BMJ Open

Effect of exercise interventions on brain-derived neurotrophic factor expression in people with overweight and obesity: protocol for a systematic review and meta-analysis

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To cite: Leung WKC, Yau SY, Suen LKP, *et al*. Effect of exercise interventions on brain-derived neurotrophic factor expression in people with overweight and obesity: protocol for a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e076118. doi:10.1136/bmjopen-2023-076118

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-076118).

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Received 29 May 2023
Accepted 27 September 2023

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ABSTRACT

Introduction Epidemic obesity ('globobesity') has led to a considerable rise in the prevalence and incidence of many disabling conditions, including cognitive dysfunction. Recent evidence has suggested that habitual exercise can alleviate the deleterious effects of obesity on cognitive functioning across the lifespan. Given that there is a potential link among obesity, exercise, cognitive health and brain-derived neurotrophic factor (BDNF), this systematic review aims to critically appraise interventional trials on exercise and BDNF and to estimate the pooled effect of exercise training on BDNF levels among healthy individuals with overweight and obesity.

Methods and analysis Six electronic databases—PubMed, MEDLINE, EMBASE, Web of Science, Ovid Nursing Database and SPORTDiscus—will be searched from their inception through December 2022. Only interventional studies, including randomised controlled trials and quasi-experimental studies, with full text available and reported in English will be included. The primary outcomes will be changes in BDNF levels among healthy subjects with overweight and obesity following either acute or chronic bouts of exercise interventions. Two reviewers will independently conduct data extraction and risk of bias assessment for included trials using the Physiotherapy Evidence Database Scale. We will produce a narrative synthesis, with findings categorised by sex, age groups and types of exercise training. Data will be extracted and pooled for meta-analyses using random-effects models.

Ethics and dissemination No formal ethical approval is required for this systematic review. The findings of this review will be disseminated through peer-reviewed publications.

PROSPERO registration number CRD42023414868.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This work will attempt to comprehensively review the evidence regarding the effects of various types of exercise interventions on brain-derived neurotrophic factor expression, which is a clinically relevant biomarker for cognitive health, in healthy people with overweight and obesity.
⇒ The study will employ rigorous methodological design and be reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
⇒ Two independent reviewers will carry out the data extraction and risk of bias assessment for the included studies.
⇒ There may be language bias as we will only consider studies reported in English.
⇒ The certainty of the evidence of this systematic review may be limited by a lack of data available for meta-analyses and the possibility of a high risk of bias of the included studies.

INTRODUCTION

Overweight/obesity and cognitive impairments

Global prevalence of overweight and obesity has increased considerably by 50% and 80% over the past 35 years, respectively.[1] Nowadays, one-third of the world's population is suffering from obesity or overweight problems. Adverse health outcomes associated with obesity include high blood pressure, cerebrovascular or cardiovascular conditions, and type 2 diabetes. Independent of underlying medical conditions, increased adiposity was also strongly associated with cognitive deficits across the lifespan.[2] In children, nearly 90% of studies showed that obesity had a detrimental influence on cognitive functioning, especially in the core domains of executive function (eg, short-term or working memory).[2] Consistent findings were also intensively observed in adults; regardless of socioeconomic status (a known positive determinant of cognition), obesity was strongly related to poorer cognitive performance, particularly executive function. In older adults, the relationship between obesity and cognitive ageing was especially high in

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midlife, but weaker in late life.[2 3] In metabolic syndrome (a cluster of obesity preceding cardiometabolic risk factors), declines in non-language executive function, including memory, attention and information processing, were highly pertaining to obesity-related cognitive impairments.[4] On the contrary, weight loss by bariatric surgery, caloric restriction or multicomponent lifestyle modification could effectively alleviate low-order executive functions, such as memory and attention.[5]

