereas Meneguzzo et al. (2021) reported a more severe clinical impact in case of repetition of adulthood trauma exposure after childhood abuse [72]. Aligning with these results, according to Pugh et al. (2018) the relative power of the ED "voice" was related to childhood emotional abuse, partly through the mediation of dissociation [76]. However, some studies did not confirm these results and showed no significant differences between patients with AN or BN reporting childhood sexual and/or physical abuse or not in terms of severity of ED psychopathology [37,54,77,78].

Furthermore, an association between the presence of early traumatic experiences and *negative body image/body dissatisfaction was observed* [41,67,71,79]. In particular, Sweetingham et al. (2008) showed that having been teased about appearance by peers and having been verbally bullied by family members were both associated with higher body dissatisfaction, and shame mediated the relationship between these variables [80].

3.2.2 Psychiatric comorbidities, psychosocial functioning, and quality of life

CM was associated with greater *general psychopathology* [38,54,56,68,72,79], worse *psychosocial functioning* [70,72] and poorer *quality of life* [72,81]. In particular, Guillaume et al. (2016) underlined a crude dose-effect between the number of traumas experienced and an increased severity of daily functioning impairment [70].

For what concerns psychiatric comorbidities, CM predicted an increased likelihood of *mood disorders* [66] including depression [38,56,59,65,68,69,71,82] and bipolar disorder type II [54]. Leraas et al. (2018) through a latent profile analysis showed that CM was associated with a "stable depressed" profile of patients with BN characterized by low affective lability and high affect intensity [83]. Furthermore, CM was associated with increased *obsessive-compulsive symptoms* [54,56,71,84], *anger/hostility* [66,85], and *anxiety* [38,47,56,66,67,82]. In particular, Stein et al. (2013) underlined that childhood sexual abuse was associated with increased fear of life [86]. Moreover, patients with CM reported increased *post-traumatic stress symptoms* [67,72,87–90]. Specifically, several studies underlined an association between CM and *dissociation* [54,59,65,79,91,92], including somatoform dissociation [91] and depersonalization [54]. Finally, Dalgleish et al. (2003) showed that self-reported parental abuse predicted a tendency to produce over general memories when exposed to negative emotional cues [93].

For what concerns the area of ***personality disorders***, an association was observed between a history of CM and comorbid borderline personality disorder psychopathology in patients with AN or BN [50,66,94], particularly in the presence of polytrauma [95]. Moreover, Rodríguez-Quiroga 2021 showed that a history of CM was associated with higher delirious, narcissistic, and paranoid personality traits in a mixed sample of patients with EDs [45]. Finally, Grilo & Masheb (2002) showed that in a sample of patients with BED, among the different types of CM only emotional abuse predicted the presence of a personality disorder [96]. In particular, patients with cluster C personality disorders, especially avoidant personality disorder, were significantly more likely to have clinically meaningful levels of emotional abuse [96].

3.2.3 Impulsivity, emotional dysregulation, and interoceptive awareness

The presence of any childhood trauma predicted greater ***impulsivity*** and impulsive behaviors [35,41,50,54,71,73,85,97–100]. Furthermore, increasing evidence showed a significant association between CM and ***emotional dysregulation*** [74,85,100,101]. In particular, Racine et al. 2015 showed that of the three forms of childhood abuse (physical, sexual and emotional), emotional abuse was the most strongly related to emotion dysregulation in patients with AN, both in restricting and binge-eating/purging subtypes [74]. Moreover, Monteleone et al. (2021) provided an experimental evidence of the heightened emotional reactivity of patients reporting CM when exposed to social stress throught the adoption of the TSST [41]. Finally, a severer deficit in ***interoceptive awareness***, an indirect measure of emotion regulation, was underlined among patients reporting CM [41,71,73].

