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Meta-analyses

Effects of weight changes in the autonomic nervous system: A systematic review and meta-analysis

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SUMMARY

Background: Obesity has been linked to autonomic dysfunction, which is thought to be one of the main contributors for hypertension, cardiac remodelling and death. Exercise and diet-based weight loss are the mainstay therapy for obesity, but there is a paucity of data regarding the effect of weight changes in autonomic nervous system (ANS) activity.
Objective: To describe the impact of weight changes in autonomic nervous system.
Methods: A systematic literature search of four biomedical databases was performed evaluating effects of weight changes, thorough diet and/or exercise-based interventions, in the following ANS outcomes: heart rate variability, namely low frequency (LF)/high frequency (HF) ratio (LF/HF ratio), normalized units of LF (LFnu) and HF (HFnu), muscle sympathetic nerve activity (MSNA), noradrenaline spillover rate (NA-SR), standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (RMSSD), baroreflex sensitivity and pupillometry. Quality appraisal was performed using the GRADE methodology and, where fitting, studies with comparable outcomes were pooled for meta-analysis.
Results: Twenty-seven studies - 7 controlled clinical trials and 20 observational studies - were included. Weight gain was reported in 4 studies and weight loss in all the other studies. Interventions inducing weight changes included: hypocaloric or hypercaloric diets, exercise (strength, endurance or aerobic training) and hypocaloric diet coupled with exercise programs. Most studies which resulted in weight loss reported decreases in LF/HF ratio, LFnu, MSNA burst frequency and incidence, NA-SR, and an increase of baroreflex sensitivity, HF, HFnu and RMSSD, pointing to a parasympathetic nervous system activation. Meta-analysis regarding weight loss interventions showed a significant pooled effect size (95% CI) with a decreased of MSNA burst frequency −5.09 (−8.42, −1.75), MSNA incidence −6.66 (−12.40, −0.62), however this was not significant for SDNN 14.32 (−4.31, 32.96). Weight gain was associated with an increase in LF/HF, LFnu, MSNA burst frequency and incidence. The weight loss effects were potentiated by the association of hypocaloric diet with exercise. Nevertheless, weight changes effects in these outcomes were based in low or very low quality of evidence.

Abbreviations: ANS, Autonomic nervous system; BRS, Baroreflex sensitivity; BMI, Body mass index; CCT, Controlled clinical trial; DASH, Dietary approach to stop hypertension; GRADE, Grading of recommendations assessment; development, and evaluation; HF, High frequency; HFnu, High frequency in normalized units; HRR, Heart rate recovery; HRV, Heart rate variability; LF, Low frequency; LF/HF ratio, Low frequency/high frequency ratio; LFnu, Low frequency in normalized units; MSNA, Muscle sympathetic nerve activity; NA-SR, Noradrenaline spillover rate; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; RMSSD, Root mean square of successive differences; SD1, Standard deviation of instantaneous beat-to-beat R−R interval variability; SD1nu, Standard deviation of instantaneous beat-to-beat R−R interval variability normalized; SDNN, Standard deviation of normal-to-normal intervals; TP, Total Power; UCT, Uncontrolled clinical trial (with or without control group measured at baseline); VLF, Very low frequency.

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Conclusions: Diet and exercise based weight loss appears to increase parasympathetic and decrease sympathetic activity, the opposing effects being observed with weight gain. These findings are not uniformly reported in the literature, possibly due to differences in study design, methodology, characteristics of the participants and techniques used to estimate autonomic nervous activity.

1. Introduction

The epidemiological association between obesity as a risk factor for diabetes, cardiovascular disease, cancer and premature death has long been established [1]. One of the mechanisms involved in the pathogenesis of these comorbidities is autonomic dysfunction. Overweight and obesity are associated with an increased sympathetic and decreased parasympathetic activity [2,3]. This is supported by previous findings showing an increase of serum noradrenaline, noradrenaline excretion, renal and heart NA-SR, MSNA and HRV indexes in obese individuals [4,5]. Autonomic dysfunction in obese has been linked to target organ damage, such as diastolic dysfunction, ventricular hypertrophy or cardiac remodelling [4]. Prevention of autonomic dysfunction could be a target to reduce these comorbidities.

Reducing weight, through diet and exercise improves the lipid profile and decreases mean arterial blood pressure, as well as the risk of developing type 2 diabetes and coronary heart disease [4,6–8]. Although many studies evaluated biochemical and haemodynamic parameters in weight change interventions, there is still a paucity of data regarding the effect of dietary and physical activity interventions with weight change in the autonomic profile [5]. The role of sympathetic inhibition through diet, exercise, surgery and pharmacological interventions as a target in the treatment of obesity and to prevent cardiovascular and metabolic consequences, is currently under research [5]. Diet and exercise-based weight loss are the mainstay therapy for obesity; understanding its effect on the ANS could help clarify regional activity patterns of the ANS and its potential applicability as an adjuvant to novel therapies.

The aim of this study is to evaluate the modulation of the sympathetic and parasympathetic nervous systems activity induced by weight gain or weight loss, through dietary and/or exercise interventions.

2. Materials and methods

This review is reported in accordance with PRISMA guidelines [9]. The protocol for the systematic review was registered with the International Prospective Register of Systematic Review (PROSPERO 2016: CRD42016038732).

2.1. Study design and population

We selected randomised controlled trials and observational studies assessing the effect of weight changes in ANS activity. No restrictions were imposed on language, publication date or status. We included participants of any age, gender, ethnic group or body mass index (BMI).

Participants with a history of acquired or inherited diseases associated with autonomic neuropathy or autonomic dysfunction [10–12] were excluded. Specifically, cardiovascular diseases, such as hypertension [13], heart failure [14], cerebrovascular and neurological disease [15,16], diabetes [5] and psychiatric, eating or sleep disorders. Participants who were smokers or under the effect of any drug that could influence directly or indirectly the ANS activity [17], were also not included.

2.2. Study interventions and outcomes

Interventions considered for this meta-analysis included all diet and/or exercise-based weight change regimens. Trials that evaluated pharmacological or surgery based interventions were excluded, due to previous reports of autonomic dysfunction after surgery [18] and acute effects of sibutramine in the ANS [19]. Despite exercise training-induced modifications in ANS are well recognized [20], our aim was to assess if there was an additional effect related to weight change, besides exercise training.

The primary outcome measures were HRV parameters. As secondary outcomes, MSNA, NA-SR, pupillometry parameters and BRS were assessed. The studied parameters and their definitions are described in Appendix A. Neurotransmitter levels, measured by catecholamine levels, namely plasma or urinary noradrenaline or adrenaline levels were not evaluated due to the limitations inherent to this method in assessing sympathetic nervous system [21]: circulating noradrenaline levels represent only a minor fraction of the amount of neurotransmitters secreted from the sympathetic nerve terminals; they do not express the regional differences in sympathetic nerve activity and are influenced by clearance, metabolism and uptake from the circulating blood [12].

2.3. Data sources and study selection

Studies were identified by searching electronic databases and reference lists of articles. The search was conducted in MEDLINE (1946 – Present), PubMed, CINAHL Plus (1937 – Present), SPORTDiscus (1800 – Present), Web of Science™ Core Collection (1900 – Present) and Scopus (1823 – Present). The following terminology was used: autonomic nervous system AND body weight or weight changes. The search queries for each database are specified in Appendix B.

Two authors independently (DS and JC) reviewed the titles and abstracts in accordance with the pre-defined inclusion criteria. This first approach selected which of the retrieved articles a evaluating weight changes using exercise/diet interventions. Reference lists of pertinent studies were hand searched to identify relevant studies. Afterwards, both reviewers analyzed, independently, the selected articles and agreed on which studies were to be included in the systematic review, for further analysis. Discrepancies between reviewer's selections were solved by authors consensus prior to data extraction.

2.4. Data extraction

Quantitative data was extracted from studies included in the review using a data extraction sheet developed by the authors, which included specific details about the study groups, methodology and intervention characteristics, outcomes and results. Data

was independently extracted by two reviewers (JC and DS). Measures were taken to avoid the inclusion of duplicated studies, including comparing author names, sample sizes, intervention characteristics and outcomes. When necessary, authors were contacted for additional information. If the data was only available in a graphical image and the quantitative data was not provided by the authors, WebPlotDigitizer software was used for quantitative data extraction from graphics (Rohatgi A, 2017, version 3.11, Austin, TX, USA).

The following data were extracted from each study [1]: study design (randomization, blinding) [2], characteristics of the participants (sample size, age range) [3], characteristics of the intervention and protocol (duration, diet composition and total calorie consumption, characteristics of the exercise training program) [4],

