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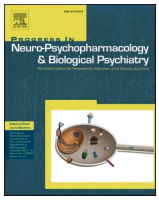

The relationship between BDNF and physical activity on depression

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ABSTRACT

Background/objective: Major depressive disorder (MDD) is one of the leading causes of disease burden and disability worldwide. Brain-derived neurotrophic factor (BDNF) seems to have an important role in the molecular mechanisms underlying MDD aetiology, given its implication in regulating neuronal plasticity. There is evidence that physical activity (PA) improves depressive symptoms, with a key role of BDNF in this effect. We aim to perform a systematic review examining the relationship between the *BDNF* Val66Met polymorphism and the BDNF protein, PA and MDD.

Methods: Both observational and experimental design original articles or systematic reviews were selected, according to the PRISMA statement.

Results: Six studies evaluated the Val66Met polymorphism, suggesting a greater impact of physical activity on depression depending on the Val66Met genotype. More discordant findings were observed among the 13 studies assessing BDNF levels with acute or chronic exercise interventions, mainly due to the high heterogeneity found among intervention designs, limited sample size, and potential bias.

Conclusions: Overall, there is cumulative evidence supporting the potential role of BDNF in the interaction between PA and MDD. However, this review highlights the need for further research with more homogeneous and standardised criteria, and pinpoints important confounding factors that must be considered in future studies to provide robust conclusions.

1. Introduction

Major depressive disorder (MDD) or depression is one of the most common mental disorders globally, affecting around >300 million people (WHO, 2020). The molecular mechanisms that lead to depression are currently unknown, although different factors that could be associated with this disorder have been proposed. Some studies have observed an increased cellular dysfunction in brain cortical and limbic areas in depressed patients (Guilloux et al., 2012; Sen et al., 2008), which has long been related to decreased neurotrophic activity (Duman and Monteggia, 2006). This lower neurotrophic activity has been reported to be associated with a reduced number of cells in the prefrontal cortex (Drevets et al., 1997; Rajkowska, 2000), in the amygdala (Bowley et al., 2002; Hamidi et al., 2004), and with a decrease in hippocampus volume (Campbell et al., 2004; Videbech and Ravnkilde, 2004). These neurobiological alterations are commonly expressed in neuroplasticity loss. Neuroplasticity is a key brain attribute in learning and memory processes (Dishman et al., 2006), and recent reviews suggest that it could be influenced by the brain-derived neurotrophic factor (BDNF) (De Vincenti et al., 2019; Miranda et al., 2019).

BDNF belongs to the family of neurotrophins, which are brain-synthesised proteins that contribute to the survival, growth and maintenance of neurons, and take part in a variety of learning and memory related functions, with an important role in the regulation of activity-dependent neuronal plasticity (Ateaque et al., 2023). BDNF protein induces dendritic spines formation and promotes cellular growth and the survival of serotonergic neurons (Y. Lu et al., 2008; Messaoudi et al., 2002), which has been involved in the pathophysiology of depression and synaptic plasticity (Kang and Schuman, 1996).

A functional polymorphism in *BDNF*, causing the substitution of

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Valine amino acid to Methionine in codon 66 (*BDNF* Val66Met), disrupts BDNF release and intracellular trafficking. This polymorphism has been associated with an increased risk of suffering depression (Cardoner et al., 2013; Egan et al., 2003; Pei et al., 2012; Phillips, 2017). Similarly, different studies have found a reduction in serum and plasmatic BDNF levels in depressed patients (Birkenhäger et al., 2012; Bus et al., 2015; Kim et al., 2007; Lee et al., 2007; Yoshida et al., 2012). Furthermore, the current understanding, based on previous reviews, is that depressed patients have decreased BDNF levels and function in hippocampus and medial prefrontal cortex (Autry and Monteggia, 2012). These changes have been described leading to the dysfunction of astrocytes and microglia cells in depressive circuits (Phillips, 2017; H. Wang et al., 2022). Similarly, a comprehensive meta-analysis performed by Molendijk et al. (2014) reported decreased BDNF serum levels in depressed patients, although no association was observed with the symptom severity of depression (Molendijk et al., 2014).

Currently, antidepressant medication is the first line of treatment for depression (Holsboer et al., 1995), specially selective serotonin reuptake inhibitors (SSRIs), although the remission rate is only between 60 and 70%, according to relevant randomized controlled trials (Kennard et al., 2009; Rush et al., 2006). Moreover, side effects of these drugs, as well as the poor adherence associated to antidepressant therapies (Keyloun et al., 2017; Sansone and Sansone, 2012), have caused an increased interest in alternative treatments, such as personalised medicine (Sinyor et al., 2010), and physical activity (Malhi et al., 2015).

Physical activity is the development of activities that require an energetic expense which involve body movements produced by skeletal muscles (Bherer et al., 2013). When physical activity is structured, planned, and aims improving or maintaining physical fitness it is known as exercise (Caspersen et al., 1985). It is well-established that regular exercise usually changes the mood through various mechanisms, e.g., an increase in self-efficacy, motivation and energy and a better psychosocial functioning (Ross et al., 2019). Regular exercise also involves positive neurobiological adaptations such as an increase in neurogenesis in the hippocampus, monoamine transmission and synaptic growth (Dishman et al., 2006; van Praag et al., 1999). Therefore, it has been suggested in key reviews that the regular practice of physical activity may be involved in the observed improvement of depressive symptoms, memory and other cognitive functions (Cotman and Berchtold, 2002; Liu-Ambrose and Donaldson, 2008) although the molecular mechanisms underlying this improvement have not been fully described yet (Coelho et al., 2012; Cotman and Berchtold, 2002; Laske et al., 2010).

The study of the neurobiological pathways involved in the reduction of depressive symptoms by exercise is required to optimise the efficacy of this potential therapeutic strategy (Dinoff et al., 2018). One of the hypotheses currently under research is the involvement of BDNF, since physical activity affects the production of this neurotrophin and improves neuroplasticity (Coelho et al., 2012; Cotman and Berchtold, 2002; Laske et al., 2010). It has been shown that physical exercise increases BDNF levels in the hippocampus and in other brain regions (Cotman and Berchtold, 2002; Phillips, 2017; Voss et al., 2013). Furthermore, benefits of exercise include an improvement on the release and function of BDNF in synapsis, which promotes the integrity of dendritic spines, avoids the hippocampus atrophy, reduces the astrocytic dysfunction and activates different cellular pathways involved in neuronal plasticity (Duman and Monteggia, 2006; Krishnan and Nestler, 2008; Patterson, 2015). For these reasons, it has been proposed that consequences of practising regular exercise allow for the homeostatic processes involved in maintenance, repair and reorganisation of the circuits that are damaged in depressed patients (Phillips, 2017).

The relationship between depression, physical activity and BDNF emerges as an interesting potential interaction to be explored in the development of an effective therapy for MDD. The therapeutic potential is of high value due to the easy manipulation and long-term monitoring that physical activity allows (Erickson et al., 2012). Nevertheless, the molecular mechanisms involved in this relationship remain unclear. Our aim was to carry out a systematic review of the scientific literature about the potential role of BDNF, both *BDNF* genetic variability and protein levels, in the relationship between physical activity and depression.

2. Methods

2.1. Search strategy and study selection

A comprehensive systematic search was conducted from April to May 2023 in PubMed, Scopus, Web of Science and PsychInfo databases to identify eligible references. The combination of controlled descriptors previously selected using MESH thesaurus, along with the boolean operators "AND" and "OR" led to the following search equation that was used across all databases: (BDNF OR "level* of protein") AND (gene* OR "polymorphism" OR "SNP" OR "Single Nucleotide Polymorphism") AND ("physical exercise" OR "exercise" OR "physical activity") AND (depress* OR "MDD" OR "unipolar disorder").

The search strategy and selection of eligible documents was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Page et al., 2021). Two authors screened all titles and abstracts.

