Systematic review PRISMA protocol 2015

ADMINISTRATIVE INFORMATION

1a Title

Echocardiographic abnormalities in anorexia nervosa.

2 Registration

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 12 February 2018 and was last updated on 23rd February 2017 (registration number CRD42018088509).

3a Authors

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3b Describe contributions of protocol authors and identify the guarantor of the review

JS is the guarantor. JS and CC drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. JS developed the search strategy along with a librarian. CC and PL provided statistical expertise. CC and PL provided expertise on echocardiography. All authors read, provided feedback and approved the final manuscript.

4 Amendments

N/A

5a Sources

Nil.

5b Sponsor

Nil.

5c Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol

N/A

INTRODUCTION

6 Describe the rationale for the review in the context of what is already known

Anorexia nervosa (AN) is a serious psychiatric condition, with a standardised mortality ratio of 6.2.[1] 80% of AN patients have cardiovascular complications,[1] along with a twofold increased risk of death from cardiovascular causes.[1]

Known echocardiographic abnormalities include a decreased left ventricular mass, reduced left ventricular dimensions, a decreased cardiac output, mitral valve prolapse and pericardial effusions. No meta-analysis has been performed on the data available so it remains uncertain as to whether these changes correlate with the severity of AN.

The National Institute of Clinical Excellence published revised guidelines in 2017 on eating disorders and advocate acute medical care for those with significant complications.[2] The Management of Really Sick Patients with Anorexia Nervosa (MARSIPAN) working group

recommend specialist eating disorder units (SEDU) for patients with severe AN, but medical admission and intensive care where appropriate for treatments not available on a psychiatric ward.[3] Neither guideline mentions the use of echocardiography in the management of these patients.

Given the lack of randomised trials or comparative effectiveness data on this subject, our aim is to systematically review the data and perform meta-analysis where possible, with the aim of using our findings to support clinical guideline development.

7 Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)

The aim of this systematic review is to ascertain the echocardiographic abnormalities seen in anorexia nervosa. Participants will be sufferers of anorexia nervosa; in the majority of the studies, there will not be any interventions involved, although some studies will be looking at the effects of weight restoration on the echocardiographic findings; in the case control studies included, the comparators will be the control group and finally the specific outcomes will be lthe echocardiographic abnormalities seen.

METHODS:

8 Specify the study characteristics

Study designs

We will include all types of studies: case reports, case series, cross-sectional studies and case controls. There are no randomised control studies. We will exclude conference abstracts and animal studies.

Participants

All sufferers of anorexia nervosa, irrespective of age or gender. We will not look at other eating disorders, such a bulimia nervosa or drug-induced anorexia. We will use the Diagnostic and Statistical Manual definition of anorexia nervosa and quantify the degree of anorexia nervosa by the body mean index (BMI) where provided.

Intervention

It most studies, there will be no intervention. In some, the intervention will be the effects of weight restoration on the echocardiographic findings.

Comparators

Where there is a control group, this will be our comparator. It may be a healthy control of normal weight or a reduced weight.

Outcome

The outcomes we are looking at are any echocardiographic abnormalities, that may affect:

- Left ventricular dimensions
- Left ventricular systolic function including cardiac output and cardiac index
- Left ventricular diastolic function
- Mitral valve prolapse (MVP)
- Left atrial size
- Right ventricular dimension
- Right ventricular function
- Other valvular abnormalities
- Pulmonary hypertension
- Pericardial effusion

We will extract all individual outcomes reported in the studies.

Timing

There will be no date restrictions. For studies looking weight restoration and echocardiographic changes in anorexia nervosa, there will be no stipulation on the length of follow up.

Setting

There will be no restrictions by type of setting.

Language

We will exclude any non-English citations.

9 Describe all intended information sources with planned dates of coverage

We will look at Medline, EMBASE and Cochrane library of systematic reviews. We will cross reference but not look at any grey literature. If the data to meta-analyse is incomplete, we will contact the authors directly for the raw data.

10 Present draft of search strategy to be used (draft Medline search)

#	Database	Search term
1	Medline	"FEEDING AND EATING DISORDERS"/
2	Medline	"ANOREXIA NERVOSA"/
3	Medline	"BULIMIA NERVOSA"/
4	Medline	"BINGE-EATING DISORDER"/
5	Medline	"FEEDING AND EATING DISORDERS OF CHILDHOOD"/
6	Medline	("eating disorder*").ti,ab
7	Medline	(anorexi*).ti,ab
8	Medline	(bulimi*).ti,ab
9	Medline	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8)
10	Medline	exp ECHOCARDIOGRAPHY/
11	Medline	(echocardiogra*).ti,ab
12	Medline	(10 OR 11)
13	Medline	(9 AND 12)
14	Medline	13 [Languages English] [Humans]

11a Describe the mechanism(s) that will be used to manage records and data throughout the review

Literature searches will be uploaded in the 'ris' format onto Mendeley. Duplicates will be easy to remove from the Mendeley software.

The two reviewers (JS and CC) will initially screen several studies to refine the screening questions. They will then independently screen the titles and abstracts against the inclusion criteria.

