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REVIEW

The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis

Adam Dinoff,[1,2] Nathan Herrmann,[1,3] Walter Swardfager[1,2] and Krista L. Lanctôt[1,2,3]

[1]Neuropsychopharmacology Research Group, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, 2075 Bayview Avenue, Toronto, ON, M4N 3M5, Canada

[2]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, 1 King's College Circle, Toronto, ON, Canada

[3]Department of Psychiatry, Faculty of Medicine, University of Toronto, 250 College Street, Toronto, ON, M5T 1R8, Canada

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Abstract

It has been hypothesized that one mechanism through which physical activity provides benefits to cognition and mood is via increasing brain-derived neurotrophic factor (BDNF) concentrations. Some studies have reported immediate benefits to mood and various cognitive domains after a single session of exercise. This meta-analysis sought to determine the effect of a single exercise session on concentrations of BDNF in peripheral blood, in order to evaluate the potential role of BDNF in mediating the beneficial effects of exercise on brain health. MEDLINE, Embase, PsycINFO, SPORTDiscus, Rehabilitation & Sports Medicine Source, and CINAHL databases were searched for original, peer-reviewed reports of peripheral blood BDNF concentrations before and after acute exercise interventions. Risk of bias within studies was assessed using standardized criteria. Standardized mean differences (SMDs) were generated from random effects models. Risk of publication bias was assessed using a funnel plot and Egger's test. Potential sources of heterogeneity were explored in subgroup analyses. In 55 studies that met inclusion criteria, concentrations of peripheral blood BDNF were higher after exercise (SMD = 0.59, 95% CI: 0.46–0.72, $P < 0.001$). In meta-regression analysis, greater duration of exercise was associated with greater increases in BDNF. Subgroup analyses revealed an effect in males but not in females, and a greater BDNF increase in plasma than serum. Acute exercise increased BDNF concentrations in the peripheral blood of healthy adults. This effect was influenced by exercise duration and may be different across genders.

Introduction

It has been observed that in addition to benefits to fitness, exercise may provide cognitive benefits and alleviate psychiatric symptoms in some individuals (Wipfli *et al.*, 2008; Rethorst *et al.*, 2009; Basso *et al.*, 2015; Best *et al.*, 2015; Bossers *et al.*, 2015; Dauwan *et al.*, 2015; Hagovska *et al.*, 2015; Kerling *et al.*, 2015; Knapen *et al.*, 2015; Pedersen & Saltin, 2015; de Souza Moura *et al.*, 2015). The mechanisms by which exercise achieves these brain benefits have yet to be elucidated. One proposed mechanism by which exercise may accomplish these benefits is via stimulating an increase in brain-derived neurotrophic factor (BDNF) concentrations (Gomez-Pinilla *et al.*, 2008; Gligoroska & Manchevska, 2012). BDNF is a protein of the neurotrophin family required for the growth, survival, and differentiation of many neurons (Acheson *et al.*, 1995; Huang & Reichardt, 2001; Greenberg *et al.*, 2009; Numakawa *et al.*, 2010). BDNF may also affect the growth and survival of glial cells, through activation of signal transduction pathways (Roback *et al.*, 1995; Rose *et al.*, 2003). Indeed, glial cells have been shown to express BDNF receptors including trkB and p75 (Frisen *et al.*, 1993; Casaccia-Bonnefil *et al.*, 1996).

Increased brain BDNF concentrations may result in increased neuronal growth, survival, and synaptogenesis, leading to the cognitive and affective benefits observed after exercise (Tolwani *et al.*, 2002; Scharfman *et al.*, 2005; Cotman & Berchtold, 2007; Arancibia *et al.*, 2008; Ma, 2008). Moreover, BDNF has been shown to be lower in the periphery of individuals with various psychiatric disorders (Green *et al.*, 2011; Suliman *et al.*, 2013; Molendijk *et al.*, 2014; Fernandes *et al.*, 2015a,b; Polyakova *et al.*, 2015) and metabolic disorders (Krabbe *et al.*, 2007). In Alzheimer's disease, reduced BDNF concentrations and mRNA expression have been observed in the hippocampus, frontal cortex, and parietal cortex of post-mortem brain tissue (Connor *et al.*, 1997; Ferrer *et al.*, 1999; Peng *et al.*, 2005). Furthermore, BDNF concentrations may decrease with age, and may be associated with cognitive function in some populations (Lommatzsch *et al.*, 2005; Ziegenhorn *et al.*, 2007;

Correspondence: K. L. Lanctôt, [1]Neuropsychopharmacology Research Group, as above.
E-mail: Krista.Lanctot@sunnybrook.ca

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Gunstad *et al.*, 2008; Komulainen *et al.*, 2008; Tapia-Arancibia *et al.*, 2008). As a result of these observations, interventions that increase BDNF concentrations are of interest.

Evidence in animals suggests that exercise increases BDNF concentration in multiple brain regions (Berchtold *et al.*, 2001a; Klintsova *et al.*, 2004; Gustafsson *et al.*, 2011). These regions include the hippocampus (Berchtold *et al.*, 2001a; Marlatt *et al.*, 2012; Fang *et al.*, 2013; Lu *et al.*, 2014) and prefrontal cortex (Geng *et al.*, 2013), areas involved in cognition, as well as the amygdala (Liu *et al.*, 2009), a brain region imperative to emotional processing. Voluntary wheel-running has been shown to increase BDNF mRNA production in the hippocampus and neocortex of rats (Neeper *et al.*, 1996), suggesting that exercise induces BDNF production via upregulation of BDNF gene transcription. While *in vivo* measurement of central BDNF in humans is not feasible, numerous studies have measured peripheral BDNF concentrations after exercise, with some studies finding increases (Griffin *et al.*, 2011; Cho *et al.*, 2012; Coelho *et al.*, 2012; Schmolesky *et al.*, 2013; El-Tamawy *et al.*, 2014; Salehi *et al.*, 2014; Jeon & Ha, 2015) and others reporting no significant changes in BDNF after exercise (Correia *et al.*, 2010; Stroehle *et al.*, 2010; Bos *et al.*, 2011; McDonnell *et al.*, 2013; Gapin *et al.*, 2015; Schuch *et al.*, 2015). Thus, evidence regarding the effects of acute exercise on peripheral BDNF is inconsistent.

Recently, our group provided meta-analytic evidence that regular aerobic exercise results in an increase in resting concentrations of peripheral BDNF in humans (Dinoff *et al.*, 2016). Here, we provide meta-analytic data on the effect of a single session of exercise (acute exercise) on peripheral concentrations of BDNF. Acute exercise has been observed to produce modest immediate benefits to cognitive performance and mood (Petruzzello *et al.*, 1991; Yeung, 1996; Tomporowski, 2003; Bartholomew *et al.*, 2005; Barella *et al.*, 2010; Chang *et al.*, 2012; Hogan *et al.*, 2013). Identification of the mechanisms by which acute exercise results in these benefits is useful to determine the clinical significance of acute exercise. A previous meta-analysis (Szuhany *et al.*, 2015) found that acute exercise increases peripheral BDNF concentration and that this effect size is moderate. Since that meta-analysis, numerous clinical studies on this effect have been published, allowing for a stronger evaluation of the evidence for this effect. Furthermore, that report did not include subgroup analyses or other investigations of heterogeneity due to a limited number of studies. Questions remain regarding the length and intensity of acute exercise required to produce benefits to cognition and affect. Therefore, this meta-analysis sought to determine whether an acute exercise session alters peripheral BDNF concentrations in humans and to investigate potential moderators of this effect.

