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REVIEW

How do different physical exercise parameters modulate brain-derived neurotrophic factor in healthy and non-healthy adults? A systematic review, meta-analysis and meta-regression

Comment différents paramètres de l'exercice physique modulent-ils le facteur neurotrophique dérivé du cerveau (BDNF) chez des adultes sains et non sains ? Une revue systématique, méta-analyse et méta-régression

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KEYWORDS
Brain;
Brain-derived neurotrophic factor;
Exercise;
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Summary
Objectives. — Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays crucial role on synaptic plasticity, neurogenesis, and neuroprotection. Exercise has been established as capable to increase BDNF level in the elderly, leading to improvement in brain functions, including learning and memory. However, there is no data regarding recommendation protocol that may lead to BDNF increase in this population. Then, we conducted a systematic review and meta-analysis to address this issue.
News. — We searched on nine large electronic databases until September 2018. Articles that evaluated the effect of exercise training on BDNF level were included. Regarding meta-analysis, random effect and meta-regression were conducted. Across twenty-five included studies in

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meta-analysis ($n = 2152$), we found exercise could lead to significant increase in BDNF level in adults (596.33 pg/ml) (95% CI: 471.76—720.89; $P < 0.001$; $I^2 = 97.5\%$; $n = 921$) comparing to control groups. Interestingly, this increase was independent of age group and health status. Meta-regression analyses found that variables such as age, exercise intensity, session and intervention duration, and exercise modality contribute to heterogeneity in terms of the entire population.

Conclusions. — Respecting study limitations, we suggest based on our results and available evidence, the following FITT-based exercise recommendation to improve BDNF level: Frequency: 2—3 times per week; Intensity: at least 65% of VO_2max; Type: moderate-intensity continuous training; Time: at least 40 minutes. Also, exercise is more effective at improving the BDNF level in lengthier intervention, and exercise intensity is linearly associated with BDNF changes.

MOTS CLÉS
Cerveau ;
Facteur neurotrophique dérivé du cerveau ;
Exercice ;
neuroprotection

Résumé

Objectifs. — Le facteur neurotrophique dérivé du cerveau (BDNF) est une neurotrophine qui joue un rôle crucial dans la plasticité synaptique, la neurogenèse et la neuroprotection. L'exercice a été établi comme étant capable d'augmenter le niveau de BDNF chez les personnes âgées, conduisant à une amélioration des fonctions cérébrales, y compris l'apprentissage et la mémoire. Cependant, il n'existe aucune donnée concernant le protocole de recommandation susceptible d'entraîner une augmentation du BDNF dans cette population. Nous avons ensuite procédé à un examen systématique et à une méta-analyse pour résoudre ce problème.

Informations. — Nous avons effectué des recherches dans neuf grandes bases de données électroniques jusqu'en septembre 2018. Les articles qui évaluaient l'effet de l'entraînement sur le niveau d'exercice de BDNF étaient inclus. En ce qui concerne la méta-analyse, un effet aléatoire et une méta-régression ont été réalisés. Parmi les vingt-cinq études incluses dans la méta-analyse ($n = 2152$), nous avons constaté que l'exercice pouvait entraîner une augmentation significative du taux de BDNF chez l'adulte (596,33 pg/mL) (IC 95 % : 471,76—720,89 ; $p < 0,001$; $I^2 = 97,5$). Des analyses de méta-régression ont montré que des variables telles que l'âge, l'intensité de l'exercice, la durée de la séance et de l'intervention, et la modalité de l'exercice contribuaient à l'hétérogénéité.

Conclusions. — En ce qui concerne les limites de l'étude, nous suggérons, en fonction de nos résultats et des preuves disponibles, la recommandation d'exercice suivante basée sur l'évaluation FITT pour améliorer le niveau de BDNF : fréquence : 2 à 3 fois par semaine ; intensité : au moins 65 % de la VO_2 max ; type : MICT ; temps : au moins 40 minutes. En outre, l'exercice est plus efficace pour améliorer le niveau de BDNF lors d'interventions plus longues et son intensité est associée de manière linéaire aux modifications du BDNF.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin found in the brain, primarily in the hippocampus, cerebral cortex, hypothalamus, and cerebellum [1]. Besides playing a critical role in modulating neuronal development and survival, and synaptic plasticity, this protein has a pivotal effect on improvement of cognitive function primarily through neurogenesis and protection against neurological diseases, such as Alzheimer's [2], and disorders such as minor and major depression [3]. Additionally, exercise-induced BDNF up-regulation at hippocampus and prefrontal cortex, where it is found in higher concentrations, has been implicated in neurogenesis [4], dendritic growth and long-term potentiation [1,5]. On the other hand, 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 disease [2].

Substantial evidence indicates that either physical exercise (hereafter referred to as exercise) or activity promotes brain function by up-regulation of different growth and neurotrophic factors especially the BDNF [6—8]. Also, it is known that continuous aerobic training (AER) could improve memory and learning in humans through an increase in BDNF expression, independently of age [9—11], health status [12—16], and intensity [15,17,18]. Likewise, other models of exercise, for example resistance (RT) and high-intensity interval training (HIIT) seems to also have neuroprotection-related effect on memory and other cognitive functions.

