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Review

Cardiac abnormalities identified with echocardiography in anorexia nervosa: systematic review and meta-analysis

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Background

Anorexia nervosa affects most organ systems, with 80% suffering from cardiovascular complications.

Aims

To define echocardiographic abnormalities in anorexia nervosa through systematic review and meta-analysis.

Method

Two reviewers independently assessed eligibility of publications from Medline, EMBASE and Cochrane Database of Systematic Reviews registries. Studies were included if anorexia nervosa was the primary eating disorder and the main clinical association in described cardiac abnormalities. Data was extracted in duplicate and quality-assessed with a modified Newcastle–Ottawa scale. For continuous outcomes we calculated mean and standardised mean difference (SMD), and corresponding 95% confidence interval. For dichotomous outcomes we calculated proportion and corresponding 95% confidence interval. For qualitative data we summarised the studies.

Results

We identified 23 eligible studies totalling 960 patients, with a mean age of 17 years and mean body mass index of 15.2 kg/m^2. Fourteen studies (469 participants) reported data suitable for meta-analysis. Cardiac abnormalities seen in anorexia nervosa compared with healthy controls were reduced left ventricular mass (SMD 1.82, 95% CI 1.32–2.31, $P < 0.001$), reduced cardiac output (SMD 1.92, 95% CI 1.38–2.45, $P < 0.001$), increased E/A ratio (SMD −1.10, 95% CI −1.67 to −0.54, $P < 0.001$), and increased incidence of pericardial effusions (25% of patients, $P < 0.01$, 95% CI 17–34%, $I^2 = 80\%$). Trends toward improvement were seen with weight restoration.

Conclusions

Patients with anorexia nervosa have structural and functional cardiac changes, identifiable with echocardiography. Further work should determine whether echocardiography can help stratify severity and guide safe patient location, management and effectiveness of nutritional rehabilitation.

Declaration of interest

None.

Keywords

Anorexia nervosa; eating disorder; echocardiography; cardiac abnormalities; systematic review.

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Background

Anorexia nervosa is a serious psychiatric condition with a standardised mortality ratio of 6.2 as reported in a recent Swedish registry study.[1] Diagnosis requires persistent deliberate energy intake restriction, intense fear of gaining weight and a disturbed self-perception of weight or shape.[2] Although a small crude increase in the incidence of anorexia nervosa has been reported,[3] there has been a decrease in mortality over the past two decades.[1] The condition affects most organ systems with 20.8% of patients becoming chronically ill[3] and 80% of patients having cardiovascular complications, with a two-fold increased risk of death from cardiovascular causes.[1]

Guidelines

The National Institute for Health and Care Excellence published revised guidelines in 2017 on eating disorders and advocate acute medical care for those with significant complications.[4] The Management of Really Sick Patients with Anorexia Nervosa working group recommend admission to a specialist eating disorder unit for patients with severe anorexia nervosa, but medical admission and intensive care for treatments not available on a psychiatric ward.[5] As medical and psychiatric wards may have different physical locations and intensity of medical support, correct identification of those patients that require medical admission is critical to ensure appropriate management.

Echocardiography has developed to the point where high resolution and highly portable cardiac imaging is now available at the bedside. Within the critical care setting cardiac ultrasound is now used widely for diagnosis, monitoring and assessment of therapeutic interventions.[6,7] Therefore, echocardiography may provide a rapid means to evaluate cardiac pathology and risk-stratify patients with anorexia nervosa. We undertook a systematic review and meta-analysis of the literature to determine the severity of cardiac structural and functional abnormalities identifiable with echocardiography in patients with anorexia nervosa.

Method

This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO identifier CRD42018088509) and can be accessed at https://www.crd.york.ac.uk/PROSPEROFILES/88509_PROTOCOL_20180317.pdf. It is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement (Supplementary Appendix 1 available at https://doi.org/10.1192/bjp.2020.1). Ethical approval was not required because of the retrospective nature of the study. A systematic literature search of all patients with anorexia nervosa who had echocardiogram documented was conducted by a librarian (T.P.) on 19 April 2017, and then repeated on 16 January 2018. There was no essential requirement for a comparison group, but where included, healthy controls were incorporated into this review. The outcome was any echocardiographic abnormality. We searched the Medline, EMBASE, CENTRAL, Cochrane Database of Systematic Reviews and the World Health Organization International Clinical Trials Registry Platform with no date restrictions. We excluded animal studies, non-English citations and conference abstracts from EMBASE. The free-text search included ‘eating disorder’, ‘anorexia

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nervosa', 'bulimia nervosa', 'binge eating disorder' and 'echocardiography.' The free-text search was expanded with MeSH terms to ensure full coverage and we deliberately kept the terms broad to maximise the number of citations detected (Supplementary Appendix 2). Of the full-text articles assessed for eligibility ($n = 72$), we hand-searched all the reference lists.

Exclusion criteria, validity assessment and data extraction

References identified were imported into Mendeley (Mendeley Desktop v1.17.13, MacOS, Mendeley Ltd, London, UK, https://www.mendeley.com/download-desktop/), a reference management software, for de-duplication. Two authors (J.S., C.C.) screened the references independently against the following exclusion criteria: studies not pertaining to anorexia nervosa, primary disease or condition not anorexia nervosa, known other primary disease of the heart, drug-induced heart disease or drug-induced anorexia nervosa, non-cardiac complications of anorexia nervosa, transoesophageal rather than transthoracic echocardiography, normal transthoracic echocardiography findings in anorexia nervosa, literature review and case report.

Papers were excluded on title first and then on abstract. Where there was disagreement between the authors, the paper was included for the next stage of full-text review.

Data extraction

We extracted in duplicate data pertaining to study details (study design, year, country), baseline characteristics of the study population (number of participants, mean age, body mass index (BMI)), assessment details (transthoracic echocardiographic data) and details pertinent to risk of bias analysis (control group BMI, quality of the echocardiographic study, description of follow-up). As a deviation from the published protocol, we sought the assistance of two additional authors: L.P. for the statistical analysis of the data and T.P. for their expertise. Where data was not locatable in the published results, we contacted the corresponding authors of studies.

Quantitative data extraction

For the assessment of continuous outcomes we used mean and s.d. For assessment of binary outcomes we extracted the number of participants with the condition divided by the total number of participants to derive a proportion. Two reviewers (J.S., C.C.) independently assessed the risk of bias at study level, using a modified Newcastle–Ottawa scale[8] (Supplementary Appendix 3).

