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Functional Changes in the Brain of bulimia nervosa a protocol for systematic review and meta-analysis

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Keywords:	NEONATOLOGY, Eating disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Neuroradiology < RADIOLOGY & IMAGING

Functional Changes in the Brain of bulimia nervosa: a protocol for systematic review and meta-analysis

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Abstract

Introduction Bulimia nervosa (BN) is a disorder with noted social and health consequences that typically arise in later adolescent and young adult years. Accumulating neuroimaging studies have found abnormal functional brain changes in BN patients. This study aims to verify concurrence of the functional cerebral alterations and providing an examination of the latest evidence based on the neurobiology studies of individuals with bulimia nervosa.

Methods and analysis A preliminary systematic search will be performed using Cochrane Library, PubMed, Embase, and Web of Science from inception to January 1, 2021. 2 researchers will be responsible to the selection of studies, quality assessment, and data extraction independently. The Anisotropic effect size version of signed differential mapping (AES-SDM) methods will be used to conduct a coordinate-based meta-analysis. The bias of publication will be confirmed via the P value of Egger test. The quality of studies will be evaluated by the Newcastle-Ottawa Scale (NOS). This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY).

Ethics and dissemination Ethical approval is not required as this is a protocol for a systematic review and no primary data are to be collected. Findings will be disseminated through peer-reviewed journal or relevant conferences.

Registration number INPLASY202130024.

Strengths and limitations of this study

This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines.
This systematic review addresses a gap in the literature by providing an examination of the published literature on the neurobiology of individuals with Bulimia nervosa.
There is potential for significant heterogeneity in the reporting of functional MRI data

between different task.

Abbreviations BN = Bulimia nervosa, EDNOS = eating disorder not otherwise specified, AES-SDM = anisotropic effect-size version of seed-based d mapping, ReHo = Regional Homogeneity, ALFF = amplitude of low frequency fluctuation, BOLD-fMRI = blood oxygenation level-dependent magnetic resonance imaging, PRISMA = preferred reporting items for systematic reviews and meta-analyses, NOS = Newcastle-Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, ROIs = region of interests, SVC = small volume corrections.

Keywords fMRI, functional cerebral alterations, meta-analysis, neuroimaging studies, protocol, systematic review

1. INTRODUCTION

Bulimia nervosa (BN) is a psychiatry and psychology disorder that often occurs in later adolescent and young adult years, and recurrent binge eating is a core diagnostic criterion for BN. [1] People with bulimia nervosa always involve recurrent episodes of binge eating followed by inappropriate compensatory acts (purging) to avoid weight gain. such as self-induced vomiting, use of laxatives, fasting and excessive exercise. [2, 3, 4] Psychiatric comorbidity, especially depression and anxiety, is very common in BN patients, [5, 6] and over a total of one fifth BN patients may have the attempt to commit suicide. [6] Studies have shown that BN patients have attention problems [7-10] and are related to an increase in the incidence of attention deficit hyperactivity disorder (ADHD). [8,11,12]

In recent decades. With the significant advances in the neuroscience, research has demonstrated that the function of the prefrontal, insular cortex, orbitofrontal cortex (OFC) and striatum have changes in BN patients, and alterations in the cortico-striatal circuits are semblable to the individuals with substance abuse [13]. It has been reported that OFC and anterior cingulate cortex (ACC) are overactive and Impaired inhibitory control of the lateral prefrontal circuit mediate the urges to binge eating [14]. Compared to HCs, BNs manifest hyperactivity of the parieto-occipital regions and hypoactivation of executive control networks, [15] and show greater insula and ACC activation in response to pictures of food versus household items. [16] The role of inhibitory control is valued increasingly in study of BN. Facing with stimuli about eating disorder, BN patients have impaired response inhibition and inhibitory control. [17] The frontostriatal area has a central role in controlling goal-directed thoughts and behaviors, [18] and the diminution of brain activation in the frontostriatal area contributes to the severity of symptoms of BNs. [19]

Overall, neurobiological research in BN is expanding rapidly. A rigorous review is necessary to increasing our understanding of the neurological underpinnings of BN, considering the actualities that the high rates of psychiatric comorbidities and risk of suicide in BN patients. [6,20] Therefore, this systematic review aims to comprehensive investigate the functional cerebral alterations of BN to increasing understanding of the existing neuroimaging research and better informing treatments across BN. The meta-

analysis that synthesizes the latest evidence of neuroimaging will be carried out via using Anisotropic effect-size version of Seed-based d Mapping (AES-SDM), which has a higher sensitivity, overlap, and good control of false positives than other methods for neuroimaging studies.[21]

2. METHODS AND ANALYSIS

2.1. Study design

The protocol is according to PRISMA-P statement guidelines.[22] and the results of this meta-analysis will be published in a journal or conferences. A preliminary systematic search was performed using Cochrane Library, PubMed, Embase and Web of Science from inception to January 3, 2021. The searching strategy of PubMed database is presented in Table 1.

Table 1

Search strategy for PubMed.

#1	Bulimia [MeSH]
#2	"Bulimia Nervosa"[Mesh]
#3	Bulimi* [Title/Abstract]
#4	Bing* [Title/Abstract]
#5	Overeat* [Title/Abstract]
#6	"Compulsive eat*" [Title/Abstract]
#7	"Eating disorder*" [Title/Abstract]
#8	EDNOS [Title/Abstract]
#9	1-8/or
#10	fMRI [Title/Abstract]
#11	ReHo [Title/Abstract]
#12	ALFF [Title/Abstract]
#13	10-12/or
#14	9 and 13

2.2. Criteria of selection for study

Criteria for inclusion

1. Studies of comparing functional cerebral alterations of bulimia nervosa with that of healthy controls will be included.
2. Adolescents and adult patients diagnosed with BN according to the DSM-5 or any recognized diagnostic criteria.
3. Whole-brain results in three-dimensional coordinates (x, y, z) of changes in standard stereotactic space (Talairach or MNI) were reported.
4. Thresholds for significance corrected for multiple comparisons or uncorrected with spatial extent thresholds were used.
5. The study is available in the English language.

Criteria for exclusion.

1. Studies only reporting region of interests (ROIs) findings were excluded.
2. Studies using coordinates relative to analyze employing small volume corrections (SVC) in preselected ROIs were excluded.

2.3. Selection of studies

After searches, the results were exported to a database named "bulimia nervosa" created by Endnote X9. An initial 1,581 studies were identified and 732 duplicates were removed. Two reviewers will independently screen titles and abstracts from the remaining 849 searches and exclude any that clearly do not satisfy the inclusion criteria. If it is dubious basing the titles and abstracts, the full text will be screened furtherly. A third senior researcher will review articles should disputes arise over study inclusion. The diagram of the selection of studies is shown in Figure 1.

2.4. Data extraction and management

Two reviewers of our team will extract the following information from the database: general characteristics (first author, year of publication, reference ID, etc.), study characteristic (design of trial, control group, method of analysis, etc.), participants, (age, gender, country, etc.), method of acquired data (power of the MRI magnetic field, model of MRI, etc.), etc.
The disagreement between the 2 reviewers will be solved by discussion among all the reviewers. The extraction data will be listed in Microsoft Excel, and the third reviewer will check the data input to ensure the consistency and correct data entry errors.

2.5. Assessment of risk of bias

The quality of all included studies will be assessed by the Cochrane risk of bias tool. The risk of bias will be divided into 3 levels: low risk, high risk, and unclear. This assessment will be conducted independently by 2 reviewers, and any differences in the assessment process will be resolved through consultation with the third reviewer.

