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# BMJ Open

## 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

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Manuscripts

# 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

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2  
3 between different task.  
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5 **Abbreviations** BN = Bulimia nervosa, EDNOS = eating disorder not otherwise  
6 specified, AES-SDM = anisotropic effect-size version of seed-based d mapping, ReHo  
7 = Regional Homogeneity, ALFF = amplitude of low frequency fluctuation, BOLD-  
8 fMRI = blood oxygenation level-dependent magnetic resonance imaging, PRISMA =  
9 preferred reporting items for systematic reviews and meta-analyses, NOS = Newcastle-  
10 Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, ROIs =  
11 region of interests, SVC = small volume corrections.  
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14

15 **Keywords** fMRI, functional cerebral alterations, meta-analysis, neuroimaging  
16 studies, protocol, systematic review  
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## 19 1. INTRODUCTION 20

21 Bulimia nervosa (BN) is a psychiatry and psychology disorder that often occurs in later  
22 adolescent and young adult years, and recurrent binge eating is a core diagnostic  
23 criterion for BN. [1] People with bulimia nervosa always involve recurrent episodes of  
24 binge eating followed by inappropriate compensatory acts (purging) to avoid weight  
25 gain. such as self-induced vomiting, use of laxatives, fasting and excessive exercise. [2,  
26 3, 4] Psychiatric comorbidity, especially depression and anxiety, is very common in BN  
27 patients, [5, 6] and over a total of one fifth BN patients may have the attempt to commit  
28 suicide. [6] Studies have shown that BN patients have attention problems [7-10] and are  
29 related to an increase in the incidence of attention deficit hyperactivity disorder  
30 (ADHD). [8,11,12]  
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33 In recent decades. With the significant advances in the neuroscience, research has  
34 demonstrated that the function of the prefrontal, insular cortex, orbitofrontal cortex  
35 (OFC) and striatum have changes in BN patients, and alterations in the cortico-striatal  
36 circuits are semblable to the individuals with substance abuse [13]. It has been reported  
37 that OFC and anterior cingulate cortex (ACC) are overactive and Impaired inhibitory  
38 control of the lateral prefrontal circuit mediate the urges to binge eating [14]. Compared  
39 to HCs, BNs manifest hyperactivity of the parieto-occipital regions and hypoactivation  
40 of executive control networks, [15] and show greater insula and ACC activation in  
41 response to pictures of food versus household items. [16] The role of inhibitory control  
42 is valued increasingly in study of BN. Facing with stimuli about eating disorder, BN  
43 patients have impaired response inhibition and inhibitory control. [17] The frontostriatal  
44 area has a central role in controlling goal-directed thoughts and behaviors, [18] and the  
45 diminution of brain activation in the frontostriatal area contributes to the severity of  
46 symptoms of BNs. [19]  
47  
48

49 Overall, neurobiological research in BN is expanding rapidly. A rigorous review is  
50 necessary to increasing our understanding of the neurological underpinnings of BN,  
51 considering the actualities that the high rates of psychiatric comorbidities and risk of  
52 suicide in BN patients. [6,20] Therefore, this systematic review aims to comprehensive  
53 investigate the functional cerebral alterations of BN to increasing understanding of the  
54 existing neuroimaging research and better informing treatments across BN. The meta-  
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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.<sup>[21]</sup>

## 2. METHODS AND ANALYSIS

### 2.1. Study design

The protocol is according to PRISMA-P statement guidelines.<sup>[22]</sup> 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](http://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  $\geq 10$  voxels to optimally balance the sensitivity and specificity.<sup>[23]</sup> Finally, AES-SDM (<https://www.sdmproject.com/software/>)<sup>[24-25]</sup> 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.<sup>[26,27]</sup> 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:<sup>[23]</sup> 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 due 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.<sup>[27]</sup> 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 due 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.<sup>[27]</sup> 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.

## References

- 1
- 2
- 3
- 4 [1]. Hay P, et al. Burden and health-related quality of life of eating disorders, including
- 5 Avoidant/Restrictive Food Intake Disorder (ARFID), in the Australian population.
- 6 *Journal of Eating Disorders*. 2017;5(21). <https://doi.org/10.1186/s40337-017-0149-z>.
- 7 [2]. American Psychiatric Association. *Diagnostic and Statistical Manual of mental*
- 8 *disorders*. 5th ed; 2013.
- 9 [3]. Herpertz-Dahlmann B. Adolescent eating disorders: definitions, symptomatology,
- 10 epidemiology and comorbidity. *Child Adolesc Psychiatry Clin N Am*. 2009; 18: 31–47.
- 11 [4]. Hoste RR, Labuschagne Z, Le Grange D. Adolescent bulimia nervosa. *Curr*
- 12 *Psychiatry Rep*. 2012; 14: 391–397. doi: 10.1007/s11920-012-0280-0 PMID:
- 13 22614677
- 14 [5]. Ulfvebrand S, et al. Psychiatric comorbidity in women and men with eating
- 15 disorders: results from a large clinical database. *Psychiatry Research*. 2015; 230:294–
- 16 9.
- 17 [6]. Pisetsky E, et al. Depression and personality traits associated with emotion
- 18 dysregulation: Correlates of suicide attempts in women with bulimia nervosa. *European*
- 19 *Eating Disorders Review*. 2015; 23:537–44.
- 20 [7]. Duchesne M, Mattos P, Fontenelle LF, Veiga H, Rizo L, Appolinario JC.
- 21 [Neuropsychology of eating disorders: a systematic review of the literature].
- 22 *Rev Bras Psiquiatr*. 2004; 26: 107–117.
- 23 [8]. Seitz J, Kahraman-Lanzerath B, Legenbauer T, Sarrar L, Herpertz S, Salbach-
- 24 Andrae H, et al. The Role of Impulsivity, Inattention and Comorbid ADHD in Patients
- 25 with Bulimia Nervosa. Reif A, editor. *PLoS ONE*. 2013; 8: e63891. doi:
- 26 10.1371/journal.pone.0063891 PMID: 23700439
- 27 [9]. Wentz E, Lacey JH, Waller G, Rastam M, Turk J, Gillberg C. Childhood onset
- 28 neuropsychiatric disorders in adult eating disorder patients. A pilot study. *Eur Child*
- 29 *Adolesc Psychiatry*. 2005; 14: 431–437.
- 30 [10]. Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit
- 31 hyperactivity symptoms and disorder in eating disorder inpatients. *Int J Eat Disord*. 2009;
- 32 42: 375–378.
- 33 [11]. Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female
- 34 inpatients with eating disorders. *Psychosom Med*. 2006; 68: 454–462.
- 35 [12]. Yilmaz Z, Kaplan AS, Zai CC, Levitan RD, Kennedy JL. COMT Val158Met
- 36 variant and functional haplotypes associated with childhood ADHD history in women
- 37 with bulimia nervosa. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35: 948–952.
- 38 [13]. Kessler RM, et al. The neurobiological basis of binge eating disorder.
- 39 *Neuroscience and Biobehavioral Reviews*. 2016; 63:223–8.
- 40 [14]. Van den Eynde F, et al. Repetitive Transcranial Magnetic Stimulation Reduces
- 41 Cue-Induced Food Craving in Bulimic Disorders. *Biological Psychiatry*. 2010; 67:793–
- 42 5.
- 43 [15]. Seitz J, et al. Attention Network Dysfunction in Bulimia Nervosa - An fMRI Study.
- 44 *Plos One*. 2016;8. <https://doi.org/10.1371/journal.pone.0161329>.
- 45 [16] Scheinle A, Schäfer A, Herman A, Vaitl D. Binge-eating disorder: Reward
- 46 sensitivity and brain activation to images to food. *Biol Psychiatry* 2009; 65:654–661.
- 47 [17]. Wu M, et al. Inhibitory control in bulimic-type eating disorders: A systematic
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2  
3 review and meta-analysis. *Plos One*. 2013;8(12): e83412.
- 4 [18]. Celone KA, et al. An fMRI investigation of the fronto-striatal learning system in  
5 women who exhibit eating disorder behaviors. *Neuroimage*. 2011;56(3):1749–57.
- 6 [19]. Skunde M, et al. Neural signature of behavioural inhibition in women with bulimia  
7 nervosa. *Journal of Psychiatry and Neuroscience*. 2016;41(5): E69–78.
- 8 [20]. Welch E, et al. Treatment-seeking patients with binge-eating disorder in the  
9 Swedish national registers: clinical course and psychiatric comorbidity. *BMC*  
10 *Psychiatry*. 2016;16(163)
- 11 [21] Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in  
12 obsessive-compulsive disorder. *Br J Psychiatry* 2009; 195:393–402. [published Online  
13 First: 2009/11/03].
- 14 [22] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic  
15 review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4:1.
- 16 [23] Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in  
17 obsessive-compulsive disorder. *Br J Psychiatry* 2009; 195:393–402
- 18 [24] Radua J, Mataix-Cols D, Phillips ML, et al. A new meta-analytic method for  
19 neuroimaging studies that combines reported peak coordinates and statistical  
20 parametric maps. *Eur Psychiatry* 2012; 27:605–11.
- 21 [25] Radua J, Via E, Catani M, et al. Voxel-based meta-analysis of regional white-  
22 matter volume differences in autism spectrum disorder versus healthy controls. *Psychol*  
23 *Med* 2011; 41:1539–50.
- 24 [26] Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication  
25 bias in meta-analysis. *Stat Med* 2001; 20:641–54. [published Online First: 2001/02/27].
- 26 [27] Lau J, Ioannidis JP, Terrin N, et al. The case of the misleading funnel plot. *BMJ*  
27 2006; 333:597–600. [published Online First: 2006/09/16]

