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REVIEW ARTICLE

Risk factors for eating disorders: an umbrella review of published meta-analyses

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Objective: To grade the evidence about risk factors for eating disorders (anorexia nervosa, bulimia nervosa, and binge eating disorder) with an umbrella review approach.
Methods: This was a systematic review of observational studies on risk factors for eating disorders published in PubMed/PsycInfo/Embase until December 11th, 2019. We recalculated random-effect meta-analyses, heterogeneity, small-study effect, excess significance bias and 95% prediction intervals, grading significant evidence ($p < 0.05$) from convincing to weak according to established criteria. Quality was assessed with the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) tool.
Results: Of 2,197 meta-analyses, nine were included, providing evidence on 50 risk factors, 29,272 subjects with eating disorders, and 1,679,385 controls. Although no association was supported by convincing evidence, highly suggestive evidence supported the association between childhood sexual abuse and bulimia nervosa (k = 29, 1,103 cases with eating disorders, 8,496 controls, OR, 2.73, 95% CI 1.96-3.79, p = 2.1 x 10-9, AMSTAR-2 moderate quality) and between appearance-related teasing victimization and any eating disorder (k = 10, 1,341 cases with eating disorders, 3,295 controls, OR 2.91, 95%CI 2.05-4.12, p = 1.8x10-9, AMSTAR-2 moderate quality). Suggestive, weak, or no evidence supported 11, 29, and 8 associations, respectively.
Conclusions: The most credible evidence indicates that early traumatic and stressful events are risk factors for eating disorders. Larger collaborative prospective cohort studies are needed to identify risk factors for eating disorders, particularly anorexia nervosa.

Keywords: Eating disorders; anorexia nervosa; bulimia nervosa; binge eating disorder: umbrella review; systematic review; meta-analysis; risk factor; prevention

Introduction

Eating disorders (ED) are a complex group of psychiatric disorders characterized by psychopathology which results in pathological eating behaviors that can lead to medical complications.[1] For example, people with anorexia nervosa (AN) are approximately five times more likely to die from any cause and eighteen times more likely to die from suicide than the general population.[2,3] In addition, bulimia nervosa (BN) and binge eating disorders (BED) are associated with complications of vomiting, laxative abuse, and obesity, respectively.

ED outcomes have remained poor in recent decades, with high rates of chronicity,[4-6] which could suggest a lack of understanding about the underlying pathophysiological mechanisms that lead to ED onset and persistence. For example, the lack of efficacious pharmacological interventions specifically for AN might be due to a relative lack of insight about the biological mechanisms underlying it.[7-9] The fact that there is no clearly superior psychosocial

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intervention among a wide range of interventions for adults and adolescents with AN is also particularly concerning.[10]

Despite the poor mechanistic knowledge of ED, an extensive body of literature has investigated putative risk factors for ED, testing a wide range of environmental[11-15] and genetic[16-20] risk factors. However, the contrasting results of individual studies are frequently not confirmed in meta-analysis. A recent large collaborative genome-wide association study has shown that metabo-psychiatric genetic predisposition, specifically eight previously unidentified loci, might increase the risk of AN.[21]

Poor knowledge of the mechanistic processes that lead to ED and risk factors for ED might be one of the reasons why early ED intervention and prevention has been studied less than psychotic and other non-psychotic disorders.[22,23] Despite preliminary evidence suggesting the potential efficacy of ED prevention, more evidence synthesis is needed,[24,25] since the state of the art for evidence on interventions to prevent or delay ED onset seems to be relatively less explored than in other fields of psychiatry.[26,27] Although the prevention of mental disorders, particularly psychosis, is being explored, it has only been partially implemented worldwide. The results so far have shown that the pre-assessment of risk should be improved to find subjects actually at risk of developing mental disorders.[28-32] Since preventive interventions are not free from potential side effects, they must be performed only for individuals with an epidemiologically and clinically significant risk of any mental illness.[33] Putative risk factors, whose associations have been inflated by biased results, must be replaced with convincing ones, as is being done for several other mental disorders, including schizophrenia,[34,35] autism,[36,37] depression,[38] bipolar disorder,[39] post-traumatic stress disorder,[40] anxiety spectrum disorder and obsessive compulsive disorder.[41] This a necessary step for finding individuals who might be at risk of ED and could thus benefit from preventive interventions.

Therefore, the aim of the present umbrella review, which graded evidence through a systematic review of meta-analyses, identified quantitative criteria based on additional statistical tests, and re-calculated each meta-analytic association, was to grade the available evidence on risk factors for ED, identifying those that should be targeted in ED prevention and considered when assessing a person with subthreshold symptoms.