Statistical methods

In our meta-analyses for continuous outcomes, we calculated the mean and standardised mean difference (SMD) and the corresponding 95% confidence interval. For dichotomous outcomes we calculated the proportion of participants with the condition and the corresponding 95% confidence interval. SMD calculations were pooled using the Der Simonian–Laird method with random-effects model, because of the heterogeneity of different measures included. Statistical heterogeneity was determined with the Q statistic and I^2 metric. Inconsistency for each outcome not attributable to chance was assessed visually with forest plots; $I^2 < 25\%$ reflected low inconsistency and $I^2 > 75\%$ reflected high inconsistency. Meta-analyses generated a SMD expressed in s.d. units and SMD of ±0.5 s.d. or greater was considered important. A random-effect meta-regression has been conducted for the left ventricular mass (LVM) parameter, including age, BMI and heart rate as potential confounder (see Supplementary Fig. 1). Unfortunately, most studies did not report on other potential confounders that could contribute to the echo parameters' variance, such as length of anorexia diagnosis, biochemical alterations and endocrine problems. We did not conduct subgroup analyses because of the lack of consistent reporting across studies of anorexia nervosa behavioural subtypes (restrictive versus purging/binging behaviour). We did perform a sensitivity analysis by age to assess whether similar findings were evident in those aged 16 years and older. Publication bias assessment was conducted using the Fail-safe N analysis with the Rosenthal approach, and funnel plots were visually inspected and assessed with the Egger regression test (see Supplementary Table 1 and Supplementary Figs 2 and 3). To calculate differences between the means of each parameter in patients before and after weight restoration, we used the Mann–Whitney U test and considered statistical significance to be signalled by P values <0.05.

Data were analysed with the MAJOR package for meta-analysis by Kyle Hamilton (https://github.com/kylehamilton/MAJOR#major-meta-analysis-jamovi-r), developed for Jamovi version 0.9.1.10 for MacOS (The Jamovi Project (2019), Jamovi, https://www.jamovi.org).

Results

Eligibility criteria

The database search produced 332 publications in addition to five further references from bibliographic review, of which 229 were non-duplicates. Title and abstract screening excluded 170 papers. Fifty-five full-text articles were reviewed and there were thirty-two further exclusions as outlined in Fig. 1. The majority of the exclusions were owing to insufficient echocardiographic data (13 studies). Nine studies were excluded because of the outcome reported not being relevant to our review; for example, the focus being on other cardiac output measures. Twenty-three studies were included in the qualitative review, with study characteristics summarised in Table 1. Fourteen studies were included in the meta-analysis (469 patients).

Electronic communication

A summary with the results of the systematic review and meta-analysis were communicated to authors of the 23 included studies.

Description of study selection

There were fourteen (61%) case-control studies, four (17%) case series, three (13%) retrospective comparative studies and two (9%) longitudinal observational studies. Two studies, which did not report duplicate publication, from the same centre with the same authorship had identical echocardiographic and Doppler measures and therefore only one set of data was included (Table 1).

The number of patients in each study varied from 11 to 173, including a total of 960 patients with anorexia nervosa. The mean age of studied patients was 17 years (range 13–45 years). Overall, the mean BMI was 15.2 kg/m^2. BMI was classified (by mean) as 'mild' (BMI $\geq$ 17 kg/m^2) in one study, 'moderate' (BMI 16–16.99 kg/m^2) in two studies, 'severe' (BMI 15–15.99 kg/m^2) in fourteen studies and 'extreme' (BMI $\leq$ 15 kg/m^2) in five studies, using the DSM-5 criteria.[2]

Study quality assessment

Among the 23 included studies, 3 were at high risk of bias (13%), 11 were at moderate risk (48%) and 9 were at low risk (39%) (Supplementary Appendix 3)

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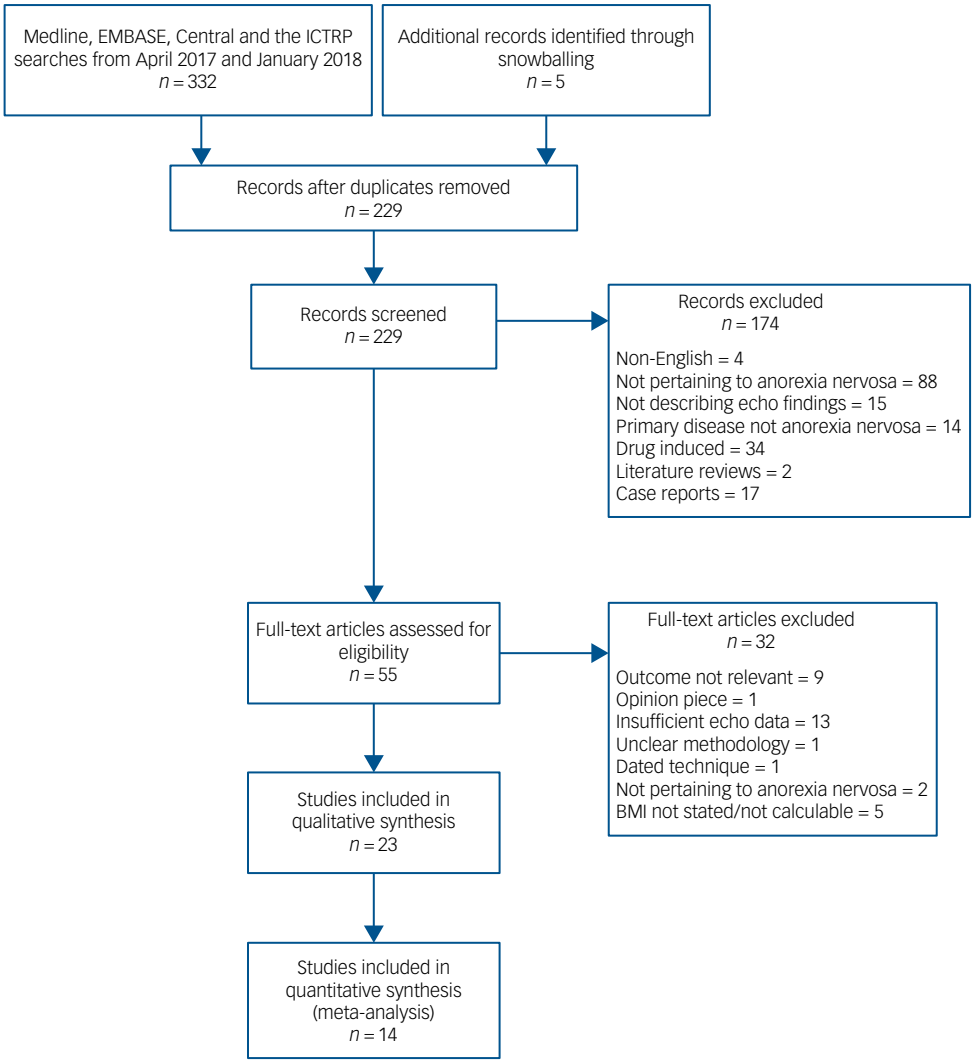

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram showing the number of articles screened at each stage.

