Autonomic Nervous System Function in Anorexia Nervosa: A Systematic Review

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Background: Autonomic nervous system (ANS) dysfunction has been suggested to contribute to the high prevalence of cardiovascular complications in individuals with anorexia nervosa (AN), yet has not been thoroughly investigated. The current review aimed to synthesize the evidence of basal ANS function in individuals with a current diagnosis of AN and those with a previous diagnosis who had achieved weight restoration, as compared to controls.

Methods: A systematic review of nine databases was conducted and studies that were published in a peer-review journal, in English, that included at least one assessment of ANS function in individuals with a current or previous diagnosis of AN were selected. Forty-six studies were included with a total of 811 participants with a current diagnosis of AN and 123 participants with a previous diagnosis of AN.

Results: ANS function was assessed through heart rate variability (n = 27), orthostatic challenge, blood pressure variability or baroreflex sensitivity (n = 11), adrenergic activity (n = 14), skin conductance level (n = 4), and pupillometry (n = 1). Individuals with AN demonstrated increased parasympathetic activity and decreased sympathetic activity, suggestive of autonomic dysregulation. Following weight restoration, autonomic function trended toward, or was equivalent to, control levels.

Discussion: Autonomic dysregulation is indicated through a range of assessments in individuals with AN. Future investigations should utilize a variety of assessments together in order to conclusively establish the nature of autonomic dysfunction in AN, and following extended weight restoration. Moreover, investigation into the co-occurrence of ANS function and cardiovascular risk is required.

Keywords: anorexia nervosa, eating disorders, autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, heartrate variability, noradrenaline, orthostatic response
INTRODUCTION

Anorexia Nervosa (AN) is an eating disorder characterized by restriction of food intake, an intense fear of gaining weight and a distorted self-perception of body image (American Psychiatric Association, 2013). AN has been recognized as an increasingly prevalent psychiatric condition among young people in Western societies, with the incidence also increasing in a variety of racial and ethnic groups (Nakai et al., 2016), mostly in women (Hoek, 2006). AN has a typical onset in adolescence (Hoek and Van Hoeken, 2003) and has an estimated lifetime prevalence of 1.7% in the general population (Smink et al., 2014). The etiology and pathophysiology of AN are complex, involving biological, psychological, and sociocultural development and maintenance factors (Phillipou et al., 2019). The chronic nature of AN is evidenced by a 50% relapse rate (Pike, 1998), with learned maladaptive behaviors becoming deeply entrenched and difficult to alter (Steinglass and Walsh, 2016).

The energy deprivation and malnutrition associated with AN places immense pressure on the cardiovascular system, with up to 80% of patients suffering from cardiovascular complications (Spaulding-Barclay et al., 2016). These include structural, conduction, and hemodynamic abnormalities (Sachs et al., 2016; Giovinazzo et al., 2019; Smythe et al., 2020), and are a major contributor to the high mortality rate in AN (Nakai et al., 2016), which is approximately six times that of the general population (Papadopoulos et al., 2009; Arcelus et al., 2011). Cardiovascular problems occur not only during the starvation state of AN; there are also specific cardiac complications that arise during the process of re-feeding, such as arrhythmia, tachycardia, and congestive heart failure (Casiero and Frishman, 2006; Vignaud et al., 2010). Despite the profound psychological and physical burdens that accompany AN, the underlying physiological mechanisms behind the cardiovascular complications of the illness remain poorly understood. It has been suggested that disturbances in cardiac autonomic regulation may contribute to the increased cardiovascular complications and mortality in AN (Mazurak et al., 2011a).

The autonomic nervous system (ANS) provides the link between the cardiovascular system and the central nervous system, and is responsible for the regulation of internal bodily processes in response to physiological and environmental changes (Palma and Benarroch, 2014). The ANS is a dynamic regulatory function that involves interpretation of sensory feedback from the organs by higher brain areas, including the brainstem and hypothalamus, in order to adapt the output of the ANS to adjust the physiological state of the body (Porges, 2007; Buiks et al., 2013). Through the regulation of heart rate (HR), blood pressure (BP), and rate of respiration among other visceral activities, the ANS maintains cardiovascular homeostasis via the opposing inputs of its two branches; the sympathetic (SNS) and parasympathetic (PNS) nervous systems (Gordan et al., 2015). Activation of the SNS results in increased arousal, such as increased HR and blood vessel constriction through the release of noradrenaline (NE), whereas the PNS (or vagal nerve) acts in opposition to decrease HR and BP. Evaluation of the ANS can be derived from various techniques including hemodynamic, biochemical and neurophysiological assessments with each presenting its own limitations (Grassi and Esler, 1999). Therefore, multiple assessments of autonomic function should be undertaken together in order to provide an overview of neural function; some of which are briefly detailed below.

Hemodynamic assessments can provide insight into the autonomic regulation of blood flow. Sinus bradycardia (Yahalom et al., 2013) and low BP levels (Sachs et al., 2016) are commonly observed in individuals with AN and are suggestive of abnormalities in autonomic regulation of HR and BP. The majority of previous investigations into autonomic function in individuals with AN have assessed heart rate variability [HRV]; the beat-to-beat variation in HR (Task Force of The European Society of Cardiology The North American Society of Pacing Electrophysiology, 1996; Billman, 2011)] as an estimation of autonomic cardiac regulation, with inconclusive findings (see Mazurak et al., 2011a for a review). While the review by Mazurak et al. (2011a) found the majority of studies that investigated HRV in AN reported parasympathetic dominance, some reported sympathetic dominance, while others found no difference in comparison to controls; this led the authors to suggest that HRV may not be suitable for the assessment of ANS in AN (Mazurak et al., 2011a). Another hemodynamic assessment of autonomic function is the orthostatic stress test, which provides a window into autonomic regulation through the baroreceptor reflex control of BP and HR (Grassi and Esler, 1999; Westerhof et al., 2006). Conditions related to orthostatic intolerance, such as orthostatic hypotension, syncope and postural orthostatic tachycardia syndrome (POTS) represent autonomic failure and have also been reported in AN (Sachs et al., 2016).

Biochemical assessment of plasma NE levels can provide an index of sympathetic neural function that have been shown to vary according to weight (Lambert et al., 2007). However, circulating NE represents only a fraction of the amount secreted from nerve terminals and is dependent on secretion, clearance and re-uptake processes (Esler et al., 1990), therefore this method provides a “confounded” index of systematic sympathetic activation (Grassi et al., 2015). Measurement of the NE metabolite, 3-methyl-4-hydroxyphenylglycol (MHPG) is another common biochemical assessment that is undertaken to further inform regional NE synthesis, release and re-uptake (Grassi and Esler, 1999).

In addition to regional NE spillover, the other “preferred” assessment for sympathetic nervous system evaluation, is the neurophysiological technique of “microneurography” (Grassi et al., 2015). Microneurography provides a direct continuous recording of muscle sympathetic nerve activity (MSNA) to give a measure of central nervous system sympathetic neural outflow to the skeletal muscles (Grassi and Esler, 1999), including blood vessels. Increased sympathetic neural drive, as assessed by microneurography, is associated with increased cardiovascular risk (Kaye et al., 1995; Grassi, 2006), yet microneurography remains less commonly used due to its semi-invasive nature.

It is beyond the scope of the current review to provide an overview of all assessments of ANS function; previous thorough reviews have been conducted (Grassi and Esler, 1999; Tjalf and Timo, 2019). To our knowledge, there has been no prior
systematic review of autonomic function in individuals with AN. Moreover, most studies have primarily assessed function in individuals in the acute state of AN and it is less clear whether any abnormalities persist after weight restoration. In order to advance the knowledge of ANS function in AN, the current systematic review aims to synthesize studies investigating resting-state ANS function in individuals with AN, including those who have achieved weight restoration, as compared to healthy controls. Given the important clinical implications of abnormalities in autonomic cardiovascular control, a greater understanding of any abnormalities in ANS function in individuals with AN, and following weight restoration, is crucial.

**MATERIALS AND METHODS**

**Search Strategy**

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) ([Supplementary Material](#)) (Moher et al., 2010) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO identifier CRD42020177195). Studies were identified through systematic searches of nine databases: Ovid MEDLINE(R) ALL 1946 to November 03, 2020; Embase 1974 to 2020 November 03 (Ovid); Ovid Embcare 1995 to 2020 Week 44; APA PsycINFO 1806 to October Week 4 2020 (Ovid); Ovid Nursing Database 1946 to October Week 4 2020; CINAHL (EBSCOhost); Health Collection, Humanities & Social Sciences Collection (Infornit); Cochrane Library and Clinical trials.gov. Search strategies were developed by a medical librarian, HW, in consultation with the review team. Strategies combined the general concepts of anorexia nervosa AND autonomic nervous system using a combination of subject headings and textwords relevant to each database. Results were limited to English language, but no date limits were applied. Animal studies were excluded. An initial strategy was developed for Medline and then adapted for other databases ([Appendix 1 in Supplementary Material](#)). All searches were updated on 5 November 2020. Reference lists of included studies were screened for additional publications.

**Study Selection**

Search results were exported to Endnote bibliographic management software, duplicates removed, and the remainder uploaded to Covidence systematic review software (www.covidence.org) by HW. Two authors (Z.J., E.L.) independently screened records on title and abstract and then full text against the following exclusion criteria: primary condition not AN, no diagnostic criteria referenced, no control group, no basal ANS assessment outcome, protocol paper, review article, dissertation, conference abstract, case series/study. A third reviewer (N.E.) resolved any conflicts. Studies that included at least one of the ANS measures in basal conditions listed in Table 1 were included (see Table 1 for a summary of ANS outcomes, description of assessment and relationship to ANS functioning). A meta-analysis was not performed as there were too few similarities between study methods and measures.

**Data Extraction**

Two reviewers (Z.J. and E.L.) independently extracted data and consensus was confirmed by a third reviewer (N.E. or A.P.) Extracted data included information on study characteristics and basal ANS assessment and outcomes.

**Risk of Bias/Quality Assessment**

The risk of bias among included studies was assessed independently by two authors (Z.J. and D.C.) using a modified version of the Newcastle-Ottawa Quality Assessment Scale (NOS; see [Appendix 2 in Supplementary Material](#)) for cohort/case-control studies, in which a high score indicates a low risk of bias (Wells et al., 2006). Studies were assessed on three domains; participant selection, comparability and outcome assessment and were classified as at low, moderate, or high risk of bias. The risk of bias was not used as an exclusion criterion in the selection of studies to provide a complete overview of available data.

**HRV Risk of Bias/Quality Assessment**

Given the large number of included studies that assessed HRV, we used a modified version of a previously published measure of study quality in studies of HRV in functional somatic disorders to specifically evaluate quality of HRV methods (Tak et al., 2009). We modified the tool to incorporate the items listed in the Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH) criteria (Quintana et al., 2016) to provide a more comprehensive assessment of HRV quality and risk of bias (see [Appendix 3 in Supplementary Material](#)). We assessed three general domains: appropriate selection of participants, appropriate quantification collection of HRV and appropriate control for confounding factors. Potential scores ranged from 0 to 22.

**RESULTS**

The literature search yielded 2,126 unique citations. The full text of 105 citations were examined and, of these, 46 articles met our inclusion criteria (see Figure 1).

**Study Characteristics**

Characteristics of the included studies for qualitative synthesis are shown in Table 2. All included studies utilized cross-sectional study design; 39 assessed participants at a single time point and seven included assessments at multiple time points after weight restoration (Gross et al., 1979; Riederer et al., 1982; Lesem et al., 1989; Kaye et al., 1990; Kreipe et al., 1994; Bar et al., 2006; Lachish et al., 2009). The 46 studies included assessments of 811 participants with a current diagnosis of AN (757 female, 11 male, 43 not specified), 123 participants with a previous diagnosis of AN who were at various stages of treatment and weight restoration (AN-WR; 100 female, 2 male, 21 not specified) and 867 control participants (834 female, 20 male, 13 not specified). Sample sizes ranged from 7 to 89 participants with a current diagnosis of AN, 4–18 weight-restored participants, and 8–39 controls. One study did not specify the sample size of their control group (Lechin et al., 2010), four studies did not specify the sex of the AN participants (Kaye et al., 1990; Pirke et al., 1992; Gross et al., 1979; Riederer et al., 1982; Lesem et al., 1989; Kaye et al., 1990; Kreipe et al., 1994; Bar et al., 2006; Lachish et al., 2009).
TABLE 1 | Description of ANS outcomes included in the review.

| Domain                        | Measure                                           | Acronym                  | Significance and methodology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Parameters | ANS indicator | Number of included studies using the measure |
|-------------------------------|---------------------------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---------------|---------------------------------------------|
| Heart rate variability (HRV)  | Standard deviation of normal-to-normal intervals  | SDNN or R-R-interval-SD  | Measured by calculating the average change in the duration of the interval (in ms) between consecutive heart-beats (R-R intervals) and deriving the standard deviation of the N-N (or R-R) intervals over a time section of the ECG.                                                                                                                                                                                                                                                                                             | SDNN       | Higher SDNN: increased HRV: increased PNS functioning: hypo-arousal | 27 (any measure of HRV) |
|                               | Root Mean Square of Successive Differences (HRV)   | RMSSD                    | A measure of HRV which is measured as the average root square of the interval between successive peaks in ECG. Compared to SDNN, it is considered more reliable in measuring HRV.                                                                                                                                                                                                                                                                                                                                   | RMSSD      | Higher RMSSD: increased HRV: higher PNS functioning: hypo-arousal |                                            |
|                               | Normal-to-normal intervals > 50 ms (% of)          | pNN50                    | Measured on ECG as the number of pairs of successive IBI intervals which are different by 50 ms or more. pNN50 is the proportion of NN50, in relation to the entire number of RR intervals.                                                                                                                                                                                                                                                                                                                                                       | Number of NN50 | Higher number of NNN50 (or higher pNN50): increased HRV: higher PNS functioning: hypo-arousal |                                            |
| Low frequency power           | LF                                                | LF power                 | As a frequency domain measure, it represents the amount of spectral power between 0.04 and 0.15 Hz on the Fast Fourier Transform (FFT) spectrum of HRV. It is indicative of the baroreflex which is a modulation (acceleration or deceleration) of HR in situations when blood pressure (BP) is too low or high (respectively), with the aim of changing BP levels through modulating HR.                                                                                                                                                                                                 | LF power   | Increased LF power: increased baroreflex effect: increased HRV |                                            |
| High frequency power          | HF                                                | HF power                 | Similarly to LF, it is a frequency domain measure of HRV which analyses activity in the 0.15–0.40 Hz range. It has been linked to cardiac-vagal activity, representing parasympathetic modulation of arousal.                                                                                                                                                                                                                                                                                                                          | HF power   | Increased HF power: increased PNS functioning: hypo-arousal |                                            |
| Low/high frequency power      | LF/HF                                             | LF/HF ratio              | The ratio between spectral power in the low and high frequency range (see above for specific ranges in Hz). It has been used as an index of the balance between SNS and PNS functioning (sympathovagal balance).                                                                                                                                                                                                                                                                                                                                 | LF/HF ratio | Increased LF/HF ratio: sympathetic dominance. Reduced LF/HF ratio: parasympathetic dominance (however a strong debate is going on in literature, regarding the association between LF/HF ratio and ANS) |                                            |
| Short-term fractal scaling exponent | α                                              | Fractal correlation       | Using detrended fluctuation analysis, the fractal scaling exponent provides a measure of complexity in heart period series (RR interval) (Peng et al., 1995).                                                                                                                                                                                                                                                                                                                                                   | Fractal correlation | Reduced α has been demonstrated in patients with congestive heart failure and depressed left ventricular function |                                            |
| Baroreflex function           | Baroreflex sensitivity                            | BRS                      | Invasive: measuring the change in heart rate in response to changes in blood pressure induced by injection of vasoactive drugs that have minimal effect on the sinus node. Non-invasive: the Valsalva maneuver, head-up-tilt, the neck chamber technique (which provides a selective manipulation of carotid baroreceptors), and the analysis of spontaneous variations of blood pressure and RR interval. Consecutive systolic pressure values and corresponding RR intervals with one-beat delay are fitted by a linear regression in the interval between the beginning and end of systolic pressure increase, the sensitivity of the baroreflex is provided by the slope of the fitted line, and expressed as the change in RR interval in milliseconds per millimeter of mercury change in systolic pressure. | ms/mmHg     | CV diseases are often accompanied by an impairment of BRS mechanisms, with a reduction of inhibitory activity and an imbalance in the physiological sympathetic-vagal outflow to the heart, thus resulting in a chronic adrenergic activation. Sustained baroreflex-mediated increase in sympathetic activity may contribute to increased end-organ damage and to the progression of the underlying disease, and a blunted baroreflex gain is predictive of increased cardiovascular risk in post-myocardial infarction and heart failure patients. | 4 |