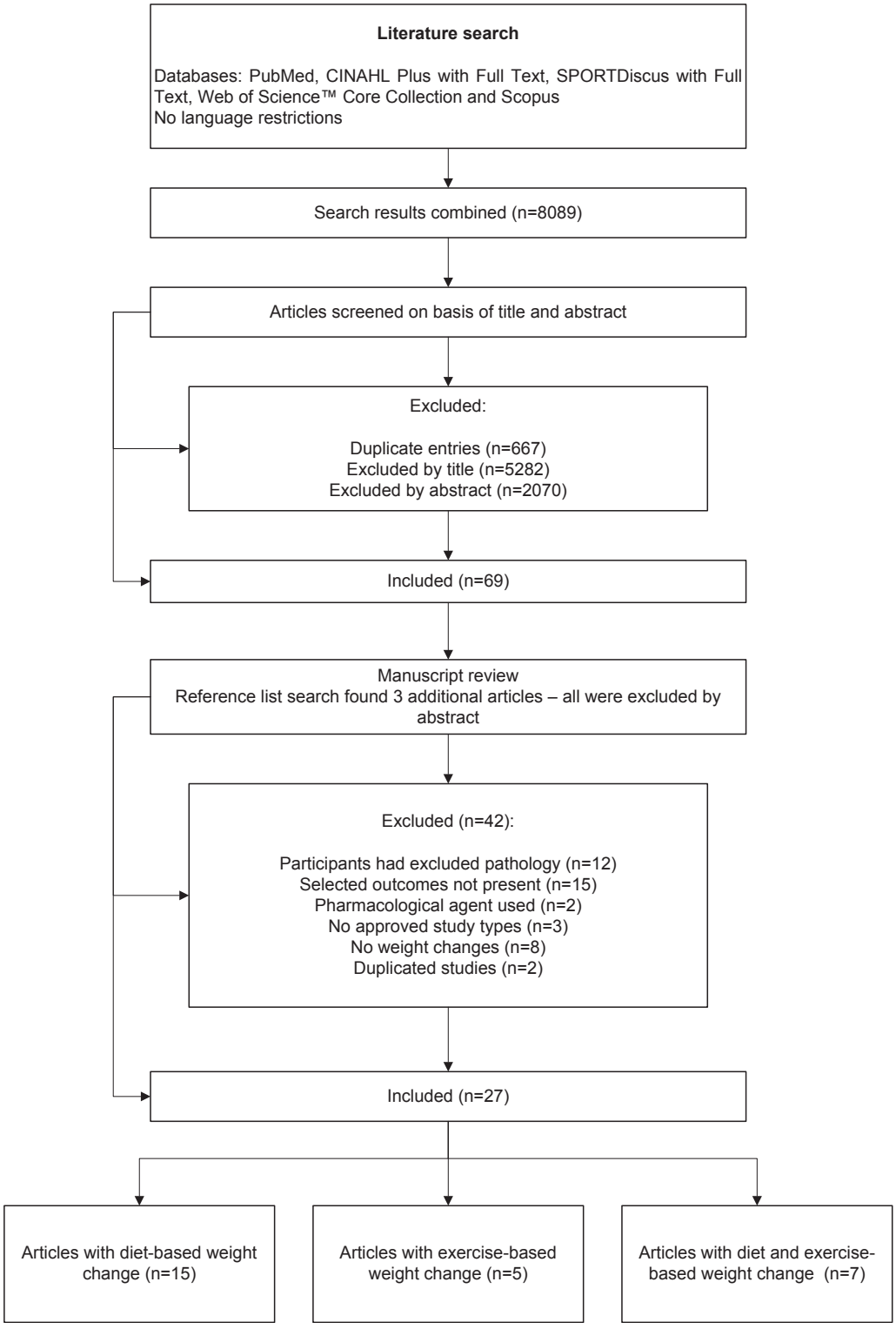

Fig. 1. PRISMA flowchart of included studies.

Table 1
Characteristics and results of the included studies.

Reference	Study design and participants	Intervention	Outcome measure	Change in BMI	Results
Weight loss					
Mazurak N et al., 2016 [34]	UCT[d] Children n = 60 (30♀) 13.0 ± 1.9 years 80.4 ± 20.5 kg Healthy matched children n = 27 (12 ♀) 12.5 ± 0.9 years 45.4 ± 8.2 kg	Weight reduction program (exercise and balanced diet) 1 year (52 children completed the intervention)	SDNN RMSSD HF; LF HF nu; LF nu LF/HF (resting vs. stress/arithmetic test)	−4.1%	SDNN, RMSSD and HF(log) increased (69.4 ± 3.7−79.7 ± 4.2 ms, p = 0.002; 58.4 ± 4.5−71.7 ± 5.8 ms, p = 0.002 and 3.00 ± 0.07 −3.17 ± 0.07 ms^2, p = 0.003, respectively). No significant differences in LF (log), HFnu, LFnu and LF/HF ratio. SDNN, RMSSD, HF(log), LF (log) and HFnu significantly decreased and LFnu and LF/HF ratio significantly increased after the stress test. When compared to the baseline control group, significant differences appeared in SDNN, RMSSD and HF(log) after intervention.
Blüher et al., 2015 [37]	UCT Children n = 31 (17 ♀) 11.2 ± 0.5 years 28.0 ± 0.8 kg/m^2	KLAKS program (diet, exercise and lifestyle counselling) 1 year	RMSSD LF; HF LF/HF Pupil diameter in darkness Pupil latency Relative reflex amplitude Constriction and Re-dilation velocity (HRV measured in 30)	−0.7%	RMSSD and LF (ln) increased from 43.5 ± 4.3 to 46.8 ± 4.0 ms, p = 0.4 and 1.45 ± 0.15 to 1.53 ± 0.16, p = 0.7, respectively. No significant differences in LF/HF(ln) and HF(ln). Pupillary constriction velocity, relative reflex amplitude and re-dilation velocity increased after intervention (4.97 ± 0.17−5.47 ± 0.18 mm/s, p < 0.001; 23.4 ± 1.1−26.3 ± 1.1; p = 0.004; 1.50 ± 0.07 −1.72 ± 0.07 mm/s; p = 0.008, respectively).
Straznicky N et al., 2015 [29]	CCT Diet group n = 17 (10 ♀) 55.0 ± 1.0 years 33.9 ± 1.7 kg/m^2 Control group n = 17 (7 ♀) 56.0 ± 1.0 years 32.8 ± 0.9 kg/m^2	Hypocaloric/DASH diet (25% prot, 30% fat and 45% carb) and increase physical activity (walk briskly for 30 min, at least 5 days per week) 16 weeks	MSNA BRS NA-SR	−8%	MSNA burst frequency and incidence decreased by 7 ± 3 bursts/min and 9 ± 5 bursts/100 beats, respectively, but did not differ from controls. NA-SR decreased by 14 ± 8% after intervention and BRS increased, but did not differ from controls.
Wijngaarden MA et al., 2013 [45]	UCT n = 12 (10 ♀) 30.0 ± 3.0 years 35.2 ± 1.2 kg/m^2	Weight-loss program with high protein low-calorie diet 8 weeks	HF LF LF/HF	−12.3%	LF increased from 755 (22−2846) to 1002 (168−4472) ms^2, p = 0.12. LF/HF increased from 0.73 (0.10−2.11) to 1.01 (0.12−2.71); p = 0.07. No significant changes in HF[b]
Sales A et al., 2012 [35]	UCT 19 ♀ Pre-hypertensive group (PTH) n = 9 39.0 ± 6.0 years 27.4 ± 2.8 kg/m^2 Normotensive group (NT) n = 10 35.0 ± 11.0 years 5.3 ± 1.7 kg/m^2	Hypocaloric diet (500 kcal/day restriction; 50−60% carb, 15 −20% prot, and <30% fat) and exercise (aerobic and resistance) 12 weeks.	SDNN TP HF LF HFnu LFnu LF/HF BRS	PTH −6.9% NT −3.2%	SDNN at baseline was lower in PTH than NT (41 ± 18 ms in PHT vs. 60 ± 19 ms in NT; p < 0.05). HF, LF and TP increased after intervention in both groups, however no significant difference was seen in comparison with baseline or between groups. SDNN increased from 41 ± 18 to 51 ± 18 ms in PHT vs. 60 ± 19 to 66 ± 22 ms in NT, but neither significantly changed versus baseline. BRS increased from 9.2 ± 3.3 to 14.8 ± 3.9 ms/mmHg in PHT (p > 0.05).
Straznicky et al., 2011 [47]	UCT Diet group (DG) n = 8 (2 ♀) 54.0 ± 2.0 years 30.6 ± 1.4 kg/m^2 Diet + exercise group (DEG) n = 10 (2 ♀) 52.0 ± 1.0 years 31.2 ± 1.1 kg/m^2	Diet/DASH (597 kcal restriction; 22% prot, 30% fat, 48% carb). Exercise (bicycle riding on alternate days for 40 min/session). 12 weeks 16 weeks (weight maintenance)	MSNA burst incidence NA-SR BRS (outcomes assessed in 11 paired participants, 4 DG and 7 DEG).	DG −7.2% DEG −11.9%	MSNA incidence decreased by 25 ± 3 bursts/100 heartbeats (p < 0.001) after weight loss and rebounded after weight maintenance (20 ± 5 bursts/100 heartbeats, p = 0.0003). NA-SR decreased by 23.0 ± 7.2% at 12 weeks (p < 0.01 vs. baseline) and this decrease was maintained at 7 months (−28.6 ± 7.8%, p < 0.01 vs. baseline). BRS increased by 5.2 ± 2.2 ms/mmHg at 12 weeks (p = 0.005), but rebounded at 16 weeks to 2.7 ± 1.3 ms/mmHg (p = 0.01 vs. baseline). There were no significant differences between interventions.
Abbas A et al., 2010 [32]	UCT 29 African American ♂ group n = 12 33.2 ± 1.5 years	Hypocaloric diet (57% carb, 20% fats, and 23% prot) ♀ 1100 kcal/day;	MSNA burst frequency MSNA burst incidence BRS	♂ −11.3% ♀ −8.8%	MSNA burst frequency reduced from 22 ± 2 to 13 ± 3 bursts/min in ♀, p = 0.006, vs. 26 ± 4 to 28 ± 3 bursts/min in ♂, p = 0.57. MSNA burst incidence reduced from 31 ± 4 to 20 ± 4 bursts/100 heartbeats in ♀, p = 0.02, vs. 42 ± 6 to 45 ± 5 bursts/100 heartbeats in ♂,

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Table 1 (*continued*)