Exercise, cognitive functioning and obesity

Numerous research has substantiated exercise as an effective non-drug treatment for improving cognitive function or preventing cognitive decline in overweight and obese people. Aerobic exercise has been extensively shown to improve cognitive functions, including improved memory function,[6] delayed brain atrophy (especially hippocampal volume loss)[6–8] and increased white matter volume.[7 8] Balance training could also stimulate both sensory (vestibular and proprioceptive) and neuromuscular systems, making connections between vestibular nuclei and the cerebellum, hippocampus, as well as some cortical regions (prefrontal and parietal).[9] The connections hence positively affect cognition, especially memory, navigation and spatial functions. In older adults, exercise training was also shown to promote recruitment of additional cortical zones to offset the neural efficiency loss associated with ageing.[10] Currently, a 2018 Cochrane Review has provided high-quality evidence for an after-exercise group to improve scores in tests of executive function in obese or overweight children and adolescents.[11] Likewise, other latest systematic reviews suggested that physical activity (PA) interventions had a favourable effect on core domains of executive function likely through amelioration of adiposity in both obese humans as well as animal models of obesity.[12 13] In older adults with overweight and obesity, being physically active also conferred cognitive and neuroprotective benefits against cognitive ageing and dementia in respect of improved global cognition and frontal function.[14]

Neural mechanisms underlying cognitive benefits of exercise training

Remarkable neural growth in the dentate gyrus of the hippocampus following habitual exercise that is strongly linked to better memory and learning has been largely implicated and extensively verified in a number of experimental rodent models.[15] Signalling pathways that were most studied in these exercise-dependent changes in cognitive functioning were brain-derived neurotrophic factor (BDNF)[15–17] and insulin-like growth factor-1.[17] Other potential neurobiological pathways were adiponectin,[18 19] irisin[20] and other PA-related myokines.[21 22] Given that both obesity and cognitive deterioration are closely related to low BDNF[23 24] and the relationship can be reversely moderated by increased PA levels via BDNF induction,[25–27] it is strongly believed that the major factor accounting for the cognitive benefits of exercise training in obesity is enhanced level of BDNF.

Exercise training and BDNF-associated cognitive functions in obesity

BDNF belongs to the family of neurotrophic polypeptides, which play a pivotal role in neurogenesis, neural growth and development, neuronal survival, neuroplasticity, synaptogenesis, brain network connectivity and cerebral blood supply. At hippocampal neurons, BDNF can attenuate deleterious effects of glutamate toxicity by binding with tropomyosin receptor kinase B, which hence orchestrates a number of intracellular signalling cascades, such as Ras/MAPK or PI3K/Akt pathways.[28] Due to muscle contraction during exercise, BDNF is largely synthesised and secreted in hippocampus[29 30] and in myocytes.[22] As BDNF is able to cross the blood–brain barrier and effectively shuttle between the brain and the blood circulation,[31] the peripheral/circulating BDNF levels have long been considered a good representation of its cortical levels.[32 33] Of note, reduced peripheral or brain levels of BDNF were strongly implicated in the pathogenesis of neurodegenerative diseases, such as dementia and Alzheimer's disease.[34–36] Meanwhile, increment in BDNF levels by drug interventions or mimic supplementation can be an effective remedy for Alzheimer's disease and its progression.[35] Beyond involvement in brain function, BDNF was also shown to have metabolic properties, particularly in response to increased blood glucose levels.[37] Research has demonstrated that prolonged hyperglycaemia and hyperlipidaemia following glucose injection, mimicking the effects of high-fat diet, hampered the expression of BDNF in some parts of the brain.[37] Recent studies using experimental animal models further provided supporting evidence for the association between BDNF improvement and exercise-associated cognitive benefits (eg, delayed cognitive decline, beta-amyloid inhibition and hippocampal anti-inflammation) in obese or pre-symptomatic rodents.[38–41] These findings suggested a potential link between low BDNF and cognitive impairments in the context of obesity.