There is an inconsistency of evidence regarding the effects of resistance training on BDNF levels [19,20]. Recent

studies [19,20] have failed to find alterations in peripheral BDNF levels among individuals exposed to a single session of resistance training. Even though resistance training seems to develop cognitive function in human and animals, this exercise-related improvement may be related to an increase in insulin-growth factor 1 (IGF-1) but no BDNF [21].

Likewise, HIIT appears to up-regulate the expression of systemic BDNF after a single bout [15] of exercise in human and after exercise training intervention in animal [15,17,22,23]. Afzalpour et al. [23] found that this model of exercise could improve BDNF expression at higher levels compared to moderate-intensity continuous training. Nevertheless, it was not found to date studies that have found an increase in BDNF after HIIT-based exercise regimen.

Although there is a body of evidence reporting the effect of aerobic exercise and activity on BDNF, little is known about a dose-response relationship between them. To now, only two studies [15,17] have tried to understand this association in humans. Nevertheless, those studies evaluated BDNF expression after a single bout of exercise. Consequently, there is still a gap regarding a possible threshold-like level of intensity or volume required to observe a significant increase in its concentration level. Then, the aim of the study was to identify a dose-response relationship between BDNF concentration and the amount of physical activit1y or exercise in humans.

2. Methods

The review follows the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [24] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) checklist (Supplementary material). This protocol was published in PROSPERO (CRD42018092137) (Supplementary material).

2.1. Search strategy

The search was conducted at September 2018 and comprised the following databases and search language: MEDLINE/PubMed (English), PsycINFO (English), CINAHL (English), Sport Discus (English), Scopus (English), Science Direct (English), Cochrane Library (English), Web of Science (English), and Scielo (English and Portuguese). The keywords used was a combination of terms related to exercise, physical activity, and different models of exercise training with BDNF and related MeSH terms. Figure S1 presents the MEDLINE search strategy and all strategies are available as electronic supplementary material. Reference sections of identified articles and relevant systematic reviews and meta-analysis were also examined to detect articles not captured by this search (Fig. 1).

Initially, two independent reviewers (RA and MGD) checked all titles and abstracts found in the electronic databases to include eligible articles for the full-text analysis. The agreement between the reviewers for the title/abstract screening was high (kappa = 0.819; $P < 0.001$). Both reviewers then reviewed the potentially eligible articles for inclusion. In case of disagreement between the first two reviewers, a third (NF) was consulted to reach a consensus. Fig. 1 presents the PRISMA flow diagram of this methodology.

2.2. Eligibility criteria

The following eligibility criteria, according to the PICOS (Population, Intervention, Comparator, Outcomes, and Study design) question, were considered for inclusion of articles in this systematic review.

2.2.1. Population

The review included adults (> 18 years) with no restriction on physical or cognitive condition. Studies including individuals with risk factors (e.g., high cholesterol, overweight, obesity, diabetes) or known cardiometabolic (e.g., Type 2 diabetes, coronary heart disease, heart failure) or neurological (e.g., Alzheimer's disease, depression, mild cognitive impairment) diseases were eligible for inclusion.

2.2.2. Intervention

The review included experimental studies with any model of exercise (e.g., AER, RT, HIIT). Studies that only aimed to increase physical activity level were not included in this review. There was no restriction on intervention duration. Interventions that aimed to verify or compare the effect of exercise and pharmacological treatment on BDNF level were not included.

2.2.3. Comparator

Control groups and baseline measurements were comparators for intervention effect values. Control groups that included any type of exercise interventions were considerate as intervention group.

2.2.4. Outcomes

BDNF concentrations were measured at serum and plasma. To be included in the meta-analysis, BDNF needed to be measured by a precise method and be reported as picogram per milliliter (pg/ml). When it was reported in other units (e.g., ng/ml, pg/dl), the original value was converted to pg/ml.

2.2.5. Study design

Experimental studies (randomized controlled trials or not) published in any language and year were considered.

2.3. Risk of bias assessment

After selecting all articles, the Cochrane Collaboration's tool for assessing the risk of bias was used [25]. All studies included in the systematic review were examined to determine the adequacy of randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.

All criteria were evaluated as a high, low, or unclear risk. Consensus was reached through discussion for all disagreements or misunderstandings. Three independent authors (N.F., M.G.D., and R.A.) conducted the quality assessment of all included publications and consensus was reached. No studies were discarded.