Methods

Data sources

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati *et al.*, 2009) guidelines (PRISMA checklist is presented in the online Supporting Information). English-language literature was searched using MEDLINE, Embase, PsychINFO, SPORTDiscus, Rehabilitation & Sports Medicine Source, and Cumulated Index to Nursing and Allied Health Literature (CINAHL) databases. Databases were searched up to October 2016 for original reports of BDNF changes after exercise. A sample search strategy (MEDLINE) is presented in the online Supporting Information. Reference lists of retrieved studies were searched for additional reports.

Study selection

Inclusion criteria were: (i) BDNF measured before and after a single session of exercise; (ii) measured serum, plasma, or whole blood BDNF concentration; (iii) exercise intensity ≥40% of peak oxygen uptake (VO_{2peak}) or described as running, cycling, or resistance training. Exclusion criteria were as follows: (i) study included a diseased population (e.g. diabetes, Parkinson's disease, multiple sclerosis, etc.) or a psychiatric population (e.g. depression, schizophrenia, etc.) without a control group; (ii) study population consisted of children below the age of 18. Diseased populations, psychiatric populations, and child populations were excluded from this meta-analysis as these populations have been shown to have altered BDNF concentrations and this may modify the effect of exercise on BDNF (Connor *et al.*, 1997; Karege *et al.*, 2002a; Palomino *et al.*, 2006; Krabbe *et al.*, 2007; Frota *et al.*, 2009; Iughetti *et al.*, 2011). Studies of diseased or psychiatric populations that included a healthy control group were included in this meta-analysis and only the healthy control group data were included in the analyses. Some studies that met these initial eligibility criteria were not included in this meta-analysis as the data were not extractable (e.g. standard deviations or variances not reported) or the exercise intensity description implied that the intervention intensity was <40% VO_{2Peak} (e.g. easy walking or yoga).

Data extraction

Each article was examined for eligibility by two independent raters. A third rater was used to settle disagreements regarding inclusion. Data on pre- and post-intervention mean BDNF concentrations and standard deviations [picograms/millilitre], population characteristics, exercise intervention characteristics, risk of bias items, and other study details were extracted into a preformatted spreadsheet by two raters. Missing data were requested from the corresponding authors. Exercise intensity prescriptions consisting of percentage of maximum heart rate or Borg rating of perceived exertion (RPE) were converted to percentage of maximum VO_{2Peak} as described by the National Council on Strength & Fitness (National Council on Strength & Fitness). In studies in which participants completed multiple trials of acute exercise, data from the trial with the least or absence of co-interventions were used in the overall analysis (examples of co-interventions included taking medication prior to exercise, or alterations of air temperature, humidity, or particulate matter, etc.). In cases of multiple trials with no co-interventions, data from the first trial, or if not reported, data from the most intense trial were included in the overall analysis. If the first reported exercise session consisted of an incremental exercise test to exhaustion, and values of peripheral blood BDNF were measured before and after this test, data from this exercise session were used in all analyses. In studies with different groups of participants completing acute exercise of different intensities and/or durations, groups were entered separately in all analyses. Studies were additionally categorized by whether the exercise intervention was aerobic or resistance training.

Statistical analyses

Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated using random-effects models (Harris *et al.*, 2008). SMDs were chosen because of variability in absolute BDNF concentrations between assays used by different laboratories and between measures of BDNF in different components of blood (Noble *et al.*, 2008). Random-effects models are preferred if significant heterogeneity is expected, as they account for variable underlying effects in estimates of uncertainty, including both within- and between- study variance. Heterogeneity across studies was summarized by Q statistics calculated in Chi-square analysis and I^2 indices were calculated to investigate inconsistencies among results of the included studies (Higgins & Thompson, 2002). Heterogeneity was further explored via subgroup analyses. Differences in the effect of acute exercise lasting longer than 30 min compared to acute exercise of 30 min or less on BDNF concentrations was explored as this was the median and modal exercise session time. In four studies that measured BDNF in both serum and plasma (Currie *et al.*, 2009; Cho *et al.*, 2012; Gilder *et al.*, 2014; Pareja-Galeano *et al.*, 2015), serum measurements were used in all analyses except subgroup analysis of serum vs. plasma (in which both measurements were used), as serum BDNF measurements were more common across studies. Inverse variance-weighted meta-regression analyses were used to investigate associations between SMDs and population characteristics and intervention characteristics. In studies with multiple different groups completing exercise of different intensities and/or durations, groups were entered separately in meta-regression analyses. Risk of publication bias was assessed visually using funnel plots and quantitatively with Egger's test (Egger *et al.*, 1997). The 'trim and fill' method was used to identify and correct for potential publication bias. Briefly, the 'trim and fill' method involves identifying and removing the smaller studies in a meta-analysis that cause funnel plot asymmetry, using the newly 'trimmed' funnel plot to estimate the true center of the funnel, then replacing the omitted studies and their missing counterparts around the centre (filling) (Duval & Tweedie, 2000; Peters *et al.*, 2007). Study quality was assessed using criteria adapted from the Cochrane Collaboration's Risk of Bias tool as done previously (Swardfager *et al.*, 2012; Dinoff *et al.*, 2016). Analyses were conducted using Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK) and STATA (Release 14.1; StataCorp, College Station, TX). Data are presented as mean ± standard deviation.

Results

Population and exercise characteristics

Fifty-five studies met inclusion criteria and presented sufficient data to be included in this meta-analysis (Fig 1). Reasons for exclusion

