The Impact of Exercise Training on Muscle Sympathetic Nerve Activity: A Systematic Review and Meta-Analysis

RUNNING HEAD: Exercise training on muscle sympathetic nerve activity

Sarah E. Meyer[1], Miranda Kimber[1], Lauren E. Maier[1], Brittany Matenchuk[1], Ramiah Moldenhauer[1], Stephanie de Waal[1], Allison Sivak[2], Margie H. Davenport[1], & Craig D. Steinback[1]

[1] Neurovascular Health Laboratory, Program for Pregnancy and Postpartum Health, Women and Children's Health Research Institute, Alberta Diabetes Institute, Faculty of Kinesiology, Sport, and Recreation, University of Alberta, Edmonton, Alberta, Canada.

[2]H.T. Coutts Education & Physical Education Library, University of Alberta, Edmonton, Alberta, Canada

Correspondence: Prof. Craig Steinback, PhD (steinbac@ualberta.ca).

ABSTRACT

The purpose of this systematic review and meta-analysis was to examine the effects of exercise training on muscle sympathetic nerve activity (MSNA) in humans. Studies included exercise interventions (randomized controlled trials [RCTs], non-randomized controlled trials [non-RCTs] or pre-to-post intervention) that reported on adults (≥18 years) where MSNA was directly assessed using microneurography, and relevant outcomes were assessed (MSNA [total activity, burst frequency, burst incidence, amplitude], heart rate, blood pressure [systolic blood pressure, diastolic blood pressure, or mean blood pressure], and aerobic capacity [maximal or peak oxygen consumption]). 40 intervention studies (n=1,253 individuals) were included. RCTs of exercise compared to no exercise illustrated that those randomized to the exercise intervention had a significant reduction in MSNA burst frequency and incidence compared to controls. This reduction in burst frequency was not different between individuals with cardiovascular disease compared to those without. However, the reduction in burst incidence was greater in those with cardiovascular disease (9 RCTs studies, n = 234, MD -21.08 bursts/100 hbs; 95% CI –16.51, -25.66; I^2 = 63%) compared to those without (6 RCTs, n = 192, MD -10.92 bursts/100 hbs; 95% CI -4.12, -17.73; I^2 = 76%). Meta-regression analyses demonstrated a dose-response relationship where individuals with higher burst frequency and incidence pre-intervention had a greater reduction in values post-intervention. These findings suggest that exercise training reduces muscle sympathetic nerve activity, which may be valuable for improving cardiovascular health.

Key Words: Muscle sympathetic nerve activity, exercise, physical activity, training, sympathetic nerve activity

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50 **NEW & NOTEWORTHY**

51 This systematic review and meta-analysis suggests exercise training reduces muscle sympathetic
52 nerve activity, which may be valuable for improving cardiovascular health. The reduction in
53 burst incidence was greater among individuals with cardiovascular disease when compared to
54 those without; exercise training may be particularly beneficial for individuals with
55 cardiovascular disease. Meta-regression analyses demonstrated a dose-response relationship,
56 where individuals with higher sympathetic activity pre-intervention had greater reductions in
57 sympathetic activity post-intervention.

58 **Keywords:** exercise; muscle sympathetic nerve activity; physical activity; sympathetic nerve
59 activity; training

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INTRODUCTION

Muscle sympathetic nerve activity (MSNA) is commonly elevated in chronic diseases characterized by cardiovascular dysfunction (e.g., cardiovascular disease, type 2 diabetes, obstructive sleep apnea). It has strong links to overall cardiovascular health and is a possible major contributor to cardiovascular disease. [1-5] Previous studies have demonstrated that elevated MSNA is an independent predictor of poor prognosis [6, 7] and mortality. [8-10] However, there is strong evidence indicating that meeting current exercise guidelines (150 min of moderate-to-vigorous physical activity each) week lowers the risk of all-cause mortality and morbidity. [11] A narrative review by Carter and Ray[12] argued the exercise-associated improvements in metrics of cardiovascular function including heart rate, blood pressure and arterial stiffness may be mediated, at least in part, by concurrent improvements in the actions of the sympathetic nervous system. [13, 14] Thus, interventions targeting the normalization of MSNA sympathetic nerve (re)activity may reduce overall morbidity and mortality. Although the actions of the sympathetic nervous system can be estimated by measuring plasma or urinary catecholamines (e.g. norepinephrine), and other neurotransmitters, the gold standard measure of muscle sympathetic nerve activity (MSNA) is via direct microneurography. Multiple studies have assessed the influence of exercise training on MSNA with varied results, likely due to limited samples sizes. No systematic review and meta-analysis has been performed to establish the effect of exercise training on MSNA. Therefore, the present systematic review and meta-analysis aims to comprehensively identify the relationship between exercise training, fitness and MSNA and concurrent changes in heart rate and blood pressure.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on systematic reviews and meta-analyses throughout the design, implementation, analysis, and reporting for this study. [15] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration no. CRD42021253325).

Information Resources

A structured search of electronic databases (MEDLINE, EMBASE, CINAHL, Scopus, Web of Science, Cochrane Library, Trip, and ProQuest Dissertations & Theses) up to October 6, 2023 was performed by a research librarian (AS; see the online supplement for complete search strategies; DOI: 10.6084/m9.figshare.25029680). The reference lists of included papers and relevant systematic reviews were checked manually to search for potentially relevant papers. The language of publication was not restricted. Studies published in languages other than English or French that were potentially relevant were translated through Google Translate, and if deemed potentially relevant were translated by a native speaker. The complete search strategy is presented in the online supplement (DOI: https://doi.org/10.6084/m9.figshare.25029680).

Eligibility Criteria

This study was guided by the participants, interventions, comparisons, outcomes, and study design (PICOS) framework.

103 *Study Design*

104 Randomized control trials (RCT) and non-randomized interventions were included. Systematic
105 reviews, Updates, Reviews or Meta-analyses were excluded from this study.

106

107 *Population*

108 All populations were eligible if they reported on muscle sympathetic nerve activity via
109 microneurography and were ≥18 years of age.

110

111 *Intervention*

112 The exercise intervention was any reported measures of exercise frequency, intensity, duration,
113 volume, or type lasting at least one week. Exercise had to be whole body in nature or utilizing
114 large major muscle groups.

115

116 *Comparison*

117 Non-exercising groups, author-defined low exercising groups, or non-exercising groups
118 receiving the same co-intervention(s).

119

120 *Outcomes*

121 MSNA (Burst frequency, burst incidence, total MSNA, burst amplitude), heart rate, systolic
122 blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MAP), and maximal
123 or peak oxygen consumption (VO2max or VO2peak).

124

125 *Study Selection*

126 Two reviewers independently assessed the titles and abstracts of articles identified by the search.
127 Studies were selected for full text review by at least one reviewer. All full text articles were
128 screened by two independent reviewers for eligibility. In the event of a disagreement, eligibility
129 was determined based on discussion between the two reviewers and by decision of a third
130 reviewer when needed. Two reviewers independently extracted the data in Microsoft Excel. If
131 the study had multiple publications, the most recent or complete publication was selected;
132 however, relevant data from all publications related to each unique study were extracted. Study
133 characteristics (e.g., study period, study design, country), population characteristics (e.g., number
134 of participants, age, BMI, height, weight, sex health complications), exposure (e.g., exercise
135 frequency, intensity, time and type of exercise) and outcomes (VO2 max or VO2peak, heart rate,
136 BP, and MSNA values: burst frequency, burst incidence, total activity, amplitude) were extracted
137 and recorded in a table (see online supplement table 1; DOI: 10.6084/m9.figshare.25029680).
138 Where data was only presented in figures and authors could not be reached via email, data were
139 extracted using WebPlotDigitizer (Web Plot Digitizer, V.3.11. Texas, USA: Ankit Rohatgi,
140 2017) [2, 5, 7, 9, 13, 14, 16-27], an online tool that supports the extraction of numeric data from graphs. [28]

141

142 *Quality Assessment (risk of bias)*

143 Two reviewers independently assessed the risk of bias at the individual level. The
144 methodological quality of the studies was assessed by both authors based on their study design.
145 The authors conducted the study using the standardized critical appraisal instruments from
146 Joanna Briggs Institute (JBI) Critical Appraisal of Evidence Effectiveness Tool. All studies were

screened using the tool for potential sources of bias including inappropriate sampling, flawed measurement of exposure, flawed measurements of outcomes, selective/incomplete outcomes, unidentified confounding factors and inappropriate statistical analysis. The differences in ratings were resolved through discussion. The overall risk of bias of a study was defined as high risk when more than one third of the factors were marked as high risk. Risk of bias tables are located in the Online Supplement Table 2 (DOI: 10.6084/m9.figshare.25029680). Funnel plots were used to assess publication bias when more than 10 studies were included in the forest plot (Figures S52-S58; DOI: https://doi.org/10.6084/m9.figshare.25029680). If there were fewer than 10 studies, publication bias was deemed non-estimable.

Data Synthesis

Review Manager v5.3 (Cochrane Collaboration, Copenhagen, Denmark) was used to conduct the statistical analyses. Due to group differences pre-intervention, mean delta and standard deviation (SD) values were calculated following the Cochrane Handbook guidelines and used in the meta-analyses. [29] SD was calculated from SEM when SD was not reported. [29] Significance was set at $p<0.05$. Inverse-variance weighting was applied to obtain change scores using a random-effects model. A priori determined subgroup analyses comparing individuals with and without cardiovascular disease were conducted. I^2 statistic was used to assess the heterogeneity between the studies. In the case of $I^2 \geq 50\%$, heterogeneity was explored further with sensitivity analyses. If data were not suitable for meta-analysis, authors were contacted to obtain additional information. Data were synthesized narratively if authors were unable to provide additional numerical data. When data from 10 or more RCTs were present for a specific physiological variable (e.g., MSNA, VO2, MAP, HR), meta-regression analyses of the mean differences were

performed using random-effects models with the restricted maximum likelihood estimation estimator for between-study variability.

RESULTS

Study Selection

A PRISMA diagram of the study search and selection process is shown in Figure 1. Forty-three primary research studies (23 RCTs [3, 5, 7, 8, 16, 20, 22, 23, 25, 30-41], 13 non-randomized interventions [2, 9, 13, 18, 21, 26, 27, 42-47], 6 pre- post- studies [14, 17, 19, 24, 45, 48], and 1 superiority trial [49]; n = 1,253) were included in this review. Co-interventions in the studies included diet (hypocaloric intake) [5, 25, 44], androgen hormone supplementation (estrogen [35] or testosterone [20]), cardiac resynchronization [34], inspiratory muscle training [41], hypoxia [44, 45], handgrip [26], cold pressor test [24], phenylephrine bolus injection [30], nitroprusside bolus injection [30], head-up tilt test [30], and controlled breathing/Valsalva maneuver [30]. We did not evaluate any reactivity tests and data from acute interventions were not extracted.