2.6. Meta-analysis

The units of each data from different trials will be converted to the International System of Units before statistical analysis. The P statistics and T statistics will be converted into Z statistics using the SDM online converter (www.sdmproject.com/utilities/?show=Statistics).
The peak date (co-ordinates, significant level, and direction of change) will be extracted and combined to recreate an effect-size map. Study maps will be voxel-wise calculated to acquire the random-effects mean, which takes study sample size, intra-study variability, and between-study heterogeneity into account. The meta-analysis of BN will be implemented with standard random-effects variance-weighted. An uncorrected $P< 0.005$ is set as the main threshold, with an additional peak height $Z > 1$ and cluster extent ≥ 10 voxels to optimally balance the sensitivity and specificity. [23] Finally, AES-SDM (https://www.sdmproject.com/software/) [24-25] will be used to quantitatively synthesize the brain functional alterations between BNs and HCs.
When more than 10 studies are included, it is sufficient to detect publication bias in

meta-analytical procedures. [26,27] The probability threshold was decreased to 0.005 to minimize the detection of false correlation.

2.7. Sensitivity analysis

Leave-one-out jackknife sensitivity analysis was used to test the stability of findings of the fMRI studies, which consists of repeating the mean analysis by systematically removing each study and repeating the analysis.

2.8. Meta-regression or subgroup analysis

If sufficient trials are included, we will explore the following potential sources of heterogeneity using subgroup analyses or meta-regression:[23] the different methods of Alff/Reho measuring including scan-T and FWHM; mean age of the patients; mean durations of the patients; mean frequency of patients, etc.

3. PATIENT AND PUBLIC INVOLVEMENT

There were no time or funds allocated to patient and public involvement， and this review does not require ethical approval duo to data that we will not endanger the individual's privacy or compromise their rights. The results of the review will provide systematically view and evidence of neuroimaging in BN, giving implication for clinical practice understanding the physiopathology of BN and further research. Result reporting and presentation will follow the Meta-analysis of Observational Studies in Epidemiology guidelines for reporting.[27] The selection process will be summarized in a flowchart, and the findings of this study may be published in a peer-reviewed journal or distributed at relevant conferences.

3. ETHICS AND DISSEMINATION

This review does not require ethical approval duo to data that we will not endanger the individual's privacy or compromise their rights. The results of the review will provide systematically view and evidence of neuroimaging of BN, giving implication for clinical practice understanding the physiopathology of BN and further research. Result reporting and presentation will follow the Meta-analysis of Observational Studies in Epidemiology guidelines for reporting.[27] The selection process will be summarized in a flowchart, and the findings of this study may be published in a peer-reviewed journal or distributed at relevant conferences.

Author contributions

SYM and DY conceived the review topic. SR drafted the search strategy after background exploratory searches. SYM and YQ co-wrote the initial protocol. DY and SR provided critical appraisal and senior oversight of the protocol. For the systematic review, WQ and LXR will perform the searches, data extraction and analysis. SR will provide oversight of the searches, data analysis and extraction. WQ will provide statistical input for data analysis. SR and DY will provide critical appraisal and senior oversight of the final manuscript.

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Figure 1. PRISMA flflow chart.

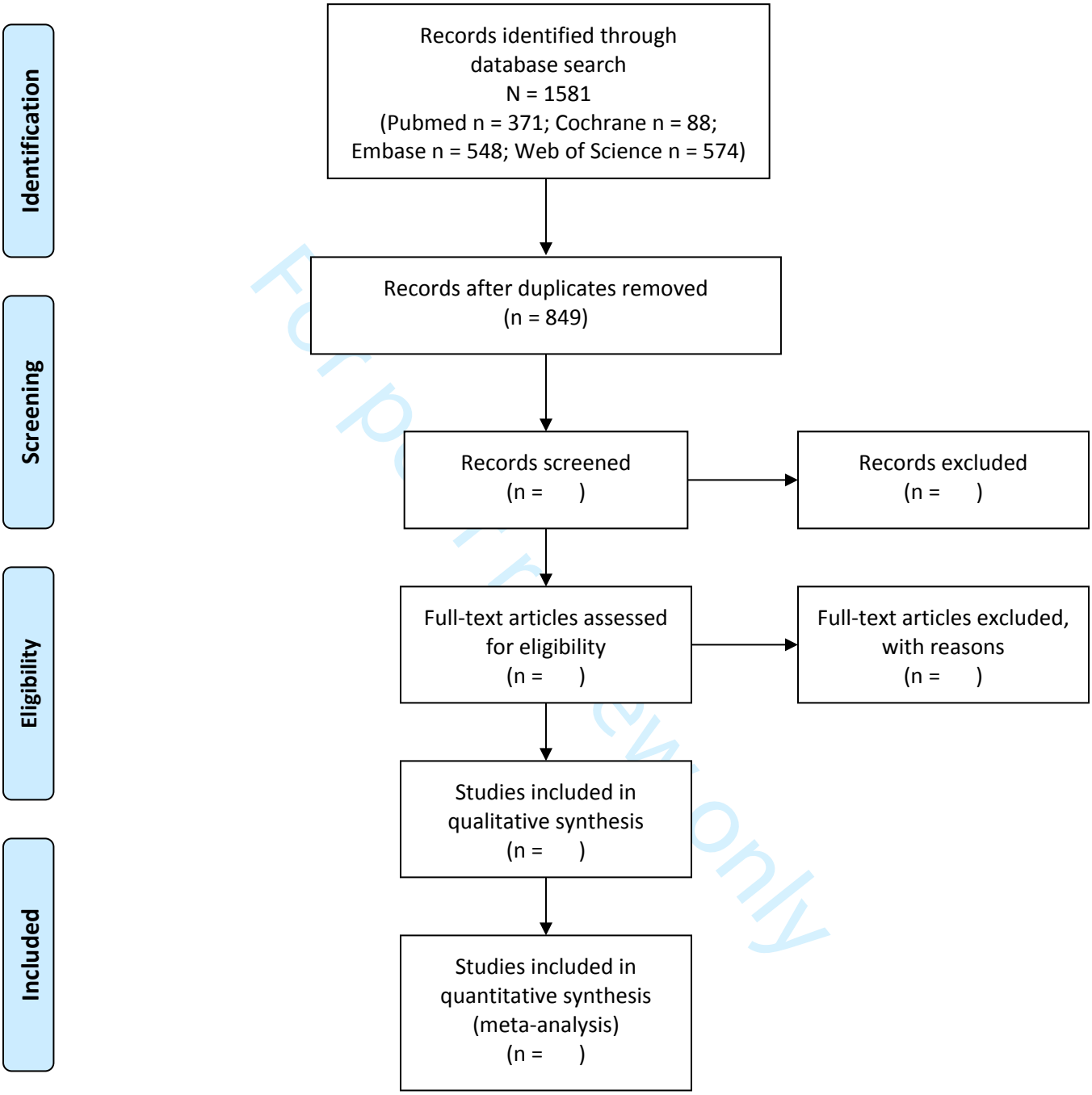

Figure 1. PRISMA flflow chart.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	#1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#1,3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	#1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	#5
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			No support
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	#3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	#3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	#3

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#3
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	#3-4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	#3-4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	#3-4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	#3-4
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#3
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	#3
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#4
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#2

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Addiction
Keywords:	NEONATOLOGY, Eating disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Neuroradiology < RADIOLOGY & IMAGING

Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

Sun, YM, MS[a]; Ye, Q, MS[a]; Wen, Q, MS[a]; Liu, XR, MS[a]; Sun,R, MD[b]; Dai, Y, MS[a]
YMS and QY are joint first authors. Correspondence: Dai, Y, Chengdu Eighth People's Hospital, Chengdu AQ3 No.1120, Rongdu Avenue, Chengdu 610083, Sichuan Province, China (e-mail: 187268806@qq.com).
[a] Chengdu Eighth People's Hospital (Geriatric Hospital of Chengdu Medical College)
[b] Chengdu University of Traditional Chinese Medicine

Abstract

Introduction Bulimia nervosa (BN) is a disorder with significant social and health consequences that typically arise in late adolescence and youth. Accumulating neuroimaging studies have found abnormal functional brain changes in BN patients. This study aims to verify the consistency of the functional cerebral alterations and provide a check on the latest evidence based on the neurobiology studies of individuals with bulimia nervosa.