(Continued)
TABLE 1 | Continued

| Domain                        | Measure                                                                 | Acronym | Significance and methodology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Parameters | ANS indicator                                                                                                                                                                                                                                                                                                                                 | Number of included studies using the measure |
|-------------------------------|-------------------------------------------------------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Blood pressure                | BP response to orthostatic challenge                                   | BP response | Orthostatic maneuvers are commonly used as a test procedure to assess autonomic nervous system control of the circulation. The physiological response to orthostatic stress is assessed by observing the difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during a change from horizontal to vertical body position.                                                                                                                                                                                                                                                                                                                                                   | SBP, DBP   | Alterations in the autonomic nervous system may contribute to an increase or decrease in resting blood pressure response to an orthostatic challenge.                                                                                                                                                                                                                                                                   | 7                                             |
| Blood pressure variability    | BPV                                                                     | BPV     | Ultrashort-term: direct continuous intra-arterial recordings coupled to spectral analysis; short-term: direct continuous intra-arterial recordings, ABPM; long-term: office blood pressure, ABPM; home blood pressure monitoring.                                                                                                                                                                                                                                                                                                                                                                      | Ultrashort-term (very low frequency, low frequency and high frequency BPV); beat-to-beat variation. Short term BPV, minutes to hours. Long-term BPV: day-to-day, visit-to-visit. | Ultrashort-term: estimation of neurohumoral systems involved in BP regulation; short-term: increased variability in daytime, night-time, and whole 24 h period associated with increased target organ damage; long-term: large visit-to-visit BPV independently associated with increased incidence of stroke. | 3                                             |
| Catecholamines                | Noradrenaline/ Norepinephrine                                          | NE      | Urine: activity of the adrenergic nervous system is inferred from 24 h urinary excretion of noradrenaline, adrenaline and their precursors or metabolites. Plasma: measurement of plasma noradrenaline concentration in venous blood.                                                                                                                                                                                                                                                                                                                                                                                                    | Urine: excretion of noradrenaline, adrenaline and their precursors or metabolites over the past 24 h. Plasma: noradrenaline levels pg/ml. | Activity of the adrenergic nervous system: increased activity indicates increased sympathetic arousal                                                                                                                                                                                                                                                                                                                                                                         | 14                                            |
|                               | 3-Methoxy-4-hydroxyphenylglycol                                        | MHPG    | MHPG is a major metabolite of NE and reflects noradrenergic neuronal tone in humans                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Urine: excretion of MHPG over the past 24 h. Plasma: MHPG levels pg/ml. | Increased levels indicate increased activity of the adrenergic nervous system: increased activity indicates increased sympathetic arousal                                                                                                                                                                                                                                                                                                                                                                         | 4                                             |
| Electrodermal activity (EDA)  | Skin conductance level                                                 | SCL     | An electrical potential is applied to two electrodes, placed next to each other on the hand palms. The electrical current, flowing between the electrodes, is measured as an index of skin conductance.                                                                                                                                                                                                                                                                                                                                                                                                   | Mean SCL, Change (slope) of SCL over time | Higher SCL: increased sympathetic arousal                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 4                                             |
| Pupillometry                  | Pupil diameter                                                         | PLR     | Pupil size or diameter is measured using eye-tracking or optometrist tools, carefully considering for any confounding effects, including changes in environmental luminance or body movements. Pupil constrictions are generally associated with increase of brightness and processing of visual information situated at a close distance (due to narrowing of visual attentional focus).                                                                                                                                                                                                                                                                                                                                       | Mean pupil size (tonic) Stimulus-or event-locked changes in pupil size (phasic) | Increased tonic pupil size; increased allocation of mental resources to the external environment. Phasic pupil size dilations: increased arousal, spontaneous or in response to a stimulus | 1                                             |
Rommel et al., 2015; Palomba et al., 2017) and three studies did not specify the sex of the AN-WR participants (Riederer et al., 1982; Kaye et al., 1990; Pirke et al., 1992). The average duration of illness ranged from 8 months to 10 years and the duration of weight restoration ranged from 2 weeks to 3 years.

**Study Quality Assessment**

The NOS scores of the included studies ranged from 3 to 10. Among the 46 included studies, two were at high risk of bias (4.3%), 17 were at moderate risk (37.0%), and 27 were at low risk (58.7%) (see Table 2 for classification or detailed assessment in Appendix 4 in Supplementary Material). The HRV quality summary score is listed in Table 3 (see Appendix 5 in Supplementary Material for a detailed assessment).

**Heart Rate Variability**

Resting HRV was an outcome measure in 27 articles (Kollai et al., 1994; Kreipe et al., 1994; Petretta et al., 1997; Rechlín et al., 1998; Casu et al., 2002; Galettà et al., 2003; Melanson et al., 2004; Roche et al., 2004; Wu et al., 2004; Bar et al., 2006; Platìsa et al., 2006; Murialdo et al., 2007; Ishizawa et al., 2008; Russell et al., 2008; Vigo et al., 2008; Lachis et al., 2009; Koschke et al., 2010; Mazurak et al., 2011b; Bomba et al., 2014; Billeci et al., 2015, 2019; Nakai et al., 2015; Rommel et al., 2015; Lonigro et al., 2017).
### TABLE 2 | Characteristics of included studies.

| References | Group | Sample size, sex | Age (years)/BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria | Exclusion criteria | Criteria used to classify AN | Patient setting | Medication | Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|------------|-------|-----------------|------------------------|-------------------|-------------|-------------------|-------------------|--------------------------|----------------|------------|------------------------------|-------------------------------|-------------|
| Abell et al. (1987) | AN | 6F, 2M | Mean: 20 NS | 27.75 months | 6 AN-R, 2 AN-BP | Met criteria for AN | NS | DSM-III | NS | NS | NS | SCL | Low |
| | HC | 6F, 2M | NS | NS | Age- and sex-matched to AN group, no history of recent dieting, weight or exercise change. Normal thyroid function. | | | | | | | | |
| | Bar et al. (2006) | AN (T1) | 15F | 16.1 ± 0.5 15.1 ± 0.5 8.6 ± 4 months | NS | Met criteria for AN | History of peripheral neuropathies, cardiac arrhythmia, or alcohol or drug abuse | DSM-IV | Inpatient | Excluded | Excluded | HRV (5 min), PLR | Low |
| | | AN-WR (T2) | 15F | NS | NS | Previous met criteria for AN, after reaching 25th percentile of normal weight | | | | | | | |
| | | AN-WR (T3) | 15F | NS | NS | Previous met criteria for AN, 6-months after reaching 25th percentile of normal weight | | | | | | | |
| | | HC | 15F | 16.6 ± 0.5 21.4 ± 0.9 | Age-, sex-, handedness- and education-matched to AN group | | | | | | | |
| | Bartak et al. (2004) | AN | 10F | 23.0 ± 1.2 15.6 ± 0.6 NS | NS | Met criteria for AN, non-smokers, no allergies and no medication for at least 1 month before the study | Professional athletes | DSM-IV | Inpatient | Excluded | NS | NE (plasma) | Low |
| | | HC | 10F | 23.3 ± 1.0 21.6 ± 0.4 | Age- and sex-matched to AN group, non-smokers, no allergies and no medication for at least 1 month before the study | History of obesity or malnutrition, CV disease, ED or other psychiatric disorders, abnormal physical examination and ECG | | | | | | | |
| | Billeci et al. (2015) | AN | 27F | 14.6 ± 2.2 15.7 ± 2.1 18 ± 14 months | All AN-R subtype, Wechsler Full Scale IQ > 80 | Met criteria for AN-R subtype, Wechsler Full Scale IQ > 80 | Psychotic symptoms, comorbid conditions not related to eating disorders, substance abuse, AN-BP subtype | DSM-IV and DSM-5 | Inpatient | NS | AN: 59.2%; MDD; Dysthymic disorder: 37%; GAD: 11.1%; ODD: 3.7% | HRV (15 min) | Low |
| | | HC | 15F | 14 ± 1.5 20.5 ± 2.2 | Sex-matched to AN group, Wechsler Full Scale IQ > 80 | | NS | | | | | | |
| | Billeci et al. (2019) | AN | 23F | 15.2 ± 1.9 15.7 ± 1.6 19.1 ± 14.5 months | All AN-R subtype | Met DSM-IV and DSM-5 criteria for AN-R subtype, Wechsler Full Scale IQ > 80, not related to eating disorders, current or previous episodes of substance abuse, AN-BP subtype | Psychotic symptoms, comorbid conditions within 3 days of hospitalization | DSM-IV and DSM-5 | Inpatient | Excluded | NS | HRV (5 min) | Low |
| | | HC | 17F | 15.7 ± 2.1 21.7 ± 2.8 | Sex-matched to AN group, Wechsler Full Scale IQ > 80 | | NS | | | | | | |

(Continued)
| References        | Group | Sample size, sex | Age (years) | BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Criteria used to classify AN | Patient setting | Medication | Comorbid psychiatric diagnoses | Basal AN variables assessed | Risk of bias |
|-------------------|-------|------------------|-------------|-------------|-------------------|------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------|-----------------|------------|-----------------------------|-----------------------------|--------------|
| Bomba et al. (2014) | AN    | 21F              | 15.9 ± 1.1  | 15.1 ± 2.6  | NS                | AN-R       | Met criteria for AN-R subtype                                                      | Drug or alcohol use                                                                | DSM-IV                      | NS             | NS             | NS             | NS             | HRV (24-h)       | Low          |
|                   | HC    | 21F              | 16 ± 2.0    | 19.7 ± 1.8  |                  | AN-R       | Age- and sex-matched to AN group, normal BMI, regular ovulatory menstrual cycles   | Neurological or psychiatric disorders, thyroid diseases, drug or alcohol use, anorexia symptoms, steroid hormone use | NS                          |                | NS             | NS             | NS             |                |              |
| Caloway et al. (1983) | AN-R  | 12F              | 20.3 ± 6.7  | NS          | 4.1 ± 3.7 years   | 12 AN-R    | Met criteria for AN                                                               | NS                                                                                 | Russell's criteria (Russell, 1970)                                           | NS                          | NS             | NS             | SCL            | Moderate     |
|                   | AN-BP | 10F              | 21.8 ± 4.3  | NS          | 4.9 ± 3.3 years   | 10 AN-BP   | Sex-matched to AN group                                                            | Taking medication known to alter blood pressure or heart rate                       | NS                          |                | NS             | NS             | NS             | HRV (5-min) and Orthostatic response | Moderate     |
| Casu et al. (2002) | AN    | 13F              | 25.0 ± 5.8  | 16.9 ± 2.6  | Range of 3–7 years | NS         | Met criteria for AN                                                               | Taking medication known to alter blood pressure or heart rate                       | NS                          |                | NS             | NS             | NS             | NE (plasma)     | Moderate     |
|                   | HC    | 16F              | 25.0 ± 2.3  | 20.9 ± 0.9  |                  |            | Sex-matched to AN group, normal diet and levels of physical activity               | NS                                                                                 | HRV (5-min) and Orthostatic response                                           | NS                          |                | NS             | NS             | NS             |                | Moderate     |
| D’Andrea et al. (2008) | AN    | 8F               | 26.2 ± 8.1  | 14.9 ± 2.5  | NS                | NS         | Met criteria for AN, BMI < 17.5                                                   | NS                                                                                 | DSM-IV                      | NS                          | NS             | NS             | NS             | NS             | NE (plasma)     | Low          |
|                   | HC    | 2F               | 27.7 ± 6.3  | NS          |                  |            | Age- and sex-matched to AN group                                                   | NS                                                                                 | NS                          |                | NS             | NS             | NS             |                |              |
| De Rosa et al. (1983) | AN    | 20F, 3M          | Mean (range): 22 (15–40) | 2.7 ± 2.3 years | NS                | AN         | Met criteria for AN, 30% below IBW                                                | NS                                                                                 | Halmi’s criteria (Halmi et al., 1977)                                         | NS                          | NS             | NS             | NE (urinary)  | High          |
|                   | HC    | 10F, 5M          | Mean (range): 25 (19–45) | NS          |                  |            |                                                | NS                                                                                 | Suspended for at least one month                                               | None taking pharmaceutical therapy                                         | NS                          |                | NS             | NE (plasma)     |               |              |
| Dostalova et al. (2007) | AN    | 10F              | 22.1 ± 1.0  | 15.7 ± 0.5  | NS                | AN-R       | Met criteria for AN, non-smokers, no allergies, free of medications for 3 weeks prior to study | Professional athletes                                                             | DSM-IV                      | Inpatient       | None           | NS             | NS             | NE (plasma)     | Low          |
|                   | HC    | 15F              | 21.3 ± 0.9  | 21.2 ± 0.4  |                  | AN-R       | Age- and sex-matched to AN group, non-smokers, no allergies, free of medications for 3 weeks prior to study | History of obesity, malnutrition, CV disease, allergies, free of medications psychiatric disorders, abnormal ECG | None taking pharmaceutical therapy                                         | NS                          |                | NS             | NS             | NS             |                |              |