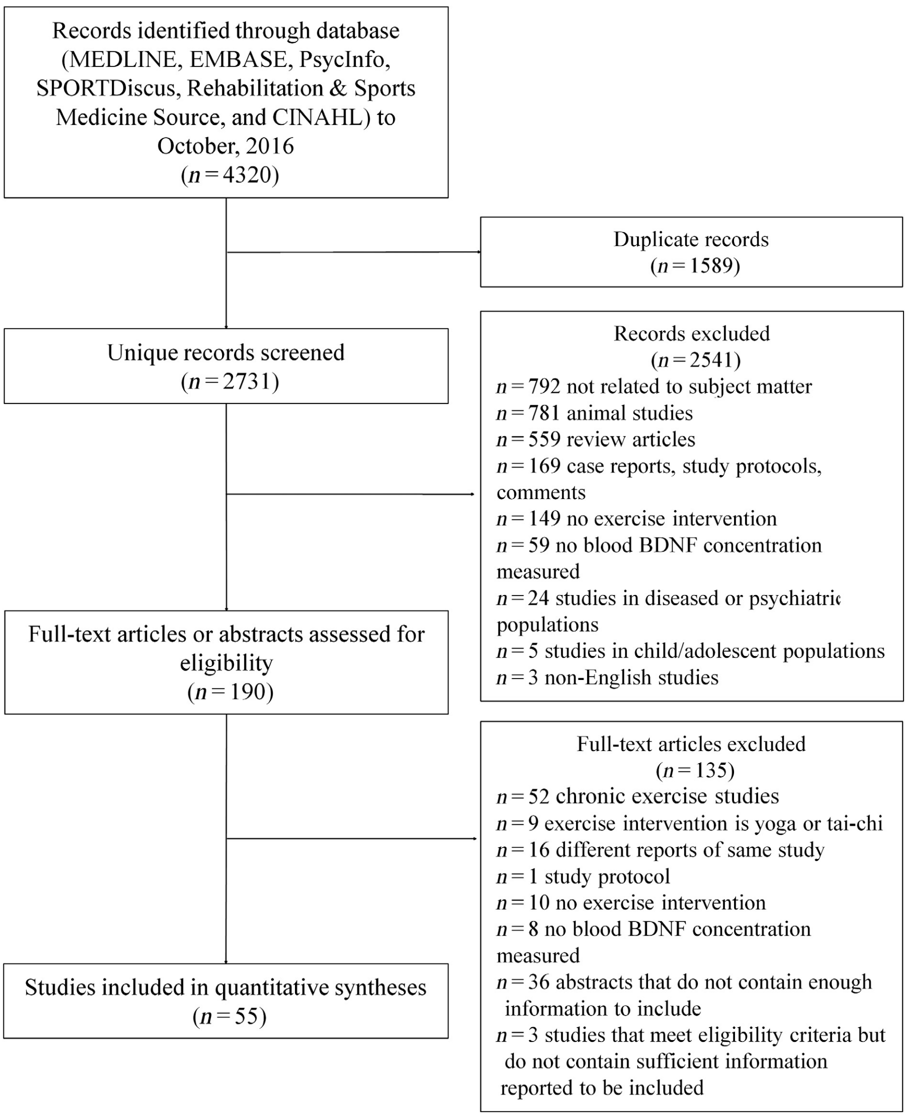

FIG 1. Search and selection of articles.

are reported in Fig 1. In total, 1180 participants (75.4% male; mean age: 27.9 ± 10.8; mean body mass index (BMI): 24.0 ± 1.7; mean $VO_{2\ Peak}$: 44.4 ± 8.1 mL/kg*min) were included. Included studies ranged in size from 4 to 95 participants. Mean exercise session time and intensity were 38.9 ± 37.5 (7–240) minutes at 78.7% ± 18.1% (45–100%) of $VO_{2\ Peak}$ respectively. A complete list of study population and exercise intervention characteristics can be found online in the Supporting Information.

Comparison of pre- and post-exercise BDNF concentration

Concentrations of peripheral blood BDNF were significantly higher after acute exercise (SMD = 0.59, 95% CI: 0.46–0.72, $P < 0.001$; Fig 2). Acute exercise caused an approximate 60% increase in BDNF concentrations in peripheral blood. Funnel plot (Supporting Information) and Egger's test ($P = 0.001$) revealed significant risk of publication bias. After adjusting for potential publication bias using the 'trim-and-fill' method, a significant increase in peripheral blood BDNF concentrations was still present (SMD = 0.40, 95% CI: 0.25–0.55, $P < 0.001$). A Chi^2 value of 131.96 ($P < 0.001$) and I^2 index of 58% signify considerable heterogeneity and inconsistency, respectively, among included studies. Qualitatively, 39% of studies reported a significant increase in peripheral blood BDNF after acute exercise, no studies reported a significant decrease in BDNF after acute exercise, and 61% reported no significant change. Fifty of the fifty-five studies were deemed likely to be high quality evidence (risk of bias assessments for each study can be found in the online Supporting Information).

Investigations of heterogeneity

Aerobic exercise vs resistance training

Eight of fifty-five studies consisted of a resistance training exercise intervention. All other studies used an aerobic exercise intervention. In subgroup analysis, there was no significant difference in effect

