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A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor

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Abstract

Consistent evidence indicates that exercise improves cognition and mood, with preliminary evidence suggesting that brain-derived neurotrophic factor (BDNF) may mediate these effects. The aim of the current meta-analysis was to provide an estimate of the strength of the association between exercise and increased BDNF levels in humans across multiple exercise paradigms. We conducted a meta-analysis of 29 studies (N = 1,111 participants) examining the effect of exercise on BDNF levels in three exercise paradigms: (1) a single session of exercise, (2) a session of exercise following a program of regular exercise, and (3) resting BDNF levels following a program of regular exercise. Moderators of this effect were also examined. Results demonstrated a moderate effect size for increases in BDNF following a single session of exercise (Hedges' g = 0.46, $p < 0.001$). Further, regular exercise intensified the effect of a session of exercise on BDNF levels (Hedges' g = 0.58, p = 0.02). Finally, results indicated a small effect of regular exercise on resting BDNF levels (Hedges' g = 0.28, p = 0.005). When analyzing results across paradigms, sex significantly moderated the effect of exercise on BDNF levels, such that studies with more women showed less BDNF change resulting from exercise. Effect size analysis supports the role of exercise as a strategy for enhancing BDNF activity in humans, but indicates that the magnitude of these effects may be lower in females relative to males.

Keywords

exercise; physical activity; brain-derived neurotrophic factor; BDNF; meta-analysis

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Conflict of Interest

In the past 3 years Dr. Otto has served as a paid consultant for MicroTransponder Inc., Concert Pharmaceuticals, and ProPhase; provided expert consensus opinion for Otsuka Pharmaceuticals; received royalty support for use of the SIGH-A from ProPhase; and received book royalties from Oxford University Press, Routledge, and Springer. The other authors have no conflicts to report.

Contributors

Kristin L. Szuhany was involved in the retrieval and review of articles, data checking, data analysis, and preparation and revision of the manuscript, tables, and figures. Matteo Bugatti was involved in retrieval and review of articles, data entering, data analysis, and review of the manuscript. Michael W. Otto was involved in the review and revision of the manuscript as well as suggested avenues of data analysis. All authors have approved the final manuscript.

Introduction

There is a wealth of evidence that exercise improves both cognition (Roig et al., 2013; Smith et al., 2010) and mood (Josefsson et al., 2014; Rethorst and Trivedi, 2013; Stathopoulou et al., 2006), with evidence suggesting that brain-derived neurotrophic factor (BDNF) activity may mediate these effects (Erickson et al., 2012; Heyman et al., 2012; van Praag et al., 2005; Vaynman et al., 2004). BDNF is a protein found in high concentrations in the central nervous system, primarily in the brain regions of the hippocampus, cerebral cortex, hypothalamus, and cerebellum (Murer et al., 2001). Central BDNF can cross the blood-brain barrier and therefore be stored in other areas of the body; however, BDNF can also be produced by tissues in the periphery, making it difficult to identify in humans whether BDNF changes in serum levels result from changes in central or peripheral BDNF (Erickson et al., 2012; Murer et al., 2001). BDNF has been implicated in neural development and functioning, including neurogenesis, dendritic growth, and long-term potentiation of neurons (Altar, 1999; Gorski et al., 2003; Huang et al., 1999; Lu et al., 2005). Non-quantitative reviews from both the animal and human literature (Huang et al., 2014; Zoladz and Pilc, 2010) provide evidence that BDNF increases following exercise in rodents and acute and programmed aerobic exercise in humans. Animal models provide more consistent evidence for exercise-induced upregulation of BDNF, given the ability to measure BDNF centrally; however, studies indicate that peripheral (serum and plasma) and central BDNF levels are correlated in mouse models (Angelucci et al., 2011; Karege et al., 2002), with some evidence for similar associations in humans (Krabbe et al., 2007). There is also tentative evidence that peripheral levels of BDNF may have central effects (Schmidt and Duman, 2010). Given the evidence for BDNF increases, exercise can be viewed as a potential strategy for inducing BDNF activity for application to the enhancement of mood or cognition.

Indeed, individual studies have demonstrated the effect of higher BDNF levels on numerous cognitive processes. For example, higher BDNF levels have been associated with better spatial (Erickson et al., 2009; Rex et al., 2006), episodic (Egan et al., 2003), recognition (Komulainen et al., 2008; Whiteman et al., 2014), and verbal memory (Grassi-Oliveira et al., 2008) as well as better hippocampal functioning (Erickson et al., 2012). In addition, decreased levels of BDNF, particularly in older adults, have been associated with hippocampal atrophy and may contribute to memory impairment, which may be linked to cognitive challenges experienced in Alzheimer's (Erickson et al., 2012; Murer et al., 2001).

Qualitative reviews (e.g., Huang et al., 2014; Zoladz and Pilc, 2010) present significant evidence that exercise enhances BDNF levels; however, they do not provide the magnitude or reliability of this effect. The goal of the present quantitative meta-analytic investigation was to document the level and reliability of the effect of exercise on changes in BDNF activity in humans. Three distinct paradigms have been used to study this effect: (1) changes in BDNF levels across a single session of acute exercise, (2) changes in BDNF levels across a session of exercise following a program of regular exercise (showing changes in BDNF release following repeated bouts of exercise), and (3) changes in resting BDNF levels following a program of regular exercise. Each of these was examined separately due to

evidence that the effects of exercise on BDNF vary across paradigms (Huang et al., 2014). In the current meta-analysis, potential moderators (e.g., sex, age, assay type, diagnostic status, and exercise frequency) of the effect of exercise on BDNF were investigated.