Methods and analysis A preliminary systematic search will be performed using Cochrane Library, PubMed, Embase, and Web of Science from inception to January 1, 2021. Two researchers will be responsible to the selection of studies, quality assessment and data extraction independently. The Anisotropic effect size version of signed differential mapping (AES-SDM) method will be used to conduct a coordinate-based meta-analysis. The bias of publication will be confirmed via the P value of Egger test. The quality of studies will be evaluated by the Newcastle-Ottawa Scale (NOS).

Ethics and dissemination No ethics approval is required for this is a systematic review protocol and does not require the collection of primary data. Findings will be disseminated through peer-reviewed journal or related conferences.

Strengths and limitations of this study

- This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines.
- This systematic review fills in the gap in the literature by providing an examination of the published literature on the neurobiology of individuals with bulimia nervosa.
- There is potential for significant heterogeneity in the reporting of functional MRI data between different tasks.

Abbreviations BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, AES-SDM = anisotropic effect-size version of seed-based d mapping, ReHo = regional homogeneity, ALFF = amplitude of low frequency fluctuation, BOLD-fMRI = blood oxygenation level-dependent magnetic resonance imaging, PRISMA =

preferred reporting items for systematic reviews and meta-analyses, NOS = Newcastle-Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, ROIs = region of interests, SVC = small volume corrections.

Keywords fMRI, functional cerebral alterations, meta-analysis, neuroimaging studies, protocol, systematic review

1. INTRODUCTION

1.1. Background

Bulimia nervosa (BN) is a psychiatry and psychology disorder that often occurs in late adolescence and youth, and recurrent binge eating is a core diagnostic criterion for BN.[1] People with bulimia nervosa always have recurrent episodes of binge eating followed by inappropriate compensatory behaviors (purging) to avoid weight gain, such as self-induced vomiting, use of laxatives, fasting and excessive exercise.[2-4] Psychiatric comorbidity, especially depression and anxiety, are very common in BN patients,[5, 6] and more than one-fifth of BN patients may have the attempt to commit suicide.[6] Studies have shown that BN patients have attention problems,[7-10] which is related to an increase in the incidence of attention deficit hyperactivity disorder (ADHD).[8, 11, 12] In recent decades. With the significant advances in the neuroscience, researches have demonstrated that the function of the prefrontal lobe, insular cortex, orbitofrontal cortex (OFC) and striatum have changed in BN patients, and alterations in the cortico-striatal circuits are semblable to the individuals with substance abuse.[13] It has been reported that OFC and anterior cingulate cortex (ACC) are overactive and impaired inhibitory control of the lateral prefrontal circuit mediate the urges to binge eating.[14] Compared with HC subjects, BN patients manifest hyperactivity of the parieto-occipital regions and hypoactivation of executive control network,[15] and show greater insula and ACC activation in response to pictures of food rather than household items.[16] The role of inhibitory control is valued increasingly in BN studies. Facing with stimuli about eating disorder, BN patients have impaired response inhibition and inhibitory control.[17] The frontostriatal area has a central role in controlling goal-directed thoughts and behaviours.[18]

Based on the new evidence generated from research framed within the food addiction hypothesis, the explanatory models for eating disorders have changed. The eating behaviour has been put into a central place in models of eating disorders.[19] Changes in the food environment interacting with individual vulnerability are considered to be the key predisposing risk factors, and neuroadaptive changes in reward circuits are thought to maintain these disorders.[19] Small sample researches have been published in recent years examining the neurobiology of the individuals with bulimia nervosa.[20-22] The frontostriatal area, which has a central role in controlling goal-directed thoughts and behaviours, including response inhibition and reward processing, is particularly associated with BN,[18] and the diminished activation of frontostriatal area in BN patients contributes to the severity of symptoms.[23] However, due to the diversity in methodology and small sample sizes within the majority of the studies reviewed, no definite conclusion have been drawn on the neurocognitive profile of individuals with

BN or BED.[24]

Overall, neurobiological research in BN is expanding rapidly. Considering the actualities that the high psychiatric comorbidity rate and high risk of suicide in BN patients, it's necessary to conduct a rigorous review to increase our understanding of the neurological underpinnings of BN,[6, 25] therefore, this systematic review aims to comprehensively investigate the functional cerebral alterations of BN to increase understanding of the existing neuroimaging research and provide better information for the treatments of BN. This meta-analysis that synthesizes the latest evidence of neuroimaging will be carried out by Anisotropic effect-size version of Seed-based d Mapping (AES-SDM), and its main features include:

Accounting for both increases and decreases of the outcome of interest (e.g. activation and deactivation) so that contradictory findings cancel each other;[26]

Use of effect size estimates with random-effects modeling, which increases reliability and performance;[27]

Potential simultaneous inclusion of available 3D statistical images (i.e. maps of t-test values);

Use of threshold-free cluster enhancement (TFCE) statistics.[28]

1.2. Objective

The purpose of this systematic review is to fully understand the functional changes that occur in the brains of BN patients and to provide evidence for the food addiction hypothesis.

2. METHODS AND ANALYSIS

2.1. Study design

This protocol is according to PRISMA-P statement guidelines,[29] and the results of this meta-analysis will be published in a journal or conference. A preliminary systematic search was performed using Cochrane Library, PubMed, Embase and Web of Science from inception to January 3, 2021. The searching strategy of PubMed database is presented in Table 1.

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#13	10-12/or
#14	9 and 13

2.2. Criteria of selection for study

We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols guidelines,[29] and reporting guidelines specific to prediction studies. In accordance with the PICO (population, interventions, comparators and outcomes) framework, inclusion and exclusion criteria will be based on the type of patients, interventions, comparisons and outcomes, as shown in table 2. The study is available in English, and we will exclude data from non-human and duplicate studies.

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
P—Population	Individuals with bulimia nervosa, with fMR	Diagnosed by unofficial diagnostic criteria
I—Intervention	None	None
C—Comparator	Datasets included within the analysis will include a comparison of bulimia nervosa patients to healthy subjects.	No comparisons
O—Outcome	1. Whole-brain results in three-dimensional coordinates (x, y, z) of changes in standard stereotactic space (Talairach or MNI) 2. Thresholds for significance corrected for multiple comparisons.	1. Studies only reporting region of interests (ROIs) findings 2. Studies using coordinates relative to analyze employing small volume corrections (SVC) in preselected ROIs

2.3. Outcomes

The primary outcome is the functional changes (activation and deactivation) in the individuals with bulimia nervosa.

2.4. Selection of studies

After searches, the results were exported to a database named “bulimia nervosa” created by Endnote. An initial 1,581 studies were identified and 732 duplicates were removed. Two reviewers will independently screen titles and abstracts from the remaining 849 searches and exclude any that clearly do not satisfy the inclusion criteria. If there was any doubt based on the titles and abstracts, the full text would be screened furtherly. A third senior researcher would review articles should disputes arise over study inclusion. The diagram of the selection of studies is shown in Figure 1.

2.5. Data extraction and management

Two reviewers of our team will extract the following information from the database: general characteristics (first author, year of publication, reference ID.), study characteristic (design of trial, control group, method of analysis.), participants, (age, gender, country.), imaging parameters (peaks coordinates, magnetic field strength, smoothing kernel, stereotactic template space, analysis software) and statistical threshold. The disagreement between the 2 reviewers will be solved by discussion among all the reviewers. The extraction data will be listed in Microsoft Excel, and the third reviewer will check the data input to ensure the consistency and correct data entry errors.