BMI, body mass index; ICTRP, International Clinical Trials Registry Platform.

Echocardiographic measures

We identified five echocardiographic themes and one clinical theme that could be examined from the included studies: LVM and size, left ventricular systolic function, diastolic function, valvular disorders, pericardial effusions, and the clinical theme of follow-up with weight restoration. We therefore describe our results below using these categories.

LVM and structure

LVM: LVM measurements are based on estimating the difference between the epicardial and endocardial left ventricular volumes, and multiplying by the standardised myocardial density. In 11 studies, patients with anorexia nervosa had reduced LVM when compared with normal-weight controls, and this was statistically significant (mean difference 32.2 g, 95% CI 23.4–40.0 g; SMD 1.82, 95% CI 1.32–2.31; $P < 0.001$; see Fig. 2).[10,12,13,17–20,22,25,26,29] This finding was consistent in four of these studies where the anorexia nervosa group was compared with a thin (normal-low BMI) control group (SMD 2.53, 95% CI 1.48–3.59; see Supplementary Fig. 1),[18,20,22,29] and when adults were studied alone (SMD 1.90, 95% CI 1.01–2.80).

Because of the lack of consistent and exhaustive reporting of possible confounders, we assessed age, BMI and heart rate as possible covariates in two models to explain the variance in the difference of LVM between anorexia nervosa and controls, respectively (Supplementary Fig. 1 of meta-regression scatterplots). In both models, these factors only partially explained the variance in LVM (Supplementary Fig. 4).

There was a statistically significant difference for LVM standardised for body surface area (LVM/BSA) between patients with anorexia nervosa and the control group (mean difference 11.8 g/m^2, 95% CI 8.69–14.93 g/m^2; SMD 0.87, 95% CI 0.64–1.10; $P < 0.001$; see Fig. 2).[10,12,19,24–27,29] Similar findings were seen when adults were studied alone (SMD 0.84, 95% CI 0.53–1.15). When the LVM was standardised for height, the anorexia nervosa group had a reduced LVM/height ratio, which was statistically significant when compared with both healthy controls with a BMI >20 kg/m^2 (mean difference 7.42 g/m, 95% CI 4.65–10.2 g/m; SMD 1.98, 95% CI 1.24–2.73; $P < 0.001$; see Fig. 2)[10,11,13,17,18,20,25,29] and thin controls with a BMI of 18 kg/m^2 (SMD 2.07, 95% CI 0.76–3.39, $P = 0.002$; see Supplementary Fig. 2).[20,22,29]

Fifteen studies[9,10,12,13,15,17–20,22–26,29] describe a reduction in LVM in patients with anorexia nervosa with correlating factors, including BMI ($r^2 = 0.34$–0.74, $P < 0.004$),[9,12,15,26] heart rate reduction ($r^2 = 0.55$, $P < 0.006$)[17] and free-thyroxine reduction ($r^2 = 0.32$, $P = 0.001$).[8]

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Table 1 Characteristics of the included studies

