



BMJ Open Exercise dose–response relationship with heart rate variability in individuals with overweight and obesity: protocol for a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Obesity is a chronic relapsing disease process and serious public health concern that can lead to chronic diseases, medical complications and a higher risk of disability. Another significant feature of obesity is dysfunction in cardiac autonomic function, which leads to changes in parasympathetic and sympathetic regulation, which can be measured using heart rate variability (HRV). The objective of this review is to estimate the extent to which exercise doses impacts on HRV among individuals living with overweight and obesity class I and II.

Methods and analysis A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science and the Cochrane Library for articles dating from 1965 to December 2021. Inclusion criteria include studies designed as parallel-arm randomised trials, enrolling adolescent and adult individuals with overweight (body mass index, BMI \geq 25 to \leq 29.9) and obesity (class I BMI: 30–34.9 and class II BMI: 35–39.9) undergoing aerobic or resistance training or concurrent exercise training. For data synthesis, sensitivity analysis, subgroup analysis and risk of bias assessment, Stata V.13.0 software will be used.

Ethics and dissemination Formal ethical approval is not required. This systematic review will be submitted to a peer-reviewed journal.

PROSPERO registration number CRD42019104154.

INTRODUCTION

Over the past 35 years, the global prevalence of obesity has tripled and current trends, if extrapolated would lead to approximately over one billion people by 2030.^{1,2} Individuals living with obesity have a significantly higher risk of developing cardiovascular disease, diabetes, hypertension, cancer, stroke and chronic disease, including osteoarthritis.¹ Obesity has also been linked to alteration in cardiac autonomic activity as seen when measuring heart rate variability (HRV).^{3,4} HRV is a non-invasive technique for analysing autonomic function by measuring beat-to-beat

Strengths and limitations of this study

- Strength of the design is the focus on dose–response analysis of intervention.
- Two reviewers will perform data extraction and risk of bias evaluation separately.
- Only English language article will be included.

changes in R-R intervals of ECG signals.⁵ Low HRV is associated with higher skinfold thickness, higher body mass index (BMI), higher body fat percentages and is an autonomous predictor of cardiovascular mortality and sudden cardiac death.^{6–8} In contrast, higher HRV is found to be associated with reduced morbidity, mortality, improved quality of life and psychological well-being.^{9–11}

Earlier studies have reported that obese individuals are relatively more susceptible to ventricular arrhythmias, which has been found to be a powerful indicator of sudden death.^{12–15} Several researchers have shown decreased HRV in obese people (BMI \geq 30) and this suggests that autonomic disturbances could be involved in the processes stimulating arrhythmia in such people.^{16–18} Weight loss by exercise training and dietary intervention, on the other hand, has been shown to reverse the detrimental impact of weight gain on autonomic function.^{6,7,18,19}

Benefits of exercise training are documented as a possible non-pharmacological weight-loss approach.^{20,21} All forms of exercise, whether aerobic, resistance or combination of aerobic and resistance (concurrent), are effective methods of improving anthropometric indicators of adiposity.^{22–24} These exercise types are characterised by multiple subdivisions such as frequency, intensity and

volume of exercise that may be considered to constitute the exercise 'dosage'. The effectiveness of the exercise intervention in reducing body weight is documented as dose-dependent and it is mediated by autonomic control.^{25–29}

Current evidence on the influence of long-term exercise training on HRV in healthy or obese individuals is inconsistent, with several studies showing significant increase in the HRV following an exercise training with varying dose ranging from 3 weeks to 12 months of exercise training in healthy and obese individuals^{7 19 30–33} while other studies did not show such an effect.^{34–36} Such differences in effect may be due to either participant attributes, a technique of measurement to estimate HRV, study design, exercise types and/or exercise dose parameter.³⁶

A meta-analysis done using data from studies carried out in healthy people suggested that aerobic exercise training can make substantial improvements in the R-R interval, and the effect size for changes in the R-R interval recorded in this study was significantly higher in long exercise interventions (>12 weeks) than in shorter treatments (<12 weeks).²⁹ Meta-analysis including studies done in the elderly³⁷ suggested endurance-type exercise is effective for increasing HRV, and exercise frequency appears to be a powerful component of training that leads to HRV improvement.

A recent meta-analysis¹⁹ reported improvement in HRV following weight-loss strategies such as dietary approaches, aerobic training, strength training and exercise programmes coupled with dietary approaches. Also, this study suggested that the impact of weight loss on the autonomic nervous system (ANS) might depend primarily on the amount of weight loss. Differences in the dosage of exercise, such as the duration, frequency and strength of exercise training, are considered to be responsible for the degree of improvement in autonomic cardiac function and the change in body weight.¹⁹

The exercise-based weight loss programmes are known to be a key part of therapy for obesity and evaluating its impact on HRV would add value to current assessments of the evidence base. In addition, no studies to date have comprehensively analysed and examined the evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore, the objective of this review is to estimate the extent to which exercise-dose increases HRV in individuals living with overweight and obesity class I and II.