3.2.4 Self-harm behaviors, suicidality, and substance abuse

Several studies underlined an association between CM and higher rates of ***non-suicidal self-injury (NSSI)*** in patients with AN, BN or BED [29,30,66,78,79,90,92,97,102–108]. In particular, Favaro & Santonastaso (2000) underlined that impulsive self-injury in patients with AN was predicted by childhood sexual abuse and anxiety, in contrast with compulsive self-injury which was predicted by obsessionality and age [107]. Furthermore, many studies found that patients with AN and/or BN with a history of CM showed a higher risk of ***suicidal ideation and suicidal attempts*** [30,78,92,103,108–112]

For what concerns ***alcohol and substance abuse***, many studies underlined an association between these risky behaviors and CM in samples of patients with different kinds of EDs, including AN, BN and BED [54,82,97,100,102].

3.2.5 Sexuality

The relationship between CM and sexuality has been investigated both in terms of sexual dysfunctions (e.g. problems in sexual desire, arousal, orgasm, and satisfaction) and of dysregulated sexuality/hypersexuality. Although CM did not show a direct effect in determining severer sexual dysfunctions before treatment in patients with AN or BN [35,113], a paradoxical association between sexual desire and increased hematic cortisol levels was observed in patients sexually or physically abused, suggesting that in this population sexual activity might elicit an automatic fear response (see also 3.2.2) [35]. Furthermore, patients with AN or BN reporting childhood sexual abuse did not show a significant improvement in sexual functioning after treatment [114]. For what concerns the issue of hypersexual behaviors, Castellini et al. (2020) showed that childhood trauma was associated with ***dysregulated sexuality*** [115]. In particular, in the subgroup of traumatized patients hypersexuality was associated with emotion dysregulation and psychopathology. Finally, Walsh et al. (2000) demonstrated that patients with both AN and history of sexual abuse had higher response times for sexual maturation words than for control-related words, and greater cognitive interference from sexual maturation words than the non-abused patients with AN [116].

3.2.6 Psychological constructs

Several psychological constructs were associated with childhood trauma exposure. In particular, feelings of ineffectiveness [34,41,43,67,69,71,73], social insecurity [34,41,43], perfectionism [71,73], asceticism [41,73], the presence of a

more external locus of control [117], self-criticism [61], low self-esteem [56,68,79], interpersonal problems [56,98], interpersonal distrust [41], negative self-directed style and self- discrepancy (i.e., the difference between one's actual self and who one believes they ought to be) [118], early maladaptive schemas (e.g. disconnection and rejection) [72] and core beliefs of abandonment, functional dependency, defectiveness/shame, emotional deprivation or inhibition, failure to achieve, mistrust/abuse, social isolation, unrelenting standards, and vulnerability to harm [65].

3.2.7 Complex relationships between psychopathological dimensions

Rodgers et al. (2019) through a Bayesian network approach showed that symptoms importance and **network structure of ED psychopathology** differed between individuals with various ED diagnosis with and without a history of CM [119]. Specifically, in patients with CM a 4-symptom pathway emerged, leading from overvaluation of weight and shape, and ending in overeating, through the mediation of loss of control and depressed mood, which emerged as the more important driving symptoms. On the other side, the ED symptom network in patients without CM was organized around the overinvestment in weight and shape and the resulting efforts to control or alter these aspects through dieting and excessive exercise. In the latter group, the driving symptoms were overeating and overvaluation of weight and shape.

The network analysis approach identified the core role of **emotional abuse** among the different kinds of CM in the phenomenology of EDs. In particular, two network analysis studies underlined that all types of CM were connected to psychopathology through the mediation of emotional abuse in samples of patients with AN-restriciting type or with binge-purging symptoms (i.e., with AN purging type or BN) [120], and with BN or BED [121]. Interoceptive awareness was involved in the associations between emotional abuse and ED-core symptoms in all the diagnostic groups [120,121] and a pivotal role in this association was also played by ineffectiveness in the binge-purge group [120,121] and by impulsivity in patients with BED [121]. Aligning with these results, a network analysis study performed in underaged patients with AN, BN, or OSFED showed that the links between physical and sexual abuse, psychopathology, and life satisfaction took place through the emotional abuse node [81]. Furthermore, emotional neglect was connected to life satisfaction both directly and via emotional abuse, feeling disliked by others, and feelings of inferiority and worthlessness before treatment [81].