	Post-exercise			Pre-exercise				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Babaei 2014a	1 215	324.4	20	775	335	20	1.7%	1.31 [0.62, 2.00]
Babaei 2014b	1 197.9	365.1	19	807.4	350	19	1.7%	1.07 [0.38, 1.75]
Bos 2011	20,668.3	8 666.7	35	18,066.7	8 666.7	35	2.3%	0.30 [−0.17, 0.77]
Brunelli 2012	1 280	315	10	940	115	10	1.1%	1.37 [0.38, 2.37]
Castellano 2008	15,940	15,383	22	15,000	12,420.5	22	2.0%	0.07 [−0.53, 0.66]
Cho 2012	37,800	2 300	18	22,944.5	9 116.6	18	1.4%	2.18 [1.34, 3.03]
Church 2016a	2 000	1 750	10	1 200	1 000	10	1.3%	0.54 [−0.36, 1.43]
Church 2016b	2 620	1 980	10	1 100	800	10	1.2%	0.96 [0.03, 1.90]
Coelho 2014	411	172.8	18	353.3	169.9	18	1.8%	0.33 [−0.33, 0.99]
Correia 2010	2 261	1 493	16	2 464	1 543	16	1.7%	−0.13 [−0.82, 0.56]
Currie 2009	15,700	3 500	4	6 970	4 020	4	0.4%	2.01 [0.05, 3.97]
Ferris 2007	22,880	8 210	15	17,620	6 894	15	1.6%	0.68 [−0.06, 1.41]
Gapin 2015	1 016.3	224.2	20	1 028.3	275.1	20	1.9%	−0.05 [−0.67, 0.57]
Gilder 2014	15,100	17,265	23	11,400	23,979.2	23	2.0%	0.17 [−0.41, 0.75]
Goda 2013	15,900	5 600	33	14,900	5 000	33	2.3%	0.19 [−0.30, 0.67]
Goekint 2008	24,187	6 430	11	16,950	3 250	11	1.2%	1.37 [0.42, 2.31]
Goekint 2010	15,760	4 160	16	15,310	3 280	16	1.7%	0.12 [−0.58, 0.81]
Goekint 2011	14,700	2 490	11	12,000	1 575	11	1.2%	1.25 [0.32, 2.18]
Gold 2003	6 740	5 000	20	4 717.2	2 199.4	20	1.9%	0.51 [−0.12, 1.14]
Griffin 2011	1 294	820.5	32	974.7	741.6	32	2.3%	0.40 [−0.09, 0.90]
Heyman 2012	14,400	2 285	11	11,950	2 285	11	1.3%	1.03 [0.13, 1.93]
Hwang 2016	25,240	6 230	29	21,666	5 079	29	2.2%	0.62 [0.09, 1.15]
Hötting 2016a	24,460	4 520	26	20,720	5 000	26	2.1%	0.77 [0.21, 1.34]
Hötting 2016b	19,167	4 420	23	19,333	4 000	23	2.0%	−0.04 [−0.62, 0.54]
Laske 2010	31,000	8 100	20	30,500	6 900	20	1.9%	0.07 [−0.55, 0.69]
Lee 2014	29,100	5 000	12	23,200	5 600	12	1.4%	1.07 [0.21, 1.94]
Mang 2014	11,918	6 404	16	5 258	3 258	16	1.5%	1.28 [0.51, 2.05]
Matthews 2009	30,480	6 730	8	24,435	5 020	8	1.1%	0.96 [−0.09, 2.02]
McDonnell 2013	29,654.9	25,572.5	25	30,573.6	23,263.5	25	2.1%	−0.04 [−0.59, 0.52]
Muders 2016	16,657.9	5 148.1	95	12,958.9	4,039.5	95	2.8%	0.80 [0.50, 1.09]
Pareja-Galeano 2015	3 540	1 860	12	3 780	1 200	12	1.5%	−0.15 [−0.95, 0.65]
Piepmeier 2015	963.9	1 557.4	29	657.9	870.4	29	2.2%	0.24 [−0.28, 0.76]
Rasmussen 2009	1 172	968	8	442	272	8	1.1%	0.97 [−0.08, 2.02]
Rojas Vega 2006	89,300	26,000	8	60,800	23,000	8	1.0%	1.10 [0.02, 2.17]
Rojas Vega 2010	8 440	2 920	8	5 900	2 340	8	1.1%	0.91 [−0.14, 1.95]
Rojas Vega 2011	14,460	6 130	20	13,333	5 460	20	1.9%	0.19 [−0.43, 0.81]
Rojas Vega 2012	10,625	3 250	11	7 125	2 875	11	1.3%	1.10 [0.19, 2.01]
Saucedo Marquez 2015	10,150	3 625	7	6 000	2 222	7	0.9%	1.29 [0.10, 2.48]
Schild 2016	0.57	0.059	36	0.44	0.089	36	2.1%	1.70 [1.16, 2.25]
Schmidt-Kassow 2012	32,424.6	7 515.4	40	32,002.9	9 724.6	40	2.4%	0.05 [−0.39, 0.49]
Schmidt-Kassow 2013	31,431.5	9 203.8	54	30,181.5	9 422.4	54	2.6%	0.13 [−0.24, 0.51]
Schmidt-Kassow 2014	37,531	7 464	11	33,071	7 355	11	1.4%	0.58 [−0.28, 1.44]
Schmolesky 2013a	30,352	13,784	9	23,002	6 625	9	1.2%	0.65 [−0.31, 1.60]
Schmolesky 2013b	30,527	8 443	9	24,830	6 437	9	1.2%	0.72 [−0.24, 1.68]
Schmolesky 2013c	30,977	20,324	8	23,855	8 584	8	1.1%	0.43 [−0.56, 1.43]
Schmolesky 2013d	38,885	12,195	9	28,549	4 366	9	1.1%	1.07 [0.07, 2.08]
Schuch 2015	190.7	1 700.4	16	222	2 031.6	16	1.7%	−0.02 [−0.71, 0.68]
Seifert 2010	3 108.3	2,392.2	12	1 958.3	1 918.6	12	1.5%	0.51 [−0.30, 1.33]
Slusher 2015	1 949.2	815.5	22	1 352.5	793.6	22	1.9%	0.73 [0.12, 1.34]
Ströhle 2010	9 680	10,500	12	10,640	8 830	12	1.5%	−0.10 [−0.90, 0.71]
Tang 2008	34,500	8 870	16	30,890	8 260	16	1.7%	0.41 [−0.29, 1.11]
Tonoli 2015	15,050	4 000	10	11,920	3 700	10	1.3%	0.78 [−0.14, 1.69]
Tsai 2014	104	83.5	40	81.8	84.9	40	2.4%	0.26 [−0.18, 0.70]
Tsai 2016	71	72	40	46.1	39	40	2.4%	0.43 [−0.02, 0.87]
Van Cutsem 2015	26,500	2 100	9	21,800	1 300	9	0.8%	2.56 [1.24, 3.89]
Wahl 2015	27,750	5 630	13	21,640	4 490	13	1.4%	1.16 [0.32, 2.00]
Walsh 2016	25,111.5	5 000	10	22,700	5 000	10	1.3%	0.46 [−0.43, 1.35]
Williams 2012	570	40	13	500	60	13	1.4%	1.33 [0.47, 2.19]
Winter 2007	1 163	338	27	1 040	239	27	2.1%	0.41 [−0.13, 0.95]
Yarrow 2010	30,853	10,350	20	23,304	8 206	20	1.8%	0.79 [0.15, 1.44]
Zoladz 2008	10.9	8.3	13	10.3	5	13	1.5%	0.08 [−0.68, 0.85]
Total (95% CI)			**1180**			**1180**	**100.0%**	**0.59 [0.46, 0.72]**

Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 131.96$, df = 60 ($P < 0.00001$); $I^2 = 55\%$
Test for overall effect: $Z = 8.81$ ($P < 0.00001$)

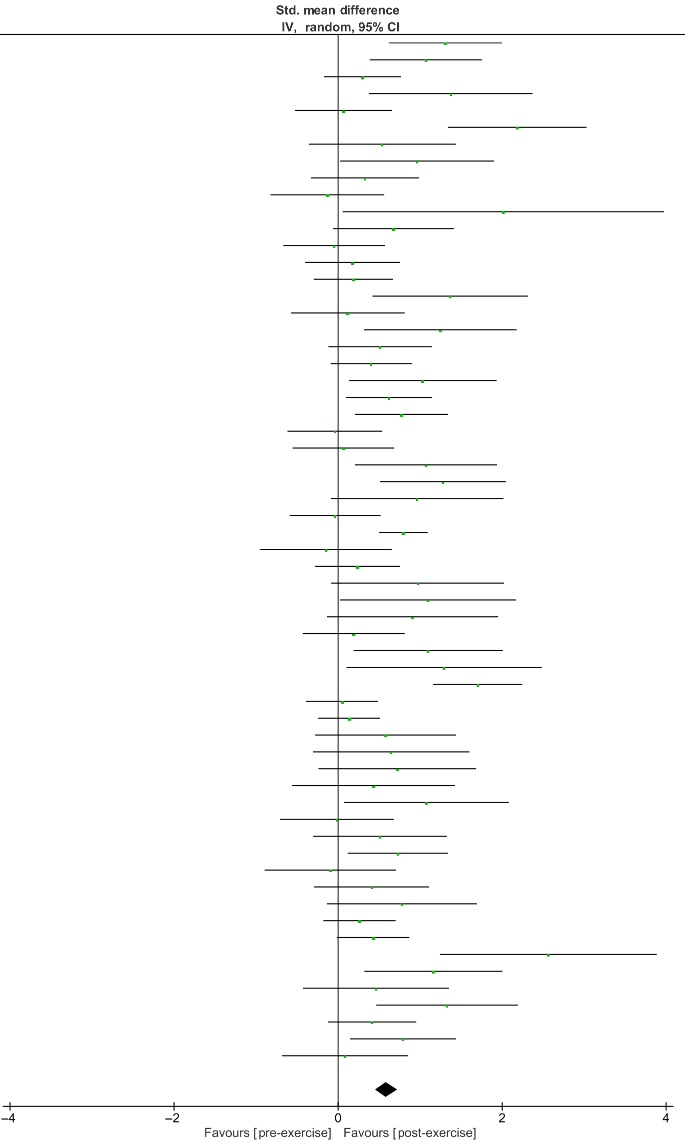

FIG 2. Peripheral blood BDNF concentration change pre- to post-exercise. Mean and SD columns indicate mean concentrations of BDNF and standard deviations of these means before and after the exercise intervention. Lines indicate 95% confidence intervals (CI) and the midpoint of each line is denoted by a square indicating the standardized mean difference (SMD) for each study. Diamond indicates overall SMD and 95% CI. Significance of overall effect: $Z = 8.47$, $P < 0.001$.

