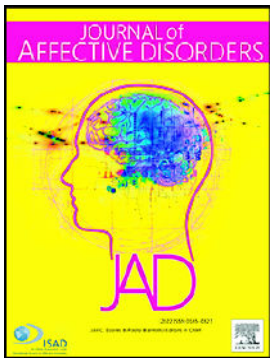

Effects of exercise training on inflammatory, neurotrophic and immunological markers and neurotransmitters in people with depression: A systematic review and meta-analysis

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Title page

Title: Effects of exercise training on inflammatory, neurotrophic and immunological markers and neurotransmitters in people with depression: a systematic review and meta-analysis.

Running title: Exercise in people with depression.

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Abstract

Background: Major depressive disorder is the most common type of mental disorder. The biological pathway by which exercise promotes its antidepressant effects remains uncleared. This study aimed to systematically review the chronic effect of exercise on blood biomarkers and its association with changes in depressive symptoms in adults with major depressive disorder.

Methods: Randomized controlled trials (RCT) published until February 2020 were screened in seven databases. Studies were systematically reviewed by two independent reviewers. Random effect meta-analysis was performed and reported as standardized mean differences (SMD) and 95% confidence interval (CI). The meta-analysis protocol was registered with PROSPERO (CRD42021221177).

Results: From 3,865 records, 12 studies (N=757 participants, mean age [SD]: 43.0 [11.0], 66.2% women) were included in this review. Exercise training resulted in superior increase in circulating BDNF (SMD: 0.44, 95%CI: 0.15, 0.73) and kynurenine (SMD: 0.29, 95%CI: 0.04, 0.54), and decrease depressive symptoms (SMD: -0.72, 95%CI: -1.08, -0.37) in adults with major depression disorder compared to control groups. Multivariate meta-regression analysis showed that improvements in circulating levels of BDNF, kynurenine and interleukyn-6 were associated with decreases in depressive symptoms.

Limitations: Results were not stratified by the type of medication used by participants due to the lack of reporting of the included studies. Few studies provided data on other biomarkers (e.g., TNF-α and IL-10) besides BNDF and kynurenine.

Conclusions: Antidepressant effect of exercise may be triggered by improved circulating levels of BNDF, kynurenine, and interleukine-6 in adults with major depressive disorder.

Keywords: Exercise, depression, biomarkers, major depression disorder, BDNF.

Effects of exercise training on inflammatory, neurotrophic and immunological markers and neurotransmitters in people with depression: a systematic review and meta-analysis

1. Background

Depression is a mental disorder that affected 350 million people worldwide in 2019 (GBD, 2019), being the sixth most disabling condition in the world (Vos et al., 2020). Major depressive disorder (MDD) is the most prevalent type of depression (Kessler et al., 2005), with a lifetime prevalence of 6–15% (Bromet et al., 2011). The pathogenesis of depression is related to changes in some physiological processes associated with neurotrophic (Hanson et al., 2011), endocrine (Berger et al., 2016), oxidative, inflammatory (Anderson & Maes, 2014; Haapakoski et al., 2015), and immunological factors (Maes, 1995). Indeed, antidepressant drugs have focused on improving several of these biomarkers. Although this treatment effectively reduces the severity and frequency of depressive symptoms, side effects like weight gain, increases in blood pressure, and impairment of sexual functions are commonly experienced (National Health System, 2022). Furthermore, the effectiveness of antidepressants was questioned by placebo-controlled clinical trials showing only a small effect size (Khan & Brown, 2015). In light of these limitations, non-pharmacological alternatives such as exercise have emerged.

Several meta-analyses have demonstrated that physical exercise is an effective treatment for depression (Cooney et al., 2013, Danielsson et al., 2013, Josefsson et al., 2014, Krogh et al., 2011, Schuch et al., 2016). However, studies examining the underlying biological mechanisms responsible for the antidepressant effect of exercise are scanty. Previous systematic reviews and meta-analyses have confirmed that exercise can induce chronic responses in hormones, neurotrophins, and inflammation biomarkers in people with depression (Feter et al., 2019, Schuch et al., 2016). Exercise-induced release of myokines such as irisin and interleukin-6 (Chow et al., 2022) and improvement in other depression-related biomarkers (Krogh et al., 2013; Schuch et al., 2014) are hypothesized as one of the antidepressant physiological pathways. However, the underlying biological mechanisms associated with the beneficial effect of exercise on depressive symptoms remained unclear.