In terms of possible **mediators between CM and ED-specific psychopathology**, many other psychopathological and psychological variables were demonstrated to be involved in patients with different ED diagnosis through mediation analysis, path analysis, or structural equation models, and included emotion dysregulation [74], attachment anxiety and avoidance [75], feelings of ineffectiveness [69], affective instability [69], depression [71], early maladaptive schemas (e.g. disconnection and rejection) [72], and negative core beliefs [65]. In particular, Waller et al. (2001) showed that depression mediated the association between childhood sexual abuse, core beliefs of abandonment and mistrust/abuse and frequency of bingeing, whereas both dissociation and depression mediated the association between core beliefs of defectiveness/shame and frequency of vomiting [65].

Several studies were performed evaluating the **mediators between CM and psychiatric comorbidities/risky behaviors** in patients with EDs. In particular, path analysis showed that emotion dysregulation and impulsivity mediated the relationship between CM and the presence of problematic alcohol/drug use in patients with BN [100]. In terms of predicting NSSI, structural equation modeling analyses showed that the latent variable related to childhood abuse was associated to NSSI through the latent variables related to general psychopathology and low self-esteem, which in turn predicted dissociative symptoms and body dissatisfaction, respectively (Muehlenkamp 2011). Furthermore, simple mediation analysis in the context of path analysis in a mixed sample of patients with EDs indicated that childhood sexual abuse was associated with the presence of two or more stressful life events in the 12 months preceding the first ED symptoms, which in turn were associated with the presence of non-suicidal self-injury [30]. Furthemore, childhood physical abuse had an indirect effect on non-suicidal self-injury through higher levels of negative self-evaluation, substance use and suicide

attempts [30]. Finally, Dodd et al. (2022) showed that among women with BN childhood trauma indirectly predicted NSSI through atypical cognitions such as odd thinking, unusual perceptual experiences, and quasi-psychotic thinking.

3.3 The maltreated eco-phenotype of EDs: longitudinal characteristics and treatment outcomes

Several studies investigated whether a history of CM was associated with a distinct longitudinal outcome (e.g. drop-out, diagnostic cross-over, hospitalization), and different response to treatment, according to different therapeutic approaches.

First of all, CM was associated with increased likelihood of **drop-out** in patients with AN or BN, both in patients treated with CBT [54,122,123] or interpersonal psychotherapy approaches [122,123]. In particular, Castellini et al. (2018) showed that subjects with both childhood abuse and neglect had the greatest probability of drop-out [54]. Furthermore, Carter at al. (2006) evaluated the impact of CM on treatment outcome of an intensive group therapy in patients with AN and showed that patients with AN-bp and childhood sexual abuse terminated treatment earlier as compared to other patients [56]. However, an overall difference on the rate or timing of premature termination of treatment between patients reporting or not childhood sexual abuse was not observed [56].

Regarding the longitudinal trend of **ED symptoms**, several studies are available involving patients with AN or BN treated with CBT. In particular, Cassioli et al. (2022) showed that as the severity of CM increased, the longitudinal trend of ED-psychopathology worsened in patients with AN, and higher baseline levels of emotional dysregulation mediated this effect [101]. Accordingly, Lelli et al. (2019) showed that ED psychopathology did not improve after treatment in patients with BN reporting childhood sexual and/or physical abuse [37]. In contrast with these results, Calugi et al. (2018) showed that patients with AN reporting childhood sexual abuse similarly improved in terms of BMI and ED-specific psychopathology as compared to those not reporting it [77], and the same result regarding ED-psychopathology was found in sexually and/or physically abused patients with AN by Lelli et al. (2019) or with both AN or BN by Castellini et al. (2018) [37,54]. Moreover, Castellini et al. (2018) and Lelli et al. (2019) showed that traumatized and non-traumatized patients did not differ in terms of remission rates from the ED [37,54]. However, Castellini et al. (2018) showed that patients reporting childhood trauma underwent diagnostic cross-over and were hospitalized more frequently [54]. In terms of outcomes regarding various eating behaviors, Rienecke et al., 2022 showed that among patients with various ED diagnoses treated with individual and group psychotherapy including trauma specific interventions, those reporting higher adverse childhood experiences had higher binge eating scores at follow-up, but not purging or restrictive behaviors [60]. Concerning patients with BED, Hazzard et al. (2021) demonstrated that lifetime PTSD and childhood abuse were associated with higher binge-eating frequency at follow-up both in patients treated with Integrative Cognitive-Affective Therapy for BED and with CBT administered through guided self-help [89]. The association between childhood abuse and binge-eating frequency at follow-up was moderated by lifetime PTSD, such that childhood abuse was associated with higher binge-eating frequency only in the presence of a history of PTSD [89].