Reference	Study design and participants	Intervention	Outcome measure	Change in BMI	Results
	32.6 ± 1.1 kg/m^2 ♀ group n = 9 32.5 ± 1.7 years 32.9 ± 1.7 kg/m^2	♂ 1700 kcal/day 16 weeks			p = 0.31[c] No significant changes in BRS in both genders.
Prado D et al., 2010 [40]	UCT Children Diet group (DG) n = 15 10.2 ± 0.3 years 30.6 ± 1.3 kg/m^2 Diet & exercise group (DEG) n = 18 10.3 ± 0.2 years 29.0 ± 0.8 kg/m^2	Hypocaloric diet (65% carb, 15% prot, 20% fat) Exercise training (60-min aerobic sessions 3/week) for 4 months.	HF LF HFnu LFnu •LF/HF Heart rate recovery at 1 min (difference between heart rate at peak exercise and at 1 min post exercise) (ΔHRR1)	DG −10.5% DEG −13.1%	LF, LFnu and LF/HF decreased after the intervention in the DEG group (p < 0.05), with larger decreases in the DEG group vs. DG group (p < 0.05). HF and HFnu increased after the intervention in DEG (p < 0.05), with significantly larger increases in DEG group vs. DG group (p < 0.05).
Drbošalová V et al., 2010 [36]	UCT 43.2 ± 9.3 years Diet (DG) n = 10 ♀ 31.9 ± 2.8 kg/m^2 Diet & Exercise (DEG) n = 9♀ 33.4 ± 4.1 kg/m^2	DG vs. DEG 10 weeks.	HF LF VLF	DG −6.9% DEG −8.1%	LF increased after intervention (242.3 ± 154.2−400.3 ± 197.0 ms^2 in DEG, p = 0.03 and 229.1 ± 159.3−303.1 ± 339.0 ms^2 in DG, p = 0.375). No significant changes in VLF or HF with each intervention. There were no significant differences between groups.
Fujibayashi et al., 2009 [48]	UCT 28 ♀ 49.8 ± 1.6 years 28.3 ± 3.2 kg/m^2	Diet (1200 kcal/day) 8 weeks	TP HF LF VLF	−6.7%	There were no significant differences after the intervention in TP, HF, LF or VLF[b]
Straznicky N et al., 2009 [51]	UCT n = 34 (13 ♀) 55.0 ± 1.0 years 31.6 ± 0.6 kg/m^2	DASH diet (reduction 600 kcal/day, 30% fat, 48% carb, 23% prot) Exercise (30−40 min of aerobic cycling on alternate days) 12 weeks	NA-SR (included results from both exercise and diet group, exercise training was done in 16 participants)	−8.2 kg	NA-SR decreased by 126.0 ± 31.0 ng/min after intervention (p < 0.01).
Kaufman C et al., 2008 [33]	UCT Overweight children n = 15 (9 ♀) 11.4 ± 0.5 years 6.8 ± 4.4 kg/m^2	Shapedown program® (Diet, exercise, behaviour intervention) 5 months	SDNN RMSSD HFnu; LFnu LF/HF (3 drop-outs)	−5.6%	SDNN increased from 90 ± 29 to 98 ± 30 ms, p = 0.35. RMSSD increased from 68.5 ± 28.1 to 113.3 ± 44.0 ms, p = 0.003. HFnu increased from 46.3 ± 9.5 to 57.6 ± 21.2, p = 0.05. LFnu decreased from 53.7 ± 9.5 to 42.4 ± 21.2, p = 0.05. LF/HF decreased from 1.3 ± 0.7 to 0.7 ± 0.5, p = 0.01[c]
Ishii K et al., 2006 [38]	UCT 10 ♀ 22.3 ± 2.6 years 24.5 ± 1.1 kg/m^2	Exercise on a cycle ergometer ≥ 30 min, ≥3 times/week. 12 weeks	TP HF LF	−2.8%	HRV data was available for 8 subjects. No differences in TP, LF or HF after the intervention[c]
Alvarez G et al., 2005 [49]	UCT[d] Old obese (OB-O) n = 6 ♂ 60.0 ± 2.7 years 28.9 ± 1.1 kg/m^2 Obese young (OB-Y) n = 10♂ 32.9 ± 2.3 years 30.4 ± 1.0 kg/m^2 Normal weight (NW) n = 13 ♂ 21.1 ± 1.0 years 21.5 ± 0.5 kg/m^2	Diet (reduce intake by 500 −800 kcal/day; 55−60% carbohydrates, 20−25% fat, and 15−20% protein) 3 months	BRS	OB-O −2.8% OB-Y −7.9%	At baseline, BRS was ≈35 and ≈60% lower in OB-Y and OB-O compared with NW and higher in OB-Y compared with the OB-O group (11.5 ± 1.9 vs. 6.7 ± 1.2 vs. 17.5 ± 2.2 ms/mmHg, p < 0.05). BRS increased with weight loss to 18.5 ± 2.6 and to 12.8 ± 4.2 ms/mmHg in the OB-Y and OB-O (p < 0.05), respectively. After intervention, BRS in OB-Y and OB-O was ≈105% and ≈75% of the observed in normal individuals.
Trombetta et al., 2003 [30]	CCT Diet (DG) n = 24 ♀ 32.2 ± 1.4 years 34.7 ± 0.5 kg/m^2 Diet & Exercise (DEG)	Diet (energy intake reduced by 600 kcal/day; 50−70% carb, 10 −15% prot; 15−30% fat). Exercise (30−40 min aerobic cycling; 20 resistance and	MSNA burst frequency MSNA burst incidence (assessed at rest and during mild or moderate handgrip exercise)	DG −10.1% DEG −10.3%	MSNA burst frequency decreased after intervention in DG and DEG (37 ± 1−29 ± 1 and 37 ± 1−29 ± 1 bursts/min, p < 0.05 for both, respectively). MSNA incidence decreased after intervention in DG and DEG (53 ± 2 −44 ± 2 and 56 ± 2−45 ± 2 bursts/100 heartbeats; p < 0.05 for both,

	n = 25♀ 32.3 ± 1.4 years 32.9 ± 0.4 kg/m^2 Control group n = 10 34.9 ± 2.1 years 33.1 ± 0.8 kg/m^2	flexibility 3 times/week). 16 weeks			respectively).These changes were significant when compared with non-adherent group. During mild and moderate handgrip exercise, there was a reduction of MSNA response after diet or diet and exercise interventions.
Esposito K et al., 2003 [46]	UCT[d] 71 ♀ premenopausal 34.4 ± 5.1 years 37.4 ± 2.6 kg/m^2 Control 28 ♀ premenopausal 34.5 ± 4.7 years 23 ± 2.0 kg/m^2	Diet (1300 kcal/day), exercise (1-h walk three times a week), behavioural and nutritional counselling 1 year	HF LF LF/HF	−13.4%	HF(ln) increased from 5.6 ± 1.3 to 6.1 ± 1.1, p < 0.05. LF/HF ratio decreased from 0.97 ± 0.3 to 0.85 ± 0.2, p < 0.01. LF (ln) did not change significantly (5.3 ± 1.1 to 5.2 ± 1.6)[c]
Poirier P et al., 2003 [42]	UCT n = 8 (6 ♀) Between 18 and 50 years 45.4 ± 6.8 kg/m^2	1st Hypocaloric diet (1000 −1500 kcal/d) 12 weeks 2nd Weight maintenance (1500 −2500 kcal/d) 12 weeks 3rd Cross over High Carb (HC) (60% carb, 25% fat, 15% prot) vs. High Fat diet (HIF) (30% carb, 55% fat, 15% prot) 2 weeks Washout 4–6 weeks	SDNN RMSSD HF LF VLF LF/HF	HC −10.1% HIF −10.8%	SDNN increased from 116 ± 32 ms to 152 ± 31, p < 0.001, with HC, versus 145 ± 36, p < 0.01 with HIF. RMSSD increased only with HC (p < 0.01). HF increased after both HC and HIF (p < 0.01 and p < 0.05, respectively). LF increased from 6.0 ± 0.8 to 6.9 ± 1.0 ms^2, p < 0.01 with HC versus 6.6 ± 0.9, p < 0.05 with HIF. VLF increased from 6.7 ± 0.7 to 7.4 ± 0.6 ms^2, p < 0.001 with HC, versus 7.2 ± 0.7, p < 0.01 with HIF. LF/HF did not change significantly with both HC and HIF[d]
Emdin M et al., 2001 [41]	UCT n = 9 (2 ♀) 35 ± 3 years 31.6 ± 1.2 kg/m^2	Hypocaloric diet (1170.3 kcal/day; 55% carb, 25% fat, 20% prot) 8 ± 1 weeks and 4 weeks of weight maintenance	LF LF/HF	−11.8%	LF increased from 608 ± 420 to 824 ± 799 ms^2, p < 0.05. LF/HF ratio was not significantly changed.
Akehi Y et al., 2001 [50]	UCT n = 16 (14 ♀) 47 ± 3 years 31.4 ± 1.1 kg/m^2	Weight-maintenance (1600–2000 kcal/day) 5 d Very-low-calorie conventional Japanese diet (VLCD-CJ): 1200, 1000, 700 kcal/day (3 days' intervals) 380 kcal/day 14 days 700,1000, 1200 kcal/day (3 days' intervals)	SDNN RMSSD HF LF LF/HF ratio	−18.5%	SDNN increased from 143 ± 10 to 184 ± 9 ms, p < 0.01. RMSSD increased from 27 ± 2 to 38 ± 4 ms, p < 0.01. HF increased from 12 ± 1 to 16 ± 2 ms^2, p < 0.01. LF increased from 21 ± 2 to 24 ± 2 ms^2, p < 0.01. LF/HF ratio decreased from 1.9 ± 0.1 to 1.5 ± 0.1, p < 0.01. Correlation between reduction rate in BMI and change in SDNN (r = 0.750, p = 0.001), RMSSD (r = 0.610, p = 0.012) and HF (r = 0.623, p = 0.010).
Yamamoto K et al., 2000 [27]	CCT Endurance group n = 7 ♂ 21 ± 1 years 72.5 ± 10.4 kg Control group n = 5♂ 22 ± 1 years 65.4 ± 6.5 kg	Cycle-endurance training 6 weeks	SDNN TP HF LF LF/HF (at rest and after exercise challenge)	−2.5%	LF/HF(ln) at rest decreased after intervention (p = 0.09), as well as the response to exercise challenge. HF(ln) and SDNN at rest increased after one week and kept significantly higher than baseline during follow-up, but stable from the 1st to 6th week. No differences in exercise challenge response. TP increased at rest one week after intervention (5.99 ± 0.33 to 6.63 ± 0.28 ms^2, p < 0.05) and slightly increased during follow-up (not significant).
Amano M et al., 2000 [39]	UCT n = 18 (9 ♀) 41.6 ± 1.2 years 27.3 ± 0.4 kg/m^2	Aerobic exercise training cycle-ergometer (30 min/session; 3 times/week) 12 weeks	TP HF LF	−5.1%	LF increased from 348.5 ± 66.8 to 694.7 ± 91.5 ms^2, p < 0.01. HF increased from 146.3 ± 30.4 to 347.7 ± 96.5 ms^2, p < 0.05. TP increased from 494.8 ± 88.5 vs. 1042.4 ± 180.9 ms^2, p < 0.01.
Grassi G et al., 1998 [25]	CCT n = 20 (6 ♀) Diet group n = 10 29.3 ± 3.0 years 38.1 ± 1.0 kg/m^2 Control group n = 10 33.2 ± 3.3 years 37.2 ± 1.3 kg/m^2	Hypocaloric diet (50% carb, 25% fats, and 25% prot with 1099 −1195 kcal) vs. unchanged diet 16 weeks	MSNA burst incidence BRS	−12.6%	MSNA burst incidence decreased from 50.0 ± 5.1 to 32.9 ± 4.6 bursts/100 heartbeats, p < 0.01. BRS modulation for heart rate increased 71.5 ± 11%, p < 0.01, after hypocaloric diet BRS modulation of MSNA increased 124.5 ± 22%, p < 0.001, after hypocaloric diet. Changes in MSNA burst incidence correlated with BMI reduction (r = 0.68, p < 0.05) and body weight reduction (r = 0.65, p < 0.05).