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37 Figure 1. PRISMA flflow chart.  
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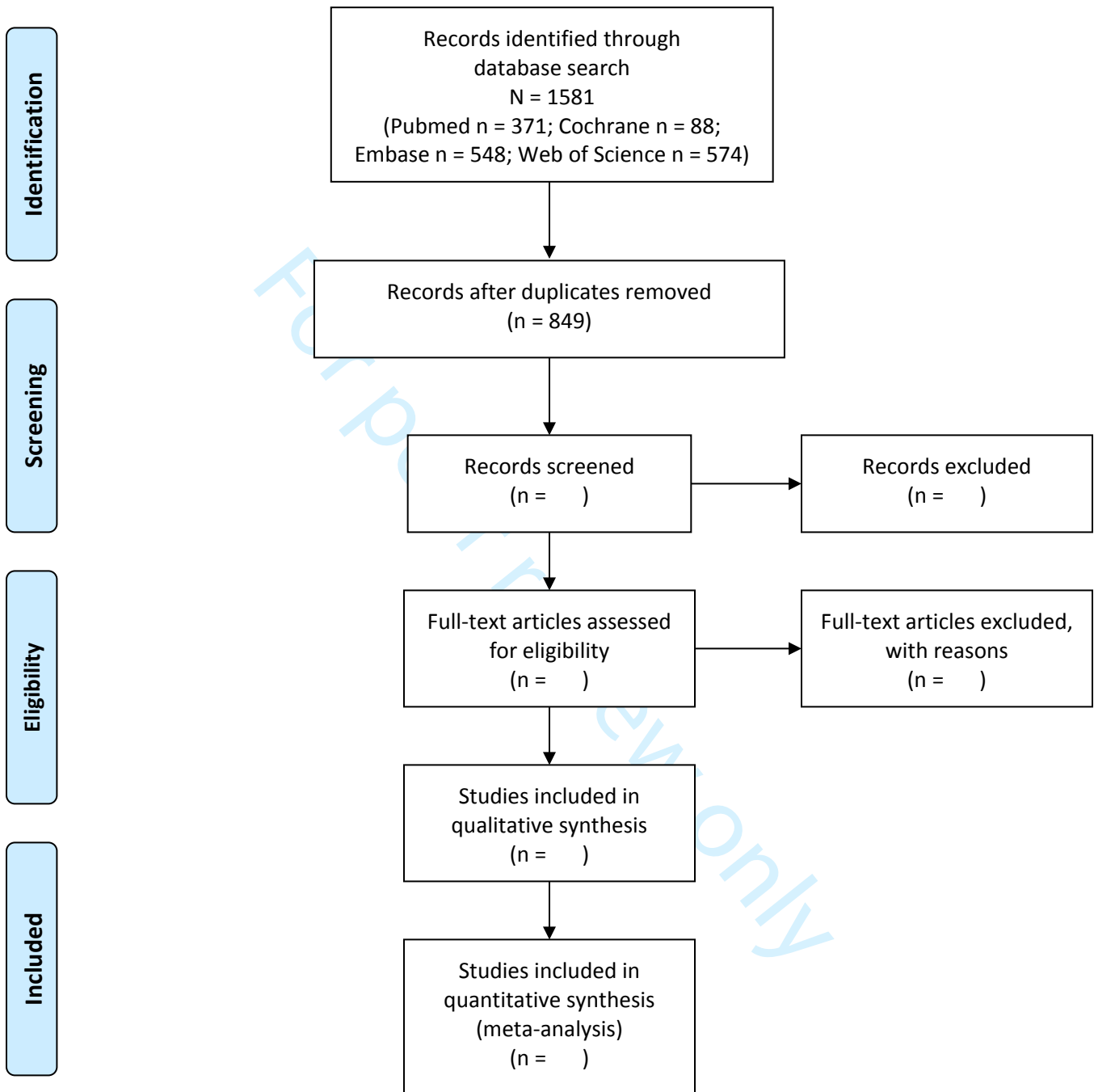


Figure 1. PRISMA flflow chart.

**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 #
<b>ADMINISTRATIVE INFORMATION</b>			
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	
<b>INTRODUCTION</b>			
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)	
<b>METHODS</b>			
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 <sup>2</sup> , Kendall's $\tau$ )	#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.**

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

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# 1 **Brain functional changes in individuals with bulimia nervosa: a** 2 **protocol for systematic review and meta-analysis**

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8 <sup>b</sup> Chengdu University of Traditional Chinese Medicine

## 9 **Abstract**

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

16 **Methods and analysis** A preliminary systematic search will be performed using  
17 Cochrane Library, PubMed, Embase, and Web of Science from inception to January 1,  
18 2021. Two researchers will be responsible to the selection of studies, quality assessment  
19 and data extraction independently. The Anisotropic effect size version of signed  
20 differential mapping (AES-SDM) method will be used to conduct a coordinate-based  
21 meta-analysis. The bias of publication will be confirmed via the P value of Egger test.  
22 The quality of studies will be evaluated by the Newcastle-Ottawa Scale (NOS).

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

## 26 **Strengths and limitations of this study**

27 This systematic review protocol follows the Preferred Reporting Items for Systematic  
28 Review and Meta-Analyses Protocols (PRISMA-P) guidelines.

29 This systematic review fills in the gap in the literature by providing an examination of  
30 the published literature on the neurobiology of individuals with bulimia nervosa.

31 There is potential for significant heterogeneity in the reporting of functional MRI data  
32 between different tasks.

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

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3 37 preferred reporting items for systematic reviews and meta-analyses, NOS = Newcastle-  
4 38 Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, ROIs =  
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8 40 **Keywords** fMRI, functional cerebral alterations, meta-analysis, neuroimaging  
9 41 studies, protocol, systematic review

## 10 42 **1. INTRODUCTION**

### 11 43 **1.1. Background**

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14 44 Bulimia nervosa (BN) is a psychiatry and psychology disorder that often occurs in late  
15 45 adolescence and youth, and recurrent binge eating is a core diagnostic criterion for BN.

16 46 <sup>(1)</sup> People with bulimia nervosa always have recurrent episodes of binge eating followed  
17 47 by inappropriate compensatory behaviors (purging) to avoid weight gain, such as self-  
18 48 induced vomiting, use of laxatives, fasting and excessive exercise.<sup>(2-4)</sup> Psychiatric  
19 49 comorbidity, especially depression and anxiety, are very common in BN patients,<sup>(5, 6)</sup>  
20 50 and more than one-fifth of BN patients may have the attempt to commit suicide.<sup>(6)</sup>  
21 51 Studies have shown that BN patients have attention problems,<sup>(7-10)</sup> which is related to  
22 52 an increase in the incidence of attention deficit hyperactivity disorder (ADHD).<sup>(8, 11, 12)</sup>  
23 53 In recent decades. With the significant advances in the neuroscience, researches have  
24 54 demonstrated that the function of the prefrontal lobe, insular cortex, orbitofrontal cortex  
25 55 (OFC) and striatum have changed in BN patients, and alterations in the cortico-striatal  
26 56 circuits are semblable to the individuals with substance abuse.<sup>(13)</sup> It has been reported  
27 57 that OFC and anterior cingulate cortex (ACC) are overactive and impaired inhibitory  
28 58 control of the lateral prefrontal circuit mediate the urges to binge eating.<sup>(14)</sup> Compared  
29 59 with HC subjects, BN patients manifest hyperactivity of the parieto-occipital regions  
30 60 and hypoactivation of executive control network,<sup>(15)</sup> and show greater insula and ACC  
31 61 activation in response to pictures of food rather than household items.<sup>(16)</sup> The role of  
32 62 inhibitory control is valued increasingly in BN studies. Facing with stimuli about eating  
33 63 disorder, BN patients have impaired response inhibition and inhibitory control.<sup>(17)</sup> The  
34 64 frontostriatal area has a central role in controlling goal-directed thoughts and  
35 65 behaviours.<sup>(18)</sup>

36 66 Based on the new evidence generated from research framed within the food addiction  
37 67 hypothesis, the explanatory models for eating disorders have changed. The eating  
38 68 behaviour has been put into a central place in models of eating disorders.<sup>(19)</sup> Changes  
39 69 in the food environment interacting with individual vulnerability are considered to be  
40 70 the key predisposing risk factors, and neuroadaptive changes in reward circuits are  
41 71 thought to maintain these disorders.<sup>(19)</sup> Small sample researches have been published in  
42 72 recent years examining the neurobiology of the individuals with bulimia nervosa.<sup>(20-22)</sup>  
43 73 The frontostriatal area, which has a central role in controlling goal-directed thoughts  
44 74 and behaviours, including response inhibition and reward processing, is particularly  
45 75 associated with BN,<sup>(18)</sup> and the diminished activation of frontostriatal area in BN  
46 76 patients contributes to the severity of symptoms.<sup>(23)</sup> However, due to the diversity in  
47 77 methodology and small sample sizes within the majority of the studies reviewed, no  
48 78 definite conclusion have been drawn on the neurocognitive profile of individuals with

79 BN or BED.<sup>(24)</sup>

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

89 Accounting for both increases and decreases of the outcome of interest (e.g. activation and  
90 deactivation) so that contradictory findings cancel each other;<sup>(26)</sup>

91 Use of effect size estimates with random-effects modeling, which increases reliability and  
92 performance;<sup>(27)</sup>

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

94 Use of threshold-free cluster enhancement (TFCE) statistics.<sup>(28)</sup>

## 95 1.2. Objective

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

## 98 2. METHODS AND ANALYSIS

### 99 2.1. Study design

100 This protocol is according to PRISMA-P statement guidelines,<sup>(29)</sup> and the results of this meta-  
101 analysis will be published in a journal or conference. A preliminary systematic search was  
102 performed using Cochrane Library, PubMed, Embase and Web of Science from  
103 inception to January 3, 2021. The searching strategy of PubMed database is presented  
104 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



## 105 2.2. Criteria of selection for study

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

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
<b>P—Population</b>	Individuals with bulimia nervosa, with fMR	Diagnosed by unofficial diagnostic criteria
<b>I—Intervention</b>	None	None
<b>C—Comparator</b>	Datasets included within the analysis will include a comparison of bulimia nervosa patients to healthy subjects.	No comparisons
<b>O—Outcome</b>	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

## 112 2.3. Outcomes

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

## 115 2.4. Selection of studies

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

## 123 2.5. Data extraction and management

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

1  
2  
3 133 The units of each data from different trials will be converted to the International System  
4 134 of Units before statistical analysis. The P statistics and T statistics will be converted  
5 135 into Z statistics using the SDM online converter ([http://www.sdmproject.com/utilities/?](http://www.sdmproject.com/utilities/?show=Statistics)  
6 136 [show=Statistics](http://www.sdmproject.com/utilities/?show=Statistics)). The peak data (co-ordinates, significant level, and direction of change)  
7 137 will be extracted and combined to recreate an effect-size map. Peak coordinates not in  
8 138 (Montreal Neurological Institute) MNI space will be converted using coordinate  
9 139 mapping software. Aggregate data on participants' demographic characteristics will be  
10 140 conducted in the form of mean  $\pm$  SD for outcome variables. Standard processing steps  
11 141 will be used in accordance with software documentation.