2.2. Selection criteria

Studies that fulfilled the following criteria were eligible for inclusion: (1) original articles using experimental or observational design (cross-sectional or longitudinal), reviews and/or meta analyses of published studies; (2) studies that analysed the relationship between exercise, depression and BDNF in adult population; (3) and in English or Spanish. Finally, we selected those manuscripts that were considered potential sources of evidence due to an optimal methodological quality. This was assessed using the Scottish Intercollegiate Guideline Network (SIGN) checklists for case-control studies, randomized controlled trials and systematic reviews and meta-analyses, accordingly (SIGN, 2019). Two reviewers assessed the eligibility of the studies independently. If there was disagreement between the reviewers, this was resolved by consensus.

2.3. Data extraction

We created two independent spreadsheets to depict the relevant information from the selected manuscripts. The first one included manuscripts studying the relationship between *BDNF* Val66Met polymorphism, physical activity or exercise and depression; the second one included records focused on the relationship between BDNF protein levels, physical activity or exercise and depression. Both spreadsheets contained document's reference, article type, epidemiological design, objectives, type of sample (sample size and main characteristics), principal variables explored (exercise or physical activity, depression and *BDNF* Val66Met polymorphism or BDNF protein levels); techniques and measurements, and main results.

3. Results

Fig. 1 shows the search and selection process of the scientific works included in this review. Tables 1a and 1b summarise the most relevant information regarding methodology and results of the selected studies.

3.1. Characteristics of the selected studies

Among 537 records included in our initial search, a total of 18 scientific articles met the inclusion criteria stated above (Fig. 1). For this review, the studies were classified in two groups: the first group focuses on the relationship between physical activity, depression and the *BDNF* gene ($n = 6$), and the second one evaluates the relationship between physical activity, depression and the BDNF protein ($n = 13$). Also, the

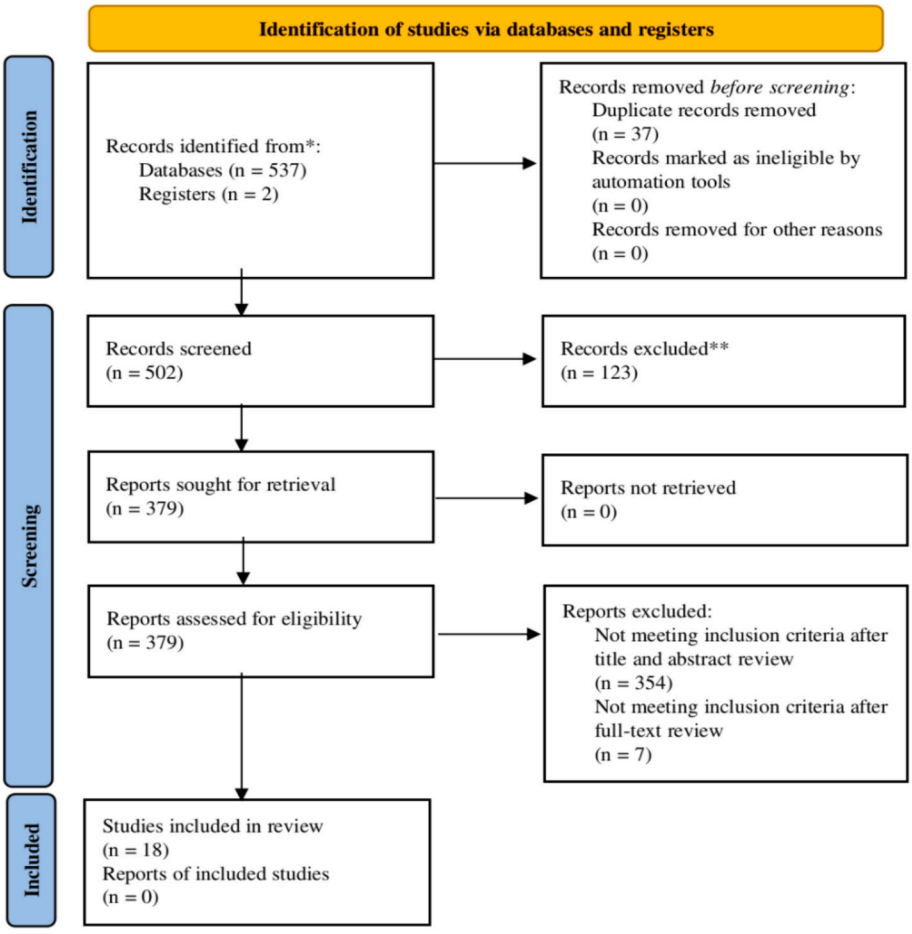

Fig. 1. PRISMA flow diagram of the search and selection process.

latter group was divided into manuscripts that evaluated the change in BDNF levels after an acute exercise intervention ($n = 4$), and manuscripts that assessed this change after chronic exercise intervention ($n = 9$). One article included results of both *BDNF* gene and protein, thus it was included in both sections. Two of the 18 articles included in this manuscript were systematic reviews and meta-analyses.

Considering the study design, from the six studies analysing the *BDNF* gene, four were observational case-control studies with a cross-sectional design, whereas two studies were randomized controlled trials (Table 1a). The four studies assessing the acute effect of exercise on the BDNF protein followed pre-experimental designs (Table 1b). From the nine studies analysing the chronic effect of exercise on the BDNF protein, we found two systematic reviews and meta-analyses, and seven randomized controlled trials (Table 1b). In order to be faithful to the selected studies, the terms "physical activity", "exercise" or "physical exercise" have been used according to the form in which they were stated in the original manuscripts.

3.2. Characteristics of the samples

The population of the selected scientific articles were young and medium-age adults in 10 studies, while 5 articles performed the study in elderly people (older than 60 years), and another one included participants from 18 to 75 years old. The population of 3 out of the 18 studies was composed exclusively by women (Laske et al., 2010; Meyer et al., 2016; Pereira et al., 2013).

Within the experimental studies, six works were conducted integrally on cases with depression. Among these, two studies included outpatients (Krogh et al., 2014; Toups et al., 2011), and three of them included inpatients (Kerling et al., 2017; Salehi et al., 2016; Schuch et al., 2014). Three other experimental studies were conducted on community-dwelling samples (Dotson et al., 2016; Pereira et al., 2013; Rahman et al., 2017), although one of them consisted of sedentary participants (Dotson et al., 2016). Among the pre-experimental studies, two of them only included cases with depression (Kallies et al., 2019; Meyer et al., 2016), and the remaining ones assessed cases versus controls (Laske et al., 2010; Ross et al., 2019). Two observational studies were representative of the general population (Gujral et al., 2014; Zarza-Rebollo et al., 2022), whereas one of them compared athletes versus controls (Haslacher et al., 2015), and the remaining one was composed of military veterans (Pitts et al., 2020).

Due to the high heterogeneity found among studies, and in order to provide a comprehensive overview of the current state of the topic, the following Results' sections show the results found in each of the studies separately. A more integrative perspective is offered in the Discussion.

3.3. Studies exploring the BDNF Val66Met polymorphism

A total of 6 documents evaluated the effect of *BDNF* Val66Met polymorphism on depression and physical activity.

Gujral et al. (2014) conducted an observational study to assess the effect of *BDNF* Val66Met polymorphism in the association between physical activity and depressive symptoms in 1072 middle-aged adults. The authors found that there were more depressive symptoms in Met allele carriers than in Val allele homozygous, even though the relationship was only significant in men ($p = 0.03$); while physical activity was associated with less depressive symptoms only in women ($p = 0.01$). Nonetheless, the moderation effect of the Val66Met polymorphism on

Table 1a
Summary of eligible studies analysing *BDNF* Val66Met polymorphism.