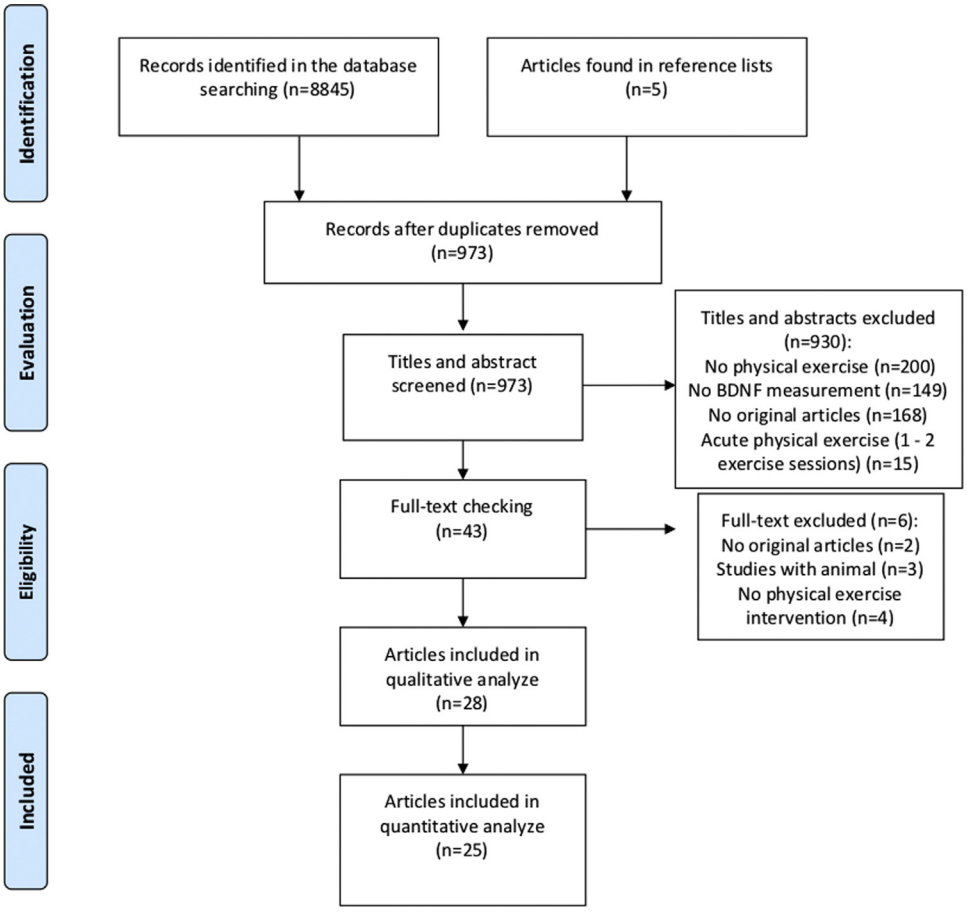

Figure 1 PRISMA flow diagram.

2.4. Data extraction

Data were extracted in duplicate and the information was cross-checked by two independent reviewers (N.F. and M.G.D.). Data about sample characteristics (gender, health status, age, body mass index, weight), exercise intervention [volume (e.g., minutes per week, minutes per session), intensity (e.g., percentage of VO_2 maximum (%VO_2max), % of maximum heart rate (%MHR)), training frequency (days per week)], blood sample (i.e., serum, plasma), primary outcome (BDNF concentration), secondary outcomes (attendance at the exercise training sessions), and quality assessment of included studies were extracted using a data extraction form (spreadsheet format).

A data extraction form was created and tested by the review team prior to full data extraction. In case of disagreement between the first two reviewers (R.A. and M.G.D.), a third independent reviewer (N.F.) helped to resolve the issue by consensus. Missing data were requested from the authors of the original data.

2.5. Statistical analyses

Data were reported as mean difference (WMD) and 95% confidence interval (CI). The use of mean differences (''difference in means'') was based on the adequateness of this standard statistic when outcome measurements in all studies are made on the same scale [24]. When data were reported in different units (e.g., nanograms per milliliter, picograms per milliliter) the data were converted to picograms per milliliter (pg/ml). When a study had more than one intervention, the interventions were included in the analysis individually. If a study has data from different time periods, only baseline and post-intervention measurements were retrieved. Where the change in standard deviation (ΔSD) was available it was collected alongside the preintervention and post-intervention SD. Where ΔSD was not reported, the correlation coefficient (corr) for each primary outcome was calculated according to the *Cochrane Handbook for Systematic Reviews of Interventions* [24]:

$$corr = \frac{SDpre^2 + SDpost^2 - \Delta SD^2}{2 \times SDpre \times SDpost}$$

and the ΔSD was calculated as:

$$\Delta SD = \sqrt[2]{\left(SDpre^2 + SDpost^2 + 2 \times corr \times SDpre \times SDpost\right)}$$

The change in BDNF concentration mean (ΔMean) and ΔSD were calculated for each condition and uploaded to Review Manager 5.0. Data analysis was also performed in statistical software STATA 13.0.