Materials and Methods

Search Strategy

Studies published in English through February 2013 were identified using the search engines PubMed, PsycINFO, and Google Scholar. The following search terms were used in combination: *brain-derived neurotrophic factor, BDNF, exercise,* and *physical activity.* Reference sections of identified articles and relevant reviews were also examined to detect articles not captured by this search.

Study Selection and Data Abstraction

Identified studies were selected for inclusion in analyses based on the following criteria: (1) focus on a human population, (2) use of a precise measure of BDNF concentration levels (i.e., plasma or serum), and (3) administration of an exercise procedure or measure (i.e., acute exercise test, programmed regular exercise). If levels of BDNF were not able to be determined in the text of the article, such data were requested from the study authors. In the current report, data were abstracted from the articles by one of the first two authors and independently checked for accuracy. Any inconsistencies regarding inclusion or data extraction were resolved in a consensus meeting with the senior author.

Study Characteristics

Within each of the identified studies, several variables were evaluated to determine if they moderated the association between exercise and changes in BDNF levels from pre-exercise to post-exercise. These included sex (expressed as % female), age, assay type (i.e., serum or plasma), diagnostic status, and exercise frequency (defined as greater than or equal to American College of Sports Medicine guidelines, Garber et al., 2011).

Most studies of programmed exercise included for analysis involved a training program of aerobic exercise (n = 15); however, five studies included strength or resistance training, with two studies examining both strength and endurance (aerobic) training. Aerobic exercises varied among programs, with some programs combining multiple exercises, in the following frequencies: cycling (n = 8), running (n = 5), walking (n = 3), swimming (n = 1), rowing (n = 1), and unspecified/individualized (n = 4). Most programs required supervised training sessions (n = 16), whereas a few offered home-based interventions (n = 2). All but one of the programs that reported exercise intensity required moderate intensity exercise, with the other program involving high intensity exercise. Several 0 compared a training vs. sedentary control (or other active control, such as stretching) group (n = 9); eight studies utilized within-subject designs.

Data Synthesis

Random-effects analyses were used in this meta-analysis. Random-effects analyses are considered to be superior to fixed-effects methods, which assume homogeneous population

effect sizes, due to minimization of type I error rates (Hunter and Schmidt, 2004; Lipsey and Wilson, 2000) and more realistic representations of heterogeneous effect sizes in the population (Field, 2001).

Effect sizes were calculated using Hedges' g (Hedges and Olkin, 1985), a variation of Cohen's d that corrects for biases due to sample sizes. To keep samples independent, one estimate of effect size was used per study; if a study included multiple effect sizes for a single construct, these effect sizes were averaged prior to data synthesis with other studies. Effect sizes of exercise at different intensities were averaged for overall study effect size; however, control groups (e.g., stretching) were not included in the overall effect size. We completed a separate moderator analysis of active (e.g., stretching) versus non-active (e.g., sedentary, waitlist) control groups, which revealed no moderation effects of control group type across paradigms ($Q(1) = 0.06$, $p = 0.81$) or within paradigm (all $p > 0.07$). Analyses were conducted combining both aerobic and strength/resistance training as well as with strength/resistance training examined separately, given the potential differential effect of these styles of interventions. Effect sizes were interpreted in the following manner: small effect ($g = 0.2$), medium effect ($g = 0.5$), and large effect ($g = 0.8$), based on Cohen's (1992) standards.

For categorical moderators (e.g., assay type, diagnostic status, exercise frequency), effects were tested by computing *Q* tests to evaluate if effects varied systematically between groups. For continuous moderators (e.g., sex, age), we used bivariate correlational analyses to evaluate significance.

Finally, publication bias was assessed. Publication bias allows for protection against the "file drawer effect," which posits that studies with null findings are less likely to be published and therefore unrepresented in the literature search and following meta-analysis. We evaluated publication bias using multiple methods. First, we examined the fail-safe N, which determines the number of additional studies with a null result required to reduce the overall effect size to non-significance (Rosenthal, 1991; Rosenthal and Rubin, 1988). If the fail-safe N is greater than 5 times the number of studies in the analysis, the results can be interpreted as robust (Rosenthal, 1991). Second, we visually inspected the funnel plot for symmetry relative to the mean effect size. Greater symmetry indicates lesser likelihood of publication bias. All data analyses were conducted using Comprehensive Meta-Analysis Software (Bornstein et al., 2005).

Results

Trial Flow

A total of 61 studies was initially identified as likely meeting inclusion criteria; evaluation of these studies resulted in a final sample for analysis that included 29 studies (see Figure 1). Studies were excluded when sufficient data were not available (following several contact attempts with authors), when outcomes were not based on BDNF levels following a bout of exercise, or when BDNF genotypes rather than levels were assessed.

Table 1 displays the characteristics of the 29 studies, representing 1,111 participants (mean age = 42.1, % female = 46.6%), included in the analysis. Fourteen studies (48%) examined changes in BDNF levels after a single session of exercise, eight studies (27%) examined changes in BDNF levels immediately post-exercise in a design evaluating the effects of a program of regular exercise, and thirteen studies (45%) examined changes in resting BDNF levels following a program of regular exercise. Four studies included patients with a diagnosis of a mental disorder: three of individuals with major depressive disorder (Gustafsson et al., 2009; Laske et al., 2010; Toups et al., 2011) and one of individuals with panic disorder (Strohle et al., 2010). Of these studies, three examined the effect of acute exercise (Gustafsson et al., 2009; Laske et al., 2010; Strohle et al., 2010), whereas one (targeting depression) examined the effect of programmed exercise on resting BDNF levels (Toups et al., 2011).