Therefore, this systematic review aimed to identify the chronic effects of exercise training on biomarkers and depressive symptoms and their association in adults with major depressive disorder.

2. Methods

The present systematic review was performed according to the PRISMA statement (Page et al., 2020) (Supplementary Table 1). The present study was registered on PROSPERO (CRD42021221177). Some changes were made to the original protocol. Initially, we had designed to use any experimental study, with or without a comparator group, in addition to including acute effects of physical exercise. After reviewing and discussing the design, we decided to include only randomized clinical trials with a comparator (control group or studies with two or more groups with different interventions). Moreover, for a better comparator effect, we decided to assess only the chronic effects of physical exercise on the outcomes.

2.1. Literature Search

Two independent authors (LLC and RA) conducted searches from August 2021 until February 2022 at MEDLINE/PubMed, Embase, Scopus, Sportdiscus, Web of Science, PsycINFO, Cochrane Library, and in the list of references from de articles included. We included RCT published in English, Portuguese or Spanish with no publication time restriction.

The following search strategy was used: (“exercise” OR “physical activity” OR “High-Intensity Interval Training” OR “resistance training” OR “aerobic training”) AND (“depress*”) AND (“biomark*” OR “oxidative stress” OR “immun*” OR “inflammat*” OR “neurotrophin” OR “brain-derived neurotrophic factor” OR “cytokines” OR “serotonin” OR “cortisol” OR “Interleukin” OR “ “growth-hormone” OR “insuline like fator-1” OR “kynurenine”) AND (randomi* OR rct OR "clinical trial*"). All databases searches strategies are presented in Supplementary table 2.

2.2. Eligibility criteria

All retrieved reports were imported for Mendeley reference management software and duplicates were removed. Two independent reviewers (LLC and RA) read the titles and abstracts independently. Disagreements were decided by a third researcher (NF). All abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were assessed in the full text. Only randomized clinical trials examining the effect of chronic exercise intervention in biomarkers presenting pre and post-blood markers were included. The exercise was defined as a planned, structured, and repetitive intervention to improve or maintain one or more components of physical conditioning (Caspersen et al., 1985). Chronic exercise constitutes exercise bouts that last a period per session, multiple sessions per week, over weeks with specific aims such as improving physical fitness, performance, or health (Kenney, Wilmore, & Costill, 2019; Xue, Yang, & Huang, 2019). Other inclusion criteria included studies with samples composed of adults with unipolar depressive disorder diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders (DSM), International Classification of Diseases (ICD) or Diagnostic and assessed by psychiatrists and/or through the use of standardized instruments such as Mini International Neuropsychiatric Interview (MINI), Composite International Diagnostic Interview (CIDI), and Structured Clinical Interview (SCID). We excluded studies in which the sample had another associated psychiatric illness (e.g., schizophrenia), comorbidities (e.g., cancer), with children or adolescents, and with animal models. Studies were limited to Portuguese, English, and Spanish and published in peer-reviewed journals.

2.3. Data Extraction

All studies that met the eligibility criteria at the full-text level were included in the data extraction process. Characteristics of samples (age, sex) and exercise intervention (type of exercise, session duration, intervention duration, session intensity, supervision), and values (baseline and post-intervention [mean and standard deviation]) of biomarkers and depressive symptoms were extracted by two authors (LLC and RA). Studies in which authors did not reply were included in the qualitative analysis only (Imboden et al., 2019; Krogh et al., 2013; Krogh et al., 2014b). For biomarkers or depressive symptoms data that were presented only in graphic form, we used the GetData Graph Digitizer software to extract these values. If these data

were missing in any study, an attempt was made to contact the authors of the articles. Data were extracted to an Excel spreadsheet and subsequently transferred to the statistical software (STATA/MP 14.2).

2.4. Outcomes measures

The primary outcome of this study was the mean difference in changes from baseline to post-intervention between exercise and control groups in circulating biomarkers after a chronic exercise intervention. Measures of depressive symptoms were considered a secondary outcome. Studies with data on biomarkers were included in this review regardless of the presence of data on depressive symptoms.

2.5. Methodological quality

Two authors (LLC and RA) evaluated the methodological quality of the studies by the Downs and Black checklist (Downs & Black, 1998). It is a validated tool to assess the methodological quality of randomized clinical trials. The checklist comprises 27 questions divided into five sub-items (reporting; external validity; bias; confounding factors/selection bias; the power of study). The score ranges from 0 to 32 points. Studies scoring between 16 and 18 points were classified as moderate quality, and studies scoring 19 points or higher were classified as high quality.