First author	Country	Type of study	Patients with anorexia nervosa	Mean age	Mean BMI	Key findings
Kuwabara *et al*, 2018[9]	Japan	Cross sectional	13	35	16	12 out of 13 patients had normal ejection fraction. Patients with anorexia nervosa had reduced LVM and LVMI. Lower BMI correlated to a lower LVMI.
Billeci *et al*, 2017[10]	Italy	Case control	44	15	15	The anorexia nervosa group had a statistically significantly reduced LVEDD, LVESD, LVMI, LVM adjusted for height and left atrium dimensions compared with the controls. The incidence of PEf was statistically higher in the anorexia nervosa group. The E peak and A peak were both statistically significantly reduced.
Morris *et al*, 2017[11]	USA	Cross sectional	30	13	16	LVMI was significantly less in patients with anorexia nervosa with versus without purging behaviour. There was no significant difference between ejection fraction and fractional shortening. Healthy controls and non-purging patients with anorexia nervosa displayed similar apex-to-base SLS when compared with the purging anorexia nervosa group.
Escudero *et al*, 2016[12]	Canada	Case control	95	16	16	LVMI, LVEDD, LVESD, IVSD and LVPWDd were significantly smaller in patients with anorexia nervosa, and correlated with BMI percentile. Left atrium was reduced in the anorexia nervosa group. The subgroup with the BMI in the lowest 10th percentile had a statistically significant increased E/A.
Lelli *et al*, 2015[13]	Italy	Case control	14	28	16	LVEDV, LVEDV/BSA, LVM, LVMI, stroke volume, SVI, cardiac output and cardiac index were all statistically significantly reduced in the anorexia nervosa group. The reduction in left ventricular dimensions and mass correlates with the degree of being underweight.
Kastner *et al*, 2012[14]	Germany	Retrospective comparative	173	15	15	Statistically higher prevalence of PEf in patients with lower BMI. Statistically significant reduced LVEDD and LVESD in anorexia nervosa compared with controls. Non-complete reversibility of TTE findings with weight restoration.
DiVasta *et al*, 2010[15]	USA	Longitudinal observational	38	17	16	BSA-corrected left ventricular mass was reduced in 11 of 38 patients. posterior wall thickness (9/38) and septal thickness (12/38) were lower. Afterload reduced in 23 out of 38 patients as measured by end systolic stress.
Docx *et al*, 2010[16]	Belgium	Longitudinal observational	128	14	15	29 of 128 (22.2%) patients had PEf. Those with PEf had significantly lower BMI, LVM, LVMI, heart rate and insulin growth factor.
Ülger *et al*, 2006[17]	Turkey	Case control	11	15	14	The PEf in two patients with anorexia nervosa resolved with weight restoration. LVEDD, IVSTd and LVPWTd, LVM and LVMI were all significantly reduced in the anorexia nervosa compared with controls.
Galetta *et al*, 2005[18]	Italy	Case control	20	22	15	In the anorexia nervosa group: EDD, IVS thickness, LVPW thickness, LVM, LVMI, peak A and E/A were all significantly reduced. The anorexia nervosa group exhibited a lower S wave peak, indicating a reduced left ventricular systolic function.
Olivares *et al*, 2005[19]	Spain	Case control	40	–	15	LVED, LVSD, LVM, LVMI and cardiac output were all significantly reduced in the anorexia nervosa group at baseline compared with weight recovery. LVPW and IVS thickness, fractional shortening and ejection fraction were similar in the two groups. Eight out of 40 had MVP at baseline versus 3 out of 40 after weight recovery.
Franzoni *et al*, 2003[20,a]	Italy	Case control	25	22	15	EDD, ESD, stroke volume, cardiac output, LVM, LVMI, peak A wave and E/A ratio were all significantly reduced in the anorexia nervosa group. IBS cyclical variation was reduced significantly in the anorexia nervosa group, reflecting contractile performance of the myocardial wall.
Galetta *et al*, 2002[21,a]	Italy	Case control				A strong relationship was found between QT segment length (dispersion) and left ventricular mass in patients with anorexia nervosa but neither control group.
Galetta *et al*, 2003[22]	Italy	Case control	25	18	15	In the anorexia nervosa group: end diastolic and systolic diameters and LVM and LVMI were significantly reduced; ejection fraction and fractional shortening were preserved. The anorexia nervosa group had a reduced peak A and E/A.
Mont *et al*, 2003[23]	Spain	Case series	31	16	15	The LVEDD, LVESD, left atrium, LVM, LVMI, cardiac output, cardiac index, A wave and E wave were all significantly reduced at baseline when compared with after refeeding.
Ramacciotti *et al*, 2003[24]	Italy	Case control	15	23	14	PEf in 71.3% patients and 30% in the thin control group. The LVM/BSA was significantly lower in the PEf group, whereas their isovolumetric relaxation time was significantly lower.
Romano *et al*, 2003[25]	Italy	Case control	91	21	16	The LVM, left ventricular diastolic diameter, cardiac output, ejection fraction and stroke volume were all significantly reduced in the anorexia nervosa group, potentially because of the reduced haemodynamic load.
Vázquez *et al*, 2003[26]	Spain	Case control	30	16	15	EDD, ESD, IVS thickness, LVM and LVMI were all significantly reduced in the anorexia nervosa group.
Eidem *et al*, 2001[27]	USA	Retrospective comparative	13	17	18	In the anorexia nervosa group, LVM was significantly reduced and the mitral valve closure to opening interval was increased. The left ventricular ejection time was unchanged, with an elevated ratio of left ventricular MPI.
Frölich *et al*, 2001[28]	Germany	Case series	65	15	14	PEf in 10 (15.4%) of 65 patients during in-patient treatment, varying from minimal to 2.24 cm. In 7 of 10 patients there was complete remission. Nine of 10 patients had low fT3 levels.
de Simone *et al*, 1994[29]	Italy	Case control	21	22	15	Left ventricular dimension, LVM, LVMI, left atrium dimensions, cardiac output, cardiac index and LVM when adjusted for height were all reduced compared with the controls. Left ventricular relative wall thickness was higher for anorexia nervosa. Mid-wall fractional shortening when predicted from end systolic stress was significantly lower in the anorexia nervosa group. The peak A was significantly less in the anorexia nervosa group, increasing E/A.
Meyers *et al*, 1987[30]	USA	Case control	15	19	16	8 out of 15 patients with anorexia nervosa had MVP versus 2 out of 15 controls. After weight restoration to 75% of ideal body weight, only one patient had MVP. The ratio of mitral leaflet length to left ventricular systolic dimension at the lowest weight was significantly different between patients with anorexia nervosa with MVP and those without, suggestive of valvulo-ventricular disproportion.
Oka *et al*, 1987[31]	Japan	Case series	23	20	14	MVP was found in 19 of 23 patients (82.6%). There was no correlation between MVP and body weight reduction. Heart rate was significantly lower in the MVP group.

BMI, body mass index; LVM, left ventricular mass; LVMI, left ventricular mass index; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; PEf, pericardial effusion; SLS, segmental longitudinal strain; IVSD, interventricular septal diameter; LVPWDd, left ventricular posterior wall diameter in diastole; LVEDV, left ventricular end diastolic volume; LVEDV/BSA, left ventricular end diastolic volume/body surface area; SVI, stroke volume index; TTE, transthoracic echocardiogram; BSA, body surface area; IVSTd, interventricular septal diameter diastole; LVPWTd, left ventricular posterior wall thickness diastole; EDD, end diastolic diameter; IVS, interventricular septum; LVPW, left ventricular posterior wall; MVP, mitral valve prolapse; ESD, end systolic diameter; IBS, integrated backscatter; LVM/BSA, left ventricular mass/body surface area; MPI, myocardial performance index; fT3, free triiodothyronine.
a. Same data-set.

Table 2 Effect of weight restoration on echocardiography findings

Study	Interval	*N*	Baseline (mean (s.d.))	Weight restoration (mean (s.d.))	*P* value
Body mass index (kg/m^2)					<0.001
Billeci *et al*, 2017[10]	N/A	9	15.4 (0.5)	18.1 (0.4)	
Ülger *et al*, 2006[17]	2.45 ± 1.17 years	11	13.71 (1.54)	21.23 (3.3)	
DiVasta *et al*, 2010[15]	11–57 weeks	19	15.9 (1.9)	18.1 (1.7)	
Olivares *et al*, 2005[19]	9–18 months	40	15.26 (2.06)	18.51 (2.33)	
Mont *et al*, 2003[23]	3–18 months	31	15.2 (2)	19.2 (1)	
Meyers *et al*, 1987[30]	75% weight gain	15			
Frölich *et al*, 2001[28]	N/A	10			
LVEDD (cm)					0.02
Billeci *et al*, 2017[10]	N/A		4.02 (0.33)	4.29 (0.26)	
Ülger *et al*, 2006[17]	2.45 ± 1.17 years		3.69 (0.52)	4.26 (0.55)	
Olivares *et al*, 2005[19]	9–18 months		4.13 (0.36)	4.37 (0.33)	
Mont *et al*, 2003[23]	3–18 months		4.2 (0.3)	4.6 (0.3)	
LVM (g)					0.09
Billeci *et al*, 2017[10]	N/A		53.02 (14.3)	95.39 (17.8)	
Ülger *et al*, 2006[17]	2.45 ± 1.17 years		105.5 (28)	104.4 (17.6)	
DiVasta *et al*, 2010[15]	11–57 weeks		76.8 (17.7)	91.5 (18.9)	
Olivares *et al*, 2005[19]			84 (20)	104 (24)	
LVMI (g/m^2)					0.12
Billeci *et al*, 2017[10]	N/A		56.1 (11.1)	56.6 (11.2)	
Olivares *et al*, 2005[19]	9–18 months		58.5 (10.6)	66.5 (12.6)	
Mont *et al*, 2003[23]	3–18 months		59 (11)	67 (13)	
LVM/height (g/m$^{2.7}$)					N/A
Billeci *et al*, 2017[10]	N/A		17.1 (3)	22.5 (5.8)	
Ülger *et al*, 2006[17]	2.45 ± 1.17 years		14.53 (3.53)	23.71 (5.13)	
Cardiac output (L/min)					N/A
Olivares *et al*, 2005[19]	9–18 months		2.9 (0.3)	3.5 (0.4)	
Mont *et al*, 2003[23]	3–18 months		2.84 (0.8)	3.92 (0.99)	
E/A					N/A
Mont *et al*, 2003[23]	3–18 months		2.41 (0.65)	2.03 (0.56)	
Pericardial effusion					0.05
Billeci *et al*, 2017[10]	N/A		67%	22%	
Ülger *et al*, 2006[17]	2.45 ± 1.17 years		18%	0%	
Frölich *et al*, 2001[28]	N/A		100%	2%	
MVP					N/A
Meyers *et al*, 1987[30]			53%	7%	