## 12 142 **2.6. Assessment of risk of bias**

13 143 The risk of bias assessment will be performed qualitatively for each study. The  
14 144 Cochrane Handbook for Systematic Reviews of Interventions will be used. Two authors  
15 145 will evaluate six areas of selection bias which include selection, performance, detection,  
16 146 attrition, reporting and other sources. Trials are going to be rated as low risk, high risk  
17 147 or unclear after evaluation.<sup>(30)</sup> Any lack of consensus will be adjudicated by consensus  
18 148 with the participation of the third author.

## 19 149 **2.7. Quality assessment**

20 150 The quality of all included studies will be assessed using the Newcastle-Ottawa Scale  
21 151 (NOS), which focuses on subjects, comparability between groups, and measurement of  
22 152 exposure factors. Quality levels of evidence for each study were defined as high ( $\geq 8$ ),  
23 153 medium (6–7), and low ( $\leq 5$ ). Any discrepancies in quality assessment between the two  
24 154 authors were resolved by a third author who served as an arbiter.

## 25 155 **2.8. Meta-analysis**

26 156 The meta-analysis of BN will be implemented with standard random-effects variance-  
27 157 weighted. An uncorrected  $P < 0.005$  is set as the main threshold, with an additional peak  
28 158 height  $Z > 1$  and cluster extent  $\geq 10$  voxels to optimally balance the sensitivity and  
29 159 specificity.<sup>(26)</sup> Study maps will be voxel-wise calculated to acquire the random-effects  
30 160 mean, which takes study sample size, intra-study variability, and between-study  
31 161 heterogeneity into account. AES-SDM (<https://www.sdmproject.com/software/>) will  
32 162 be used to quantitatively synthesize the brain functional alterations. SDM is a statistical  
33 163 technique used in meta-analysis papers, examining differences in brain activity for  
34 164 neuroimaging techniques including fMRI.<sup>(28, 31)</sup>

35 165 SDM includes five primary steps:

- 36 166 1) Coordinates of cluster peaks (significant BNs-vs-HCs voxels of activation) are  
37 167 selected.
- 38 168 2) The lower and upper bounds of possible effect size images are estimated.
- 39 169 3) MetaNSUE is used to estimate the most likely effect size and its standard error.  
40 170 Several imputations are generated premised on adding noise to these estimations within  
41 171 the bounds.
- 42 172 4) Each imputed dataset is meta-analysed. Rubin's rules are implemented to combine  
43 173 imputed meta-analysed datasets.

1  
2  
3 174 5) A standard permutation test is ran by the recreated of subject images. The process is  
4 175 repeated with each set of permuted images. The maximum statistic of the final image  
5 176 is saved. The distribution of these maxima is used to family-wise error-correct for  
6 177 multiple comparisons.

7  
8 178 The minimum number of studies required for synthesis will be three per analysis. When  
9 179 more than 10 studies are included, it is sufficient to detect publication bias in meta-  
10 180 analytical procedures.<sup>(32, 33)</sup> The probability threshold was decreased to 0.005 to  
11 181 minimize the detection of false correlation.

## 12 13 14 182 **2.9. Sensitivity analysis**

15  
16 183 Leave-one-out jackknife sensitivity analysis will be used to test the stability of findings  
17 184 of the fMRI studies, which consists of repeating the mean analysis by systematically  
18 185 removing each study and repeating the analysis.

## 19 20 21 186 **2.10. Meta-regression or subgroup analysis**

22  
23 187 If sufficient trials are included, we will explore the following potential sources of  
24 188 heterogeneity using subgroup analyses or meta-regression:<sup>(26)</sup> the different methods of  
25 189 Alff/Reho measuring including scan-T and FWHM; mean age of the patients;-mean  
26 190 course of the BN; mean frequency of BEs, etc.

## 27 28 29 191 **3. PATIENT AND PUBLIC INVOLVEMENT**

30  
31 192 There were no time or funds allocated to patient and public involvement, and this  
32 193 review does not require ethical approval duo to data that we will not endanger the  
33 194 individual's privacy or compromise their rights. The results of the review will provide  
34 195 systematically view and evidence of neuroimaging in BN, giving implication for  
35 196 clinical practice understanding the physiopathology of BN and further research. Result  
36 197 reporting and presentation will follow the Meta-analysis of Observational Studies in  
37 198 Epidemiology guidelines for reporting.<sup>(33)</sup> The selection process will be summarized in  
38 199 a flowchart, and the findings of this study may be published in a peer-reviewed journal  
39 200 or distributed at relevant conferences.

## 40 41 42 43 201 **3. ETHICS AND DISSEMINATION**

44  
45 202 This review does not require ethical approval duo to data that we will not endanger the  
46 203 individual's privacy or compromise their rights. The results of the review will provide  
47 204 systematically view and evidence of neuroimaging of BN, giving implication for  
48 205 clinical practice understanding the physiopathology of BN and further research. Result  
49 206 reporting and presentation will follow the Meta-analysis of Observational Studies in  
50 207 Epidemiology guidelines for reporting.<sup>(33)</sup> The selection process will be summarized in  
51 208 a flowchart, and the findings of this study may be published in a peer-reviewed journal  
52 209 or distributed at relevant conferences.

## 53 54 55 56 210 **Author contributions**

57  
58 211 SYM and DY conceived the review topic. SR drafted the search strategy after  
59 212 background exploratory searches. SYM and YQ co-wrote the initial protocol. DY and  
60

1  
2  
3 213 SR provided critical appraisal and senior oversight of the protocol. For the systematic  
4 214 review, WQ and LXR will perform the searches, data extraction and analysis. SR will  
5 215 provide oversight of the searches, data analysis and extraction. WQ will provide  
6 216 statistical input for data analysis. SR and DY will provide critical appraisal and senior  
7 217 oversight of the final manuscript.  
8  
9

## 10 218 **Competing Interests**

11  
12 219 No competing interests exist.  
13

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15  
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18

## 19 223 **References**

- 20  
21  
22 224 1. Hay P, Mitchison D, Collado AEL, González-Chica DA, Stocks N, Touyz S. Burden and  
23  
24 225 health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake  
25  
26 226 Disorder (ARFID), in the Australian population. *Journal of eating disorders*. 2017;5:21.  
27  
28  
29 227 2. Organization AP. *Diagnostic and statistical manual of mental disorders (5th ed.)*:  
30  
31 228 *Diagnostic and statistical manual of mental disorders (5th ed.)*; 2013.  
32  
33  
34 229 3. Herpertz-Dahlmann B. Adolescent eating disorders: definitions, symptomatology,  
35  
36 230 epidemiology and comorbidity. *Child and adolescent psychiatric clinics of North America*.  
37  
38 231 2009;18(1):31-47.  
39  
40  
41  
42 232 4. Hoste RR, Labuschagne Z, Le Grange D. Adolescent bulimia nervosa. *Current psychiatry*  
43  
44 233 *reports*. 2012;14(4):391-7.  
45  
46  
47  
48 234 5. Ulfvebrand S, Birgegård A, Norring C, Högdahl L, von Hausswolff-Juhlin Y. Psychiatric  
49  
50 235 comorbidity in women and men with eating disorders results from a large clinical database.  
51  
52 236 *Psychiatry research*. 2015;230(2):294-9.  
53  
54  
55  
56 237 6. Pisetsky EM, Wonderlich SA, Crosby RD, Peterson CB, Mitchell JE, Engel SG, et al.  
57  
58 238 *Depression and Personality Traits Associated With Emotion Dysregulation: Correlates of*  
59  
60

- 1  
2  
3  
4 239 Suicide Attempts in Women with Bulimia Nervosa. *European eating disorders review : the*  
5  
6 240 *journal of the Eating Disorders Association.* 2015;23(6):537-44.
- 7  
8  
9 241 7. Duchesne M, Mattos P, Fontenelle LF, Veiga H, Rizo L, Appolinario JC. [Neuropsychology  
10  
11 242 of eating disorders: a systematic review of the literature]. *Revista brasileira de psiquiatria (Sao*  
12  
13 243 *Paulo, Brazil : 1999).* 2004;26(2):107-17.
- 14  
15  
16  
17 244 8. Seitz J, Kahraman-Lanzerath B, Legenbauer T, Sarrar L, Herpertz S, Salbach-Andrae H,  
18  
19 245 et al. The role of impulsivity, inattention and comorbid ADHD in patients with bulimia nervosa.  
20  
21 246 *PloS one.* 2013;8(5):e63891.
- 22  
23  
24  
25 247 9. Wentz E, Lacey JH, Waller G, Råstam M, Turk J, Gillberg C. Childhood onset  
26  
27 248 neuropsychiatric disorders in adult eating disorder patients. A pilot study. *European child &*  
28  
29 249 *adolescent psychiatry.* 2005;14(8):431-7.
- 30  
31  
32  
33 250 10. Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit hyperactivity  
34  
35 251 symptoms and disorder in eating disorder inpatients. *The International journal of eating*  
36  
37 252 *disorders.* 2009;42(4):375-8.
- 38  
39  
40 253 11. Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with  
41  
42 254 eating disorders. *Psychosomatic medicine.* 2006;68(3):454-62.
- 43  
44  
45 255 12. Yilmaz Z, Kaplan AS, Zai CC, Levitan RD, Kennedy JL. COMT Val158Met variant and  
46  
47 256 functional haplotypes associated with childhood ADHD history in women with bulimia nervosa.  
48  
49 257 *Progress in neuro-psychopharmacology & biological psychiatry.* 2011;35(4):948-52.
- 50  
51  
52  
53 258 13. Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-  
54  
55 259 eating disorder. *Neuroscience and biobehavioral reviews.* 2016;63:223-38.
- 56  
57  
58  
59 260 14. Van den Eynde F, Claudino AM, Mogg A, Horrell L, Stahl D, Ribeiro W, et al. Repetitive  
60