The units of each data from different trials will be converted to the International System of Units before statistical analysis. The P statistics and T statistics will be converted into Z statistics using the SDM online converter (http://www.sdmproject.com/utilities/?show=Statistics). The peak data (co-ordinates, significant level, and direction of change) will be extracted and combined to recreate an effect-size map. Peak coordinates not in (Montreal Neurological Institute) MNI space will be converted using coordinate mapping software. Aggregate data on participants' demographic characteristics will be conducted in the form of mean ± SD for outcome variables. Standard processing steps will be used in accordance with software documentation.

2.6. Assessment of risk of bias

The risk of bias assessment will be performed qualitatively for each study. The Cochrane Handbook for Systematic Reviews of Interventions will be used. Two authors will evaluate six areas of selection bias which include selection, performance, detection, attrition, reporting and other sources. Trials are going to be rated as low risk, high risk or unclear after evaluation.[30] Any lack of consensus will be adjudicated by consensus with the participation of the third author.

2.7. Quality assessment

The quality of all included studies will be assessed using the Newcastle-Ottawa Scale (NOS), which focuses on subjects, comparability between groups, and measurement of exposure factors. Quality levels of evidence for each study were defined as high (⩾8), medium (6–7), and low (⩽5). Any discrepancies in quality assessment between the two authors were resolved by a third author who served as an arbiter.

2.8. Meta-analysis

The meta-analysis of BN will be implemented with standard random-effects variance-weighted. An uncorrected $P< 0.005$ is set as the main threshold, with an additional peak height $Z > 1$ and cluster extent ≥10 voxels to optimally balance the sensitivity and specificity.[26] Study maps will be voxel-wise calculated to acquire the random-effects mean, which takes study sample size, intra-study variability, and between-study heterogeneity into account. AES-SDM (https://www.sdmproject.com/software/) will be used to quantitatively synthesize the brain functional alterations. SDM is a statistical technique used in meta-analysis papers, examining differences in brain activity for neuroimaging techniques including fMRI.[28, 31]

SDM includes five primary steps:

1) Coordinates of cluster peaks (significant BNs-vs-HCs voxels of activation) are selected.

2) The lower and upper bounds of possible effect size images are estimated.

3) MetaNSUE is used to estimate the most likely effect size and its standard error. Several imputations are generated premised on adding noise to these estimations within the bounds.

4) Each imputed dataset is meta-analysed. Rubin's rules are implemented to combine imputed meta-analysed datasets.

5) A standard permutation test is ran by the recreated of subject images. The process is repeated with each set of permuted images. The maximum statistic of the final image is saved. The distribution of these maxima is used to family-wise error-correct for multiple comparisons.

The minimum number of studies required for synthesis will be three per analysis. When more than 10 studies are included, it is sufficient to detect publication bias in meta-analytical procedures.[32, 33] The probability threshold was decreased to 0.005 to minimize the detection of false correlation.

2.9. Sensitivity analysis

Leave-one-out jackknife sensitivity analysis will be used to test the stability of findings of the fMRI studies, which consists of repeating the mean analysis by systematically removing each study and repeating the analysis.

2.10. Meta-regression or subgroup analysis

If sufficient trials are included, we will explore the following potential sources of heterogeneity using subgroup analyses or meta-regression:[26] the different methods of Alff/Reho measuring including scan-T and FWHM; mean age of the patients;-mean course of the BN; mean frequency of BEs, etc.

3. PATIENT AND PUBLIC INVOLVEMENT

There were no time or funds allocated to patient and public involvement, and this review does not require ethical approval duo to data that we will not endanger the individual's privacy or compromise their rights. The results of the review will provide systematically view and evidence of neuroimaging in BN, giving implication for clinical practice understanding the physiopathology of BN and further research. Result reporting and presentation will follow the Meta-analysis of Observational Studies in Epidemiology guidelines for reporting.[33] The selection process will be summarized in a flowchart, and the findings of this study may be published in a peer-reviewed journal or distributed at relevant conferences.

3. ETHICS AND DISSEMINATION

This review does not require ethical approval duo to data that we will not endanger the individual's privacy or compromise their rights. The results of the review will provide systematically view and evidence of neuroimaging of BN, giving implication for clinical practice understanding the physiopathology of BN and further research. Result reporting and presentation will follow the Meta-analysis of Observational Studies in Epidemiology guidelines for reporting.[33] The selection process will be summarized in a flowchart, and the findings of this study may be published in a peer-reviewed journal or distributed at relevant conferences.

Author contributions

SYM and DY conceived the review topic. SR drafted the search strategy after background exploratory searches. SYM and YQ co-wrote the initial protocol. DY and

SR provided critical appraisal and senior oversight of the protocol. For the systematic review, WQ and LXR will perform the searches, data extraction and analysis. SR will provide oversight of the searches, data analysis and extraction. WQ will provide statistical input for data analysis. SR and DY will provide critical appraisal and senior oversight of the final manuscript.

Competing Interests

No competing interests exist.

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Figure 1. PRISMA flflow chart.

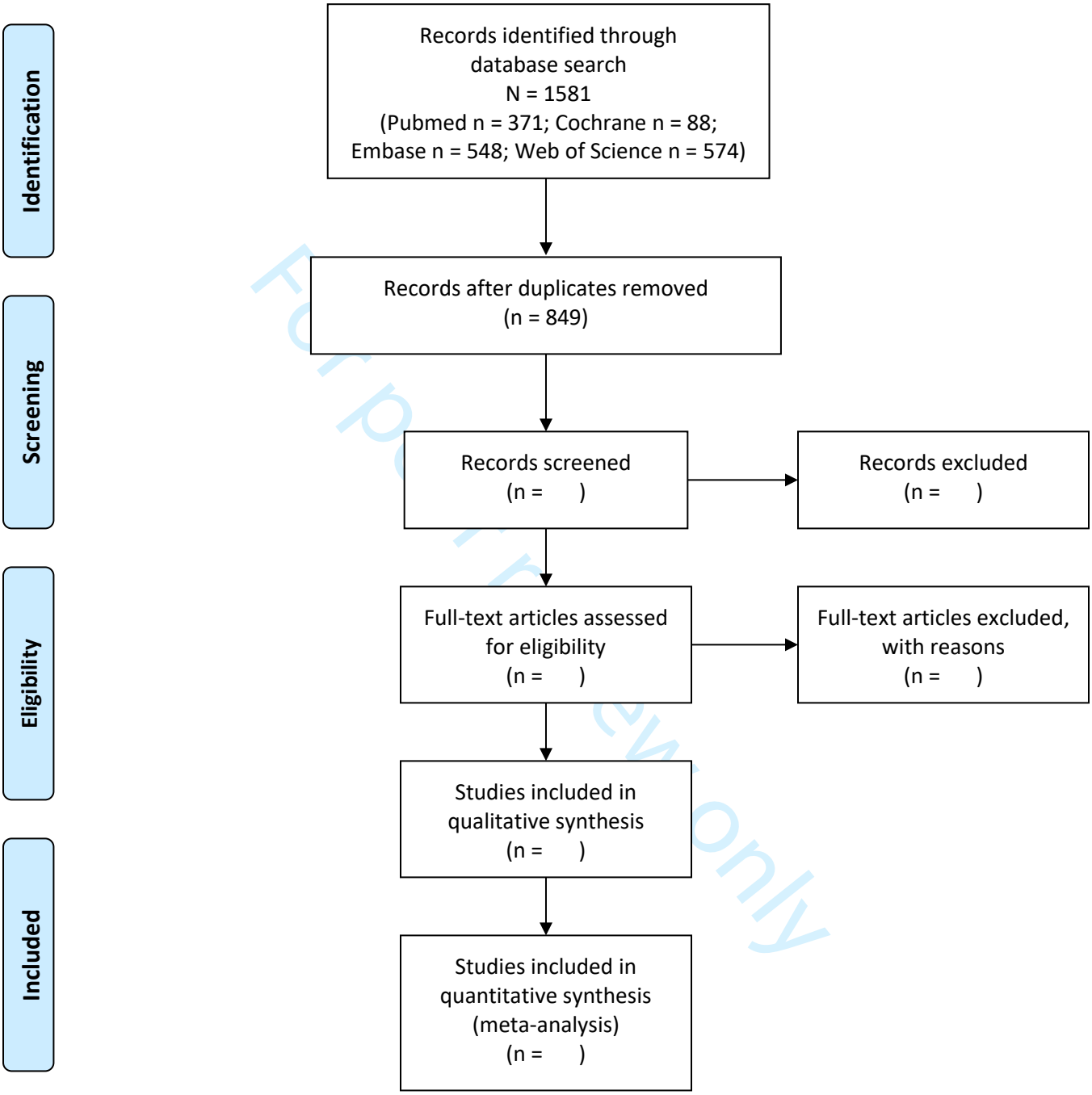

Figure 1. PRISMA flflow chart.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	#1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	-
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	#1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	#7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			No support
Sources	5a	Indicate sources of financial or other support for the review	-
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	#4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	#3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	#3-4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#4-5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	#4-5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	#4-5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	#4-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	#5-6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#4-5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	#4-5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#5-6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