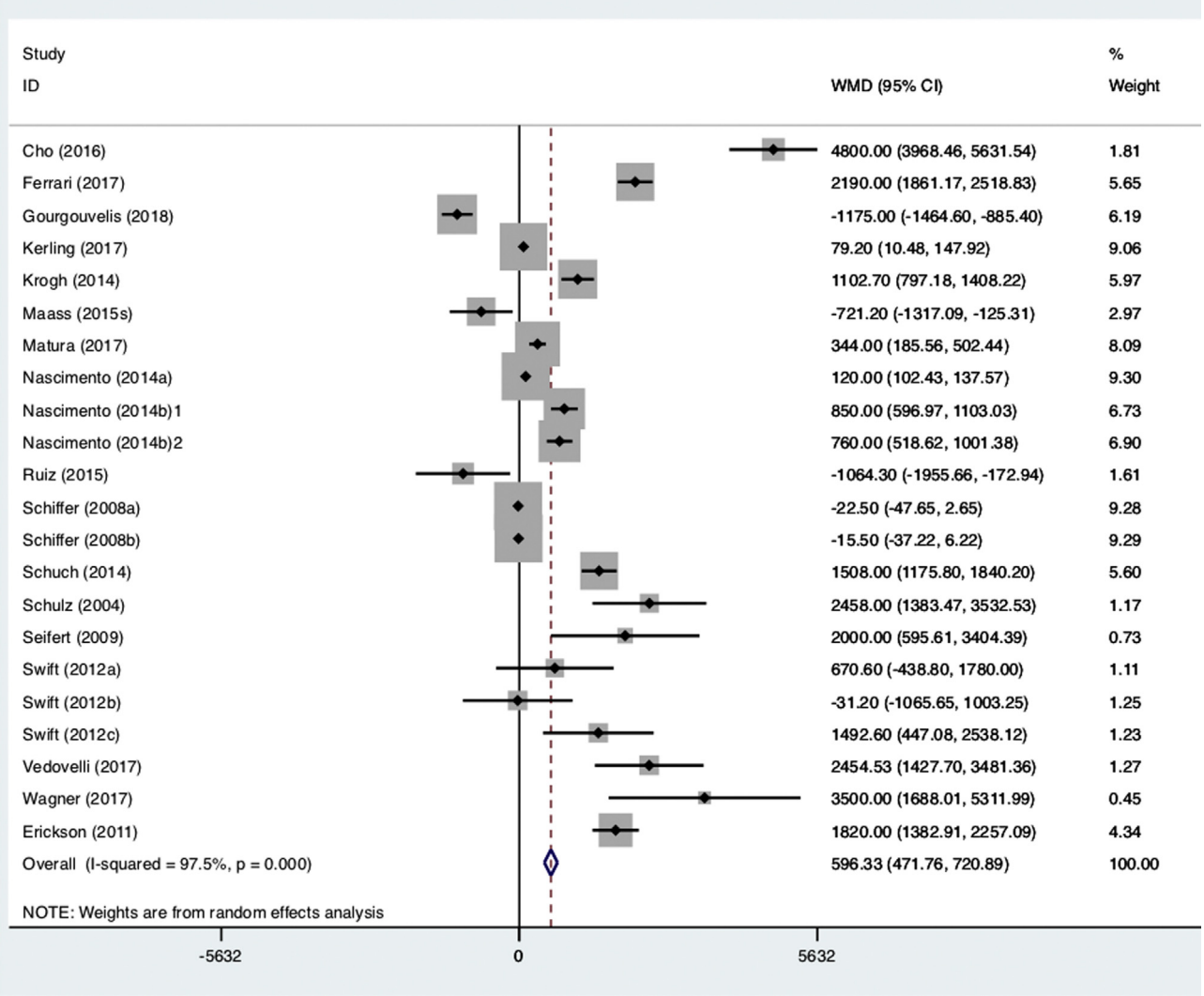

Figure 2 Forest plot of the results from a random-effect meta-analysis shown as mean difference with 95% CIs on brain-derived neurotrophic factor level (BDNF; pg/ml) in adults. For each study, the circle represents the mean difference of the intervention effect with the horizontal line intersecting it as the lower and upper limits of the 95% CI.

Cochran's Q test was used to assess the heterogeneity between the studies and the I^2 statistic refers to a ratio of true effect variance to observed error variance [26]. According to Higgins et al. [26], as the analysis showed moderate to high heterogeneity in most of the analyzed outcomes, a random-effect analysis model was used. Furthermore, a subgroup analysis was conducted to identify their effect on BDNF concentration change.

The subgroups analyzed were generated based on blood sample (i.e. serum and plasma), age, gender, health status (i.e. sample diagnosed with any disease or disorder), physical exercise model, intervention length, session frequency and duration, exercise intensity, use of anti-depressive drugs, and risk of bias. Publication bias was assessed using Egger's test and by visual inspection of funnel plots.

In order to understand the sources of heterogeneity, we conducted a meta-regression analysis using minutes per week, intensity (%VO_2max), age, intervention and session duration and model of exercise as covariates because they could influence the exercise-induced increase in BDNF concentration, had considerable unexplained heterogeneity (I^2) and had a sufficient number of studies (≥ 10). Exercise intensity and volume were limited to %VO_2max and minutes per week and per session, respectively, because there were few study groups that used %MHR and MET per minutes per week (< 10). These covariates were meta-regressed individually and together in a random-effects meta-regression model using STATA 13.0.