size between resistance training interventions and aerobic exercise interventions (Aerobic exercise: SMD = 0.61, 95% CI: 0.46–0.75, $P < 0.001$; Resistance training: SMD = 0.48, 95% CI: 0.15–0.80, $P = 0.004$; Test for subgroup differences: $Chi^2 = 0.52$, df = 1, $P = 0.47$). Both types of exercise produced a significant increase in peripheral blood BDNF after acute exercise. Significant heterogeneity and inconsistency were present in the aerobic subgroup ($Chi^2 = 117.09$, $P < 0.001$, $I^2 = 56\%$) but not the resistance training subgroup ($\chi^2 = 13.64$, $P = 0.09$, $I^2 = 41\%$).

Exercise duration and intensity

In meta-regression analysis, exercise duration showed a trending association ($\beta = 1.822$, $P = 0.075$, df = 46) with effect size of BDNF increase after exercise (Fig 3). Removal of one study data point (Rasmussen *et al.*, 2009) with an exercise duration of twice as long as the next longest duration and greater than five standard deviations from the mean exercise duration (online Supporting Information), yielded a significant association ($\beta = 2.078$, $P = 0.043$, df = 45) between exercise duration and effect size (Fig 4). A positive association indicates that longer exercise times were associated with greater effect sizes. The median and modal exercise duration was 30 min. In subgroup analysis, exercise sessions of greater than 30 min resulted in significantly greater increases in peripheral BDNF than those produced after exercise sessions of 30 min or less (Greater than 30 min: SMD = 0.81, 95% CI: 0.53–1.09, $P < 0.001$; 30 min of less: SMD = 0.47, 95% CI: 0.31–0.63, $P < 0.001$; Test for subgroup differences: $Chi^2 = 4.24$, df = 1, $P = 0.04$). Exercise intensity also showed a trend ($\beta = 1.766$, $P = 0.085$, df = 43) for a significant association with effect size in meta-regression analysis (Fig 5).

Serum vs. plasma

Forty-two studies measured BDNF in serum only, nine studies (Zoladz *et al.*, 2008; Rasmussen *et al.*, 2009; Correia *et al.*, 2010; Seifert *et al.*, 2010; Babaei *et al.*, 2014; Coelho *et al.*, 2014; Slusher *et al.*, 2015; Church *et al.*, 2016; Schild *et al.*, 2016) measured BDNF in plasma only, and four studies (Currie *et al.*, 2009; Cho *et al.*, 2012; Gilder *et al.*, 2014; Pareja-Galeano *et al.*, 2015) measured BDNF in both serum and plasma. In subgroup analysis, a significantly greater increase in BDNF was found in plasma compared to serum (Serum: SMD = 0.55, 95% CI: 0.41–0.68, $P < 0.001$; Plasma: SMD = 0.99, 95% CI: 0.58–1.40, $P < 0.001$; Test for subgroup differences: $\chi^2 = 4.12$, df = 1, $P = 0.04$). Importantly, the serum subgroup contained more than four times as many participants as the plasma subgroup. In both subgroups, BDNF was significantly increased after acute exercise.

Gender

Meta-regression analysis revealed a significant association ($\beta = 3.624$, $P = 0.001$, df = 58) between percent of study population being male and effect size of increase in BDNF after exercise (Fig 6). A positive association indicates that greater increases in BDNF were observed in studies consisting of a greater proportion of males. In subgroup analysis, a significant increase in BDNF after acute exercise was found in males but not in females (Males: SMD = 0.75, 95% CI: 0.57–0.92, $P < 0.001$; Females: SMD = 0.13, 95% CI: −0.10–0.37, $P = 0.26$; Test for subgroup differences: $Chi^2 = 16.62$, df = 1, $P < 0.001$). Of note, approximately three quarters of all participants in studies included in this

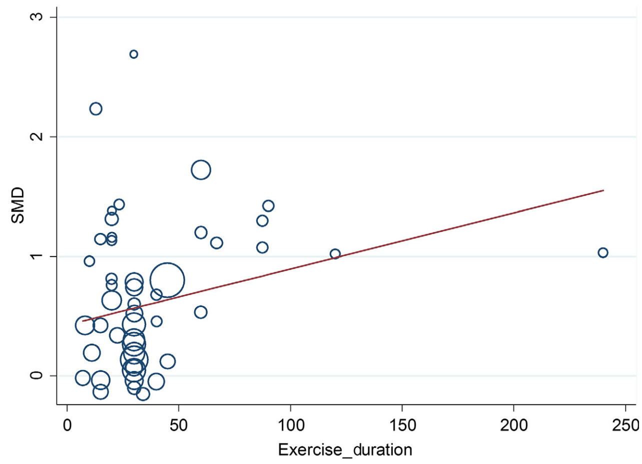

FIG 3. Meta-regression analysis of BDNF changes against exercise duration in minutes. A trending positive association ($\beta = 1.822$, $P = 0.075$, df = 46) was found between length of exercise session and effect size. SMD, standardized mean difference.

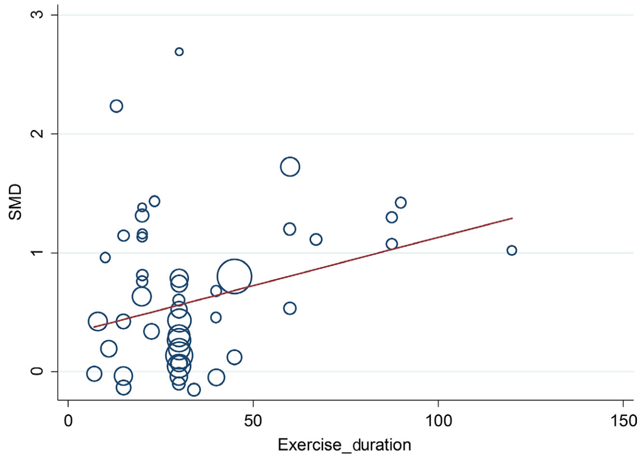

FIG 4. Meta-regression analysis of BDNF changes against exercise duration in minutes after removal of Rasmussen *et al.* (2009). A significant positive association ($\beta = 2.078$, $P = 0.043$, df = 45) was found between length of exercise session and effect size. SMD, standardized mean difference.