Methods

A protocol for this study is publicly available on the Center for Open Science platform (https://osf.io/hu8yd/?view_only=269352b4b1e040bcb825f48b567032a4). We performed a systematic review, considering the Preferred Reporting Items for Systematic Reviews and Meta-analyses[42] and the Meta-analysis of Observational Studies in Epidemiology guidelines.[43]

Search strategy and selection criteria

We searched the PubMed, PsycInfo and Embase databases (final search on December 11th, 2019) to identify systematic reviews with meta-analyses pooling longitudinal observational studies that examined any association between putative risk factors for ED, defined according to clinical records, any version of the DSM or ICD, or validated scales with cut-off points. The following keywords were used in PubMed (meta-analysis OR meta-analysis OR systematic review) AND (anorexia nervosa OR binge* OR bulimi* OR eating disorder*), and equivalent ones were used in PsycInfo and Embase. Two reviewers (DM, DB) independently searched the titles/abstracts for eligibility and assessed the full text of articles that passed this phase. A third reviewer (MS) resolved any conflicts. When more than one meta-analysis assessed the same risk factor, we only included the one with the most studies, as previously described.[34,38,39,44,45] The exclusion criteria were: 1) meta-analyses of randomized controlled trials; 2) those published in languages other than English; 3) those that included cross-sectional studies from which no causal inference could be made; 4) systematic reviews without meta-analyses.

The same two investigators who independently performed the screening extracted the data in a predefined Excel spreadsheet. For each meta-analysis, we extracted the PMID/DOI, first author, publication year, population, risk factor, study design, ED type (AN, BN, BED, or mixed), number of included studies and total sample size to identify the largest meta-analysis. For each primary study in the largest meta-analyses, we recorded data on the first author, year of publication, study design, number of cases (subjects who developed ED), subjects who did not develop ED, effect size with 95% confidence intervals (95%CI), ED definition criteria, and study location. The methodological quality of each included meta-analysis was assessed with the Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool (a recent update of AMSTAR,[46] available at https://amstar.ca/Amstar-2.php) by the same two investigators.

Data analysis

For each association in each meta-analysis, we re-performed a random-effect meta-analysis that calculated the pooled effect size and the 95% confidence intervals.[47] Heterogeneity was assessed with the I^2 statistic.[48] We calculated the 95% prediction intervals for the summary random effect sizes, which provide the possible range in which the effect sizes of future studies are expected to fall.[49] We also tested for the presence of small-study effect bias,[38,39,44,50] which was deemed to be present in cases of pooled estimates larger than the largest individual study, as well as publication bias (Egger's regression asymmetry test [$p \leqslant 0.10$]). Finally, we assessed excess significance bias by evaluating whether the observed number of studies with nominally statistically significant results ($p \leqslant 0.05$) were different from the expected number of studies with statistically significant results (significance threshold set at $p \leqslant 0.10$).[51,52]

Grading the evidence

The credibility of the meta-analyses was assessed according to stringent criteria based on previously published

umbrella reviews.[38,39,44,50,53] In brief, associations that presented nominally significant random-effects summary effect sizes (i.e., $p < 0.05$) were ranked as convincing, highly suggestive, suggestive, or weak evidence based on the number of events, the strength of the association, and the presence of several biases (criteria presented in Box 1). The quality of included meta-analyses was assessed with the AMSTAR-2 tool.

Results

Search

A flowchart of the search, selection and inclusion process is presented in Figure 1. Out of 2,197 articles screened at the title/abstract level, we assessed the full text of 45 publications. Of these, 36 were excluded for including only cross-sectional studies (n=26), not conducting a meta-analysis of risk factors for ED (n=4), not being the largest meta-analysis (n=3), not focusing on ED as defined according to the inclusion criteria of the present umbrella review (n=2), or performing a pooled, rather than a meta-analysis (n=1). A reference list of the 36 excluded articles is provided in Table S1, available as online-only supplementary material. Nine meta-analyses were ultimately included, providing evidence on 49 risk factors from a total of 29,272 individuals with ED and 1,679,385 controls.

Grading the evidence

The evidence grade for ED risk factors is reported in Table 1. Nine meta-analyses[11,12,54-60] investigated a wide range of risk factors for ED. Early menarche was investigated in one meta-analysis, peripartum events were investigated in four (APGAR score, C-section, vaginal instrumental delivery, and gestational age lower than 37 weeks), pre-existing medical or psychiatric conditions were investigated in seven (attention deficit and hyperactivity disorder, substance use, type I diabetes), initial psychological features and BMI at baseline assessment in longitudinal studies were investigated in nine, and the remaining investigated risk factors were lifetime or childhood traumatic events or physical, emotional, sexual abuse.