The random-effects meta-regression used residual restricted maximum likelihood to measure between-study variance (τ^2) with a Knapp-Hartung modification as recommended. When all covariates were analyzed together, permutation tests were performed ($n = 1000$) to address the issue of multiple testing by calculating adjusted P-values [27]. Also, we generated correlations to test the association between BDNF changes with variables explaining heterogeneity in meta-regression analyses as well as with key exercise variables, based on clinical judgment of their importance. All correlation analyses were weighted by the inverse of the variance of each observation, and scatter

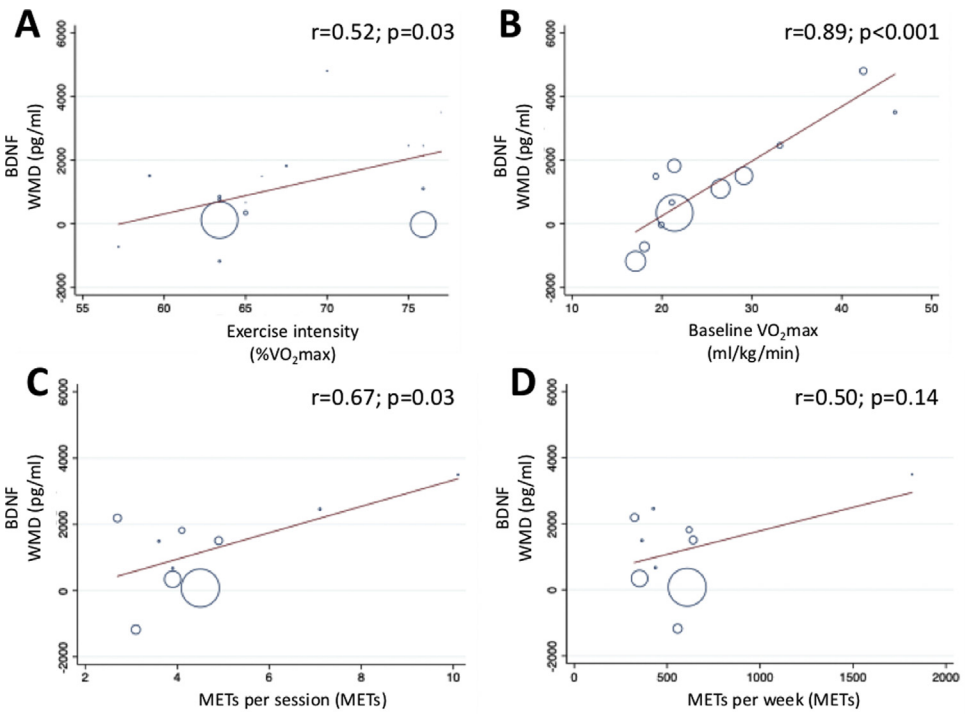

Figure 3 Association between intensity-related training variables and changes in brain-derived neurotrophic factor (BDNF) in adults. The size of the symbols is proportional to the inverse variance of each study in the pooled analysis.

'bubble' plots were constructed to graphically display the proportional weights of the different trials.

3. Results

3.1. Systematic review

The original search yielded 8845 articles. Randomized trials were identified by consulting other reviews and meta-analyses on the subject and were added in manually (5 studies). After deduplication and screening for inclusion criteria, 43 articles were independently read/reviewed by three authors (NF, MGD, and RA). A total of 28 RCTs were selected for inclusion in this meta-analysis (Fig. 1).

The sample ranged from 14 [28] to 120 [29] adults with age mean of 47.4 (±21.1) years (Table S1—Supplemental material). Among articles included in the qualitative analysis, three evaluated the effect of exercise in adults with depression [12,13,30], two in subjects with overweight or obesity [31,32], and eleven used healthy individuals in their sample [10,11,19,28,29,33—40]. Also, 60% of the samples were sedentary before the intervention period. In average, the exercise programs were performed for 13.34 (±11.7) weeks, with a frequency of 3.0 (±0.7) days per week and session duration of 48.2 (±11.9) minutes. The mean exercise intensity was approximately at 66.6 (±6.6) % of VO_2max. Most exercise intervention was based on AER (70%), followed by concurrent training (AER + RES; 22%) and RT (7%).

Exercise was able to increase BDNF concentration level in 13 (48%) of included studies. Curiously, 11 (85%) from those studies used only AER in their exercise program.

3.2. Bias evaluation

From seven studies that reported use anti-depressive drug by the sample during intervention period [12—14,30,41—43], two [13,42] did not report the appropriate control of the variable in articles (Figure S2—Supplemental material).

On selection, performance and detection bias, there was a high incidence of unclear risks (69,2%). Studies with a high risk of selection bias actually reported that randomization occurred at sample selection and allocation, but they did not specify properly how it was done [24]. Similarly, there was a lack of detail in articles regarding blinding in participants, personnel, and evaluator.

Considering reporting bias, nineteen [7,10,11,13,14,28,29,32,35—39,41—44,16,45,46] (64.5%) of the included studies were classified as high risk, mainly because they did not report the exact *P*-value ($P < 0.05$).

Regarding publication bias, the analysis showed no significant effect on BDNF concentration change ($P = 0.712$; Figure S3—supplementary material).

3.3. Meta-analysis

All studies included in the systematic review evaluated the effect of exercise on BDNF concentration level. Nevertheless, only 31 studies had enough data to be added to the meta-analysis. The outcome (BDNF concentration change) was reported in mean change (95% CI). The analysis showed that exercise groups increased changes in BDNF concentration levels in 596.33 pg/ml (95% CI: 471.76—720.89; $P < 0.001$; $I^2 = 97.5\%$; $n = 921$) in adults comparing to control groups (Fig. 2). Also, at

Table 1 Results from random-effects meta-analysis shown as weighted mean difference (WMD) with 95% CIs on BDNF changes (pg/ml) on different subgroups.

