

DOES PHYSICAL EXERCISE INCREASE BRAIN-DERIVED NEUROTROPHIC FACTOR IN MAJOR DEPRESSIVE DISORDER? A META-ANALYSIS

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SUMMARY

Background: Major depressive disorder (MDD) is one of the most common disorders in the world, but is generally refractory to antidepressant treatment. However, physical exercise has been demonstrated to improve MDD symptoms, though the mechanism through which this is achieved is not clear. This systematic review and meta-analysis aimed to clarify whether physical exercise increased brain-derived neurotrophic factor (BDNF) in patients with MDD to either establish or rule out this effect as a possible mechanism.

Subjects and methods: We searched five electronic databases (PubMed, PsycINFO, CHINAL, Cochran Library, and Japanese Central Review of Medicine) for interventional studies released prior to 24 October 2017, examining the effects of physical exercise on BDNF in patients with MDD that compared the experimental group with an MDD control group. Those studies meeting the inclusion criteria were subjected to a meta-analysis in which changes of BDNF from baseline to post-exercise were quantified, with a standard mean difference and random effect model.

Results: Five studies were eligible and included 199 participants. All articles included subjects with severe symptoms; three articles studied inpatient populations. All articles introduced aerobic exercise. We found no significant effect of physical exercise on BDNF levels ($Z=0.32$, $p=0.75$), and no heterogeneity ($I^2=0\%$). The risk of bias was moderate.

Conclusions: We conclude that physical exercise does not significantly increase BDNF in patients with MDD. Thus, while increased BDNF has been shown to be beneficial in patients with MDD, physical exercise likely produces its benefits through a different mechanism. However, the small number of included articles and lack of multiple reviewers increase the risk of the result being a false negative.

Key words: BDNF – MDD – depression – antidepressant – meta-analysis

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common disorders in the world, and its symptoms impair mood and cognition, physical health, and social and occupational functioning. MDD is generally refractory to antidepressant treatment, and can cycle between symptomatic activation and remission; notably, remitted patients do not show any MDD symptoms. However, recent developments in neurocognitive measurement have demonstrated that cognitive dysfunction is still present in patients with MDD despite their being symptomatically remitted (Rock et al. 2014).

The lack of antidepressant response in patients with MDD has forced the development of other treatment strategies, one of which is physical exercise. Exercise has shown some benefit in patients with MDD. For example, a systematic review and meta-analysis by Schuch et al. (2016) showed that physical exercise decreased depressive symptoms in patients with MDD, while Stubbs et al. (2016) also demonstrated improved cardiorespiratory fitness in patients with MDD. Thus, physical exercise intervention improved not only MDD symptoms but also physical health. The relative safety and lack of side effects of physical exercise as a treatment for depression are well-known (Lam et al. 2016), and its efficacy rivals that of psychopharma-

cological treatment (Cooney et al. 2013). These traits make physical exercise a strong candidate treatment option for MDD.

However, the mechanism underlying the effects of physical exercise on depressive symptoms remains unclear. An increase in brain-derived neurotrophic factor (BDNF) is one putative mechanism. BDNF concentrations in patients with depression were significantly lower than those in healthy controls (Sen et al. 2008), and were negatively correlated with depressive symptoms (Caldieraro et al. 2017). A meta-analysis by Zhou et al. (2017) determined that antidepressant drugs increase BDNF concentrations as well as decrease depressive symptoms. However, it is unclear whether physical exercise increases BDNF in patients with MDD. The aim of this meta-analysis was to clarify whether physical exercise increases BDNF in patients with MDD, and thus determine if such a mechanism could be at work in the benefits of physical exercise on depressive symptoms in patients with MDD.

SUBJECTS AND METHODS

Subjects

This meta-analysis included only previously published literature; therefore, its subjects were ethically protected.

Methods

Search strategy

Five electronic databases (PubMed, PsycINFO, CHINAL, Cochrane Library, and Japanese Central Review of Medicine) were searched for records dated up to 24 October 2017, using the following 3 keyword groups (with wildcards):

- Major depressive disorder;
- (Tai-chi or exergame or yoga or lift* or resistance or “physical medicine” or train* or fitness or activity* or strength* or bicycle* or cycling or aquatic* or swim* or hiking or walk* or jogging or running or aerobic* or exercise*);
- (“Brain-derived neurotrophic factor” or BDNF).

Each group was searched separately; then, the collected results from all 3 search groups were searched by joining all three keyword groups into one search formula with Boolean AND operators.