Effect of Acute Exercise on BDNF Levels

Figure 2 shows the effect sizes for the 14 studies analyzing the effect of acute exercise on change in BDNF levels. For these studies, BDNF levels were measured prior to and following (from immediately to 60 minutes after) a single exercise session in the laboratory. Pre- to post-exercise change in BDNF levels across a single exercise session reflected a moderate effect size (Hedges' $g = 0.46$, $SE = 0.08$, 95% CI = 0.29–0.62, $z = 5.49$, $p < 0.001$).

Effect of Programmed Regular Exercise on BDNF Levels

The effect of programmed regular exercise on BDNF levels was examined for two different outcome variables. First, we examined the effect of a program of regular exercise, ranging from 3 to 24 weeks, on changes in BDNF levels across a single session of exercise. In a sample of 8 studies, pre- to post-exercise change in BDNF levels intensified following a program of regular exercise (Hedges' $g = 0.58$, $SE = 0.25$, 95% CI = 0.10–1.07, $z = 2.35$, $p = 0.02$). Results are displayed in Figure 3.

Second, we examined the effect of a program of regular exercise, ranging from 3 weeks to 2 years, on resting BDNF levels. In a sample of 13 studies, programs of exercise also exhibited changes in resting levels of BDNF; however, this result was on the order of a small effect size (Hedges' $g = 0.28$, $SE = 0.10$, 95% CI = 0.08–0.48, $z = 2.79$, $p = 0.005$). Results are displayed in Figure 4.

Effects of Strength Training on BDNF Levels

Removing a resistance paradigm (i.e., arm and elbow strength) from examination of effects of acute exercise on BDNF levels did not significantly impact the results (Hedges' $g = 0.49$, $SE = 0.08$, 95% CI = 0.34–0.64, $z = 6.48$, $p < 0.001$). However, removing a resistance training intervention from the effect of programmed exercise on acute BDNF levels reduced the effect size previously observed (Hedges' $g = 0.26$, $SE = 0.15$, 95% CI = −0.03–0.54, $z = 1.78$, $p = 0.075$), potentially due to the very large effect size obtained in the removed study ($g = 3.53$). Finally, removing one strength training study and two strength/resistance training study groups did not significantly affect the observed effect for resting BDNF levels

following programmed exercise (Hedges' g = 0.29, SE = 0.10, 95% CI = 0.09–0.50, z = 2.82, p = 0.005).

When examining the five studies which included strength/resistance training groups, the effect did not reach significance (Hedges' g = 0.57, SE = 0.41, 95% CI = −0.24–1.37, z = 1.39, p = 0.17), perhaps due to two studies exhibiting moderate to strong positive effects and three studies exhibiting negative effects.

Moderators of Exercise Effects on BDNF Levels

Of the moderators of interest, the proportion of women in studies, participant age, and assay type (i.e., serum or plasma) were not confounded with the type of exercise program. Across all studies, we found a significant negative correlation between effect size and percentage of women in studies (r(33) = −0.38, p = 0.03). Effect sizes were smaller for studies with a greater proportion of women and retained significance when the one outlying effect size estimate (g = 3.53) was excluded from the analysis (r(32) = −0.37, p = 0.04). Across all studies, participant age was not significantly related to changes in BDNF levels following exercise (r(32) = −0.24, p = 0.19), nor was assay type (serum or plasma; Q(1) = 0.54, p = 0.46).

The potential moderators of diagnostic status and exercise frequency were specific to the type of exercise paradigm; hence, the latter variables were examined only within the relevant paradigms, albeit at low power. Within studies of resting BDNF levels, exercise frequency category was not significantly related to BDNF levels (Q(1) = 0.001, p = 0.98). Of note, effect sizes for two psychiatric samples studied (major depressive disorder and panic disorder) were at least that of healthy samples for both acute exercise (0.49 for psychiatric versus 0.40 for healthy; Q(1) = 0.86, p = 0.36) and resting BDNF following regular exercise (0.40 for psychiatric versus 0.17 for healthy).

Publication Bias

Publication bias was evaluated separately for each of the three paradigms examined.

Acute exercise—Evaluation of publication bias indicated that 191 studies reporting a null effect would be required to shift the observed effect to a non-significant level. A fail-safe N of 191 is substantially greater than the number of studies needed for a robust effect (N = 80) according to guidelines suggested by Rosenthal (1991), indicating that our effect is robust for this paradigm. Also, the funnel plot is for this paradigm is roughly symmetrical by visual inspection (see Supplemental Materials).

Programmed regular exercise—The fail-safe N of 50 for the effect of programmed regular exercise on BDNF levels immediately following exercise equaled the number of studies needed for a robust effect (N = 50), and the funnel plot appeared roughly symmetrical by visual inspection. Finally, the fail-safe N of 54 for the effect of programmed regular exercise on resting BDNF levels was marginally less than that needed for a robust effect (N = 80). The funnel plot also appears asymmetrical with more studies with small sample sizes appearing above the mean than below the mean, indicating that studies with

smaller sample sizes are more likely to get published if the effect sizes are greater. Funnel plots are presented in Supplemental Materials.