Reference	Study design	Objectives	Sample characteristics	Study variables		Summary of findings
				Physical activity	Depression	
Gujral et al. (2014)	Observational study. Cases and controls.	To assess the effect of the *BDNF* Val66Met polymorphism in the association between physical activity and depressive symptoms in adults.	$N = 1072$ non-Hispanic Caucasians (525 males/ 547 females; avg. age = 44.7 years old). 378 Met allele carriers; 694 Val/Val.	PPAQ (self-assessed) Estimation of average energy expended per week.	CES-D	In men, greater depressive symptoms were observed in Met allele carriers compared to ValVal homozygous ($p = 0.03$). In women, physical activity was linked with reduced depressive symptoms ($p = 0.01$). The effect of physical activity on depressive symptoms was not increased nor reduced depending on the Val66Met genotype ($p = 0.94$).
Haslacher et al. (2015)	Observational study. Cases and controls.	To evaluate the relationship between resistance sports and the attenuation of the genetic susceptibility to depression in elderly marathon athletes.	$N = 55$ athletes/58 controls, >60 years old. Inclusion criteria: ≥ 1 participation in established competitions in the three years prior to the study, and ≥ 2 h of physical activity per week.	Participants were endurance sports athletes (marathon runners and endurance cyclists).	BDI and GDS	A statistically significant interaction was found between groups (athletes vs controls) and genotypes (BDI: $p = 0.027$; GDS: $p = 0.013$). An increased relative risk of 3.54 (95%CI = 1.28–9.80) of obtaining a BDI score ≥ 10 was found among ValVal homozygous, although only in controls. This effect was not found in Met allele carriers.
Dotson et al. (2016)	Experimental study. Randomized controlled trial	To assess the relationship of the *BDNF* Val66Met polymorphism and depressive symptoms in elderly adults after a physical activity intervention. To evaluate the effects of this intervention on depressive symptoms.	$N = 365$ adults (70–89 years old). Inclusion criteria: sedentary, able to walk 400 m in <15 min.	The intervention consisted in: 12 months with sessions of mainly 40 min of moderate-intensity walking, modulating the intensity and location of the sessions. The control group received an intervention about ageing health.	CES-D	After an intervention with physical activity, a greater decrease in somatic symptoms was observed only in men, with a higher benefit in Met allele carriers, compared with ValVal homozygous and women ($p = 0.043$).
Rahman et al. (2017)	Experimental study. Randomized controlled trial.	To assess the relationship between the *BDNF* Val66Met polymorphism and treatment response of an intervention with either physical activity or ICBT. To assess the interaction between *BDNF* Val66Met and childhood adversity in response to treatment.	$N = 547$ Swedish adults with mild-to-moderate depression. Randomized controlled trial with physical exercise, ICBT and treatment as usual, during 12 weeks.	Participants in the intervention group were allocated in randomly assigned groups (low, medium and high intensity). Assistance was recommended to be 3 weekly 60-min sessions in gyms.	Inclusion criteria: PHQ-9 score > 10. Depressive symptoms: MADRS and social attachment ability (5 questions from ISIS subscale)	In participants that had not reported an exposure to childhood adversity, Met allele carriers were observed to have a greater response to an intervention with physical exercise ($p < 0.05$), compared to ValVal homozygous.
Pitts et al. (2020)	Observational study. Cases and controls.	To evaluate the effect of depression in cognitive functions in US veterans. To assess the role of the *BDNF* Val66Met polymorphism and physical exercise (or their interaction) in this effect.	$N = 1386$ US veterans of European-American descent (avg. age = 63 years old).	Participants were divided into two groups: those who self-reported no exercise, or those who reported practising any exercise ($\geq$1 days per week, median of 3 days per week).	PHQ-2. Cognitive functioning: MOS-CFS and CBB for psychomotor speed, attention, visual learning and working memory.	Among Met allele carriers that were depressed at the moment of the study, those who exercised obtained better results than those who did not exercise, in all the MOS-CFS measures ($p > 0.003$ in all p's), and CBB measures of visual learning ($p > 0.001$) and working memory ($p > 0.001$).
Zarza-Rebollo et al. (2022)	Observational study. Cases and controls.	To analyse the effect of the *BDNF* Val66Met genotype in the relationship between physical activity and depression.	$N = 209$ cases and 2914 controls from the general population, with ages between 18 and 75 (avg. age = 43.18 years old)	Self-reported number of hours per week of physical activity.	MINI (DSM-IV criteria)	A lower prevalence of depression was observed in Met allele carriers with a higher reported number of hours of physical activity, compared to ValVal homozygous. An interaction effect was observed in the total sample (OR = 0.95, 95%

(*continued on next page*)

Table 1a (*continued*)

Reference	Study design	Objectives	Sample characteristics	Study variables		Summary of findings
				Physical activity	Depression	
						CI = 0.90–0.99, p = 0.027) and in women (OR = 0.93, 95%CI = 0.87–0.98, p = 0.019).

Abbreviations: BDI: Beck Depression Inventory; CBB: Cogstate Brief Battery; CES-D: Center for Epidemiology Scale for Depression; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Version Four; GDS: Geriatric Depression Scale; ICBT: Internet-based Cognitive Behavioural Therapy; ISIS: Interview Schedule for Social Interaction; MADRS: Montgomery Åsberg Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; MOS-CFS: Medical Outcomes Study Cognitive Functioning Scale; PHQ-2: Patient Health Questionnaire 2-Item Depression Screener; PHQ-9: Patient Health Questionnaire 9-Item Depression Scale; PPAQ: Paffenbarger Physical Activity Questionnaire.

the interaction between physical activity and depressive symptoms in middle-aged adults was not significant (Gujral et al., 2014).

In 2015, Haslacher et al. investigated whether intensive endurance sports mitigated the genetic vulnerability to depression in a cohort of elderly marathon athletes (> 60 years old) (58 controls and 55 athletes). Athletes must have participated in at least one competition in the 3 years prior to the study, and performed physical training for >2 h per week. Beck Depression Inventory (BDI) (Beck et al., 1961) and Geriatric Depression Scale (GDS) (Yesavage and Sheikh, 1986) were used to assess the depressive state of the participants. The results showed a statistically significant interaction between the group (athletes vs controls) and *BDNF* genotypes in depressive symptoms (BDI: p = 0.027, GDS: p = 0.013). Moreover, among *BDNF* Val/Val participants, only controls showed a higher risk of getting a score of ≥10 in the BDI (RR = 3.537; 95% CI = 1.276–9.802), while this effect did not appear in Met allele carriers. They concluded that physical exercise positively influences the effect of *BDNF* on mood and that this effect was greater in Val/Val allele homozygous, suggesting a counteracting effect of physical exercise in the genetic susceptibility to depression (Haslacher et al., 2015).

More recently, Pitts et al. (2020) aimed to evaluate whether the *BDNF* Val66Met polymorphism and physical activity had a role in the effect of depression on cognitive functioning in 1386 USA veteran soldiers. Two groups were established: those who practised any exercise (median of 3 days per week), and those who did not. The Patient Health Questionnaire-2 (PHQ-2) was used to assess the depressive symptoms, and the Medical Outcomes Study Cognitive Functioning Scale (MOS-CFS), and Cogstate Brief Battery (CBB) were used for assessing different cognitive functioning aspects, subjective and objective, respectively. They reported a statistically significant interaction between depression, the Val66Met genotype and physical activity. They observed better score results for all the MOS-CFS measures (p < 0.003), the CBB measures of visual learning (p < 0.001) and working memory (p < 0.001) in depressed veterans that carried the Met allele and exercised in comparison to Met allele carriers nonexercisers (Pitts et al., 2020).

In a recently published research, Zarza-Rebollo et al. (2022) aimed to investigate the existing relationship between the Val66Met polymorphism, physical activity and depression in a cross-sectional study. Their sample consisted of a total of 3123 participants representative of the general population, with ages between 18 and 75 years old, including 209 cases with depression and 2914 controls. The Spanish version of the Mini-International Neuropsychiatric Interview (MINI) interview was used to diagnose major depression, following Diagnostic and Statistical Manual of Mental Disorders (Fourth edition) (DSM-IV) criteria. The results showed an interaction effect between the Val66Met polymorphism and the number of hours of self-reported physical activity on the risk of depression. This effect was observed in the total sample (OR = 0.95, 95%CI = 0.90–0.99, p = 0.027) and was strengthened in women (OR = 0.93, 95%CI = 0.87–0.98, p = 0.019). The results suggested that participants carrying the Met allele decreased their risk of depression as more hours of physical activity were reported, compared to Val/Val individuals (Zarza-Rebollo et al., 2022).