(Continued)
| References                | Group          | Sample size, sex | Age (years) | BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                                          | Exclusion criteria | Criteria used to classify AN | Patient setting | Medication | Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|---------------------------|----------------|------------------|-------------|-------------|-------------------|------------|------------------------------------------------------------|-------------------|-------------------------------|-----------------|------------|-------------------------------|---------------------------|--------------|
| Galetta et al. (2003)     | AN 25F         | 17.5 ± 4.2       | 15.3 ± 1.4  | 2.6 ± 1.8 years NS | Met criteria for AN, stable BW for 3 months, no signs of CV disease | NS         | DSM-IV, Excluded for treatment                            | None              | NS                            | NS              | HRV (24-h) | Low                          | HRV (24-h) |   |
|                           | HC-T 25F       | 17.7 ± 3.9       | 18.7 ± 1.7  | 2.6 ± 1.8 years NS | Age-and sex-matched to AN group, BMI <20 | Family history of arterial hypertension | NS              | NS                            | NS              | NS        | NS                            | HRV (24-h) | Low          |
|                           | HC-NW 25F      | 18.1 ± 4.5       | 21.9 ± 2.8  | 2.6 ± 1.8 years NS | Age- and sex-matched to AN group, BMI >20 | NS              | NS                            | NS              | NS        | NS                            | HRV (24-h) | Low          |
| Green et al. (2020)       | AN 7F NS       | 18.5 ± 1.7       | 21.9 ± 3.0  | 2.6 ± 1.8 years NS | Met criteria for AN, aged between 14 and 35 years, female | Pregnancy | DSM-5, Excluded for treatment                            | None              | NS                            | NS              | NS        | NS                            | HRV (5 min) | Low          |
|                           | HC 32F         | 23.6 ± 5.3       | 23.1 ± 5.6  | 2.6 ± 1.8 years NS | No disordered eating, aged between 14 and 35 years, female | NS              | NS                            | NS              | NS        | NS                            | HRV (5 min) | Low          |
| Gross et al. (1979)       | AN (T1) 15F    | 22 ± 2           | 22 ± 2      | 2.6 ± 1.8 years NS | Met criteria or AN | NS              | NS                            | NS              | NS        | NS                            | NS                  | Moderate     |
|                           | AN-WR (T2) 13F | 23 ± 2           | 23 ± 2      | 2.6 ± 1.8 years NS | After significant weight gain | Medical or psychiatric illnesses | NS              | NS                            | NS              | NS        | NS                            | NS                  | Moderate     |
|                           | HC 39F         | 23 ± 2           | 23 ± 2      | 2.6 ± 1.8 years NS | Age- and sex-matched AN group, normal BW | NS              | NS                            | NS              | NS        | NS                            | NS                  | Moderate     |
| Ishizawa et al. (2008)    | AN 35F         | 22.9 ± 5.9       | 14.4 ± 2.0  | Mean (range): AN: 19 (4–192) months | Met criteria for AN, aged between 16 and 35 years | Physical comorbidities aside from AN, medication that influences ANS function (SSRIs or tranquilizers) | NS              | NS                            | NS              | NS        | NS                            | NS                  | Moderate     |
|                           | HC 37F         | 24.3 ± 3.2       | 20.6 ± 1.4  | AN: 16 (4–192) months | Age- and sex-matched to AN group, BMI between 18.5 and 24.9 | Any past or current physical or psychiatric disease and treatment with any drugs | DSM-IV | 26 outpatient/9 inpatient | None | AN: 2 MDD, 1 dysthymic disorder | BPV, BRS, HRV (10 min) | Low          |
| Kaye et al. (1990)        | AN (T1) NS     | NS               | NS          | NS          | NS               | Met criteria for AN | NS              | DSM-III | NS | NS | NS | NE (plasma) | High |
|                           | AN-WR (T2) NS  | NS               | NS          | NS          | NS               | Previously met criteria for AN | DSM-III | NS | NS | NS |                  | |
|                           | HC 11F         | NS               | NS          | NS          | NS               | Previously met criteria for AN, long-term WR, stable BW for 6 months | NS              | DSM-III | Excluded | NS | NS | MHPG (plasma and CSF), NE (plasma and CSF), Orthostatic response | Moderate       |
| Kaye et al. (1985)        | AN-WR 11F      | 24 ± 19.8 months | AN-R/7      | AN-BP       | Previously met criteria for AN, long-term WR, stable BW for 6 months | Weight below 85% of IBW, medication use | NS              | DSM-III | Excluded | NS | NS |                  | |
|                           | HC 8F          | 25.6 ± 2.8       | NS          | NS          | Sex-matched to AN group, stable BW for 6 months | Medication use | NS              | NS | NS | NS |                  | |

(Continued)
| References       | Group                  | Sample size, sex | Age (years) | BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Criteria used to classify AN | Medication | Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|------------------|------------------------|------------------|-------------|-------------|-------------------|------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------|------------|-------------------------------|-----------------------------|--------------|
| Kollai et al. (1994) | AN 11F                | 13.6 ± 1.8       | NS          | NS          | NS                | Met criteria for AN, <80% IBW for 6 months, medication free for 6 weeks | NS | DSM-III Inpatient None AN: none met criteria for MDD | BRS (Valsalva Moderate Maneuver, Neck chamber technique, Atropine sulfate injection), HRV (5 min) |
|                   | HC 11F                | 14.2 ± 1.9       | NS          | NS          |                   | Height, age and sex-matched to AN group, no current or past psychopathology, normal menstrual cycles. | NS |                      |                                      |
| Koschke et al. (2010) | AN 20F               | Mean (range): 24 (19–43) | Mean (range): 15.7 | Mean (range): 70 (6–228) months | Met DSM-IV criteria for AN, free from medical/psychiatric/Neuropathies, cardiac arrhythmia, substance abuse | NS | DSM-IV Inpatient None None | HRV (30 min) Low |
|                   | HC 20F                | Mean (range): 25 (22–43) | Mean (range): 21.9 |                   | Age, physical activity- and sex-matched to AN group, free from medical/psychiatric disease | NS |                      |                                      |
| Kreipe et al. (1994) | AN (T1) 8F            | 18.6 ± 3.9       | NS          | NS          | All AN-R          | Met criteria for AN | NS | DSM-III Inpatient NS NS | HRV (Supine for 256 s, Orthostatic for 15 min), Orthostatic response |
|                   | AN-WR (T2) 4F         | NS               | NS          | NS          | All AN-R          | Previously met criteria AN, 2 weeks after inpatient treatment with variable amount of weight gain | NS |                      |                                      |
|                   | HC 8F                 | 20.9 ± 5.7       | NS          | NS          |                   | Age- and sex-matched to AN group, normal diet and activity level | NS |                      |                                      |
| Lachish et al. (2009) | AN (T1) 24F           | 15.9 ± 0.5       | 15.5 ± 0.3  | 2.5 ± 2.8 years | All AN-R          | Met criteria for AN, stable medical condition | NS | DSM-IV Inpatient AN, HC, AN-WR (T3): Social phobia; 7 NS | AN-WR (T2): HRV (length) Low |
|                   | AN-WR (T2) 12F        | NS               | 19.5 ± 0.4  | 2 weeks     | All AN-R          | Previously met criteria for AN, at discharge when achieved desired BW for 2 weeks | NS |                      |                                      |

(Continued)
| References                | Group | Sample size, sex | Age (years) | BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Criteria used to classify AN | ANS setting | Medication Comorbid psychiatric diagnoses | Basal ANS variables assessed | Baseline | Risk of bias |
|---------------------------|-------|------------------|-------------|-------------|-------------------|------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------|--------------|------------------------------------------|-------------------------------|----------|--------------|
| Lechin et al. (2010)      | AN    | 22F              | 22.0 ± 6.4  | NS          | NS                | 10 AN-R, 12 AN-BP | Met criteria for AN, no other physical illness | Pregnancy, lactation, smoking and alcohol abuse | DSM-IV                     | NS           | NS                                      | AN and HC: no medication for 15 days prior to study | NE (plasma), Low | Orthostatic response |
|                           | HC    | All F            | NS          | NS          | NS                | NS         | Age-, sex-, and race-matched to AN group, no other physical illness                | NS                                                                                | NS                          | SCL          | Moderate                                                       |
| Léonard et al. (1998)     | AN    | 14F              | 23.9 ± 8.3  | 16.2 ± 3.1  | 5.9 ± 4.2 years   | NS         | Met criteria for AN                                                                  | NS                                                                                | DSM-IV                      | Inpatient    | NS                                      | NS                                               | NS       | Moderate     |
|                           | HC    | 18F              | 29.3 ± 9.7  | 21.1 ± 2.7  | NS                | NS         | Age- and sex-matched to AN group                                                    | NS                                                                                | NS                          | NS           | NS                                      | SCL                                               | Moderate  | Orthostatic response |
| Lesem et al. (1989)       | AN (T1)| 11F             | 25.2 ± 5.3  | NS          | NS                | NS         | Met criteria for AN, admitted to clinical unit                                      | NS                                                                                | DSM-III                     | Inpatient    | NS                                      | NS                                               | NS       | Moderate     |
|                           | AN-WR (T2) | 11F      | 3 weeks     | NS          | NS                | NS         | Previously met criteria for AN, after 3 weeks of treatment (no significant change in BW) | NS                                                                                | NS                          | NS           | NS                                      | NS                                               | NS       | Moderate     |
|                           | HC    | 9F               | 27.6 ± 3.4  | NS          | NS                | NS         | Sex-matched to AN group, normal BW, no history or current psychiatric illness       | NS                                                                                | NS                          | NS           | AN and HC: no psychotropic medications for 4 weeks prior to study | NE (plasma), Moderate Orthostatic response |
| Lonigro et al. (2019)     | AN    | 13F              | 15.0 ± 0.9  | 16.3 ± 1.5  | NS                | All AN-R   | Met criteria for AN-R, female, aged between 13 and 17 years, absence of severe physical condition, no SCX, or associated medication that may impact on neurological conditions on ANS function | Diagnosed with intellectual disabilities, developmental disorders, psychiatric disorder that may impact on autonomic functioning | DSM-5                       | Day patient   | AN: no medication that may impact on autonomic functioning | AN: 2 MDD, 1 GAD     | HRV (5 min) | Low          |
|                           | HC    | 12F              | 15.3 ± 1.4  | 20.1 ± 1.2  | NS                | NS         | Sex-matched to AN group, no lifetime history of ED or psychiatric disorder       | NS                                                                                | DSM-5                       | Day patient   | AN: no medication that may impact on autonomic functioning | AN: 2 MDD, 1 GAD     | HRV (5 min) | Low          |
| Luck et al. (1983)        | AN    | 18F              | Mean: 17.5  | NS          | NS                | NS         | Met criteria for AN, normal plasma sodium levels, no evidence of dehydration or over-hydration | Russell’s criteria (Russell, 1970)                                             | Inpatient and outpatient | No medication 2 weeks prior to study | NS                                               | NE (plasma), Moderate     | Moderate  | Orthostatic response |
| References            | Group | Sample size, sex | Age (years)/BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria | Exclusion criteria | Criteria used to classify AN | Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|-----------------------|-------|-----------------|-------------------------|-------------------|------------|-------------------|-------------------|---------------------------|-------------------------------|-----------------------------|------------|
| Lutz et al. (2019)    | AN    | 19F             | 25.2 ± 5.3 / 15.79 ± 1.67 / 9.7 ± 6.7 years | 10 AN-R, 9 AN-BP |            | Met criteria for AN; >18 years age | Age- and sex-matched to AN group, no recent weight loss, normal plasma sodium levels, no clinical evidence of de- or over-hydration | DSM-5 disorders, current substance use, current PTSD | AN: 6 taking SSRIs | HRV (5 min) | Low |
| HC                    | 20F   | Mean: 18.0 NS    |                          |                   |            |                   |                   |                           |                               | HRV (5 min) | Moderate |
| Mazurak et al. (2011b)| AN    | 21F             | 23.8 ± 6.9 / 16.1 ± 1.5 |            | NS         | Met criteria for AN | Taking medication, pregnant or lactating, history of alcohol or drug abuse or failed to follow instructions during testing | ICD-10 | Inpatient | None | HRV (3 min) | Low |
| HC                    | 21F   | 25.0 ± 8.1 / 20.1 ± 1.5 |                   |                   |            |                   | Age- and sex-matched to AN group, no history of AN, IBS or chronic somatic or psychiatric disorder |                   |                           |                               | HRV (5 min; 24h) | Moderate |
| Melanson et al. (2004)| AN    | 6F              | 29 ± 3 NS | Mean (range): 19 (2–72) months | NS         | Met criteria for AN | NS | DSM-IV | Outpatient | NS | NS | HRV (5 min) | Moderate |
| HC                    | 10F   | 24 ± 3 NS       |                          |                   |            |                   | Sex-matched to AN group, no history of congenital or acquired heart disease or hypertension | NS |                           |                               | HRV (330 s), Orthostatic response | Moderate |
| Murialdo et al. (2007)| AN    | 34F             | Mean (CI): 24.2 (21.4–27.1) / 15.7 (15.1–16.4) | Mean (CI): 55.4 (38.6–72.1) months | NS         | Met criteria for AN | NS | DSM-IV | Inpatient | NS | NS | HRV (5 min) | Low |
| HC                    | 30F   | Mean (CI): 25.9 (23.3–28.5) / 22.9 (22.3–23.6) |                   |                   |            |                   | Sex-matched to AN group, normal menstrual cycle and BMI | NS |                           |                               | Orthostatic response | Moderate |
| Nakai et al. (2015)   | AN    | 14F             | 27.9 ± 9.4 / 13.2 ± 1.9 / 121.9 ± 105.3 | All AN-R subtypes |               | Met criteria for AN-R subtype | Anxiety disorders, emotional disorders | DSM-IV | Inpatient | None | NS | HRV (5 min) | Low |
| HC                    | 22F   | 23.2 ± 4.2 / 18.5 ± 1.7 |                   |                   |            |                   | Age- and sex-matched to AN group, no current Axis I disorder, no history of EDs or CV diseases | NS |                           |                               |                           | Low |
| Nedvidkova et al. (2004)| AN  | 5F              | 23.0 ± 1.3 / 14.7 ± 0.7 |                   | NS         | Met criteria for AN, non-smokers, no allergies, medication free for 1 month prior to the study | NS | DSM-IV | Inpatient | None | NS | NE (plasma and adipose tissue) | Low |

(Continued)
| References          | Group | Sample size, sex | Age (years)/BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Criteria used to classify AN | Patient setting | Medication | Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|---------------------|-------|------------------|-------------------------|-------------------|------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------|----------------|------------|-------------------------------|-----------------------------|-------------|
|                     |       |                  |                         |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
| Jenkins et al.      | AN    | 13 (sex NS)      | 22.3 ± 1.0 22.2 ± 0.3   |                   |            | Age- and sex-matched to AN group, non-smokers, no malnutrition, endocrine or CV disease, EDs, psychiatric disorders | History of obesity, hypertension, endocrine or CV disease, EDs, psychiatric disorders | DSM-IV                 | Outpatient        | Excluded                  | Excluded                   | SCL          | Low                      |
|                     | HC    | 6F               | 22.3 ± 1.0 22.2 ± 0.3   |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     |       |                  |                         |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
| Palomba et al.      | AN    | 13 (sex NS)      | 23.92 ± 3.38            | 1.66              |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | HC    | 13 (sex NS)      | 20.31 ± 7.74            | 1.66              |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     |       |                  |                         |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
| Petretta et al.     | AN    | 13F              | 20 ± 2                  | 1.64              | 7.46 ± 1.64 |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | HC-T  | 10F              | 22 ± 3                  | 16.6 ± 1.1        |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | HC-NW | 10F              | 21 ± 3                  | 23.4 ± 2.4        |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     |       |                  |                         |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
| Pirke et al.        | AN    | 13F              | 22.9 ± 9.8 15.1 ± 1.5 3.6 ± 4.6 years | 6AN-R, 1AN-BP |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | AN-WR | NS               | 25.4 ± 3.7 20.0 ± 4.5 4.0 ± 2.0 years | 8AN-R, 2AN-BP |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | HC    | 12F              | 23.5 ± 1.9 21.5 ± 1.4   |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     |       |                  |                         |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
| Platisa et al.      | AN-C  | 9F               | 21.0 ± 9.0 14.4 ± 0.6 36 ± 9 months | NS                |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | AN-A  | 8F               | 20.4 ± 0.8 15.7 ± 0.6 12 ± 15 months | NS                |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | HC    | 8F               | 20.4 ± 0.8 20.6 ± 0.4   |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | AN-PWR| 16F, 2M          | Mean: 23.8 NS           |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |
|                     | AN-PWR| 17F, 1M          | Mean: 22.0 NS           |                   |            |                                                                                   |                                                                                  |                            |                |                       |                              |              |