Research gaps and objectives

A 2015 meta-analytical review demonstrated moderate effect sizes for increments in BDNF acutely after a single bout of exercise, while chronic exercise further intensified BDNF enhancement.[42] However, a 2020 systematic review has revealed that the directionality of changes in circulating BDNF levels in response to exercise was equivocal, especially in obesity-related pathophysiological contexts (eg, type 2 diabetes).[43] Therefore, this study will be conducted to settle controversies arising from these two apparently conflicting systematic reviews, which are of the strongest strength of evidence. Besides, to the best of our knowledge, the present review is the first to document the strength and reliability of the effects of exercise interventions on BDNF changes in obesity contexts. The objective of this review is to systematically evaluate

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the effects of varying exercise interventions on BDNF in healthy individuals with overweight and obesity.

METHODS AND ANALYSIS

Study design

The study protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines.[44 45] Reporting of the study flow and findings will be in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 updated guideline for reporting systematic reviews.[46 47]

Types of studies

This review will include interventional studies, including both randomised controlled trials (RCTs) and quasi-experimental studies, which aimed at examining the effects of exercise interventions (eg, aerobic training, resistance training, functional training, exergaming, etc) on BDNF levels in healthy individuals with overweight or obesity. Only studies with full text available and in English language will be included.

Types of participants

The present review will only include healthy human subjects with overweight or obesity. Obese or overweight subjects comorbid with other pathological conditions (eg, type 2 diabetes) will not be considered. Studies involving only non-human subjects (eg, experimental animals) will also be excluded.

Type of interventions

Standalone or multicomponent exercise interventions have to be included in at least one experimental arm within the studies. Exercise interventions in combination with other types of non-exercise (eg, diet control) interventions in a multimodal programme will be excluded. It is because the effects of exercise interventions on BDNF levels may be blinded by other non-exercise interventions and cannot be solely studied.

Types of comparison controls

Comparison groups across the included controlled trials will be categorised into either active or non-active controls. For active controls, we define them as exercise interventions at a lower intensity/training dosage or active strategies interrupting sedentary time/behaviour. For non-active controls, we define them as non-exercise interventions, including 'diet control', 'usual care', 'no treatment' and 'wait-list control'.

Outcome measures

The primary outcome of interest is the change in BDNF levels (protein and RNA) in response to either acute or chronic exercise interventions. The biological samples of interest include blood (whole blood, serum and plasma), urine, adipose tissues, brain tissues (eg, hippocampus and cerebral cortex), muscles, saliva, etc. The BDNF levels should be numerically quantified using biological laboratory techniques, including ELISA, routine chemistry analyser, western blot, quantitative PCR, histological examination, immunofluorescence staining, cell cytometry, etc.

Electronic database search

Potential studies will be identified using six electronic databases—PubMed, MEDLINE, EMBASE, Web of Science, Ovid Nursing Database and SPORTDiscus—from their inception through December 2022. To avoid missing any eligible studies, the reference lists of all included articles or searched review papers will also be screened. The text word terms used in the electronic database search (title/abstract/subject/keywords) will be obes*, overweight, metabolic syndrome, physical activity, exercis*, resistance training, aerobic training, functional training, exergam*, cogniti*, BDNF, brain-derived neurotrophic factor and brain derived neurotrophic factor. The search queries for each database with limiters are summarised in online supplemental appendix 1.

Data collection and analysis

Study selection

A two-stage screening approach will be adopted to initially screen the titles and abstracts, followed by the full texts. The population, intervention, comparison, outcome, study design framework will be employed to guide the inclusion of the searched studies. If the information of the searched studies cannot be verified in the initial screening stage (eg, key information not clearly provided in the abstract), full-text assessment for these studies along with other potentially eligible studies will be conducted. The study selection process will be reported according to the PRISMA 2020 flow diagram (http://prisma-statement.org/) (figure 1).

Data extraction

The extracted information, including authors, publication year, number of participants in the intervention group and their characteristics, details of interventions and controls (eg, training volume (frequency×intensity×time), programme duration and attrition/dropout) and key findings (ie, changes in the BDNF levels), will be summarised into an evidence table. All data obtained will be independently checked by two review authors.