Individual study characteristics can be found in the Online Supplementary Table 1 (DOI: https://doi.org/10.6084/m9.figshare.25029680). Seventeen studies included aerobic only training interventions[14, 19, 21, 24, 25, 33-35, 38-43, 45, 46, 49], twenty-four studies utilized combined aerobic and resistance training interventions[2, 3, 5, 7-9, 16-18, 20, 22, 23, 26, 27, 30-32, 36, 37, 40, 41, 44, 47, 48], and 2 studies examined resistance training only interventions[13, 40]. Duration of training intervention ranged from 3 weeks to 1 year. Thirty-three studies examined populations with pre-existing medical conditions, including obesity, [5, 25] heart diseases/pathologies (heart failure, [2, 3, 8, 9, 17, 20, 23, 27, 34, 36, 47] chagastic disease, [37] Fontan patients, [41] coronary artery disease, [18] post-myocardial infraction,

192 [7, 46, 48]), sleep apnea, [22, 26, 27] postmenopausal women, [35] hypertension, [23, 43, 44] pregnancy, [38] neural
193 mediated syncope, [30] metabolic syndrome, [26, 44] and polycystic ovary syndrome. [39]
194
195 **Quality Assessment and Certainty Assessment**
196 JBI tools were used to assess the quality of each individual study (See Tables S2-5; DOI:
197 https://doi.org/10.6084/m9.figshare.25029680). Common sources of bias included a lack of
198 concealment of the allocation to the treatment group, as well as participant and assessor blinding
199 to the treatment assignment.
200
201 **MSNA BURST FREQUENCY**
202 *RCTs:*
203 The pooled estimate from 23 RCTs [3, 5, 7, 8, 16, 20, 22, 23, 25, 30-41, 50, 51] (exercise groups, n = 341;
204 control groups, n = 317 participants) indicated that individuals randomized to an exercise
205 intervention had significantly greater reductions in resting MSNA bust frequency compared to
206 those randomized to control conditions (mean difference [MD] = -8.41 bursts/min; 95% CI -5.59,
207 -11.22, I^2 = 89%, P < 0.00001; Figure S1; DOI: 10.6084/m9.figshare.25029680). Test for
208 subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 4.43, P =
209 0.11, I^2 = 54.8%). The pooled estimate of 3 studies (n = 124 participants) revealed that
210 reductions in burst frequency following randomization to a diet and exercise experimental group
211 or diet only control group were not significantly different between the groups (MD = 0.85
212 bursts/min, 95% CI -2.73, -1.02, P = 0.27, Figure S2; DOI: 10.6084/m9.figshare.25029680). [5, 25,
213 51] One study could not be included in the meta-analysis as the comparator group continued
214 regular endurance training throughout the study (n = 17 participants). [49] In this study,

recreational endurance athletes were randomly divided into a control, in which they continued their regular training, or an overload training group for four weeks. Burst frequency among the overload training group increased significantly (20 ± 7 vs. 24 ± 5 bursts/minute, P = 0.006), while burst frequency did not change in the control condition (17 ± 3 vs. 15 ± 4 burst/minutes, P = 0.33).

Subgroup analyses:

A sub-group analysis of RCTs was conducted to evaluate any differences between participants with and without cardiovascular disease. Patients with cardiovascular disease had higher basal burst frequency (Mean 38.57 bursts/min, CI 35.5, 41.4) compared to healthy individuals (Mean 32.34, CI 28.40, 36.28, P=0.01). The pooled estimate of 11 RCTs (exercise group, n = 156; control group, n = 143 participants [5, 22, 25, 30, 32, 35, 38-40]{Ray, 2010 #60;Trombetta, 2003) which only enrolled participants *without* cardiovascular disease, revealed significantly greater reductions in burst frequency among participants randomized to an exercise intervention compared to a control condition (MD = -5.37 bursts/min, 95% CI -2.56, -8.19 I^2 = 81%, P < 0.00001). Similarly, the pooled estimate of 12 RCTs (exercise group, n = 156; control group, n=143 participants, [3, 7, 8, 16, 20, 23, 31, 33, 34, 36, 37, 41]) which only enrolled participants *with* cardiovascular conditions, indicated significant reductions in burst frequency (MD = -11.54 bursts/min, 95% CI -7.38, -15.70, I^2 = 85%, P = <0.00001, Figure 2). The subgroup comparison indicated that individuals with cardiovascular disease tended to have greater reductions in burst frequency following randomization to an exercise intervention compared to individuals without cardiovascular disease (Chi^2 = 5.79, I^2 = 82.7%, P = 0.02).

Non-RCTs:

Data from 5 non-RCTS [2, 9, 21, 26, 27] (exercise group, n=76; control group, n=67 participants) were included in this analysis. These data demonstrated that individuals exposed to an exercise intervention had greater reductions in burst frequency compared to control participants (MD, -9.95 bursts/min; 95% CI -5.89, -14.005, I^2 = 75%, P =0.0005, Figure S3; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 1.10, P = 0.30, I^2 = 8.8%). Two studies could not be included within the meta-analysis as control participants only underwent an assessment at one time point and thus were not assigned to an intervention (n = 89 participants [18, 47]). Badrov et al. (2019) and Notarius et al. (2019) found that an exercise program significantly reduced resting burst frequency in those with heart failure (HF) (Notarius: 52.6 ± 13 to 47 ± 11, bursts/minute, P = 0.01; Badrov: 48 ± 8 to 39 ± 11 bursts/minute, P < 0.001) and post-intervention burst frequency in patients was not different than a cohort of healthy controls.

Subgroup analyses:

Among non-RCTs where individuals *without* cardiovascular disease completed an exercise intervention [21, 26, 27], the pooled estimate revealed significantly greater reductions than the control intervention (MD = -9.41 bursts/min, 95% CI -3.69, -15.13, I^2 = 87%, P = 0.001, Figure S4; DOI: 10.6084/m9.figshare.25029680). The pooled estimate of 3 non-RCTs (exercise group, n=34; control group, n=32 participants [2, 9, 26]) revealed individuals *with* cardiovascular disease who completed an exercise intervention also had a greater reduction in burst frequency of -10.63 bursts/minute (95% CI -5.00, -16.26, I^2 = 20%, P < 0.0002, Figure S4; DOI: 10.6084/m9.figshare.25029680) than those in the control intervention. However, subgroup

comparison indicated no differences in the reduction in burst frequency in those with and without cardiovascular disease ($Chi^2 = 0.09$, $I^2 = 0\%$, $P = 0.77$).

Pre to Post Studies

The pooled estimate from 7 pre to post studies[14, 17, 19, 24, 42, 45] {Svedenhag, 1984 #61} (n=101 participants) also indicated that burst frequency was reduced among individuals who completed an exercise training intervention (MD = -4.83 bursts/min, 95% CI -0.35, -9.31, $I^2 = 73\%$, $P = 0.0001$, Figure S5; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed a difference on burst frequency due to the type of exercise intervention ($Chi^2 = 11.84$, $P = 0.0006$, $I^2 = 91.6\%$).

Subgroup analyses:

Subgroup analysis of pre to post studies revealed individuals with cardiovascular disease had significant reductions in burst frequency following exercise training (1 study, n = 45, MD = -12.66 bursts/min, 95% CI -6.02, -19.30, $I^2 = 62\%$, $P = 0.0002$, Figure S6; DOI: 10.6084/m9.figshare.25029680). However, burst frequency was not affected among healthy participants (6 studies, n = 56, MD = -0.15 bursts/min, 95% CI -2.74, 2.43, $I^2 = 0\%$, $P = 0.87$, Figure S6). Comparison of subgroups suggested that individuals with cardiovascular disease exhibited significantly greater reductions in burst frequency following an exercise intervention compared to individuals without cardiovascular disease ($Chi^2 = 11.84$, $I^2 = 92\%$, $P = 0.0006$).

284 **BURST INCIDENCE**

285 *RCTs:*

286 The pooled estimate of 16 RCTs[3, 5, 7, 8, 16, 20, 23, 25, 30-32, 34, 36, 38, 40] (exercise group, n=249; control
287 group, n=226 participants) revealed a significantly greater reduction in burst incidence following
288 randomization to an exercise training intervention compared to a control condition (MD -15.67
289 bursts/100 beats, 95% CI -10.38, -20.95, I^2 = 86%, P < 0.00001, Figure S7; DOI:
290 10.6084/m9.figshare.25029680). Test for subgroup differences showed an effect of the type of
291 exercise intervention on the change in burst incidence (Chi^2 = 15.63, P = 0.0004, I^2 = 87.2%).
292 The pooled estimate of 3 studies (n = 124 participants) revealed that reductions in burst
293 incidence following randomization to a diet and exercise experimental group or diet only control
294 group were not significantly different between the groups (MD = -1.58 bursts/min, 95% CI -
295 4.53, 1.36, P = 0.58, Figure S8; DOI: 10.6084/m9.figshare.25029680). One randomized
296 superiority trial could not be included in the meta-analysis due to an active control group [49] (n =
297 17 participants). In this study, Coates et al. 2018 observed that burst incidence did not
298 significantly change in recreational athletes randomized to a general (30.9 ± 8.1 vs 30.1 ± 10.6
299 bursts/100 hbs) or overload endurance training (40.4 ± 13.8 vs. 48.6 ± 12 bursts/100 hbs).
300

301 *Subgroup analyses:*

302 Patients with cardiovascular disease had higher basal burst incidence (Mean 57.3 bursts/100 hbs,
303 CI 51.2, 63.3) compared to healthy individuals (Mean 39.6 CI bursts/100 hbs, P<0.0001).The
304 pooled estimate of 9 RCTs (n = 234 participants [3, 7, 8, 16, 20, 23, 31, 34, 36, 40]) revealed that individuals
305 with cardiovascular disease experienced significant reductions in burst incidence following
306 exercise intervention compared to controls (MD = -21.08 bursts/100 hbs, 95% CI -16.51, -25.66,

I^2 = 63%, P < 0.00001, Figure 3). A significant reduction in burst incidence from pre- to post-intervention was also observed among individuals *without* cardiovascular disease [5, 25, 30, 32, 38] compared to the control condition (n = 241, MD = -9.20 bursts/100 hbs, 95% CI -3.52, -14.88, I^2 = 77%, P < 0.0001, Figure 3); however, an assessment of subgroup differences indicated that individuals with cardiovascular disease had significantly greater reductions in burst incidence following an exercise intervention compared to those without (Chi^2 = 10.20, I^2 = 90%, P = 0.001).

Non-RCTs:

The pooled estimate from 3 non-RCTs [9, 13, 46] (n = 78 participants) indicated that the change in burst incidence among individuals exposed to an exercise intervention was not significantly different than those exposed to a control intervention (MD, -12.38 bursts/100 beats; 95% CI 6.50, -31.25, I^2 = 94%, P = 0.20, Figure S9; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed a significant difference between the type of exercise intervention (Chi^2 = 34.45, P < 0.00001, I^2 = 94.2%). However, two studies could not be included within the meta-analysis [18, 47] as control participants only underwent an assessment at one time point and thus were not assigned to an intervention (n = 89 participants). Notarius et al 2019 and Badrov et al. 2019 both found that exercise training significantly reduced resting burst incidence in those with HF (Notarius: 83.7 ± 18.2 to 76 ± 23.4 bursts/100 hbs, P < 0.05; Badrov: 81 ± 7 to 66 ± 17 bursts/100 hbs, P <0.01).