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Table 1 (*continued*)

Reference	Study design and participants	Intervention	Outcome measure	Change in BMI	Results
Seals D et al., 1989 [31]	CCT Exercise group n = 11 ♂ 53 ± 2 years 81.2 ± 3.5 kg Control group n = 8 ♂ 54 ± 3 years 84.0 ± 4.4 kg	Endurance exercise 30 weeks (walked/jogged first 14 weeks 3.0 days/week, 33 min/day at 68% of heart rate reserve (HRR), then for 16 weeks jogged 4 days/week for 43 min/day at 81% of their HRR).	BRS	−3.1%[a]	BRS did not differ between groups after intervention.
Weight gain					
Hu M et al., 2009 [28]	CCT Training group (TG) n = 52 ♂ 32.2 ± 7.2 years 1.5 ± 10.2 kg. Control group (CG) n = 22 ♂ 31.0 ± 7.5 years 79.4 ± 9.7 kg.	Strength training 10 weeks Two sets training groups (n = 26 + 26) differed in training facilities (same training volume and intensity)	SD1 SD1nu (assessed during exercise challenge)	+0.8%	Only 48 subjects in TG and 21 in CG completed the intervention. Average SD1 and SD1nu, measured at 100 W in $V0_2$ max test, increased significantly in TG in comparison with the CG after intervention ($p < 0.05$).
Gentile C et al., 2007 [44]	UCT 12 ♂ 23 ± 2 years 23.8 ± 0.7 kg/m^2	Overfed using a liquid dietary supplement of more 1000 kcal/day 6–8 weeks until a 5-kg weight gain	MSNA burst frequency MSNA burst incidence	+6.7%	MSNA burst frequency increased from 32 ± 2 to 38 ± 2 bursts/min, $p = 0.002$. MSNA burst incidence increased from 52 ± 4 to 59 ± 3 bursts/100 beats, $p = 0.026$. ΔMSNA burst frequency and burst incidence correlated with Δ body weight (%) ($r = 0.59$, $p = 0.022$), and ($r = 0.56$, $p = 0.029$), respectively.
Weight gain followed by weight loss					
Müller M et al., 2015 [43]	UCT 32 ♂ 20 to 37 years 77.7 ± 7.6 kg	10-week normal diet 1 week of overfeeding (4059 ± 52 kcal/d), 3 weeks caloric restriction (1353 ± 154 kcal/d) 2 weeks of refeeding (4059 ± 452 kcal/d).	SDNN RMSDD LF HF LF/HF	Overfeeding[a] +2.3% Restriction −7.6% Refeeding +4.8%	HF increased during caloric restriction vs. overfeeding Δ 436 ± 757 ms^2, $p < 0.05$. LF/HF ratio decreased during restriction vs. baseline or overfeeding (Δ-1.01 ± 1.197; Δ-1.27 ± 1.350, $p < 0.001$, respectively), after refeeding it increased (Δ1.53 ± 1.458, $p < 0.001$). RMSSD and SDNN increased during caloric restriction vs. overfeeding (Δ19.38 ± 20.73 ms and Δ10.87 ± 10.67 ms, $p < 0.001$, respectively). During the initial overfeeding period RMSDD and SDNN decreased (Δ-14.08 ± 14.39 ms, $p < 0.001$ and Δ −10.72 ± 18.71 ms, $p < 0.05$, respectively), similar results occur during overfeeding (Δ-14.58 ± 16.32 and Δ-23.26 ± 22.61, $p < 0.001$).
Adachi T et al., 2011 [26]	CCT n = 36 (14 ♀) 29.6 ± 1.3 years Weight gainer group (WGG) n = 20 29.7 ± 1.4 years 24.4 ± 0.9 kg/m^2 Weight maintainer group (WMG) n = 16 29.6 ± 2.3 years 24.2 ± 0.9 kg/m^2	Diet (40% carb, 40% fat, and 20% prot) WGG received more 1000 kcal/day for 8 weeks then a supervised diet for 8 weeks to weight reduction. WMG kept same diet	HFnu LFnu LF/HF (measured during wakefulness, non-REM sleep and REM sleep)	+5.3% −4.7% (return baseline weight)	During wakefulness, HFnu significantly decreased after weight gain (0.39 ± 0.03–0.31 ± 0.03) and increased after weight loss (0.31 ± 0.03 −0.38 ± 0.04)0. LFnu and LF/HF increased after weight gain (0.61 ± 0.03 to 0.69 ± 0.03, $p < 0.016$; (2.00 ± 0.32–2.99 ± 0.43, $p < 0.016$) and decreased after weigh loss (0.69 ± 0.03–0.62 ± 0.03, $p < 0.016$; 2.99 ± 0.43–2.39 ± 0.53, $p < 0.016$). During REM sleep, HFnu decreased with weight gain (0.29 ± 0.03 −0.23 ± 0.02, $p < 0.016$) and increased after weight loss (0.23 ± 0.02 −0.29 ± 0.02, $p < 0.016$). LF/HF decreased after weight loss (4.16 ± 0.48–2.95 ± 0.46, $p < 0.016$).

Data is expressed in mean ± SEM, except if otherwise specified.
BRS – Baroreflex sensitivity | CCT – Controlled clinical trial (control group followed throughout the time of the intervention) | UCT – uncontrolled clinical trial | DASH – Dietary Approaches to Stop Hypertension | KLAKS program – Concept Leipzig: Adiposity therapy for school-aged children program | HRR – Heart rate recovery | HF – High Frequency | HRV – Heart rate variability | LF – Low frequency | MSNA – Muscle sympathetic nerve activity | NA-SR – Noradrenaline spillover rate | RMSSD – Root mean square of successive differences | SD1 – Standard deviation of instantaneous beat-to-beat R–R interval variability | nu – normalized units | SD1nu – Standard deviation of instantaneous beat-to-beat R–R interval variability normalized | SDNN – Standard deviation of normal-to-normal intervals TP – Total Power | VLF – Very low frequency | (ln) – values underwent logarithmic transformation.

[a] Percentage referring to weight variation.
[b] Data expressed in median (range.)
[c] Data expressed in mean ± standard deviation.
[d] Control group measured at baseline.

Table 2
GRADE profile for studies evaluating the effects of weight loss in autonomic nervous system activity.