Regarding the experimental approaches, Dotson et al. (2016) examined the impact of the *BDNF* Val66Met polymorphism and sex in depressive symptoms after an intervention with physical activity in 365 sedentary adults. The intervention consisted of a 12-month program in specialised centres, whereas the control group attended instruction sessions on health education. Depressive symptoms were analysed at baseline and at 12-months. The results showed the most pronounced decrease in somatic symptoms in men that participated in the physical activity intervention, with a preferential benefit on Met allele carriers (p = 0.043). Furthermore, the impact of physical activity in depressive symptoms was marginally dependent on the *BDNF* Val66Met genotype and sex (p = 0.079) (Dotson et al., 2016).

The experimental study performed by Rahman et al. (2017) aimed to investigate the predictive ability of the Val66Met polymorphism in the improvement of depressive symptoms due to physical exercise, considering the influence of childhood adversity. The study sample was composed of 547 adults from the general population with mild-to-moderate depression, determined with a score of ≥10 on the Patient Health Questionnaire (PHQ-9). The depressive symptoms were assessed before and after the intervention. The experimental group was randomly divided into three intensity levels and was recommended to exercise in a gym 3 sessions per week during 12 weeks. Among Met allele carriers, they found a greater response to the intervention with physical exercise in those patients that did not report childhood adversity (p < 0.05) in comparison to Val/Val participants (Rahman et al., 2017).

3.4. Studies analysing the levels of BDNF protein

3.4.1. Acute exercise interventions

This section includes four articles whose main objective was to assess the effect of single bouts of physical exercise. All studies followed an experimental design, determining BDNF protein levels before and after performing the requested exercise bout.

Laske et al. (2010) conducted a study to investigate the effects of exercise in BDNF serum concentration. A total of 55 women older than 50 years participated in the study: 35 of them were diagnosed with MDD (20 were treated with SSRI antidepressants during the 3 months prior to the study), and 20 were control women. BDNF serum concentrations were measured before and after an incremental exercise test in a treadmill. These concentrations did not significantly differ between MDD patients with medication and those who did not have any treatment. Furthermore, compared to controls, MDD cases showed significantly lower BDNF levels before the exercise test (p = 0.001), whereas no significant differences were observed after performing exercise (p = 0.233). Following a unique short-term exercise, a statistically significant increase in BDNF serum levels was found in MDD patients (p < 0.001). After a 30-min break following exercise, both groups showed a significant reduction of BDNF serum levels, even below the levels prior to the exercise (Laske et al., 2010).

Later, Ross et al. (2019) analysed the effect of different intensity aerobic exercise in BDNF serum levels in a sample of 26 individuals: 13 MDD cases and 13 controls. A total of three exercise sessions were performed. Sessions consisted of 15 min of work with different

Table 1b
Summary of eligible studies analysing the BDNF protein.

Reference	Study design	Objectives	Sample characteristics	Study variables		Summary of findings
				Physical activity	Depression	
ACUTE EFFECT OF PHYSICAL ACTIVITY						
Laske et al., 2010	Experimental study with cases and controls	To assess the association between acute exercise and serum BDNF in MDD female patients.	$N = 35$ MDD cases (21 with SSRI treatment during prior 3 months) and 20 controls. Only women, >50 years old.	An incremental exercise test (on a treadmill) was conducted, starting with a speed of 3 km/h and inclination of 0%, increasing linearly every 3 min. The test concluded when the participant was physically unable to continue.	HDRS. Participants were considered cases when their score was ≥18.	Cases had lower BDNF levels before exercise than controls ($p = 0.001$), although this difference was not statistically significant after exercise ($p = 0.233$). After acute exercise, greater BDNF level increases were observed in cases ($p < 0.001$). After 30 min of rest following exercise, serum BDNF decreased below baseline levels.
Meyer et al. (2016)	Experimental study.	To evaluate the response of serum BDNF concentration to acute exercise in MDD female patients, comparing intensity levels. Relationship between antidepressant use, pre-exercise psychological health and BDNF.	$N = 24$ women (20–60 years old) with depression. Able to perform physical activity. Participants had no psychiatric treatment regimen, or with a stable regimen for 8 weeks prior to the study.	3 sessions of 30 min of exercise in a cycle ergometer at one of the prescribed intensities, including a 5-min warm-up and a 5-min cool-down. Sessions were separated by one week. A control session consisted of a rest session of the same time in the cycle ergometer.	MDD diagnosis was confirmed using MINI. Before exercise, 10 and 30 min after exercise, subjects completed the POMS rating scale.	An acute improvement in depressive mood and a significant increase of BDNF ($p = 0.006$) were found after exercise, independently of its intensity. Changes in serum BDNF concentrations did not correlate to changes in depressive mood. Participants not taking medication had higher serum BDNF levels than those taking medication ($p = 0.015$), with similar depressive mood changes.
Kallies et al. (2019)	Experimental study	To evaluate the effect of incremental aerobic exercise on serum BDNF level in MDD patients, considering changes in plasma volume and platelets count.	$N = 30$ MDD cases (7 with a single depressive episode) (18–65 years old). All were sedentary (<90 min per week).	An incremental exercise test on a cycle ergometer was conducted, starting at 25 W and increasing 25 W every 2 min. The test concluded when the participant was physically unable to continue.	MDD diagnosis was assessed for a larger project. Severity of depressive symptoms was assessed using BDI.	BDNF significantly increased after exercise ($p < 0.001$), after adjusting for change in plasma volume and platelet count. An interaction between change in BDNF and platelet count ($p = 0.001$) suggested a greater increase in BDNF in participants with lower number of platelets.
Ross et al. (2019)	Experimental study with cases and controls.	To evaluate the effect of different intensities of aerobic exercise on the level of BDNF and serum cortisol in depressed patients and controls.	N = 13 MDD cases and 13 controls (18–50 years old). Participants were able and safe to perform physical activity.	3 sessions of 15 min. Different procedures were performed by three groups: LI cycling (35% of heart rate reserve), HI cycling (70% of heart rate reserve), or sitting (control condition).	MDD diagnosis was confirmed using MINI, and severity of depressive symptoms using MADRS (considering a score > 10 for cases).	No group effect was observed in post-exercise BDNF response. BDNF immediately after HI exercise was significantly greater than LI ($p = 0.003$) and control condition ($p = 0.027$). BDNF significantly increased from baseline to immediately after exercise in HI ($p < 0.001$) and LI ($p = 0.019$) conditions. 15 min after exercise (or any time further) BDNF was not significantly different from baseline levels in any condition.
CHRONIC EFFECT OF PHYSICAL ACTIVITY						
Toups et al. (2011)	Experimental study.	To analyse the changes in BDNF levels after exercise	$N = 126$ adults (18–70 years old). Only 70 with blood	Participants were divided into two	Participants were partial or non-	Baseline serum BDNF concentration did not

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Table 1b (*continued*)