Differences between baseline and weight restoration calculated with the Mann–Whitney U test. LVEDD, left ventricular end diastolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; MVP, mitral valve prolapse.

Left ventricular dimensions: Left ventricular dimensions were quantified in the included studies, using M-Mode assessment of the left ventricular internal diameters. Eleven out of twelve studies describing left ventricular dimensions found a difference in either the systolic, diastolic or wall dimensions in the anorexic population compared with the normal range.[10,12,15,17–20,22,25,26,29] Eleven studies describe a reduction in end diastolic left ventricular cavity dimensions[10,12,14,17–20,22,25,26,29] ranging from 3.69 to 4.13 cm. This represents 4–16.1% absolute reduction compared with controls. Five studies demonstrated a significant reduction in wall thickness: one study affecting the interventricular septum only[26] (mean BMI 15.3 kg/m^2, 0.61 ± 0.11 cm *v.* 0.69 ± 0.1 cm in the control group, $P = 0.006$) and four studies affecting both the interventricular septum and LVPW (mean BMI 15.2 kg/m^2).[12,15,17,18]

Left ventricular systolic function

Fractional shortening represents the change in left ventricular mid-cavity size with left ventricular ejection. Ejection fraction represents the fraction of blood ejected from the left ventricle during each cardiac cycle. Stroke volume is the volume of blood that forms the ejection fraction per cardiac cycle, and cardiac output is stroke volume multiplied by heart rate. Data describing the effect of anorexia nervosa on cardiac output were available for seven studies.[12,13,19,20,25,26,29] There was a statistically significant reduction in cardiac output for the anorexia nervosa group compared with healthy controls (mean difference 1.43 l/min, 95% CI 1.03–1.83 l/min; SMD 1.92, 95% CI 1.38–2.45; $P < 0.001$; see Fig. 3), which was also evident in the adult subgroup (SMD 1.84, 95% CI 1.26–2.42).

There were six studies examining the effect of anorexia nervosa on stroke volume. In all six studies the stroke volume was significantly reduced,[12,13,20,21,25,29] but in only two studies was the stroke volume index (adjusted for height) significantly reduced compared with the control group.[13,29]

Based on ejection fraction and fractional shortening eight studies did not report left ventricular function outside the normal range.[11,12,15,17,18,20,23,26] In two studies the ejection fraction was significantly reduced compared with the control group.[13,25]

Beyond ejection fraction, fractional shortening, stroke volume and cardiac output, other techniques for assessing the left ventricular were described. There were five studies that described impaired systolic function in patients with anorexia nervosa,[11,18,20,27,29] including a subgroup of patients with anorexia nervosa with purging behaviour with significantly decreased apical segmental longitudinal strain (the rate at which the myocardium develops contractile power) values.[11] Franzoni *et al* found that cyclic variation in myocardial integrated backscatter was significantly lower in the anorexia group than in the control group when adjusted for body weight, reflecting poor contractile performance of the myocardial wall.[20] de Simone *et al* found the percentage predicted m-shortening (mid-wall fractional shortening as a percentage of that predicted from end systolic stress) and percentage predicted e-shortening (endocardial fractional shortening as a percentage of predicted) were significantly reduced in the anorexia nervosa group.[29]

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Diastolic function

Diastolic function is measured in the apical four chamber view, using pulsed wave Doppler at the tips of the mitral valve leaflets. This determines peak early filling (E wave) and late diastolic filling (A wave). The E/A ratio is the ratio of these velocities and is normally between 1 and 2. A ratio of greater than two suggests restrictive filling owing to stiffening of the left ventricular wall. In the pooled data of six studies, there was a significant increase in the E/A ratio in the anorexia nervosa group compared with the control group (mean difference 0.61, 95% CI 0.93–0.30; SMD −1.10, 95% CI −1.67 to −0.54; $P < 0.001$; see Fig. 3).[12,18,20,22,27,29] This finding was also seen when compared with thin controls, in data from four pooled studies (SMD −1.79, 95% CI −2.14 to −1.45; $P < 0.001$; see Fig. 3).[18,20,22,29]

Four studies reported a normal transmitral E wave velocity and a reduced transmitral A wave velocity (ranging from 33.7 to 43 cm/s, representing an absolute reduction of 23–26%) and an increased E/A ratio (1.96 to 2.8, representing an absolute increase of 22 to 32%) (mean BMI 15.2 kg/m^2).[18,20,22,29] One study reported this finding in the subgroup analysis of the patients with less than 10th percentile of BMI (mean BMI 15 kg/m^2).[12] Multivariable linear regression analysis showed that heart rate was the only independent predictor of E/A ratio.[12,18]

Valvular disorders

Mitral valve prolapse (MVP) is the most consistently described valvular abnormality, with the two oldest studies reporting primarily on the prevalence of MVP in the anorexia nervosa population.[30,31] To make the diagnosis of MVP one study used M-mode,[30] and one study looked at mitral leaflet movement into the left atrium beyond the functional mitral annulus.[31] The studies include a total of 38 patients with anorexia nervosa and report a prevalence of MVP ranging from 53.3 to 82.6%. Only one study used case controls and they report a prevalence of 13% in the control group.[30] The study with the highest reported prevalence describes both double- and single-leaflet MVP in 19 out of the 23 patients with anorexia nervosa studied.[31]