Inclusion criteria

The inclusion criteria for this review were:

- all participants (intervention and control groups) were patients with MDD;
- BDNF quantified in plasma or serum;
- conducted physical activity or exercise as the intervention;
- a randomized controlled study design;

- not a review article. The overall search strategy is summarized in Figure 1.

Analysis

Two types of analyses of eligible articles were utilized, a narrative analysis and a meta-analysis.

Narrative analysis

Eligible articles were narratively analyzed for aspects including: (1) features of subjects; (2) type of physical exercise used for intervention; (3) duration of intervention; (4) drop-out rates.

Meta-analysis

The change in plasma/serum BDNF from the pre-intervention baseline levels to those after the intervention were calculated for all participants with a standard mean difference and random effect model. All meta-analyses were performed using Review Manager 5 (The Nordic Cochrane Center, The Cochrane Collaboration 2011, Copenhagen, Denmark). All eligible articles were assessed for the risk of bias using the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011), which assesses 6 aspects of potential risk: Random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, and selective reporting.

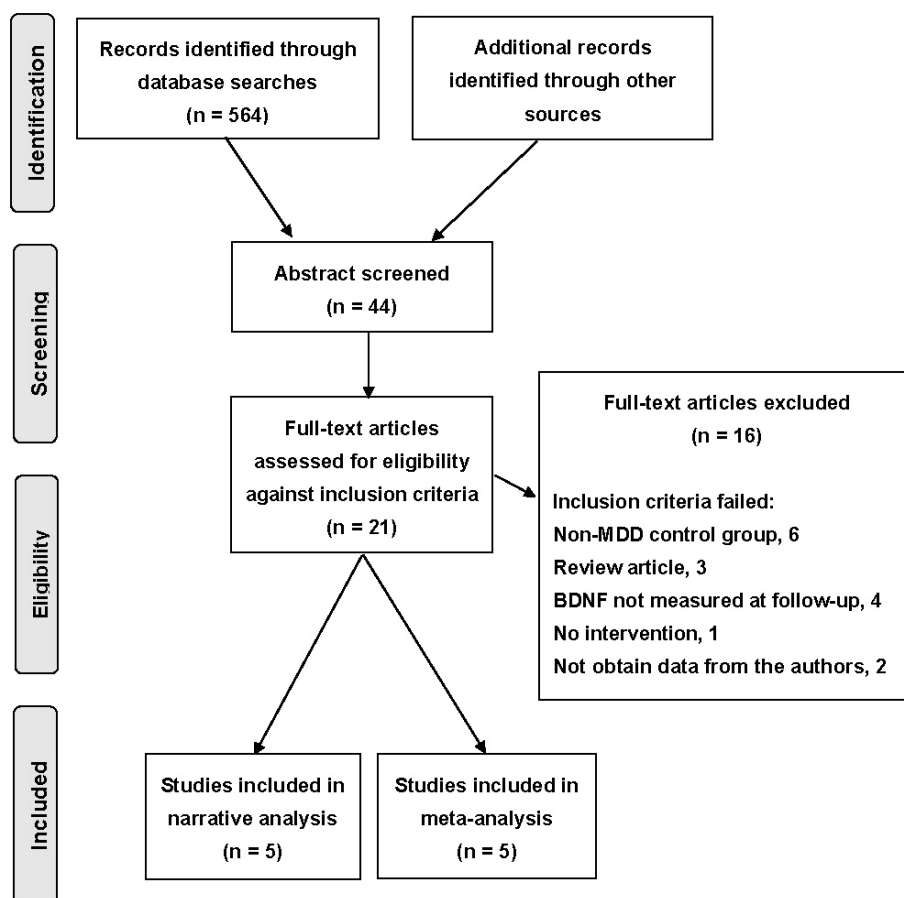


Figure 1. Flow diagram

Table 1. Summary of eligible articles

Authors	Published year	Exercise (n)	Control (n)	Mean age (exercise group or whole) (years)	Subjects' features at baseline		Treatment site	Inclusion/exclusion criteria regarding symptom severity
					Severity of symptoms, scales at baseline in exercise group or whole			
Heissel et al.	2015	7	7	68.7±3.1	31.3±6.7 BDI	severe	inpatient	Inclusion - diagnosed MDD Exclusion - ≤13 BDI
Kerling et al.	2017	22	20	44.2±8.5	29.4±10.9 BDI	severe	inpatient	Inclusion - Between ages 18 and 60 years Exclusion - Not within inclusion age range
Krogh et al.	2014	41	38	38.9±11.7	19.0±3.9 HAM-D ₁₇	severe	outpatient	Inclusion - aged between 18 to 60 years old - >12 HAM-D ₁₇ Exclusion - any antidepressant medication within the last two months - suicidal behavior according to HAM-D ₁₇
Salehi et al.	2016	20	20	30.25±6.21	44.65±8.13 HDRS	severe	inpatient	Inclusion - >30 BDI - > 25 HDRS
Schuch et al.	2014	15	11	42.81±12.4	26.68±2.6 Hamilton scale for depression	very severe	inpatient	Inclusion - severe symptoms of MDD - >25 Hamilton-17 - aged between 18 to 60 years old
Authors	Published year	Intervention		Intervention for control group	Drop-out rate in exercise group	Duration and frequency of intervention of exercise		
		Exercise as intervention						
Heissel et al.	2015	Combining aerobic, strength and coordinative exercise - 10 minute warm up - 20-25 minute exercise		Relaxation	14.30%	60 minutes, twice a week, 4 weeks		
Kerling et al.	2017	Using bicycle ergometer, treadmill, crosstrainer, and rowing according to the preference of participants. Intensity was in aerobic-anaerobic transition zone.		Treatment as usual	0%	45 minutes, three times a week, 6 weeks		
Krogh et al.	2014	Supervised aerobic training using stationary bikes at 80% of their maximal heart rate		Stretching, rowing, and catching balls.	19.50%	45 minutes, three times a week, 3 months		
Salehi et al.	2016	Combining aerobic exercise + electroconvulsive therapy in aerobic exercise, supervised cycling exercise was introduced. Intensity was 60-70% of VO ₂ max.		Electroconvulsive therapy	0%	40-45 minutes, twice a week, 4 weeks		