Variables	Interventions	Participants	WMD (95% CI)	I^2 (%)
Blood sample				97.4
Serum	19	873	941.94 (659.20—1224.68)	
Plasma	4	88	23.95 (—38.86—86.75)	
Gender				94.6
Male	6	197	1947.16 (1211.57—2682.75)	
Female	18	798	319.78 (225.46—414.10)	
Age (years)				0
Less than 40	7	161	549.98 (315.56—784.41)	
40—60	7	368	1186.28 (291.19—2081.36)	
More than 60	8	392	550.33 (170.86—929.80)	
Health status				90.4
Healthy subject	11	422	377.74 (198.20—557.29)	
Diagnosed patients	10	470	965.66 (656.97—1274.35)	
Physical exercise model				92
Moderate-intensity continuous training	15	644	1021.62 (744.31—1298.94)	
Resistance training	2	85	134.68 (—77.84—347.20)	
Concurrent training	5	192	767.62 (—1116.11—2651.35)	
Intervention length (weeks)				85.9
11 or less	7	214	1115.77 (—436.78—2668.33)	
12	7	249	208.47 (80.06—336.88)	
13 or more	8	459	1120.62 (642.19—1599.05)	
Training frequency (sessions per week)				0
2—3	25	1652	1189.24 (779.87—1598.62)	
5	2	104	1705.54 (—3079.40—6490.48)	
Session duration (minutes)				0
Less than 40	5	247	86.96 (—525.61—1699.52)	
40—59	7	347	1044.18 (670.50—1417.86)	
60 or more	9	276	1446.07 (621.00—2271.14)	
Exercise intensity (%VO_2max)				87.3
Less than 65%	6	200	178.83 (—649.81—1007.47)	
65% or higher	12	555	1682.51 (1159.40—2205.61)	
Exercise intensity (%maxHR)				14.2
76% or less	8	300	—52.83 (—305.59—199.92)	
More than 76%	3	140	773.30 (—704.69—2251.30)	
Anti-depressive drugs				38.7
Use	4	172	1099.24 (152.26—2046.22)	
No use	20	823	450.41 (365.22—535.59)	
Risk of bias (categories with ''high risk of bias'')				87.4
Less than 3	12	384	290.66 (130.59—450.74)	
3 or more	13	1133	751.30 (473.23—1029.37)	

MET: metabolic equivalent; %maxHR: maximum heart rate; VO_2max: maximum oxygen uptake; Coeff.: coefficient; CI: confidence interval.

post-intervention period, BDNF concentration was higher in individual from exercised groups compared to control group (795.71 pg/ml; 95% CI: 382.45—1208.97; $P < 0.001$; I^2:98%; $n = 2152$) (Figure S4—Supplemental material).

3.4. Subgroup analysis

All figures from subgroup analysis are presented in Table 1. The limits used in each categorization were chosen in order to provide to all categories the most similar number of individuals.

Briefly, exercise could produce positive changes in BDNF in adults, regardless age group, gender, and health status. However, it seems that training-related variables have some influence on BDNF variation. For example, lengthier intervention periods, with longer and more intense sessions seems to be more effective to increase BDNF in adults.

Moreover, our sensitivity analysis showed even when ten studies [13,19,29,35—37,16,45—47] showing high risk of bias in as least 3 categories was separated from analysis,

Table 2 Results from univariate and multivariate meta-regression models.

Model	*n*	Coeff. (95% CI)	τ^2	Adj. R^2 (%)	I^2 (%)	*P*-value
No covariates	25	596.33 (471.76 to 720.89)	4.33		97.50	< 0.001
Univariate						
Minutes per week	15	0.00 (−0.02 to 0.01)	1.33	−7.31	98.40	0.68
Intensity (%VO_2max)	13	0.09 (−0.01 to 0.20)	0.82	21.41	98.78	0.07
Age	15	−0.03 (−0.06 to 0.01)	1.02	17.89	97.79	0.16
Intervention length	15	0.00 (−0.05 to 0.05)	1.36	−9.47	98.95	0.99
Type of physical exercise	15	−0.09 (−0.69 to 0.50)	1.36	−9.38	98.97	0.74
Baseline VO_2max	9	0.06 (0.01 to 0.11)	0.26	56.47	85.93	0.02
Session duration	15	0.00 (−0.06 to 0.06)	1.36	−9.09	98.75	0.88
Volume-related covariates	15		1.54	−23.58	98.53	0.83
Minutes per week		−0.03 (−0.10 to −0.04)				0.38
Intervention length		0.00 (−0.06 to 0.06)				0.89
Session duration		0.89 (−0.14 to 0.32)				0.42
Intensity-related covariates	7		0	100.00	0.00	0.24
Intensity (%VO_2max)		3.63 (−5.29 to 12.56)				0.12
Baseline VO_2max		8.05 (−11.87 to 27.97)				0.12
MET per session		−40.23 (−140.04 to 59.57)				0.12
MET per week		0.01 (−0.01 to 0.02)				0.12
Total MET		0.02 (−0.04 to 0.08)				0.17
Multivariate model	9		0	100.00	0.00	0.03
Minutes per week		0.97 (0.94 to 1.02)				0.15
Intervention length		1.03 (1.01 to 1.06)				0.02
Session duration		1.07 (0.91 to 1.26)				0.19
Intensity (%VO_2max)		0.96 (0.92 to 1.01)				0.09
Baseline VO_2max		1.03 (0.95 to 1.12)				0.22
Age		0.96 (0.91 to 1.01)				0.07

MET: metabolic equivalent; VO_2max: maximum oxygen uptake; Coeff.: coefficient; Adj. R^2: Adjusted R^2; CI: confidence interval.

exercise could increase BDNF level (321.66 pg/ml; 95% CI: 159.60—483.73; $P < 0.001$; $I^2 = 97\%$; $n = 418$).