Question: Should weight loss be used for the modulation of autonomic system activity?										
Quality assessment							Summary of findings			
Participants (studies) follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With control	With weight loss		Risk with control	Risk difference with weight loss (95% CI)
LF/HF ratio (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by several methods[f]; Better indicated by lower values)										
RCT										
48 (2 studies[a]) 8 weeks	Serious[b]	Serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,c,d] due to risk of bias, inconsistency, imprecision	21	27	–	Not pooled	Not pooled[e]
Observational										
361 (11 studies[g]) 26 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	55	295	–	–	–
LF in normalized units (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by several methods[f]; Better indicated by lower values)										
RCT										
36 (1 study[a]) 8 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊕⊖⊖ **LOW**[a,d,i,j] due to imprecision	16	20	–	The mean LF in normalized units in the control groups was **−0.010 n.u.**	The mean LF in normalized units in the intervention groups was **0.07 lower** (0.0892 −0.0508 lower)[j]
Observational										
159 (4 studies[k]) 26 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	27	126	–	–	–
HF in normalized units (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by several methods[f]; Better indicated by higher values)										
RCT										
36 (1 study[a]) 8 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊕⊖⊖ **LOW**[d,i] due to imprecision	16	20	–	The mean HF in normalized units in the control groups was **−0.010 n.u.**	The mean HF in normalized units in the intervention groups was **0.070 higher** (0.0474 −0.0926 higher)[s]
Observational										
159 (4 studies[k]) 26 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	27	126	–	–	–
Very low frequency (OBS) (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by several methods[l]; Better indicated by lower values)										
55 (3 studies[m]) 15 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	–	47	–	–	–
Low frequency (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by several methods[f]; Better indicated by lower values)										
RCT										
12 (1 study[n]) 6 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊕⊖⊖ **LOW**[d,i] due to imprecision	5	7	–	–	–
Observational										
396 (14 studies[o]) 22 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	55	356	–	–	–
High frequency (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by several methods[f]; Better indicated by higher values)										
RCT										
12 (1 study[n]) 6 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊕⊖⊖ **LOW**[d,i] due to imprecision	5	7	–	The mean HF in the control groups was **−0.05 ms²**	The mean HF in the intervention groups was **1.300 higher** (0.876–1.172 higher)[p]
Observational										
	Serious[h]	Very serious[c]		Very serious[d]	Undetected		55	347	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Question: Should weight loss be used for the modulation of autonomic system activity?										
Quality assessment							Summary of findings			
Participants (studies) follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With control	With weight loss		Risk with control	Risk difference with weight loss (95% CI)
387 (13 studies[q]) 21 weeks			No serious indirectness			⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision					
Total power (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by ECG, except by Amano et al. [39] which used a bedside monitor; Better indicated by higher values)											
RCT											
12 (1 study[o]) 6 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	⊕⊕⊖⊖ **LOW**[d] due to imprecision	5	7	–	–	The mean TP in the intervention group was **0.860 higher** (0.524 −1.196 higher)[p]
Observational											
73 (4 studies[r]) 11 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	–	73	–	–	–
Standard deviation of normal to normal intervals (CRITICAL OUTCOME; measured with: RR intervals collected by several methods[f]; Better indicated by higher values)											
RCT											
31 (2 studies[s]) 18 weeks	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,d,t] due to risk of bias, imprecision	13	18	–	–	The mean Standard deviation of normal to normal intervals in the intervention groups was **14.32 higher** (4.31 lower to 32.96 higher)
Observational											
167 (6 studies[u]) 18 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	27	140	–	–	–
Root mean square of successive differences (OBS) (CRITICAL OUTCOME; measured with: RR intervals collected by several methods[f]; Better indicated by higher values)											
178 (6 studies[v]) 24 weeks	Serious[h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h] due to risk of bias, inconsistency, imprecision	27	152	–	–	–
MSNA burst frequency (CRITICAL OUTCOME; measured with: Data collected by microneurography in the peroneal nerve.; Better indicated by lower values)											
RCT											
92 (3 studies[w]) 16 weeks	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,d] due to risk of bias, imprecision	27	66	–	–	The mean MSNA burst frequency in the intervention groups was **5.09 lower** (8.42 −1.75 lower)
Observational											
29 (1 study[x]) 16 weeks	Serious[h]	Serious[p]	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊖⊖⊖ **VERY LOW**[h,i,d] due to risk of bias, inconsistency, imprecision	–	21	–	–	–
MSNA burst incidence (CRITICAL OUTCOME; measured with: Data collected by microneurography in the peroneal nerve.; Better indicated by lower values)											
RCT											
112 (4 studies[y]) 16 weeks	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,d] due to risk of bias, imprecision	37	76	–	–	The mean MSNA burst incidence in the intervention groups was **6.66 lower** (12.4 −0.92 lower)
Observational											
40 (2 studies[z]) 23 weeks	Serious[h,aa]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[c,d,h,aa] due to risk of bias, inconsistency, imprecision	–	32[aa]	–	–	–

Noradrenaline spillover rate (CRITICAL OUTCOME; measured by subtracting the clearance of radiolabelled NA from plasma NA values; Better indicated by lower values)											
RCT											
34 (1 study[ab]) 16 weeks	Serious[b]	No serious inconsistency[i]	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊖⊖⊖ **VERY LOW**[d,i] due to risk of bias, imprecision	17	17	–	The mean Noradrenaline spillover rate in the control groups was −**21 ng/min**	The mean Noradrenaline spillover rate in the intervention groups was **176 lower** (361.3 lower to 9.3 higher)
Observational											
34 (2 studies[ac]) 21 weeks	Very serious[b]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,c,d,ad] due to risk of bias, inconsistency, imprecision	–	34[ad]	–	–	–
Baroreflex sensitivity (CRITICAL OUTCOME; measured with: Calculated by different methods[ae]; Better indicated by higher values)											
RCT											
73 (3 studies[af]) 21 weeks	Serious[b]	Serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,c,d] due to risk of bias, inconsistency, imprecision	35	38	–	–	–
Observational											
95 (4 studies[ag]) 17.72 weeks	Serious[b,h]	Very serious[c]	No serious indirectness	Very serious[d]	Undetected	⊕⊖⊖⊖ **VERY LOW**[b,c,d,h] due to risk of bias, inconsistency, imprecision	13	74	–	–	–
Pupillometry parameters (OBS) (CRITICAL OUTCOME; measured with: redilation velocity, constriction velocity, relative light reflex amplitude and pupil latency)											
30 (1 study[ah]) 52.14 weeks	Serious[b,h]	Very serious[i]	No serious indirectness	Very serious[d]	Undetected[i]	⊕⊖⊖⊖ **VERY LOW**[b,d,h,i] due to risk of bias, inconsistency, imprecision	–	31	–	–	–

HF – High frequency, LF – Low frequency, LF/HF ratio – Low frequency/High frequency ratio, MSNA – Muscle sympathetic nerve activity, OBS – Observational studies, RCT – Randomized clinical trial.

[a] Different interventions. Hypocaloric diet [26] (only one presenting in normalized units) and accounted for 8 weeks of weight loss and exercise (endurance training) [27].

[b] Lack of allocation concealment [25,29,32,35,49]. Incomplete accounting of patients in Nora E. Straznicky et al., 2015 [29] (paired measurements were presented for 13/17 of the intervention group and 10/17 of the control group). N. E. Straznicky et al., 2011 [47] included 18 of the 34 participants of N. E. Straznicky et al., 2009 [51] (repeated participants in both studies).

[c] Different populations and interventions characteristics or used different study designs.

[d] Different populations and interventions, small population size, large 95% confidence interval with no effect.

[e] Not possible to calculate estimate of effect due to Yamamoto et al., 2001 [27] presented values after logarithmic transformation.

[f] All studies collected outcome data from measurements made through ECG, except Müller et al., 2005 [43] and Amano et al., 2001 [39], which used a bedside monitor and Poirier et al., 2003 [42], Esposito et al., 2003 [46] and Akehi et al., 2001 [50], which used a Holter.

[g] Hypocaloric diet [33,34,41–43,45,46,50] | Hypocaloric diet and exercise [35,37,40].

[h] Uncontrolled trials, comparison with control group only at baseline, selected populations for comparison [47].

[i] Single study.

[j] Calculated with different follow up periods controls versus intervention (where only weight loss period was assessed).

[k] Hypocaloric diet [33,34] | Hypocaloric diet and exercise [35,40].

[l] All studies collected outcome data from measurements made through ECG, except Poirier et al. [42] which used a Holter recording device.

[m] Hypocaloric diet [42,48] | Hypocaloric diet and exercise [36].

[n] Exercise (endurance training) [27].

[o] Hypocaloric diet [34,41–43,45,46,48,50]; Hypocaloric diet and exercise [35–37,40] | Exercise (aerobic training) [39] | Exercise (strength training) [38].

[p] Values from logarithmic transformation were presented, driven from graphical presented data.

[q] Hypocaloric diet [34,42,43,45,46,48,50] | Hypocaloric diet and exercise [35–37,40] | Exercise (aerobic training) [39] | Exercise (strength training) [38].

[r] Hypocaloric diet [48] | Hypocaloric diet and exercise [35] | Exercise (aerobic training) [39] | Exercise (strength training) [38].

[s] Exercise (endurance training) [27,31].

[t] Heterogeneity: $P > 0.05$; $I2 = 0\%$.

[u] Hypocaloric diet [33,34,42,43,50] | Hypocaloric diet and exercise – [35].

[v] Hypocaloric diet [33,34,42,43,50] | Hypocaloric diet and exercise [37].

[w] Hypocaloric diet [29,30] | Hypocaloric diet and exercise [30] (data split accordingly to each arm intervention).

[x] Hypocaloric diet [32].

[y] Hypocaloric diet [25,29,30] | Hypocaloric diet and exercise [30] (data split accordingly to each arm intervention).

[z] Hypocaloric diet [32] | Hypocaloric diet and exercise [47].

[aa] In Straznicky et al., 2011 [47], paired MSNA was performed in 11 subjects of total population (n = 18), only 11 were included in intervention group.

[ab] Hypocaloric diet [29].

[ac] Hypocaloric diet and exercise (aerobic) [47,51].

[ad] N. E. Straznicky et al., 2011 [47] included 18 of the 34 participants of N. E. Straznicky et al., 2009 [51]. In N. E. Straznicky et al., 2009, 16 of the 34 participants also participated in an exercise program. The study was originally designed as a RCT, but all participants were subsequently pooled because dietary weight loss and dietary weight loss plus exercise resulted in similar lowering of whole-body noradrenaline spillover rate.

[ae] Phenylephrine and nitroprusside method [25,32,49] | Sequence method [29] | Neck suction and pressure method [31] | Alpha coefficient method [35] | Sequence method [4].

[af] Hypocaloric diet [25]| Hypocaloric diet and exercise [29] | Exercise (endurance training) [31].

[ag] Hypocaloric diet [32,49] | Hypocaloric diet and exercise [35,47].

[ah] Hypocaloric diet and exercise [37].

Table 3
GRADE profile for studies evaluating the effects of weight gain in autonomic nervous system activity.