328 *Subgroup analyses:*

329 A test for subgroup differences indicated individuals *with* cardiovascular disease had
330 significantly greater reductions in burst incidence compared to those *without* ($Chi^2 = 14.02$, $I^2 =$
331 93%, P =0.0002). The pooled estimate 2 non-RCTs (exercise group, n = 27; control group, n=33
332 participants) [9, 46] indicated individuals *with* cardiovascular disease had significant reductions in
333 burst incidence following randomization to an exercise intervention (-20.93 bursts/100 beats;
334 95% CI 9.70, 32.22, $I^2 = 71\%$, P = 0.0003, Figure S10; DOI: 10.6084/m9.figshare.25029680). In
335 contrast, the pooled estimate of 1 study [13] (n = 18 participants) indicated that burst incidence was
336 not altered among those *without* cardiovascular disease following an exercise intervention (MD =
337 4.00 bursts/100 hbs, 95% CI 10.62, -42.62, P = 0.24, Figure S10; DOI:
338 https://doi.org/10.6084/m9.figshare.25029680).

339

340 *Pre to Post Studies*

341 The pooled estimate from 3 pre to post studies [17, 42, 48] (n=97 participants) demonstrated that
342 exercise intervention significantly reduced burst incidence by -13.99 bursts/100 heartbeats (95%
343 CI -20.87, -7.10, $I^2 = 52\%$, P < 0.04, Figure S11; DOI: 10.6084/m9.figshare.25029680). Test for
344 subgroup differences showed a difference between the type of exercise intervention ($Chi^2 = 4.60$,
345 P = 0.03, $I^2 = 78.2\%$).

346 *Subgroup analyses:*

347 A test for subgroup differences showed individuals *with* cardiovascular disease had a reduction
348 in burst incidence from pre- to post-intervention (MD -18.19 bursts/100 hbs, 95% CI -10.54, -
349 25.84; $I^2 = 49\%$, P < 0.00001, Figure S12, DOI: 10.6084/m9.figshare.25029680). The group
350 *without* cardiovascular disease group did not show a difference between pre- and post-

intervention burst incidence (MD -5.23 bursts/100 hbs, 95% CI 3.82, -14.28, I^2 = 0%, P = 0.26, Figure S12, DOI: https://doi.org.10.6084/m9.figshare.25029680).

TOTAL ACTIVITY

RCTs:

There was evidence from 1 RCT [16] (n=17 participants) demonstrating that exercise training had no significant effect on the change in total sympathetic activity among individuals randomized to an exercise intervention compared to control intervention (MD = 23.00 a.u., 95% CI 63.20, -17.20, p = 0.26, Figure S13; DOI: https://doi.org10.6084/m9.figshare.25029680).

VO_2 PEAK

RCTs:

There were 19 RCTs [2, 3, 5, 7, 8, 20, 22, 23, 25, 30-37, 40, 41] (exercise group, n = 333; control group, n = 320 participants) that reported on changes in VO2peak following intervention. The pooled estimate from these studies demonstrated that exercise training significantly increased VO2peak in exercise groups compared to controls (MD = +3.66 mL/min/kg, 95% CI 4.43, 2.89, I^2 = 45%, P < 0.00001, Figure S14; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 1.42, P = 0.49, I^2 = 0%).

Subgroup analyses:

Subgroup analyses revealed that the increase in VO2 peak was similar in individuals with and without cardiovascular disease when randomized to exercise interventions (P = 0.37). The pooled estimate of 12 RCTs[2, 3, 7, 8, 20, 23, 31, 33, 34, 36, 37, 41] (exercise group, n = 158; control group, n = 146 participants) indicted a MD = +3.26 mL/min/kg, in VO2 peak following randomization to an

exercise intervention compared to control intervention in individuals *with* cardiovascular disease (95% CI 4.14, 2.38, I^2 = 14%, P < 0.00001, Figure 4). Among individuals *without* cardiovascular disease, the pooled estimate of 9 studies [5, 22, 25, 30, 32, 35, 40, 50, 51] (n = 304 participants) demonstrated that the increase in VO2 peak was MD = +3.26 mL/min/kg following exercise intervention versus the control intervention (95% CI 4.14, 2.38, I^2 = 44%, P < 0.00001, Figure 4).

Non-RCTs:

The pooled estimate of 4 non-RCTs [2, 9, 21, 26] (exercise group, n=67; control group n=58 participants) also demonstrated that VO2 peak increased significantly among individuals exposed to an exercise intervention compared to control intervention (MD = 3.41 mL/min/kg, 95% CI 4.61, 2.22, I^2 = 6%, P < 0.00001, Figure S15; DOI: 10.6084/m9.figshare.25029680). Two studies could not be included within the meta-analysis [18, 47] as control participants only underwent an assessment at one time point and thus were not assigned to an intervention (n = 89 participants). Notarius et al 2019 and Badrov et al. 2019, both found that exercise training significantly increased VO2peak in those with HF (Notarius: 18.3 ± 7.8 to 21.4 ± 8.8 mL/min/kg, P < 0.05; Badrov: 26.5 ± 6.9 to 28.7 ± 8.9 mL/min/kg, P < 0.05).

Subgroup analyses:

The pooled estimate of 4 non-RCTs [2, 9, 21, 26] (n = 125 participants) indicated individuals *with* and *without* cardiovascular disease both had significant increases in VO2 peak following randomization to an exercise intervention (MD = +2.55 mL/min/kg, 95% CI 3.93, 1.17, I^2 = 0%, P = 0.0003; MD = +5.31 mL/min/kg, 95% CI 7.45, 3.17, I^2 = 0%, P < 0.00001, respectively,

Figure S16; DOI: 10.6084/m9.figshare.25029680). However, the change in VO2 peak following an exercise intervention appeared greater in individuals *without* compared to *with* cardiovascular disease (P = 0.03).

Pre to Post Studies

The pooled estimate from 1 pre- post- study [17] (n=45 participants) demonstrated that exercise training significantly increased VO2peak among individuals with heart failure (MD = +3.30 mL/min/kg; 95% CI 1.76, 4.85; P < 0.0001, Figure S17; DOI: 10.6084/m9.figshare.25029680).

HEART RATE

RCTs:

The pooled estimate from 21 RCTs [3, 5, 7, 8, 16, 20, 22, 23, 25, 30, 32-41 50, 51] (exercise group, n = 350; control group, n = 344 participants) revealed a modest, yet significant reduction in resting heart rate (-1.64 bpm) among individuals randomized to an exercise intervention (95% CI -0.31, -2.97, I^2 = 39%, P = 0.03, Figure S18; DOI: 10.6084/m9.figshare.25029680) compared to controls. Test for subgroup differences showed a difference in the heart rate response to exercise training depending on the type of exercise intervention (Chi^2 = 18.10, P = 0.0001, I^2 = 89%). One randomized superiority trial could not be included in the meta-analysis due to an active control group [49] (n = 17 participants). Coates et al., 2018 found that four weeks overload training had no effect on resting heart rate (54 ± 6 vs. 52 ± 5 bpm).

Subgroup analyses:

Subgroup analyses determined that individuals *with* cardiovascular disease randomized to an exercise intervention [3, 7, 8, 16, 20, 23, 33, 34, 36, 37, 40, 41] did not have a significantly different change in

resting heart rate compared to those randomized to the control condition (MD = -1.68 bpm, 95% CI, 0.53, -3.89, I^2 = 37%, P = 0.14, Figure 5), while a difference in the change in resting heart rate was observed among individuals *without* cardiovascular disease randomized to exercise [5, 22, 25, 30, 32, 35, 38, 39 50, 51] versus control condition (MD = -1.74 bpm, 95% CI -0.03, -3.45, I^2 = 30%, P = 0.03, Figure 5). Nonetheless, the analysis of subgroup differences determined the change in resting heart rate from pre to post exercise intervention was not significantly different between the groups (Chi^2 = 0.00, P = 0.97, I^2 = 0%).

Non-RCTs:

The pooled estimate of 4 non-RCTs [2, 9, 13, 45] (n = 101 participants) revealed the change in resting heart rate was not different following an exercise versus control intervention (MD = -1.71 bpm, 95% CI 2.93, -6.36, I^2 = 62%, P = 0.47, Figure S19; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 5.30, P = 0.07, I^2 = 62.2%). Two studies could not be included within the meta-analysis [18, 47] as control participants only underwent an assessment at one time point and thus were not assigned to an intervention (n = 89 participants). Notarius et al. (2019) and Badrov et al. (2019) found that an exercise program had no significant effect on resting heart rate in those with HF post-training (Notarius: 63 ± 10.4 to 63 ± 10.4 bpm, P > 0.05; Badrov: 59.7 ± 7 to 58.8 ± 8 bpm, P > 0.05).

Subgroup analyses:

Subgroup analyses revealed that resting heart rate was not different following exercise intervention among both individuals *with* and *without* cardiovascular disease. The pooled estimate of 2 studies (n = 66 participants) revealed that resting heart rate did not change

following an exercise intervention among individuals *with* cardiovascular disease [2, 9] (MD = -0.54 bpm, 95% CI -5.29, 4.20, I^2 = 47%, P = 0.82, Figure S20; DOI: 10.6084/m9.figshare.25029680). The pooled estimate of 2 studies (n = 35 participants) revealed resting heart rate was significantly reduced following an exercise intervention in exercise compared to controls among those *without* cardiovascular disease [13, 45] (MD = 6.45 bpm, 95% CI 11.60, 1.31, I^2 = 7%, P = 0.01, Figure S20; DOI: 10.6084/m9.figshare.25029680). However, the analysis of subgroup differences indicated changes in resting heart rate were not different between those *with* and *without* cardiovascular disease (P = 0.05).

Pre to Post Studies

The pooled estimate of 6 pre- post- studies [14, 17, 19, 42, 48 52] (n=117 participants) demonstrated that resting heart rate was reduced from pre to post-exercise training intervention (MD = -2.39 bpm, 95% CI -0.31, -4.47, I^2 = 0%, P = 0.02, Figure S21; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 1.17 P = 0.28, I^2 = 14.7%).

Subgroup analyses:

Subgroup analyses of pre to post studies revealed reductions in heart rate were non-significant among individuals *with* [14, 19] (MD = -4.71 bpm, 95% CI 6.60, -16.03, I^2 = 0%, P = 0.41, Figure S22; DOI: 10.6084/m9.figshare.25029680) but were significant in those *without* [17, 43, 48 52] (MD = -2.31 bpm, 95% CI -0.19, -4.43, I^2 = 0%, P = 0.03, Figure S22; DOI: 10.6084/m9.figshare.25029680) cardiovascular disease following exercise training. There were no differences in these changes between groups (Chi^2 = 0.17, P=0.86, I^2 = 0%).