Overall, no association was supported by convincing evidence. Highly suggestive evidence supported the association between childhood sexual abuse and BN (k = 29, 1,103 ED cases, 8,496 controls, OR, 2.73, 95%CI 1.96-3.79, p = 2.1 x 10-9, AMSTAR-2 moderate quality)[54] and between appearance-related teasing victimization and any ED (k = 10, 1,341 ED cases, 3,295 controls, OR 2.91, 95%CI 2.05-4.12, p = 1.8 x 10-9, AMSTAR-2 moderate quality).[57] Suggestive, weak, or no evidence was provided for 10, 29, and 8 risk factor, respectively. More specifically, the 12 meta-analyses that investigated risk factors for AN had the lowest evidence among all ED (one provided suggestive evidence, seven provided weak evidence, and four provided no evidence). Ten meta-analyses investigated risk factors for BED (three provided suggestive evidence and seven provided weak evidence). Ten meta-analyses investigated BN (one provided highly suggestive evidence, one provided suggestive evidence, and eight provided weak evidence). The remaining 17 meta-analyses investigated risk factors for any ED (one provided highly suggestive evidence, five provided suggestive evidence, seven provided weak evidence, and four provided no evidence). The median number of studies per meta-analysis was 32 (interquartile range [IQR] 17-82). The median number of ED cases per risk factor was 514 (IQR 196-1,103), and the median total population was 3,147 (IQR 993-8,478).

Detailed sources of bias are reported in Table 2 for all significant associations. Overall, the following bias pattern emerged: associations based on evidence from at least 1,000 subjects with ED (18%), 95% prediction intervals excluding the null value (18%), small study effect absent (72%), excess significance bias absent (60%), low overall heterogeneity of associations (8% with significant heterogeneity), significance of the largest study (68%), and publication bias (70%). The quality of included meta-analyses was high for one,[60] critically low for one,[59] and moderate for the reaming seven.

Box 1 Credibility assessment criteria for meta-analyses of observational studies

Classification	Criteria
Convincing evidence (Class I)	1. More than 1,000 cases 2. Significant summary associations ($p < 10\text{-}6$) per random-effects calculations 3. No evidence of small-study effects 4. No evidence of excess of significance bias 5. Prediction intervals not including the null value 6. Largest study nominally significant ($p < 0.05$) 7. Not large heterogeneity (i.e., $I^2 < 50\%$)
Highly suggestive evidence (Class II)	1. More than 1,000 cases 2. Significant summary associations ($p < 10\text{-}6$) per random-effects calculation 3. Largest nominally significant study ($p < 0.05$)
Suggestive evidence (Class III)	1. More than 1,000 cases 2. Significant summary associations ($p < 10\text{-}3$) according to random effect calculations
Weak evidence	1. All other associations with $p < 0.05$
Non-significant associations	1. All associations with $p < 0.05$