Schuch et al.	2014	The objective is consumption of up to 16.5 kcal/kg/week. Modality could be chosen by participants by their preference among stationary bike, treadmill, and transport.		Treatment as usual	0%	three times a week while hospitalized		

RESULTS

As shown in Figure 1, of the 564 articles identified by the search terms, 5 articles (n=199 participants) met the inclusion criteria. The key features of the eligible articles are summarized in Table 1.

Narrative analysis

Features of subjects

The severity of the depressive symptoms in the subjects at baseline in all eligible articles was assessed by either the Beck Depression Inventory or a variant of the Hamilton Depression Rating Scale. Average severity scores were categorized as severe or worse according to the categorical definitions for each scale (Sajatovic et al. 2012). Of the 5 eligible articles, 4 articles applied inclusion or exclusion criteria based on symptom severity, and 2 articles included only patients with symptom severity categorized as worse than “moderate” (Schuch et al. 2014, Salehi et al. 2016). One article applied inclusion or exclusion criteria based on suicidal behavior (Krogh et al. 2014). The average ages in all eligible articles were around 40 years, except for one article in which the average age was 68 years. Four studies recruited inpatients, whereas one recruited outpatients.

Type of physical exercise as intervention

All eligible articles introduced aerobic exercise in some form. Most studies used bicycles, but treadmills, rowing, and other forms of aerobic training were introduced; in two articles, the participants could choose the exercise modality from a list of 3-5 choices according to their preference.

Duration of intervention

Four of the five studies conducted interventions lasting less than 40 minutes per session, and one article did not describe the session length. In terms of frequency, three studies conducted sessions 3 times per week, and the other two studies conducted two sessions per week. Four studies conducted sessions for over 3 weeks.

Drop-out rates

In all eligible articles, drop-out rate was reported to be less than 20%. Notably, the two studies which allowed participants to choose their exercise had no drop-outs (0%).

Meta-analysis

The risk of bias

The results of the risk of bias calculations are shown in Table 2 and Figure 2. Two articles (Krogh et al. 2014, Salehi et al. 2016) were found to be low-risk with respect to random sequence generation, allocation concealment, and blinding of participants and personnel. Three articles (Krogh et al. 2014, Salehi et al. 2016, Kerling et al. 2017) were found to be low-risk with respect to blinding of data analysis. Four articles (Heissel et al. 2015, Schuch et al. 2014, Krogh et al. 2014, Kerling et al. 2017) were found to be low-risk with respect to the blinding of outcome assessment and incomplete outcome data categories. However, three articles (Heissel et al. 2015, Schuch et al. 2014, Kerling et al. 2017) were unclear in the random sequence generation and blinding of participants and personnel, two articles (Schuch et al. 2014, Kerling et al. 2017) were unclear in allocation concealment, and all five articles were unclear in selective reporting categories.