(Continued)
| References          | Group      | Sample size, sex | Age (years)BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                  | Exclusion criteria | Criteria used to classify AN | Patient setting | Medication | Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|---------------------|------------|------------------|------------------------|-------------------|------------|-------------------------------------|--------------------|-------------------------------|------------------|------------|-------------------------------|-----------------------------|---------------|
|                     |            |                  |                        |                   |            |                                     |                    |                               |                  |            |                               |                             |               |
| Jenkins et al.      | AN-WR      | 11F, 1M          | Mean: 23.5 NS years    | NS                | NS         | Previously met criteria for AN, >90% IBW | NS                 |                               |                  |            |                               |                             |               |
|                     | HC         | 14F, 2M          | Mean: 23.4 NS years    | NS                | NS         | Age- and sex-matched to AN group     | NS                 |                               |                  |            |                               |                             |               |
| Riederer et al.     | AN (T1)    | 14F, 2M          | 15.3 ± 0.5 NS          | NS                | NS         | Met criteria for AN                  | NS                 |                               |                  |            |                               |                             |               |
|                     | AN-WR (T2) | NS               |                        |                   |            |                                      |                    |                               |                  |            |                               |                             |               |
| Roche et al.        | AN         | 23F, 2M          | 19.0 ± 3.0 15.2 ± 2.1 | NS                | NS         | Age- and sex-matched to AN group     | NS                 |                               |                  |            |                               |                             |               |
|                     | HC         | 23F, 2M          | 19.0 ± 2.0 22.5 ± 1.9  | NS                |            |                                      |                    |                               |                  |            |                               |                             |               |
| Rommel et al.       | AN         | NS               | Median (1st-3rd Q): 19.5 (17.3–21) | Median (1st-3rd Q): 15.2 (14.5–15.4) years | All AN-R | Met criteria for AN                  | NS                 | DSM-IV criteria for AN; average BMI of 15 | Inpatient | NS          |                                   |                             | Low           |
|                     | HC         | 24F              | Median (1st-3rd Q): 19 (19-21) | Median (1st-3rd Q): 21.0 (19.6-22.3) | NS         | Age- and education-matched to AN group | NS                 | AN-BP, high anxiety, neurological disorders, PTSD, SUD, intellectual deficits, missing data | Inpatient | NS          |                                   |                             |               |
| Russell et al.      | AN         | 17F              | 23.6 ± 10.6 16.2 ± 2.2 | NS                | NS         | Met criteria for AN                  | NS                 | DSM-IV and ICD-10              | Inpatient | NS          | Patients were NS started on antidepressants and antipsychotic agents depending on clinical need | HRV (20 min)         | Moderate     |
|                     | HC         | 35F              | 22.9 ± 5.0 21.3 ± 3.0  | NS                |            |                                      |                    |                               |                  |            |                               |                             |               |
| Takimoto et al.     | AN         | 21F              | 23.9 ± 6.0 14.9 ± 1.9  | 50 (7–192) months | 13 AN-R, 8 AN-BP | Met criteria for AN                  | NS                 | DSM-IV                         | Excluded | Excluded | BPV, BRS, HRV, Orthostatic response | Low             |               |
|                     | HC         | 30F              | 22.5 ± 3.3 20.7 ± 1.6  |                    | NS         | Age- and sex-matched to AN group     | NS                 |                               |                  |            |                               |                             |               |
| References                | Group   | Sample size, sex | Age (years)/BMI (kg/m²) | Duration of AN/WR | AN subtype | Inclusion criteria                                                                 | Exclusion criteria                          | Criteria used to classify AN | Patient setting | Medication Comorbid psychiatric diagnoses | Basal ANS variables assessed | Risk of bias |
|---------------------------|---------|------------------|-------------------------|-------------------|-----------|------------------------------------------------------------------------------------|---------------------------------------------|-----------------------------|-----------------|-------------------------------------------|-------------------------------|----------------|
| Tonhajzerova et al. (2020) | AN      | 20F              | 14.6 ± 2.1, 16.4 ± 2.6  | 8.6 ± 2.8 months  | All AN-R  | Met criteria for AN; AN-R subtype                                                   | AN-BP (AN group), smoking, CV, respiratory; endocrine, neurological, metabolic, or infectious diseases or mental disorders (excluding AN), medication or dietary supplementation which could affect CV or ANS function | DSM-5 Inpatient              | Excluded        | Excluded BPV, BRS, HRV                   | Basal ANS variables assessed | Low          |
|                          | HC      | 20F              | 16.1 ± 1.0, 21.6 ± 2.9  |                   |            |                                                                                   | Age- and sex-matched to AN group             |                             |                 |                                           |                               |              |
| Van Binsbergen et al. (1991) | AN      | 10F              | Mean: 24.5 years        |                   | NS        | Met criteria for AN; aged between 18 and 36; weight <75% IBW; no medication use; amenorrhea for 6 months; acrocyanosis; lanugo | Substance use, psychotropic medication usage, professional athlete | DSM-III Outpatient              | Excluded NS    | MHPG (24-h urine excretion), NE (plasma; 24-h urine excretion), Orthostatic response |                                 | Low          |
|                          | HC-T    | 10F              | Mean: 26.4 years        |                   | Sex-matched to AN group, regular ovulatory cycles, 80–90% IBW                  | Acrocyanosis, lanugo, distorted attitudes toward eating, food, or weight, extreme fear of becoming obese, professional athlete |                             |                 |                              |                               |              |
|                          | HC-NW   | 10F              | Mean: 25.1 Mean: 20.7   |                   | Sex-matched to AN group, regular ovulatory cycles, 90–120% IBW                |                                                                 |                             |                 |                              |                               |              |
| Vigo et al. (2008)       | AN      | 14F              | 26.6 ± 8.0, 17.7 ± 2.2  | Range of 0.5–15 years | All AN-R  | Met criteria for AN                                                                  | Abnormal cardiac rhythm, DSM-IV anticholinergic medication use in week prior to the study, psychotic symptoms. AN: history of binging | DSM-IV Inpatient              | Excluded        | Excluded HRV (10 min)                     |                                 | Low          |
|                          | HC      | 19F              | 26.2 ± 1.8, 20.2 ± 1.1  |                   | Age- and sex-matched to ED group                                                |                                                                 |                             |                 |                              |                               |              |
| Wu et al. (2004)         | AN      | 14F              | 18.5 ± 5.0, 13.2 ± 2.0  | NS                | Met criteria for AN                                                                  | Autonomic disorders, diabetes mellitus, CV diseases or arrhythmias | DSM-IV Inpatient              | NS              | NS                                        | HRV (5 min)                       | Low          |
|                          | HC      | 12F              | 19.5 ± 1.2, 21.2 ± 1.4  |                   | No family history of hypertension or CV disease                                 |                                                                 |                             |                 |                              |                               |              |

AN, anorexia nervosa; AN-A, acute AN; AN-BP, anorexia nervosa, binge-purge subtype; AN-C, chronic AN; AN-PWR, previous diagnosis of anorexia nervosa, partial weight-restoration; AN-R, anorexia nervosa, restricting subtype; ANS, autonomic nervous system; AN-WR, previous diagnosis of anorexia nervosa, weight-restored; BP, blood pressure; BPD, bipolar disorder; BPV; blood pressure variability; BRS, baroreflex sensitivity; BW, body weight; CI, confidence interval; CV, cardiovascular; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ECG, electrocardiogram; ED, eating disorder; F, female; GAD, Generalized anxiety disorder; HC, healthy controls; HC-NW, Normal weight healthy controls; HC-T, Constitutionally thin healthy controls; HC-W, previous diagnosis of anorexia nervosa, weight-restored; HRV, heart rate variability; IBW, ideal body weight; ICD-10, International Classification of Diseases, Tenth Revision; IQ, Intelligence Quotient; M, male; MDD, Major depressive disorder; MHPG, 3-methyl-4-hydroxyphenylglycol; NE, noradrenaline; NS, not specified; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; OH, orthostatic hypotension; PLR, pupillometry response; PTSD, post-traumatic stress disorder; SCL, skin conductance level; SCX, schizophrenia spectrum disorder; SD, standard deviation; SSRI, Selective Serotonin Reuptake Inhibitor; SUD, substance use disorder; T1, time 1; T2, time 2; T3, time 3; Q, quartile.
### TABLE 3 | Heart-rate variability, as compared to controls.

| References          | HRV duration | Group    | SDNN/RR | RMSSD | NN50/pNN50 | TP  | LF   | HF   | LF/HF | α   | Outcome                                                                 | Quality (score between 0 and 22) |
|---------------------|--------------|----------|---------|-------|------------|-----|------|------|-------|-----|--------------------------------------------------------------------------|----------------------------------|
| Bar et al. (2006)   | 5 min        | AN       | ↑       |       |            |     |      |      |       | NS  | Increased pain thresholds are associated with increased parasympathetic tone in AN but not AN-WR | 12                               |
| Billeci et al.      | 5 min        | AN-WR    | NS      |       |            |     |      |      |       | NS  | Prevalence of parasympathetic over sympathetic activity in AN            | 14                               |
| Billeci et al. (2015)| 15 min       | AN       | ↑ ↑ ↑   | ↓     | ↑ ↓ ↓      |     |      |      |       | ↑ ↓ | Patients with AN demonstrated an altered autonomic response to light exercise (indicated SNS activation and PNS withdrawal) | 19                               |
| Billeci et al. (2019)| 5 min        | AN       | ↑ ↑ ↑   | ↓     | ↑ ↓ ↓      |     |      |      |       | ↑ ↓ | Patients with AN demonstrated increased PNS at rest, which were mirrored (to a lesser magnitude) by patients with functional hypothalamic amenorrhea | 19                               |
| Bomba et al. (2014) | 24-h         | AN       | ↑ ↑ ↑   | NS    | ↑ ↓        |     |      |      |       | ↑ ↓ | Patients with AN have a preserved sympathetic and increased parasympathetic HRV response to an orthostatic challenge, which may be compensatory mechanisms to starvation | 14                               |
| Casu et al. (2002)  | 5 min each:  | AN       | ↑ ↑ ↑   |       |            |     |      |      |       | ↑ ↓ | Patients with AN demonstrated abnormally persistent parasympathetic HRV modulation during an orthostatic challenge | 7                                |
|                     | supine and   | Supine   | NS; Orthostatic |       |            |     |      |      |       | ↑ ↓ | Patients with AN demonstrated increased SNS, increased PNS and increased complexity of inter-beat intervals, which may be a protective cardiovascular mechanism | 19                               |
|                     | orthostatic  |          | ↓       |       |            |     |      |      |       | ↑ ↓ |                                                                      |                                   |
| Galetta et al.      | 24-h         | AN       | ↑ ↑ ↑   | ↑     |            |     |      |      |       | ↑ ↓ |                                                                      |                                   |
| Green et al. (2020) | 5 min        | AN       | ↑       |       |            |     |      |      |       | ↑ ↓ | There was no difference in cardiac autonomic balance between individuals with AN and HCs | 13                               |
| Ishizawa et al.     | 10 min       | AN       | ↑       |       |            |     |      |      |       | ↑ ↓ | HRV in patients with AN demonstrated decreased SNS, increased PNS and increased complexity of inter-beat intervals, which may be a protective cardiovascular mechanism | 19                               |

(Continued)
| References                  | HRV duration | Group       | SDNN/RR | RMSSD | NN50/pNN50 | TP | LF | HF | LF/HF | α  | Outcome                                                                 | Quality score between 0 and 22 |
|-----------------------------|--------------|-------------|---------|--------|-------------|----|----|----|--------|----|---------------------------------------------------------------------------|--------------------------------|
| Kollai et al. (1994)        | 5 min AN     | ↑           |         |        |             |    |    |    |        |    | Patients with AN demonstrated high resting vagal activity                | 8                              |
| Koschke et al. (2010)       | 30 min AN    | ↑           |         |        |             |    |    |    |        |    | AN patients demonstrated resting vagal predominance which remained after controlling for BMI | 19                             |
| Kreipe et al. (1994)        | Supine: 256s; Orthostatic: 15 min AN (T1) | Supine ↓; Orthostatic NS | Supine ↓; Orthostatic NS | | | | | | | AN patients demonstrated persistent PNS modulation in response to an orthostatic challenge and decreased resting SNS activity. This trended toward control values after 2 weeks of inpatient treatment | 10                             |
| Lachish et al. (2009)       | NR AN (T1)   | ↓           |         |        |             | NS | NS | NS |        |    | Individuals with AN demonstrated cardiovascular vagal hyperactivity, which persisted after short- and long-term weight restoration | 17                             |
| Lonigro et al. (2019)       | 5 min AN     | ↑           |         |        |             |    |    |    |        |    | Patients with AN demonstrated delayed recovery and stronger PNS activity in response to emotional attachment test, which may reflect altered emotion regulation | 13                             |
| Lutz et al. (2019)          | 5 min AN     | NS          |         |        |             |    |    |    |        |    | Patients with AN demonstrated no significant difference in sympathetic cardiac modulation to HCs | 15                             |
| Mazurak et al. (2011b)      | 3 min each: supine, orthostatic, recovery AN | Supine, recovery NS; Orthostatic ↑ |         |        |             |    |    |    |        |    | Patients with AN longer inter-beat intervals and weaker vagal withdrawal during an orthostatic test (independent from BMI) | 18                             |
| Melanson et al. (2004)      | 5 min; 24 h  | Short-term NS; 24-h, daytime: ↓ | Short-term NS; 24-h, daytime, night-time: ↓ | Short-term NS; 24-h, daytime, night-time: ↓ | Short-term NS; 24-h, daytime, night-time: ↓ | NS |    |    |        |    | Patients in various stages of recovery and refeeding demonstrated decreased resting and ambulatory measures of HRV with decreased parasympathetic activity | 12                             |
| Murialdo et al. (2007)      | 5.5 min each: supine, orthostatic AN | Supine NS; Orthostatic ↓ |         |        |             |    |    |    |        |    | Patients with AN demonstrated reduced SNS response to an orthostatic challenge. Disease duration and BMI were not correlated with HRV parameters | 10                             |
| References            | HRV duration | Group | SDNN/RR | RMSSD | NN50/pNN50 | TP | LF  | HF  | LF/HF | α  | Outcome                                                                 |
|-----------------------|--------------|-------|---------|--------|-------------|----|-----|-----|-------|----|-------------------------------------------------------------------------|
| Nakai et al. (2015)   | 5 min        | AN    | NS      | NS     | NS          | NS | NS  | NS  | NS    |    | Illness duration was negatively correlated with increased parasympathetic tone (HF) and positively correlated with lower vagal tone/high sympathetic tone (LF/HF ratio). This may indicate an initial adaptive response in AN with increased cardiac risk over a longer illness duration |
| Petretta et al. (1997)| 24 h         | AN    | ↑       | ↑      | ↑           | ↑  | ↑   | ↑   | ↑     |    | Patients demonstrated longer inter-beat intervals and increased parasympathetic activity over 24-h compared to thin and normal weight controls |
| Platisa et al. (2006) | 24 h         | AN-C  | ↓       | ↓      | NS          |    | ↓   | ↓   | ↑     |    | Difference in HRV measures for acute and chronic AN; increased HRV in acute AN and decreased HRV in chronic AN. This may indicate the compensatory increased PNS tone in acute AN is attenuated over illness duration |
| Rechlin et al. (1998) | 5 min each:  | AN    | ↑       | ↑      | ↑           | ↑  | ↑   | ↓   | ↑     |    | Patients with AN demonstrated decreased sympathetic activity at rest and in response to an orthostatic challenge which trended to be reversed with weight restoration. Resting and orthostatic SNS activity were positively correlated with body weight. |
|                       | supine and  |       |         |         |             |    |     |     |       |    | 24-h HRV assessment demonstrated enhanced parasympathetic activity and withdrawal of sympathetic control In response to an emotional induction test, patients with AN displayed increased time required for parasympathetic activity to return to baseline, which may be a physiological disturbance due to emotion regulation deficits |
| References                  | HRV duration | Group         | SDNN/RR | RMSSD | NN50/pNN50 | TP | LF | HF | LF/HF | α | Outcome                                                                                                                                                                                                 | Quality |
|-----------------------------|--------------|---------------|---------|-------|------------|----|-----|----|-------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Russell et al. (2008)       | 20 min       | AN            | NS      | NS    | ↓           |    | NS | NS | NS    | NS | Patients with AN demonstrated decreased pNN50 compared to HCs but did not differ in any other HRV parameters. HRV parameters in AN group differed from individuals with other EDs                                                                                   | 9       |
| Tonhajzerova et al. (2020)  | 5 min        | AN            |         |       |             |    |     |     |               | NS | There were no significant differences in cardiac-linked vagal modulation indexed by HRV HF in patients with anorexia nervosa, compared to controls                                                                 | 21      |
| Vigo et al. (2008)          | 10 min       | AN            | NS      | NS    | ↓           |    | NS | NS | ↓     |     | Patients with AN demonstrated decreased HRV fractal scaling exponent and LF than controls. This pattern is similar to patients after myocardial infarction and may represent increased randomness of HR.                                                             | 17      |
| Wu et al. (2004)            | 5 min        | AN            |         |       |             |    | ↑  | ↑  | ↓     |     | Patients with AN demonstrated decreased SNS and enhanced PNS HRV activity. SNS (LF) was negatively correlated with anxiety and illness duration whereas PNS (HF) was positively associated with anxiety and illness duration                              | 13      |