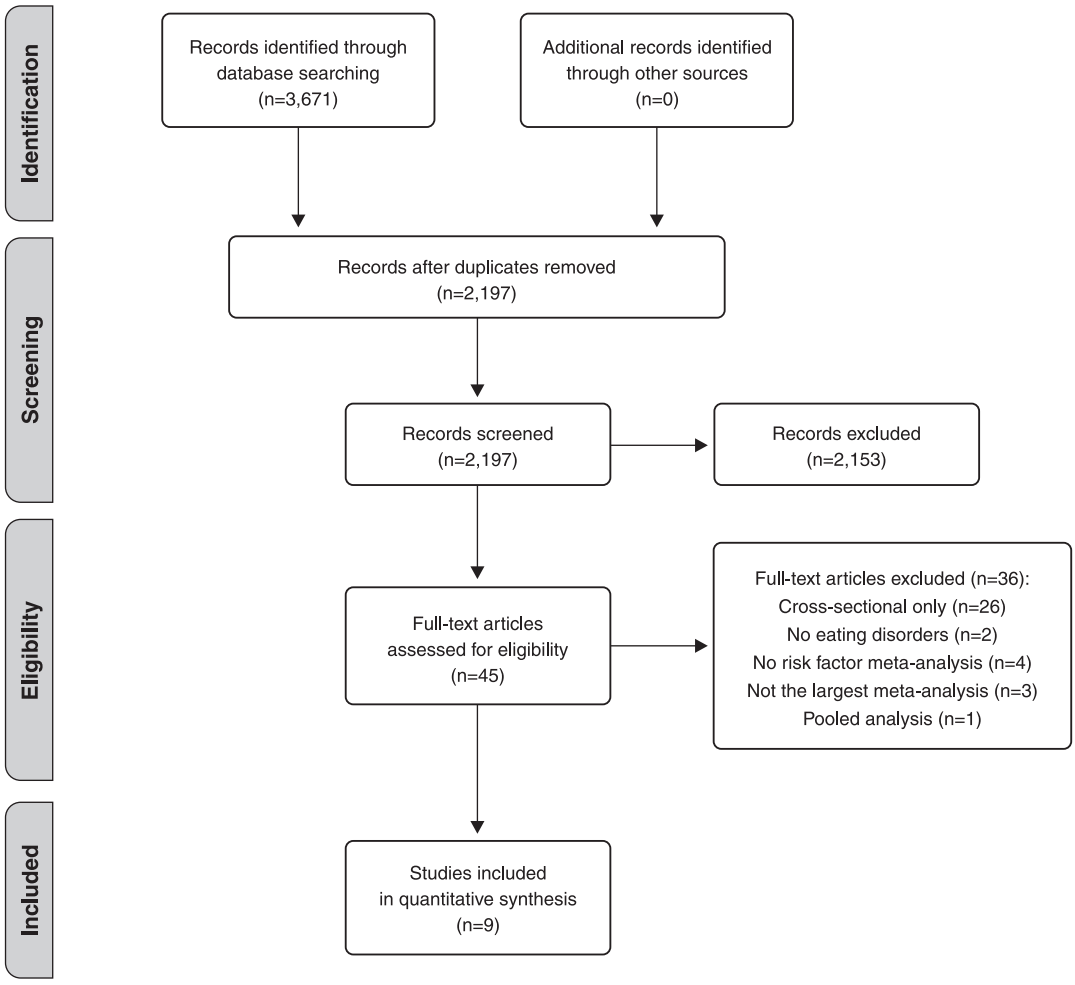

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart.

Discussion

This is the first comprehensive umbrella review of meta-analyses on risk factors for ED, which goes beyond mere pooling of available meta-analyses by including additional stringent statistical tests and evidence grading based on quantitative criteria. This review included 50 associations from nine meta-analyses, showing a lack of convincing evidence supporting all ED risk factors. Highly suggestive evidence was found for childhood sexual abuse as risk factor for BN and appearance-related teasing victimization for any ED.

These results can advance clinical knowledge in the field of ED on various points. First, none of the putative risk factors for ED are supported by convincing evidence, and several types of bias may have inflated the estimates reported in meta-analyses. This is particularly concerning when we compare the evidence of risk factors for ED with the evidence of risk factors for schizophrenia[34,35] (seven factors overall supported by convincing evidence), autism[36,37] (seven factors), depression[38] (eight factors), bipolar disorder[39] (one factor), post-traumatic stress disorder[40] (three factors), and anxiety spectrum disorder and obsessive compulsive disorder[41] (one). Environmental factors play an important role in the pathogenesis of mental disorders, while genetic predisposition still explains only a very small portion of the risk of schizophrenia, depressive disorders, bipolar disorders.[61] The lack of established risk factors for ED may be due to limited research in this field or to the heterogeneity of the clinical pictures, which have common characteristics and frequent overlap with other mental disorders. There are common general psychopathologic features in ED (e.g., depressive, anxious, obsessive-compulsive), as well as feelings of ineffectiveness and interpersonal sensitivity, which appear to be even more central than behavioral and specific psychopathologies.[62] This could reduce the specificity of risk factors.

Second, while a number of mental disorders have specific risk factors, such as high clinical risk for psychosis,[34] or irritable bowel syndrome for bipolar disorder,[39] the risk factors for ED found in the present review appear to be relatively unspecific. For example, childhood sexual abuse has been connected with a number of adverse health outcomes, including borderline personality disorder, anxiety, depression, post-traumatic stress disorder, psychosis, and non-suicidal self-injury, in addition to pain, risky sexual behavior, obesity, and HIV infection.[63] This is not surprising,

Table 1 Evidence grading for meta-analyses of observational studies on risk factors for ED