- 1  
2  
3  
4 261 transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders.  
5  
6 262 Biological psychiatry. 2010;67(8):793-5.  
7  
8  
9 263 15. Seitz J, Hueck M, Dahmen B, Schulte-Rüther M, Legenbauer T, Herpertz-Dahlmann B, et  
10  
11 264 al. Attention Network Dysfunction in Bulimia Nervosa - An fMRI Study. PloS one.  
12  
13 265 2016;11(9):e0161329.  
14  
15  
16 266 16. Schienle A, Schäfer A, Hermann A, Vaitl D. Binge-eating disorder: reward sensitivity and  
17  
18 267 brain activation to images of food. Biological psychiatry. 2009;65(8):654-61.  
19  
20  
21 268 17. Wu M, Hartmann M, Skunde M, Herzog W, Friederich HC. Inhibitory control in bulimic-type  
22  
23 269 eating disorders: a systematic review and meta-analysis. PloS one. 2013;8(12):e83412.  
24  
25  
26 270 18. Celone KA, Thompson-Brenner H, Ross RS, Pratt EM, Stern CE. An fMRI investigation of  
27  
28 271 the fronto-striatal learning system in women who exhibit eating disorder behaviors. NeuroImage.  
29  
30 272 2011;56(3):1749-57.  
31  
32  
33 273 19. Treasure J, Leslie M, Chami R, Fernández-Aranda F. Are trans diagnostic models of eating  
34  
35 274 disorders fit for purpose? A consideration of the evidence for food addiction. European eating  
36  
37 275 disorders review : the journal of the Eating Disorders Association. 2018;26(2):83-91.  
38  
39  
40 276 20. Coutinho J, Ramos AF, Maia L, Castro L, Conceição E, Geliebter A, et al. Volumetric  
41  
42 277 alterations in the nucleus accumbens and caudate nucleus in bulimia nervosa: a structural  
43  
44 278 magnetic resonance imaging study. The International journal of eating disorders.  
45  
46 279 2015;48(2):206-14.  
47  
48  
49 280 21. Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD, et al.  
50  
51 281 Monetary reward processing in obese individuals with and without binge eating disorder.  
52  
53 282 Biological psychiatry. 2013;73(9):877-86.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 283 22. Schäfer A, Vaitl D, Schienle A. Regional grey matter volume abnormalities in bulimia  
5  
6 284 nervosa and binge-eating disorder. *NeuroImage*. 2010;50(2):639-43.  
7  
8  
9 285 23. Skunde M, Walther S, Simon JJ, Wu M, Bendszus M, Herzog W, et al. Neural signature of  
10  
11 286 behavioural inhibition in women with bulimia nervosa. *Journal of psychiatry & neuroscience* :  
12  
13 287 JPN. 2016;41(5):E69-78.  
14  
15  
16 288 24. Van den Eynde F, Guillaume S, Broadbent H, Stahl D, Campbell IC, Schmidt U, et al.  
17  
18 289 Neurocognition in bulimic eating disorders: a systematic review. *Acta psychiatrica Scandinavica*.  
19  
20 290 2011;124(2):120-40.  
21  
22  
23 291 25. Welch E, Jangmo A, Thornton LM, Norring C, von Hauswolff-Juhlin Y, Herman BK, et al.  
24  
25 292 Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical  
26  
27 293 course and psychiatric comorbidity. *BMC psychiatry*. 2016;16:163.  
28  
29  
30 294 26. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-  
31  
32 295 compulsive disorder. *The British journal of psychiatry : the journal of mental science*.  
33  
34 296 2009;195(5):393-402.  
35  
36  
37 297 27. Bossier H, Seurinck R, Kühn S, Banaschewski T, Barker GJ, Bokde ALW, et al. The  
38  
39 298 Influence of Study-Level Inference Models and Study Set Size on Coordinate-Based fMRI  
40  
41 299 Meta-Analyses. *Frontiers in neuroscience*. 2017;11:745.  
42  
43  
44 300 28. Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, et al. A new  
45  
46 301 meta-analytic method for neuroimaging studies that combines reported peak coordinates and  
47  
48 302 statistical parametric maps. *European psychiatry : the journal of the Association of European*  
49  
50 303 *Psychiatrists*. 2012;27(8):605-11.  
51  
52  
53 304 29. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred  
54  
55  
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57  
58  
59  
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- 1  
2  
3  
4 305 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.  
5  
6 306 Systematic reviews. 2015;4(1):1.  
7  
8  
9 307 30. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane  
10  
11 308 Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed).  
12  
13 309 2011;343:d5928.  
14  
15  
16 310 31. Radua J, Via E, Catani M, Mataix-Cols D. Voxel-based meta-analysis of regional white-  
17  
18 311 matter volume differences in autism spectrum disorder versus healthy controls. Psychological  
19  
20 312 medicine. 2011;41(7):1539-50.  
21  
22  
23 313 32. Macaskill P, Walter SD, Irwig LJSiM. A comparison of methods to detect publication bias  
24  
25 314 in meta-analysis. 2010;20(4):641-54.  
26  
27  
28 315 33. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot.  
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30 316 BMJ (Clinical research ed). 2006;333(7568):597-600.  
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35 318 Figure 1. PRISMA flflow chart.  
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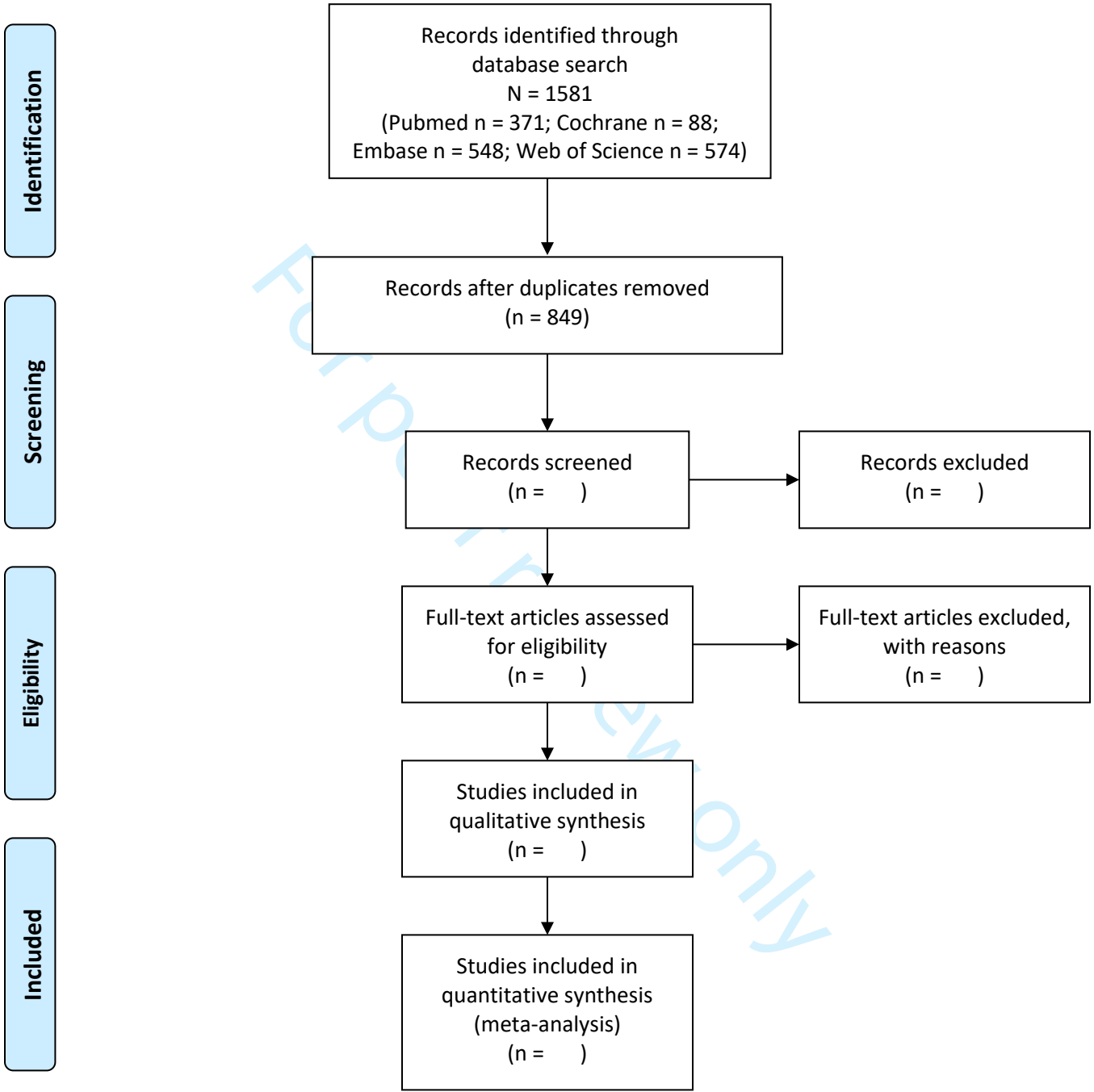


Figure 1. PRISMA flflow chart.