Discussion

This meta-analysis provides reliable evidence that both acute and regular exercise have a significant impact on BDNF levels. Evidence from 14 studies indicated that a single session of exercise increases BDNF levels, reflecting a moderate effect size. Moreover, regular exercise intensifies the magnitude of these effects with increased BDNF responsivity, reflecting a moderate effect size, following a regular program of exercise relative to those completing acute exercise alone. Both of these findings are reliable as evaluated by fail-safe N and funnel plot analyses. Finally, 13 studies demonstrated that programs of regular exercise also impact resting BDNF levels; however, this effect was more modest than that seen immediately after exercise, and this effect was not considered robust.

Considering these findings, there is reliable evidence from human studies indicating that each episode of exercise results in a “dose” of BDNF activity and that the magnitude of this “dose” can be enhanced over time by regular exercise. The relative importance of these episodic BDNF doses, relative to the more subtle increases in resting BDNF levels seen across an exercise program, is not clear. Much more information is needed on the time course of benefits from exercise, particularly cognitive benefits, and the potential importance of BDNF activity at the time of learning, rather than as a general prime in the days before a learning task (Korol et al., 2013). Moreover, the staying power of brief exercise interventions needs to be elucidated, particularly given evidence in animal models that cognitive gains from brief exercise training (e.g., 4 weeks) can be lost within several weeks (e.g., Hopkins et al., 2011).

More generally, animal studies provide evidence for a variety of mechanisms by which BDNF enhancement from exercise results in improved cognition. For example, as little as one week of exercise improves subsequent learning in animals, an effect that is eliminated by blockade of BDNF in the hippocampus (Vaynman et al., 2004). Also, exercise-induced BDNF activity can reduce the threshold for successful encoding and memory (Intlekofer et al., 2013) and has been hypothesized to place the brain in a state of readiness for plasticity (Cotman et al., 2007). The precise mechanism of this readiness is made challenging by the host of pre-synaptic enhancement of neurotransmitter release and post-synaptic N-methyl-D-aspartate receptor (NMDA) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor changes as well as important downstream activity (e.g., cAMP response element-binding protein; CREB) associated with exercise-induced BDNF activity (Christie et al., 2008; Vaynman et al., 2004), all of which could play a role in long-term potentiation effects. In addition, in terms of longer-term structural changes, exercise appeared to reverse hippocampal degeneration and declining hippocampal network efficiency in aged animals, with enhancement of presynaptic densities and greater connectivity (Siette et al., 2013). These changes appear to explain the observed improvements in recognition memory associated with exercise in animals (Cotman et al., 2007). In addition to the rescue of hippocampal neurons from the negative effects of aging, exercise-induced BDNF activity helps reduce the effects of specific stressors, including oxidative DNA changes (Yang et al.,

2014) and disruption of synaptic plasticity from sleep deprivation (Zagaar et al., 2013). Also, relative to models for cognition, models for exercise-induced BDNF effects on mood have undergone only limited development, drawing from the stress-protective aspects of BDNF, as well as the effects of antidepressant medications on BDNF (for review, Duman and Monteggia, 2006), but otherwise not offering detailed mechanisms. Greater specification of the role of BDNF in mood disorders awaits additional study.

Concerning human studies, we had limited power to examine moderating influences of interpersonal and exercise characteristics, due to the limited sample size within each of the exercise paradigms investigated. When examining moderators across paradigms, sex significantly moderated the effect of exercise on BDNF levels, such that BDNF did not increase as much in females following exercise as in males. Given these data, we encourage further evaluation of this discrepancy in BDNF production and the use of sex as a covariate to hone the evaluation of exercise effects on BDNF, as well as outcomes assumed to be mediated by BDNF activity.

Also of interest is the magnitude of exercise effects on BDNF levels for psychiatric populations and healthy populations. In our meta-analysis, effect sizes between these populations were in similar ranges for acute exercise, but raised the question whether regular exercise may have greater effects in psychiatric than healthy participants, given a tentative 2:1 difference in mean effect sizes for BDNF changes across exercise (0.40 for psychiatric versus 0.17 for healthy). More studies are needed to see if these potential differences become reliable. Yet, our tentative results raise the possibility that programs of exercise may help rescue the low resting BDNF levels often observed in depressed patients (Brunoni et al., 2008; Piccinni et al., 2008) and exercise produces effects in a similar range to those of antidepressants ($d = 0.62$ for antidepressants, Sen et al., 2008). Future research may also focus on differences in exercise effects on BDNF in populations with medical conditions. In our meta-analysis, we did not find significant differences between healthy individuals and those with medical conditions (e.g., obesity, MS, diabetes), but conclusions are limited due to few studies examining medical populations.

Future studies also need to examine the effects of strength/resistance training on BDNF levels in comparison to effects of aerobic exercise on BDNF levels. Our meta-analysis had limited power to assess these affects due to the small number of studies including strength training. These studies also included considerable variation in the strength and direction of effects, with three studies indicating negative effects of strength training (Correia et al., 2010; Schiffer et al., 2009; Swift et al., 2012) on BDNF levels and two studies indicating positive effects (Goekint et al., 2010; Yarrow et al., 2010), with one of these studies showing a very large positive effect (Yarrow et al., 2010). Given the importance of both aerobic and strength exercises in an exercise program, it would be beneficial to identify BDNF changes across both paradigms.