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MEAN ARTERIAL BLOOD PRESSURE (MAP)

RCTs:

The pooled estimate from 18 RCTs [2, 3, 5, 7, 20, 23, 30, 32-38, 40 50, 51] (exercise group, n = 295; control group n = 285 participants) demonstrated a non-significant reduction in MAP among individuals randomized to an exercise intervention compared to control condition (MD = -1.51 mmHg, 95% CI 0.13, -3.15, I^2 = 51%, P = 0.07, Figure S23; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 1.84, P = 0.40, I^2 = 0%).

Subgroup analyses:

The pooled estimate of 10 RCTs [2, 3, 7, 8, 20, 23, 33, 34, 36, 37] (exercise group, n = 132; control group, n = 126 participants) which only enrolled participants *with* cardiovascular conditions, indicated a non-significant change in MAP following an exercise intervention (MD = -1.97 mmHg, 95% CI -5.48, 1.54, I^2 = 70%, P = 0.27, Figure 6). In contrast, a significant reduction in MAP was observed among participants *without* cardiovascular disease randomized to exercise interventions [5, 30, 32, 35, 38, 40 50, 51] (MD = -1.83 mmHg, 95% CI -0.42, -3.24, I^2 = 0%, P = 0.01, Figure 6). However, subgroup analysis did not identify a significant difference in the MAP responses following exercise interventions between sub-groups (Chi^2 = 0.01, P = 0.94, I^2 = 0%).

Non-RCTs:

The pooled estimate of 3 non-RCTs [2, 9, 13] (exercise group, n=46; control group, n=40 participants) also demonstrated that exercise training had no significant effect on MAP in both

individuals exposed to exercise compared to control interventions (MD = -3.90 mmHg, 95% CI 1.07, -8.87, I^2 = 52%, P = 0.12, Figure S24; DOI: 10.6084/m9.figshare.25029680). Test for subgroup differences showed no difference in the type of exercise intervention (Chi^2 = 1.63, P = 0.20, I^2 = 38.7%). One study could not be included within the meta-analysis [18] as control participants only underwent an assessment at one time point and thus were not assigned to an intervention (n = 44 participants). Badrov et al. (2019) found that those with HF after a six-month cardiac rehabilitation program had significantly lowered resting MAP (86 ± 10 mmHg to 82 ± 7 mmHg, P < 0.05).

Subgroup analyses:

Subgroup analyses revealed that MAP was not different following exercise intervention among individuals *with* cardiovascular disease. The pooled estimate of 2 studies [2, 9] (exercise group, n = 34; control group, n = 32 participants) indicated that MAP did not change following an exercise intervention among individuals *with* cardiovascular disease (MD = -2.02 mmHg, 95% CI 4.52, -8.57, I^2 = 47%, P = 0.54, Figure S25). The results of 1 study [13] (exercise group, n = 12; control group, n = 8 participants) suggested MAP reduced significantly following exercise intervention among participants *without* cardiovascular disease (MD = -7.00 mmHg, 95% CI -3.07, -10.93, P = 0.0005, Figure S25). Test for subgroup differences indicated changes in MAP were not different between those *with* and *without* cardiovascular disease (Chi^2 = 1.63, P = 0.20, I^2 = 38.7%).

513 *Pre to Post Studies*

514 The pooled estimate of 4 pre- post- studies [14, 17, 24, 48] (n=92 participants) demonstrated that MAP
515 was not affected among individuals who completed an exercise training intervention (MD = -
516 1.68, 95% CI 1.87, -5.22, I^2 = 22%, P = 0.35, Figure S26; DOI: 10.6084/m9.figshare.25029680).
517 Test for subgroup differences showed no difference in the type of exercise intervention on MAP
518 from pre- to post-intervention (Chi^2 = 0.16, P = 0.69, I^2 = 0%).

519

520 *Subgroup analyses:*

521 Subgroup analyses of pre to post studies revealed MAP was not affected following exercise
522 intervention among individuals *with* [17, 48] (MD = -1.37, 95% CI 3.68, -6.41, I^2 = 38%, P = 0.60,
523 Figure S27; DOI: 10.6084/m9.figshare.25029680) and *without* [14, 20, 24] (MD = -2.83, 95% CI
524 2.24, -7.91, I^2 = 0%, P = 0.27, Figure S27; DOI: 10.6084/m9.figshare.25029680) cardiovascular
525 disease following exercise training. There were no differences between subgroups in the effect of
526 exercise on MAP (Chi^2 = 0.16, P = 0.69, I^2 = 0%).

527

528 **SYSTOLIC BLOOD PRESSURE**

529 The pooled estimate from 14 RCTs [2, 5, 7, 20, 22, 23, 25, 32, 33, 35, 37-40] demonstrated that exercise
530 training had no significant effect on the change in SBP among individuals randomized to an
531 exercise compared to a control intervention (MD = -2.24 mmHg, 95% CI 0.28, -4.77, I2 = 48%,
532 P = 0.08, Figure S28; DOI: 10.6084/m9.figshare.25029680). Subgroup analyses revealed no
533 change in SBP following exercise intervention in both individuals *with* and *without*
534 cardiovascular disease (Figure S29; DOI: 10.6084/m9.figshare.25029680). However, 5 non-
535 RCTs [9, 13, 26, 27, 45] indicated that SBP was 7.68 mmHg lower (95% CI -2.33, -13.02, I^2 = 63%, P <
536 0.005, Figure S30) from pre- to post-intervention in the exercise group compared to the control

group. Subgroup analyses revealed no differences in SBP in individuals with cardiovascular disease, but SBP was lower in the exercise group in individuals without cardiovascular disease (Figure S31; DOI: 10.6084/m9.figshare.25029680). The pooled estimate of 4 pre- post- studies [17, 19, 24, 42] demonstrated that SBP significantly decreased following exercise training (MD = -3.01 mmHg, 95% CI -0.02, -6.01, I^2 = 0%, P = 0.05, Figure S3; DOI: 10.6084/m9.figshare.25029680). SBP was lower in the exercise training group for individuals with cardiovascular disease, but not those without (Figure S33; DOI: 10.6084/m9.figshare.25029680).

DIASTOLIC BLOOD PRESSURE

The pooled estimate of 14 RCTs [2, 5, 7, 20, 22, 23, 25, 32, 33, 35, 37-40] (exercise group, n = 237; control group, n= 241 participants) demonstrated the change in DBP was not significantly different following randomization to exercise training (MD = -1.78 mmHg, 95% CI 0.41, -3.97, I^2 = 77%, P = 0.11, Figure S34; DOI: 10.6084/m9.figshare.25029680). Subgroup analyses revealed no difference in the DBP response to exercise training between individuals *with* and *without* cardiovascular disease (Chi^2 = 0.04. P = 0.84, I^2 = 0%, Figure S35). The pooled estimate of 5 non-RCTs [9, 13, 26, 27, 45] showed no difference in the change in DBP among individuals exposed to an exercise versus control intervention (MD, -3.96 mmHg, 95% CI 0.76, -8.68, I^2 = 68%, P = 0.10, Figure S36; DOI: 10.6084/m9.figshare.25029680). Subgroup analyses revealed that the change in DBP following intervention was not different following exposure to an exercise versus control intervention among individuals *with* and *without* cardiovascular disease (Chi^2 = 0.35. P = 0.55, I^2 = 0%, Figure S37, DOI: 10.6084/m9.figshare.25029680). The pooled estimate of 4 pre-

post- studies [17, 19, 24, 42] (n= 85 participants) demonstrated that DBP was not significantly affected among individuals who completed an exercise training intervention (MD = -2.27 mmHg, 95% CI 0.82, -5.35, I^2 = 56%, P = 0.15, Figure S38; DOI: 10.6084/m9.figshare.25029680), and test for subgroup differences determined there were no differences between individuals *with* and *without* cardiovascular disease (Chi^2 = 0.00, P = 0.97, I^2 = 0%, Figure S39, DOI: 10.6084/m9.figshare.25029680).

Meta Regressions

Linear meta-regression analyses were conducted using data from RCTs when at least 10 studies with sufficient data were available. Meta-regression analyses were performed for the change in burst frequency and burst incidence following an exercise intervention in relation to the initial pre-training values. A significant positive relationship was identified between initial burst frequency and the change in burst frequency following an exercise intervention in randomized control trials (slope=0.582, adjusted R^2=0.415, p=0.003, Figure 7). Similarly, a positive relationship exists between initial burst incidence and the change in burst incidence following an exercise intervention in randomized control trials (slope=0.635, adjusted R^2=0.624, p=0.002, Figure 7). However, when the improvements in VO2peak were assessed in relation to MSNA burst frequency and incidence (BF, slope = -0.536, adjusted R^2 = -0.0526, P = 0.552, Figure S40; BI, slope = -1.651, adjusted R^2 = 0.0145, P = 0.262, Figure S45; DOI: 10.6084/m9.figshare.25029680), no significant relationships were found. Meta-regression analyses did not identify any relationships between the change in burst frequency and incidence with the change in heart rate (BF, slope = 0.2699, adjusted R^2 = 0.1997, P = 0.06, Figure S41;

BI, slope = 0.147, adjusted R^2 = 0.0463, P = 0.295, Figure S46; DOI: 10.6084/m9.figshare.25029680). Further, meta-regression of changes in MSNA burst frequency and incidence in relation to changes in mean arterial pressure (BF, slope = -0.1508, adjusted R^2 = 0.4218, P = 0.514, Figure S42; BI, slope = -0.083, adjusted R^2 = -0.2589, P = 0.705, Figure S47; DOI: 10.6084/m9.figshare.25029680), and changes in burst frequency with systolic and diastolic blood pressure (SBP, slope = -0.5385, adjusted R^2 = 1.00, P = 0.161, Figure S43; DBP, slope = -0.2382, P = 0.442, Figure S44; DOI: 10.6084/m9.figshare.25029680), were also not significant. Meta-regression analyses were performed between the change in sympathetic activity (burst frequency and incidence) and training volume, but no relationships were identified (Figures S48-S51; DOI: 10.6084/m9.figshare.25029680).

DISCUSSION

Main Findings

This systematic review and meta-analysis of 21 RCTs, 13 non-RCTs, 5 pre-post-studies and 1 superiority trial demonstrates clearly that exercise interventions (which improved VO2peak/max) significantly reduces sympathetic nervous system activity, as measured by MSNA burst frequency and incidence. Analysis of secondary cardiovascular outcomes from included studies also demonstrated reductions in heart rate in those taking part in exercise training, but not blood pressure.