METHODS

Patient and public involvement

No patient involved as it is a systematic review. The results will be disseminated by the publication of the manuscript in a peer-reviewed journal.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols guidelines are used for the current study. PRISMA will be used to assist reporting of the SR, once completed.³⁸ This systematic

review will consider only randomised controlled trials (RCTs). Any amendments to this study protocol will be reported.

Electronic search

Seven databases will be searched; PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science and the Cochrane Library, for articles dating from 1965 to December 2021.⁵ We will also refer to ClinicalTrials.gov, the WHO's registry platform ICTRP, the reference lists of key articles identified via Scopus and articles that cited the included articles. Also, authors will be contacted to obtain for studies that have been completed but not published. If more than one publication describes the same study, the one that provides the most data will be included in the meta-analysis. Studies will be limited to publications in the English language. The search will be carried out by the first author and a medical librarian. **Box 1** Shows the search strategy for PubMed.

Eligibility criteria and study selection

The titles and abstracts screening will be done for eligibility and the article considered appropriate will be reviewed in full-text papers. This process will be conducted using Covidence (www.covidence.org)³⁹ and it is expected to be completed by December 2021.

Inclusion criteria

Studies will be included if they report data from (1) parallel-arm RCTs, (2) enrolled adolescent (age ≥ 10 years) and adult individuals with overweight (BMI ≥ 25 to ≤ 29.9) and obesity (class I BMI: 30–34.9 and class II BMI: 35–39.9) undergoing aerobic or resistance exercise training or concurrent exercise training (**table 1**)²⁷ and had an outcome of interest as HRV (3) exercise intervention is reported in terms of frequency, intensity, time and type, and (4) measurement of at least one variable of HRV before and after the training intervention is reported.

Exclusion criteria

Exclusion criteria will be (1) observational studies, (2) studies measuring acute exercise effects, (3) obesity class III (BMI ≥ 40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and (4) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.^{37 40 41}

Study selection

Following different database searches, retrieved articles will be imported to the Covidence platform³⁹ where the results will be combined and duplicates will be removed. As a large number of papers are expected to require screening, four authors will be involved in screening. These authors will also perform pilot-testing of eligibility criteria on the first 10% of titles and abstracts. To harmonise the screening process, a training session will be provided to all reviewers. During this session,

Box 1 Shows the search strategy for PubMed

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Word]) OR exercise[Title]) OR exercise[Title/Abstract])) OR (((aerobic
exercise) OR aerobic exercise[Text Word]) OR aerobic exercise[Title]) OR
aerobic exercise[Title/Abstract])) OR (((resistance exercise) OR resis-
tance exercise[Text Word]) OR resistance exercise[Title]) OR resistance
exercise[Title/Abstract])) OR (((concurrent exercise) OR concurrent
exercise[Text Word]) OR concurrent exercise[Title]) OR concurrent exer-
cise[Title/Abstract])) OR (((combination exercise) OR combination
exercise[Text Word]) OR combination exercise[Title]) OR combination
exercise[Title/Abstract])) OR (((("resistance training"[MeSH Terms]) OR
resistance training) OR resistance training[Text Word]) OR resistance
training[Title]) OR resistance training[Title/Abstract])) OR (((aerobic
training) OR aerobic training[Text Word]) OR aerobic training[Title]) OR
aerobic training[Title/Abstract])) exercise dose OR dose response OR
aerobic dose OR resistance dose OR concurrent dose OR combina-
tion dose OR (((("cardiorespiratory fitness"[MeSH Terms]) OR cardio-
respiratory fitness[Text Word]) OR cardiorespiratory fitness[Title]) OR
cardiorespiratory fitness[Title/Abstract]) OR cardiorespiratory fitness))
OR (((physical activity) OR physical activity[Text Word]) OR physical
activity[Title]) OR physical activity[Title/Abstract])) OR (((cardiorespi-
ratory endurance) OR cardiorespiratory endurance[Text Word]) OR cardio-
respiratory endurance[Title]) OR cardiorespiratory endurance[Title/
Abstract])) OR (((strength training) OR strength training[Text Word])
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(((strengthening) OR strengthening[Text Word]) OR strengthening[Title])
OR strengthening[Title/Abstract]))
AND
((((("overweight"[MeSH Terms]) OR overweight) OR overweight[Text
Word]) OR overweight[Title]) OR overweight[Title/Abstract])) OR
(((("obesity"[MeSH Terms]) OR obesity) OR obesity[Text Word]) OR
obesity[Title]) OR obesity[Title/Abstract])) OR (((healthy individuals[Text
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Abstract]) OR healthy individuals))
AND
(((((((heart rate variability) OR heart rate variability[Text Word]) OR heart
rate variability[Title]) OR heart rate variability[Title/Abstract])) OR (((au-
tonomic function) OR autonomic function[Text Word]) OR autonomic
function[Title]) OR autonomic function[Title/Abstract])) OR (((sympa-
thetic function) OR sympathetic function[Text Word]) OR sympathetic
function[Title]) OR sympathetic function[Title/Abstract])) OR (((para-
sympathetic function) OR parasympathetic function[Text Word]) OR
parasympathetic function[Title]) OR parasympathetic function[Title/
Abstract])) OR (((vagal function) OR vagal function[Text Word]) OR vagal
function[Title]) OR vagal function[Title/Abstract]))
  