Question: Should weight gain be used for the modulation of autonomic system activity?											
Quality assessment							Summary of findings				
Participants (studies) follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With weight gain		Risk with control	Risk difference with weight gain (95% CI)
LF/HF ratio (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by ECG; Better indicated by higher values)											
RCT											
36 (1 study[a]) 8 weeks[f]	No serious risk of bias[b]	No serious inconsistency[c]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊕⊖⊖ **LOW**[b,c,d,e] due to imprecision	16	20	–	The mean LF/HF ratio in the control groups was **0.08**	The mean LF/HF ratio in the intervention groups was **0.91 higher** (0.5–1.32 higher)[g]
Observational											
32 (1 study[h]) 3 weeks[k]	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	–	32	–	–	–
LF in normalized units (RCT) (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by ECG; Better indicated by higher values)											
36 (1 study[a]) 8 weeks[f]	No serious risk of bias[b]	No serious inconsistency[c]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊕⊖⊖ **LOW**[b,c,d,e] due to imprecision	16	20	–	The mean LF in normalized units in the control groups was **0.01 n.u.**	The mean LF in normalized units in the intervention groups was **0.07 higher** (0.04–0.10 higher)[g]
HF in normalized units (RCT) (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by ECG; Better indicated by lower values)											
36 (1 study[a]) 8 weeks[f]	No serious risk of bias[b]	No serious inconsistency[c]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊕⊖⊖ **LOW**[b,c,d,e] due to imprecision	16	20	–	The mean HF in normalized units in the control groups was **−0.01 n.u.**	The mean HF in normalized units in the intervention groups was **0.07 lower** (0.10–0.04 lower)[g]
Low frequency (OBS) (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by bedside monitor; Better indicated by higher values)											
32 (1 study[h]) 3 weeks[k]	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	–	32	–	–	–
High frequency (OBS) (CRITICAL OUTCOME; measured with: Fourier transformation of RR intervals collected by bedside monitor; Better indicated by lower values)											
32 (1 study[h]) 3 weeks[k]	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	–	32	–	–	–
Standard deviation of normal to normal intervals (CRITICAL OUTCOME; measured with: RR intervals collected a wrist-top computer; Better indicated by higher values)											
RCT											
69 (1 study[l]) 10 weeks	Serious[m]	No serious inconsistency[c]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,m] due to risk of bias, imprecision	21	48	–	The mean Standard deviation of normal to normal intervals in the control groups was **−0.24 ms**.[n]	The mean Standard deviation of normal to normal intervals in the intervention groups was **0.99 higher** (0.00–0.94 higher)[n]
Observational											
32 (1 study[h]) 3 weeks[k]	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	–	32	–	–	–
Root mean square of successive differences (OBS) (CRITICAL OUTCOME; measured with: RR intervals collected by bedside monitor; Better indicated by higher values)											
32 (1 study[h]) 3 weeks[k]	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	–	32	–	–	–
MSNA burst frequency (OBS) (CRITICAL OUTCOME; measured with: Data collected by microneurography in the peroneal nerve.; Better indicated by lower values)											
20 (1 study[o]) 7 weeks	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	–	12	–	–	–

MSNA burst incidence (OBS) (CRITICAL OUTCOME; measured with: Data collected by microneurography in the peroneal nerve.; Better indicated by lower values)								
20 (1 study[o]) 7 weeks	Serious[i]	Serious[j]	No serious indirectness[d]	Very serious[e]	Undetected[c]	⊕⊖⊖⊖ **VERY LOW**[c,d,e,i,j] due to risk of bias, inconsistency, imprecision	12	–	–	–

HF – High frequency, LF – Low frequency, LF/HF ratio – Low frequency/High frequency ratio, MSNA – Muscle sympathetic nerve activity, OBS – Observational studies, RCT – Randomized clinical trial.

[a] Hypercaloric diet [26].
[b] Potential limitations (lack of allocation concealment) are unlikely to lower confidence in the estimate of effect.
[c] Single study.
[d] No sources of indirectness.
[e] Total population size is less than 400.
[f] 16 weeks in total (Hypercaloric diet with weight gain in the first 8, followed by hypocaloric diet with weight loss in the last 8 weeks). In this part, only the initial 8 weeks were taken into account.
[g] Calculated with different follow up periods controls versus intervention (where only weight gain period was assessed).
[h] Hypercaloric diet [43].
[i] No control group.
[j] Single study and observational study.
[k] 3 weeks (6 weeks in total – 1 of overfeeding, 3 of caloric restriction and 2 of refeeding). Only the week of overfeeding and the 2 weeks of refeeding were accounted here.
[l] Exercise (strength training) [28].
[m] Incomplete accounting of patients and outcome events (4 participants were excluded for inconsistent participation in the intervention and measurements and 1 participant dropped out). Potential limitations (lack of allocation concealment) are unlikely to lower confidence in the estimate of effect.
[n] Values solely presented in logarithmic transformation. Measured at 100 W exercise intensity in bicycle ergometer.
[o] Hypocaloric diet [44].

weight change (presented as relative percentage of change in weight in BMI, or when not available in kg) [5] outcomes (type, characteristics of the outcome measurement conditions and main results). In case of exclusion, the justification based on the inclusion and exclusion criteria.

2.5. Grading system and meta-analysis

Quality of evidence assessment was made in accordance to the GRADE methodology. Evidence for each outcome was classified using 5 criteria [1]: risk of bias [2], inconsistency [3], indirectness [4], imprecision, and [5] publication bias. These criteria allow the establishment of four levels of quality: high, if multiple RCTs with a low risk of bias reported consistent, generalizable results for an outcome; moderate, if one of the criteria was not met; low, if two of the criteria were not met; and very low, if three of the criteria were not met. In case of one of the outcomes was reported in a single study, data was considered sparse and the corresponding evidence classified as low. GRADE profiler software (version 3.6) was used for the analysis.

Quality of evidence is a reflection of the extent of confidence the reviewers place in an estimate of effect and whether it is adequate to support a recommendation. The GRADE system classifies the strength of the recommendation as strong or weak in accordance to the quality of the supporting evidence and the balance between desirable and undesirable outcomes [22–24].

Quantitative analysis was performed using studies of similar design and comparable outcomes and their results were pooled using a random effect model in Review Manager software (version 5.2). I^2 test was used for heterogeneity evaluation and funnel plot symmetry for the assessment of the risk of publication bias. Selective reporting bias was accessed by comparing outcomes of interest listed in the methods of each included study with the ones presented in the results.

3. Results

3.1. Studies and participants' characteristics

After a systematic literature search, 27 studies met inclusion criteria. Fig. 1 shows the flowchart of studies selection strategy. The included articles encompassed 7 controlled clinical trials [25–31], 3 of which were randomized, and 20 were observational studies [32–51]. Characteristics and results of the studies are described in Table 1. A list of the excluded studies as well as the reasons for exclusion is available in Appendix C.

The population in the evaluated studies included 787 participants (632 in the intervention groups and 155 in controls). The age ranged from 10 to 60 years, 347 were male, and three studies were conducted in children [34,37,40]. Overweight/obese represented 71% of the participants [25,29,30,32–34,36,37,39–42,45–51], nevertheless, obesity's definition differed between studies, particularly in children [34,37,40].

The studies differed in targets for intervention, four focused in weight gain [26,28,43,44] and others on weight loss [25–27,29–43,45–51]. Interventions for inducing weight changes included: hypocaloric [25,26,29,30,32–34,36,40–43,45–50] or hypercaloric diets [26,43,44]; exercise programs (strength [28,38], endurance [27,31] and an aerobic training [39]) and hypocaloric diets associated with an exercise programs (aerobic training [30,36,40,47,51], resistance and aerobic training [35] and resistance and endurance [37]). Dietary composition differed between interventions (Table 1), some applied Dietary Approach to Stop Hypertension (DASH) [29,47,51], one study focused on Japanese diet

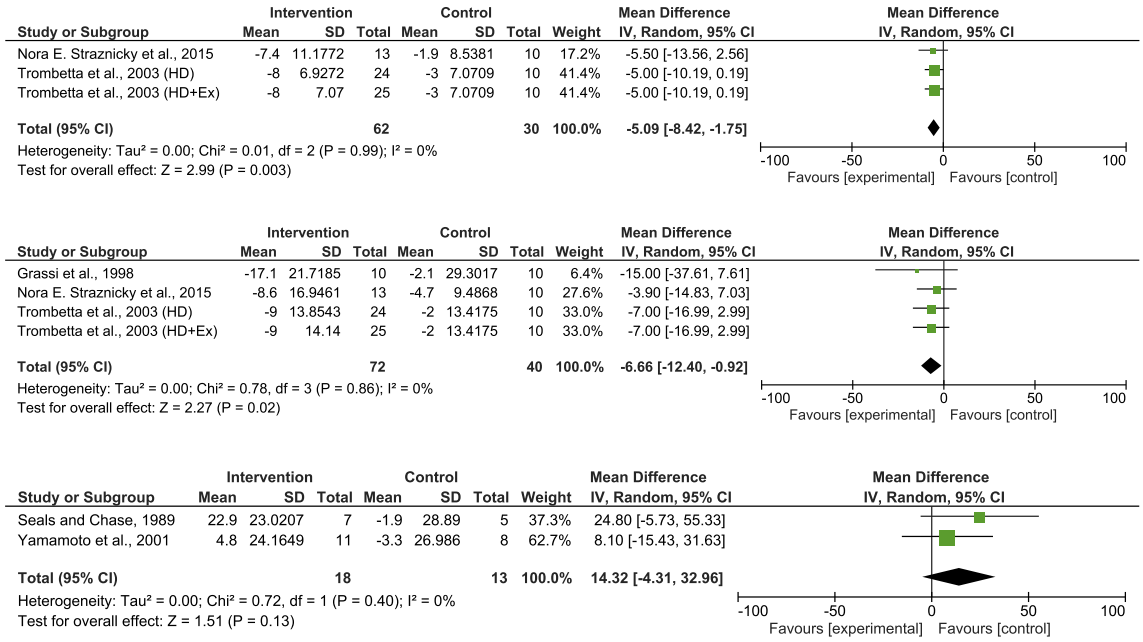

Fig. 2. Meta-analysis of muscle sympathetic nerve activity (MSNA) burst frequency (top), MSNA burst incidence (middle) and standard deviation of normal-to-normal intervals (bottom) changes with weight loss.

using a very low calorie diet [50]. In some studies, interventions included also lifestyle counselling [33,37].