The negative impact of CM on the longitudinal trend of **general psychopathology and psychiatric comorbidities** was underlined by several studies adopting both CBT and psychodynamic approaches. In particular, for what concerns CBT, Lelli et al. (2019) and Castellini et al. (2018) showed that patients with AN or BN reporting CM did not improve in terms of general psychopathology at follow-up [37,54]. Furthermore, Castellini et al. (2018) showed that at follow-up patients with childhood abuse reported greater rates of use of antidepressants and had higher levels of psychiatric comorbidity, specifically a mood disorder comorbidity or obsessive-compulsive disorder [54]. In studies of psychodynamic therapy, Strangio et al. (2019) showed that in a mixed sample of patients with various ED diagnosis, those with a history of CM reported a significant decrease only in psychoticism, whereas those not reporting CM had a significant decrease in somatization, obsessive–compulsive symptoms, general psychopathology, phobic anxiety, interoceptive deficits, and

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dissociation [85]. In contrast with these results, Calugi et al. (2018) showed that patients with AN and a history of sexual abuse similarly improved after intensive CBT-E in terms of work, social functioning and general psychopathology as compared to those without a history of childhood sexual abuse [77].

Finally, patients with AN and BN and a history of CM treated with CBT did not improve in terms of ***hypocortisolemia*** [37], nor in ***sexual functioning***, unlike those without CM [114]. Moreover, Castellini et al. (2020) evaluated the impact of CM on the longitudinal trajectory of ***amenorrhea*** in patients with AN treated with CBT-E, and time-to-event analysis demonstrated that a history of CM predicted an earlier resumption of menses [124].

For what concerns the ***mediators of treatment response*** in traumatized patients, Kopland et al. (2023) demonstrated in a sample of patients with AN, BN or OSFED treated with compassion-focused therapy that improvements in ED psychopathology were predictive of enhancements in self-compassion, but only when CM levels were low. Conversely, in the presence of higher CM levels, an inverse relationship between these variables was observed and the reduction in ED symptoms was predicted by improvements in self-compassion [125]. Furthermore, Cassioli et al. (2022) demonstrated the pivotal role of emotional dysregulation in the maintenance of higher levels of ED psychopathology in patients treated with CBT-E in the presence of early trauma [101]. Finally, Monteleone et al. (2023) evaluated the ***modification of the relationship between variables after treatment*** through the comparison of the network structure of psychopathology before and after a CBT-oriented multimodal treatment in underaged patients with AN, BN or OSFED. This study showed that prior to treatment, emotional neglect was connected to life satisfaction both directly and via emotional abuse, feeling disliked by others, and feelings of inferiority and worthlessness (as previously mentioned, see paragraph 3.2.7). Following discharge, only the negative association between emotional neglect and excellent life conditions persisted [81].

4. Discussion

The present systematic review provided an accurate description of the evidence about the existence of a maltreated eco-phenotype of EDs and a comprehensive picture of its defining features from a biological, psychopathological, clinical, and treatment response perspective, which are graphically represented in Figure 2.