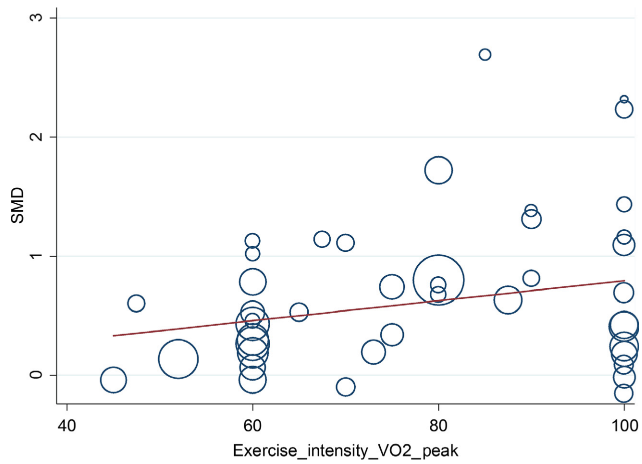

FIG 5. Meta-regression analysis of BDNF changes against exercise intensity (% of $VO_{2\ Peak}$). A trending positive association ($\beta = 1.766$, $P = 0.085$, df = 43) was found between exercise intensity and effect size. SMD, standardized mean difference.

meta-analysis were male, and in subgroup analysis five times as many males were included in the analysis than females.

Age, body mass index (BMI), and cardiorespiratory fitness

Mean age ($\beta = -0.877$, $P = 0.38$, df = 58) and BMI ($\beta = 1.000$, $P = 0.33$, df = 32) of study participants were not significantly associated with effect size (Figs 7 and 8). Interestingly, mean $VO_{2\ Peak}$ of study participants was significantly associated ($\beta = 3.548$, $P = 0.002$, df = 23) with effect size in studies that reported mean $VO_{2\ Peak}$ of study participants (Fig 9). This association was positive indicating greater increases in peripheral BDNF after acute exercise in those with greater cardiorespiratory fitness.

Discussion

Results from this meta-analysis suggest that peripheral blood concentrations of BDNF are increased after a single session of exercise. The effect of acute exercise on peripheral BDNF concentrations is heterogeneous and inconsistent. This phenomenon was found to have a medium effect size (Cohen, 1988), with the average increase in peripheral BDNF after acute exercise being approximately 60%. Interestingly, it appears the increase in peripheral BDNF after acute exercise is transient (Gold *et al.*, 2003; Rojas Vega *et al.*, 2006, 2012; Matthews *et al.*, 2009; Yarrow *et al.*, 2010; Goekint *et al.*, 2011; Brunelli *et al.*, 2012; Heyman *et al.*, 2012; Schmidt-Kassow *et al.*, 2012; Saucedo Marquez *et al.*, 2015; Tonoli *et al.*, 2015; Wahl *et al.*, 2015; Walsh *et al.*, 2016). Multiple studies have examined the kinetics of BDNF after acute exercise and have consistently reported decreases of BDNF back to baseline concentrations after 15–60 min of rest post exercise (Gold *et al.*, 2003; Rojas Vega *et al.*, 2006, 2012; Matthews *et al.*, 2009; Yarrow *et al.*, 2010; Goekint *et al.*, 2011; Brunelli *et al.*, 2012; Heyman *et al.*, 2012; Schmidt-Kassow *et al.*, 2012; Saucedo Marquez *et al.*, 2015; Tonoli *et al.*, 2015; Wahl *et al.*, 2015; Walsh *et al.*, 2016).

One hypothesized mechanism by which exercise enhances brain health is via upregulating BDNF production (Gomez-Pinilla *et al.*, 2008; Gligoroska & Manchevska, 2012). Evidence from this meta-analysis supports this hypothesis; however, this meta-analysis only assessed concentrations of BDNF in the periphery and therefore it cannot be concluded that concentrations of BDNF in the brain were increased after acute exercise. Although one human study suggested an association between peripheral and central BDNF concentrations (Pillai *et al.*, 2010), the evidence in humans is limited. It has been reported that BDNF can cross the blood-brain barrier (BBB) of mice and rats (Poduslo & Curran, 1996; Pan *et al.*, 1998); however, evidence of the ability of BDNF to cross the BBB is inconsistent (Pardridge *et al.*, 1994; Pilakka-Kanthikeel *et al.*, 2013) and the human BBB is structurally and functionally different from those in animal models. The roles of BDNF in the periphery are not well characterized and may involve modification of peripheral neuron function, regulation of energy homeostasis, and modification of insulin activity (Ono *et al.*, 1997; Lommatzsch *et al.*, 1999; Vanevski & Xu, 2013).

Numerous mechanisms may be responsible for BDNF increases observed after exercise. Changes in cerebral blood flow during exercise may contribute to increased BDNF production in the brain (Querido & Sheel, 2007). Furthermore, changes in circulating hormones, such as insulin-like growth factor and norepinephrine, may contribute to upregulated BDNF mRNA production (Ding *et al.*, 2006; Chen *et al.*, 2007). Upregulation of BDNF transcription

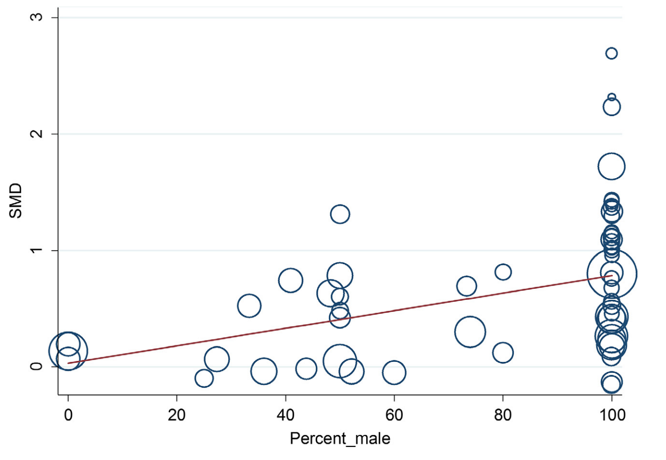

FIG 6. Meta-regression analysis of BDNF changes against percent of study population that are male. A significant positive association ($\beta = 3.624$, $P = 0.001$, df = 58) was found between percent of study population that are male and effect size. SMD, standardized mean difference.

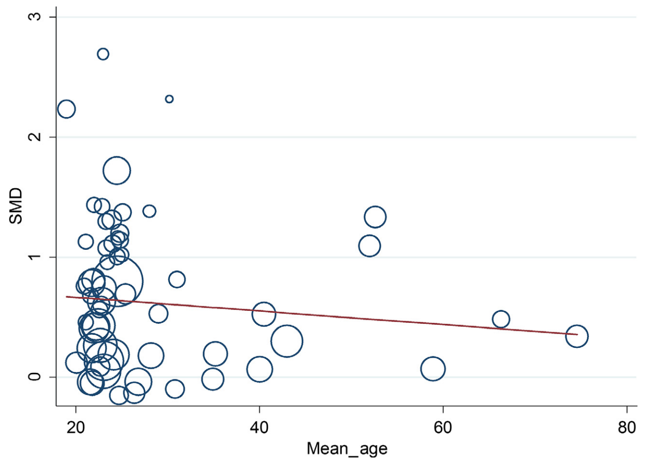

FIG 7. Meta-regression analysis of BDNF changes against mean age of study population. No association ($\beta = -0.877$, $P = 0.38$, df = 58) was found between mean age of study population and effect size. SMD, standardized mean difference.