3.5. Meta-regression

The results from the full model meta-regressions are presented in Table 2. When combined, weekly volume, VO_2max-based physical exercise intensity, age, intervention length, baseline VO_2max, and session duration did explain 100% of the variance in BDNF level changes ($P = 0.03$).

As showed in Fig. 3, higher cardiorespiratory fitness at baseline (Fig. 3b) and exercise intensity (Fig. 3a and c) were associated with increased changes in BDNF level. Also, the impact of physical exercise in increasing serum BDNF level was augmented with higher weekly volume of physical training (1.03 pg/ml (1.01, 1.06), $P = 0.02$) (Figure S5—Supplemental material).

4. Discussion

To the best of our knowledge, this is the first study that aimed to determine an optimal frequency, duration, intensity, and physical exercise model to improve the concentration of this important neurotrophin. Based on our findings and on literature, physical exercise-induced BDNF improvement was more effective in interventions based on MICT, using frequency between 2 and 3 days per week, each session lasting 40 minutes or more, target VO_2max-based intensity equal to 65% and total exercise intervention duration of at least 13 weeks. Our data showed MICT was both sufficient and necessary to increase serum BDNF concentration in adults.

BDNF has been associated with neuronal protection and survival, axonal and dendritic growth and remodeling, neuronal differentiation and synaptic plasticity [1,4]. The neurotrophin is implicated in many neural processes and can prevent or delay neurodegenerative diseases. BDNF is also essential for angiogenesis and strengthening neural connectivity during childhood, biological activities important for learning and memory and required for enhanced academic performance and brain health [48]. Importantly, BDNF can cross the blood-brain barrier in a bidirectional manner [49] and can be measured peripherally in serum and plasma. This characteristic makes BDNF action extends beyond the brain, as it is also involved in regulating metabolic functions, such as fat oxidation and glucose uptake [50,51] and is believed to be downregulated in people suffering obesity and type 2 diabetes [52].

Exercising promotes changes in different levels of a human being's organization, including metabolic adaptations. Those modifications occur in accordance with the exercise volume, intensity, duration, and frequency [53]. Besides differences in age, gender, health condition, or exercise model, analysis of metabolic alterations during exercise is an appropriate way of controlling its metabolic

dynamics [54]. Thus, exercise effects observed for cognition is expected to occur within this integrated machinery that comprises the aerobic energy expenditure and the synthesis of BDNF as a hub for the promotion of neural plasticity and protection.

Previous meta-analysis [5,54,55] has consistently reported beneficial effects of MICT on BDNF concentration. However, RT has lead authors to different conclusions about its influence on BDNF concentration. These divergences could be addressed to sample age. Coelho et al. [56] evaluated the effect of RT on plasma BDNF level in older women (mean age: 71 years). Authors used only knee extensors and flexors in exercises session, which lasted 60 minutes and occurred 3 times per week. Regarding intensity, authors established a load equal to 75% of one repetition maximum (1RM). Using this protocol, they reported an increase in plasma BDNF level after RT training. Goekint et al. [19], although established a very similar RT protocol (10-week duration; 3 times per week; 65% of 1RM), could not find a significant increase in serum BDNF level in young adults (mean age: 20 years). Similarly, Schiffer et al. [38] also aimed to identify some effect of RT on BDNF in plasma in students (mean age: 22 years). Using RT protocol similar to those previously described (12-week duration; 3 times per week; 75% of 1RM), the authors also could not find a significant improvement in plasma BDNF level.

Based on those results previously reported, and on our findings, we showed young (less than 40 years), middle (41 to 59 years) and older adult (60 years old or more) seems to be susceptible to positive changes in BNDF induced by exercise, especially RT. This finding is relevant since circulating BDNF levels have been shown to be affected by a host of factors including age. The concentrations of BDNF change with increasing age, and neuronal loss in older persons has been shown to be related to low peripheral BDNF levels.

MICT seems as a non-pharmacological neuroprotective strategy due to its effects on BDNF concentration [6,54,55], hippocampus volume [29] and on neurogenesis [4,57]. However, as stated by Coelho and colleagues [54] and later by Dinoff and colleagues [58], the available evidence does not allow us to reproduce a recommended protocol (i.e., type, intensity, volume) of physical exercise that aims to increase in levels BDNF. Our findings here suggest a FITT-based recommendation of physical exercise aimed to promote BDNF augmentation: Frequency: 2—3 times per week; Intensity: at least 65% of VO_2max; Type: MICT; Time: at least 40 minutes. This FIIT model is adopted by the American College of Sports Medicine in guidelines for exercise prescription [53].