While significant reductions in burst frequency and incidence were observed among healthy participants following an exercise intervention, the analysis of subgroups categorized by cardiovascular health status revealed more profound reductions in burst incidence among

individuals with cardiovascular disease compared to those without. Although significant subgroup differences in burst frequency were not uniform across experimental type, the subgroup comparison for burst frequency was noted as p=0.07 for RCTs and achieved significance in pre- post designs. When interpreting MSNA burst frequency data, it should be considered that burst frequency (by nature of its pulse-synchrony) is heavily influenced by prevailing heart rate, and in this scenario any concurrent influence of exercise training on heart rate. Indeed, the current analyses indicated a reduction in heart rate in individuals engaged in training programs. However, these reductions were modest, and generally consistent between those with and without cardiovascular disease. Therefore, based on the sum of evidence, it appears that MSNA is reduced following exercise training and that reductions in MSNA were most robust in patients with cardiovascular disorders. Although the specific underlying mechanisms linking exercise training to reductions in MSNA are beyond the scope of this review, it is possible that enhanced baroreflex control mediated by exercise training could be a driver in the drop in resting MSNA. Laterza et al. 2007 specifically noted in their exercise trial on those with hypertension, that regular exercise enhances baroreflex control of MSNA.[23] This is consistent with the observed decrease in burst incidence with a modest (or non-significant) reduction in blood pressure. Meta-regression analyses revealed a significant relationship between initial sympathetic activity and the degree of change in sympathetic activity from pre- to post-exercise intervention. Indeed, participants with cardiovascular disease (n = 12 RCTs) had higher basal burst frequency than participants without. This is internally consistent with the greater reduction in burst frequency observed in patient groups. Our analysis empirically supports the hypothesis put forward by Carter and Ray[12] that improvements in cardiovascular function with exercise may be related to improvements in sympathetic nerve activity and reactivity. To further

assess whether efficacy of the exercise intervention, as evidenced by changes in VO2peak/max, influenced the degree to which sympathetic activity changed, we conducted meta-regressions of change in MSNA burst frequency and incidence against change in VO2peak/max. However, these were not significant. This suggests that exercise may impart separate but parallel improvements in aerobic fitness and sympathetic outflow via distinct mechanisms.

Exercise training has been suggested to improve cardiovascular health via augmented endothelial function, vasodilation and muscle blood flow, and reduced MSNA and blood pressure. [36] We were able to extract secondary outcomes related blood pressure from most studies. However, reductions in blood pressure were modest and non-significant across most study types. A recent large network meta-analysis (n = 15 827 pooled participants) demonstrated clear, clinically meaningful, reductions in systolic and diastolic pressure following exercise interventions. [53] Thus our non-significant findings may be due to a relatively small sample size to detect differences in these secondary outcomes. Also, we can not rule out the possibility that the exercise interventions used in the studies lacked the volume or intensity required to stimulate significant remodeling of the cardiovascular system to reduce resting BP. [54] However we were unable to comment on training volume. Although training resulted in clear increases in aerobic fitness, these changes were not correlated with concurrent reductions in MSNA. It is possible that the reductions in MSNA are related to other process not linked to augmented VO2peak. We observed an effect of intervention type on the magnitude of change in burst incidence with training but not burst frequency, suggesting some training types (i.e., aerobic training) may have a greater influence of resting heart rate than others. Test for subgroup differences in the heart rate response was also significant, supporting that differences in burst frequency from intervention

types are driven by heart rate. Although we were able to extract data on MSNA burst frequency and incidence, burst amplitude and associated MSNA total activity (the product of amplitude and frequency) were reported less frequently. This lack of reporting does limit interpretations, particularly if exercise training differentially influences the number or gating of bursts of activity and descending drive via the active pool of sympathetic neurons (i.e. burst amplitude). As research in this area continues, authors are encouraged to fully report MSNA frequent, incidence and amplitude as well as associated total activity. Nonetheless, the results of this meta-analysis are important as sympathetic hyperactivity has been linked to cardiovascular morbidity and mortality. These findings present strong rationale for the use of exercise intervention as a measure to reduce sympathetic activity.

Perspectives and Significance

Our findings demonstrate that exercise training can reduce MSNA activity, which we now know is tightly linked with the control of our peripheral and central vasculature. With these comprehensive findings, exercise training could be used at a clinical level for those with underlying health complications to improve MSNA levels and therefore overall health of the cardiovascular system.

There were several strengths of this current review. The inclusion criteria were comprehensive, allowing articles with various exercise protocols (type (strength & aerobic), duration (longer than two weeks), modality, and involvement of other interventions (i.e. drug intervention)), to not be limiting factors to the inclusion of articles into this review. Similarly, we allowed the inclusion of any primary research study design to be included in the analysis published in two languages

(English and French). Studies that provided only narrative results were also included in this study. Therefore, our review was widely inclusive of studies that involved exercise training, creating a diverse pooling of previous literature. Most studies looked at populations with underlying health complications. However, there were a few limitations to our review. First, the heterogeneity for some subgroup analyses and overall analysis was high. Secondly, there were only few of studies that included the comparison or measured the effects of exercise training in healthy individuals. Further, tests for bias identified higher risk areas including a lack of blinding of participants and researchers due to the nature of exercise interventions, inconsistency across groups regarding other treatments and care, and lack of follow up and high dropout rates. These limitations are inherent to longitudinal exercise training programs but should still be considered when interpreting the data. Finally, there was a lack of diversity among the exercise interventions and duration of the trials. Seventy percent of all exercise programs involved cycling on a stationary cycle for about forty minutes. There were no exercise trials that compared the effects of strength training to aerobic training nor the effects of different modalities of exercise on MSNA. Future research should look at the effects that multimodal exercise interventions have on MSNA. Additionally, future research should look at the effects of long-term exercise programs lasting longer than six months as only three studies looked at the effects of exercise training after six months, while the majority lasted four months.

CONCLUSIONS

This review and meta-analysis present strong evidence that exercise intervention can significantly reduce MSNA and that this effect is even greater among individuals with

cardiovascular disease. These findings suggest that exercise training should be used among clinical populations as a method to reduce sympathetic activity and improve overall health.

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DISCLOSURES

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

S.E.M. and M.K. were primarily responsible for data collection and analysis, interpretation of results, manuscript preparation and approval of final manuscript. L.E.M. was involved in data collection and analysis, figure preparation, and editing and revising the final manuscript. B.M. contributed to research design, data collection and analysis, interpretation of results, and approval of final manuscript. R.M. and S.d.W. A.S. was responsible for data collection through systematic searches of all relevant online databases. M.H.D. and C.D.S. were responsible for conception and design of the research, interpretation of results, revising and approval of final manuscript.

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FIGURE CAPTIONS

Figure 1: PRISMA diagram. Includes the inclusion criteria for this review.

Figure 2: Effect of exercise (randomized controlled trials) on the change in burst frequency from pre- to post-intervention. Subgroups include 1) Non-cardiovascular disease group, 2) Cardiovascular disease group, Analyses conducted with a random effects model. IV, inverse variance; SD, standard deviation; I^2= heterogeneity; CI, confidence interval (24 studies, n=658). HF, heart failure; ET, exercise-trained; UT, untrained; OSA, obstructive sleep apnea; NT, not trained; PCOS, polycystic ovary syndrome; MetSyn, metabolic syndrome; WL, dietary weight loss; EX, exercise weight loss; AT, aerobic training.

Figure 3: Effect of exercise vs. control (randomized controlled trials) on the change in burst incidence from pre- to post-intervention. Subgroups include 1) Non-cardiovascular disease group and 2) Cardiovascular disease group. Analyses conducted with a random effects model. IV, inverse variance; SD, standard deviation; I^2= heterogeneity; CI, confidence interval (15 studies, n=426). MetSyn, metabolic syndrome; WL, weight loss; EX, exercise; HF, heart failure; ET, exercise training; IMT, inspiratory muscle training; UT, untrained.

Figure 4: Effect of exercise (randomized controlled trials) on the change VO2 peak from pre- to post-intervention. Subgroups include 1) Non-cardiovascular disease group and 2) Cardiovascular disease group, Analyses conducted with a random effects model. IV, inverse variance; SD, standard deviation; I^2= heterogeneity; CI, confidence interval (21 studies, n=653). OSA, obstructive sleep apnea; ET, exercise training; NT, no training; MetSyn, metabolic syndrome; WL, weight loss; HF, heart failure; UT, untrained; IMT, inspiratory muscle training.

Figure 5: Effect of exercise (randomized controlled trials) on the change in resting heart rate from pre- to post-intervention. Subgroups include 1) Non-cardiovascular disease group and 2)-Cardiovascular disease group, Analyses conducted with a random effects model. IV, inverse variance; SD, standard deviation; I^2= heterogeneity; CI, confidence interval (22 studies, n=694). OSA, obstructive sleep apnea; ET, exercise training; NT, no training; MetSyn, metabolic syndrome; WL, weight loss; HF, heart failure; IMT, inspiratory muscle training; UT, untrained.

Figure 6: Effect of exercise (randomized controlled trials) on the change in mean blood pressure from pre- to post-intervention. Subgroups include 1) Non-cardiovascular disease group and 2) Cardiovascular disease group. Analyses conducted with a random effects model. IV, inverse variance; SD, standard deviation; I^2= heterogeneity; CI, confidence interval (18 studies, n=580). HF, heart failure; ET, exercise training; NT, no training; IMT, inspiratory muscle training.

960

961 Figure 7: Meta-regressions representing the relationship between initial sympathetic activity and
962 the change in sympathetic activity following an exercise intervention. Top panel represents
963 sympathetic burst frequency (bursts/min) and bottom panel represents sympathetic burst
964 incidence (bursts/100 hbs). Sympathetic activity was considered a continuous variable and data
965 from randomized control trials for all participants randomized to exercise interventions were
966 included.