Reference	Study design	Objectives	Sample characteristics	Study variables		Summary of findings
				Physical activity	Depression	
	Randomized controlled trial.	training in MDD patients. To assess the relationship between baseline BDNF levels and treatment response.	samples completed the study. All participants were being treated with SSRIs for 2 to 6 months (with partial or no response).	groups: high energy expenditure and low energy expenditure. The intervention consisted of 12 weeks of education and personalised training with an exercise regimen appropriate to the dose.	responders to the prior SSRI treatment (in case their HDRS score was ≥14), with MDD diagnosis confirmation with the SCID. The severity of depressive symptoms was assessed using IDS-C and HDRS.	significantly vary between before and after completing the intervention, and was not correlated with energy expenditure ($p = 0.15$) or improvement in depressive symptoms ($p = 0.89$). Subjects with higher baseline BDNF had faster depressive symptoms improvements ($p = 0.003$).
Pereira et al. (2013)	Experimental study. Randomized controlled trial.	To assess the effect of 2 standardised exercise programs (SE and AE) on BDNF plasma levels and depressive symptoms in elderly women.	$N = 451$ elderly sedentary women (65–89 years old).	Participants were divided into two groups, with two exercise programs: SE and AE. The protocols include 3 one-hour sessions a week, for a total of 30 supervised sessions in 10 weeks.	GDS	Plasma BDNF levels significantly differed between SE and AE ($p = 0.009$). Pre- and post-intervention differences in BDNF levels were only observed within the SE group ($p = 0.008$). Pre- and post-intervention GDS scores were significantly different in both exercise protocols ($p = 0.001$).
Krogh et al. (2014)	Experimental study. Randomized controlled trial.	To evaluate the changes in hippocampal volume and serum levels of neurotrophins (BDNF, VEGF and IGF-1) after an exercise intervention, compared to a control condition, in patients with depression.	$N = 79$ sedentary MDD patients (38 in control condition, 41 in aerobic exercise condition). Inclusion criteria: 18 to 60 years old, <1 h of exercise per week, no current psychotherapeutic or antidepressant treatment in the past 2 months.	Two groups were differenciated: (1) Experimental group: exercise bikes at 80% of their maximum heart rate. (2) Control group: stretching, low impact exercise. Interventions consisted of 3 sessions/week for 3 months.	The Danish version of the MINI was used for DSM-IV diagnosis, and HDRS score > 12 was the threshold to consider cases with MDD.	No differences in BDNF were found between groups, in any of the reported measures, nor in any group during the intervention. A significant association between the change in the hippocampus volume and the depressive symptoms was reported ($p = 0.03$).
Szuhany et al. (2015)	Experimental study. Randomized controlled trial.	The evaluate the effects of adding exercise to the treatment of patients with depression on the serum levels of BDNF.	$N = 26$ MDD patients (15 in exercise plus treatment as usual condition, 11 followed usual treatment). Participants were 18 to 60 years old.	The intervention consisted of supervised aerobic exercise 3 times a week (16.5 kcal/kg/week, with a median of 9 sessions (3 weeks)). The modality and intensity was free to choose until completing the indicated kcal/kg. All the sessions were composed of: warm-up, main part and cool-down.	MDD diagnosis was ascertained using the MINI, with DSM-IV criteria. Considered cases with score ≥ 25 in HDRS.	A significant association was found between time and BDNF concentrations ($p < 0.001$), whereas no differences between groups were observed ($p = 0.13$). Serum BDNF levels were not modified after the addition of exercise to the usual treatment.
Salehi et al. (2016)	Experimental study. Randomized controlled trial.	To analyse the differential effects of electroconvulsive therapy (ECT), aerobic exercise (AET) and their combination in depressive symptoms and in plasma BDNF, in MDD patients.	$N = 60$ MDD patients from 25 to 40 years old. Participants were randomly assigned in three groups: ECT, ECT + AET and AET. All patients maintained their standard SSRI medications.	In the AET condition sessions consisted of 45 min of treadmill (3 sessions per week during 4 weeks).	MDD diagnosis was confirmed using DSM-IV criteria, score ≥ 30 in BDI, score ≥ 25 in HDRS.	BDNF increased with time in the three conditions. BDI and HDRS scores significantly decreased after the intervention in the three conditions. A significant association between the treatment condition and remission rate ($p < 0.001$) was found. The combined treatment showed the highest remission rate, while the lowest was found in the ECT condition.
Kerling et al. (2017)	Experimental study. Randomized controlled trial	To assess the effect of an exercise intervention on serum BDNF levels in MDD	$N = 42$ MDD patients from 18 to 60 years old. 22 were assigned to the exercise group, and 20 to the control	The intervention consisted of 3 weekly 45-min training sessions of moderate intensity	MDD diagnosis was confirmed using the SCID. MADRS was employed	BDNF increased in the exercise condition and decreased in controls, finding a significant

(*continued on next page*)

Table 1b (*continued*)

Reference	Study design	Objectives	Sample characteristics	Study variables		Summary of findings
				Physical activity	Depression	
		patients, added to their usual treatment.	group. Their medication did not change during the intervention.	for a total of 6 weeks. These sessions were 25 min on a cycle ergometer and 20 min on machines of their choice. The control exercise consisted of walking, ball games and stretching for 20 min.	to assess the severity of depressive symptoms.	time x group effect regarding serum BDNF concentrations (p = 0.03). BDNF serum levels did not significantly differ between before and after the intervention in any group.
Rahman et al. (2017)	Experimental study. Randomized controlled trial.	To analyse the association between serum mature-BDNF or pro-BDNF levels and the response to treatment with physical exercise.	N = 547 Swedish adults with mild-to-moderate depression.	Three groups participated in three interventions: physical exercise, ICBT, or treatment as usual, during a 12-weeks intervention. Among the participants following the physical activity intervention, 3 intensities were randomly assigned: low, medium and high. Assistance to 3 weekly 60-min sessions in gyms was recommended.	Inclusion criteria were having a PHQ-9 score $\geq$ 10. Depressive symptoms were assessed using MADRS and evaluating social attachment ability (5 questions from ISIS subscale)	Met allele carriers had higher baseline concentrations of mature BDNF than Val/Val participants (p = 0.019). No differences in BDNF levels were found after the intervention.
Dinoff et al. (2018)	Systematic review and meta-analysis	To review and meta-analyse the effect of exercise intervention on BDNF concentrations in MDD patients, and to assess the role of sex, age, intensity or duration of exercise.	6 original articles included, with a total of 176 participants with MDD.	Inclusion criteria included: chronic exercise intervention (prolonged over various weeks), with intensity $\geq$50% of maximum oxygen uptake.	MDD cases included should have been diagnosed following DSM criteria.	Six studies met the inclusion criteria. BDNF concentrations were not significantly higher after the chronic aerobic exercise intervention (p = 0.09) in the meta-analysis.
Kurebayashi and Otaki (2018)	Systematic review and meta-analysis	To review and meta-analyse the effect of physical exercise on BDNF levels in MDD patients.	5 original articles included, with a total of 199 MDD patients with severe symptoms.	Inclusion criteria included: chronic aerobic exercise intervention.	All subjects were MDD patients. Depressive symptoms were assessed by BDI or HDRS.	The meta-analysis showed no significant effect of physical exercise on BDNF levels (p = 0.75).

objectives: 1) low intensity cycling at 35% heart rate reserve (LO); 2) high intensity cycling at 70% heart rate reserve (HI); or 3) remaining seated as a control group (CON). BDNF concentration was measured before, immediately after exercise, and every 15 min post-exercise for 1 h. No significant differences were observed between MDD cases and controls. BDNF serum levels were significantly higher immediately after exercise in HI compared to LO (p = 0.003) and to CON (p = 0.027). Furthermore, BDNF levels after exercise were significantly higher than levels measured before exercise in HI (p < 0.001) and LO (p = 0.019) conditions. BDNF levels at 15 min after exercise in HI and LO conditions were not significantly different from the values obtained before exercise, and no differences were found at any time later (Ross et al., 2019). Overall, this work reported a positive effect of a single session aerobic exercise on BDNF production, both in healthy and depressed individuals.

The group of Meyer et al. (2016) analysed the response in serum BDNF to exercise bouts in 24 female MDD patients between 20 and 60 years old. Three 30-min sessions of exercise in a cycle ergometer at different prescribed intensities (light, moderate or hard) were performed, one session per week. A control session consisting of a resting session in the cycle ergometer was included. Blood was drawn from the participants before exercise and 10 min later, while they completed a Profile of Mood States (POMS) and a BDI-II questionnaire to assess depressive symptoms at those moments and 30 min after each exercise session. Results in POMS suggested an improvement in the depressive mood after exercise. In addition, there was a significant increase in serum BDNF (p = 0.006), independent of the intensity of the exercise. Nevertheless, the changes in BDNF serum levels were not significantly correlated with changes in the POMS questionnaire, nor 10 or 30 min after exercise (p > 0.05). This correlation was not present with changes in BDI-II either. The 14 participants who had antidepressants showed lower BDNF protein serum levels post-exercise than the participants without medication (p = 0.015), but similar mood changes were observed (Meyer et al., 2016).

Later, Kallies et al. (2019) analysed changes in BDNF serum levels before and after an incremental exercise test, in a sample of 30 adult MDD patients. These participants, previously diagnosed in a larger study (Heinzel et al., 2018), were from 18 to 65 years old and did not exercise for >90 min per week. The change in plasma volume and the number of platelets was considered in the analyses. The incremental exercise test took place in a cycle ergometer, with periodical progressions until the participant was physically unable to continue. The results indicated a significant increase of serum BDNF induced by exercise (p < 0.001) after adjustment by plasma volume shift and platelet count. Furthermore, they found a significant interaction effect between the change in BDNF serum levels and the number of platelets (p = 0.001), showing a higher increase of these levels in participants who had a smaller amount of platelets (Kallies et al., 2019).