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Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

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Abstract

Introduction Bulimia nervosa (BN) is a disorder with high health and socioeconomic burdens that typically arises in late adolescence and early adulthood. Previous neuroimaging studies have found functional brain changes in patients with BN. This study aims to review the latest neurobiological evidence from studies of individuals with BN, examine the consistency of these findings, and evaluate the food addiction hypothesis of the disease.

Methods and analysis A systematic search will be performed using the Cochrane Library, PubMed, Embase, and Web of Science databases, covering the period from database inception to November 30, 2021. Two researchers will be responsible for study selection, quality assessment, and data extraction. The anisotropic effect size version of the signed differential mapping method will be used to conduct a coordinate-based meta-analysis. Publication bias will be examined with the Egger test. The quality of studies will be evaluated using the Newcastle-Ottawa Scale.

Ethics and dissemination No ethics approval is required for this is a systematic review protocol and does not require the collection of primary data. Findings will be disseminated through peer-reviewed journal or related conferences.

Strengths and limitations of this study

1. This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.
2. The present findings are potentially relevant to researchers and clinicians focused on the neurobiology of BN.
3. High heterogeneity is expected in the reporting of functional magnetic resonance imaging findings from different tasks.

Abbreviations BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, AES-SDM = anisotropic effect-size version of seed-based d mapping, BOLD-fMRI = blood oxygenation level-dependent magnetic resonance imaging, PRISMA = preferred reporting items for systematic reviews and meta-analyses, NOS

= Newcastle-Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, ROIs = region of interests, SVC = small volume corrections.

Keywords fMRI, functional cerebral alterations, meta-analysis, neuroimaging studies, protocol, systematic review

1. INTRODUCTION

1.1. Background

Bulimia nervosa (BN) is a psychiatric and psychological disorder that often occurs in late adolescence and early adulthood; recurrent binge eating is a core diagnostic criterion for BN. [1] People with bulimia nervosa have recurrent episodes of binge eating followed by inappropriate compensatory behaviors (purging) to avoid weight gain, such as self-induced vomiting, use of laxatives, fasting, and excessive exercise.[2-4] Psychiatric comorbidity, including depression and anxiety, is very common in BN patients,[5, 6] and more than one-fifth of BN patients have attempted suicide.[6] Studies have shown that BN patients have attention deficits,[7-10] which are associated with an increase in the incidence of attention deficit hyperactivity disorder.[8, 11, 12]

Recent neuroscience studies have shown that the function of the prefrontal lobe, insular cortex, orbitofrontal cortex (OFC), and striatum differ in BN patients from those in healthy controls, and that alterations in the cortico-striatal circuits are similar to those observed in individuals with substance abuse.[13] It has been suggested that the OFC and anterior cingulate cortex (ACC) are overactive in this patient group, and that impaired inhibitory control of the lateral prefrontal circuit mediates the urges to binge eat.[14] Compared with healthy controls, BN patients manifest hyperactivity of the parieto-occipital regions and hypoactivation of the executive control network[15] and show insula and ACC activation that is greater in response to pictures of food than that in response to pictures of household items.[16] The role of inhibitory control disruption is increasingly recognized in BN studies. Faced with stimuli related to eating, BN patients have impaired response inhibition and inhibitory control.[17] The frontostriatal area plays a central role in controlling goal-directed thoughts and behaviors, including response inhibition and reward processing.[18]

The evidence from research examining the food addiction hypothesis has changed the explanatory models of eating disorders. Eating behavior is central in models of eating disorders.[19] Changes in the food environment that interact with individual vulnerability may be key risk factors for BN, and neuroadaptive changes in reward circuits are likely to maintain these disorders.[19] Recent small sample studies have examined the neurobiology of individuals with BN,[20-22] showing a strong association between the frontostriatal area function and BN.[18] In fact, the diminished activation of the frontostriatal area in BN patients has been shown to contribute to the severity of symptoms.[23] However, small sample sizes and heterogenous protocols of the previous studies preclude any meaningful conclusions on the neurocognitive profile of individuals with BN or binge eating disorder.[24]

Neurobiological research on BN is expanding rapidly. Given the high psychiatric comorbidity and suicide rates in BN patients, a rigorous review of the evidence on the

neurological underpinnings of BN is required.[6, 25] Therefore, this systematic review aims to comprehensively examine the evidence on functional brain changes in patients with BN to evaluate the food addition hypothesis and support disease management. This meta-analysis, which synthesizes the latest neuroimaging evidence, will be performed using the anisotropic effect-size version of seed-based d mapping (AES-SDM). This software's main features include:

Accounting for both increases and decreases of the outcome of interest (e.g. activation and deactivation) so that contradictory findings cancel each other;[26]

Use of effect size estimates with random-effects modeling, which increases reliability and performance;[27]

Potential simultaneous inclusion of available 3D statistical images (i.e. maps of t-test values);

Use of threshold-free cluster enhancement (TFCE) statistics.[28]

1.2. Objective

The purpose of this systematic review is to fully understand the functional changes that occur in the brains of BN patients and to provide evidence for the food addiction hypothesis.

2. METHODS AND ANALYSIS

2.1. Study design

This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.[29] The results of this systematic review and meta-analysis will be published in a specialist journal or presented at a conference. A preliminary search was performed using the Cochrane Library, PubMed, Embase, and Web of Science, including records from database inception to November 30, 2021. The search strategy for the PubMed database is presented in Table 1.

Table 1

Search strategy for PubMed.

#1	Bulimia [MeSH]
#2	"Bulimia Nervosa"[MeSH]
#3	Bulimi* [Title/Abstract]
#4	Bing* [Title/Abstract]
#5	Overeat* [Title/Abstract]
#6	"Compulsive eat*" [Title/Abstract]
#7	"Eating disorder*" [Title/Abstract]
#8	EDNOS [Title/Abstract]
#9	1-8/or
#10	fMRI [Title/Abstract]
#11	functional MRI[Title/Abstract]
#12	functional magnetic resonance imaging [Title/Abstract]
#13	BOLD [Title/Abstract]
#14	10-13/or
#15	9 and 14

2.2. Criteria of selection for study

The present study will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols guidelines.[29] Following the PICO (population, interventions, comparators, and outcomes) framework, inclusion and exclusion criteria will be based on the type of patients, interventions, comparisons, and outcomes reported (Table 2). Only studies published in the English language will be included, and we will exclude data from non-human and duplicate studies.

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
P—Population	Individuals with bulimia nervosa, with fMRI	Diagnosed by unofficial diagnostic criteria
I—Intervention	None	None
C—Comparator	Bulimia nervosa patients vs. healthy controls	No comparisons
O—Outcome	1. Whole-brain results in three-dimensional coordinates (x, y, z) of changes in standard stereotactic space (Talairach or MNI) 2. Thresholds for significance corrected for multiple comparisons (cluster level corrected, $P < 0.05$ FWE/FDR).	1. Studies only reporting region of interests (ROIs) findings 2. Studies using coordinates relative to analyze employing small volume corrections in preselected ROIs.