Table 2. Risk of bias graph

	A	B	C	D	E	F
Heissel et al. 2015	?	-	?	?	+	?
Kerling et al. 2017	?	?	?	+	+	?
Krogh et al. 2014	+	+	+	+	+	?
Salehi et al. 2016	+	+	+	+	?	?
Schuch et al. 2014	?	?	?	?	+	?

A - random sequence generation
 B - allocation concealment
 C - blinding of participants and personnel
 D - blinding of data analyst
 E - incomplete outcome data
 F - selective reporting

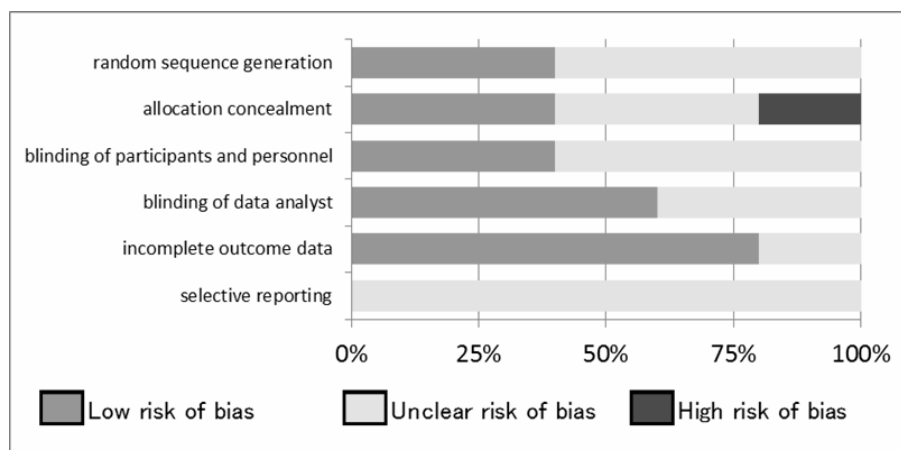


Figure 2. Risk of bias summary

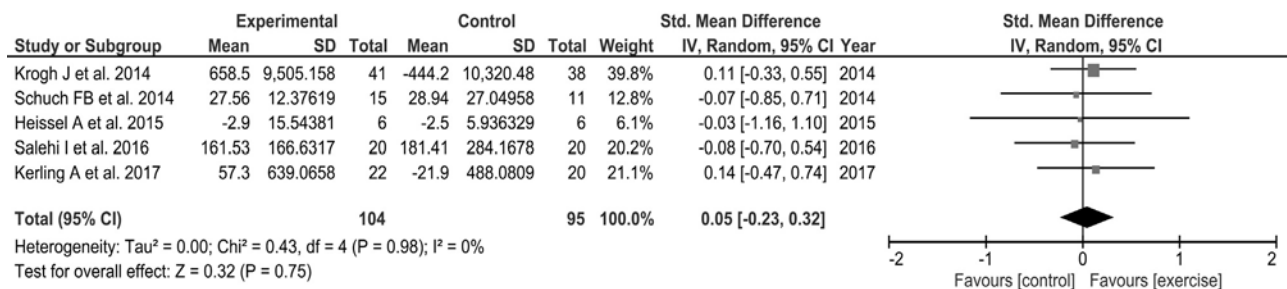


Figure 3. Forest plot of meta-analysis

BDNF quantification

As shown in Figure 3, the five eligible studies included 104 participants in the exercise (intervention) group and 95 participants in the control (no exercise) group. The standard mean difference did not reach significance ($Z=0.32$, $p=0.75$); furthermore, the heterogeneity was low ($I^2=0\%$).

DISCUSSION

The result of this meta-analysis indicates that physical exercise had no effect on BDNF in serum/plasma, at least in so far as the eligible articles are concerned.