Other potential moderators for future study include exercise intensity (e.g., mild, moderate, vigorous), sedentary status (e.g., sedentary, regular exercise completer, athlete), and genotype (e.g., val66met) as well as further investigating the potential negative association between age and effect size. Exercise intensity was reported in several studies as estimated

% of VO_{2max}. However, several studies failed to report intensity and many studies only evaluated moderate intensity exercise. Future studies should clearly report exercise intensity level, utilizing estimated metabolic equivalents (METs) in order to better uniformly describe results. In addition, future studies should consider investigating the effect of varying degrees of exercise intensity on BDNF production. Sedentary status (e.g., as quantified by the Physical Activity Recall Questionnaire: (Blair et al., 1985); or the International Physical Activity Questionnaire: (Craig et al., 2003)) and genotype expressions were rarely reported in detail in the studies examined, therefore, making these variables difficult to assess as moderator variables. The val66met polymorphism in particular may be important for understanding age-related cognitive decline and degree of BDNF response to exercise (Erickson et al., 2012; Phillips et al., 2014).

Despite these unanswered questions, the available evidence indicates that exercise should be considered as a successful strategy for enhancing BDNF activity. Accordingly, use of exercise to enhance cognitive abilities and living skills has recently been successful in dementia patients according to meta-analytic review (Forbes et al., 2013), with preliminary promising evidence in Parkinson's disease (Ahlskog, 2011), and schizophrenia (Oertel-Knochel et al., 2014). The fact that exercise offers wide ranging physical health benefits (Alford, 2010) in addition to effects on mood (Asmundson et al., 2013; Josefsson et al., 2014; Stathopoulou et al., 2006) and cognition (Erickson et al., 2012; Smith et al., 2010) encourages the regular application of exercise as a particularly broad spectrum intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Meta-analysis of brain-derived neurotrophic factor (BDNF) levels following exercise
- We found a moderate effect of increased BDNF following a single session of exercise
- Regular exercise intensified effect of a single session of exercise on BDNF levels
- We found a small effect of increased resting BDNF levels after regular exercise
- Sex moderated effect of exercise on BDNF levels with smaller effects for females