2.3. Outcomes

The primary outcomes are functional changes (activation and deactivation) in individuals with BN.

2.4. Selection of studies

Search results will be exported to an Endnote database. Two reviewers will independently screen study titles and abstracts and exclude those studies that do not meet the eligibility criteria. Studies whose eligibility is not clear from title and abstract screening will undergo full-text reading. In case of between-reviewer discrepancies on study eligibility, a third reviewer will arbitrate. Study flow is presented in Figure 1

2.5. Data extraction and management

Two reviewers will extract data on the following variables: publication characteristics (first author name, year of publication, reference ID), study characteristics (study design, control group, method of analysis), participant characteristics (age, sex, and country of origin), task paradigm (task details, specific contrasts of interest, cognitive processes interrogated), imaging parameters (peak coordinates, magnetic field strength, smoothing kernel, stereotactic template space, analysis software), and statistical thresholds. Disagreements between the two reviewers will be resolved by consensus. Data sheets will be created in Microsoft Excel. Data quality control will be performed by the third reviewer.

The units from each study dataset will be converted to the International System of Units before statistical analysis. The P-statistics and T-statistics will be converted into Z-statistics using the SDM online converter (http://www.sdmproject.com/utilities/?show=Statistics). The peak data (coordinates, significance level, and direction of

change) will be extracted and combined to recreate an effect-size map. Peak coordinates not in the Montreal Neurological Institute space will be converted using coordinate mapping software. Aggregate data on participants' demographic characteristics will be reported as means with standard deviations. Data processing will be performed according to the manufacturer's instructions.

2.6. Risk of bias and quality assessment

Qualitative risk of bias assessment will be performed for each study. The Cochrane Handbook for Systematic Reviews of Interventions will be used in this study. Two authors will evaluate six areas of selection bias: selection, performance, detection, attrition, reporting, and other sources. Trials will be rated as "low", "high", or "unclear" risk.[30] Any discrepancies in assessment will be resolved by consensus or third-author arbitration.

Study quality will be assessed using the Newcastle-Ottawa Scale, which accounts for study participants, comparability of groups, and measurement of exposure factors. The quality of evidence in each study will be defined as high (≥8 points), medium (6–7 points), or low (≤5 points). Any discrepancies in quality assessments between the two authors will be resolved by third-author arbitration.

2.7. Meta-analysis

The meta-analysis of eligible studies will involve a variance-weighted standard random effects model. An uncorrected P-value of < 0.005 will be set as the main threshold, with an additional peak height Z-value of > 1 and a cluster extent of ≥10 voxels to optimally balance sensitivity and specificity. [26] Study maps will be calculated voxel-wise to estimate the random-effects mean, which considers the sample size, intra-study variability, and between-study heterogeneity. AES-SDM (https://www.sdmproject.com/software/) will be used to quantitatively synthesize findings of functional brain alterations. SDM is a statistical technique for meta-analysis that examines differences in brain activity detected by neuroimaging techniques, including functional magnetic resonance imaging. [28, 31]

SDM includes five primary steps:

1) Coordinates of cluster peaks (significant BNs-vs-HCs voxels of activation) are selected.

2) The lower and upper bounds of possible effect size images are estimated.

3) MetaNSUE is used to estimate the most likely effect size and its standard error. Several imputations are generated premised on adding noise to these estimations within the bounds.

4) Each imputed dataset is meta-analysed. Rubin's rules are implemented to combine imputed meta-analysed datasets.

5) A standard permutation test is ran by the recreated of subject images. The process is repeated with each set of permuted images. The maximum statistic of the final image is saved. The distribution of these maxima is used to family-wise error-correct for multiple comparisons.

The minimum number of studies required for synthesis is three per analysis. When more

than 10 studies are included, it was sufficient to detect publication bias in the meta-analytical procedures.[32, 33] The probability threshold will be decreased to 0.005 to minimize the detection of false correlations.

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Leave-one-out jackknife sensitivity analysis will be used to test the stability of estimates derived from the functional magnetic resonance imaging studies; this technique involves repeating the main analysis and systematically removing one study at a time before repeating the analysis.

2.9. Meta-regression or subgroup analysis

If enough studies are included, the following potential sources of among-study heterogeneity will be explored using subgroup analyses or meta-regression:[26] task paradigm; FEW or FDR; participants' mean age, mean BN duration, and mean frequency of binge eating, among others.

3. PATIENT AND PUBLIC INVOLVEMENT

Neither time nor funding has been allocated to public engagement pertaining to this study. The review findings will provide a summary of evidence on neuroimaging characteristics in BN, which may be relevant to clinicians and researchers focused on the physiopathology of BN.

3. ETHICS AND DISSEMINATION

This review does not require an ethics board approval, as the data used are anonymized and do not infringe on individuals' rights. The results will be reported and discussed, as required by the Meta-analysis of Observational Studies in Epidemiology guidelines.[33] The present findings will be published in a peer-reviewed journal or presented at relevant conferences.

Author contributions

SYM and DY conceived the review topic. SR drafted the search strategy after background exploratory searches. SYM and YQ co-wrote the initial protocol. DY and SR provided critical appraisal and senior oversight of the protocol. For the systematic review, WQ and LXR will perform the searches, data extraction and analysis. SR will provide oversight of the searches, data analysis and extraction. WQ will provide statistical input for data analysis. SR and DY will provide critical appraisal and senior oversight of the final manuscript.

Competing Interests

No competing interests exist.

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Figure 1. PRISMA flflow chart.