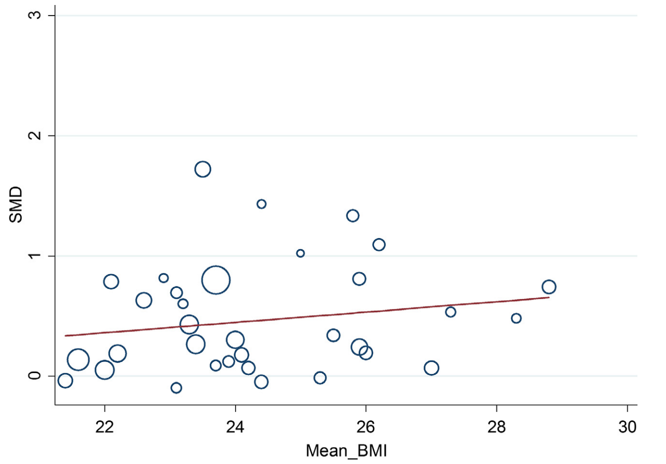

FIG 8. Meta-regression analysis of BDNF changes against mean BMI of study population. No association ($\beta = 1.000$, $P = 0.33$, df = 32) was found between mean BMI of study population and effect size. SMD, standardized mean difference.

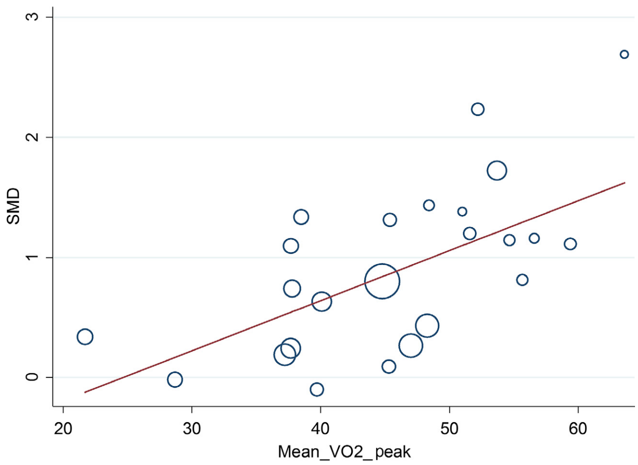

FIG 9. Meta-regression analysis of BDNF changes against mean $VO_{2\ Peak}$ of study population. A significant positive association ($\beta = 3.548$, $P = 0.002$, df = 23) was found between mean $VO_{2\ Peak}$ of study population and effect size. SMD, standardized mean difference.

appears to be dependent on cAMP-response-element binding protein (CREB), as mutant mice with repressed CREB activity showed no significant increases in BDNF mRNA nor protein levels after acute exercise (Chen & Russo-Neustadt, 2009; Aguiar *et al.*, 2011). The possibility exists that increases in BDNF concentrations observed after exercise may be due to a decrease in blood volume resulting from water loss during exercise (McConell *et al.*, 1997). Adjusting for blood volume loss post-exercise may provide a solution for determining whether increased BDNF concentrations after exercise are due to blood water loss or upregulation of BDNF production (Pareja-Galeano *et al.*, 2015).

Previous reviews on the effect of exercise on BDNF concentrations in humans have largely concluded that acute exercise transiently increases peripheral BDNF concentration (Knaepen *et al.*, 2010; Zoladz & Pilc, 2010; Coelho *et al.*, 2013; Huang *et al.*, 2014). The results of this meta-analysis are similar to an earlier analysis with fewer studies (Szuhany *et al.*, 2015). This current meta-analysis differs from that one by the inclusion of 41 additional reports that were added due to a different search strategy and a later search period (October 2016). There have been many reports published on the effect of acute exercise on peripheral BDNF concentrations since the previous meta-analysis, underscoring the importance of this topic. A larger number of included studies allowed for a stronger evaluation of current evidence and a more robust exploration of heterogeneity across studies.

Results from this meta-analysis suggest that exercise duration modifies the effect of acute exercise on peripheral BDNF concentrations. Longer exercise duration was associated with a greater increase in BDNF. Exercise durations of greater than 30 min were found to result in a significantly greater increase in peripheral BDNF than exercise durations of 30 min or less. This suggests that different exercise durations may enhance brain function differently. Interestingly, in a meta-analysis on the effects of acute exercise on cognitive performance, cognitive benefits after acute exercise were only observed after exercise durations longer than 20 min (Chang *et al.*, 2012).

In contrast to the effect of chronic exercise training on resting concentrations of peripheral BDNF (Dinoff *et al.*, 2016), no difference was observed in the effect of acute exercise on peripheral BDNF concentrations between aerobic and resistance training interventions. It has been observed that blood lipoprotein response to chronic exercise training differs between aerobic and resistance training interventions (Tambalis *et al.*, 2009). Perhaps longer time periods are required to observe differences in protein concentration changes induced by aerobic vs resistance training exercises. Short-term changes in protein concentrations may be similar in both aerobic and resistance training interventions. This finding suggests that with respect to changes in BDNF concentrations, aerobic exercise differs from resistance training only in chronic exercise training.

Interestingly, a greater mean $VO_{2\ Peak}$ of the study population was associated with greater effect size, indicating that greater increases in BDNF after acute exercise were observed in those with greater cardiorespiratory fitness. This may indicate that individuals with greater cardiorespiratory fitness are better 'primed' for acute physiological changes occurring after exercise and may receive greater acute benefits to cognition and mood (Castellano & White, 2008; Zoladz *et al.*, 2008; Chang *et al.*, 2012). Indeed, a meta-analysis of the effects of acute exercise on cognition determined that positive effects of acute exercise on cognition were greater in those with greater cardiorespiratory fitness (Chang *et al.*, 2012). It has been observed that blood pressure increase in response to exercise is lower in those with greater cardiorespiratory fitness (Kokkinos *et al.*, 2002), suggesting that those with greater fitness are more adapted to the physiological changes triggered by acute exercise. Perhaps those with greater exercise experience produce greater increases in BDNF because previous exercise experience has rendered their bodies more efficient at producing BDNF in response to exercise. Contrariwise, increased BDNF response to exercise may result in greater effects of exercise on cardiorespiratory capacity, explaining why those with greater increases in BDNF concentrations display greater cardiorespiratory fitness.

Gender differences in the effect of acute exercise on peripheral BDNF concentrations were observed in this meta-analysis, with a significant increase in BDNF post-exercise found in males but not females. This finding may be explained by several possible factors. This subgroup analysis was significantly limited by the fact that more than three quarters of the subjects included in this meta-analysis were male. A significantly larger male subgroup compared to females limits the confidence of this finding, as an effect in females may have been detected if more female participants were included. Differences in resting serum concentrations of BDNF across genders may be present, with some reports indicating greater resting serum BDNF concentrations in males than females (Lommatzsch *et al.*, 2005; Ozan *et al.*, 2010). This suggests that BDNF production and or breakdown differs between genders (Chan & Ye, 2017). In addition, differences in body composition and muscle mass may account for the difference in acute BDNF response to exercise found in this meta-analysis. Matthews *et al.* observed increases in BDNF mRNA and protein expression in rat muscle tissue after electrical stimulation and muscle contraction, suggesting that BDNF may be produced in muscle tissue during exercise (Matthews *et al.*, 2009). Thus, a greater proportion of muscle mass in males may explain the larger increase in BDNF after acute exercise. Furthermore, steroid hormone concentration differences across genders may account for some of the difference in acute BDNF response to exercise (Pluchino *et al.*, 2013). Interestingly, both estrogen and testosterone have been observed to have the potential to induce BDNF expression (Rasika *et al.*, 1999; Berchtold *et al.*, 2001b; Zhao *et al.*, 2003; Sohrabji & Lewis, 2006; Pluchino *et al.*, 2013). Perhaps testosterone is a more potent inducer of BDNF than estrogen, as this would explain an observed greater concentration of resting serum BDNF in males than females. Of note, differences in resting BDNF concentration changes after chronic exercise training were not found across genders, with similar increases in resting BDNF concentrations being observed in both males and females (Dinoff *et al.*, 2016). Age and BMI were not found to be modifiers of the effect of acute exercise on peripheral BDNF concentrations in this meta-analysis.