Regarding the biological correlates, the majority of available studies concerned neuroanatomical modifications and alterations in the endogenous stress response system. Specifically, neuroimaging studies revealed variations in both gray and white matter, along with reduced cortical thickness and a diminished gyrification index in specific brain regions among individuals with EDs and a history of childhood trauma (see Supplementary Table 1), supporting the hypothesis of the role of CM in influencing the course of brain development [9,126,127]. As for the endogenous stress response system, results seem to suggest that CM may determine a functional exhaustion of the HPA axis. Indeed, several studies showed lower urinary and plasmatic cortisol levels, and lower saliva CAR in individuals reporting CM (see Supplementary Table 1). Furthermore, Lelli et al. (2019) showed that these alterations persisted after treatment [37], matching with what was demonstrated in other populations regarding the long-lasting effects of early trauma on the HPA axis [128,129]. Moreover, the studies evaluating the emotional and biological reactivity to an experimental psychosocial stressor (TSST) showed that CM predicted a different emotional reactivity and a diverse response of the HPA axis in this type of context [41,43], aligning with the hypothesis that childhood traumatic experiences lead to increased interpersonal vulnerability and changes in threat-related social and emotional processing [7,8]. Although studies related to other biological correlates of CM in patients with EDs are few, the literature seemed to indicate an association with modifications in inflammation markers, ghrelin levels, fecal short chain fatty acids, and microbiome composition (see Supplementary Table 1), supporting the role of CM as a factor that impacts the entire organism, including the immune system and the gut-brain axis [130–132]. Moreover, CM has been shown to influence the expression of phenotypic characteristics associated with the presence of specific genes among patients with EDs (see Supplementary Table 1), including DRD2 and 5-HTTLPR, alinigning with the hypothesis of CM as an epigenetic modifier [8,133,134].

CM was also associated with specific clinical features, including an earlier age at onset, the bingeing/purging subtypes of EDs, and greater severity of pathological eating behaviors (see Supplementary Table 2). As for the psychopathological aspect, early trauma showed a clear impact on determining greater severity of general psychopathology, more psychiatric comorbidity, including personality disorders, worse psychosocial functioning and quality of life, higher levels of impulsivity, emotional dysregulation, deficits in interoceptive awareness, dysregulated sexuality, risky behaviors such as non-suicidal self-injury, suicidality, and alcohol and substance abuse (see Supplementary Table 2. Various studies have also highlighted that specific psychological constructs were more represented in patients with a history of CM, attaining both the interpersonal area, such as social insecurity, and the intrapsychic area, such as increased self-criticism and core beliefs of defectiveness/shame (see Supplementary Table 2).

Data on the severity of ED-specific psychopathology exhibited some inconsistencies, with most studies showing a positive association between CM and worse ED psychopathology, including a poorer body image, but there were also studies that did not confirm this association (see Supplementary Table 2). Regarding this topic, studies adopting innovative statistical methods allowing an accurate evaluation of the relationship between variables highlighted that the complex associations between psychopathological dimensions and the network structure of ED psychopathology differed in patients reporting CM (see Supplementary Table 2). In light of this evidence, it appears that the maltreated eco-phenotype of EDs should not be exclusively observed from the quantitative perspective of severity, particularly concerning ED-specific psychopathology. Instead, it should be considered from the viewpoint of a possible distinct psychopathological structure of the disorder.

Regarding the longitudinal outcomes, the literature showed that the maltreated eco-phenotype of EDs is characterized by a worse response to currently proposed treatments, particularly in terms of higher dropout rates, diagnostic cross-over, hospitalization rates, long-term maintenance of higher levels of general psychopathology, psychiatric comorbidity, and sexual dysfunctions (see Supplementary Table 3). Furthermore, specific psychopathological dimensions were demonstrated to be involved in the maintenance of ED psychopathology in the presence of CM, including emotional dysregulation and low self-compassion (see Supplementary Table 3). However, data on the course of ED-specific psychopathology over time were somewhat discordant. In particular, some studies adopting the CBT approach showed that the longitudinal trajectory of ED psychopathology was not affected by the presence of CM [37,54,77], while Cassioli et al. (2022) found that as trauma severity increased, treatment response worsened also in the area of ED-specific symptoms [101]. It should be noted that the studies that did not show an impact of CM on the longitudinal course of ED psychopathology did not consider the severity of the experienced trauma. Furthermore, they neglected the area of emotional abuse in the definition of childhood trauma, considering exclusively that of sexual and/or physical abuse. This is a fundamental fact to consider, given that several studies seemed to suggest that emotional abuse represents the core element of CM involved in modifying the phenotypic characteristics of EDs [81,120,121]. Another apparently controversial result was that reported by Castellini et al. (2020) regarding the fact that CM predicted an earlier menses resumption in amenorrheic patients with AN [124]. However, it should be noted that other factors associated with the presence of early trauma and weight recovery also predicted menses resumption, including diagnostic cross-over, making it possible to speculate that in patients with CM menses resumption should not be necessarily viewed as a marker of recovery from the ED, but rather of a transition to a new phase of the disease [124].