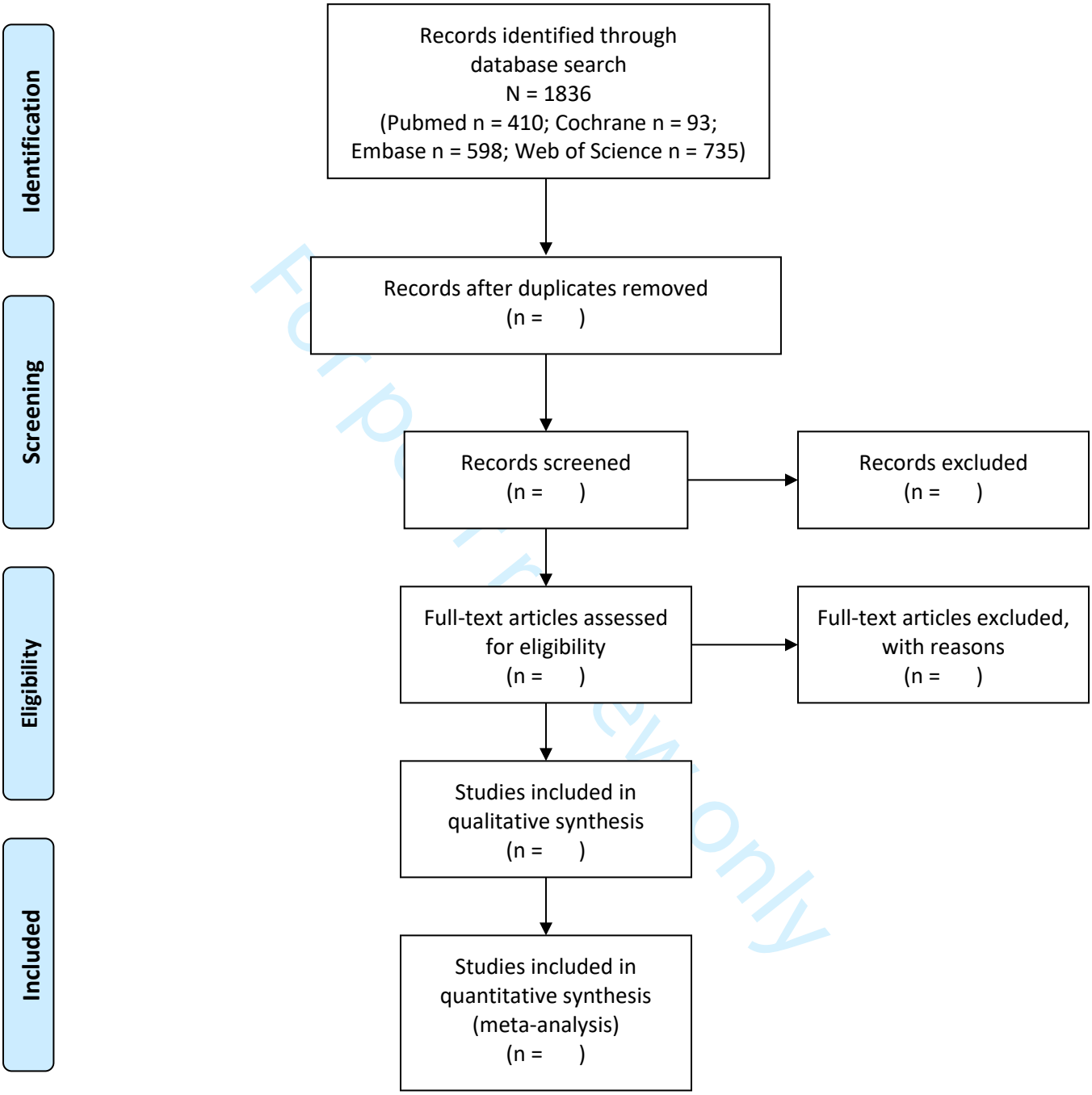

Figure 1. PRISMA flflow chart.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	#1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	-
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	#1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	#7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			No support
Sources	5a	Indicate sources of financial or other support for the review	-
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	#4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	#3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	#3-4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#4-5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	#4-5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	#4-5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	#4-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	#5-6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#4-5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	#4-5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#5-6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

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Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

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Abstract

Introduction Bulimia nervosa (BN) is a disorder with high health and socioeconomic burdens that typically arises in late adolescence and early adulthood. Previous neuroimaging studies have found functional brain changes in patients with BN. This study aims to review the latest neurobiological evidence from studies of individuals with BN, examine the consistency of these findings, and evaluate the food addiction hypothesis of the disease.

Methods and analysis A systematic search will be performed using the Cochrane Library, PubMed, Embase, and Web of Science databases, covering the period from database inception to November 30, 2021. Two researchers will be responsible for study selection, quality assessment, and data extraction. The anisotropic effect size version of the signed differential mapping method will be used to conduct a coordinate-based meta-analysis. Publication bias will be examined with the Egger test. The quality of studies will be evaluated using the Newcastle-Ottawa Scale.

Ethics and dissemination No ethics approval is required for this is a systematic review protocol and does not require the collection of primary data. Findings will be disseminated through peer-reviewed journal or related conferences.

PROSPERO registration number: CRD42022307233

Strengths and limitations of this study

1. This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.
2. Two or more reviewers will independently perform the study selection, data extraction and assessment of the risk of bias.
3. High heterogeneity is expected in the reporting of functional magnetic resonance imaging findings from different tasks.

Abbreviations BN = bulimia nervosa, EDNOS = eating disorder not otherwise

specified, AES-SDM = anisotropic effect-size version of seed-based d mapping, BOLD-fMRI = blood oxygenation level-dependent magnetic resonance imaging, PRISMA = preferred reporting items for systematic reviews and meta-analyses, NOS = Newcastle-Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, ROIs = region of interests, SVC = small volume corrections.

Keywords fMRI, functional cerebral alterations, meta-analysis, neuroimaging studies, protocol, systematic review

1. INTRODUCTION

1.1. Background

Bulimia nervosa (BN) is a psychiatric and psychological disorder that often occurs in late adolescence and early adulthood; recurrent binge eating is a core diagnostic criterion for BN. [1] People with bulimia nervosa have recurrent episodes of binge eating followed by inappropriate compensatory behaviors (purging) to avoid weight gain, such as self-induced vomiting, use of laxatives, fasting, and excessive exercise.[2-4] Psychiatric comorbidity, including depression and anxiety, is very common in BN patients,[5, 6] and more than one-fifth of BN patients have attempted suicide.[6] Studies have shown that BN patients have attention deficits,[7-10] which are associated with an increase in the incidence of attention deficit hyperactivity disorder.[8, 11, 12]

Recent neuroscience studies have shown that the function of the prefrontal lobe, insular cortex, orbitofrontal cortex (OFC), and striatum differ in BN patients from those in healthy controls, and that alterations in the cortico-striatal circuits are similar to those observed in individuals with substance abuse.[13] It has been suggested that the OFC and anterior cingulate cortex (ACC) are overactive in this patient group, and that impaired inhibitory control of the lateral prefrontal circuit mediates the urges to binge eat.[14] Compared with healthy controls, BN patients manifest hyperactivity of the parieto-occipital regions and hypoactivation of the executive control network[15] and show insula and ACC activation that is greater in response to pictures of food than that in response to pictures of household items.[16] The role of inhibitory control disruption is increasingly recognized in BN studies. Faced with stimuli related to eating, BN patients have impaired response inhibition and inhibitory control.[17] The frontostriatal area plays a central role in controlling goal-directed thoughts and behaviors, including response inhibition and reward processing.[18]

The evidence from research examining the food addiction hypothesis has changed the explanatory models of eating disorders. Eating behavior is central in models of eating disorders.[19] Changes in the food environment that interact with individual vulnerability may be key risk factors for BN, and neuroadaptive changes in reward circuits are likely to maintain these disorders.[19] Recent small sample studies have examined the neurobiology of individuals with BN,[20-22] showing a strong association between the frontostriatal area function and BN.[18] In fact, the diminished activation of the frontostriatal area in BN patients has been shown to contribute to the severity of symptoms.[23] However, small sample sizes and heterogenous protocols of the previous studies preclude any meaningful conclusions on the neurocognitive profile of

individuals with BN or binge eating disorder.[24]

Neurobiological research on BN is expanding rapidly. Given the high psychiatric comorbidity and suicide rates in BN patients, a rigorous review of the evidence on the neurological underpinnings of BN is required.[6, 25] Therefore, this systematic review aims to comprehensively examine the evidence on functional brain changes in patients with BN to evaluate the food addition hypothesis and support disease management. This meta-analysis, which synthesizes the latest neuroimaging evidence, will be performed using the anisotropic effect-size version of seed-based d mapping (AES-SDM). This software's main features include:

Accounting for both increases and decreases of the outcome of interest (e.g. activation and deactivation) so that contradictory findings cancel each other;[26]

Use of effect size estimates with random-effects modeling, which increases reliability and performance;[27]

Potential simultaneous inclusion of available 3D statistical images (i.e. maps of t-test values);

Use of threshold-free cluster enhancement (TFCE) statistics.[28]

1.2. Objective

The purpose of this systematic review is to fully understand the functional changes that occur in the brains of BN patients and to provide evidence for the food addiction hypothesis.

2. METHODS AND ANALYSIS

2.1. Study design

This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.[29] The results of this systematic review and meta-analysis will be published in a specialist journal or presented at a conference. A preliminary search was performed using the Cochrane Library, PubMed, Embase, and Web of Science, including records from database inception to November 30, 2021. The search strategy for the PubMed database is presented in Table 1.

Table 1

Search strategy for PubMed.