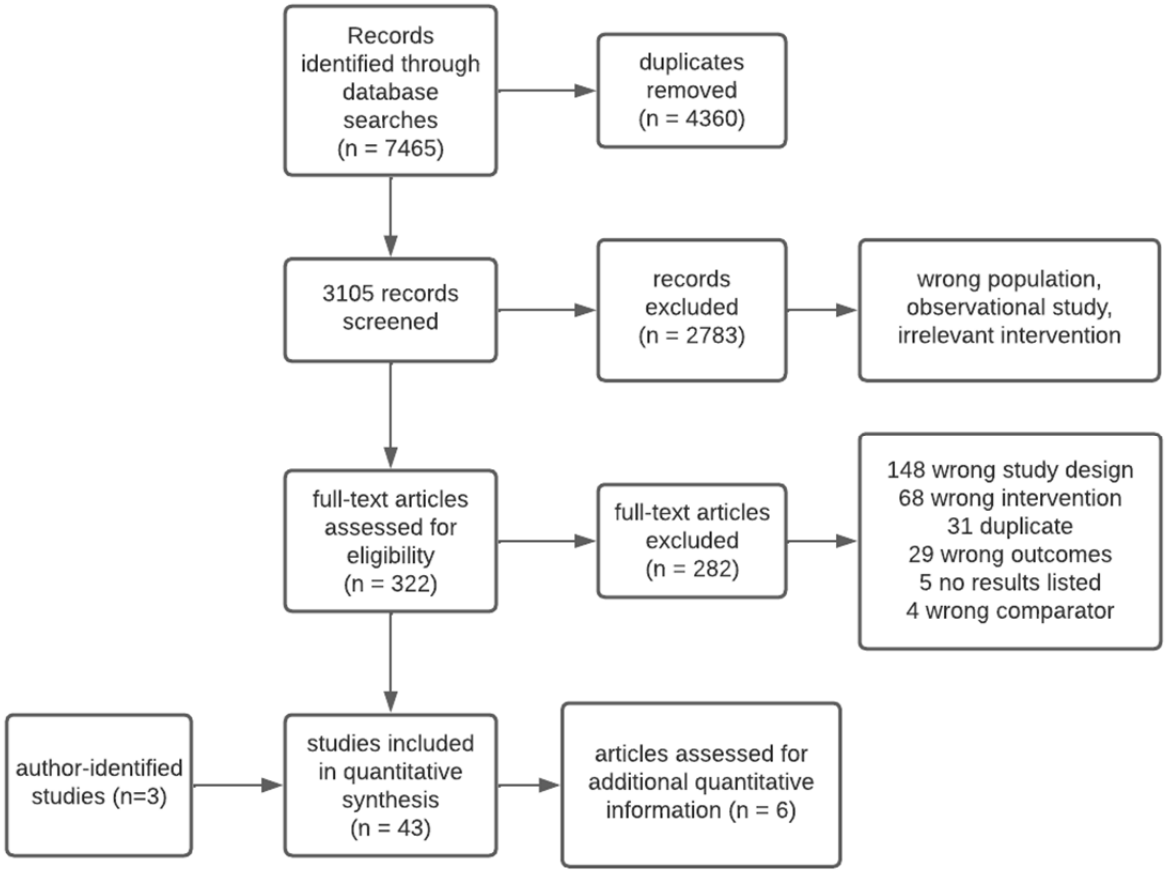
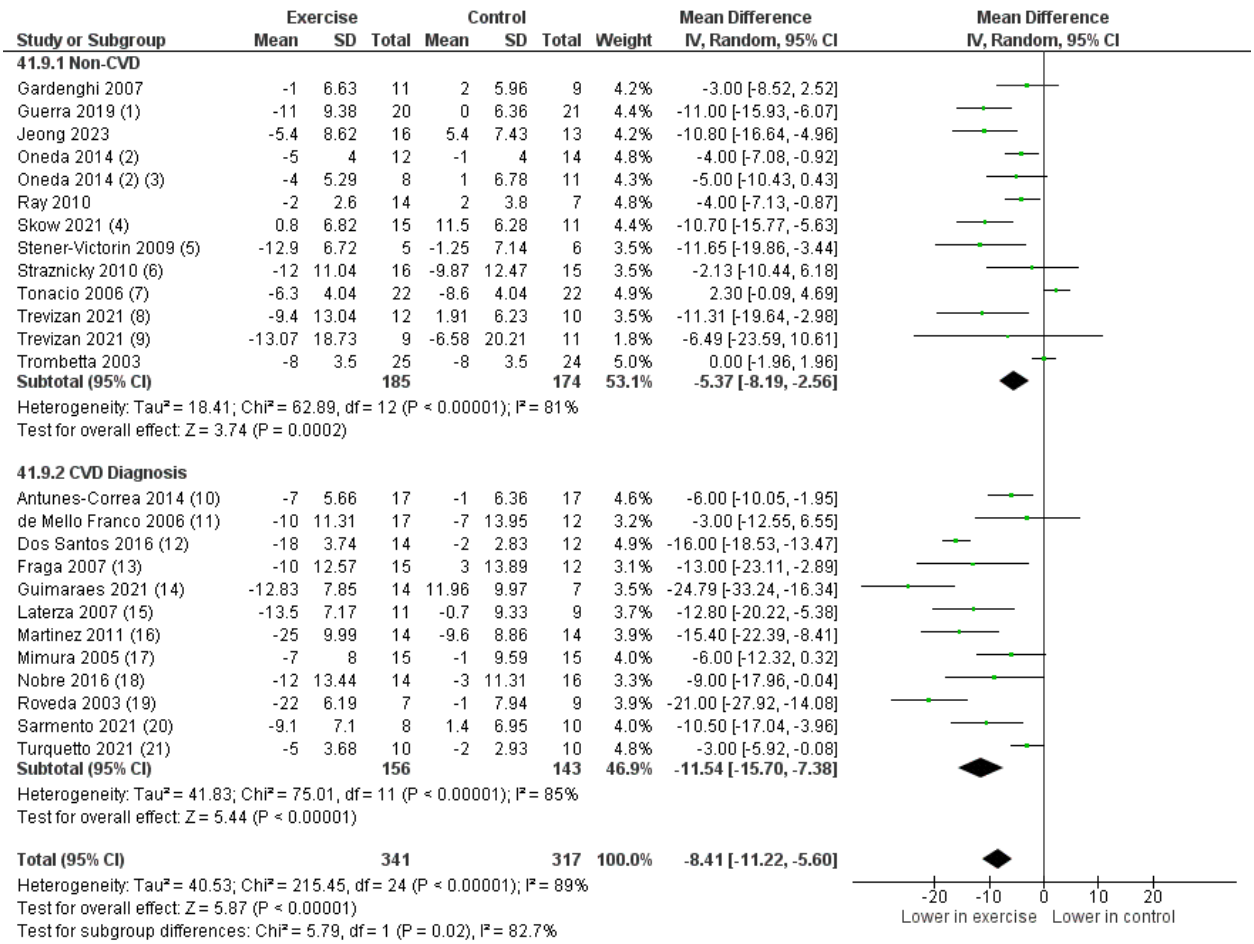


Figure 1



Footnotes

(1) OSA ET VS. UT
(2) Placebo group
(3) Estrogen therapy
(4) Pregnant
(5) PCOS ET VS. UT
(6) MetSyn: WL + ET vs. UT
(7) Obese: ET + diet vs. diet
(8) HF ET VS. UT
(9) HF ET + IMT VS. IMT
(10) Heart Failure
(11) HF ET VS. UT
(12) HF ET + Testosterone vs. testosterone
(13) HF ET VS. UT
(14) Heart Failure
(15) Hypertensive
(16) Post myocardial infarction
(17) Acute myocardial infarction
(18) HF
(19) HF
(20) Chronic chagastic cardiomyopathy
(21) Fontan Patients

Figure 2

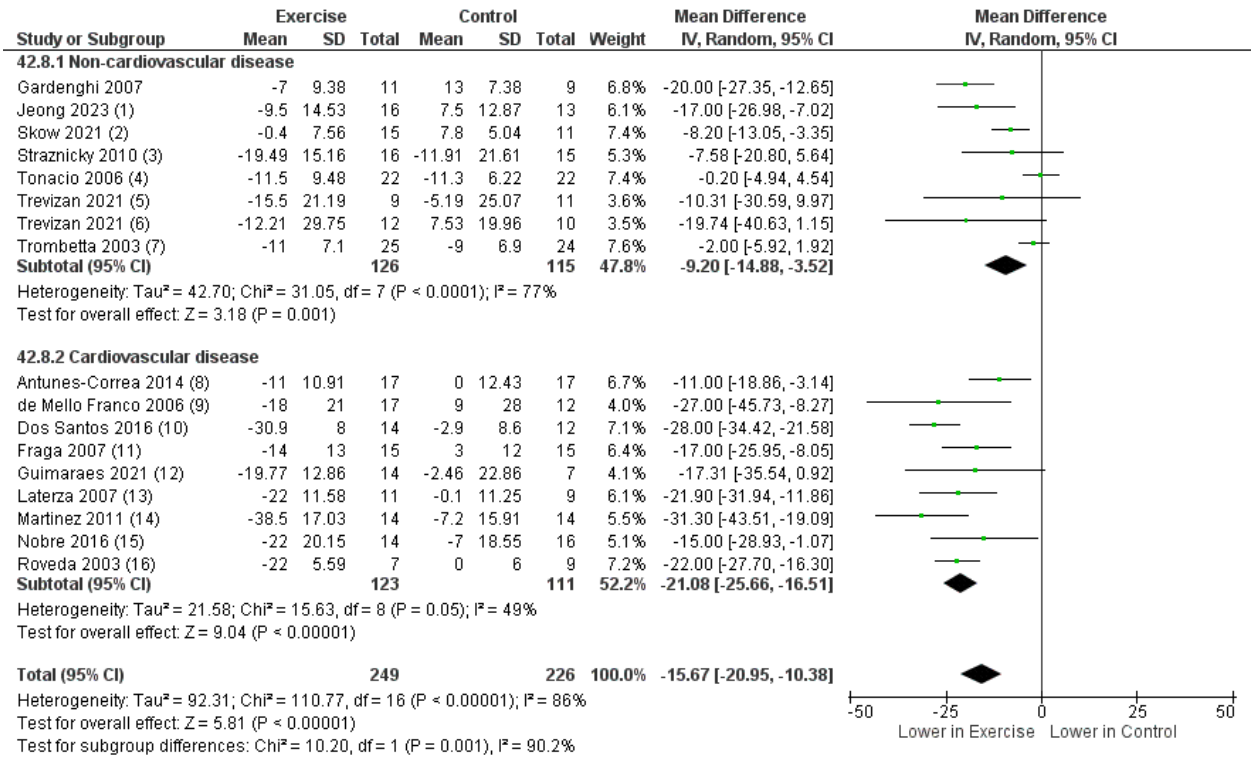
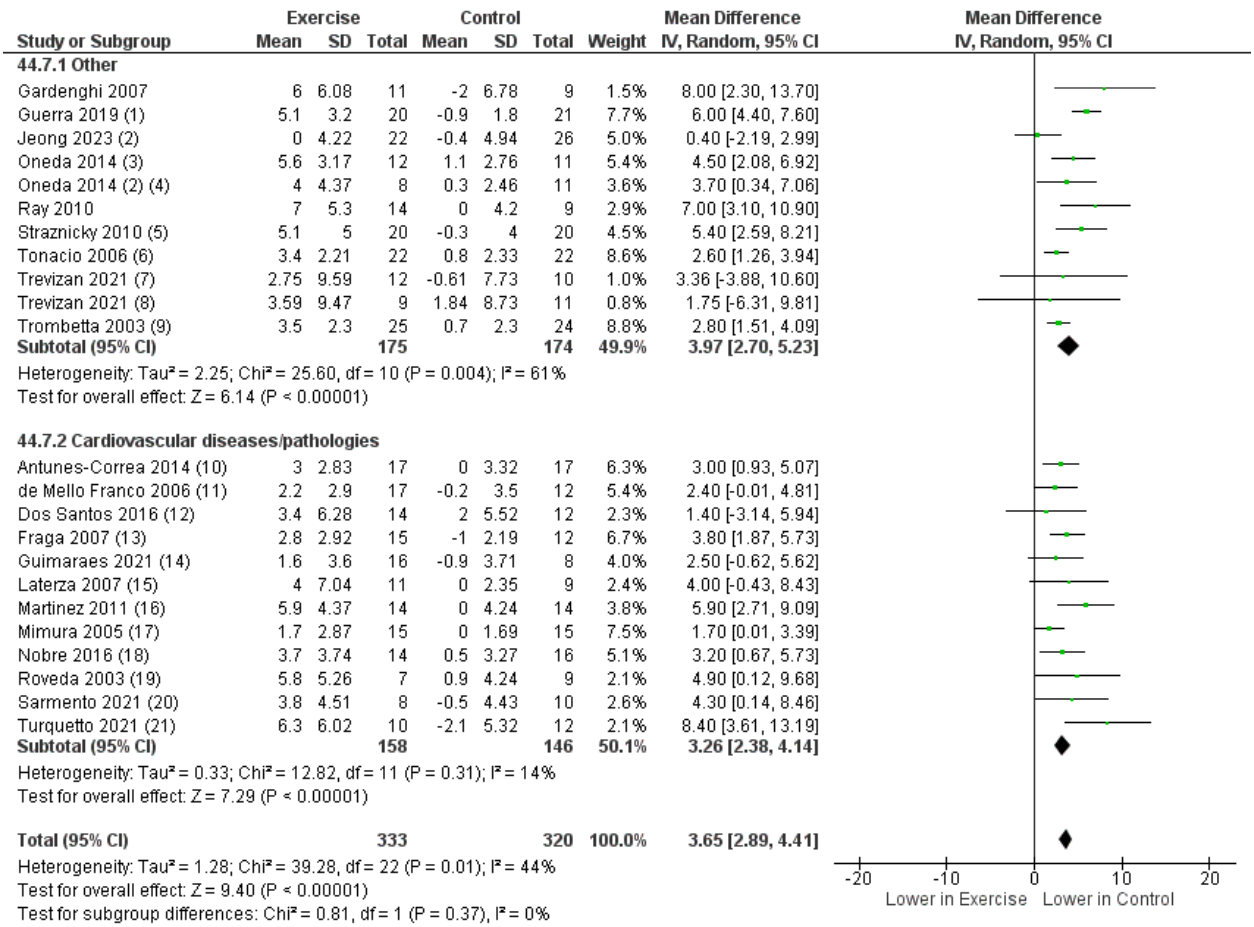