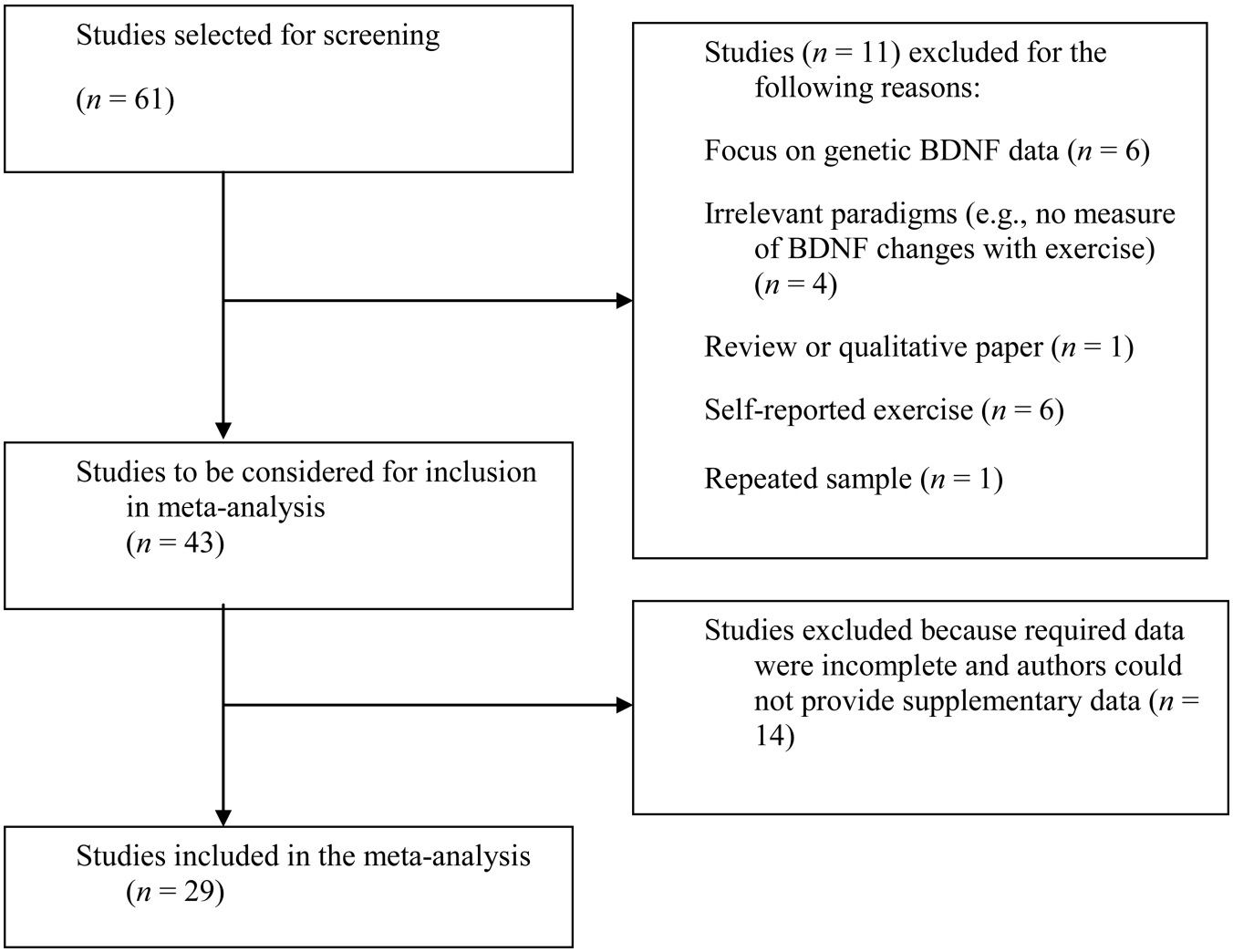

Figure 1.
Study selection process

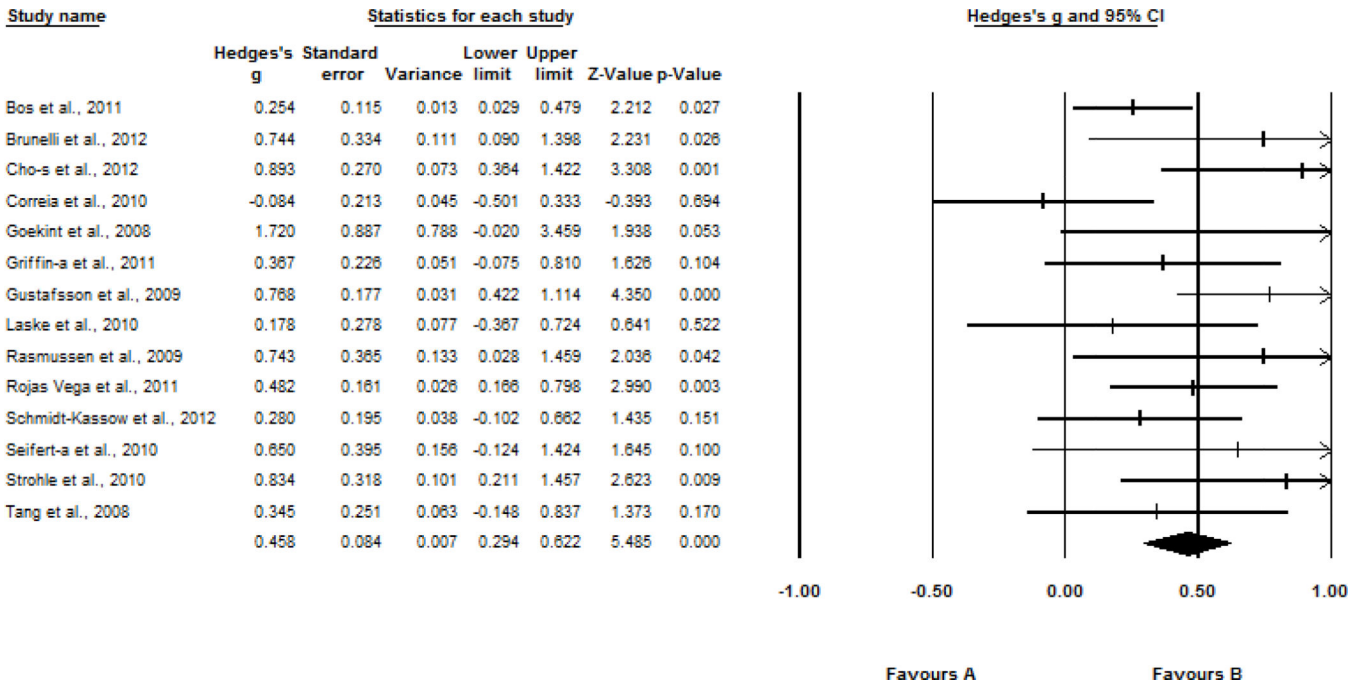

Figure 2.

Effect sizes of the association between exercise and BDNF levels following acute exercise. s, serum; a, acute exercise.

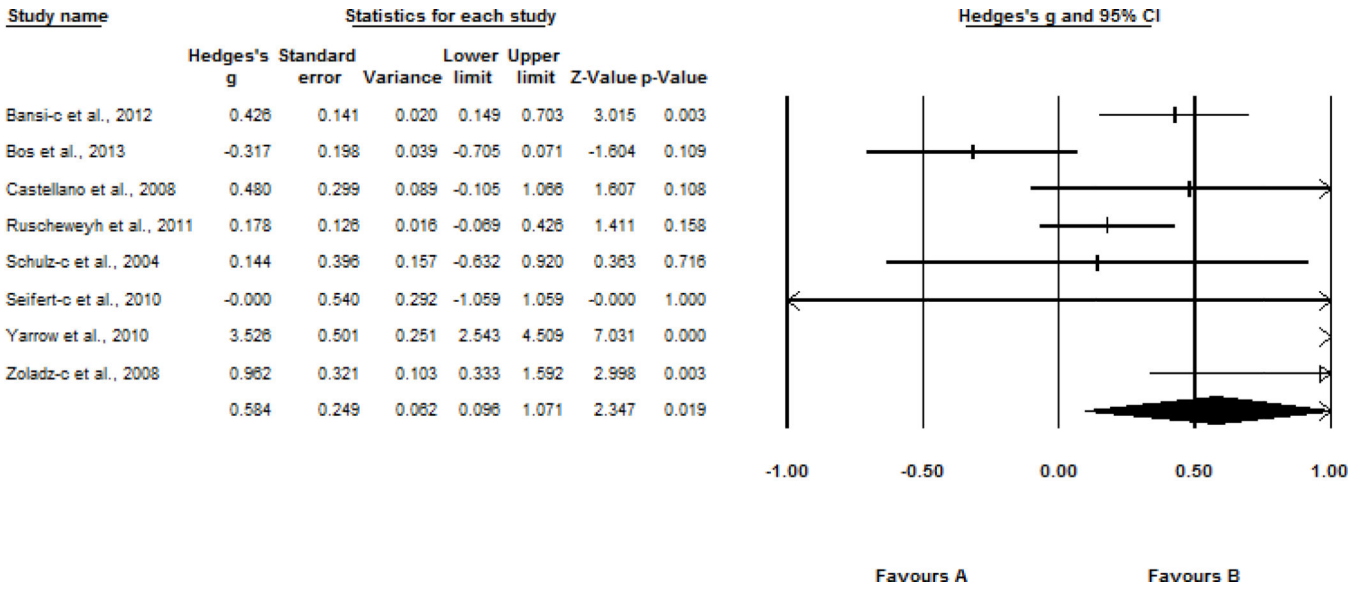

Figure 3.