The results of this review underlined that the correlates of CM did not show significant differences across the various ED diagnosis. Furthermore, many of the characteristics of the maltreated eco-phenotype of EDs highlighted in this review were found to be similar to those observed in other psychiatric disorders, including the presence of trauma-related neuroanatomical alterations, modifications of the HPA axis, a higher prevalence of comorbidity, emotional dysregulation, and risky behaviors [2,3]. Moreover, changes in social information processing as well as high levels of self-criticism and low self-compassion have been consistently acknowledged as transdiagnostic factors conferring heightened risk for multiple types of psychopathology in individuals reporting childhood traumatic experiences [7,135–137]. Similarly, several studies showed an association of CM not just with a severer clinical presentation [2,3], but also with a qualitative modification of the symptomatic expression and network structure of the core psychopathological features of other mental disorders [138,139], and with worse responses to standard treatments [10,11,140,141]. The overlapping of the characteristics of the maltreated eco-phenotype of EDs with those of the maltreated eco-phenotypes of other mental disorders from a biological and clinical point of view, and in terms of longitudinal course, underlined the role of early trauma as a factor which is transdiagnostically associated with specific modifications of the phenotypic expression of mental disorders. These findings align with the hypothesis that CM triggers alterations that are intrinsically tied to the traumatic experience itself, regardless of whether psychopathology subsequently develops or not, and irrespective of the specific disorder the individual may eventually develop [7,142], which will then depend on the interaction with other risk and resilience factors including genetic and biological components [3].

Beyond identifying shared characteristics with the maltreated eco-phenotypes of other psychiatric conditions, the findings of this systematic review allowed to underline distinct features inherent to the maltreated eco-phenotype of EDs. These distinguishing traits seem to arise from the interaction between the biological and psychopathological changes induced by early trauma and the specific psychopathological and clinical features of EDs. For instance, within this context, low self-esteem, shame, and the early maladaptive schemas typical of post-traumatic psychopathology manifested in terms of greater body dissatisfaction [79,80] and higher tendence to overvalue the importance of body shapes and weight [72]. Furthermore, binge/purge eating behaviors were

the behavioral correlate of negative core beliefs (e.g., defectiveness and shame) [65]. Trauma-related psychopathological dimensions, including emotional dysregulation, affective instability, and the tendency to lose control, were expressed in this populations in terms of an exacerbation of ED-specific psychopathology [69,74,101], whereas dissociation predicted binge-eating and purging symptoms [65]. Feelings of ineffectiveness phenotypically manifested in terms of more severe ED symptoms [69], specifically greater body dissatisfaction and bulimia [120,121], whereas depressive symptoms were linked to greater drive for thinness [71], body dissatisfaction [71], overeating [119], and bingeing/vomiting behaviors [65]. Finally, difficulties in interoceptive awareness correlated with drive for thinness [120], bulimic symptoms [120,121], and body dissatisfaction [121]. It is also noteworthy that in the area of sexuality aspects of post-traumatic and ED-specific psychopathology intertwined in a unique way [35,114,115]. Furthermore, these findings highlighted a specific interplay between trauma-induced biological changes and those resulting from malnutrition and disordered eating behaviors (see Supplementary Table 1). A notable example of this was the elevation of ghrelin levels [46], which increase in response to both stress and purging behaviors, as well as the alterations in the endogenous stress-response system, particularly within the HPA axis, which have been observed in response to both early trauma and underweight conditions. Furthermore, the pattern of menstrual alterations found in these patients is typical of the maltreated eco-phenotype of EDs and not of what was observed in other areas of mental health [124]. Finally, the evidence related to changes in the gut microbiota seems to suggest that they may be attributable not only to the effects of early trauma but also to those of disordered eating [47]. Regarding the neuroanatomical aspects, studies in this field are still preliminary. However, it is intriguing to note that the brain areas implicated in trauma-related modifications in patients with EDs have been shown to be involved with functions such as higher-order visual perception, emotional regulation processes, self-awareness, brain reward systems, the recognition and interpretation of body image-related information, the processing of stimuli from one's own body, and taste processing [31,32,34]. Future studies will need to clarify to what extent the neuroanatomical alterations observed in patients with EDs are specific to this population as opposed to others, and whether they may be involved in promoting the development of ED-specific psychopathology as opposed to other types of psychopathology in individuals exposed to CM. Thoroughly understanding the interaction between post-traumatic psychopathological and biological features and ED-specific expressions as they manifest in the maltreated eco-phenotype of EDs is crucial to ensure the identification and treatment of both aspects appropriately. Focusing solely on the non-specific aspects, which are common to all maltreated eco-phenotypes, would indeed cause to overlook those post-traumatic manifestations that are expressed through the specific features of the disorder.