Follow-up periods ranged from 1 week to 1 year. In Adachi et al. [26], a hypercaloric diet for weight increase was followed by a hypocaloric diet to reduce weight. A similar approach was taken by Mullër et al. [43], where the participants underwent 1 week of overfeeding, followed by 3 weeks of caloric restriction and 2 weeks of refeeding. Poirier et al. [42] conducted a study design where a three months' hypocaloric diet was followed by a weight-maintenance period of 3 months, followed by a high-fat diet vs. high-carbohydrate diet targeting weight-maintenance. This type of design allowed to assess both weight changes and the impact of each diet in the ANS outcomes.

HRV parameters were accessed from the RR intervals collected by ECG [26,27,31,33–38,40,45,48], using an Holter [41,42,46,50], by a bedside monitor [39,43] or by a wrist top monitor [28]. In most of the studies, periods of 5 min epochs were selected, except in two where regression from an algorithm of 24 h was used [40,41]. Another study differed between daytime and night time analysis [42]. In Hu et al. [28], measures of RR intervals were averaged for each 60 and 90 s' work load. In four studies, the epoch used wasn't specified [35,38,43,48]. HRV outcomes were determined according to the standards of measurement of HRV put forth by the Task Force of the ESC/NASPAE, 1996 [52], including Seals & Chase, 1989 [31] recommendations. However, some studies presented slight differences in the definition of the power spectrum intervals' range, particularly for the VLF outcome.

MSNA parameters were accessed by a microneurography technique with a tungsten needle in the peroneal nerve [53]. Whole-body NA-SR measured according to the isotope dilution technique [54]. BRS was accessed by: phenylephrine and nitroprusside technique [25,32,49], sequence method [29,47], α-coefficient method [35], and by the neck pressure and suction [31]. Pupillometry parameters were ascertained using a pupilometer [55].

The GRADE approach was applied to assess if weight loss had an impact on ANS activity (Table 2) or if weight increase influenced ANS (Table 3). For both questions, all the included studies had a low and very low quality of evidence.

3.2. Effects of weight loss

3.2.1. Heart rate variability

Two controlled clinical trials (CCT) [26,27] and eleven observational studies [33–35,37,40–43,45,46,50] presented data on the Low frequency/High frequency (LF/HF) ratio. Both CCTs didn't present significant differences after weight loss intervention [26,27]. Five observational studies showed decreases of the ratio after weight loss [33,42,43,46,50], which ranged from 12% [46] to 46% [33]. Prado et al. [40], compared LF/HF in a diet and exercise group vs. diet and showed a significantly larger decrease when exercise was associated, despite similar weight loss between groups. The remaining observational studies [34,35,37,41,45] did not show any significant differences. Data pooling was precluded, as outcomes were assessed in different populations and dietary interventions, using different techniques [27].

Low frequency (LF) was measured in one CCT [27] and fourteen observational studies [34–43,45,46,48,50]. Five observational studies [36,39,41,42,50] showed significant increases after weight loss. In Drbošalová et al. [36], a significant increase was only seen when diet was associated with exercise. Prado et al. [40] differed, showing a decrease in LF that was greater in the diet and exercise group in non-obese children. The remaining observational studies did not present any differences with weight loss.

One CCT [26] and four observational studies [33–35,40] measured low frequency in normalized units (LFnu). Adachi et al. [26] showed a significant decrease with weight loss with hypocaloric diet. All but one observational study [35] had a reduction of LFnu after weight loss. In Prado et al. [40], LFnu declined more in the diet and exercise group when compared with diet alone. HFnu showed similar results, though in the opposing direction. After the interventions an increase was seen in the CCT [26], and in all observational studies that assessed this outcome, except in Sales et al. [35]. Diet and exercise had a more pronounced effect [40].

Very low frequency (VLF) was evaluated in three observational studies [36,42,48]. VLF increased significantly after weight loss both in high carbohydrate or high fat diets [42].

High frequency (HF) was measured in one CCT [27], which reported a significantly increase immediately after the first week of an exercise intervention, that was kept until the end of follow-up. Of the thirteen observational studies [34–40,42,43,45,46,48,50] that assessed this outcome, seven [27,34,39–42,50] reported significant increases in HF with weight loss. This increase was more pronounced when diet was associated with an exercise program [40]. Similar results occurred for total power (TP) in the same CCT [27], where an increase was seen at day 7 and after 4 weeks of intervention. One observational study [39], reported significant increases in TP after weight loss from the four observational studies [35,38,39,48] that measured this outcome.

Standard deviation of normal-to-normal intervals (SDNN) increased with the intervention in two CCTs [27,31]. Four [34,42,43,50] out of six observational studies [33–35,42,43,50] that reported this outcome had a significant increase after weight loss.

Root mean square of successive differences (RMSSD) was reported in six observational studies [33,34,37,42,43,50], of which five showed an increase [33,34,42,43,50] that ranged from 8% [37] to 65% [33]. In Poirier et al. [42], it only increased under the high-carbohydrate maintenance diet. Mazurak et al. [34] observed a significant post-intervention group effect versus the control group. The remaining observational studies did not present any significant differences.

Several studies reported significant correlations involving changes in HRV parameters. In Ishii et al. [38] TP variation correlated negatively both with body fat and body fat ratio. In Poirier et al. [42], during daytime, after weight loss, there were positive correlations between changes in LF/HF and with both total calories and carbohydrate oxidation. Changes in both HF and RMSSD were positively correlated with the energy balance. In the high-fat diet, the authors describe a positive correlation between LF/HF and fat oxidation. In another study [48], VLF changes correlated negatively with body mass, BMI, body fat percentage, fat mass and waist circumference changes. Akehi et al. [50] reported positive correlations between the reduction rate of the BMI and ΔSDNN, ΔRMSSD and ΔHF.

3.2.2. Muscle sympathetic nerve activity

The changes of muscle sympathetic nerve activity (MSNA) parameters with weight loss were evaluated in three CCTs [25,29,30] and two observational studies [32,47].

MSNA burst frequency decreased after interventions in two CCTs [29,30], in the hypocaloric diet groups in both studies and in the hypocaloric diet associated with exercise group in Trombetta et al. [30]. One observational study [32] found a decrease after the intervention in black women, but this was not significant in black men.

MSNA burst incidence was evaluated in three CCTs [25,29,30] and in two observational studies [32,47]. MSNA showed significant decreases in all intervention groups, except in the black men group in Abbas et al. [32].

Variation of MSNA incidence with the intervention correlated positively both with Δ body weight, ΔBMI [25] and Δ abdominal fat mass [47]. The increase in the baroreflex sensitivity modulation of heart rate and MSNA was positively correlated with the MSNA reduction induced by body weight loss. In Straznicky et al. [29], a stepwise regression analysis model in the hypocaloric diet group showed that ΔBRS ($r^2 = 0.36$) and Δ body weight ($r^2 = 0.6$) were predictors of Δ MSNA incidence.

3.2.3. Noradrenaline spillover rate

Three studies accessed noradrenaline spillover rate (NA-SR), one CCT [29], and two observational studies [47,51]. Hypocaloric diet [29] did not elicit significant changes in the outcome, however in a subgroup analysis by baseline insulin status showed a significant decrease in the hyperinsulinemic subgroup (n = 7/17). In the remaining studies, NA-SR decreased significantly. A 75 g oral glucose test was performed in Straznicky et al. [51], with measurements of NA-SR at 30, 60, 90 and 120 min after ingestion. A significant decrease occurred in both hyperinsulinemic and normoinsulinemic groups, however a more intense increase in sympathetic response to glucose ingestion was seen in the hyperinsulinemic subgroup.

3.2.4. Baroreflex sensitivity and pupillometry parameters

A total of seven studies (three CCTs [25,31,51] and four observational studies [32,35,47,49]) evaluated baroreflex sensitivity (BRS). Grassi et al. [25] and Straznicky et al. [51] showed a significant increase in baroreflex modulation of heart rate and MSNA. Seals & Chase [31], showed no significant changes with the intervention. Two observational studies [47,49] reported a significant increase with weight loss.

Pupillometry parameters (pupil diameter in darkness (mm), pupil latency (s), relative reflex amplitude, constriction velocity (mm/s), re-dilation velocity (mm/s)) were accessed in Bluher et al. [37]. With the exception of pupil diameter in darkness and pupil latency, all other outcomes significantly increased with weight loss.

3.2.5. Meta-analysis

We conducted a meta-analysis for changes in SDNN, MSNA burst frequency and MSNA burst incidence with interventions resulting in weight loss (Fig. 2). Data was pooled for MSNA burst frequency [30,51], MSNA burst incidence [25,30,51] and SDNN [27,31]. Trombetta et al. [30] evaluated the effects of and hypocaloric diet alone or together with an exercise program. We considered these two interventions as separate for data pooling in MSNA burst frequency and incidence.

The meta-analysis of MSNA burst frequency and burst incidence data yielded a large overall effect and low heterogeneity in both outcomes. These results should be considered carefully as in one of the studies was also included a change in physical activity habits [51] and in one of the studies it was conducted solely in premenopausal obese women [30].

The meta-analysis of SDNN showed no significant overall effect and low heterogeneity. Follow-up periods varied from 6 to 30 weeks [27,31]. Both studies were conducted solely on males, although Yamamoto et al. included younger individuals [27]. Forest plots were visually analysed and presented no indication of publication bias.

3.3. Effects of weight gain

Two CCTs [26,28] and one observational study [43] described changes in the included variables with weight gain. Adachi et al. [26] evaluated LF/HF, LFnu and HFnu, reporting significant increases in the first two and a significant decrease in the latter during daytime, as well as a significant decrease in HFnu during REM sleep. Müller et al. [43], reported data on LF/HF, LF, HF, SDNN and RMSSD across two different periods that resulted in weight gain. SDNN and RMSSD decreased significantly in both periods and LF/HF increased significantly in the 14 days refeeding period.