A greater relative increase in BDNF was found in plasma compared to serum. However, this subgroup analysis was also limited by a large difference in subgroup size, with more than four times as many participants in the serum subgroup than the plasma subgroup. The relatively small size of the plasma subgroup rendered this subgroup more susceptible to outliers. Removal of the study by Cho *et al.* (with an SMD in plasma greater than one and half times as large as any other SMD) eliminated the significant difference in effect size between these two subgroups. BDNF is stored in platelets, which are activated and release their contents in serum (Fujimura *et al.*, 2002). This results in substantially higher concentrations of BDNF in serum measurements than plasma (Pareja-Galeano *et al.*, 2015). Exercise has been associated with increases in platelet count and may result in platelet activation (Kestin *et al.*, 1993; el-Sayed, 1996). It is possible that platelet activation during exercise results in the release of stored BDNF into plasma, contributing to increases in plasma BDNF after exercise. Since platelet activation during exercise would not affect serum concentrations of BDNF, serum measurements may be better for determining the effect of acute exercise on blood BDNF concentrations.

Plasma BDNF represents freely floating BDNF and thus may have a different physiological role from serum BDNF (Lommatzsch *et al.*, 2005). It is likely that if BDNF is able to cross the human BBB, only BDNF in plasma would be able to do so as serum BDNF is normally stored in platelets (Pan *et al.*, 1998). Increased BDNF in the brain may result in enhanced neuronal survival and synaptogenesis, resulting in structural changes and enhanced brain function (Tolwani *et al.*, 2002; Erickson *et al.*, 2011; Swardfager *et al.*, 2011). On the other hand, if BDNF is able to cross the BBB, elevated peripheral BDNF concentrations may indicate increased BDNF production in the brain (Klein *et al.*, 2011). Indeed, associations between central and peripheral BDNF concentrations have been reported in animals (Karege *et al.*, 2002b; Angelucci *et al.*, 2011; Klein *et al.*, 2011) and in one human study (Pillai *et al.*, 2010).

The effect of exercise on BDNF concentrations may be altered by the presence of a single nucleotide polymorphism (SNP) in the gene encoding BDNF (Canivet *et al.*, 2015; Nascimento *et al.*, 2015; Lemos *et al.*, 2016). The Val66Met SNP is a gene variation resulting in an amino acid substitution from valine to methionine that is present in approximately 30% of the global population (Petryshen *et al.*, 2010). This SNP is associated with altered BDNF secretion and altered serum BDNF concentration (Lang *et al.*, 2009; Arija *et al.*, 2010). Two studies included in this meta-analysis (McDonnell *et al.*, 2013; Schmidt-Kassow *et al.*, 2013) examined differences in the effect of acute exercise on peripheral BDNF concentrations between those with and without the Val66met SNP. Schmidt-Kassow *et al.* reported no differences between groups (Schmidt-Kassow *et al.*, 2013) while McDonnell *et al.* reported group differences due to significantly lower resting serum BDNF concentrations in those with the SNP (McDonnell *et al.*, 2013). As only two studies examined this phenomenon, there is not enough evidence to conclude whether this SNP modifies the effect of acute exercise on BDNF concentrations.

This meta-analysis was limited by the heterogeneity in exercise intervention and study populations across different studies. We attempted to address this heterogeneity via subgroup and meta-regression analyses. Some of the subgroup analyses, such as the gender and blood component subgroup analyses, were limited by large differences in subgroup size. Another limitation to the results of this meta-analysis is that most studies included did not account for potential effects of dehydration on changes in BDNF concentrations post-exercise. Reduction in blood volume resulting from water loss during exercise may have contributed to higher concentrations of BDNF after exercise. One study that corrected for blood volume loss after exercise still observed significant increases in BDNF post-exercise in whole blood and serum coagulated for 24 h, but not in plasma nor serum coagulated for 10 min (Pareja-Galeano *et al.*, 2015). Additionally, more than half of the studies included in this meta-analysis lacked a control group that did not undertake exercise. This may have detracted from the quality of the evidence; however, fifty of the fifty-five studies included in this meta-analysis were deemed of high methodological quality in risk of bias analysis based on standardized criteria which included items such as adequately described interventions, objective reporting of outcomes, and reporting of adherence to intervention (see risk of bias analysis in the online Supporting Information).

Conclusion

Overall, this meta-analysis provides evidence for an increase in peripheral blood concentrations of BDNF after a single session of exercise. This effect is heterogeneous and may differ between genders. This effect appears to be modified by exercise duration. Further research to elucidate other modifiers of this effect, such as the presence of the Val66Met SNP, is warranted. Future studies in humans evaluating the relationship between peripheral and central BDNF and determining whether BDNF can cross the BBB are needed to assess the importance of the results of this meta-analysis. In addition, more work to determine whether transient increases in BDNF mediate clinical benefits, such as improvements in mood and cognition, would help in evaluating the impact of these results.

Supporting Information

Additional supporting information can be found in the online version of this article:

Table S1 PRISMA Checklist.
Table S2 Sample search strategy (Medline database).
Table S3 Study population and exercise intervention characteristics for each study included in the meta-analysis.
Table S4 Funnel plot of studies included in the meta-analysis. This funnel plot indicates a risk of publication bias.
Table S5 Risk of bias analysis of all studies included in the meta-analysis using criteria adapted from Cochrane Collaboration's Risk of Bias tool.
Table S6 Investigation of heterogeneity in subgroup analyses.

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Conflict of interest

All authors declare that they have no conflicts of interest relevant to the content of this review.

Author contributions

Walter Swardfager and Adam Dinoff conceived the study and formulated the systematic search strategy. All authors contributed to the analysis and interpretation of the data. Adam Dinoff prepared the first draft of the manuscript and all authors contributed to drafting and editing the manuscript for important intellectual content.

Data accessibility

All data used for these analyses and all supporting information files can be accessed online. Data used for these analyses are in the form of a Review Manager Version 5.3 file as well as an excel spreadsheet.

Abbreviations

1RM, One Repetition Maximum; BBB, Blood-Brain Barrier; BDNF, Brain-Derived Neurotrophic Factor; BMI, Body Mass Index; CI, Confidence Interval; CINAHL, Cumulative Index to Nursing and Allied Health Literature; HR Max, Maximum Heart Rate; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RPE, Rating of Perceived Exertion; SMD, Standardized Mean Difference; SNP, Single Nucleotide Polymorphism.

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