Four further studies describe the presence of MVP in their populations as a secondary observation without describing how it was measured. The reported prevalence of MVP amongst this second group of studies ranged from 9 to 21%.[12,13,19,29]

Pericardial effusions

Pericardial effusions are classified according to depth: trace <0.5 cm, small 0.5–1.0 cm, moderate 1.0–2.0 cm and large >2.0 cm. The overall proportion of patients with anorexia nervosa with pericardial effusion in 10 studies was 25% ($P < 0.01$; 95% CI 0.17–0.34; $I^2 = 80\%$; Supplementary Fig. 3).[9–17,24] The effusions were all silent, with the majority being mild to moderate in size. In six out of seven case controlled studies healthy controls were not diagnosed with pericardial effusion.[10–14,17] Only one study[24] demonstrated three cases (30%) of pericardial effusion in healthy controls. One study found the LVM/BSA to be significantly lower in the group of patients with anorexia nervosa and a pericardial effusion (54.8 ± 11 *v.* 68 ± 18 g/m^2, $P < 0.001$).[24]

Follow-up after weight restoration

There was a significant increase in left ventricular end diastolic diameter and a significant decrease in the proportion of patients with anorexia nervosa with pericardial effusion following weight restoration. The remaining data demonstrates trends in improvement with weight restoration: an increase in the LVM, LVM index, LVM/height, cardiac output; and a reduction in the E/A ratio and the proportion of patients with an MVP (see Table 2).

Four studies describe improvements in left ventricular dimensions, left ventricular mass and size with weight restoration.[13,17,19,23] LVM index and left ventricular end diastolic diameter significantly increased in four studies following refeeding,[10,17,19,23] with a mean increase of 13.5%[19,23] and 10.3%, respectively.[17,19,23] Two studies describe a significant increase in left ventricular end systolic diameter of between 5 and 9%.[14,19] Cardiac output improved by 21–38% with weight recovery in two studies.[19,23]

In two studies demonstrating evidence of MVP, this improved with weight gain.[24,30] Oka *et al* reported a pre-treatment prevalence of MVP at 83%, and after 2–24 months of weight restoration the prevalence reduced to 45%.[31] Meyers *et al* found that after achieving more than 75% of ideal body weight, the ratio of leaflet length to end systolic dimension (longer length reflecting increased prolapse) in patients with anorexia nervosa changed from 0.86 ± 0.14 to 0.7 ± 0.11 ($P < 0.02$).[30]

Five studies including 354 patients describe resolution of pericardial fluid in 62%,[16] 66%,[10] 70%,[28] 88%[14] and 100%[17] of patients with weight restoration.

Discussion

This review demonstrates anorexia nervosa has significant effects on the structure and the function of the heart, which are easily identifiable by echocardiography. Our key findings are that anorexia nervosa is associated with a reduction in LVM, a reduction in cardiac output, diastolic dysfunction, MVP and pericardial effusions, the resolution of which seemingly occurs with weight restoration.

The reduction in LVM is an observation that persists even when the control group is thin. Malnutrition and immobility may cause cardiac atrophy as it does in skeletal muscle.[15,22,25] Other postulated mechanisms for the reduction in muscle mass seen in this condition are reduced preload causing left ventricular remodeling;[11,29] and reduction in afterload, which acts as a stimulus for the downregulation of left ventricular mass to subnormal levels.[25,32] The cellular and molecular components of this myocyte volume loss are imperfectly understood. This phenomenon is seen in other animals, such as the Burmese python, which infrequently feeds and can increase its heart mass by 40% following a large meal. This significant hypertrophy, not hyperplasia, is an adaptive response to the increased metabolic rate, with increased triglycerides, free fatty acids and activation of P13 K/Akt/mTOR signalling pathways.[33] Although age, BMI and heart rate explain some of the differences in LVM between anorexia nervosa and controls, it is only partially explained, and therefore other features of anorexia nervosa are likely to be contributing, such as the length of diagnosis, or associated metabolic and endocrine abnormalities. Heart rate might be a consequence of the cardiac abnormalities seen in patients with anorexia nervosa rather than a biological contributor to these morphological changes.

Our second key finding is that anorexia nervosa is associated with a reduction in cardiac output. Abnormalities in left ventricular systolic function may be related to the changes in structural properties of the myocardium,[15] reduced contractility owing to atrophy,[34] ventricular remodelling and altered regional function,[11] nutritional deficiencies (magnesium, phosphorus, thiamine or selenium)[35] and reduced adherence.[18]

There is a statistically significant increased E/A ratio in patients with anorexia nervosa compared with normal-weight and thin controls, and comparison with thin controls demonstrates homogeneity. There is evidence that left atrial dysfunction and impaired

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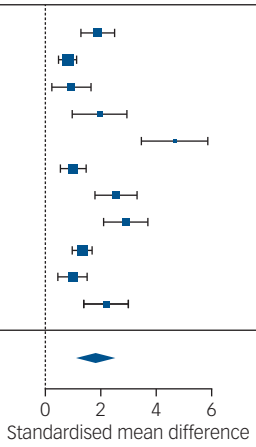
(a) LVM in normal controls and patients with anorexia nervosa

Study	Control N	Control Mean (s.d.)	Anorexia N	Anorexia Mean (s.d.)	Weight	SMD (95% CI)
Billeci *et al.* 2017	20	108.3 (19.5)	44	77.9 (14)	9.44%	1.89 (1.27–2.51)
Escudero *et al.* 2016	58	133.1 (41.8)	95	105.1 (28.9)	10.55%	0.81 (0.47–1.15)
Lelli *et al.* 2015	23	137.8 (30.9)	14	111.2 (20)	9.08%	0.95 (0.25–1.65)
Ûlger *et al.* 2006	12	84.4 (16.4)	11	53 (14.3)	7.65%	1.96 (0.96–2.95)
Galetta *et al.* 2005	20	109.5 (9.8)	20	66.2 (8.3)	6.71%	4.67 (3.48–5.87)
Oliveres *et al.* 2005	40	94.5 (17.5)	40	76.8 (17.7)	10.11%	1.00 (0.53–1.46)
Franzoni *et al.* 2003	25	126.1 (16.4)	25	82.9 (17.1)	8.86%	2.54 (1.79–3.28)
Galetta *et al.* 2003	25	126.1 (14.2)	25	82.7 (15.3)	8.63%	2.89 (2.10–3.69)
Romano *et al.* 2003	62	96.9 (21.2)	91	71.2 (17.6)	10.50%	1.34 (0.98–1.69)
Vázquez *et al.* 2003	30	98.3 (21.2)	30	76.2 (22.6)	9.81%	1.00 (0.46–1.53)
de Simone *et al.*1994	19	124 (22.8)	21	73.3 (22.3)	8.66%	2.20 (1.42–2.99)
Random-effects model	334		416		100.00%	1.82 (1.32–2.31)