Overall, this review indicates that the wounds of childhood trauma can create both biological and relational vulnerability, potentially triggering psychopathological imbalances which may not merely manifest as a generic ED, but rather as a distinct disease eco-phenotype, characterized by unique psychopathological and biological expressions, and by a specific longitudinal trajectory. Therfore, this findings support the hypothesis proposed by Teicher et al. regarding the need to modify the approach to mental disorders from a clinical, research, and nosographic perspective, moving towards considering early trauma as a fundamental phenotypic and, consequently, diagnostic modifier [2,3]. Specifically, Teicher et al. recommended a moderate revision of the DSM consisting in the addition of the new diagnostic specifier *"with maltreatment history"* or *"with early life stress"* to the primary DSM diagnosis when a history of early trauma is present as a first step to acknowledge the critical role of CM as a phenotypic modifier of psychiatric disorders and to move towards the development of an etiologically informed classification system [2,3]. Adopting this perspective in EDs would allow for the identification of the specific needs of patients reporting CM, improving clinical management. Furthermore, it would improve research in this field, allowing to stratify patient groups according to the presence or not of CM and therefore making it more targeted. Finally, it would enable the adoption of trauma-focused treatments when a post-traumatic etiopathogenesis is recognized. Recently, Rossi et al. (2023) demonstrated that the add-on of Eye Movement Desensitizaion and Reprocessing (EMDR), a treatment originally developed for PTSD, to CBT-E in patients with AN and a history of CM improved treatment response, not just in terms of ED-

specific psychopathology and weight recovery, but also of reduction of general psychopathology and dissociative symptoms. Furthermore, the RCT performed by Trottier at al. proved the benefits of an integrated ED-PTSD approach comprehending cognitive processing therapy for PTSD [143] and CBT-E interventions in terms of improvements in post-traumatic symptoms and anxiety in patients with EDs and comorbid PTSD as compared to standard CBT. Furthermore, potential innovative pharmacological interventions targeting biological maintenance mechanisms, such as alterations in the stress-response system or gut microbiota, could be studied in order to improve the prognosis of patients reporting a history of CM. A trauma-informed nosography would be particularly important in the field of EDs, given the poor response to standard treatments [144–146], the burden of these diseases [147,148], and the consequent need to find new therapeutic strategies that move towards personalized approaches.