Effect sizes of the association between acute exercise and BDNF levels following programmed regular exercise. c, change after programmed exercise.

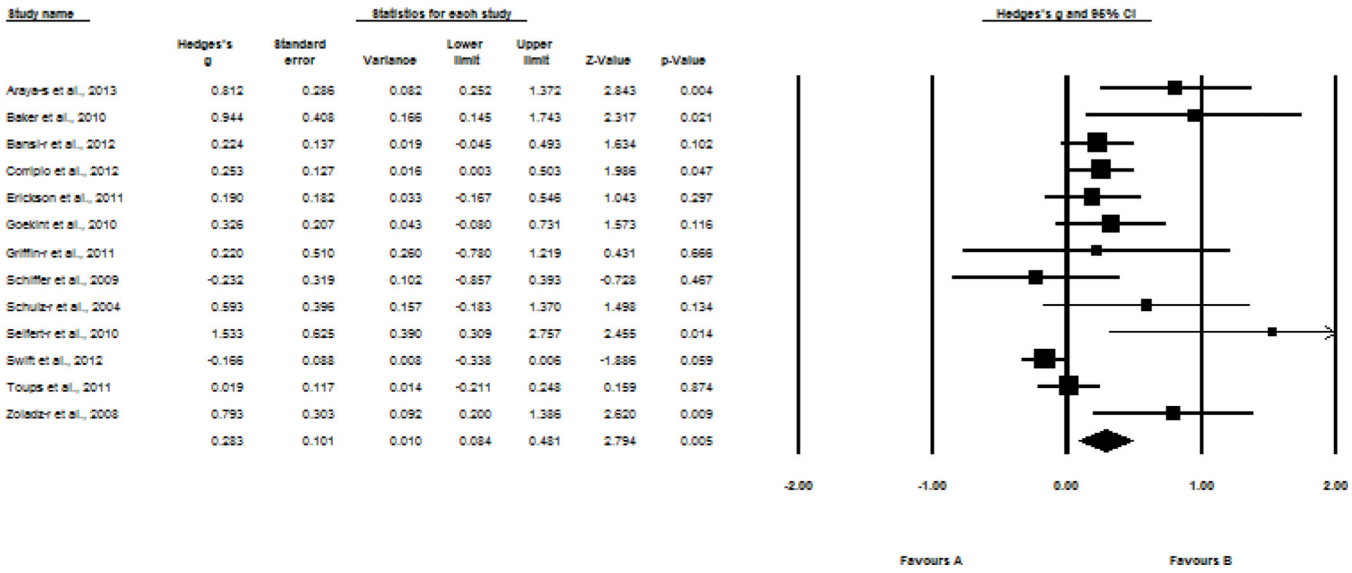

Figure 4.

Effect sizes of the association between exercise and resting BDNF levels following programmed regular exercise. s, serum; r, resting BDNF levels after programmed exercise.

Table 1

Sample characteristics for studies of the association between exercise and BDNF levels

Study	Population studied	N	% female	Mean Age	BDNF measure	Duration of exercise program	Type of exercise	Intensity of exercise	Supervised/ Home-based	Randomized/ control group	Hedge's g
BDNF collected after acute exercise											
Goekint et al., 2008	Healthy	11	0	22.9	serum	n/a	60 min ergometric cycling	Moderate (55–75% of VO_{2max})	n/a	Placebo vs. reboxetine	1.72
Tang et al., 2008	Healthy	16	50	UN	serum	n/a	15 min stepping	Not reported	n/a	n/a	0.35
Rasmussen et al., 2009	Healthy	8	0	UN	plasma	n/a	4h rowing	High (85–95% VO_{2max})	n/a	n/a	0.74
Cho et al., 2012	Healthy	18	0	19	plasma & serum	n/a	Bruce maximal treadmill	Until volitional exhaustion	n/a	n/a	0.89
Correia et al., 2010	Healthy	16	0	24.6	plasma	n/a	Strength (knee/elbow)	Maximal knee and elbow contractions	n/a	n/a	−0.08
Seifert et al., 2010	Healthy	12	0	29.8	plasma	n/a	Ergometer cycling	Until exhaustion	n/a	n/a	0.65
Bos et al., 2011	Healthy	38	26	43	serum	n/a	cycling	Moderate (74% VO_{2max})	n/a	n/a	0.25
Griffin et al., 2011	Healthy	47	0	22	serum	n/a	Ergometer graded exercise test	until exhaustion	n/a	Exercisers vs. sedentary control	0.37
Rojas Vega et al., 2011	Healthy	20	100	35.2	serum	n/a	Graded exercise test	To 150bpm	n/a	n/a	0.48
Brunelli et al., 2012	Healthy	10	0	22	serum	n/a	Cycling	Volitional exhaustion	n/a	n/a	0.74
Schmidt-Kassow et al., 2012	Healthy	40	50	23	serum	n/a	30 min cycle ergometer		n/a	Light vs. intense exercise	0.28
Gustafsson et al., 2009	MDD	36	50	UN	plasma	n/a	Computerized ergometer	Until exhaustion	n/a	Depressed vs. healthy controls	0.77
Laske et al., 2010	MDD	55	100	60.3	serum	n/a	Incremental exercise test on treadmill	Until volitional exhaustion	n/a	Depressed vs. healthy	0.18
Strohle et al., 2010	Panic	12	75	31.9	serum	n/a	30 min treadmill test	Moderate (70%) VO_{2max})	n/a	Exercise vs. quiet rest; panic vs. healthy	0.83
Acute BDNF measured after regular programmed exercise											