Risk of bias assessment

Given that more than 15 000 records were indexed on the Physiotherapy Evidence Database (PEDro) Scale and more than 60% of PEDro records were coded as highly relevant to sports physiotherapy,[48] the PEDro Scale will be used to examine the methodological quality of the included studies (online supplemental appendix 2). The PEDro Scale is a reliable and valid instrument for assessing the methodological quality of RCTs and non-RCTs about the effects of exercise interventions on cognitive functioning.[49 50] In brief, the PEDro Scale consists of 11 items (eligibility, randomisation, allocation concealment,

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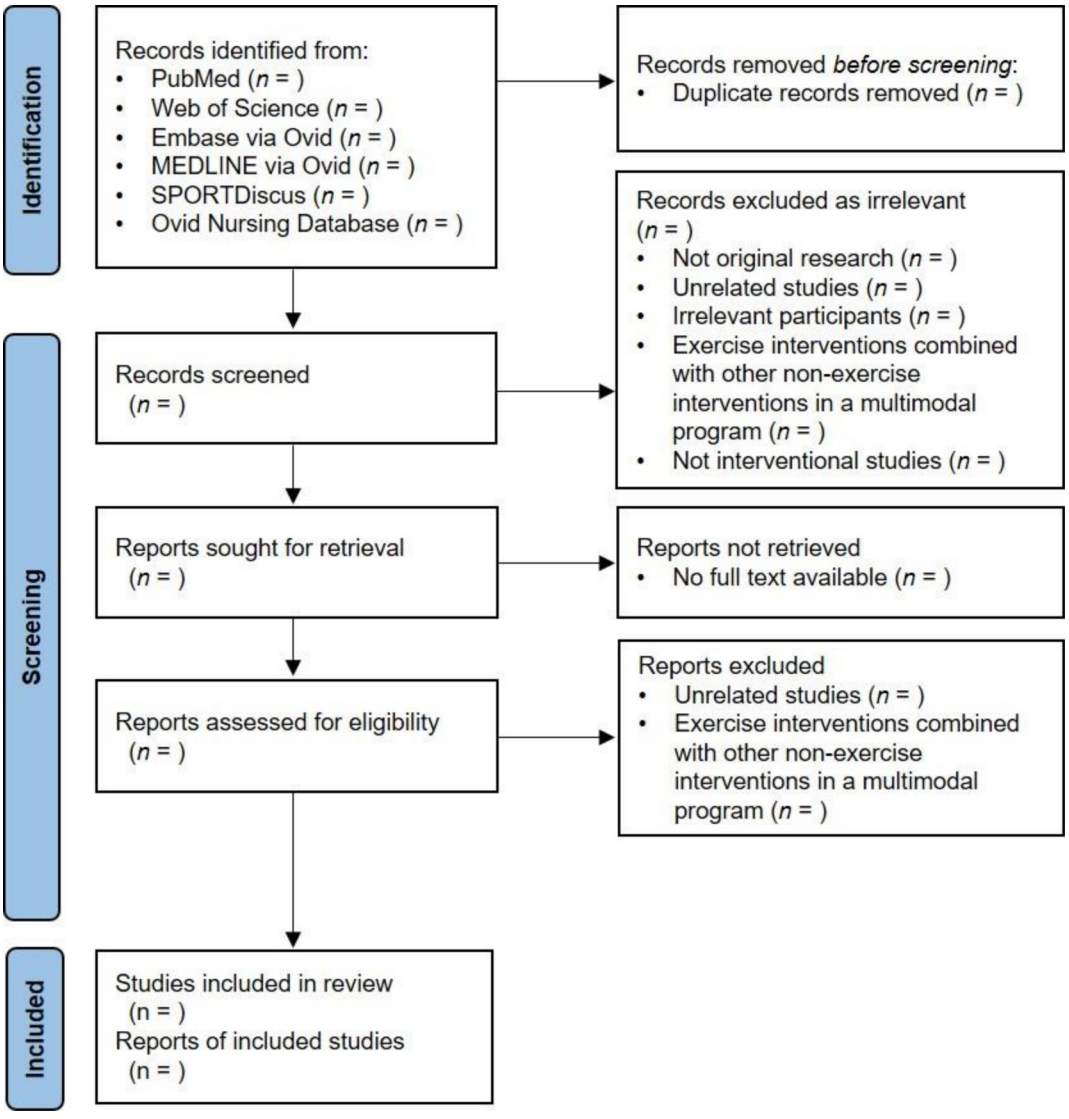