Despite the large number of studies included in this systematic review, it is necessary to underline the limitations of the literature on this subject. First, all the included studies evaluated female populations, with only a very small minority including male subjects. Moreover, only a few studies considered underage populations, or patients with BED, and studies related to the biological correlates of the maltreated eco-phenotype are still scarce. There was a general lack of reporting and consideration of sociodemographic factors in the studies reviewed, underscoring the need for further research in this area. Considering that the age of first exposure appears to modulate the impact of CM on mental health [9,149,150], this remains an unresolved issue in the field of the maltreated eco-phenotype in EDs due to the lack of data. Most of the studies included were cross-sectional, and the longitudinal ones were still mostly observational in design. However, while this generally means that the evidence reported should be considered of low quality, it does not mean that they cannot provide valuable insights, and it is important to make some considerations. In the field of CM correlates, especially in a single diagnostic area like EDs, it would be unreasonable to expect studies such as RCTs, beyond studies on treatment outcomes. Therefore, in this context, high-quality evidence would typically mean that the study design minimizes bias, using appropriate statistical methods controlling for potential confounding variables, and using recognized diagnostic criteria and psychometric tools. As indicated by the quality assessment, these points were present in most of the included studies. Moreover, many of the findings were confirmed by multiple studies, which strengthens the level of evidence. On the contrary, results reported by a single study or those on which there was no agreement in different reports should be considered more preliminary, pending future data on the subject. Regarding longitudinal studies on treatment outcomes, it is advisable that future RCTs in the field of EDs consider the presence or absence of CM as a moderator of outcome. It would also be essential to expand research with longitudinal studies to more thoroughly investigate the psychopathological dimensions that are associated with the maintenance of symptoms over time in the presence of a history of trauma, and to identify increasingly specific targets for structuring innovative treatments. Finally, many studies, especially the less recent ones, considered only childhood sexual/physical abuse, neglecting the importance of emotional abuse and neglect. However, more recent studies have overcome this limitation. It might also be relevant to investigate the impact of other types of early trauma, such as bereavement. Adverse childhood events different from CM could lead to a distinct traumatized eco-phenotype with characteristics that are more or less overlapping with those of the maltreated one, which was the subject of this review.

The present study shows various strengths, particularly the investigation of a wide range of correlates of childhood trauma through a very inclusive research string, which allowed the inclusion of a large number of studies and thus a comprehensive description of the maltreated eco-phenotype of EDs from various perspectives. In addition, the screening of papers was extensively discussed among multiple researchers, allowing for accurate verification of the extrapolated data. However, it also has some weaknesses, notably that the research was confined to two databases (PubMed and ClinicalTrials.gov), and only reports published in English were considered. Moreover, negative results that did not represent the primary outcome of the study were excluded, as they did not provide data for which an adequate power calculation had been performed.

While this represents a strength in terms of statistical accuracy, it also may introduce a bias related to giving more relevance to positive results.

In conclusion, this systematic review provided, for the first time, an accurate and comprehensive description of the maltreated eco-phenotype of EDs. It highlighted the importance of moving towards an etiologically informed nosography that considers the role of early trauma not just as a risk factor for the development of these disorders, but also as an etiologic agent capable of producing eco-phenotypic variants of EDs from the multifaceted perspectives of biology, psychopathology, and longitudinal course. Recognizing the importance of CM as a phenotypic modifier would improve the clinical approach to EDs, facilitate and empower research in this field, and guide the development of new therapeutic strategies that consider the specific needs and psychopathological features of individuals reporting a history of childhood trauma.

CRediT Statement

Conceptualization: E.R., E.C. and G.C.; Data curation: E.R., E.C., C.D. and G.M.; Investigation: E.R., E.C.,

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Figure Captions

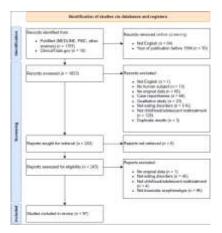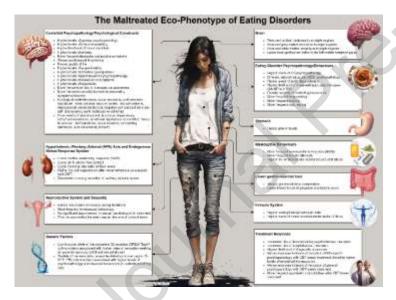**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

Figure 2 Graphical summary of main results.

Graphical abstract

Highlights

- Patients with Eating Disorders (EDs) and Childhood Maltreatment (CM) show distinct features.
- CM is linked to neuroanatomical changes and altered stress responses in ED patients.
- CM correlates with severe eating behaviors, higher psychiatric comorbidity, and impulsivity.
- CM is associated with poorer treatment outcomes in ED patients.
- CM should be recognized as an etiologic agent shaping ED eco-phenotypic variants.