3.4.2. *Chronic exercise interventions*

A total of eight manuscripts analysing the effect of chronic exercise intervention -extended for various weeks- have been included in this section, with the aim of assessing differences between before and after a long-lasting intervention. Seven studies were randomized controlled trials and two works were systematic reviews and meta-analyses.

Toups et al. (2011) conducted a study to evaluate the change in BDNF levels after an intervention with exercise in 126 MDD adult patients, partially responders to a 2 to 6-months treatment with SSRIs. The

intervention lasted 12 weeks and 70 participants completed the study. Subjects were randomly divided into two groups: high and low energy expenditure. The high energy expenditure group performed supervised physical activity aiming to burn 16 kcal per kilogram of body weight per week, whereas 4 kcal per kilogram of body weight per week was the target for the low energy expenditure group. Results showed that basal BDNF serum concentration was stable and did not correlate with the energetic expenditure ($p = 0.15$) or the improvement of the clinician rated version of the Inventory of Depression Symptomatology (IDS-C) score ($p = 0.89$) in the entire sample. However, subjects with higher baseline BDNF levels improved their IDS-C score with exercise in a shorter period of time and independently of the group of energy expenditure ($p = 0.003$) (Toups et al., 2011).

The study conducted by Rahman et al. (2017), previously mentioned in the *Influence of the BDNF Val66Met polymorphism* section, also measured the concentrations of serum proBDNF and mature BDNF. They did not find any effect of the intervention with physical exercise in these concentrations. The intervention consisted of a 12-weeks program of physical exercise in which 547 participants with mild-to-moderate depression attended 3 gym sessions per week. They found a statistically significant difference between *BDNF* Val66Met Met allele carriers and Val/Val participants in their baseline levels of mature BDNF, which were higher in Met allele carriers ($p = 0.019$). Nonetheless, these levels were not altered by the intervention (Rahman et al., 2017).

Pereira et al. (2013) investigated the effect of two standardised exercise programmes in BDNF plasma levels and depressive symptoms in 451 inactive women (65–89 years old). Participants were divided into two groups to follow a supervised protocol of muscle strength exercises (SE) or aerobic exercises (AE) (1-h, 3 times a week for 10 weeks). The Geriatric Depression Scale (GDS) was used to evaluate depressive symptoms. A significant difference in BDNF levels was found between groups ($p = 0.009$), but the difference between before and after intervention was only present in the SE group ($p = 0.008$). There was a significant difference between pre- and post-intervention in GDS scores in both groups ($p = 0.001$), suggesting a positive effect of both standardised exercise programmes on depressive symptoms in elderly women, but independent on BDNF (Pereira et al., 2013).

Following a similar strategy, Salehi et al. (2016) also evaluated the changes in BDNF plasma levels after different types of intervention in 60 patients with MDD. Participants were young adults and had a BDI score higher than 30 and a Hamilton Depression Rating Scale (HDRS) higher than 25. Depending on the intervention, participants were randomly assigned to one of the three following groups: electroconvulsive therapy (ECT), aerobic exercise training (AET), or the combination of both interventions (ECT + AET). The intervention lasted 4 weeks and was combined with a standard SSRI treatment. Here, BDNF plasma levels increased with time in all groups. The ECT + AET and the AET conditions showed the highest and the lowest increases, respectively. Moreover, the BDI and HDRS scores significantly decreased between pre- and post- intervention. The differences were stronger in the combined intervention than in the ECT and AET conditions. Furthermore, they reported a significant association between the treatment condition and the remission rate ($p < 0.001$), with the highest remission rate observed in the combined intervention (more than half of the patients showed complete remission). However, no association between BDNF levels and depressive symptoms were observed, leading to inconclusive results for the potential of BDNF as a reliable MDD biomarker (Salehi et al., 2016).

Krogh and colleagues (Krogh et al., 2014) conducted a randomized clinical trial to assess the effect of exercise intervention on the hippocampus volume and serum levels of BDNF, VEGF and IGF-1 proteins in 79 MDD patients. Patients were diagnosed using the Danish version of the MINI interview and had a score higher than 12 in the HDRS. Participants did not receive antidepressant medication for the 2 previous months to the study and were randomly assigned in two groups. Experimental intervention (41 individuals) consisted of 45-min sessions of exercising on stationary bikes at 80% of their maximum heart rate, whereas control intervention (38 individuals) consisted of low impact exercise for the same time interval. The intervention lasted 3 months and participants were advised to participate in 3 sessions per week. The results showed that the hippocampus volume and the serum concentrations of BDNF, VEGF and TFG-1 did not vary between groups, although they found a significant association between the change in the hippocampus volume and the depressive symptoms ($p = 0.03$) (Krogh et al., 2014).

In 2014, Schuch et al. (2014) evaluated the effect of the combination of exercise to a pre-established treatment in BDNF serum levels of 26 MDD patients. MDD diagnosis was assessed with the MINI and depressive symptoms were assessed using the HDRS (all participants must have a score ≥ 25). Participants were splitted into two groups: 11 patients maintained their usual treatment, and 15 of them added aerobic exercise sessions to the treatment. The intervention consisted of 3 weekly sessions for 3 weeks where they could choose the intensity and the modality according to their preferences. The results showed a significant association between BDNF levels and the time ($p < 0.001$), but no differences between groups were observed ($p = 0.13$), concluding that the combination of exercise with the usual treatment does not have any effect on BDNF serum levels in MDD patients (Schuch et al., 2014).

Later, Kerling et al. (2017) analysed the effect of additional exercise in BDNF serum levels in 42 patients diagnosed with MDD according to the DSM-IV criteria. The control group maintained their treatment with no changes throughout the intervention, whereas the experimental group added an intervention with exercise. This intervention consisted of 45-min sessions (3 per week) of moderate intensity for 6 weeks. A significant effect was found between time and groups regarding BDNF serum levels ($p = 0.03$), with an increase of BDNF concentrations in the experimental group in comparison to controls. Nonetheless, the differences in BDNF serum levels before and after the intervention were not statistically significant in any group (Kerling et al., 2017).

Finally, Dinoff et al. (2018) conducted a systematic review and meta-analysis which included 6 studies with a total of 176 individuals. Their aim was to investigate whether chronic aerobic exercise interventions had, consequently, an increase in BDNF blood concentration in MDD patients diagnosed using DSM guidelines. They also assessed whether the effect was dependent on individuals' variables (age or sex) or the parameters of the intervention (exercise duration or intensity). They considered interventions where intensity of the exercise was $\geq$50% of the maximum oxygen absorption. The meta-analysis including the 6 studies showed that BDNF concentrations were not significantly higher after chronic aerobic exercise intervention, although a trend towards association was observed ($p = 0.09$) (Dinoff et al., 2018).

Similarly, in the review and meta-analysis by Kurebayashi and Otaki (2018), the authors explored the effect of physical exercise on BDNF levels in MDD patients, in order to establish or reject this effect as a potential mechanism by which the exercise improves depressive symptoms. The review included 5 experimental studies with a total of 199 patients with severe depressive symptoms. The intervention consisted of chronic aerobic exercise. The results of the meta-analysis showed that there was no significant effect of physical exercise in BDNF levels ($Z = 0.32$, $p = 0.75$). Thus, they suggested that, given the benefits of exercise on MDD, this effect may occur through a different mechanism than that involving BDNF (Kurebayashi and Otaki, 2018), although the possibility of a false negative due to studies' limitations was not discarded.

3.4.3. BDNF serum/plasma levels quantification techniques

The quantification of BDNF serum concentration was performed with an ELISA assay in all the included studies. The majority of them used the Quantikine Human BDNF Immunoassay kit (R&D Systems) (Kallies et al., 2019; Kerling et al., 2017; Krogh et al., 2014; Laske et al., 2010; Meyer et al., 2016; Rahman et al., 2017; Ross et al., 2019; Toups et al., 2011), although Schuch et al. (2014) used an ELISA Sandwich assay commercial kit from Chemicon (USA) (Schuch et al., 2014). It is worth mentioning that Kerling et al. (2017) analysed several forms of serum

BDNF, such as free BDNF, BDNF connected to Trk, pro-BDNF and mature-BDNF (Kerling et al., 2017). Regarding the measurement of BDNF plasma concentration, also an ELISA assay (R&D Systems) was the preferred technique (Pereira et al., 2013; Salehi et al., 2016).