Several studies have examined the effect of physical activity on BDNF in various disease states. Dinoff et al. (2016) conducted a meta-analysis of 29 articles ($n=1212$), and reported that aerobic exercise, but not resistance training, increased the resting concentration of BDNF in healthy people (standard mean difference = 0.66). In several mental disorders, systematic reviews and meta-analyses showed a positive effect of physical exercise on BDNF. Jensen et al. (2016) examined whether physical exercise increased BDNF in patients with mild cognitive impairment and dementia in a systematic review, and reported that almost all of the research showed physical exercise to have a positive effect. Sanada et al. (2016) examined the effect in patients with schizophrenia in a meta-analysis of six articles ($n=252$), and also reported a positive effect on BDNF (standard mean difference = 0.95). Finally, Mackay et al. (2017) investigated the effect in patients with neurological disorders with a meta-analysis of five articles ($n=142$), and reported that aerobic exercise increased BDNF (standard mean difference = 0.84). Therefore, it is likely that physical activity increases BDNF in a number of different neuropsychiatric diseases.

However, the data herein on patients with MDD did not confirm the effect; furthermore, heterogeneity was low, lending credence to the data. The reason may be related to the duration of the effects of physical activity on BDNF. In healthy people, Szuhany et al. (2015) conducted a meta-analysis examining differences among the effects of physical activity on BDNF according to three different exercise conditions: A single session of exercise; a session of exercise following a program of regular exercise; and resting BDNF levels following a program of regular exercise. They found that the effect

size of resting BDNF levels was small, a finding similar to that observed among patients with MDD. Laske et al. (2010) conducted a single exercise session for elderly patients with MDD and age-matched healthy controls, and tracked serum BDNF concentration over baseline, end-of-session, and end-of-session +30 min time points. They noted a decrease in serum BDNF at the final (30 min post-session) time point versus baseline in both groups. Thus, in patients with MDD, the effects of physical activity on BDNF may be very short-lasting.

Associations between BDNF and neurocognitive functions have been reported. De Assis et al. (2017) conducted a systematic review and reported that exercise increased BDNF and executive function in healthy people. Ahmed et al. (2015) conducted a meta-analysis examining the association of BDNF concentration with neurocognitive function in schizophrenia, and found a positive association between the variables. Therefore, it is likely that the improvement of neurocognitive function induced by physical exercise was at least partially mediated by BDNF in healthy people, as well as in patients with schizophrenia.

In patients with MDD, a meta-analysis of eight studies by Brondino et al. (2017) noted that the effects of physical activity on global neurocognition were negligible, but those on visual learning were significant. This suggests that in patients with MDD, exercise may have limited effects on neurocognitive functions aside from visual learning. Oertel-Knöchel et al. (2014) compared the patterns of influence of aerobic exercise on neurocognition between patients with schizophrenia and those with MDD, and found a greater effect in schizophrenia than MDD. Finally, considering our meta-analysis' results, BDNF may not be a likely candidate for mediating the mechanism which underlies the limited benefit of physical exercise in patients with MDD. In a pharmacological study, serum BDNF in treatment-resistant MDD was unaffected by antidepressant treatment, whereas serum BDNF in treatment-responsive MDD was significantly different (Yoshimura et al. 2007). All participants in this meta-analysis had severe symptoms of MDD, and three of the five studies analyzed inpatients. Thus, the participants in some or all of these studies might have antidepressant-resistant MDD, which could alter the results herein. Future studies are needed to assess the effect of physical exercise in patients with MDD who responded to antidepressant therapy.

This meta-analysis has several limitations. First, risk of bias was difficult to assess. Only two categories clearly showed low risk of bias (less than half of the categories). Interventions such as physical exercise tend to be recognized as interventions by many healthcare workers, suggesting a moderate risk of bias in selective reporting and blinding of personnel. Second, only one author reviewed and assessed the articles and risk of bias. Considering that Cochran recommends two authors at least, a future review with multiple assessors is needed. Third, the number of eligible articles was relatively small, with only five articles and 199 participants included. Therefore, there are the risk of false-zero heterogeneity, our results may differ when more studies can be included.

CONCLUSION

This review and meta-analysis aimed to examine whether physical exercise increases BDNF in people with MDD. Five studies were eligible and their features were as follows: subjects had severe symptoms of MDD; subjects in 4 of the 5 eligible studies were inpatients; interventions lasted more than 40 minutes per session; the drop-out rates were low; and risk of bias was moderate. However, the effect of physical exercise on BDNF did not reach statistical significance. The mechanism of the effect of physical exercise on depressive symptoms of MDD was not related to BDNF.

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Conflict of interest: None to declare.

Contribution of individual authors:

Yusuke Kurebayashi: research idea, study design, literature search, statistical analysis, manuscript writing, approval of the final version;

Junichi Otaki: research idea, study design, statistical analysis, approval of the final version.

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