Study	Study design	Risk factor	ED type	ED definition	k	Grading of evidence	AMSTAR-2	eOR
Caslini 2016[54]	Case-control	Childhood sexual abuse	BN	DSM-III	32	Highly suggestive	Moderate	2.73
Lie 2019[57]	Case-control	Appearance-related teasing victimization	ED	DSM-III, DSM-IV, ICD-10	10	Highly suggestive	Moderate	2.91
Caslini 2016[54]	Case-control	Childhood sexual abuse	BED	DSM-IV	32	Suggestive	Moderate	2.31
Caslini 2016[54]	Case-control	Childhood physical abuse	BED	DSM-IV	32	Suggestive	Moderate	3.10
Krug 2013[55]	Case-control	APGAR score at 5 minutes < 7	AN	ICD-9	6	Suggestive	Moderate	1.32
Nazar 2016[56]	Cohort	ADHD	ED	DSM-IV	17	Suggestive	Moderate	4.24
Nazar 2016[56]	Cohort	ADHD	ED	DSM-IV	17	Suggestive	Moderate	4.21
Nazar 2016[56]	Cohort	ADHD	BED	Clinical interview	17	Suggestive	Moderate	3.93
Stice 2002[11]	Cohort	Initial body dissatisfaction	ED	EDI	NA	Suggestive	Moderate	1.67
Stice 2002[11]	Cohort	Initial self-reported dieting	BN	EDI	NA	Suggestive	Moderate	2.26
Stice 2002[11]	Cohort	Initial negative affect	ED	EDI	NA	Suggestive	Moderate	1.38
Stice 2002[11]	Cohort	Initial perceived pressure to be thin	ED	EDI	NA	Suggestive	Moderate	1.51
Caslini 2016[54]	Case-control	Childhood sexual abuse	AN	DSM-IV	32	Weak	Moderate	1.92
Caslini 2016[54]	Case-control	Physical abuse	AN	DSM-IV	32	Weak	Moderate	3.35
Caslini 2016[54]	Case-control	Physical abuse	BN	DSM-IV	32	Weak	Moderate	3.44
Chen 2010[12]	Case-control	Sexual abuse	ED	Clinical interview	37	Weak	Moderate	2.72
Lie 2019[57]	Case-control	Bullying victimization	ED	DSM-III, DSM-IV, ICD-10	6	Weak	Moderate	2.22
Molendijk 2017[58]	Case-control	Sexual abuse	AN	DSM-III-R	82	Weak	Moderate	1.74
Molendijk 2017[58]	Case-control	Sexual abuse	AN BP	DSM-III-R	82	Weak	Moderate	2.80
Molendijk 2017[58]	Case-control	Sexual abuse	BED	DSM-IV	82	Weak	Moderate	1.88
Molendijk 2017[58]	Case-control	Sexual abuse	BN	DSM-III-R	82	Weak	Moderate	2.48
Molendijk 2017[58]	Case-control	Sexual abuse	ED	DSM-IV	82	Weak	Moderate	2.29
Molendijk 2017[58]	Case-control	Physical abuse	AN BP	DSM-IV	82	Weak	Moderate	2.76
Molendijk 2017[58]	Case-control	Physical abuse	AN R	DSM-IV	82	Weak	Moderate	2.65
Molendijk 2017[58]	Case-control	Physical abuse	BED	DSM-IV	82	Weak	Moderate	2.57
Molendijk 2017[58]	Case-control	Physical abuse	BN	DSM-IV	82	Weak	Moderate	3.43
Molendijk 2017[58]	Case-control	Physical abuse	ED	DSM-IV	82	Weak	Moderate	2.96
Molendijk 2017[58]	Case-control	Emotional abuse	AN R	DSM-IV	82	Weak	Moderate	3.52
Molendijk 2017[58]	Case-control	Emotional abuse	BED	DSM IV	82	Weak	Moderate	2.44
Molendijk 2017[58]	Case-control	Emotional abuse	BN	DSM-III-R	82	Weak	Moderate	5.13
Molendijk 2017[58]	Case-control	Double abuse	ED	DSM-III-R	82	Weak	Moderate	2.09
Nazar 2016[56]	Cohort	ADHD	ED	DSM-IV	17	Weak	Moderate	3.33
Stice 2002[11]	Cohort	Initial modeling of body image	BED	EDE Q	NA	Weak	Moderate	1.81
Stice 2002[11]	Cohort	Initial thin ideal internalization	BED	BULIT R, EAT 26	NA	Weak	Moderate	1.51
Stice 2002[11]	Cohort	Initial perfectionism	BN	EDI	NA	Weak	Moderate	1.24
Stice 2002[11]	Cohort	Impulsivity	BED	BULIT R, EAT 26	NA	Weak	Moderate	1.28
Stice 2002[11]	Cohort	Substance use	BN	DSM-III-R	NA	Weak	Moderate	1.44
Stice 2002[11]	Cohort	Initial BMI	BN	EDI	NA	Weak	Moderate	1.67
Young 2013[59]	Cohort	Diabetes type I	BN	EAT-26	NA	Weak	Critically low	1.94
Young 2013[59]	Cohort	Diabetes type I	ED	DSM-IV	NA	Weak	Critically low	2.30
Krug 2013[55]	Case-control	Vaginal instrumental delivery	AN	ICD-9	6	No evidence	Moderate	1.07
Krug 2013[55]	Case-control	Gestational age < 37 weeks	AN	ICD-9	6	No evidence	Moderate	0.80
Lie 2019[57]	Case-control	Appearance-unrelated teasing victimization	ED	DSM-III, DSM-IV, ICD-10	6	No evidence	Moderate	1.5
Molendijk 2017[58]	Case-control	Sexual abuse	AN R	DSM-III-R	82	No evidence	Moderate	1.65
Molendijk 2017[58]	Case-control	Physical abuse	AN	DSM-III-R	82	No evidence	Moderate	1.23
Molendijk 2017[58]	Case-control	Sexual abuse	ED	DSM-III-R	82	No evidence	Moderate	1.29
Stice 2002[11]	Cohort	Early menarche	ED	EAT 26	NA	No evidence	Moderate	1.19
Zhang 2019[60]	Case-control	Caesarean delivery	ED	ICD-9, ICD-10	4	No evidence	High	1.18