Study	Population studied	N	% female	Mean Age	BDNF measure	Duration of exercise program	Type of exercise	Intensity of exercise	Supervised/ Home-based	Randomized/ control group	Hedge's g
Zoladz et al., 2008	Healthy	13	0	22.7	plasma	5 weeks	Endurance cycling (4d/wk), test: cycloergometer to exhaustion	Moderate	Supervised	n/a	0.96
Seifert et al., 2010	Healthy	12	0	29.8	plasma	12 weeks (3 months)	Cycling, running, swimming, rowing	Moderate (70% VO_{2max})	Supervised	Training vs. sedentary	0.00
Yarrow et al., 2010	Healthy	20	0	21.9	serum	5 weeks	Resistance training (3d/wk)	Traditional: 75% 1RM; eccentric: 50–120% 1RM	Supervised	Traditional vs. eccentric enhanced resistance training	3.53
Ruscheweyh et al., 2011	Healthy	62	69.4	60.2	serum	24 weeks (6 months)	Nordic walking and gymnastics	Moderate (Nordic walking: 50–60% VO_{2max}, gymnastics: 30–40% VO_{2max})	Supervised	Nordic walking vs. gymnastics vs. control	0.18
Bos et al., 2013	Healthy	24	62.5	32.1	serum	12 weeks	Walking and running	Moderate (75% VO_{2max})	Supervised	Urban vs. rural environment	−0.32
Schulz et al., 2004	MS	28	68	39.5	serum	8 weeks	Individualized aerobic training (2d/wk)	Moderate (60% VO_{2max})	Home-based	Training vs. control	0.14
Castellano et al., 2008	MS	22	72.7	40	serum	4 weeks, 8 weeks	Cycling (3d/wk)	Moderate (60% VO_{2max})	Supervised	MS vs. control	0.48
Bansi et al., 2012	MS	52	67.3	51.1	serum	3 weeks	Cycling (5d/wk)	Moderate (60% VO_{2max})	Supervised	Land ergometer vs. aquatic bike training	0.43
Resting BDNF measured after regular programmed exercise											
Zoladz et al., 2008	Healthy	13	0	22.7	plasma	5 weeks	Endurance cycling (4d/wk)	moderate	Supervised	n/a	0.79
Schiffer et al., 2009	Healthy	27	UN	23	plasma	12 weeks	Endurance: running; strength: curl, press, rows, crunches, etc.	Endurance: high (80% VO_{2max}); strength: 70–80% 1RM	Supervised	Endurance vs. strength vs. control	−0.23
Goekint et al., 2010	Healthy	16	21.7	21.2	serum	10 weeks	Strength exercises (3d/wk)	Not reported	Supervised	Training vs. sedentary	0.33
Seifert et al., 2010	Healthy	12	0	29.8	plasma	12 weeks (3 months)	Cycling, running, swimming, rowing	Moderate (70% VO_{2max})	Supervised	Training vs. sedentary	1.53
Erickson et al., 2011	Healthy	120	66.7	66.6	serum	52 weeks (1 year)	Aerobic walking	Moderate (60% VO_{2max})	Supervised	Exercise vs. stretching control	0.19
Griffin et al., 2011	Healthy	47	0	22	serum	3 weeks, 5 weeks	Aerobic cycling (3d/wk)	Moderate	Supervised	Exercise vs. sedentary	0.22
Swift et al., 2012	Diabetes	150	55.1	56.9	serum	36 weeks (9 months)	Aerobic exercise, resistance training, combined (3d/wk)	Moderate (50–80% VO_{2max})	Supervised	Aerobic exercise, resistance training, combined, stretching control	−0.17

Study	Population studied	N	% female	Mean Age	BDNF measure	Duration of exercise program	Type of exercise	Intensity of exercise	Supervised/ Home-based	Randomized/ control group	Hedge's g
Toups et al., 2011	MDD	70	78.6	49.4	serum	12 weeks	unspecified	16 KKW (high expenditure) or 4KKW (low expenditure)	Supervised	High vs. low energy expenditure	0.02
Schulz et al., 2004	MS	28	68	39.5	serum	8 weeks	Individualized aerobic training (2d/wk)	Moderate (max 75% VO_{2max})	Home-based	Training vs. control	0.59
Baker et al., 2010	MCI	33	51.5	70	plasma	24 weeks (6 months)	Treadmill, bike, elliptical (4d/wk)	Moderate to high (75–85% VO_{2max})	Supervised	High intensity exercise vs. stretching control	0.94
Bansi et al., 2012	MS	52	67.3	51.1	serum	3 weeks	Cycling (5d/wk)	Moderate (60% VO_{2max})	Supervised	Land ergometer or aquatic bike	0.22
Corripio et al., 2012	Obese	120	44.2	7.9	plasma	104 weeks (2 years)	Unspecified (3d/wk)	Moderate	Home-based	n/a	0.25
Araya et al., 2013	Obese	15	60	38.3	plasma & serum	12 weeks (3 months)	Treadmill, bike (3d/wk)	Moderate (65% VO_{2max})	Supervised	n/a	0.81

Note. MDD = major depressive disorder; MS = multiple sclerosis; MCI = mild cognitive impairment, KKW = kcal/kg/week; RM = repetition maximum; UN = unknown.