## 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 #
<b>ADMINISTRATIVE INFORMATION</b>			
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:			
Sources	5a	Indicate sources of financial or other support for the review	No support
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	-
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 <sup>2</sup> , Kendall's $\tau$ )	#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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# BMJ Open

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

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Manuscripts

# 1 **Brain functional changes in individuals with bulimia nervosa: a** 2 **protocol for systematic review and meta-analysis**

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## 9 **Abstract**

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

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

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

## 26 **Strengths and limitations of this study**

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

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

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

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

## 41 1. INTRODUCTION

### 42 1.1. Background

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

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

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

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

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

85 Accounting for both increases and decreases of the outcome of interest (e.g. activation  
 86 and deactivation) so that contradictory findings cancel each other;<sup>(26)</sup>

87 Use of effect size estimates with random-effects modeling, which increases reliability  
 88 and performance;<sup>(27)</sup>

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

91 Use of threshold-free cluster enhancement (TFCE) statistics.<sup>(28)</sup>

## 92 1.2. Objective

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

## 96 2. METHODS AND ANALYSIS

### 97 2.1. Study design

98 This protocol followed the Preferred Reporting Items for Systematic Review and  
 99 Meta-Analyses guidelines.<sup>(29)</sup> The results of this systematic review and meta-analysis  
 100 will be published in a specialist journal or presented at a conference. A preliminary  
 101 search was performed using the Cochrane Library, PubMed, Embase, and Web of  
 102 Science, including records from database inception to November 30, 2021. The search  
 103 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

## 104 2.2. Criteria of selection for study

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

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
<b>P—Population</b>	Individuals with bulimia nervosa, with fMRI	Diagnosed by unofficial diagnostic criteria
<b>I—Intervention</b>	None	None
<b>C—Comparator</b>	Bulimia nervosa patients vs. healthy controls	No comparisons
<b>O—Outcome</b>	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.

## 111 2.3. Outcomes

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

## 114 2.4. Selection of studies

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

## 120 2.5. Data extraction and management

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

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



1  
2  
3 134 change) will be extracted and combined to recreate an effect-size map. Peak coordinates  
4 135 not in the Montreal Neurological Institute space will be converted using coordinate  
5 136 mapping software. Aggregate data on participants' demographic characteristics will be  
6 137 reported as means with standard deviations. Data processing will be performed  
7 138 according to the manufacturer's instructions.  
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9

## 10 139 **2.6. Risk of bias and quality assessment**

11  
12 140 Qualitative risk of bias assessment will be performed for each study. The Cochrane  
13 141 Handbook for Systematic Reviews of Interventions will be used in this study. Two  
14 142 authors will evaluate six areas of selection bias: selection, performance, detection,  
15 143 attrition, reporting, and other sources. Trials will be rated as "low", "high", or "unclear"  
16 144 risk.<sup>(30)</sup> Any discrepancies in assessment will be resolved by consensus or third-author  
17 145 arbitration.

18  
19 146 Study quality will be assessed using the Newcastle-Ottawa Scale, which accounts for  
20 147 study participants, comparability of groups, and measurement of exposure factors. The  
21 148 quality of evidence in each study will be defined as high ( $\geq 8$  points), medium (6–7  
22 149 points), or low ( $\leq 5$  points). Any discrepancies in quality assessments between the two  
23 150 authors will be resolved by third-author arbitration.  
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## 27 151 **2.7. Meta-analysis**

28  
29 152 The meta-analysis of eligible studies will involve a variance-weighted standard random  
30 153 effects model. An uncorrected P-value of  $< 0.005$  will be set as the main threshold, with  
31 154 an additional peak height Z-value of  $> 1$  and a cluster extent of  $\geq 10$  voxels to optimally  
32 155 balance sensitivity and specificity.<sup>(26)</sup> Study maps will be calculated voxel-wise to  
33 156 estimate the random-effects mean, which considers the sample size, intra-study  
34 157 variability, and between-study heterogeneity. AES-SDM  
35 158 (<https://www.sdmproject.com/software/>) will be used to quantitatively synthesize  
36 159 findings of functional brain alterations. SDM is a statistical technique for meta-analysis  
37 160 that examines differences in brain activity detected by neuroimaging techniques,  
38 161 including functional magnetic resonance imaging.<sup>(28, 31)</sup>

39 162 SDM includes five primary steps:

- 40 163 1) Coordinates of cluster peaks (significant BNs-vs-HCs voxels of activation) are  
41 164 selected.
- 42 165 2) The lower and upper bounds of possible effect size images are estimated.
- 43 166 3) MetaNSUE is used to estimate the most likely effect size and its standard error.  
44 167 Several imputations are generated premised on adding noise to these estimations within  
45 168 the bounds.
- 46 169 4) Each imputed dataset is meta-analysed. Rubin's rules are implemented to combine  
47 170 imputed meta-analysed datasets.
- 48 171 5) A standard permutation test is ran by the recreated of subject images. The process is  
49 172 repeated with each set of permuted images. The maximum statistic of the final image  
50 173 is saved. The distribution of these maxima is used to family-wise error-correct for  
51 174 multiple comparisons.

52 175 The minimum number of studies required for synthesis is three per analysis. When more  
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3 176 than 10 studies are included, it was sufficient to detect publication bias in the meta-  
4 177 analytical procedures.<sup>(32, 33)</sup> The probability threshold will be decreased to 0.005 to  
5 178 minimize the detection of false correlations.

## 179 **2.8. Sensitivity analysis**

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

## 184 **2.9. Meta-regression or subgroup analysis**

185 If enough studies are included, the following potential sources of among-study  
186 heterogeneity will be explored using subgroup analyses or meta-regression:<sup>(26)</sup> task  
187 paradigm; FEW or FDR; participants' mean age, mean BN duration, and mean  
188 frequency of binge eating, among others.

## 189 **3. PATIENT AND PUBLIC INVOLVEMENT**

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

## 194 **3. ETHICS AND DISSEMINATION**

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

## 200 **Author contributions**

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

## 208 **Competing Interests**

209 No competing interests exist.

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## 213 **References**

- 214 1. Hay P, Mitchison D, Collado AEL, González-Chica DA, Stocks N, Touyz S. Burden and  
215 health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake  
216 Disorder (ARFID), in the Australian population. *Journal of eating disorders*. 2017;5:21.
- 217 2. Organization AP. *Diagnostic and statistical manual of mental disorders (5th ed.)*:  
218 *Diagnostic and statistical manual of mental disorders (5th ed.)*; 2013.
- 219 3. Herpertz-Dahlmann B. Adolescent eating disorders: definitions, symptomatology,  
220 epidemiology and comorbidity. *Child and adolescent psychiatric clinics of North America*.  
221 2009;18(1):31-47.
- 222 4. Hoste RR, Labuschagne Z, Le Grange D. Adolescent bulimia nervosa. *Current psychiatry*  
223 *reports*. 2012;14(4):391-7.
- 224 5. Ulfvebrand S, Birgegård A, Norring C, Högdahl L, von Hausswolff-Juhlin Y. Psychiatric  
225 comorbidity in women and men with eating disorders results from a large clinical database.  
226 *Psychiatry research*. 2015;230(2):294-9.
- 227 6. Pisetsky EM, Wonderlich SA, Crosby RD, Peterson CB, Mitchell JE, Engel SG, et al.  
228 *Depression and Personality Traits Associated With Emotion Dysregulation: Correlates of*  
229 *Suicide Attempts in Women with Bulimia Nervosa*. *European eating disorders review : the*  
230 *journal of the Eating Disorders Association*. 2015;23(6):537-44.
- 231 7. Duchesne M, Mattos P, Fontenelle LF, Veiga H, Rizo L, Appolinario JC. [Neuropsychology  
232 of eating disorders: a systematic review of the literature]. *Revista brasileira de psiquiatria (Sao*  
233 *Paulo, Brazil : 1999)*. 2004;26(2):107-17.
- 234 8. Seitz J, Kahraman-Lanzerath B, Legenbauer T, Sarrar L, Herpertz S, Salbach-Andrae H,

- 1  
2  
3  
4 235 et al. The role of impulsivity, inattention and comorbid ADHD in patients with bulimia nervosa.  
5  
6 236 PloS one. 2013;8(5):e63891.  
7  
8  
9 237 9. Wentz E, Lacey JH, Waller G, Råstam M, Turk J, Gillberg C. Childhood onset  
10  
11 238 neuropsychiatric disorders in adult eating disorder patients. A pilot study. *European child &*  
12  
13 239 *adolescent psychiatry*. 2005;14(8):431-7.  
14  
15  
16  
17 240 10. Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit hyperactivity  
18  
19 241 symptoms and disorder in eating disorder inpatients. *The International journal of eating*  
20  
21 242 *disorders*. 2009;42(4):375-8.  
22  
23  
24  
25 243 11. Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with  
26  
27 244 eating disorders. *Psychosomatic medicine*. 2006;68(3):454-62.  
28  
29  
30 245 12. Yilmaz Z, Kaplan AS, Zai CC, Levitan RD, Kennedy JL. COMT Val158Met variant and  
31  
32 246 functional haplotypes associated with childhood ADHD history in women with bulimia nervosa.  
33  
34 247 *Progress in neuro-psychopharmacology & biological psychiatry*. 2011;35(4):948-52.  
35  
36  
37  
38 248 13. Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-  
39  
40 249 eating disorder. *Neuroscience and biobehavioral reviews*. 2016;63:223-38.  
41  
42  
43 250 14. Van den Eynde F, Claudino AM, Mogg A, Horrell L, Stahl D, Ribeiro W, et al. Repetitive  
44  
45 251 transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders.  
46  
47 252 *Biological psychiatry*. 2010;67(8):793-5.  
48  
49  
50  
51 253 15. Seitz J, Hueck M, Dahmen B, Schulte-Rüther M, Legenbauer T, Herpertz-Dahlmann B, et  
52  
53 254 al. Attention Network Dysfunction in Bulimia Nervosa - An fMRI Study. *PloS one*.  
54  
55 255 2016;11(9):e0161329.  
56  
57  
58 256 16. Schienle A, Schäfer A, Hermann A, Vaitl D. Binge-eating disorder: reward sensitivity and  
59  
60