ADHD = attention deficit hyperactivity disorder; AMSTAR = Assessment of Multiple Systematic Reviews; AN = anorexia nervosa; BED = binge eating disorder; BMI = body mass index; BN = bulimia nervosa; BULIT R = Bulimia Test; EAT = Eating Attitude Test; ED = eating disorders; EDE Q = Eating Disorder Examination Questionnaire; EDI = Eating Disorders Inventory; eOR = equivalent odds ratio; NA = not available; OR = odds ratio; PI = prediction interval.

Table 2 Grading criteria for highly suggestive, suggestive, and weak evidence of risk factors for eating disorders

Study	Risk factor	k	Cases	Non cases	Total	Above1,000 cases	Heterogeneity	PI includes null	p-value ES*
Caslini 2016[54]	Childhood sexual abuse	26	1,103	7,393	8,496	1	1	1	1
Lie 2019[57]	appearance-related teasing victimization	10	1,341	1,954	3,295	1	1	1	1
Caslini 2016[54]	Childhood physical abuse	4	NA	NA	NA	NA	0	0	1
Caslini 2016[54]	Childhood sexual abuse	7	NA	NA	NA	NA	0	0	1
Krug 2013[55]	APGAR score at 5 minutes < 7	33	2,701	65,443	68,144	1	0	0	2
Nazar 2016[56]	ADHD	12	3,618	23,398	27,016	1	1	1	1
Nazar 2016[56]	ADHD	6	1,814	7,709	9,523	1	1	1	2
Nazar 2016[56]	ADHD	4	1,263	7,163	8,426	1	1	1	2
Stice 2002[11]	Initial body dissatisfaction	11	NA	NA	17,332	NA	1	1	1
Stice 2002[11]	Initial negative affect	11	NA	NA	17,411	NA	1	1	1
Stice 2002[11]	Initial perceived pressure to be thin	4	NA	NA	7,517	NA	0	1	1
Stice 2002[11]	Initial self-reported dieting	7	NA	NA	9,436	NA	1	1	1
Caslini 2016[54]	Childhood sexual abuse	13	196	2,264	2,460	0	1	1	3
Caslini 2016[54]	Emotional abuse	2	NA	NA	NA	NA	0	NA	2
Caslini 2016[54]	Physical abuse	4	30	1,024	1,054	0	0	1	3
Caslini 2016[54]	Physical abuse	9	222	1,906	2,128	0	0	0	1
Chen 2010[12]	Sexual abuse	11	292	13,035	13,327	0	0	0	1
Lie 2019[57]	Bullying victimization	6	554	911	1,465	0	0	0	2
Molendijk 2017[58]	Double abuse	3	125	4,393	4,518	0	0	1	3
Molendijk 2017[58]	Emotional abuse	3	129	159	288	0	0	1	3
Molendijk 2017[58]	Emotional abuse	3	437	2,288	2,725	0	0	1	1
Molendijk 2017[58]	Emotional abuse	2	61	1,379	1,440	0	0	NA	1
Molendijk 2017[58]	Physical abuse	4	83	218	301	0	0	1	3
Molendijk 2017[58]	Physical abuse	6	176	333	509	0	0	1	3
Molendijk 2017[58]	Physical abuse	5	591	2,556	3,147	0	0	0	1
Molendijk 2017[58]	Physical abuse	9	514	1,853	2,367	0	1	0	1
Molendijk 2017[58]	Physical abuse	7	521	172	693	0	0	0	1
Molendijk 2017[58]	Sexual abuse	7	314	1,770	2,084	0	1	1	3
Molendijk 2017[58]	Sexual abuse	6	175	341	516	0	1	1	3
Molendijk 2017[58]	Sexual abuse	5	591	2,556	3,147	0	0	1	2
Molendijk 2017[58]	Sexual abuse	18	997	3,969	4,966	0	1	1	2
Molendijk 2017[58]	Sexual abuse	7	521	172	693	0	0	1	3
Nazar 2016[56]	ADHD	3	1,174	6,954	8,128	1	1	1	3
Stice 2002[11]	Initial BMI	10	NA	NA	11,063	NA	1	1	2
Stice 2002[11]	Impulsivity	3	NA	NA	933	NA	0	1	3
Stice 2002[11]	Initial modeling of body image	2	NA	NA	449	NA	0	NA	3
Stice 2002[11]	Initial perfectionism	4	NA	NA	2,124	NA	0	1	3
Stice 2002[11]	Initial thin ideal internalization	4	NA	NA	15,182	NA	1	1	3
Stice 2002[11]	Substance use	4	NA	NA	2,236	NA	0	1	2
Young 2013[59]	Diabetes	9	NA	NA	927	NA	1	1	3
Young 2013[59]	Diabetes	7	NA	NA	4,515	NA	1	1	3