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reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement (ie, thresholds: <0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement and >0.80 almost perfect agreement).⁴² Disputes will be settled by

Table 1 Operational definitions of exercises type used for the current systematic review according to the American College of sports Medicine²⁷

Exercise type	Operational definition
Aerobic/endurance exercise training	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training programme

agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed (figure 1).⁴³

Data extraction and analysis

Outcomes

In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD, pNN50) and frequency domain variables of HRV (total power, VLF, LF, HF, LF/HF ratio) (table 2).

Secondary outcomes include cardiorespiratory endurance, muscular strength, adiposity/anthropometric measures. These outcomes are chosen based on the previous research.^{7 19 30–33} If data are available in qualifying studies, the relationship of exercise training with other endpoints, such as time effect and interaction effect with sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence and life stress, will also be analysed.

Data extraction

A data extraction form will be adopted from published literature.^{44–46} Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/publication year, duration, place of the trial conducted, number of participating centres, study design), the participants (sample size, participants randomised and patients analysed in each group, age, sex, socioeconomic status, height, weight, BMI, waist circumference, waist-hip ratio, waist-height ratio and body fat per cent), intervention (aerobic, resistance and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration and progression), control group treatment, method of randomisation, method of allocation, blinding process, outcome time point and follow-up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement HRV reported either in absolute or log transformed or both. Two independent reviewers will pilot test the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session