4. Discussion

Here, we have performed a systematic review of the scientific literature about the role of BDNF (*BDNF* Val66Met polymorphism and/or protein level) in the potential relationship between physical exercise and MDD or the improvement of depressive symptoms.

4.1. The role of BDNF Val66Met polymorphism

Regarding the *BDNF* Val66Met polymorphism, a total of 6 studies were selected, which mainly included advanced aged people.

The results of four out of the six studies included in this section suggested a greater impact of physical activity on depression depending on the *BDNF* Val66Met genotype. In particular, physically active participants or individuals following an intervention with physical activity that carried the Met allele showed lower risk of depression and greater effects on the improvement of depressive symptoms compared to Val/Val homozygous individuals. Opposite to these findings, the other two studies included in this section did not find a statistically significant interaction between the *BDNF* polymorphism, physical activity and depression, although one of the works argued an insufficient sample that might have hindered obtaining significant results (Gujral et al., 2014).

It is worth mentioning that the six studies included in this section were not easily comparable due to the heterogeneity found in different aspects between them. First, there were two longitudinal studies (Dotson et al., 2016; Rahman et al., 2017), whereas four of them were cross-sectional studies. Second, the inclusion criteria and sample size also varied, (e.g., two of the articles included adults of all ages (Rahman et al., 2017; Zarza-Rebollo et al., 2022), one study included middle-aged adults (Gujral et al., 2014), and three studies analysed an older sample (Dotson et al., 2016; Haslacher et al., 2015; Pitts et al., 2020). Within the latter group, one sample consisted of veteran soldiers (Pitts et al., 2020), another compared athletes and controls (Haslacher et al., 2015), and one study included advanced aged adults from the general population (Dotson et al., 2016). Furthermore, they differed on how the included variables were considered. In this sense, the variable “depression” or “depressive symptoms” was assessed using different methods and scales, e.g., CES-D (Dotson et al., 2016; Gujral et al., 2014), BDI and GDS (Haslacher et al., 2015), MADRS (Rahman et al., 2017), PHQ-2 (Pitts et al., 2020), or following DSM-IV criteria using the MINI interview (Zarza-Rebollo et al., 2022). Moreover, there were also differences on how the variable “physical activity” was measured. Whereas only one cross-sectional study compared athletes with a control group (Haslacher et al., 2015), the remaining three cross-sectional studies compare self-evaluated physical activity, using different parameters and scales (Gujral et al., 2014; Pitts et al., 2020; Zarza-Rebollo et al., 2022). These differences were also apparent in the interventions performed in the two longitudinal studies (Dotson et al., 2016; Rahman et al., 2017). In addition, Rahman and colleagues considered childhood adversity as an additional parameter suggesting that this event may play an important role in the response to the physical exercise treatment in depressed patients (Rahman et al., 2017).

Regarding the effect of the *BDNF* Val66Met polymorphism, the association between the Met allele and the risk of depression has largely been addressed. The first study assessing the effect of this polymorphism in humans found a deficient intracellular trafficking and secretion derived from the Met allele, potentially causing impaired episodic memory and reduced hippocampal volume (Egan et al., 2003). Subsequent studies achieved diverse findings, both in agreement (Miyajima et al., 2008; L. Wang et al., 2012), and in disagreement with these prior results (Benjamin et al., 2010; Harris et al., 2006). In addition, Lang et al. (2009) reported increased serum BDNF concentrations in Val/Val individuals compared to Val/Met subjects (Lang et al., 2009). Therefore, the Val66Met polymorphism has become a contentious study field without a conclusive role on the susceptibility that conferred to different aspects of cognition and psychiatric disorders (Notaras et al., 2015). Focusing on depression, a meta-analysis of 14 studies did not find any association between this polymorphism and depression in the total sample, neither after stratifying according to ethnicity (Verhagen et al., 2010). However, this meta-analysis reported a significant risk effect of the Met allele in men after sex stratification. Given the conflicting results, the observations obtained from the present systematic review could be explained by an interaction effect between this polymorphism and physical activity rather than by a genetic association between *BDNF* Val66Met and depression. It would be of great interest to investigate whether different types of physical activity lead to this effect or whether particular benefits occur with different types of interventions. Including sex as a relevant factor for the interaction effect would also provide more conclusive results. Future research should also clearly state the characteristics of the interventions, as a lack of a detailed description on the procedure followed was a generalised weak point across studies.

4.2. The role of BDNF protein levels

4.2.1. Acute exercise intervention

Four articles assessing the effect of an acute exercise intervention on the relationship between BDNF levels, depression and physical activity were included in this section. The results of the four studies pointed to a significant change of BDNF levels after physical activity in depressed patients, although two of the studies found that these concentrations were restored after a short period of time (Laske et al., 2010; Ross et al., 2019). This finding is consistent with the main results from a recent meta-analysis evaluating the acute effect of physical activity on BDNF concentration (Szuhany et al., 2015). Despite the heterogeneity of the meta-analysed samples, the authors observed an increase in BDNF levels following a single bout of physical activity. Similarly, in a recent study the authors found a significant increase in BDNF levels in partially-remitted MDD patients after strenuous exercise in comparison to an active control group (Kramer et al., 2023). It is remarkable that Kallies et al. (2019) only reported this increment effect when an adjustment with changes in platelets count and plasma volume was considered (Kallies et al., 2019). Platelets count may be responsible for certain differences in BDNF levels, given their well-known function of BDNF storing and releasing (Fujimura et al., 2002; Yamamoto and Gurney, 1990). Thus, given their key relevance, it is surprising that the study by Kallies et al. (2019) is the only one that considered platelets count as a covariate to adjust their results. Further studies analysing peripheral BDNF concentrations should take into consideration platelets levels, as well as other characteristics, e.g., platelet reactivity, that are also sources of heterogeneity (Naegelin et al., 2018; Serra-Millàs, 2016). Interestingly, in the two studies comparing cases with depression and controls, no differences were found depending on this condition (Kallies et al., 2019; Ross et al., 2019). The effect of acute exercise or BDNF levels alterations on depressive symptoms was only determined in one study, which reported an improvement in depressive mood after exercise, although the changes in these symptoms were not correlated with changes in BDNF levels (Meyer et al., 2016).

Although the sample sizes of these studies were similar, several sources of heterogeneity were found between them. As an example, concerning the study cohorts, one of the studies included exclusively elderly women (Laske et al., 2010), whereas another study only considered middle-aged women (Meyer et al., 2016). This fact hinders the comparison with the studies by Kallies et al. (2019) and Ross et al. (2019) that included samples of middle-aged men and women (Kallies et al., 2019; Ross et al., 2019). Moreover, two of the four studies exclusively included patients with depression, thus case-control comparison was not assessed (Kallies et al., 2019; Meyer et al., 2016). The

structure of the interventions with exercise also differed between the studies: two studies performed incremental exercise tests -although they differed in logistic aspects- (Kallies et al., 2019; Laske et al., 2010), whereas the other two works reported different sessions of physical activity at certain defined intensities (Meyer et al., 2016; Ross et al., 2019). Thus, future studies considering a more standardised approach would ease our current understanding of the observed effect.

4.2.2. Chronic exercise intervention

Seven original works performing a prolonged exercise intervention and evaluating the relationship between BDNF levels, depression and chronic physical activity were included. Similar to what was described in the previous sections, we found a high heterogeneity in different aspects that made it impossible to meta-analyse the studies. Two systematic reviews with meta-analyses were also included in this section. Due to the complexity of this approach, sample sizes were limited and smaller than the observed in the previous section.

Among the original articles, there was one study including a sample from the general population, which did not include MDD cases but evaluated depressive symptoms instead (Pereira et al., 2013). The remaining six articles included cases with MDD diagnosis. These six studies were randomized controlled trials, and their samples were entirely composed of depression cases.