AN, anorexia nervosa; AN-A, acute anorexia nervosa; AN-C, chronic anorexia nervosa; AN-PWR, previous diagnosis of anorexia nervosa, partially weight-restored; AN-WR, previous diagnosis of anorexia nervosa, weight-restored; BMI, body mass index; ED, eating disorder; HC, healthy controls; HF, High frequency power; HRV, heart rate variability; LF/HF, Low/high frequency power; LF, Low frequency power; NN50, Normal-to-normal intervals > 50 ms (% of); NR, not reported; NS, not significant; PNS, parasympathetic nervous system; RMSSD, Root Mean Square of Successive Differences; SDNN, Standard deviation of normal-to-normal intervals; SNS, sympathetic nervous system; TP, Total power; T1, time 1; T2, time 2; T3, time 3; α, Short-term fractal scaling exponent.
et al., 2019; Lutz et al., 2019; Green et al., 2020; Tonhajzerova et al., 2020) (see Table 3). Studies used various durations of HRV assessment; 21 reported HRV outcomes from short-term recordings (Kollai et al., 1994; Kreipe et al., 1994; Rechlin et al., 1998; Casu et al., 2002; Wu et al., 2004; Bar et al., 2006; Murialdo et al., 2007; Ishizawa et al., 2008; Russell et al., 2008; Vigo et al., 2008; Lachish et al., 2009; Koschke et al., 2010; Mazurak et al., 2011b; Billeci et al., 2015, 2019; Nakai et al., 2015; Rommel et al., 2015; Lonigro et al., 2015; Green et al., 2020; Tonhajzerova et al., 2020), five used ambulatory HRV recordings taken over 24 h (Petretta et al., 1997; Galetta et al., 2003; Roche et al., 2004; Platisa et al., 2006; Bomba et al., 2014) and one study reported both (Melanson et al., 2004). Regarding the HRV measures reported, 15 of the included studies reported on time domain HRV (Kollai et al., 1994; Petretta et al., 1997; Casu et al., 2002; Galetta et al., 2003; Melanson et al., 2004; Roche et al., 2004; Bar et al., 2006; Platisa et al., 2006; Russell et al., 2008; Vigo et al., 2008; Lachish et al., 2009; Koschke et al., 2010; Bomba et al., 2014; Billeci et al., 2015, 2019), 16 reported low frequency (LF) (Kreipe et al., 1994; Petretta et al., 1997; Rechlin et al., 1998; Casu et al., 2002; Galetta et al., 2003; Melanson et al., 2004; Roche et al., 2004; Wu et al., 2004; Platisa et al., 2006; Murialdo et al., 2007; Ishizawa et al., 2008; Lachish et al., 2009; Bomba et al., 2014; Billeci et al., 2015, 2019; Nakai et al., 2015), 22 reported high frequency (HF) (Kreipe et al., 1994; Petretta et al., 1997; Rechlin et al., 1998; Casu et al., 2002; Galetta et al., 2003; Melanson et al., 2004; Roche et al., 2004; Wu et al., 2004; Platisa et al., 2006; Murialdo et al., 2007; Ishizawa et al., 2008; Lachish et al., 2009; Mazurak et al., 2011b; Bomba et al., 2014; Billeci et al., 2015, 2019; Nakai et al., 2015; Rommel et al., 2015; Lonigro et al., 2019; Lutz et al., 2019; Green et al., 2020; Tonhajzerova et al., 2020) and 14 studies reported on calculated ratios of LF to HF (LF/HF) (Kreipe et al., 1994; Casu et al., 2002; Galetta et al., 2003; Melanson et al., 2004; Wu et al., 2004; Bar et al., 2006; Ishizawa et al., 2008; Lachish et al., 2009; Koschke et al., 2010; Bomba et al., 2014; Billeci et al., 2015, 2019; Nakai et al., 2015; Green et al., 2020). Four studies used detrended fluctuation analysis (DFA) to calculate the scaling exponent (α) of HRV (Platisa et al., 2006; Ishizawa et al., 2008; Russell et al., 2008; Vigo et al., 2008).

(i) Current AN

Basal time domain HRV in individuals with a current diagnosis of AN was reported in 15 studies. Of the ten studies that assessed short-term time domain HRV, individuals with AN had increased HRV in five studies (Kollai et al., 1994; Bar et al., 2006; Koschke et al., 2010; Billeci et al., 2015, 2019), decreased in two studies (Russell et al., 2008; Lachish et al., 2009) and unchanged in three studies (Casu et al., 2002; Melanson et al., 2004; Vigo et al., 2008), as compared to controls. Of the six studies that assessed time domain HRV using ambulatory recordings, four reported increased HRV (Petretta et al., 1997; Galetta et al., 2003; Roche et al., 2004; Bomba et al., 2014), one reported decreased HRV (Melanson et al., 2004) and one reported unchanged HRV (Platisa et al., 2006). Two studies demonstrated increased time domain HRV, as compared to lean controls (Petretta et al., 1997; Galetta et al., 2003).

Frequency domain HRV was assessed in 20 short-term recordings and 6 ambulatory recordings. Of the 16 studies that reported resting LF, seven reported decreased LF (Kreipe et al., 1994; Rechlin et al., 1998; Roche et al., 2004; Vigo et al., 2008; Lachish et al., 2009; Billeci et al., 2015, 2019), two reported increased LF (Petretta et al., 1997; Wu et al., 2004) and six reported unchanged LF (Galetta et al., 2003; Murialdo et al., 2007; Ishizawa et al., 2008; Russell et al., 2008; Bomba et al., 2014; Nakai et al., 2015), compared to controls. One study reported decreased HF HRV in acute AN (average illness duration of 12 months) and increased LF in chronic AN (average illness duration of 36 months) (Platisa et al., 2006). Of the 22 studies that reported resting HF in individuals with a current diagnosis of AN, nine reported increased HF (Petretta et al., 1997; Galetta et al., 2003; Roche et al., 2004; Wu et al., 2004; Ishizawa et al., 2008; Lachish et al., 2009; Bomba et al., 2014; Billeci et al., 2015, 2019), two reported decreased HF (Rechlin et al., 1998; Roche et al., 2004) and ten reported unchanged HF (Kreipe et al., 1994; Murialdo et al., 2007; Russell et al., 2008; Vigo et al., 2008; Mazurak et al., 2011b; Nakai et al., 2015; Lonigro et al., 2015; Green et al., 2020; Tonhajzerova et al., 2020), as compared to controls. Platisa et al. (2006) found increased HF in acute AN and decreased HF in chronic AN, while Melanson et al. (2004) assessed both short-term and ambulatory HRV, reporting no difference between groups in short-term recording of LF or HF, yet ambulatory results demonstrated both decreased LF and HF in individuals with AN, compared to controls. Of the 14 studies that reported a calculated LF/HF ratio, nine reported decreased LF/HF ratio (Kreipe et al., 1994; Galetta et al., 2003; Wu et al., 2004; Ishizawa et al., 2008; Lachish et al., 2009; Koschke et al., 2010; Bomba et al., 2014; Billeci et al., 2015, 2019) and five reported unchanged LF/HF ratios (Melanson et al., 2004; Bar et al., 2006; Russell et al., 2008; Nakai et al., 2015; Green et al., 2020), as compared to controls.

Of the four studies that reported non-linear assessments of HRV and reported the scaling exponent (α), two found decreased α (Ishizawa et al., 2008; Vigo et al., 2008) and one reported no difference in α compared to controls (Russell et al., 2008). Platisa et al. (2006) again highlighted differences according to duration of AN, reporting decreased α in those with a shorter illness duration and no difference to controls in those with an extended illness duration.

Overall, three studies indicated differences in HRV modulation according to duration of illness. A shorter illness duration was demonstrated by increased parasympathetic modulation which was attenuated over time in two studies (Platisa et al., 2006; Nakai et al., 2015). However, Wu et al. (2004) found a negative correlation between enhanced SNS activity and illness duration and a positive correlation between PNS activity and illness duration.

(ii) Weight-Restored AN

Four studies reported on HRV in individuals with a previous diagnosis of AN who were in varying stages of weight restoration. Two reported time domain HRV; one reported decreased HRV (no change from the current AN group) as compared to controls (Lachish et al., 2009) and the other reported no difference.
between AN-WR and controls (Bar et al., 2006). Three reported LF HRV in AN-WR; two reported maintenance of decreased LF (Rechlin et al., 1998; Lachish et al., 2009) and one reported no difference in LF (Kreipe et al., 1994) between AN-WR and controls. The same three studies also recorded HF in AN-WR; one reported maintenance of high HF in AN-WR (Lachish et al., 2009) and two reported no difference in HF (Kreipe et al., 1994; Rechlin et al., 1998) between AN-WR and controls. Three studies calculated the LF/HF ratio; one reported sustained low LF/HF after weight restoration (Lachish et al., 2009) and two reported no difference in LF/HF between AN-WR and controls (Kreipe et al., 1994; Bar et al., 2006).

Orthostatic Response, Blood Pressure Variability, and Baroreflex Sensitivity

Eleven studies reported the response to an orthostatic challenge, blood pressure variability (BPV), or baroreflex sensitivity (BRS) as an outcome measure (Gross et al., 1979; Lesem et al., 1989; Van Binsbergen et al., 1991; Kollai et al., 1994; Kreipe et al., 1994; Casu et al., 2002; Murialdo et al., 2007; Ishizawa et al., 2008; Lechin et al., 2010; Takimoto et al., 2014; Tonhajzerova et al., 2020) (see Table 4).

(i) Current AN

Six studies assessed BP response to an orthostatic challenge in individuals with a current diagnosis of AN; five reported decreased systolic BP (SBP) and/or diastolic BP (DBP) (Gross et al., 1979; Lesem et al., 1989; Kreipe et al., 1994; Casu et al., 2002; Murialdo et al., 2007) and one did not directly compare the response to controls (Lechin et al., 2010). Four studies investigated NE levels in response to an orthostatic challenge; two found a decreased response (Gross et al., 1979; Lechin et al., 2010), one an increased response (Lesem et al., 1989), and one found no difference (Van Binsbergen et al., 1991), as compared to controls.

Three studies reported increased BRS in individuals with a current diagnosis of AN (Kollai et al., 1994; Ishizawa et al., 2008; Takimoto et al., 2014) but Tonhajzerova et al. (2020) reported no difference in BRS to controls. All three studies that assessed BPV in individuals with AN reported decreased LF variability of BP (Ishizawa et al., 2008; Takimoto et al., 2014; Tonhajzerova et al., 2020).

(ii) Weight-Restored AN

Two studies assessed BP response to an orthostatic challenge in AN-WR groups, with both reporting maintenance of decreased BP response (Gross et al., 1979; Lesem et al., 1989). However, both reports of NE response to an orthostatic challenge were no different from controls (Gross et al., 1979), or trended toward control levels (Lesem et al., 1989) following weight restoration.

Adrenergic Assessment

Fourteen studies reported basal NE or MHPG as an outcome measure (Gross et al., 1979; Riederer et al., 1982; De Rosa et al., 1983; Luck et al., 1983; Kaye et al., 1985; Lesem et al., 1989; Van Binsbergen et al., 1991; Pirke et al., 1992; Bartak et al., 2004; Nedvidkova et al., 2004; Dostalova et al., 2007; D’Andrea et al., 2008; Lechin et al., 2010) (see Table 5).

(i) Current AN

Thirteen studies reported basal NE or MHPG levels in individuals with a current diagnosis of AN. Of these studies, 11 reported basal plasma NE levels; four reported decreased plasma NE (Gross et al., 1979; Luck et al., 1983; Pirke et al., 1992; D’Andrea et al., 2008), one reported increased plasma NE (Van Binsbergen et al., 1991) and six reported no difference in basal plasma NE (Lesem et al., 1989; Kaye et al., 1990; Bartak et al., 2004; Nedvidkova et al., 2004; Dostalova et al., 2007; Lechin et al., 2010), as compared to controls. Lechin et al. (2010) proposed that individuals with AN present with adrenal sympathetic overactivity, as evidenced by the low NE: adrenaline plasma ratio, yet did not directly compare NE levels to controls. Beta-adrenergic receptor activity was assessed by Kaye et al. (1990) who found an erratic response to increasing doses of isoproterenol in individuals with AN, as compared with controls, proposing that altered regulation of presynaptic adrenoreceptors may account for the discrepancy in assessments of NE levels across studies.

Two studies assessed adipose tissue levels of NE and both reported increased NE (Bartak et al., 2004; Nedvidkova et al., 2004). Two studies assessed urinary NE levels and both found decreased urinary NE, as compared to normal weight controls (De Rosa et al., 1983; Van Binsbergen et al., 1991) and lean controls (Van Binsbergen et al., 1991), despite one also reporting increased plasma NE levels (Van Binsbergen et al., 1991). Three studies assessed urinary excretion levels of MHPG; in two, MHPG levels were decreased in individuals with AN (Gross et al., 1979; Riederer et al., 1982) and in the third, there was no difference to controls (Van Binsbergen et al., 1991).