- 1  
2  
3  
4 257 brain activation to images of food. *Biological psychiatry*. 2009;65(8):654-61.  
5  
6  
7 258 17. Wu M, Hartmann M, Skunde M, Herzog W, Friederich HC. Inhibitory control in bulimic-type  
8  
9 259 eating disorders: a systematic review and meta-analysis. *PloS one*. 2013;8(12):e83412.  
10  
11  
12 260 18. Celone KA, Thompson-Brenner H, Ross RS, Pratt EM, Stern CE. An fMRI investigation of  
13  
14 261 the fronto-striatal learning system in women who exhibit eating disorder behaviors. *NeuroImage*.  
15  
16  
17 262 2011;56(3):1749-57.  
18  
19  
20 263 19. Treasure J, Leslie M, Chami R, Fernández-Aranda F. Are trans diagnostic models of eating  
21  
22 264 disorders fit for purpose? A consideration of the evidence for food addiction. *European eating*  
23  
24 265 *disorders review : the journal of the Eating Disorders Association*. 2018;26(2):83-91.  
25  
26  
27 266 20. Coutinho J, Ramos AF, Maia L, Castro L, Conceição E, Geliebter A, et al. Volumetric  
28  
29 267 alterations in the nucleus accumbens and caudate nucleus in bulimia nervosa: a structural  
30  
31 268 magnetic resonance imaging study. *The International journal of eating disorders*.  
32  
33 269 2015;48(2):206-14.  
34  
35  
36  
37 270 21. Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD, et al.  
38  
39 271 Monetary reward processing in obese individuals with and without binge eating disorder.  
40  
41 272 *Biological psychiatry*. 2013;73(9):877-86.  
42  
43  
44  
45 273 22. Schäfer A, Vaitl D, Schienle A. Regional grey matter volume abnormalities in bulimia  
46  
47 274 nervosa and binge-eating disorder. *NeuroImage*. 2010;50(2):639-43.  
48  
49  
50  
51 275 23. Skunde M, Walther S, Simon JJ, Wu M, Bendszus M, Herzog W, et al. Neural signature of  
52  
53 276 behavioural inhibition in women with bulimia nervosa. *Journal of psychiatry & neuroscience :*  
54  
55 277 *JPN*. 2016;41(5):E69-78.  
56  
57  
58 278 24. Van den Eynde F, Guillaume S, Broadbent H, Stahl D, Campbell IC, Schmidt U, et al.  
59  
60

- 1  
2  
3  
4 279 Neurocognition in bulimic eating disorders: a systematic review. *Acta psychiatrica Scandinavica*.  
5  
6 280 2011;124(2):120-40.  
7  
8  
9 281 25. Welch E, Jangmo A, Thornton LM, Norring C, von Hausswolff-Juhlin Y, Herman BK, et al.  
10  
11 282 Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical  
12  
13 283 course and psychiatric comorbidity. *BMC psychiatry*. 2016;16:163.  
14  
15  
16 284 26. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-  
17  
18 285 compulsive disorder. *The British journal of psychiatry : the journal of mental science*.  
19  
20 286 2009;195(5):393-402.  
21  
22  
23 287 27. Bossier H, Seurinck R, Kühn S, Banaschewski T, Barker GJ, Bokde ALW, et al. The  
24  
25 288 Influence of Study-Level Inference Models and Study Set Size on Coordinate-Based fMRI  
26  
27 289 Meta-Analyses. *Frontiers in neuroscience*. 2017;11:745.  
28  
29  
30 290 28. Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, et al. A new  
31  
32 291 meta-analytic method for neuroimaging studies that combines reported peak coordinates and  
33  
34 292 statistical parametric maps. *European psychiatry : the journal of the Association of European*  
35  
36 293 *Psychiatrists*. 2012;27(8):605-11.  
37  
38  
39 294 29. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred  
40  
41 295 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.  
42  
43 296 *Systematic reviews*. 2015;4(1):1.  
44  
45  
46 297 30. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane  
47  
48 298 Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*.  
49  
50 299 2011;343:d5928.  
51  
52  
53 300 31. Radua J, Via E, Catani M, Mataix-Cols D. Voxel-based meta-analysis of regional white-

1  
2  
3  
4 301 matter volume differences in autism spectrum disorder versus healthy controls. Psychological  
5  
6 302 medicine. 2011;41(7):1539-50.

7  
8  
9 303 32. Macaskill P, Walter SD, Irwig LJSiM. A comparison of methods to detect publication bias  
10  
11 304 in meta-analysis. 2010;20(4):641-54.

12  
13  
14 305 33. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot.  
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16 306 BMJ (Clinical research ed). 2006;333(7568):597-600.

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20 308 Figure 1. PRISMA flflow chart.  
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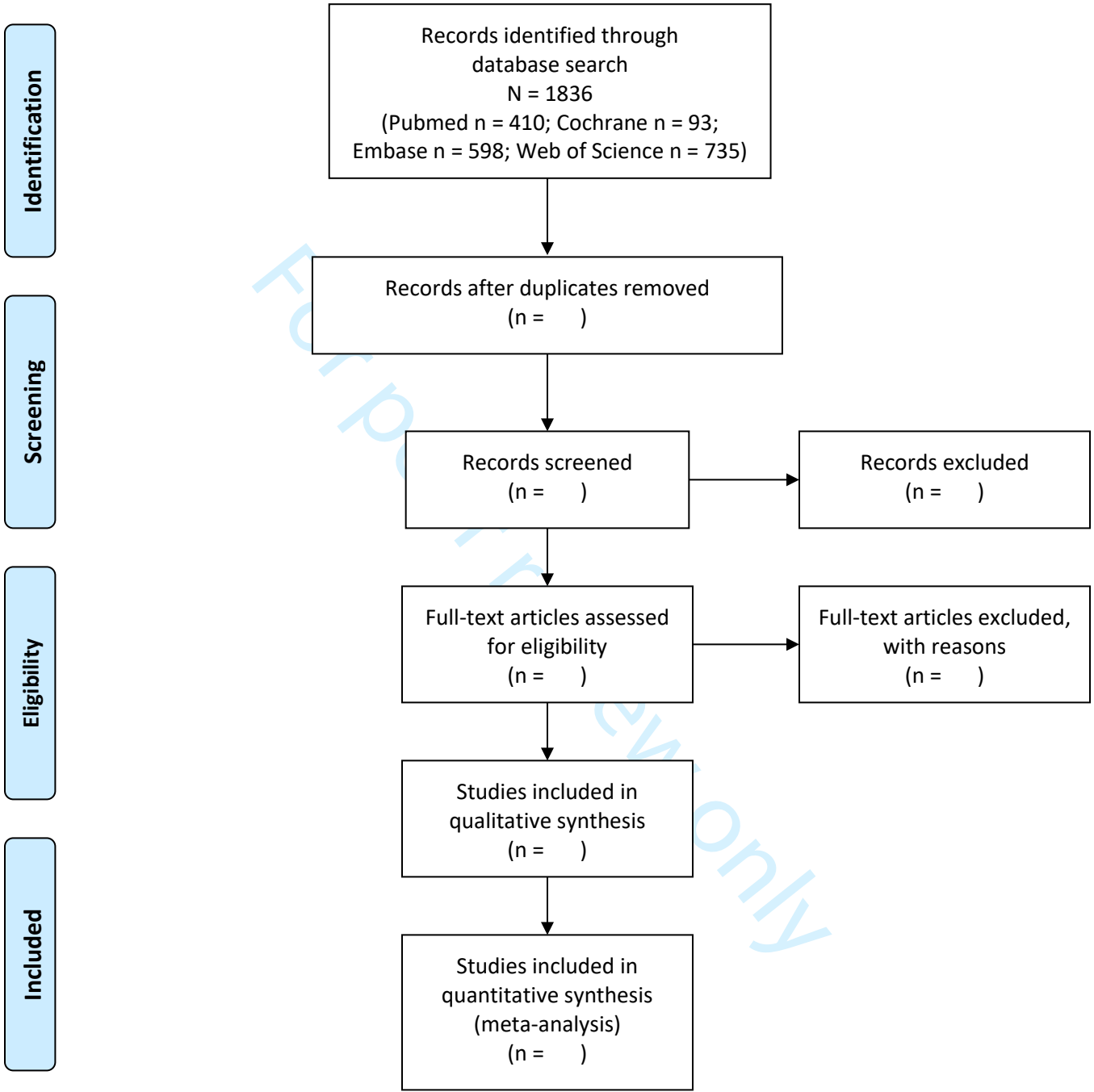


Figure 1. PRISMA flflow chart.



## 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 #
<b>ADMINISTRATIVE INFORMATION</b>			
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:			
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	-
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 <sup>2</sup> , Kendall's $\tau$ )	#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.*

# BMJ Open

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

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

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Manuscripts

# 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

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4 37 specified, AES-SDM = anisotropic effect-size version of seed-based d mapping,  
5 38 BOLD-fMRI = blood oxygenation level-dependent magnetic resonance imaging,  
6 39 PRISMA = preferred reporting items for systematic reviews and meta-analyses, NOS  
7 40 = Newcastle-Ottawa Scale, OFC = orbitofrontal cortex, ACC = anterior cingulate  
8 41 cortex, ROIs = region of interests, SVC = small volume corrections.