Figure 3



Footnotes

(1) OSA-ET vs OSANT
(2) Chronic kidney failure
(3) Placebo group
(4) Estrogen therapy
(5) MetSyn: WL +EX vs WL
(6) Obese: ET + diet vs. diet
(7) HF ET VS. UT
(8) HF ET + IMT VS. IMT
(9) Obese women: ET + diet vs. diet
(10) Heart failure
(11) HF-ET vs HF-UT
(12) Heart failure
(13) Heart failure
(14) Heart failure
(15) Hypertensive
(16) Myocardial infarction
(17) Acute myocardial infarction
(18) heart failure
(19) Heart failure
(20) Chronic chagastic cardiomyopathy
(21) Fontan patients

Figure 4

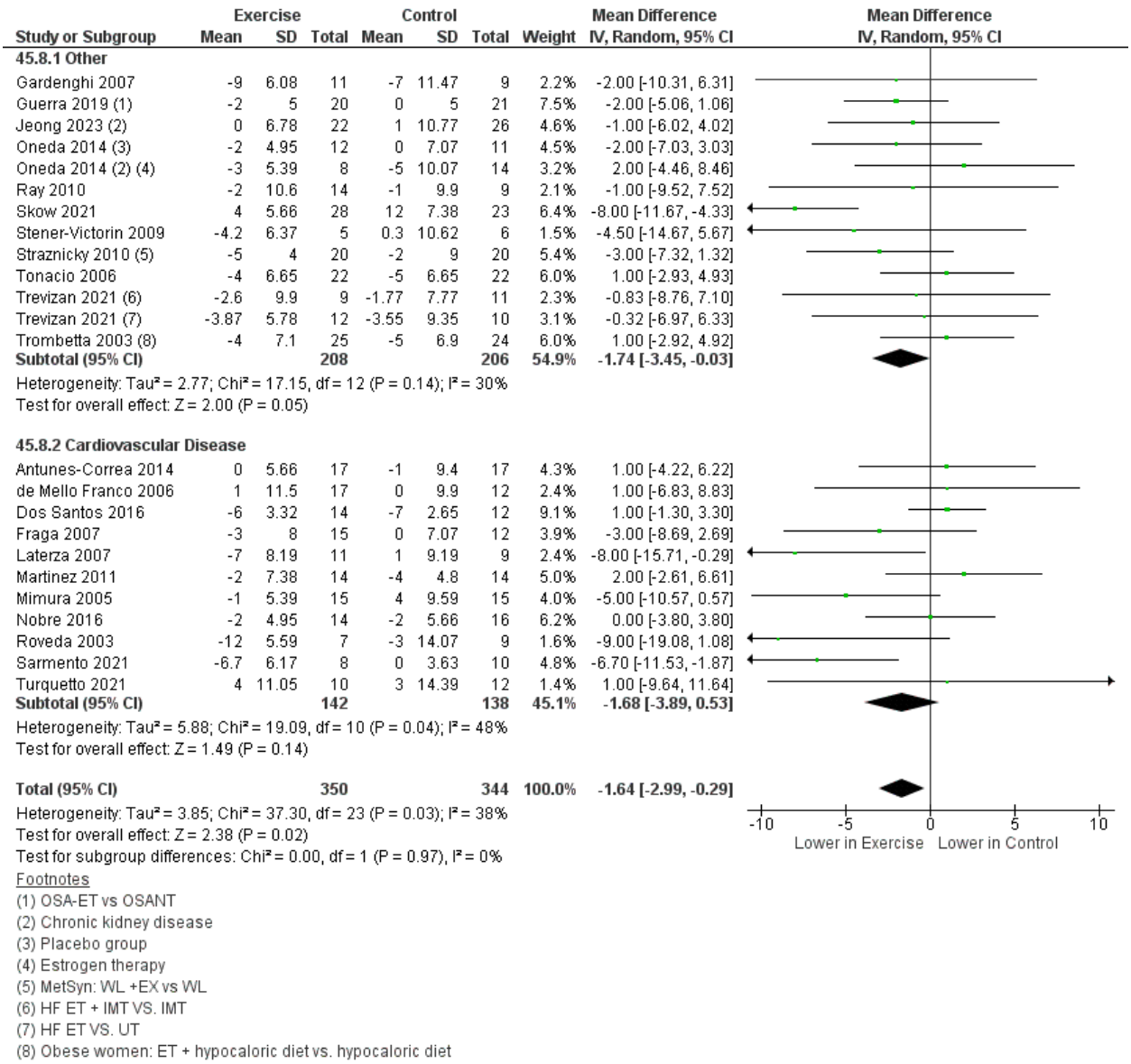
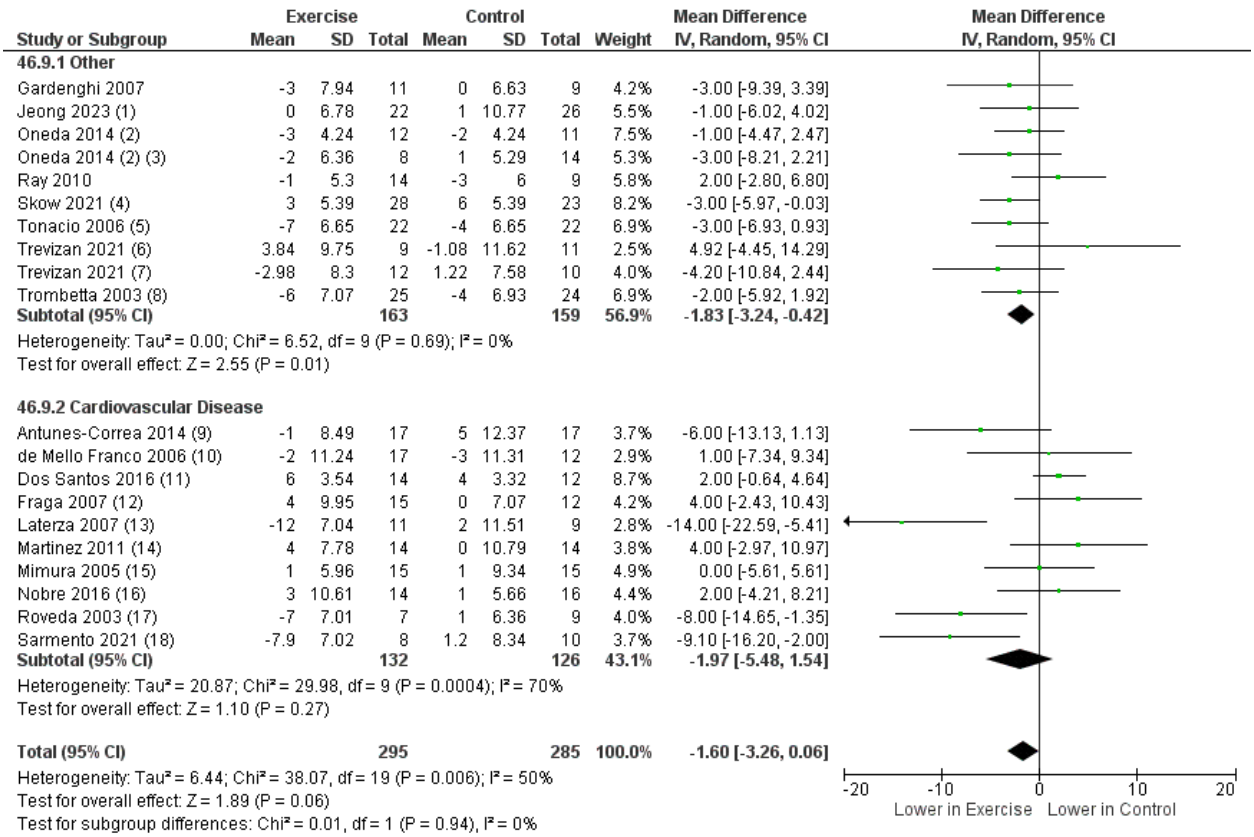