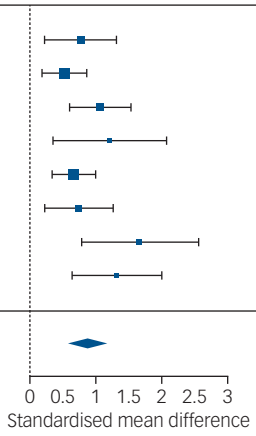
Heterogeneity: $Tau^2 = 0.57$; $Chi^2 = 7.74$; d.f. = 10 ($P < 0.001$); $I^2 = 87.07\%$
Test for overall effect $Z = 7.22$ ($P < 0.001$)



(b) LVM/BSA in normal controls and patients with anorexia nervosa

Study	Control N	Control Mean (s.d.)	Anorexia N	Anorexia Mean (s.d.)	Weight	SMD (95% CI)
Billeci *et al.* 2017	20	65.2 (8.4)	44	58.1 (9.4)	11.97%	0.77 (0.23–1.32)
Escudero *et al.* 2016	58	85.9 (21.5)	95	75.8 (17.5)	20.31%	0.53 (0.19–0.86)
Oliveres *et al.* 2005	40	70 (10.5)	40	58.5 (10.6)	14.41%	1.08 (0.61–1.55)
Ramacciotti *et al.* 2003	10	69 (18)	15	54.8 (1.1)	5.98%	1.22 (0.35–2.08)
Romano *et al.* 2003	62	61.3 (15.1)	91	52.2 (12.2)	20.33%	0.67 (0.34–1.00)
Vázquez *et al.* 2003	30	64 (12.4)	30	53.9 (14.4)	12.62%	0.74 (0.22–1.27)
Eidem *et al.* 2001	13	106 (17.4)	13	79.4 (13.1)	5.70%	1.67 (0.78–2.57)
de Simone *et al.*1994	19	75.2 (12.6)	21	54.9 (16.8)	8.68%	1.33 (0.64–2.02)
Random-effects model	252		349		100.00%	0.87 (0.64–1.10)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.63$; d.f. = 7 ($P < 0.12$); $I^2 = 38.85\%$
Test for overall effect $Z = 7.29$ ($P < 0.001$)



(c) LVM/height in normal controls and patients with anorexia nervosa

Study	Control N	Control Mean (s.d.)	Anorexia N	Anorexia Mean (s.d.)	Weight	SMD (95% CI)
Billeci *et al.* 2017	20	23.4 (3.6)	44	17.4 (2.8)	11.61%	1.93 (1.31–2.56)
Morris *et al.* 2017	14	23.6 (3.5)	25	24.2 (5.9)	11.52%	–0.11 (–0.77 to 0.54)
Lelli *et al.* 2015	23	34.4 (7.4)	14	28 (8.2)	11.40%	0.81 (0.12–1.50)
Ûlger *et al.* 2006	12	22.5 (4.6)	11	14.5 (3.5)	10.37%	1.86 (0.88–2.84)
Galetta *et al.* 2005	20	30.1 (2.2)	20	20.3 (2.1)	9.68%	4.47 (3.31–5.62)
Franzoni *et al.* 2005	25	31.2 (3.1)	25	21.4 (3.3)	11.00%	3.01 (2.20–3.82)
Galetta *et al.* 2003	25	31.4 (3.2)	25	21.2 (3.1)	10.91%	3.19 (2.35–4.02)
Romano *et al.* 2003	62	26 (5)	91	20 (4)	12.29%	1.35 (0.99–1.70)
de Simone *et al.* 1994	19	33.2 (6.3)	21	21.1 (6.5)	11.23%	1.85 (1.11 –2.59)
Random-effects model	220		276		100.00%	1.98 (1.24–2.73)

Heterogeneity: $Tau^2 = 1.14$; $Chi^2 = 10.51$; d.f. = 8 ($P < 0.001$); $I^2 = 90.48\%$
Test for overall effect $Z = 5.22$ ($P < 0.001$)

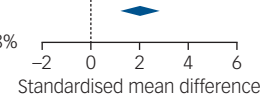


Fig. 2 (a) LVM in normal controls and patients with anorexia nervosa. (b) LVM/BSA in normal controls and patients with anorexia nervosa. (c) LVM/height in normal controls and patients with anorexia nervosa. LVM, left ventricular mass; LVM/BSA, left ventricular mass standardised for body surface area.

SMD, standardised mean difference.

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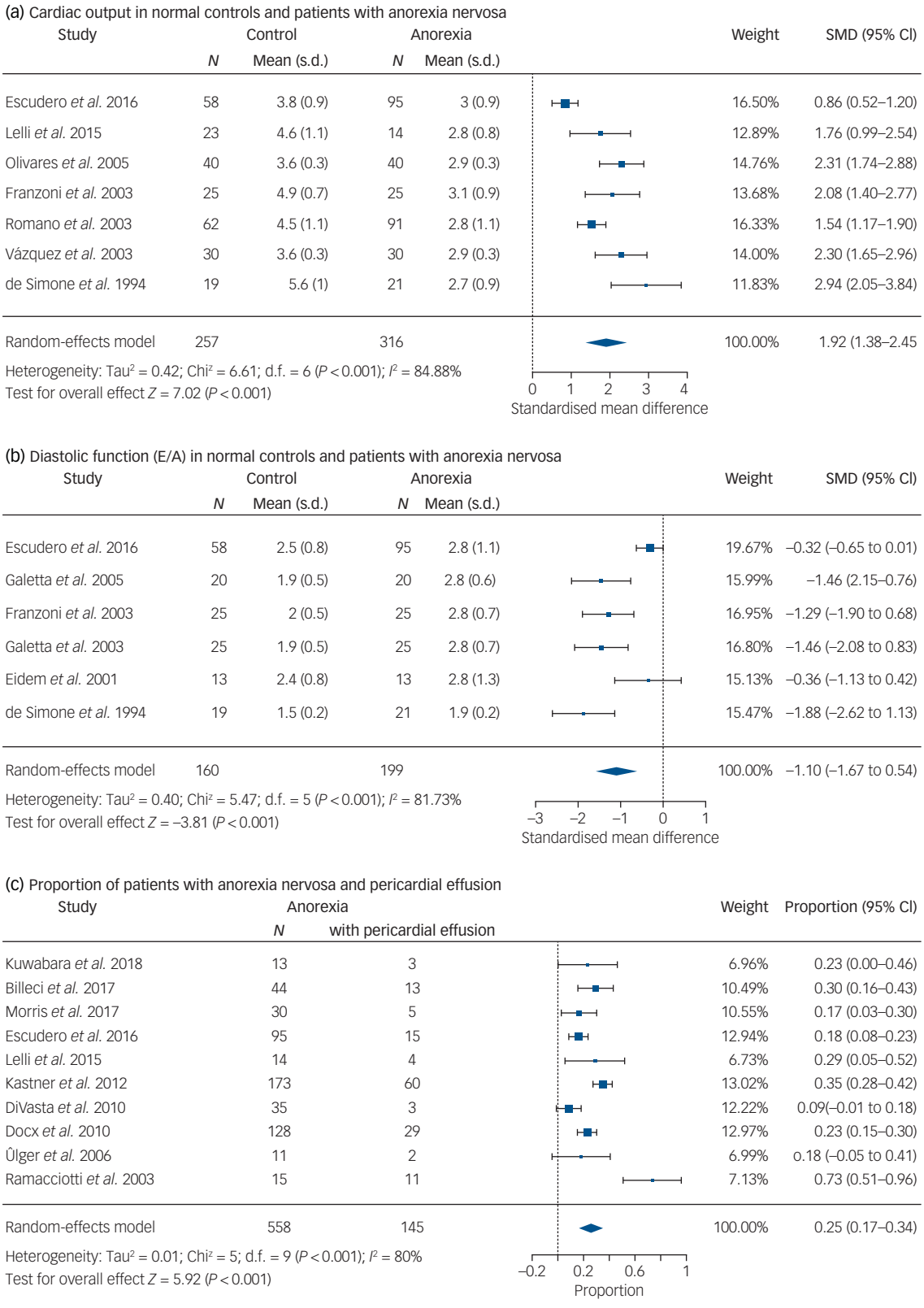