Regarding frequency, sensitivity analysis reported that exercising five times per week do not promote BDNF concentration increase compared to 2—3 times/week. Baker et al. [59,60] and Ruscheweyh [18] examined the effects of MICT (75—85% maximum heart rate) and Nordic walking, respectively, on BDNF level in older adults. The exercise protocol was executed four and five times per week in each study. At the end of experiments, the authors did not report an improvement in BDNF level among both samples. However, in one experiment [59], researchers reported physical exercise-induced BDNF increase only in men. Although several studies have been reporting that MICT realized 3 times per week on BDNF level [6,54,55], some researches did not achieve the same conclusion with exercise between 4 to 5 times per week. One explanation could be the lower rest interval between sessions especially with older samples. Still, we intensely encourage more researches to verify the effect of different exercise frequencies in BDNF concentration in adults.

Still, on volume, it seems that exercise for at least 12 weeks consecutively and session duration of 40 minutes or more is the optimal recommendation for BDNF release. Dinoff et al. [58], the latest published meta-analysis about physical exercise and BDNF, used subgroups analysis to verify any differences between intervention lasting less than 12 weeks vs. 12 weeks or more. The authors failed to find this relationship. One explanation could be different criteria between the present study and the one above mentioned. For example, we did not include studies that did not have a control group. There is consistent evidence supporting that acute bouts of moderate to vigorous intensity aerobic exercise increase circulating BDNF in adults [6,61]. Also, as intensity and duration increases, effect size becomes greater [6]. At the mitochondrial level, Bishop et al. [62] suggested that training intensity may be an important determinant of improvements in mitochondrial function, but not mitochondrial content. On the other hand, training volume seems to be more significant than intensity for exercise-induced increases in mitochondrial content.

BDNF binds to the tyrosine kinase receptor TrkB and activates molecules such as SHC (SHC1) and PLC-gamma (PLCG1). These lead to activation of various signaling modules such as PI3K/AKT pathway, RAS/MAPK/ERK pathway, and AMPK/ACC [63]. These different pathways are responsible for crucial neuronal processes. For instance, BDNF stimulation of PI3K/AKT signaling pathway is essential for proliferation, protection, and survival of neuronal cells. Moreover, ERK1/2-induced BDNF (MAPK3/MAPK1) has a major function in differentiation, protection of neuronal cells, and release of neurotransmitters [62].

In the last years, researchers around the world have reported that either MICT [64] or resistance exercise [65] increase in phosphorylation of ERK 1/2 and p38 MAPK in adults. Similarly, stimulation of PI3K/AKT signaling cascade has been shown to be induced by swimming [66], treadmill training [67] and running wheel [68]. Indeed, Bruel and colleagues [93] indicated that exercise-mediated improvement of adult neurogenesis and synaptic plasticity is blockage by inhibited of PI3K/AKT. Based on thus conclusions, it is established that physical exercise may improve neurological architecture through the activation of different pathways.

Yuan et al. [21] showed that resistance training-induced increase in IGF-1 promotes proliferation of neural cells by activating the PI3K/Akt or the MAP kinase pathways. Also, MICT activated the same pathway, but it initiated with BDNF release. This leads us to hypothesize that either MICT or RT could be responsible for enhancement in adult neurogenesis, synaptic plasticity, and cognitive function. MICT-mediated improvements are mainly coordinated by increased BDNF release, leading to stimulation of PI3K/AKT and RAS/MAPK/ERK signaling cascade pathway. Similarly, RT may contribute to the development of neural function by an augmented release of IGF-1, which promotes proliferation of neural cells by activating the same pathways [21]. Nevertheless, it is recommended by the present study and the literature [6,57], more studies evaluating the effect of

RT in cerebral parameters especially regarding neurotrophic and growth factors. On same though, the authors encourage scientific community to identify how physical activity and different models of physical exercise may affect not only healthy individuals but essentially in people with neurodegenerative conditions, such as Alzheimer's disease.

One important limitation from the present study is the high heterogeneity among studies. In order to understand and reduce the effect of heterogeneity on results, we performed sensitivity and meta-regression analysis. First, sensitivity analysis showed the exercise-induced effect on BDNF level is affected by blood sample, age, gender, health status, exercise model, intervention length, session frequency and duration, and VO_2max-based exercise intensity. Anti-depression drug use and risk of bias did not affect exercise benefits on BDNF concentration. Also, meta-regression analysis reported that minutes per week, VO_2max-based exercise intensity, age, intervention length, baseline cardiorespiratory fitness, and session duration explained 100% of the variation in serum BDNF level change.

5. Conclusion

We not only agreed with literature that physical exercise especially MICT is able to augment BDNF level, but suggest, based on our results and available evidence, following FITT-based physical exercise recommendation to improve BDNF concentration: Frequency: 2—3 times per week; Intensity: at least 65% of VO_2max; Type: MICT; Time: at least 40 minutes. Exercise is more effective at improving the BDNF level in lengthier intervention. Furthermore, it seems that exercise intensity is linearly associated with BDNF changes. The authors encourage scientific community to deeply understand how physical activity and different model of physical exercise may affect the central nervous system especially in the prevention of some neurodegenerative conditions, such as Alzheimer's disease.

Ethical statement

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.scispo.2019.02.001.

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