(ii) Weight-Restored AN

Six studies reported basal NE or MHPG levels in individuals with a previous diagnosis of AN (Gross et al., 1979; Riederer et al., 1982; Kaye et al., 1985; 1990; Lesem et al., 1989; Pirke et al., 1992). Five studies reported plasma NE levels; two of which reported decreased NE (Kaye et al., 1985; Pirke et al., 1992) and three reported no difference to controls (Gross et al., 1979; Lesem et al., 1989; Kaye et al., 1990). Two studies reported urinary MHPG levels and both found them to be comparable to control levels (Gross et al., 1979; Riederer et al., 1982) whereas one study assessed plasma MHPG, which was decreased in AN-WR participants (Kaye et al., 1985).

Skin Conductance Level and Pupil Response

Four studies reported skin conductance level (SCL) as an outcome measure in individuals with a current diagnosis of AN (see Table 6); two reported decreased SCL (Abell et al., 1987; Palomba et al., 2017) and two reported no difference in SCL compared to controls (Calloway et al., 1983; Léonard et al., 1998).

The only study that assessed pupil response (PLR) found decreased PLR response in individuals with a current diagnosis of AN, which did not persist after weight restoration (Bar et al., 2006).
### TABLE 4 | Orthostatic response, blood pressure variability and baroreflex sensitivity, as compared to controls.

| References        | Variables assessed | Group | Orthostatic | Orthostatic | BPV | BRS | NE | Outcome                                                                 |
|-------------------|--------------------|-------|-------------|-------------|-----|-----|----|------------------------------------------------------------------------|
| Casu et al. (2002)| Orthostatic BP     | AN    | ↓           | ↓           |     |     |    | Patients with AN demonstrated discorded sympathovagal balance during an orthostatic challenge, with a trend toward a high degree of vagal tone |
| Gross et al. (1979)| Orthostatic BP, NE | AN    | ↓           | NS          |     |     | NS | AN-WR patients demonstrated higher BP than acute AN patients, yet the levels were still below controls in response to an orthostatic challenge. Patients with AN demonstrated decreased LF variability of BPV, indicating decreased SNS responsiveness. Increased BRS is associated with increased PNS responsiveness. |
| Ishizawa et al. (2008)| BPV, BRS | AN    |             | LF ↓        | ↑   |     |    | Patients with AN demonstrated high resting vagal activity, which is partly explained by enhanced BRS and likely contributes to bradycardia |
| Kollai et al. (1994)| BRS              | AN    |             |             |     | ↑   |    | AN patients demonstrated abnormal autonomic control of cardiovascular activity in response to an orthostatic challenge, showing low sympathetic modulation compared to HCs. This trended toward control values after 2 weeks of inpatient treatment |
| Kreipe et al. (1994)| Orthostatic BP     | AN    | ↓           |             |     |     |    | There were no significant variations in BP in individuals with AN or controls in response to orthostasis |
| Lechin et al. (2010)| Orthostatic BP     | AN    | NS          | NS          |     |     | ↓ | Patients with AN demonstrated decreased BP in response to an orthostatic challenge, which trended toward controls after weight stabilization. NE levels were higher in individuals with AN during orthostasis, and trended toward normal levels following weight restoration |
| Leisem et al. (1989)| Orthostatic BP, NE | AN (T1)| ↓           |             |     | ↑   |    | Patients with AN demonstrated decreased BP response to an orthostatic challenge, compared to HCs |
| Murialdo et al. (2007)| Orthostatic BP     | AN    | ↓           |             |     |     | ↓ | Individuals with AN demonstrated altered autonomic changes in response to head-up tilting. Activation of the SNS was weak, whereas the PNS was strongly inhibited |
| Takimoto et al. (2014)| Orthostatic SBP, BPV, BRS | AN | NS | LF ↓ | Phase shift ↑ |    | | At rest, individuals with AN demonstrated lower sympathetically mediated BPV, indicative of insufficient sympathetic cardiovascular control. BRS was significantly higher than participants with obesity but not controls. |
| Tonhajzerova et al. (2020)| BPV, BRS | AN    |             | LF ↓        |     |     | NS | The NE response to a postural change did not differ between individuals with AN and HCs |

### DISCUSSION

The current review provides the first synthesis of investigations into ANS function in individuals with AN and those who have a previous diagnosis and have achieved weight restoration. The assessment of ANS function across modalities is discussed below.

**Heart Rate Variability**

The majority of studies that assessed HRV in the time domain demonstrated increased beat-to-beat variability in HR in individuals with a current diagnosis of AN, consistent with a recent review (Peyser et al., 2020). Moreover, increased time domain HRV parameters were demonstrated in patients with AN when compared to lean controls (Petretta et al., 1997; Galetta et al., 2003). The studies that reported decreased time domain HRV presented some methodological limitations. One did not specify duration of AN and stated that participants had recently started various antidepressant and antipsychotic agents (Russell et al., 2008), which have been associated with decreased HRV (Licht et al., 2010), another did not report the length of HRV assessment (Lachish et al., 2009) and the third reported results from a small sample size of six patients (Melanson et al., 2004). Following weight restoration, one reported no difference to controls and the other reported decreased HRV, yet did not report the HRV assessment length (Lachish et al., 2009). Therefore, based on the current review results, beat-to-beat variability in HR is increased in
| References | Group          | Plasma NE | Urinary NE | Adipose tissue NE | Plasma MHPG | Urinary MHPG | Outcome                                                                 |
|------------|---------------|-----------|------------|-------------------|-------------|--------------|--------------------------------------------------------------------------|
| Bartak et al. (2004) | AN | NS | ↑ |                       |             |              | Basal plasma NE levels were not different between AN and control groups, but controls demonstrated increased NE levels during exercise. The local SNS activity in abdominal adipose tissue was increased in AN patients. |
| D'Andrea et al. (2008) | AN | ↓ |             |                      |             |              | Individuals with AN and BN demonstrated decreased basal levels of urinary NE compared to controls. AN and BN differed in other measures of biochemical profile. |
| De Rosa et al. (1983) | AN | ↓ |             |                      |             |              | Decreased basal urinary NE was accompanied by multiple endocrine abnormalities in AN which are consistent with hypothalamic dysfunction. |
| Dostalova et al. (2007) | AN | NS |             |                      |             |              | No difference in basal or exercise-induced plasma NE levels between individuals with AN and controls. |
| Gross et al. (1979) | AN | ↓ |             |                      |             |              | Plasma NE and urinary excretion of MHPG were lower in AN group than controls but increased to normal levels after weight restoration, suggesting that they were secondary to malnutrition and not etiological factors. |
| Kaye et al. (1990) | AN (T1) | NS |             |                      |             |              | No difference in basal NE levels between individuals with acute AN, during refeeding or after weight restoration, compared to controls. |
| Kaye et al. (1990) | AN-WR (T2) | NS |             |                      |             |              | Reduced noradrenergic activity was present in long-term weight restored individuals. |
| Lechin et al. (2010) | AN | NR |             |                      |             |              | Individuals with AN demonstrated predominance of circulating adrenaline over NE during resting, orthostasis and exercise. |
| Lesem et al. (1989) | AN (time 1) | Supine NS; Orthostatic ↑ |          | Supine NS; Orthostatic ↑ |             |              | Patients with AN had elevated plasma NE levels at hospital admission, which gradually declined over 3 weeks of treatment. |
| Luck et al. (1983) | AN | ↓ |             |                      |             |              | Resting plasma NE levels were reduced in patients with AN, which may be a consequence of SNS suppression in response to starvation. |
| Nedvidkova et al. (2004) | AN | NS | ↑ |                      |             |              | Patients with AN demonstrated increased basal adipose tissue NE levels, but no difference in plasma NE levels, demonstrating the existence of different SNS activity at whole body level and at adipose tissue level. |
| Pirke et al. (1992) | AN | ↓ |             |                      |             |              | Basal plasma NE levels were lower in AN and AN-WR individuals, compared to HCs. Patients with AN also demonstrated a lower plasma NE to a test meal. Plasma NE was negatively correlated with ‘eating restraint’, which may be the causal factor for NE suppression despite weight restoration. |
| Riederer et al. (1982) | AN (T1) | AN-WR (T2) | ↓ |          | ↓ | NS | Food intake and body composition influence urinary MHPG, with normalization after treatment. |
| Van Binsbergen et al. (1991) | AN | Supine ↑; Orthostatic NS | |                      |             |              | Patients with AN had higher plasma NE levels at rest but a normal NE plasma response to an orthostatic challenge. AN patients had lower urinary NE excretion levels than lean controls, which may reflect an altered metabolism of biogenic amines. |

AN, anorexia nervosa; AN-WR, previous diagnosis of anorexia nervosa, weight-restored; BP, blood pressure; BPV, blood pressure variability; BRS, baroreflex sensitivity; DBP, diastolic blood pressure; HC, healthy controls; LF, low frequency; NE, noradrenaline; NR, not reported; NS, not significant; PNS, parasympathetic nervous system; SBP, systolic blood pressure; SNS, sympathetic nervous system.

the acute state of AN, which does not continue following weight restoration.

Assessment of HRV in the frequency domain, specifically in the LF and HF frequency bands, trended toward increased HF and decreased LF which was reflected in a trend toward decreased LF/HF ratios in patients with a current diagnosis of AN. Assessment of HRV in the frequency domain in WR participants primarily suggested normalization of HRV, with either no difference or levels trending toward controls. Akin to HRV assessed in the time domain, the acute state of AN is marked...
by increased parasympathetic activity and decreased sympathetic activity in the frequency domain, which appears to normalize following weight restoration.

Non-linear analysis of HRV was also assessed to provide a measure of complexity ($\alpha$), or randomness, in heart period series that has been demonstrated to be reduced in individuals with congestive heart failure (Peng et al., 1995) and a prognostic indicator of cardiac mortality (Huikuri et al., 2000). Decreased $\alpha$ values were demonstrated in individuals with a current diagnosis of AN (Ishizawa et al., 2008; Vigo et al., 2008) and in those with a shorter duration of AN (termed "acute") (Platisa et al., 2006), reflective of HRV patterns seen in patients with heart failure, which was postulated to be a mechanism of cardiac autonomic dysfunction and sudden death in AN (Vigo et al., 2008).

While the majority of studies indicated concordant results in HRV assessment, discrepancies are likely to be due in part to the duration of AN, the potential for comorbid conditions to impact HRV and the assessment methodology. The impact of chronicity (or duration of AN) was repeatedly highlighted as a distinguishing feature of HRV profile HRV (Platisa et al., 2006; Nakai et al., 2015). It was suggested that the HRV profile was so distinct between initial and chronic stages of illness that it could be used to distinguish between phases of illness, whereby initial starvation is typified by increased parasympathetic activity (increased HF) and an extended duration of illness was characterized by increased sympathetic activity (LF) (Petretta et al., 1997; Melanson et al., 2004; Roche et al., 2004; Platisa et al., 2006; Nakai et al., 2015). A single study found contrasting results (a positive correlation between increased illness duration and HF but a negative correlation between duration and LF), yet did not specify illness duration, therefore potential extrapolation is uncertain (Wu et al., 2004). A tentative conclusion may be that the relative increase or decrease in HF and LF is dependent on duration of AN. However, further investigation is required to confirm this hypothesis.

In addition to duration of illness, another potential influence on HRV that must be taken into account is the potential impact of comorbid psychiatric conditions on HRV parameters (Shinba et al., 2008). Anxiety and stress have been demonstrated to increase sympathetic activity (Lucini et al., 2002) and evoke cardiac vagal withdrawal, a physiological response thought to be related to the hypersensitivity engendered in anxiety disorders (for a review on the topic, see Friedman, 2007). Similarly, decreased HRV has frequently been associated with depression (independent from cardiovascular disease) (Musselman et al., 1998; Kemp et al., 2010) and antidepressant use (Licht et al., 2010; Michael and Kaur, 2021). Given that the majority of studies did not specify comorbid psychiatric conditions or psychoactive medication use, the impact of these in the current review cannot be ascertained. There is a wide literature on the influence of psychological state on HRV (Thayer et al., 2012), with common reference to Porges’ polyvagal theory which stipulates that HRV is associated with experience and expression of social and emotional behavior (Porges, 2007). Given the high rate of comorbid psychiatric disorders in individuals with AN (O’Brien and Vincent, 2003), it may be difficult to extrapolate reliably, the influence of AN alone on HRV.

### Table 6: Skin conductance and pupil response, as compared to controls.

| References          | Variables assessed | Group      | SNS | PNS | Outcome                                                                 |
|---------------------|--------------------|------------|-----|-----|------------------------------------------------------------------------|
| Abell et al. (1987) | SCL                | AN         | ↓   |     | Patients with AN demonstrated a decreased SNS in response to cold, compared to HCs |
| Bar et al. (2006)   | PLR                | AN-BP      |     | ↑   | No difference between AN and HC in skin conductance.                  |
| Leonardi et al. (1988) | SCL              | AN         |     |     | There was no difference between AN and HCs in baseline skin conductance but meal intake induced significantly higher increase in SCL in individuals with AN, compared to HCs. The SCL was negatively correlated with BMI and positively correlated with anxiety, depression and ED psychopathology. Individuals with AN demonstrated reduced resting SCL, which was independent from BMI but negatively correlated with metacognitive scale (negative beliefs about thoughts in general). Dysfunctional metacognitions about worry might yield also a reduced sympathetic activity. |
| Palomba et al. (2017) | SCL               | AN         |     |     | No difference between AN and HC in skin conductance.                  |

AN, anorexia nervosa; AN-BP, anorexia nervosa, binge-purge subtype; AN-R, anorexia nervosa, restricting subtype; BMI, body mass index; SCL, skin conductance level; ED, eating disorder; HC, healthy controls; NS, not significant; PLR, pupillometry response; PNS, parasympathetic nervous system; SNS, sympathetic nervous system.
Further consideration must be applied when considering the HRV assessment methodology. Assessments of HRV in the current review were derived from both ambulatory recordings and short-term recordings of varying length. While HRV analyses of different lengths of time are generally closely correlated (Costa et al., 1994), results between short-term and ambulatory recordings can differ (Li et al., 2019) and should not be compared (Task Force of The European Society of Cardiology The North American Society of Pacing Electrophysiology, 1996). Indeed, the only study that assessed both short-term and ambulatory HRV in the current review reported no difference in short-term HRV but decreased HRV over long-term recordings (Melanson et al., 2004).

A separate consideration is concern over whether HRV is a reflection of the autonomic state of the entire body or the regulation of the sinoatrial node alone (Hayano and Yuda, 2019). The use of HRV as a sole index of ANS activity is potentially problematic given that frequency domain analysis of HRV reportedly over-simplifies the non-linear interactions between the SNS and PNS (Billman, 2013). While HRV provides some insight into vagal activity, it has the disadvantage of giving a poor indication of sympathetic activity (Esler and Lambert, 2003; Billman, 2013). Indeed, LF heart rate spectral power (often interpreted as sympathetic activity) has been demonstrated as unrelated to direct assessments of sympathetic activity, such as NE spillover, MSNA (Kingwell et al., 1994), and cardiac sympathetic innervation quantified by positron emission tomographic neuroimaging (Rahman et al., 2012). Moreover, in the current review, 17 out of the 25 studies that assessed HRV did not use any other method to assess autonomic function in individuals with AN, a limitation underscored by Ishizawa et al. (2008) and Takimoto et al. (2014).