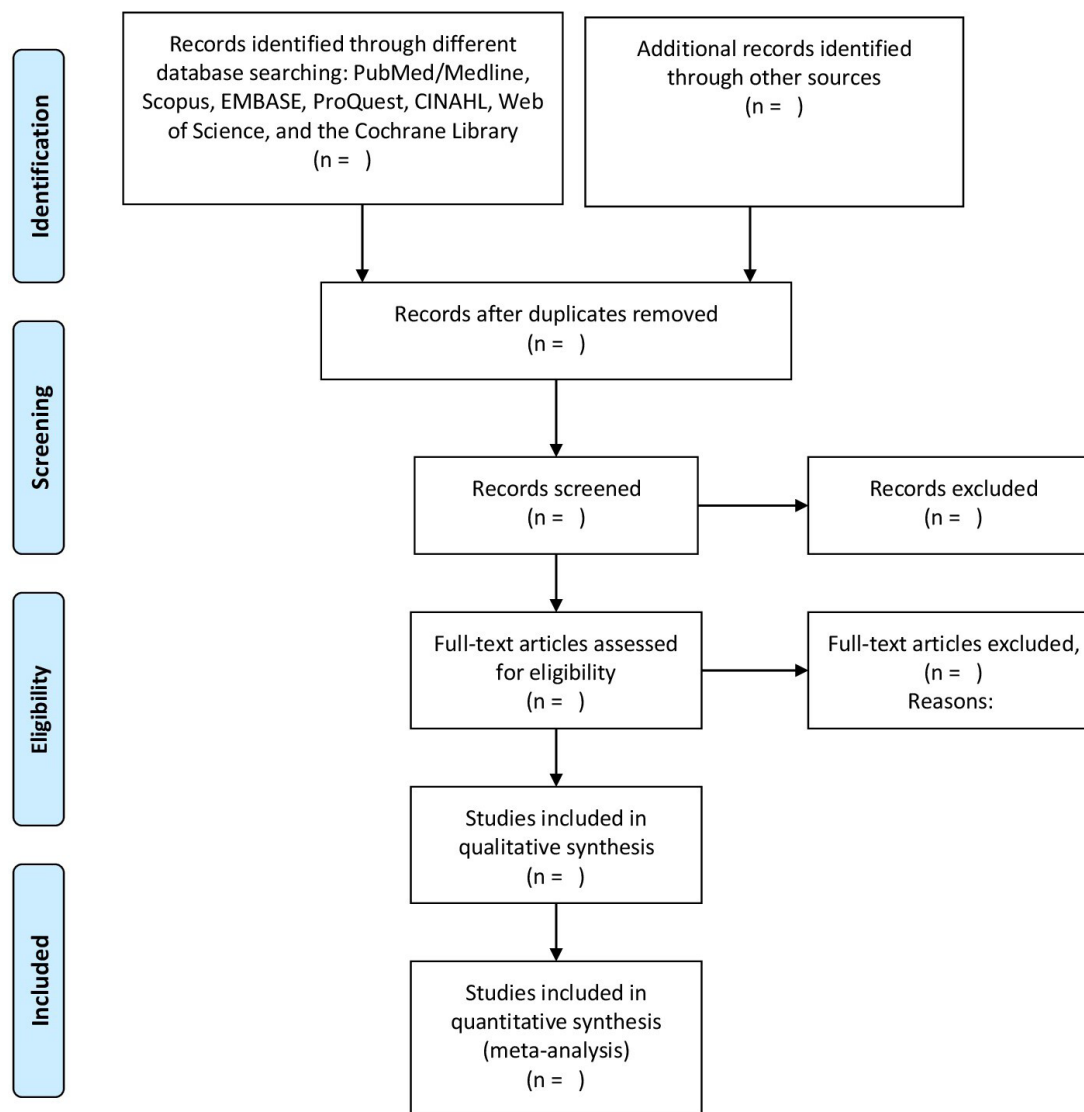


Figure 1 Flow diagram for study selection based on the PRISMA guidelines.⁵⁵ PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 2 Heart rate variability (HRV) domains⁵

Time domain measures of HRV: variable (units) and description	
SDNN (ms)	SD of all NN intervals
SDANN (ms)	SD of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total no of all NN intervals
Frequency domain measures of HRV: variable (units) and description	
Total power ms ²	The variation of NN intervals over the temporal segment
VLF (ms ²)	Power in very low frequency range
LF (ms ²)	Power in low frequency range
HF (ms ²)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

will be held to harmonise the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written ‘Data Extraction Guide’ with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and risk of bias assessment

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration’s Risk of Bias Tool 2.0⁴⁷ for risk of bias assessment across five domains. Assessments will be carried out

using an iterative online form available.⁴⁸ The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim *et al.*^{49 50} For each domain, the probability of bias will be evaluated as ‘low risk’, ‘some concerns’ or ‘high risk’. If at least one area is listed as ‘high risk’, studies will be deemed to have an overall high risk of bias. Quality of evidence will be measured using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) rating system.⁵¹ Publication bias will be evaluated using visual inspection of funnel plot asymmetry.⁵²

Data synthesis strategy: meta-analysis

We will primarily examine the training effect (aerobic, resistance and concurrent exercise training) on HRV. We will also explore possible sources of heterogeneity among studies by examining aerobic, resistance and concurrent exercise impact with time point. To attain the standardised mean difference and 95% CI, the data of interest given as continuous will be used for meta-analysis. The Q -statistic and I^2 tests will be used to test for heterogeneity between the included studies. Heterogeneity will be considered low if I^2 is $\leq 40\%$, and high if I^2 is $\geq 75\%$. We will use a random-effects model for meta-analysis. If substantial heterogeneity ($I^2 > 40\%$) or fixed effects for homogeneous effects ($I^2 < 40\%$).⁵³ Aggregate data obtained from the included studies will be used for quantitative synthesis. By plotting the data on a forest plot, heterogeneity will be evaluated visually.⁵⁴

Analysis of subgroups or subsets

The subanalysis will include baseline participant characteristics and exercise intervention characteristics. Interaction effects between variables will be identified for subgroup analysis.⁵⁴

Significance

Due to modernisation and mechanisation of lifestyle, there is an increase in overweight and obesity globally. Exercise is a key element to prevent lifestyle disease, therefore, it is important to explore dose–response benefits specifically towards HRV to maximise the physiological benefits. The study would help to understand the autonomic response of the heart (ie, HRV) at different doses of exercise training. Also can help to recommend the training regimen for overweight and obese people for optimum gain in HRV.

ETHICS AND DISSEMINATION

This review will not require an ethical authorisation, since participant privacy issues do not exist. Our results will provide data on the various forms of exercise dose–response on the HRV in overweight and obese people. The results of this study will be published in a peer-reviewed international journal, displayed at relevant conferences and disseminated to obesity-focused public organisations.

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Contributors MKS, VK, AMM and GAM conceived of the study and provided guidance for drafting the protocol. AMM and MKS designed the search strategy. MKS, VK, AMM, SKN, RSN and GAM drafted and reviewed the final version systematic review protocol manuscript for submission. All the contributors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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