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Table 2 (*continued*)

Study	Egger's test	Largest study significant	Small study effect	Excess of significance bias	Class of evidence	ES type	ES	95% low CI	95% upper CI
Caslini 2016[54]	0	1	0	0	2	OR	2.73	1.96	3.79
Lie 2019[57]	0	1	0	0	2	OR	2.91	2.05	4.12
Caslini 2016[54]	0	1	0	NA	3	OR	3.10	2.48	3.88
Caslini 2016[54]	0	1	0	NA	3	OR	2.31	1.66	3.20
Krug 2013[55]	0	0	0	1	3	OR	1.32	1.17	1.49
Nazar 2016[56]	1	0	1	1	3	OR	4.24	2.62	6.87
Nazar 2016[56]	0	1	0	0	3	OR	4.21	2.22	7.97
Nazar 2016[56]	0	1	0	0	3	OR	3.93	2.09	7.38
Stice 2002[11]	0	1	0	NA	3	r	0.14	0.11	0.17
Stice 2002[11]	0	1	0	1	3	r	0.09	0.06	0.12
Stice 2002[11]	0	1	0	NA	3	r	0.11	0.08	0.14
Stice 2002[11]	1	1	1	1	3	r	0.22	0.14	0.30
Caslini 2016[54]	1	0	1	0	4	OR	1.92	1.13	3.27
Caslini 2016[54]	NA	1	NA	NA	4	OR	3.69	2.07	6.59
Caslini 2016[54]	0	0	0	0	4	OR	3.35	1.43	7.85
Caslini 2016[54]	1	1	1	1	4	OR	3.44	2.56	4.60
Chen 2010[12]	0	1	0	0	4	OR	2.72	2.04	3.63
Lie 2019[57]	0	1	0	0	4	OR	2.22	1.50	3.28
Molendijk 2017[58]	0	0	0	0	4	OR	2.09	1.32	3.30
Molendijk 2017[58]	0	0	0	0	4	OR	3.52	1.68	7.38
Molendijk 2017[58]	0	1	0	0	4	OR	2.44	1.73	3.48
Molendijk 2017[58]	NA	1	0	0	4	OR	5.13	2.80	9.39
Molendijk 2017[58]	0	0	0	0	4	OR	2.76	1.44	5.29
Molendijk 2017[58]	0	1	0	0	4	OR	2.65	1.33	5.28
Molendijk 2017[58]	0	1	0	0	4	OR	2.57	1.99	3.30
Molendijk 2017[58]	1	0	1	1	4	OR	3.43	2.19	5.39
Molendijk 2017[58]	0	1	0	0	4	OR	2.96	1.89	4.62
Molendijk 2017[58]	0	0	0	0	4	OR	1.74	1.09	2.79
Molendijk 2017[58]	0	0	0	1	4	OR	2.80	1.23	6.36
Molendijk 2017[58]	0	1	0	0	4	OR	1.88	1.38	2.55
Molendijk 2017[58]	1	1	1	0	4	OR	2.48	1.70	3.60
Molendijk 2017[58]	0	1	0	0	4	OR	2.29	1.36	3.87
Nazar 2016[56]	0	1	0	0	4	OR	3.33	1.39	7.97
Stice 2002[11]	1	0	1	NA	4	r	0.14	0.06	0.22
Stice 2002[11]	0	0	0	1	4	r	0.07	0.00	0.13
Stice 2002[11]	NA	1	NA	NA	4	r	0.16	0.07	0.25
Stice 2002[11]	0	1	0	0	4	r	0.06	0.02	0.10
Stice 2002[11]	0	1	0	NA	4	r	0.11	0.04	0.20
Stice 2002[11]	0	1	0	0	4	r	0.10	0.06	0.14
Young 2013[59]	0	1	0	1	4	d	0.36	0.13	0.60
Young 2013[59]	1	0	1	0	4	d	0.46	0.10	0.82