Overall, the assessments of HRV indicated alterations in autonomic regulation of heart rate in AN characterized by increased heart rate variance and increased vagal activity. While persistent sympathetic excitation and depressed vagal activity are associated with ventricular arrhythmias and sudden cardiac death (Task Force of The European Society of Cardiology The North American Society of Pacing Electrophysiology, 1996), the implications of persistent vagal activation and autonomic dysregulation remain unclear. However, there have been indications of increased parasympathetic activity and autonomic dysregulation at the onset of acute myocardial infarction (Webb et al., 1972), with the suggestion that autonomic dysregulation is a risk factor for sudden cardiac death in individuals with amyotrophic lateral sclerosis (Asai et al., 2007). Therefore, it remains to be determined whether consistent elevation of HRV and increased vagal modulation of cardiac control represent cardiovascular risk for individuals with AN.

Orthostatic Response, Blood Pressure Variability, and Baroreflex Sensitivity
Assessment of the physiological response to an orthostatic challenge can provide powerful insight into cardiac autonomic regulation. During a head-up tilt, the resultant peripheral venous pooling and decreased cardiac output triggers stimulation of aortic, carotid and cardiopulmonary baroreceptors, resulting in increased sympathetic outflow and inhibition of parasympathetic activity in healthy individuals (Ramirez-Marrero et al., 2007).

Observations that assessed the change in BP from a supine to upright position were limited; while BP response to orthostasis was blunted in individuals with AN in one study (Casu et al., 2002), it did not differ from controls in others (Lechin et al., 2010; Takimoto et al., 2014). Multiple studies compared absolute BP levels between AN and HC groups during an orthostatic challenge; a methodology which is limited in providing an indication of autonomic regulation given that BP is principally decreased in individuals with AN. However, assessments of HRV, BPV and adrenergic response to orthostasis revealed that individuals with AN failed to exhibit an increased sympathetic response to a head-up tilt. While a normal response is demonstrated by a decrease in the HF and increase in LF components of HRV and BPV, these reflex mechanisms were not seen in individuals with AN (Casu et al., 2002; Murialdo et al., 2007; Takimoto et al., 2014). Furthermore, individuals with AN did not demonstrate increased adrenergic outflow during a change in position (Gross et al., 1979; Lechin et al., 2010), yet were comparable to controls after weight restoration (Gross et al., 1979; Lesem et al., 1989).

While at rest, individuals with AN demonstrated decreased variability in BP and increased baroreflex sensitivity, further suggesting increased parasympathetic control over the heart. Together, these assessments of orthostatic response, BPV and BR in individuals with AN demonstrate an abnormal regulation of the cardiovascular system through a failure to activate a sympathetic response and inhibit parasympathetic activity. Altered orthostatic regulation suggests that individuals with AN are at risk of a range of conditions associated with altered orthostatic regulation, such as syncope, orthostatic hypertension, and POTS (Grubb, 2005), many of which have indeed been reported in AN. Following weight-restoration, responses tended toward those of controls, reflective of the suggestion that resolution of a normal orthostatic response can determine medical stability and readiness for discharge following treatment (Shamim et al., 2003).

Adrenergic Assessment
While many of the studies that assessed static adrenergic activity in the current review found no difference in plasma NE levels between individuals with AN and controls, there was a trend toward decreased plasma NE or MHPG levels. Decreased NE was interpreted as a chronic adaptation to malnutrition by some authors (Riederer et al., 1982; Dostalova et al., 2007), which contributed to hypothalamic dysfunction during the acute state of AN (Gross et al., 1979; De Rosa et al., 1983). Another interpretation suggested that NE levels varied over the course of treatment according to stress levels and psychological (as opposed to physical) stabilization (Lesem et al., 1989). Moreover, altered regulation of presynaptic beta-adrenoreceptors was reported, suggesting that altered noradrenergic receptor function may also be present in individuals with AN (Kay et al., 1990).
Similarly, urinary excretion of NE and MHPG was decreased in individuals with AN compared to both normal weight (Gross et al., 1979; De Rosa et al., 1983) and lean controls (Van Binsbergen et al., 1991), which increased following treatment (Gross et al., 1979; Riederer et al., 1982). While MHPG is the major metabolite of NE in the brain, urinary MHPG is predominantly the product of peripheral SNS, rather than central nervous system NE metabolism. Given that urinary catecholamine excretion is dependent on renal function (Esler et al., 1988), which has previously been shown to be impaired in individuals with AN (Stheneneur et al., 2014), interpretation of decreased urinary excretion of NE and MHPG in AN is constrained.

In contrast, assessment of NE levels in adipose tissue revealed localized elevated levels of sympathetic activity in individuals with AN, compared to controls (Bartak et al., 2004; Nedvidkova et al., 2004), despite no difference in overall plasma NE (Bartak et al., 2004). Given that local adipose tissue sympathetic activity is not a reflection of overall whole body sympathetic activity (Patel et al., 2002), an increase in localized sympathetic activity within adipose tissue was suggested to be a protective mechanism to protect fat stores from further depletion through downregulation of lipolysis (Bartak et al., 2004), a process supported by prolonged fasting models (Migliorini et al., 1997).

Each assessment of adrenergic activity in individuals with a current diagnosis of AN, and after weight restoration, provided an alternate assessment of NE presence and metabolism. Given that circulating NE levels represent a small proportion of NE secreted from nerve terminals (Grassi and Esler, 1999), it is difficult to surmise a conclusive interpretation of sympathetic activity from these results. However, there was a trend toward decreased NE levels in individuals with a current diagnosis of AN, which normalized after weight restoration.

**Skin Conductance Level and Pupillary Response**
In comparison to alternate measurements of autonomic function, SCL and PLR were less commonly assessed. Notwithstanding this, reduced sympathetic activation in SCL (Abell et al., 1987; Palomba et al., 2017) and altered SCL responses between AN subtype (Calloway et al., 1983) were reported. All assessments of SCL were conducted on the palms, of which are prone to emotional sweating (Vetrugno et al., 2003). Indeed, alterations to SCL in AN were observed to be correlated with psychological factors (including anxiety and metacognitive dysfunction) (Léonard et al., 1998; Palomba et al., 2017). Given that sympathetic skin response has been demonstrated to be emotionally activated (Cheshire et al., 2020), the use of SCL to provide insight into thermoregulatory autonomic function is therefore limited.

The only study that investigated PLR found decreased sympathetic and increased parasympathetic pupil response in individuals with AN, yet only in the acute state, which normalized following weight restoration (Bar et al., 2006). Given that only a single investigation has been conducted into PLR, which identified changes in autonomic nervous system activity in individuals with AN, further investigations of this non-invasive parameter should be undertaken in future studies.

**Limitations**
The purpose of the current review was to synthesize the evidence of ANS function associated with AN. Several methodological factors must be taken into account when comparing the assessments of ANS function in the current review. Given the serious nature and medical instability associated with AN, many studies utilized small sample sizes, which no doubt contributed to the lack of consistency among results in individual studies. Moreover, the studies investigating individuals with a previous diagnosis of AN included varied durations of weight restoration, precluding the ability to draw a succinct conclusion. Many studies did not detail or compare differences between restrictive and binge eating-purging subtypes of AN, therefore any differences related to specific AN behaviors cannot be determined by the current review. Future investigations into ANS function after a prolonged period of weight restoration would allow a better understanding of the impact of AN in any long-term alterations to ANS function. Similarly, delineation of AN subtype and assessment of comorbid psychiatric diagnoses in future assessments could reveal any differences in autonomic function according to subtype and comorbidities.

**Implications and Conclusion**
The current review provides a synthesis of the evidence to date assessing resting autonomic function in individuals with AN, and after weight restoration. It is indicated that individuals with AN demonstrate autonomic dysregulation characterized by decreased sympathetic activity and increased parasympathetic activity as well as increased complexity of the ANS through a variety of assessment methodologies. Given the ease and convenience of HRV assessment, it is tempting to use the measure as a sole assessment of autonomic function. However, the demonstrated impact that both illness duration and psychiatric comorbidities can have on HRV infer that assessment of autonomic activity should be established via additional accompanying measures. While the duration of weight restoration in the current review was widely varied, the majority of studies to date indicated that autonomic regulation tended to normalize after weight restoration. Moreover, there has been no assessment of SNS activity in individuals with AN to date using either microneurographic measurement of muscle sympathetic nerve activity or assessment of organ-specific NE spillover; the two “preferred” assessments of human adrenergic function (Grassi and Esler, 1999).

The underlying mechanisms that contribute to the abnormalities in ANS function in acute AN remain speculative. It has been proposed that the parasympathetic dominance seen in AN is an adaptive physiological response to conserve energy in response to malnutrition (Buchhorn et al., 2016; Sachs et al., 2016; Kalla et al., 2017). However, it remains unclear whether energy preservation alone is underlying the changes in ANS function, given that the three studies that included lean control groups did not find a linear relationship between BMI and ANS function. Specifically, HRV and NE excretion in patients with...
AN were significantly different than both normal-weight and lean controls, who satisfied the weight, but not psychological, criterion for AN (Van Binsbergen et al., 1991; Petretta et al., 1997; Galetta et al., 2003). There is growing evidence of an intrinsic connection between the brain and the heart, including interplay between frontal-vagal (brain-heart) and depression networks (Isager et al., 2020), that purportedly contributes to cardiovascular disease (Makovac et al., 2017). Given the demonstrated dysregulation of other neural regulatory systems in AN [including dopaminergic and serotonergic systems, which are thought to contribute to both physiological and psychological traits seen in AN (Kaye et al., 2005; Fladung et al., 2010)], there may be central dysregulation of ANS networks in AN, yet this remains putative.

The implications of the current review are that increased vagal activity is likely to underlie the widespread bradycardia in individuals with AN. Moreover, inhibited SNS activation during orthostasis would result in insufficient blood flow to organs and contribute to episodes of syncope. Less clear are the implications of the increased autonomic complexity demonstrated by HRV and BRS parameters. While cardiovascular disease is commonly associated with sympathetic overactivity (Malpas, 2010), the consequences of sustained parasympathetic overactivity and autonomic dysregulation are yet to be determined. It remains to be ascertained whether the autonomic dysregulation indicated in individuals with AN contributes to the widespread cardiovascular complications.

This review has demonstrated that autonomic dysregulation is indicated in individuals with AN, yet there have been no thorough assessments of autonomic function utilizing multiple methodologies. Due to the variability in both methodology and quality of assessments to date, conclusions drawn from these data should be interpreted with caution. Furthermore, in order to determine the association between autonomic dysregulation and widespread cardiovascular complications in AN conclusively, future investigations should employ a variety of assessments of autonomic function in conjunction with markers of cardiovascular risk. It will also be important to assess the impact of comorbid psychiatric conditions and duration of illness in order to conclusively establish the nature of autonomic (dys)function in AN. Similarly, future investigations in individuals with an extended duration of weight restoration are still required. Determination of autonomic function through a variety of assessment methodologies in individuals with a current, and previous, diagnosis of AN alongside assessments of cardiovascular risk will aid in determining the contributing factors to cardiovascular complications. This will allow clinicians to identify individuals at risk and aid in the prevention, treatment and development of interventions to reduce the inadvertent mortality rate of AN.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

ZJ conceived the project and drafted the manuscript. HW conducted the search. ZJ, EL, and NE conducted the study selection. ZJ, NE, AP, DC, and EL conducted the data extraction and risk of bias. All authors designed and approved the protocol, reviewed, and approved.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.682208/full#supplementary-material

REFERENCES

Abell, T. L., Malagelada, J. R., Lucas, A. R., Brown, M. L., Camilleri, M., Go, V. L., et al. (1987). Gastric electromechanical and neurohormonal function in anorexia nervosa. Gastroenterology 93, 958–965. doi: 10.1016/s0016-5085(87)90557-9

American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub. doi: 10.1176/appi.books.9780890425596

Arcelus, J., Mitchell, A. J., Wales, J., and Nielsen, S. (2011). Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. Arch. Gen. Psychiatry 68, 724–731. doi: 10.1001/archgenpsychiatry.2011.74

Asai, H., Hirano, M., Udaka, F., Shimada, K., Oda, M., Kubori, T., et al. (2007). Sympathetic disturbances increase risk of sudden cardiac arrest in sporadic ALS. J. Neurol. Sci. 254, 78–83. doi: 10.1016/j.jns.2007.01.007

Bar, K. J., Boetgter, S., Wagner, G., Wölzfost, C., Gerhard, U. J., Boetgter, M. K., et al. (2006). Changes of pain perception, autonomic function, and endocrine parameters during treatment of anorectic adolescents. J. Am. Acad. Child Adolesc. Psychiatry 45, 1068–1076. doi: 10.1097/01.chi.0000227876.19909.48

Bartak, V., Vybalr, S., Papezova, H., Dostalova, I., Pacak, K., and Nedvídikova, J. (2004). Basal and exercise-induced sympathetic nervous activity and lipolysis in adipose tissue of patients with anorexia nervosa. Eur. J. Clin. Invest. 34, 371–377. doi: 10.1111/j.1365-2362.2004.01344.x

Billeci, L., Tartarisco, G., Brunori, E., Crifaci, G., Scardigli, S., Balocchi, R., et al. (2015). The role of wearable sensors and wireless technologies for the assessment of heart rate variability in anorexia nervosa. Eat. Weight Disord. 20, 23–31. doi: 10.1007/s40519-014-0135-2

Billeci, L., Tonacci, A., Brunori, E., Raso, R., Calderoni, S., Maestro, S., et al. (2019). Autonomic nervous system response during light physical activity in adolescents with anorexia nervosa measured by wearable devices. Sensors 19:2820. doi: 10.3390/s19122820

Billman, G. E. (2011). Heart rate variability—an historical perspective. Front. Physiol. 2:86. doi: 10.3389/fphys.2011.00086

Billman, G. E. (2013). The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front. Physiol. 4:26. doi: 10.3389/fphys.2013.00026

Bombà, M., Corbetta, F., Gambera, A., Nicosa, F., Bonini, L., Neri, F., et al. (2014). Heart rate variability in adolescents with functional hypothalamic amenorrhea and anorexia nervosa. Psychiatry Res. 215, 406–409. doi: 10.1016/j.psychres.2013.11.012

Buchhorn, R., Hauk, F., Meint, S., and Willaschek, C. (2016). The impact of nutrition on the autonomic nervous system. Int. J. Food Nutr. Sci. 3, 1–16. doi: 10.15436/2377-0619.16.942
Grassi, G., and Esler, M. (1999). How to assess sympathetic activity in humans. *J. Clin. Psychiatry* 142, 38–42. doi: 10.1192/jcpr.142.1.38

Casiero, D., and Frishman, W. H. (2006). Cardiovascular complications of eating disorders. *Circ. Res. 11, 1113–1118*. doi: 10.1161/01.CIR.90.1.12572

Esler, M. D. (1995). Adverse consequences of high sympathetic nervous system activity. In *Heart rate power spectrum analysis of autonomic dysfunction*, pp. 395–400. Springer, Berlin, Heidelberg.

Buijs, R. M., Escobar, C., and Swaab, D. F. (2013). “Chapter 15 - The circadian system and the balance of the autonomic nervous system,” in *Handbook of Clinical Neurology*, eds R. M. Buijs and D. F. Swaab, (Elsevier), 173–191.

Calloway, P., Fonagy, P., and Wakeling, A. (1983). Autonomic arousal in eating disorders: further evidence for the clinical subdivision of anorexia nervosa. *Br. J. Psychiatry 142, 227–231*. doi: 10.1192/bjp.142.1.227

Casiero, D., and Frishman, W. H. (2006). Cardiovascular complications of eating disorders. *Circ. Res. 14, 216–221*. doi: 10.1161/CIRCRESAHA.104.482018

Halmi, K. A., Goldberg, S. C., Eckert, E., Casper, R., and Davis, J. M. (1977). “Pretreatment evaluation in anorexia nervosa,” in *Anorexia Nervosa ed R. A. Vigersky* (New York, NY: Raven Press), 43–54.