#1	Bulimia [MeSH]
#2	"Bulimia Nervosa"[MeSH]
#3	Bulimi* [Title/Abstract]
#4	Bing* [Title/Abstract]
#5	Overeat* [Title/Abstract]
#6	"Compulsive eat*" [Title/Abstract]
#7	"Eating disorder*" [Title/Abstract]
#8	EDNOS [Title/Abstract]
#9	1-8/or
#10	fMRI [Title/Abstract]
#11	functional MRI[Title/Abstract]
#12	functional magnetic resonance imaging [Title/Abstract]

#13	BOLD [Title/Abstract]
#14	10-13/or
#15	9 and 14

2.2. Criteria of selection for study

The present study will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols guidelines.[29] Following the PICO (population, interventions, comparators, and outcomes) framework, inclusion and exclusion criteria will be based on the type of patients, interventions, comparisons, and outcomes reported (Table 2). Only studies published in the English language will be included, and we will exclude data from non-human and duplicate studies.

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
P—Population	Individuals with bulimia nervosa, with fMRI	Diagnosed by unofficial diagnostic criteria
I—Intervention	None	None
C—Comparator	Bulimia nervosa patients vs. healthy controls	No comparisons
O—Outcome	1. Whole-brain results in three-dimensional coordinates (x, y, z) of changes in standard stereotactic space (Talairach or MNI) 2. Thresholds for significance corrected for multiple comparisons (cluster level corrected, $P < 0.05$ FWE/FDR).	1. Studies only reporting region of interests (ROIs) findings 2. Studies using coordinates relative to analyze employing small volume corrections in preselected ROIs.

2.3. Outcomes

The primary outcomes are functional changes (activation and deactivation) in individuals with BN.

2.4. Selection of studies

Search results will be exported to an Endnote database. Two reviewers will independently screen study titles and abstracts and exclude those studies that do not meet the eligibility criteria. Studies whose eligibility is not clear from title and abstract screening will undergo full-text reading. In case of between-reviewer discrepancies on study eligibility, a third reviewer will arbitrate. Study flow is presented in Figure 1

2.5. Data extraction and management

Two reviewers will extract data on the following variables: publication characteristics (first author name, year of publication, reference ID), study characteristics (study design, control group, method of analysis), participant characteristics (age, sex, and country of origin), task paradigm (task details, specific contrasts of interest, cognitive processes interrogated), imaging parameters (peak coordinates, magnetic field strength, smoothing kernel, stereotactic template space, analysis software), and statistical thresholds. Disagreements between the two reviewers will be resolved by consensus. Data sheets will be created in Microsoft Excel. Data quality control will be performed by the third reviewer.

The units from each study dataset will be converted to the International System of Units

before statistical analysis. The P-statistics and T-statistics will be converted into Z-statistics using the SDM online converter (http://www.sdmproject.com/utilities/?show=Statistics). The peak data (coordinates, significance level, and direction of change) will be extracted and combined to recreate an effect-size map. Peak coordinates not in the Montreal Neurological Institute space will be converted using coordinate mapping software. Aggregate data on participants' demographic characteristics will be reported as means with standard deviations. Data processing will be performed according to the manufacturer's instructions.

2.6. Risk of bias and quality assessment

Qualitative risk of bias assessment will be performed for each study. The Cochrane Handbook for Systematic Reviews of Interventions will be used in this study. Two authors will evaluate six areas of selection bias: selection, performance, detection, attrition, reporting, and other sources. Trials will be rated as "low", "high", or "unclear" risk.[30] Any discrepancies in assessment will be resolved by consensus or third-author arbitration.

Study quality will be assessed using the Newcastle-Ottawa Scale, which accounts for study participants, comparability of groups, and measurement of exposure factors. The quality of evidence in each study will be defined as high (≥8 points), medium (6–7 points), or low (≤5 points). Any discrepancies in quality assessments between the two authors will be resolved by third-author arbitration.

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Competing Interests

No competing interests exist.

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Figure 1. PRISMA flflow chart.

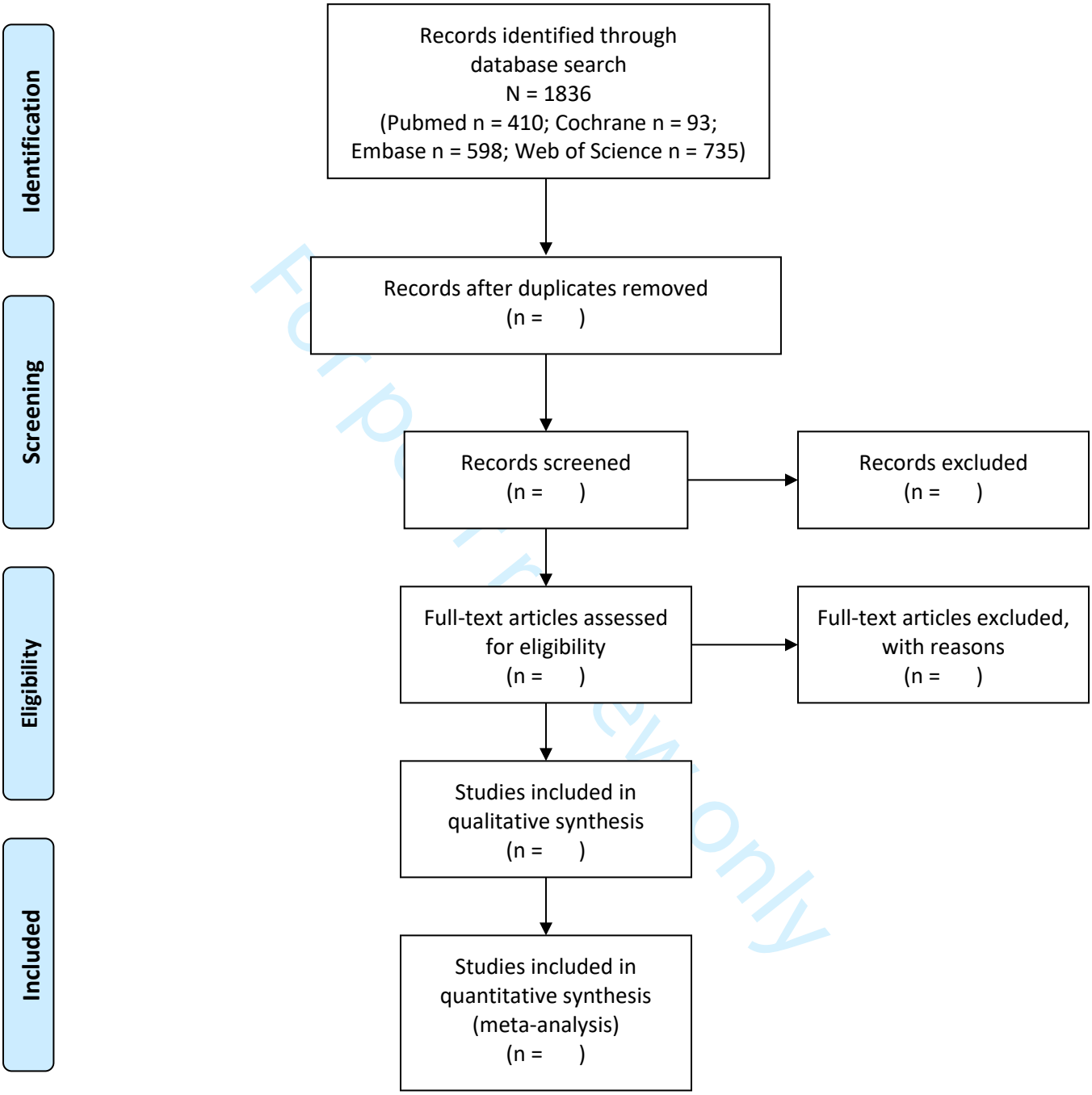

Figure 1. PRISMA flflow chart.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	#1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	-
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	#1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	#7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			No support
Sources	5a	Indicate sources of financial or other support for the review	-
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	#4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	#3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	#3-4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#4-5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	#4-5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	#4-5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	#4-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	#5-6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#4-5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	#4-5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#5-6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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