ADHD = attention deficit hyperactivity disorder; CI = confidence interval; NA = not available; OR = odds ratio; PI = prediction interval.
*1 $\leqslant$ 10-6, 2 $\leqslant$ 10-3, 3 $\leqslant$ 0.05, 4 $\leqslant$ 0.05.

given that child abuse is a risk factor for general psychopathology[64] and that the effect of sexual abuse on ED psychopathology is probably mediated by ineffectiveness, which is present beyond ED.[65] The transdiagnostic nature of these risk factors is relatively underexplored but could, at least theoretically, allow transdiagnostic early detection and intervention for these disorders.[66,67] To the best of our knowledge, only one pooled analysis of follow-up data from three randomized controlled trials on ED prevention has focused on a high-risk population with body dissatisfaction, finding that negative affect and low BMI predicted AN, elevated body dissatisfaction, overeating, and fasting predicted BN, and elevated body dissatisfaction, overeating, and functional impairment predicted BED.[68] However, such findings have not yet been replicated in larger cohort studies and have not been pooled in meta-analyses accounting for random error and heterogeneity across studies. Moreover, one more reason for the lack of evidence about risk factors for ED might be explained by a recent large GWAS study, which included 16,992 cases of anorexia nervosa and 55,525 controls, finding that eight loci linked to other psychiatric disorders, physical activity, and metabolic (including glycemic), lipid and anthropometric traits (independent of the effects of common variants associated with body-mass index) were associated with a higher risk of AN.[21] Such results might suggest that some genetic risk is shared with other psychiatric conditions, but that there are also specific metabolic pathways for AN that should be investigated in greater detail. However, an overlap between mental and physical disorders is also present in other mental disorders.[69]

Third, we found that the least evidence is available for AN, which is, on the other hand, the most severe ED in terms of clinical outcome, medical complications, and survival. Fourth, the lack of clear evidence supporting the identification of ED risk factors, especially for AN, is highly relevant in the light of the need for early ED detection as a crucial component in improving ED treatment efficacy. Some authors[70] have proposed a staging model for AN that shows poorer outcomes with illness progression. In line with this framework, the NICE (2010) ED guidelines recommend that treatment should begin at the earliest opportunity to avoid the additional effects of chronicity, psychiatric comorbidity, and complications from malnutrition.[71] Promoting mental health, a complementary strategy for preventing mental disorders, is particularly needed in young populations, such as those at risk of developing ED.[72]

Appearance-related teasing victimization was identified as a risk factor for any ED, with highly suggestive, but not convincing, evidence. This confirms that interpersonal and social functioning might be a risk factor for ED, which was suggested in a systematic review[73] that highlighted the role of interpersonal issues as a factor in ED onset. In addition, this finding confirms that emotional abuse in childhood and adolescence, which consists of humiliating and demeaning experiences, is the form of abuse most directly associated with ED psychopathology, independent of other psychiatric comorbidities.[74]

The strength of the present study is that it is the first umbrella review to demonstrate that no convincing evidence supports any ED risk factor. Moreover, it provides methodological direction for future studies, i.e., a focus on high quality evidence about ED risk factors, such as large-scale collaborative studies, harmonizing measurements, and data sharing to bridge the gap with prevention strategies implemented in other areas of psychiatry. Finally, the focus of collaborative studies should be on metabolic pathways, which were associated with AN in a large recent GWAS study. Thus, leading centers involved clinical research on ED should plan large multicenter longitudinal cohort studies investigating the role of putative risk factors for ED, focusing on metabolic pathways, which have been completely neglected to date.

The main limitation of the present study is that only one of the included meta-analyses met high quality criteria according to the AMSTAR-2 checklist. Furthermore, the lack of evidence for specific risk factors could be related to the paucity of large-scale collaborative longitudinal studies assessing the role of moderating mechanisms in the relationship between conditions preceding the onset of the disorder and the development of ED psychopathology.[75] Finally, factors not included in meta-analyses are not considered in umbrella reviews.

In conclusion, no ED risk factor is supported by convincing evidence. The field of ED is being left behind with respect to the preliminary evidence necessary to begin implementing targeted preventive interventions for individuals with subthreshold symptoms. More multi-center longitudinal cohort studies are needed to identify modifiable risk factors for ED, including the metabolic factors suggested by a recent large-scale GWAS study.[21]

Disclosure

The authors report no conflicts of interest.

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