11b State the process that will be used for selecting studies through each phase of the review

Screening: The two reviewers will review the titles and abstracts independently against the inclusion criteria:

- Studies pertaining to AN
- Primary disease or condition AN
- No other known primary disease of the heart
- Not drug induced heart disease or drug induced AN
- Only cardiac complications of AN
- Abnormal echocardiographic findings in AN
- Not a literature review

We will obtain the full study for all titles that meet the inclusion criteria or where there is any uncertainty/disagreement between the two reviewers. We will resolve disagreement through discussion or through consultation with our third author, PL. We will record the reasons for rejecting the full studies. Potential reasons would include insufficient echocardiographic details. Neither of the reviewers will be blinded to journal titles/authors/institutions.

Inclusion in the meta-analysis: The studies which are to be included in the meta-analysis will be the case control studies, with basic demographic details compulsory (i.e age and body mass index).

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

The data extracted will be in duplicate and will include demographics. For those studies where meta-analysis is not possible, we will include: methodology; a description of the echocardiographic details that would be included in a British Society of Echocardiography minimum dataset for transthoracic echocardiograms, and outcomes. For the meta-analysis, the two reviewers will grade the evidence according to the Newcastle-Ottawa Scale. The composite mean and standard deviations for both the case and control groups will be extracted. We will contact study authors where missing information is required.

12 List and define all variables for which data will be sought

Age, body mass index, trial design, trial size and country of publication will be recorded where possible for all studies. In addition, for the meta-analysis of the case control studies, we will extract data for: left ventricular dimensions, left ventricular mass, left ventricular systolic function, left ventricular diastolic function, presence of MVP and presence of pericardial effusions. If the study focuses on weight restoration, data prior to weight restoration and the data after weight restoration will be included in addition to the duration of follow-up.

13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale

The primary outcomes will be:

- the effect of severity of AN on left ventricular mass, measured in grams (g).
- the effect of the severity of AN on cardiac output, measured in litres per minute.
- the effect of the severity of AN on diastolic function, represented by the E/A ratio
- the effect of weight restoration on left ventricular mass (g)
- the effect of weight restoration on left ventricular dimensions measured in centimetres.
- The relative risk (RR) of having a pericardial effusion in the AN population, and if this varies with severity of disease

- The RR of having a MVP in the AN population, and if this varies with severity of disease

Not all these outcomes will be calculated from the total number of randomised patients, due to heterogeneity (the studies will vary in what outcomes they study).

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

To assess possible bias we will collect information using the Cochrane Collaboration tool for assessing the risk of bias, where appropriate. Our meta-analysis will be looking at case controls only so aspects such as random allocation sequence, concealment at allocation and blinding are not relevant. There will be a proportion of patients who will be lost to follow up, largely because of the psychiatric nature of the disease process.

15a Describe criteria under which study data will be quantitatively synthesized

If the studies are sufficiently homogenous then we will conduct a meta-analysis using random-effects model.

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

Measures of incidence (mitral valve prolapse and pericardial effusion):

This will be determined by using a risk ratio (RR) with 95% confidence intervals (CI).

For continuous outcomes, such as left ventricular dimensions:

We will analyse using weighted mean differences with 95% CI.

Unit of analysis issues:

Where there is more than one control group (e.g healthy controls and thin but healthy controls), we will include both.

Dealing with missing data:

We will contact the authors directly for any missing data that we encounter.

Assessment of heterogeneity:

We will test clinical heterogeneity by assessment of participant factors (e.g age), trial factors (notably losses to follow up) and outcomes measured.

Data synthesis:

Each outcome will be combined and calculated using RevMan 5.3, according to statistical guidelines specified in the *Cochrane Handbook for Systematic Reviews of Interventions.*

15c Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)

Subgroup analyses will be used to explore the effects of the severity of anorexia nervosa. This will be based on the body mass index.

15d If quantitative synthesis is not appropriate, describe the type of summary planned

For the trials which cannot be included in the meta-analysis, a systematic narrative synthesis will be provided in table format. The narrative synthesis will explore the relationship and findings within the studies included, in line with the guidance: Cochrane Consumers and Communication Review Group: data synthesis and analysis.

16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)

Our systematic review will not include randomised control trials therefore meta-bias (and preferential reporting of positive studies over negative studies) will be less of an issue. The studies whhere we can meta-analyse the data will be assessed for ‘heterogeneity’. In addition publication bias may be evident from assessing the funnel plots produced.

17. Describe how the strength of the body of evidence will be assessed.

The strength of the body of evidence will be assessed using the Newcastle-Ottawa Scale which uses a 'star system' to judge the non-randomised studies on three broad categories. It attributes a score to a paper after assessing the selection of the study groups, their comparability and the ascertainment of whether the outcome of interest or exposure for cohort and case control studies.

References

1. Papadopoulos F, Ekbom A, Brandt L et al. Excess mortality, causes of death and prognostic factors in anorexia nervosa. *British Journal of Psychiatry* (2009) 194(1) 10-17

2. National Institute for Health and Care Excellence (2017). Eating disorders: recognition and treatment. NICE guideline [NG69]

3. MARSIPAN: Management of Really. Sick Patients with Anorexia Nervosa (2014). 2nd edition. College Report [CR189].