Figure 1 Flow diagram of study selection.

baseline comparison, blinding (subjects, therapists and outcome assessors), completeness of results, intention-to-treat, between-group comparison and point measures), where we will be required to fill out 'no' or 'yes'. For each 'no' or 'yes' response, we will assign a value of 0 or 1, respectively. A total score for each included study ranges from 0 to 11. As blinding (especially subjects and therapists) was not easily implemented in exercise intervention trials,[48] the methodological quality classification of included studies will be adjusted as previously described (sum scores: ≥6 ('high quality, low risk of bias'); scores: 4–5 ('acceptable quality, moderate risk of bias') and scores: ≤3 ('low quality, high risk of bias')).[49–51] The results will be independently checked by two review authors.

Estimate of pooled effect size

For continuous outcomes that were measured using different scales, data will be summarised as standardised mean difference, while for continuous outcomes that were measured by the same unit of measures, data will be represented as weighted mean difference. The pooled estimates of effect size for each outcome will be interpreted as small (0.2–0.49), medium (0.5–0.79) or large (≥0.8) according to the Cohen's rule of thumb for effect sizes.[52]

Handling of missing data

In case of missing information (eg, mean BDNF levels), we will contact the study authors accordingly. If the authors are unable to provide the required information, we will address the possible impacts of missing data on our synthesised evidence in the discussion section. All meta-analyses will only be conducted on raw data available at the time of publication.

Assessment of heterogeneity in included studies

The degree of heterogeneity across studies will be assessed using Higgins I^2 statistics. Results of the I^2 statistics in 0–25%, 25–50% and >50% represent low, moderate and high heterogeneity, respectively.

Subgroup analysis

Subgroup analyses will be carried out for potential moderators (eg, age, sex, types of comparison controls, etc)

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given that there are sufficient number of studies included for meta-analyses.

Sensitivity analysis

To guarantee the robustness of evidence, we will perform sensitivity analysis by excluding studies of low quality. We will then compare the results to decide whether studies with high risk of bias should be excluded according to strength of evidence, pooled effect sizes and study heterogeneity.

Assessment of publication bias

Given that when there are at least 10 studies in the meta-analysis, funnel plots will be constructed to visually examine the potential for publication bias of the included studies. Asymmetry of the funnel plots (ie, 'file drawer problem') indicates possible publication bias of the included trials.

Data synthesis

For controlled trials, pairwise meta-analysis will be conducted using a random-effects model, which takes into account possible variations in effects sizes across trials.[53] All meta-analyses will be conducted using Review Manager (V.5.4) software. Stratified by age categories (children and adolescents, adults and older adults), exercise modes (eg, aerobic training or resistance training) and sex (males vs females), a narrative synthesis of the findings from the included trials will also be carried out.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

This systematic review will not require formal ethical approval because the study will only consider published articles, and all data available among included studies should be anonymous with no concerns about participant privacy or confidentiality. Our findings will provide information about the effects of various exercise interventions on BDNF in healthy individuals with overweight and obesity, where the research area is rapidly emerging, clinically relevant and short of research efforts. The findings of this review will be disseminated through peer-reviewed academic journals.

Contributors WKCL, SYY, LKPS and SCL conceived and designed the study. This protocol was drafted by WKCL, and then edited by SYY, LKPS and SCL. WL designed the search strategies, while WKCL and SYY will conduct the search, data extraction and risk of bias assessment independently. WKCL and SYY will analyse and interpret the data. LKPS and SCL will resolve any disagreements during the review. All authors have approved the final version of this study protocol.

Funding The study was supported by the College Research Grant 2022/23 (ref. CRG2022/04, peer-reviewed competitive grant), Tung Wah College, Hong Kong Special Administrative Region of China.

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 required.

Provenance and peer review Not commissioned; externally peer reviewed.

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