The effect of the chronic exercise intervention on depressive symptoms, as a variable, would be a key outcome to be considered. Nonetheless, this effect was not considered in all of the studies. Of note, three of them found a positive effect of the intervention, decreasing depressive symptomatology (Pereira et al., 2013; Salehi et al., 2016; Toups et al., 2011). These three studies did not associate this improvement to differences in BDNF levels, suggesting that the improvements in depression observed were due to independent mechanisms other than BDNF levels. Despite that, the effect of single bouts of physical activity on the increase of BDNF levels was consistent among the four studies analysed in the *Acute exercise intervention* section (Kallies et al., 2019; Laske et al., 2010; Meyer et al., 2016; Ross et al., 2019). Therefore, given this well-established link, which is in agreement with prior literature (Szuhany et al., 2015), it could be hypothesised that the long-term improvement of exercise on depressive symptoms could be, at least, partly mediated by the effect of a repeated exposure to acute increases in BDNF levels (Meyer et al., 2016). In this regard, the well-established role of BDNF on neuroplasticity and neurogenesis (Costa et al., 2022; Leal et al., 2017), the effect of physical activity on this processes (Erickson et al., 2011), and the growing evidence of the potential implication of neuroplasticity and neurotrophic factors in depression (Liu et al., 2017) would support the potential interaction between depression, physical activity and BDNF. Other mechanisms, such as the anti-inflammatory effect that physical activity exerts in the human body could also be involved (Gleeson et al., 2011; Rethorst et al., 2013).

From the interventions, only a randomized controlled trial performed on the general population obtained both improvements in depressive symptoms and increased BDNF levels following the intervention (Pereira et al., 2013). However, this result was only observed in the strength exercise branch, and was not observed in the aerobic exercise group, in opposition to the findings reported in Knaepen et al. (2010) (Knaepen et al., 2010).

It is important to note that the measurement of peripheral BDNF concentrations may not be the proper strategy for detecting changes and availability of BDNF in the brain, according to previous research (Elfving et al., 2010), although there are studies finding a positive correlation between both parameters (Klein et al., 2011). In this regard, it should be considered that a significant variation has been observed among different commercial assays for the measurement of BDNF levels (Polacchini et al., 2015). Therefore the reliability of the comparisons between studies could be jeopardised. Remarkably, different commercial assays are able to recognise both pro-BDNF and mature BDNF, or have a higher specificity for the mature form of BDNF. Considering that the physiological effects of both forms are broadly opposite, the fraction measured by each kit would be of critical interest (B. Lu et al., 2005). Other methodological considerations may involve the storage of serum and plasma for BDNF measurements, which can also be a source of heterogeneity, as BDNF stability varies depending on the source (Polyakova et al., 2017).

Furthermore, it is increasingly recognised that diverse factors, including sampling characteristics and sociodemographic variables such as age, sex, and lifestyle factors, e.g., smoking status and diet, can significantly impact peripheral BDNF levels (Bus et al., 2011). For instance, it would be important to consider the effect that age has on BDNF levels, since both a decrease in plasma and serum concentrations of this protein (Erickson et al., 2010; Lommatzsch et al., 2005) and an increase of serum BDNF throughout life has been reported (Bus et al., 2011). Therefore, the wide age ranges included in some of the included studies could be a confounding factor and a probable cause for the heterogeneity observed in the results. BDNF levels are also likely to vary between genders (Lommatzsch et al., 2005), as well as to have a lower increase in women after physical activity (Szuhany et al., 2015), and to fluctuate in women even within the course of a day (Pluchino et al., 2009). This variability underscores the importance of meticulously considering these factors to increase accuracy and reliability of study outcomes and to facilitate comparability.

Antidepressants have also been observed to increase peripheral BDNF levels, although these changes will depend on the particular antidepressant used in antidepressant therapy (Deuschle et al., 2012; Hellweg et al., 2008; Zhou et al., 2017). Thus, how they were considered across the analysed cohorts could be of relevance for understanding the results (Sheldrick et al., 2017; Zhou et al., 2017). Whereas Krogh et al. (2014) excluded participants with recent antidepressant treatment, in Salehi et al. (2016) all patients were treated, and in the remaining studies the use of them was allowed (Krogh et al., 2014; Salehi et al., 2016). Apart from the aforementioned heterogeneity provided by their use, it would be logical to consider that they might be moderating or masking the effect of physical activity on BDNF concentrations.

As an additional source of heterogeneity, important differences were also observed in the physical activity interventions performed across studies, as well as in the procedure followed for the control branch. In this regard, the use of light-intensity physical activity for the control branch in sedentary MDD cases -as in Toups et al. (2011) or Krogh et al. (2014)-, might lead to underestimating the effect of the intervention, as it has been observed with other placebo interventions (Josefsson et al., 2014; Krogh et al., 2014; Toups et al., 2011).

Finally, it is necessary to highlight the differences found on the management of depression diagnosis since clinician-rated instruments and self-assessed questionnaires have been demonstrated to not be equivalent (Cuijpers et al., 2010). Whereas most of the studies followed DSM criteria using MINI or clinically validated interviews, two studies employed self-assessed questionnaires (Pereira et al., 2013; Rahman et al., 2017).

As a final remark, we included two systematic reviews and meta-analyses, both assessing chronic exercise interventions. The novelty of these studies, together with its publication in the same year, evidences both the growing interest in this research field and the paucity of studies analysing the effect of physical activity on depression and BDNF. The conclusions of both systematic reviews and meta-analyses are in line with the limitations stated in the previous sections, highlighting the potential bias caused by antidepressants, the variability of the interventions, sex and age of the participants, along the limited sample sizes.

4.2.3. General considerations

To the best of our knowledge, this is the first systematic review covering the analysis of the relationship between BDNF (Val66Met polymorphism and BDNF protein levels), depression, and physical activity. The study of the Val66Met genotype on this relationship allowed

a more integrative perspective, providing a comprehensive vision of the state of the art in this research field. This first approach pointed towards a greater antidepressant effect of physical activity in Met allele carriers in four out of the six studies. On the contrary, we observed a considerable disparity in the results regarding the existence of a relationship between BDNF levels, depression and physical activity, with an important heterogeneity across studies in relevant parameters (e.g., type of intervention, the use of a control group in physical activity interventions, sample size, and the scales for assessing depression). The heterogeneity observed across studies highlights that standardisation towards these different methodological aspects should be considered in future research in order to obtain more comparable and conclusive results. Other important recommendations include considering the potential confounder variables, such as the use of antidepressant medication, sex and age of the cohort, or the BDNF measurement assays. Finally, it is remarkable that studies comparing peripheral BDNF from serum and plasma are not easily comparable.

One of the most robust results was the acute increase of BDNF levels following a single bout of physical activity, described in the *Acute exercise intervention* section. Together with the observed trend found in most of the studies assessing the Val66Met polymorphism, it could be hypothesised that the greater benefit found in Met allele carriers from physical activity could be related to this acute increase of BDNF. Therefore, physical activity could contribute to mitigate the previously reported detrimental effect of the Met allele on cognition and depressive symptoms.

5. Conclusions

A considerable number of studies addressing the potential role of BDNF -both the genetic variability of the Val66Met polymorphism and the protein levels- in the interaction between depression and physical exercise were found, highlighting the current interest of this research field. There is cumulative evidence supporting the involvement of BDNF in the molecular mechanisms behind the association of physical exercise and the improvement of depression. However, this systematic review pointed to a high heterogeneity between studies in important methodological aspects, and potential sources of bias, that must be considered in future research in order to obtain more robust conclusions. Overall, we still consider the recommendation to practise physical activity for the treatment of depression and depressive symptoms to be evident and effective. However, a better understanding of the different variables of exercise (type of activity, duration or intensity), and their role in the improvement of depression would be necessary, as well as a deeper knowledge of the physiopathology of depression, to identify the optimal way to properly implement this therapeutic strategy.

CRediT authorship contribution statement

Juan Antonio Zarza-Rebollo: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Elena López-Isac:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation. **Margarita Rivera:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Laura Gómez-Hernández:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Ana M. Pérez-Gutiérrez:** Writing – review & editing, Investigation. **Esther Molina:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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