Fig. 3 (a) Cardiac output in normal controls and patients with anorexia nervosa. (b) Diastolic function (E/A) in normal controls and patients anorexia nervosa. (c) Proportion of patients with anorexia nervosa and pericardial effusion.

SMD, standardised mean difference.

left ventricular filling occurs with severe weight loss.[12] Myocardial fibrosis has been demonstrated histologically and on magnetic resonance imaging in patients with anorexia nervosa,[36] and may contribute to restrictive physiology.

MVP is common in the anorexia nervosa group, with valvulo-ventricular disproportion[37] being a proposed cause. Loss of left ventricular mass causes distortion of left ventricular structure and the atrioventricular tissues, and therefore dysfunction of the valve.

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Some studies failed to demonstrate full resolution of MVP with weight restoration,[31,37,38] suggesting that high baseline prolapse is a trait-related marker reflecting a population at high risk of eating or anxiety disorder.[39]

Twenty-five per cent of patients with anorexia nervosa have a pericardial effusion that is clinically silent, unrelated to hypoproteinaemia[24,40] and mostly resolves with weight restoration. We are aware of two case reports of patients with anorexia nervosa requiring pericardiocentesis.[40,41] Although our data did not demonstrate it, risk factors include a low BMI.[16] Proposed mechanisms include myocardial wasting and the loss of pericardial fat,[16] causing pericardial layer separation.[24]

Our results strongly suggest that resolution of cardiac structural changes occur with weight restoration. However notably, re-feeding can be marked by the onset of new severe cardiac complications owing to the abrupt increase in preload, metabolic requirements and electrolyte abnormalities.[24] This is the most dangerous time in the management of patients with severe anorexia nervosa and cardiac abnormalities,[35] with four case reports describing Takotsubo's cardiomyopathy[42–45] owing to refractory hypoglycaemia, a feature of the terminal stages of starvation.[42–45]

One previous systematic review looking at cardiovascular complications in anorexia nervosa has been undertaken.[46] However this review does not meta-analyse the data and is much broader, including repolarisation and conduction abnormalities, haemodynamic changes and peripheral vascular abnormalities. In addition, there have been five key studies since its publication.[9–13]

Our results demonstrate strong messages regarding the destruction of normal cardiac structure in anorexia nervosa and include data from 960 patients. Since admission to secondary care with this disease is uncommon, this data-set represents a valuable snapshot of a condition where cardiac abnormalities are consistently seen. We aim to disseminate these findings to patients and families by incorporating them into guidelines and by publicising the results with organisations, which will facilitate dissemination.

Limitations

The current literature comes from high-income countries, limiting the external validity.[47] Although availability of echocardiography has traditionally varied between countries, the decreasing cost and greater portability means access to echocardiography for patients with anorexia nervosa will be significantly easier in the future, and therefore will provide a readily available tool to optimise cardiac care for these patients. The studies were heterogenous and many were of small sample size. We did not age restrict the studies since early work has informed current practice. However, the studies span a 25-year period, during which time significant advances have been made in echocardiography. We combined data-sets from children and adults, but it is plausible that a paediatric heart may respond differently to malnutrition compared with an adult heart, which may also be exposed to other cardiovascular risk factors that accumulate with age. Our sensitivity analysis did not demonstrate significant differences when the adult group was studied separately, but further studies with larger samples are likely to be of interest. Other limitations include the retrospective nature of some studies, inconsistent study designs, moderate to high risk of bias, the frequent lack of reporting of the anorexia nervosa subtypes, the differences in illness severity and the different methods of measurements (Supplementary Appendix 4).

In conclusion, patients with anorexia nervosa are generally young and have reversible and potentially catastrophic cardiac changes. To avoid and manage the medical complications in this cohort of patients our findings suggest due diligence should be paid to cardiac involvement. Given the increased availability of echocardiography in the acute and critical care setting, systematic assessment of cardiac changes associated with anorexia nervosa is likely to produce useful data. Longer-term cardiac follow-up of these patients would also be of value to understand the effects of loss of myocyte mass on later health. In tandem with this data collection the authors suggest that inclusion of cardiac structural assessment with agreed triggers should be considered in the next consensus statement.

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Supplementary material

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Data availability

The data-set is available from the corresponding author.

Author contributions

J.S. and C.C. designed the study. T.P. conducted the searches. J.S. and C.C. acquired, analysed and interpreted the data. J.S., C.C., L.P., T.P. and P.L. drafted the manuscript. J.S. and L.P. performed the statistical analysis. C.C. and P.L. supervised the study. All authors had full access to the data and can take responsibility for its integrity and accuracy of the analysis. J.S. is the guarantor. The manuscript guarantor (J.S.) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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