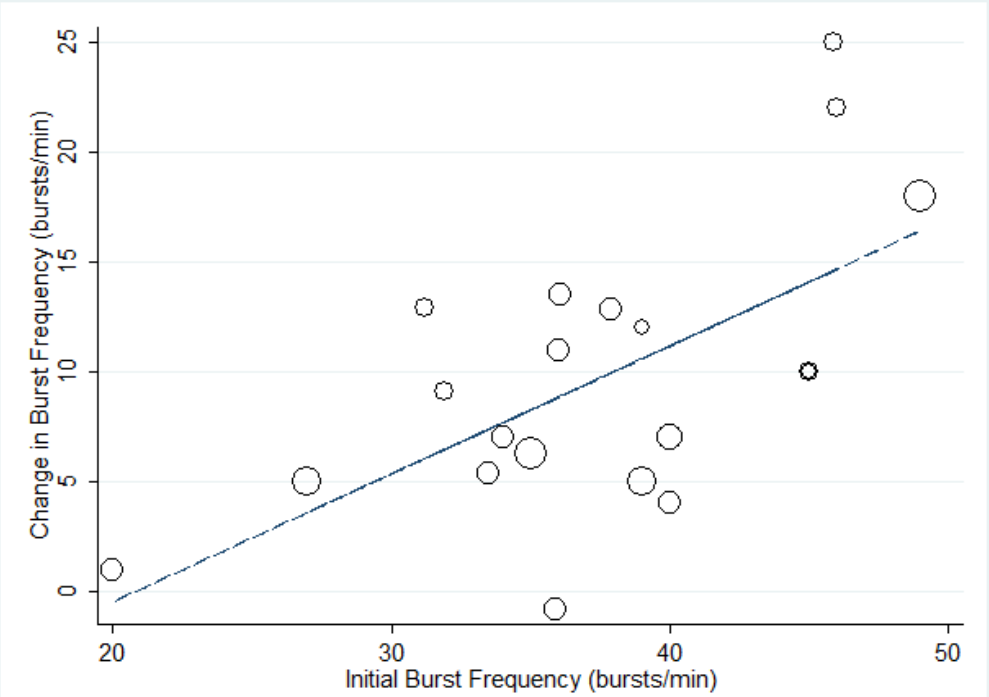
Figure 5



Footnotes

(1) Chronic kidney disease
(2) Placebo
(3) Estrogen therapy
(4) Pregnant
(5) Obese: ET + diet vs. diet
(6) IMT + ET VS IMT
(7) HF ET VS NT
(8) Obese: ET + diet vs. diet
(9) Heart failure
(10) Heart failure
(11) Heart failure
(12) Heart failure
(13) Hypertensive
(14) Myocardial infarction
(15) Acute myocardial infarction
(16) Heart failure
(17) Heart failure
(18) Chronic chagastic cardiomyopathy

Figure 6



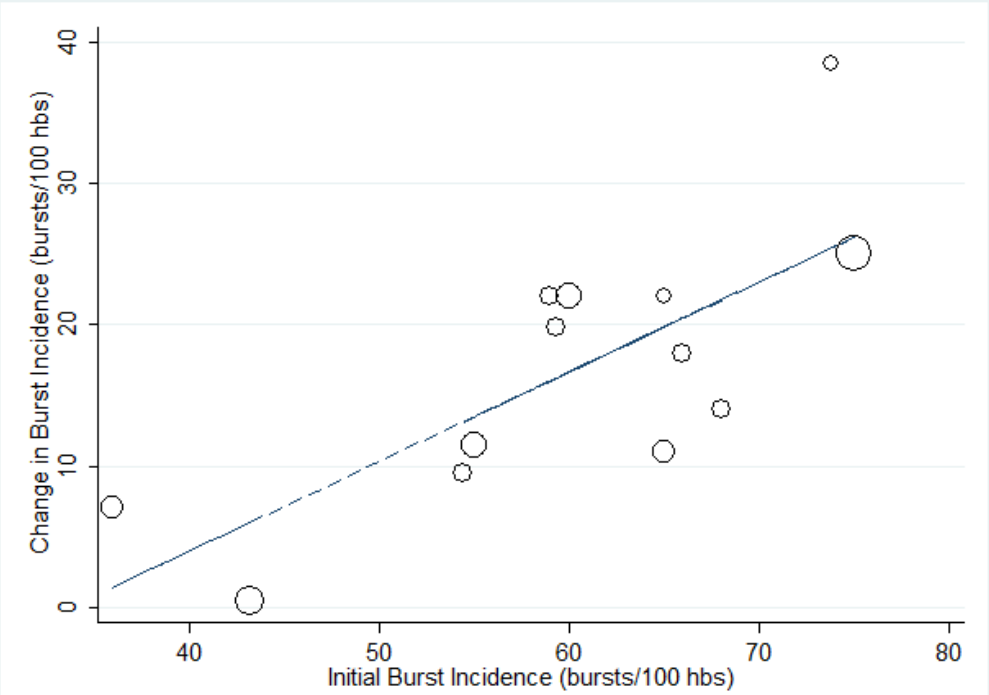
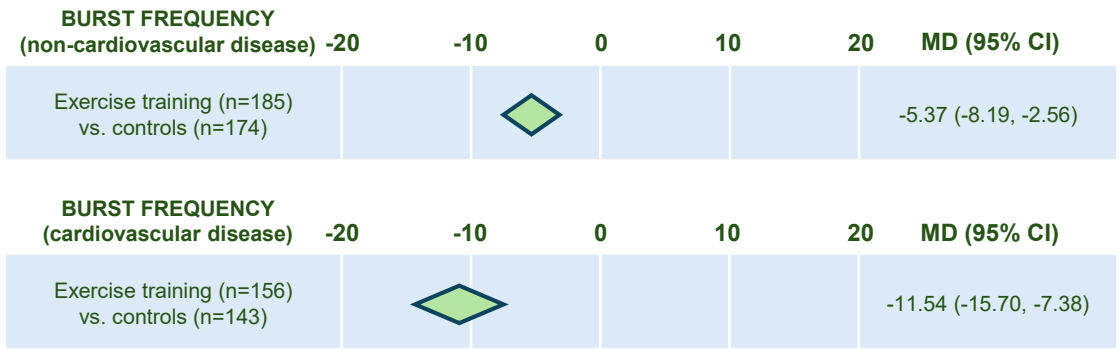


Figure 7

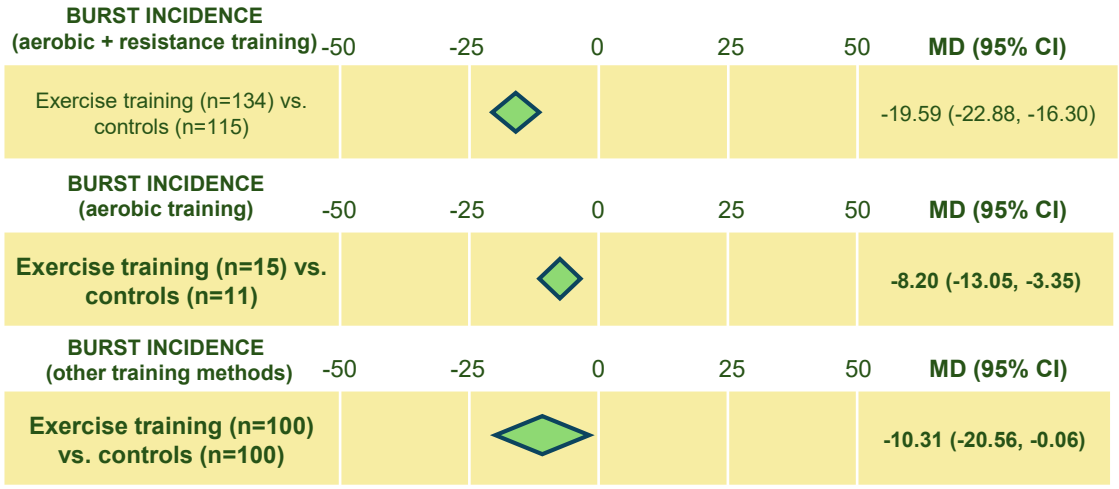
The impact of exercise training on muscle sympathetic nerve activity: A systematic review and meta-analysis

Meyer SE, Kimber M, Maier LE, Matenchuk BM, Moldenhauer R, de Waal S, Sivak A, Davenport MH, & Steinback CD

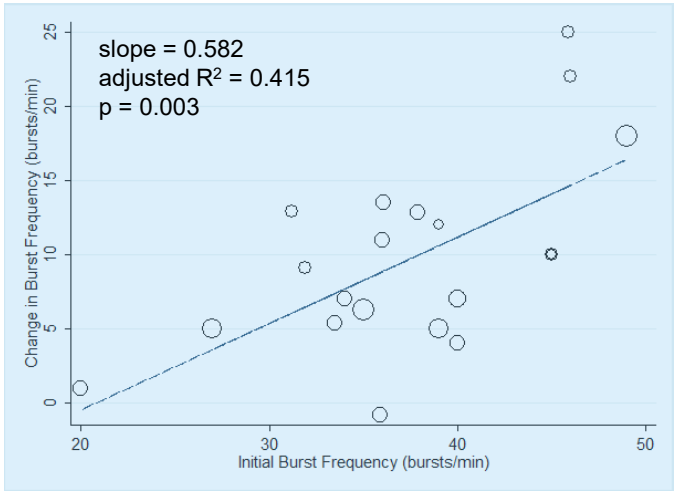
Aim: To examine the effects of exercise training on muscle sympathetic nerve activity (MSNA)

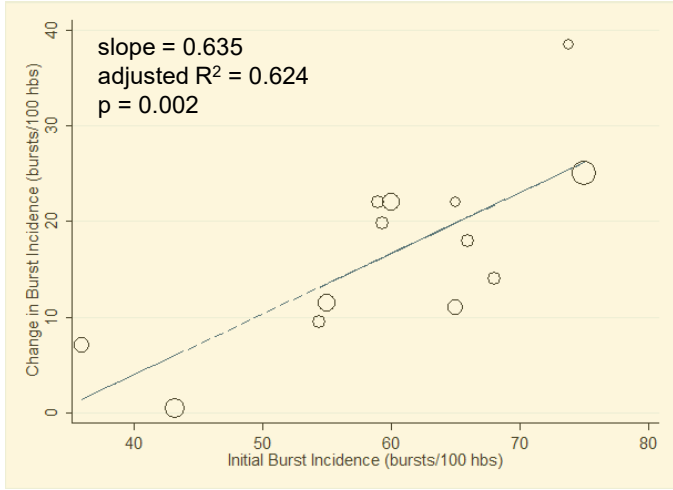


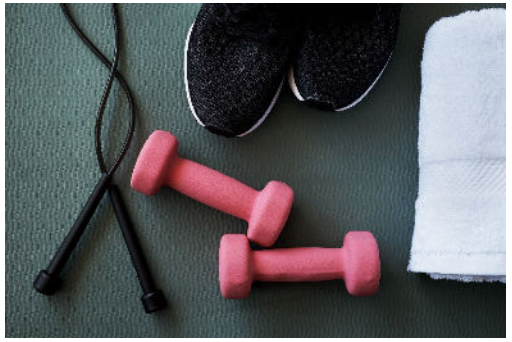
Exercise training resulted in greater reductions in burst frequency in individuals with cardiovascular disease (p=0.02)



The type of exercise training impacted the change in burst incidence following training (p=0.0004)







CONCLUSION: All types of exercise interventions significantly reduce MSNA (both burst frequency and incidence). This effect is greater among individuals with cardiovascular disease and related to prevailing MSNA.