Hayano, J., and Yuda, E. (2019). Pitfalls of assessment of autonomic function by heart rate variability. *J. Physiol. Anthrop. 38, 1–8*. doi: 10.1186/s40101-019-0193-2

Hoek, H. W. (2006). Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. *Curr. Opin. Psychiatry 19, 389–394*. doi: 10.1097/00001756-200606000-00001

Hoek, H. W., and Van Hoeken, D. (2003). Review of the prevalence and incidence of eating disorders. *Int. J. Eating Disord. 34, 383–396*. doi: 10.1002/eat.10222

Huikuri, H. V., Mikkaillo, T. H., Peng, C. K., Goldberg, A. L., Hintze, U., and Moller, M. (2000). Fractal correlation properties of RR interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation 101*, 47–53. doi: 10.1161/01.CIR.101.1.47

Isler, T. A., Van Bueren, N. E., Kenemans, J. L., Geurts, R., and Arns, M. (2020). A frontal-vagal network theory for major depressive disorder: implications for optimizing neuromodulation techniques. *Brain Stimul. 13*, 1–9. doi: 10.1016/j.brs.2019.10.006

Ishizawa, T., Yoshuichi, K., Takimoto, Y., Yamamoto, Y., and Akabayashi, A. (2008). Heart rate and blood pressure variability and baroreflex sensitivity in patients with anorexia nervosa. *Psychosom. Med. 70*, 695–700. doi: 10.1097/Psy.0b013e31817b9090

Kalla, A., Krishnamoorthy, P., Gopalakrishnan, A., Garg, J., Patel, N. C., and Figueredo, V. M. (2017). Gender and age differences in cardiovascular complications in anorexia nervosa patients. *Int. J. Cardiol. 227*, 55–57. doi: 10.1016/j.ijcard.2016.11.209

Kaye, D. M., Lefkovits, J., Jennings, G. L., Bergin, P., Broughton, A., and Esler, M. D. (1995). Adverse consequences of high sympathetic nervous system activity in the failing human heart. *J. Am. Coll. Cardiol. 26*, 1257–1263. doi: 10.1016/0735-1097(95)00332-0

Kaye, W. H., Frank, G. K., Baill, U. F., Henry, S. E., Meltzer, C. C., Price, J. C., et al. (2005). Serotonin alterations in anorexia and bulimia nervosa: new insights from imaging studies. *Physiol. Behav. 85*, 73–81. doi: 10.1016/j.physbeh.2005.04.013

Kaye, W. H., George, D. T., Gwirtsman, H. E., Jimerson, D. C., Goldstein, D. S., Ebert, M. H., et al. (1990). Isoprotenerol infusion test in anorexia nervosa: assessment of pre- and post-beta-noradrenergic receptor activity. *Psychopharmacol. Bull. 26*, 355–359.

Kaye, W. H., Jimerson, D. C., Lake, C. R., and Ebert, M. H. (1985). Altered norepinephrine metabolism following long-term weight recovery in patients with anorexia nervosa. *Psychiatry Res. 14*, 333–342. doi: 10.1016/0165-1781(85)90101-5

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., and Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biological Psychiatry 67*, 1067–1074. doi: 10.1016/j.bpyscr.2009.12.012

Kingwell, B. A., Thompson, J. M., Kaye, D. M., Mcpherson, G., Jennings, G. L., and Esler, M. D. (1994). Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation 90*, 234–240. doi: 10.1161/01.CIR.90.1.234

Kollai, M., Bonyhay, I., Jokkel, G., and Szonyi, L. (1994). Cardiac vagal hyperactivity in adolescent anorexia nervosa. *Eur. Heart J. 15*, 1113–1118. doi: 10.1093/oxfordjournals.eurheartj.a06636

Koschke, M., Boetger, M. K., Machold, C., Schulz, S., Yerganian, V. K., Voss, A., et al. (2010). Increased QT variability in patients with anorexia nervosa: an indicator for increased cardiac mortality? *Int. J. Eat. Disord. 43*, 743–750. doi: 10.1002/eat.20765

Kreipe, R. E., Goldstein, B., Deking, D. E., Tipton, R., and Kemple, M. H. (1994). Heart rate power spectrum analysis of autonomic dysfunction
in adolescents with anorexia nervosa. *Int. J. Eat. Disord.* 16, 159–165. doi: 10.1002/1098-108X(199409)16:2<159::AID-EAT2610160207>3.0.CO;2-H
Lachish, M., Stein, D., Kaplan, Z., Matar, M., Faigin, M., Korsunski, I., et al. (2009). Irreversibility of cardiac autonomic dysfunction in female adolescents diagnosed with anorexia nervosa after short- and long-term weight gain. *World J. Biol. Psychiatry* 10, 510–515. doi: 10.3109/15622970902980770
Lambert, E., Straznicky, N., Schlaich, M., Eder, M., Dawood, T., Hotchkin, E., et al. (2007). Differing pattern of sympathoexcitation in normal-weight and obesity-related hypertension. *Hypertension* 50, 862–868. doi: 10.1161/HYPERTENSIONAHA.107.094649
Lechin, F., Van Der Dijs, B., Pardey-Maldonado, B., Rivera, J. E., Baez, S., and Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6:e1000097. doi: 10.1371/journal.pmed.1000097
Murialdo, G., Casu, M., Falchero, M., Brugnolo, A., Patrone, V., Cerro, P. F., et al. (2017). Alterations in the autonomic control of heart rate variability in patients with anorexia or bulimia nervosa: correlations between sympathovagal activity, clinical features, and leptin levels. *J. Endocr. Invest.* 30, 356–362. doi: 10.1007/BF03346310
Musselman, D. L., Evans, D. L., and Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch. Gen. Psychiatry* 55, 580–592. doi: 10.1001/archpsyc.55.5.580
Nakai, Y., Fujita, M., Nin, K., Noma, S., and Teramukai, S. (2015). Relationship between duration of illness and cardiac autonomic nervous activity in anorexia nervosa. *Biopsychosoc. Med.* 9:12. doi: 10.1186/s13030-015-0032-6
Nakai, Y., Noma, S., Fukusima, M., Taniguchi, A., and Teramukai, S. (2016). Serum lipid levels in patients with eating disorders. *Intern. Med.* 55, 1853–1857. doi: 10.2169/internalmedicine.55.5632
Nedvidkova, J., Dostalova, I., Bartak, V., Papezov, H., and Pacak, K. (2004). Increased subcutaneous abdominal tissue norepinephrine levels in patients with anorexia nervosa: an in vivo microdialysis study. *Physiol. Res.* 53, 409–413. O’Brien, K. M., and Vincent, N. K. (2003). Psychiatric comorbidity in anorexia and bulimia nervosa: nature, prevalence, and causal relationships. *Clin. Psychol. Rev.* 23, 57–74. doi: 10.1016/S0272-7758(02)00201-5
Palma, J. A., and Benarroch, E. E. (2014). Enhanced cortical processing of cardio-afferent signals in anorexia nervosa. *Clin. Neurophysiol.* 125, 261–271. doi: 10.1016/j.clinph.2013.11.010
Lesem, M. D., George, D. T., Kaye, W. H., Goldstein, D. S., and Jimeron, D. C. (1997). Increased sympathetic activity, clinical features, and leptin levels. *J. Endocr. Invest.* 30, 356–362. doi: 10.1007/BF03346310
Migliorini, R. H., Garofalo, M., and Kettelhut, I. C. (1997). Increased sympathetic activity in rats while adipose tissue during prolonged fasting. *Am. J. Physiol.* 272, R656–R661. doi: 10.1152/ajpregu.1997.272.2.R656
Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PloS Med.* 6:e1000097. doi: 10.1371/journal.pmed.1000097
Palomba, D., Venturini, M., Rausa, M., Contin, S. A., Penolazzi, B., Schumann, R., et al. (2017). Reduced sympathetic activity and dysfunctional metacognition in patients with anorexia nervosa: a preliminary study. *J. Evid. Based Psychother.* 17:1. doi: 10.24193/jebp.2017.1.1
Papadopoulos, F. C., Ekborn, A., Brandt, L., and Ekseilus, L. (2009). Excess mortality, causes of death and prognostic factors in anorexia nervosa. *Br. J. Psychiatry* 194, 10–17. doi: 10.1192/bjp.bp.108.054742
Peyser, D., Scolnick, B., Hildebrandt, T., and Taylor, J. A. (2020). Heart rate variability as a measure of cardiac autonomic function in anorexia nervosa: a review of the literature. *Eat. Weight Disord.* 25, 599–612. doi: 10.1007/s40519-019-00792-8
Pirke, K. M., Kellner, M., Philipp, E., Laessle, R., Krieg, J. C., and Fichter, M. (2005). Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* 5, 82–87. doi: 10.1063/1.166141
Platisa, M. M., Nestorovic, Z., Damjanovic, S., and Gal, V. (2006). Linear and non-linear heart rate variability measures in chronic and acute remitted patients with anorexia nervosa and in healthy controls. *Clin. Physiol.* 26, 54–60. doi: 10.1111/j.1475-097X.2005.00307
Peyser, S., Scholl-Bandt, N., and Taylor, A. J. (2020). Heart rate variability as a biomarker for anorexia nervosa: a review. *Eur. Eat. Disord. Rev.* 29, 20–31. doi: 10.1002/erv.2791
Pettretta, M., Bonaduce, D., Scalì, L., De Filippo, E., Marciano, F., Migaux, M. L., et al. (1997). Plasma norepinephrine after a standardized test meal in acute and non-remitted patients with anorexia nervosa and in healthy controls. *Br. J. Nutr.* 77, 109–113. doi: 10.1079/BJN19970108
M. L., et al. (1997). Heart rate variability as a measure of autonomic nervous system function in anorexia nervosa. *Clin. Auton. Res.* 7, 3373–3377. doi: 10.1210/ciems187.7.76895
Peng, C. K., Havlin, S., Stanley, H. E., and Goldberger, A. L. (1995). Heart rate variability as a biomarker for anorexia nervosa: a review. *Eur. Eat. Disord. Rev.* 29, 20–31. doi: 10.1002/erv.2791
Phillipou, A., Music, S., and Lee Rossell, S. (2019). A biopsychosocial proposal to progress the field of anorexia nervosa. *Aust. N. Z. J. Psychiatry* 53, 1145–1147. doi: 10.1177/0004867419849487
Pike, K. M. (1998). Long-term course of anorexia nervosa: response, relapse, remission, and recovery. *Clin. Psychol. Rev.* 18, 447–475. doi: 10.1016/S0272-7358(98)00014-2
Peke, K. M., Kellner, M., Philip, E., Laessle, R., Krieg, J. C., and Fichter, M. M. (1992). Plasma norepinephrine after a standardized test meal in acute and remitted patients with anorexia nervosa and in healthy controls. *Biol. Psychiatry* 31, 1074–1077. doi: 10.1016/0006-3223(92)00102-6
Platisa, M. M., Nestorovic, Z., Damjanovic, S., and Gal, V. (2006). Linear and non-linear heart rate variability measures in chronic and acute phase of anorexia nervosa. *Clin. Psychol. Funct. Imaging* 26, 54–60. doi: 10.1111/j.1475-097X.2005.00653.x
Porges, S. W. (2007). The polyvagal theory. *Biol. Psychol.* 74, 114–126. doi: 10.1016/j.biopsycho.2006.05.008
Quintana, D., Alves, G. A., and Heathers, J. (2016). Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication. *Transl. Psychiatry* 6:e803. doi: 10.1038/tp.2016.73
Rahman, F., Pechnik, S., Gross, D., Sewell, L., and Goldstein, D. S. (2011). Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Clin. Auton. Res. 21, 133–141. doi: 10.1007/s10286-010-0098-y

Ramirez-Marrero, F. A., Charkoudian, N., Zhong, L., Hesse, C., and Eisenach, J. H. (2007). Balance between sympathetic response to head-up tilt and cardiac vagal factors in healthy humans. Clin. Auton. Res. 17, 227–230. doi: 10.1007/s10286-007-0427-y

Rechlín, T., Weis, M., Ott, C., Bleichner, F., and Joraschký, P. (1998). Alterations of autonomic cardiac control in anorexia nervosa. Biol. Psychiatry 43, 358–363. doi: 10.1016/S0006-3223(97)00026-7

Riederer, P., Toiß, K., and Kruzik, P. (1982). Excretion of biogenic amine metabolites in anorexia nervosa. Clin. Chim. Acta 123, 27–32. doi: 10.1016/0009-8981(82)90109-7

Roche, F., Estour, B., Kadem, M., Millot, L., Pichot, V., Duverney, D., et al. (2004). Alteration of the QT rate dependence in anorexia nervosa. Pacing Clin. Electrophysiol. 27, 1099–1104. doi: 10.1111/j.1540-8159.2004.00591.x

Rommel, D., Nandirino, J. L., De Jonckheere, J., Swierczek, M., Dodin, V., and Logier, R. (2015). Maintenance of parasympathetic inhibition following emotional induction in patients with restrictive type anorexia nervosa. Psychiatry Res. 225, 651–657. doi: 10.1016/j.psychres.2014.11.030

Russell, G. F. (1970). Anorexia nervosa: its identity as an illness and its treatment. Mod. Trends Psychol. Med. 2, 131–164.

Russell, J., Hijazi, S., Edington, L., Spence, I., and Jelinek, H. F. (2008). Decrease in heart rate variability response to task is related to anxiety and depressiveness in normal subjects. Psychosom. Med. 70, 603–609. doi: 10.1136/jn.1440-1819.2008.01855.x

Smirk, F. S., Van Hoeken, D., Oldehinkel, A. J., and Hoek, H. W. (2014). Cardiovascular abnormalities identified with echocardiography in anorexia nervosa: Cardiac abnormalities identified with echocardiography in anorexia nervosa. Br. J. Psychiatry doi: 10.1192/bjp.bp.113.134138

Spaulding-Barclay, M. A., Stern, J., and Mehler, P. S. (2016). Cardiovascular complications of anorexia nervosa: a systematic review. Int. J. Eat. Disord. 49, 238–248. doi: 10.1002/eat.22481

Shamim, T., Golden, N. H., Arden, M., Fülöp, L., and Shenker, I. R. (2003). Resolution of vital sign instability: an objective measure of medical stability in anorexia nervosa. J. Adolesc. Health 32, 73–77. doi: 10.1016/S1054-1393(02)00533-5

Shinba, T., Kariya, N., Matsui, Y., Ozawa, N., Matsuda, Y., and Yamamoto, K. I. (2007). Resolution of vital sign instability: an objective measure of medical stability in anorexia nervosa. J. Adolesc. Health 32, 73–77. doi: 10.1016/S1054-1393(02)00533-5

Steinglass, J. E., and Walsh, B. T. (2016). Neurobiological model of the persistence of medical stability in anorexia nervosa. Clin. Auton. Res. 24, 175–181. doi: 10.1007/s10286-014-0250-1

Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Eur. Heart J. 17, 354–381.

Thayer, J. F., Ahls, F., Fredrikson, M., Sollers III, J. I., and Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci. Biobehav. Rev. 36, 747–756. doi: 10.1016/j.neubiorev.2011.11.009

Tjal, Z., and Timo, S. (2019). The investigation of the cardiovascular and sudomotor autonomic nervous system—a review. Front. Neurol. 10:53. doi: 10.3389/fneur.2019.00053

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