10 42 **Keywords** fMRI, functional cerebral alterations, meta-analysis, neuroimaging  
11  
12 43 studies, protocol, systematic review

## 14 44 **1. INTRODUCTION**

### 16 45 **1.1. Background**

17 46 Bulimia nervosa (BN) is a psychiatric and psychological disorder that often occurs in  
18 47 late adolescence and early adulthood; recurrent binge eating is a core diagnostic  
19 48 criterion for BN.<sup>(1)</sup> People with bulimia nervosa have recurrent episodes of binge eating  
20 49 followed by inappropriate compensatory behaviors (purging) to avoid weight gain, such  
21 50 as self-induced vomiting, use of laxatives, fasting, and excessive exercise.<sup>(2-4)</sup>  
22 51 Psychiatric comorbidity, including depression and anxiety, is very common in BN  
23 52 patients,<sup>(5, 6)</sup> and more than one-fifth of BN patients have attempted suicide.<sup>(6)</sup> Studies  
24 53 have shown that BN patients have attention deficits,<sup>(7-10)</sup> which are associated with an  
25 54 increase in the incidence of attention deficit hyperactivity disorder.<sup>(8, 11, 12)</sup>

26 55 Recent neuroscience studies have shown that the function of the prefrontal lobe, insular  
27 56 cortex, orbitofrontal cortex (OFC), and striatum differ in BN patients from those in  
28 57 healthy controls, and that alterations in the cortico-striatal circuits are similar to those  
29 58 observed in individuals with substance abuse.<sup>(13)</sup> It has been suggested that the OFC and  
30 59 anterior cingulate cortex (ACC) are overactive in this patient group, and that impaired  
31 60 inhibitory control of the lateral prefrontal circuit mediates the urges to binge eat.<sup>(14)</sup>  
32 61 Compared with healthy controls, BN patients manifest hyperactivity of the parieto-  
33 62 occipital regions and hypoactivation of the executive control network<sup>(15)</sup> and show  
34 63 insula and ACC activation that is greater in response to pictures of food than that in  
35 64 response to pictures of household items.<sup>(16)</sup> The role of inhibitory control disruption is  
36 65 increasingly recognized in BN studies. Faced with stimuli related to eating, BN patients  
37 66 have impaired response inhibition and inhibitory control.<sup>(17)</sup> The frontostriatal area  
38 67 plays a central role in controlling goal-directed thoughts and behaviors, including  
39 68 response inhibition and reward processing.<sup>(18)</sup>

40 69 The evidence from research examining the food addiction hypothesis has changed the  
41 70 explanatory models of eating disorders. Eating behavior is central in models of eating  
42 71 disorders.<sup>(19)</sup> Changes in the food environment that interact with individual  
43 72 vulnerability may be key risk factors for BN, and neuroadaptive changes in reward  
44 73 circuits are likely to maintain these disorders.<sup>(19)</sup> Recent small sample studies have  
45 74 examined the neurobiology of individuals with BN,<sup>(20-22)</sup> showing a strong association  
46 75 between the frontostriatal area function and BN.<sup>(18)</sup> In fact, the diminished activation of  
47 76 the frontostriatal area in BN patients has been shown to contribute to the severity of  
48 77 symptoms.<sup>(23)</sup> However, small sample sizes and heterogenous protocols of the previous  
49 78 studies preclude any meaningful conclusions on the neurocognitive profile of

79 individuals with BN or binge eating disorder.<sup>(24)</sup>  
 80 Neurobiological research on BN is expanding rapidly. Given the high psychiatric  
 81 comorbidity and suicide rates in BN patients, a rigorous review of the evidence on the  
 82 neurological underpinnings of BN is required.<sup>(6, 25)</sup> Therefore, this systematic review  
 83 aims to comprehensively examine the evidence on functional brain changes in patients  
 84 with BN to evaluate the food addiction hypothesis and support disease management.  
 85 This meta-analysis, which synthesizes the latest neuroimaging evidence, will be  
 86 performed using the anisotropic effect-size version of seed-based d mapping (AES-  
 87 SDM). This software's main features include:  
 88 Accounting for both increases and decreases of the outcome of interest (e.g. activation  
 89 and deactivation) so that contradictory findings cancel each other;<sup>(26)</sup>  
 90 Use of effect size estimates with random-effects modeling, which increases reliability  
 91 and performance;<sup>(27)</sup>  
 92 Potential simultaneous inclusion of available 3D statistical images (i.e. maps of t-test  
 93 values);  
 94 Use of threshold-free cluster enhancement (TFCE) statistics.<sup>(28)</sup>

## 95 1.2. Objective

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

## 99 2. METHODS AND ANALYSIS

### 100 2.1. Study design

101 This protocol followed the Preferred Reporting Items for Systematic Review and  
 102 Meta-Analyses guidelines.<sup>(29)</sup> The results of this systematic review and meta-analysis  
 103 will be published in a specialist journal or presented at a conference. A preliminary  
 104 search was performed using the Cochrane Library, PubMed, Embase, and Web of  
 105 Science, including records from database inception to November 30, 2021. The search  
 106 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

## 107 2.2. Criteria of selection for study

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

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
<b>P—Population</b>	Individuals with bulimia nervosa, with fMRI	Diagnosed by unofficial diagnostic criteria
<b>I—Intervention</b>	None	None
<b>C—Comparator</b>	Bulimia nervosa patients vs. healthy controls	No comparisons
<b>O—Outcome</b>	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.

## 114 2.3. Outcomes

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

## 117 2.4. Selection of studies

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

## 123 2.5. Data extraction and management

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

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

1  
2  
3 134 before statistical analysis. The P-statistics and T-statistics will be converted into Z-  
4 135 statistics using the SDM online converter ([http://www.sdmproject.com/utilities/?](http://www.sdmproject.com/utilities/?show=Statistics)  
5 136 [show=Statistics](http://www.sdmproject.com/utilities/?show=Statistics)). The peak data (coordinates, significance level, and direction of  
6 137 change) will be extracted and combined to recreate an effect-size map. Peak coordinates  
7 138 not in the Montreal Neurological Institute space will be converted using coordinate  
8 139 mapping software. Aggregate data on participants' demographic characteristics will be  
9 140 reported as means with standard deviations. Data processing will be performed  
10 141 according to the manufacturer's instructions.

## 142 **2.6. Risk of bias and quality assessment**

143 Qualitative risk of bias assessment will be performed for each study. The Cochrane  
144 Handbook for Systematic Reviews of Interventions will be used in this study. Two  
145 authors will evaluate six areas of selection bias: selection, performance, detection,  
146 attrition, reporting, and other sources. Trials will be rated as "low", "high", or "unclear"  
147 risk.<sup>(30)</sup> Any discrepancies in assessment will be resolved by consensus or third-author  
148 arbitration.

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

## 154 **2.7. Meta-analysis**

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

165 SDM includes five primary steps:

- 166 1) Coordinates of cluster peaks (significant BNs-vs-HCs voxels of activation) are  
167 selected.
- 168 2) The lower and upper bounds of possible effect size images are estimated.
- 169 3) MetaNSUE is used to estimate the most likely effect size and its standard error.  
170 Several imputations are generated premised on adding noise to these estimations within  
171 the bounds.
- 172 4) Each imputed dataset is meta-analysed. Rubin's rules are implemented to combine  
173 imputed meta-analysed datasets.
- 174 5) A standard permutation test is ran by the recreated of subject images. The process is  
175 repeated with each set of permuted images. The maximum statistic of the final image



176 is saved. The distribution of these maxima is used to family-wise error-correct for  
177 multiple comparisons.  
178 The minimum number of studies required for synthesis is three per analysis. When more  
179 than 10 studies are included, it was sufficient to detect publication bias in the meta-  
180 analytical procedures.<sup>(32, 33)</sup> The probability threshold will be decreased to 0.005 to  
181 minimize the detection of false correlations.

## 182 **2.8. Sensitivity analysis**

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

## 187 **2.9. Meta-regression or subgroup analysis**

188 If enough studies are included, the following potential sources of among-study  
189 heterogeneity will be explored using subgroup analyses or meta-regression:<sup>(26)</sup> task  
190 paradigm; FEW or FDR; participants' mean age, mean BN duration, and mean  
191 frequency of binge eating, among others.

## 192 **3. PATIENT AND PUBLIC INVOLVEMENT**

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

## 197 **3. ETHICS AND DISSEMINATION**

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

### 203 **Author contributions**

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

### 211 **Competing Interests**

212 No competing interests exist.

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1  
2  
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## 220 **References**

- 221 1. Hay P, Mitchison D, Collado AEL, González-Chica DA, Stocks N, Touyz S. Burden and  
222 health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake  
223 Disorder (ARFID), in the Australian population. *Journal of eating disorders*. 2017;5:21.
- 224 2. Organization AP. Diagnostic and statistical manual of mental disorders (5th ed.):  
225 Diagnostic and statistical manual of mental disorders (5th ed.); 2013.
- 226 3. Herpertz-Dahlmann B. Adolescent eating disorders: definitions, symptomatology,  
227 epidemiology and comorbidity. *Child and adolescent psychiatric clinics of North America*.  
228 2009;18(1):31-47.
- 229 4. Hoste RR, Labuschagne Z, Le Grange D. Adolescent bulimia nervosa. *Current psychiatry*  
230 *reports*. 2012;14(4):391-7.
- 231 5. Ulfvebrand S, Birgegård A, Norring C, Högdahl L, von Hausswolff-Juhlin Y. Psychiatric  
232 comorbidity in women and men with eating disorders results from a large clinical database.  
233 *Psychiatry research*. 2015;230(2):294-9.
- 234 6. Pisetsky EM, Wonderlich SA, Crosby RD, Peterson CB, Mitchell JE, Engel SG, et al.  
235 Depression and Personality Traits Associated With Emotion Dysregulation: Correlates of  
236 Suicide Attempts in Women with Bulimia Nervosa. *European eating disorders review : the*  
237 *journal of the Eating Disorders Association*. 2015;23(6):537-44.
- 238 7. Duchesne M, Mattos P, Fontenelle LF, Veiga H, Rizo L, Appolinario JC. [Neuropsychology

- 1  
2  
3  
4 239 of eating disorders: a systematic review of the literature]. *Revista brasileira de psiquiatria* (Sao  
5  
6 240 Paulo, Brazil : 1999). 2004;26(2):107-17.  
7  
8  
9 241 8. Seitz J, Kahraman-Lanzerath B, Legenbauer T, Sarrar L, Herpertz S, Salbach-Andrae H,  
10  
11 242 et al. The role of impulsivity, inattention and comorbid ADHD in patients with bulimia nervosa.  
12  
13 243 *PloS one*. 2013;8(5):e63891.  
14  
15  
16  
17 244 9. Wentz E, Lacey JH, Waller G, Råstam M, Turk J, Gillberg C. Childhood onset  
18  
19 245 neuropsychiatric disorders in adult eating disorder patients. A pilot study. *European child &*  
20  
21 246 *adolescent psychiatry*. 2005;14(8):431-7.  
22  
23  
24  
25 247 10. Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit hyperactivity  
26  
27 248 symptoms and disorder in eating disorder inpatients. *The International journal of eating*  
28  
29 249 *disorders*. 2009;42(4):375-8.  
30  
31  
32 250 11. Blinder BJ, Cumella EJ, Sanathara VA. Psychiatric comorbidities of female inpatients with  
33  
34 251 *eating disorders*. *Psychosomatic medicine*. 2006;68(3):454-62.  
35  
36  
37 252 12. Yilmaz Z, Kaplan AS, Zai CC, Levitan RD, Kennedy JL. COMT Val158Met variant and  
38  
39 253 *functional haplotypes associated with childhood ADHD history in women with bulimia nervosa*.  
40  
41 254 *Progress in neuro-psychopharmacology & biological psychiatry*. 2011;35(4):948-52.  
42  
43  
44  
45 255 13. Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-  
46  
47 256 *eating disorder*. *Neuroscience and biobehavioral reviews*. 2016;63:223-38.  
48  
49  
50  
51 257 14. Van den Eynde F, Claudino AM, Mogg A, Horrell L, Stahl D, Ribeiro W, et al. Repetitive  
52  
53 258 *transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders*.  
54  
55 259 *Biological psychiatry*. 2010;67(8):793-5.  
56  
57  
58 260 15. Seitz J, Hueck M, Dahmen B, Schulte-Rüther M, Legenbauer T, Herpertz-Dahlmann B, et