A single observational study [44] described the changes of MSNA burst frequency and incidence in weight gain. Both parameters were significantly increased. The study found positive correlations between Δ MSNA burst frequency and percentage change in both body weight and body fat, as well as Δ body fat and with Δ MSNA burst incidence with body weight change.

4. Discussion

This review sheds light on the adaptations of the ANS activity occurring with diet and exercise-based weight changes. Weight loss was associated in most studies with decreases in LF/HF ratio, LFnu, MSNA burst frequency and incidence, NA-SR and with an increase of BRS, HF, HFnu, and RMSSD, pointing to sympathetic inhibition and parasympathetic activation. Weight gain, on the other side, hinted at an increase in LF/HF, LFnu, MSNA burst frequency and incidence. The weight loss effects were potentiated by the association of a hypocaloric diet with exercise program. Nevertheless, changes in these outcomes were not consistent between studies and any conclusion on the effect of weight changes on the ANS is hindered by the low and very low quality of evidence.

Our study is limited by the discrepancies found in the effect (or lack of it) of these weight changes between studies, which could be related to the studied population's characteristics, heterogeneity between the different interventions, as well as potential bias from having a large number of observational studies and a small number of controlled trials. Measurement of the ANS-related outcomes were conducted with different techniques, however, regardless of the method, a tendency towards parasympathetic hegemony with weight loss was shown. Despite the reliability of the methods used for measurement of both primary and secondary outcomes, they only provide information regarding the organ-specific ANS activity, so the results cannot be generalized, as different organs might have different regional autonomic outflows. The majority of the studies lacked control groups, possibly due to practical and ethical limitations in abstaining from a potentially beneficial intervention (diet or exercise) in a susceptible group, namely obese or participants with metabolic syndrome. The exclusion of participants with hypertension, diabetes, psychiatric or eating disorders, that could induce ANS dysfunction by mechanisms independent on weight changes, might limit the generalizability of our results to the obese with hypertension and/or diabetes as co-morbidities. Nevertheless, these criteria allowed to increase comparability between participants and to evaluate the specific effect of weight change in autonomic nervous system, without considering baseline autonomic dysfunction driven by other diseases. Still, based on limited evidence [56,57], we might infer that the reductions in sympathetic activity with weight loss could be greater in these groups.

To our knowledge, this is the first systematic review with meta-analysis detailing the effects of interventions resulting in weight change in the ANS. We have shown a specific additional effect of exercise in the ANS response to weight change. This agglomeration of data points to an important effect of weight reduction in the ANS, a potential target to reduce the development of obesity-related diseases. We have also reported improvements both with endurance and strength exercise, a deviation against the classic approach that only aerobic exercise elicited these changes. The use of the GRADE methodology for reporting the quality of the evidence of the included studies allowed to classify the evidence accordingly to its quality. The meta-analysis, despite low heterogeneity and large effects of the included few studies, had a small number of pooled participants. Therefore, results should be interpreted with caution has participants' characteristics may have an additional influence in this response.

The participants differed in gender, age, ethnicity and metabolic profile. The meta-analysis of SDNN changes with weight loss might not have achieved a significant effect due to these differences. Despite the similar exercise programs, the follow-up times were different (8–30 weeks) and the number of participants was small. Constitutive bradycardia in males and the inverse relationship between HR and HRV in this group [41] might explain the higher TP and MSNA parameters and lower vagal activity when compared to women [58]. In our review, one study reported MSNA had a higher tendency to decrease in women [32]. This may be due to gender differences in the adipose tissue distribution, greater peripheral insulin sensitivity in women and greater sympathetically-mediated vasoconstriction in men [5].

Age can also affect the response to the intervention. Similar results were found in children and young adults, except for the LF outcome in Prado et al. [40]. The divergent decrease in LF might be explained by the controversial evidence supporting it as a marker of sympathetic and parasympathetic activity and developmental changes in the ANS in children. These lifestyle interventions might have a different impact in the cardiac vagal tone in populations with lower basal vagal tone, such as older individuals, than in young healthy subjects with higher basal tone [49]. Furthermore, the degree of the weight change might influence the study's results.

Weight loss impact on the ANS might be mainly dependent on the amount of weight reduction. Those studies that did not reach a significant difference had lower BMI variation [35,37,48]. Notwithstanding, some studies [10,33] with a reduction of less than 10% of BMI had a consistent increase in parasympathetic activity. Weight loss, specifically abdominal fat loss, might be one of the major determinants of sympathetic neural adaption [47]. Fat mass, in particular visceral abdominal fat, is a strong determinant of ANS activity [59], and may explain the rebound in MSNA parameters after weight maintenance in Straznicky et al. [47]. Changes in the metabolic profile may be the main drivers in sympathetic activation with weight gain and parasympathetic tone increases with weight loss.

Hyperinsulinemia has been linked to parasympathetic withdrawal, sympathetic dominance and baroreceptor downregulation [5]. Plasma insulin and insulin resistance have been shown to decrease with weight reduction. The mechanisms and sites through which insulin increases ANS activity remain unknown [29,47]. Cytokines, such as TNF-α and IL-6, non-esterified free fatty acids, ghrelin, neuropeptide Y, melanocortins and reduced adiponectin and leptin resistance have also been suggested as possible mediators in sympathoactivation [60,61]. Increased regional sympathetic traffic induced by leptin promotes lipolysis in white adipose tissue, thermogenesis in brown adipose tissue and increase metabolic activity in liver and skeletal muscle, resulting in increased energy expenditure [5].

Cholecystokinin's response is blunted in obesity and with high fat diets [5], which might explain the increase in VLF and LF after weight loss with a high-fat diet in Poirier et al. study [42]. Incretins, such as glucagon-like peptide 1 and gastric inhibitory peptide, might act through direct modulation of ANS activity, independently of their insulin-release effects, as some studies with glucagon-like peptide 1 analogues and animal studies have suggested [5,61,62]. Reductions in the activity of the renin-angiotensin-aldosterone system and in circulating free fatty acids after weight loss are also thought to be implicated in the observed changes in ANS activity [5,63]. Several correlations backed the links between these metabolic parameters and ANS indexes [25,29,38,42,44,47,48,50].

Sympathoinhibitory and sympathoexcitatory effects induced by baroreceptor stimulation and deactivation, respectively, are impaired in metabolic syndrome [59]. The improvement in BRS, associated with an improvement in metabolic syndrome, is also a potential mechanism for explaining the decrease of MSNA after weight loss [25]. In one study [42], energy expenditure was inversely correlated with HF and RMSSD and resting metabolic rate was positively correlated with VLF. This goes into accordance with previous reports of sympathetic indexes increase, in situations of

blunted sympathetic response, possibly leading to a decreased basal metabolic rate and thermogenesis [5].

The negative energy balance, per se, might have a role in variations in ANS activity during weight changes. This has led some authors to claim that the observed changes may be smaller within periods of weight stability [29,49]. The majority of the included studies measured the outcomes of interest after either an overnight fasting or in a postprandial period, calling into question the possibility of the acute effects of a meal and fasting influencing the results [64].

Hypocaloric diet associated with exercise appeared to lead to larger improvements than hypocaloric diet alone [30,36,40,47]. MSNA burst frequency and burst incidence pooled data were shown to decrease after weight reduction. The pooled studies had slightly different follow-up periods (12–16 weeks), different dietary intervention and one of the studies included an exercise program [30]. This study had an important weight in the reported results, despite most of the included participants in the meta-analysis were submitted only to diet. The impact on ANS might be modulated by neural plastic remodelling in the paraventricular nucleus with exercise [65].

Different exercise interventions were assess including endurance [27,31], strength [28,38], and aerobic training [39]. Independently of the type of exercise these studies pointed to parasympathetic activation, including Hu et al. [28], which reported a weight increase (due to an increase in lean body mass from strength training, even though fat mass decreased significantly). The effect of exercise interventions in ANS activity is controversial. Differences in training duration, frequency and intensity, are thought to be responsible for those discrepancies [66]. Some studies report an increase in sympathetic activity during exercise and in response to other stressors that cause sympathoexcitation, including baroreceptor unloading [66].

The modulation of ANS activity by exercise is thought to be mediated by the central nervous system and peripherally modulated by baroreflexes and chemoreflexes [20,66]. Recent evidence, however, points to an altered expression of genes involved in synaptic plasticity and a role of brain-derived neuro-trophic factor and insulin-like growth factor 1 mediators [66]. Strength training effects in ANS activity are poorly studied, but current literature supports the increase in parasympathetic activity [67], even though both of the included studies reported small weight and fat mass changes. Therefore, other mechanisms might have a role in this relation, such as improvements in insulin resistance and endothelial dysfunction with exercise [66]. The increase of sympathoactivation with greater exercise intensities might be responsible for preventing the increase of SD1 and SD1n indexes in Hu et al. [28]. However in shorter term studies, no improvements in ANS were seen [27]. This may indicate different mechanisms in play in short-term and long-term exercise modulation of ANS activity.

5. Conclusion

Variations in the autonomic nervous system profile are induced by weight changes. Weight gain was associated with a sympathetic predominance, but it is uncertain whether this is due to direct sympathoactivation or, indirectly, mediated by parasympathetic inhibition. Weight loss seems to reverse this trend and lead to greater parasympathetic activity, but the same uncertainty arises. Inconsistency in the results of the existing literature may be caused by the diversity in the array of experimental designs, accessing methods as well as baseline clinical conditions. Focus on a wide population with longer follow-ups would allow a better understanding of the impact of these changes in obesity-related disease and metabolic dysfunction.

Author contributions

JC and DS contributed to study design, literature search, data selection, extraction, interpretation, and manuscript writing. AM, LD and PM contributed to study design, data interpretation and manuscript critical review.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no financial or personal conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.01.006.

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