- 1  
2  
3  
4 261 al. Attention Network Dysfunction in Bulimia Nervosa - An fMRI Study. PloS one.  
5  
6 262 2016;11(9):e0161329.  
7  
8  
9 263 16. Schienle A, Schäfer A, Hermann A, Vaitl D. Binge-eating disorder: reward sensitivity and  
10  
11 264 brain activation to images of food. Biological psychiatry. 2009;65(8):654-61.  
12  
13  
14 265 17. Wu M, Hartmann M, Skunde M, Herzog W, Friederich HC. Inhibitory control in bulimic-type  
15  
16 266 eating disorders: a systematic review and meta-analysis. PloS one. 2013;8(12):e83412.  
17  
18  
19 267 18. Celone KA, Thompson-Brenner H, Ross RS, Pratt EM, Stern CE. An fMRI investigation of  
20  
21 268 the fronto-striatal learning system in women who exhibit eating disorder behaviors. NeuroImage.  
22  
23 269 2011;56(3):1749-57.  
24  
25  
26 270 19. Treasure J, Leslie M, Chami R, Fernández-Aranda F. Are trans diagnostic models of eating  
27  
28 271 disorders fit for purpose? A consideration of the evidence for food addiction. European eating  
29  
30 272 disorders review : the journal of the Eating Disorders Association. 2018;26(2):83-91.  
31  
32  
33 273 20. Coutinho J, Ramos AF, Maia L, Castro L, Conceição E, Geliebter A, et al. Volumetric  
34  
35 274 alterations in the nucleus accumbens and caudate nucleus in bulimia nervosa: a structural  
36  
37 275 magnetic resonance imaging study. The International journal of eating disorders.  
38  
39 276 2015;48(2):206-14.  
40  
41  
42 277 21. Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD, et al.  
43  
44 278 Monetary reward processing in obese individuals with and without binge eating disorder.  
45  
46 279 Biological psychiatry. 2013;73(9):877-86.  
47  
48  
49 280 22. Schäfer A, Vaitl D, Schienle A. Regional grey matter volume abnormalities in bulimia  
50  
51 281 nervosa and binge-eating disorder. NeuroImage. 2010;50(2):639-43.  
52  
53  
54 282 23. Skunde M, Walther S, Simon JJ, Wu M, Bendszus M, Herzog W, et al. Neural signature of  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 283 behavioural inhibition in women with bulimia nervosa. *Journal of psychiatry & neuroscience* :  
5  
6 284 *JPN*. 2016;41(5):E69-78.  
7  
8  
9 285 24. Van den Eynde F, Guillaume S, Broadbent H, Stahl D, Campbell IC, Schmidt U, et al.  
10  
11 286 Neurocognition in bulimic eating disorders: a systematic review. *Acta psychiatrica Scandinavica*.  
12  
13 287 2011;124(2):120-40.  
14  
15  
16  
17 288 25. Welch E, Jangmo A, Thornton LM, Norring C, von Hausswolff-Juhlin Y, Herman BK, et al.  
18  
19 289 Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical  
20  
21 290 course and psychiatric comorbidity. *BMC psychiatry*. 2016;16:163.  
22  
23  
24 291 26. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-  
25  
26 292 compulsive disorder. *The British journal of psychiatry : the journal of mental science*.  
27  
28 293 2009;195(5):393-402.  
29  
30  
31 294 27. Bossier H, Seurinck R, Kühn S, Banaschewski T, Barker GJ, Bokde ALW, et al. The  
32  
33 295 Influence of Study-Level Inference Models and Study Set Size on Coordinate-Based fMRI  
34  
35 296 Meta-Analyses. *Frontiers in neuroscience*. 2017;11:745.  
36  
37  
38 297 28. Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, et al. A new  
39  
40 298 meta-analytic method for neuroimaging studies that combines reported peak coordinates and  
41  
42 299 statistical parametric maps. *European psychiatry : the journal of the Association of European*  
43  
44 300 *Psychiatrists*. 2012;27(8):605-11.  
45  
46  
47 301 29. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred  
48  
49 302 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.  
50  
51 303 *Systematic reviews*. 2015;4(1):1.  
52  
53  
54  
55  
56  
57  
58 304 30. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane  
59  
60

- 1  
2  
3  
4 305 Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed).  
5  
6 306 2011;343:d5928.  
7  
8  
9 307 31. Radua J, Via E, Catani M, Mataix-Cols D. Voxel-based meta-analysis of regional white-  
10  
11 308 matter volume differences in autism spectrum disorder versus healthy controls. Psychological  
12  
13 309 medicine. 2011;41(7):1539-50.  
14  
15  
16 310 32. Macaskill P, Walter SD, Irwig LJSiM. A comparison of methods to detect publication bias  
17  
18 311 in meta-analysis. 2010;20(4):641-54.  
19  
20  
21 312 33. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot.  
22  
23 313 BMJ (Clinical research ed). 2006;333(7568):597-600.  
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28 315 Figure 1. PRISMA flflow chart.  
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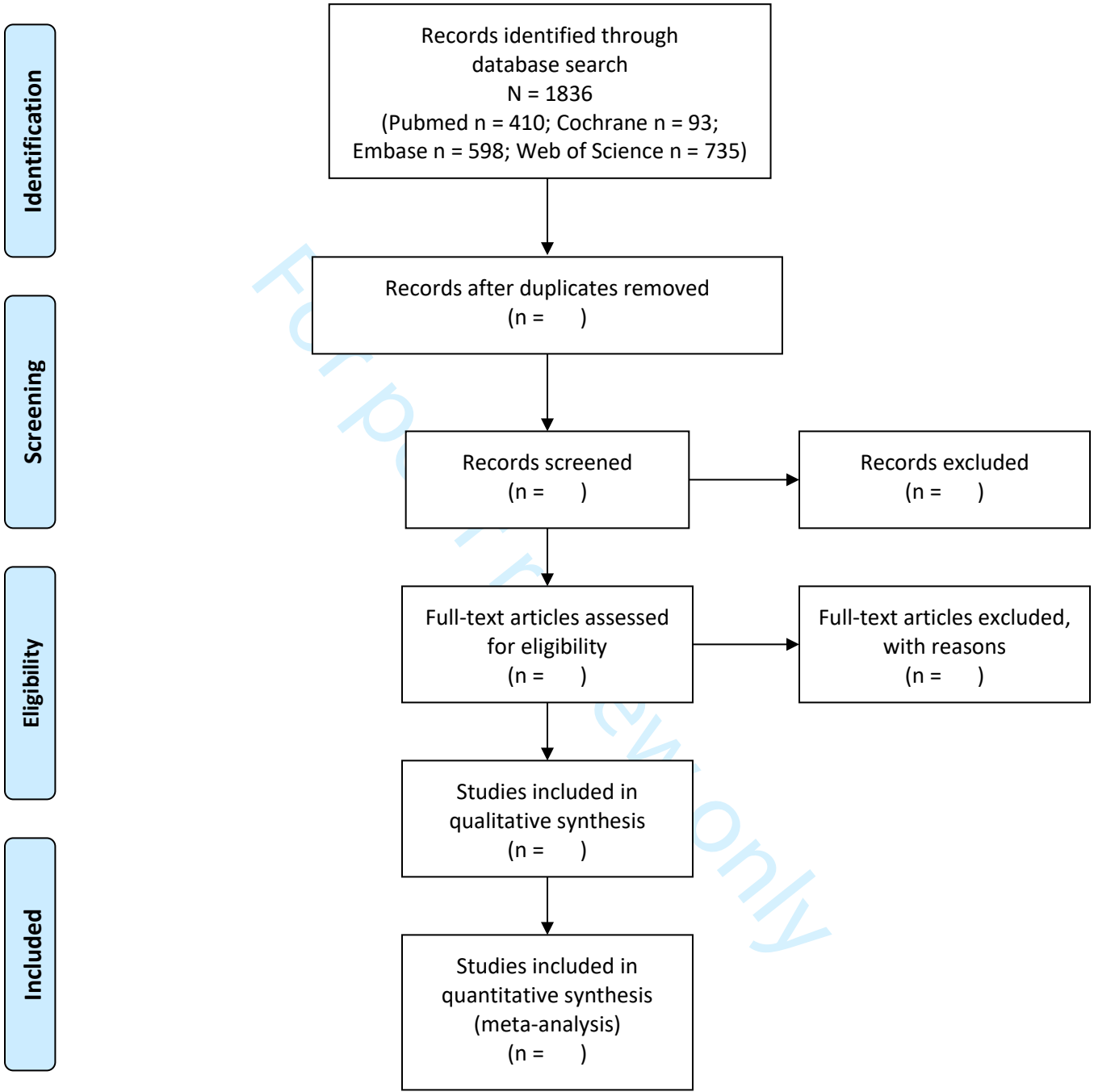


Figure 1. PRISMA flflow chart.

## 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 #
<b>ADMINISTRATIVE INFORMATION</b>			
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:			
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	-
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 <sup>2</sup> , Kendall's $\tau$ )	#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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