2.6. Quality of evidence and strength of recommendations

The GRADE system (Grading of Recommendations Assessment, Development, and Evaluation) evaluated the quality of evidence of the studies. This system classified the quality of evidence studies as high, moderate, low, and very low. Factors that can reduce the quality of evidence include study type and risk of bias, inconsistency of results, lack of generalizability, imprecise data, and other reporting biases.

2.7. Statistical analysis

Data were reported as standardized mean difference (SMD) and 95% confidence interval (CI). Units of measurements were converted to the most frequent unit used in each specific biomarker (e.g., (cortisol - µg/dL to ng/mL). Also, standard errors were converted to standard deviation (SD) when necessary. If a study had two interventions, both were included separately in the analysis. Values of cortisol and TNF-α were multiplied by -1, so increased concentration could be interpreted as a

positive exercise-induced modification. Data analysis was performed in statistical software STATA/MP 14.2. 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 (Higgins et al., 2003). Furthermore, subgroup analyses were performed to identify the factors associated with exercise-induced changes in biomarkers. Type of training, intensity, weekly volume, supervision, continent, sex, and age were considered for sub-group and meta-regression analyses. We calculated the SMD of the changes in the exercise and control group from baseline to post-intervention based on the following formula (Higgins & Green, 2006):

$$SMD = \frac{difference\ in\ mean\ outcomes\ between\ groups}{standard\ deviation\ of\ outcomes\ among\ participants}$$

In order to understand the sources of heterogeneity, we conducted a meta-regression analysis using the type of training, intensity, weekly volume, supervision, continent, sex, and age as covariates. These covariates were meta-regressed individually and together in a random-effects meta-regression model. The random-effects meta-regression used residual restricted maximum likelihood to measure between-study variance (τ^2). Method of moments was used to estimate τ^2. This is a generalization of the DerSimonian and Laird (1986) method commonly used for random-effects meta-analysis. When all covariates were analyzed together, permutation tests were performed (n = 1000) to address the issue of multiple testing by calculating adjusted P-values (Harbord & Higgins, 2008). Also, correlation coefficients were calculated to test the association between changes in biomarkers with changes in depressive symptoms. All correlation analyses were weighted by the inverse of the variance of each observation, and scatter 'bubble' plots were constructed to display the different trials' proportional weights graphically.

3. Results

3.1. Characteristics of included studies and samples

After searching in different databases and the reference list of articles, we found 3,865 records. After exclusion of duplicates and applying eligibility criteria in titles, abstracts, and full-text, a total of 12 studies were included in the systematic review (Carneiro et al., 2016; Carneiro et al., 2016b; Euteneuer et al., 2017; Fernandes et

al., 2022; Hennings et al., 2013; Imboden et al., 2021; Kerling et al., 2017; Krogh et al., 2014; Millischer et al., 2017; Rethorst et al., 2014; Schuch et al., 2014 and Toups et al., 2011), and nine were included in the meta-analysis (Carneiro et al., 2016; Euteneuer et al., 2017; Fernandes et al., 2022; Hennings et al., 2013; Imboden et al., 2021; Kerling et al., 2017; Krogh et al., 2014; Millischer et al., 2017 and Schuch et al., 2014). A flowchart of the search process is illustrated in Figure 1.

The summary of the main characteristics of the included studies is presented in Table 1. A total of 757 subjects were analyzed, with 508 in the intervention group (68.1% female) and 249 in the control group (62.2% female). The mean age of the intervention and control groups were 44.6±9.9 and 41.6±12.7 years, respectively. Of the total interventions, 93.3% used aerobic training (one study used combined training), at moderate intensity (46.7%), with professional supervision (60%) and a total weekly volume of more than 150 minutes (46.7%) in the exercise interventions.

3.2. Methodological quality

The mean score of the D&B checklist was 16.7 points, ranging from 13 (Toups et al., 2011) to 22 (Euteneuer et al., 2017) (Supplementary Table 3). Five studies were classified as moderate quality (Hennings et al., 2013; Krogh et al., 2014; Millischer et al., 2017; Rethorst et al., 2013 and Schuch et al., 2014), and two as high methodological quality (Euteneuer et al., 2017 and Imboden et al., 2021). Certainty of effect was determined to be moderate for overall and kynurenine circulating levels, low for BNDF, and very low for IL-6 via GRADE analysis (Supplementary Table 4).

3.3. Primary outcome

Across the 12 articles included in the study, a total of 32 different biomarkers were reported. The most prevalent were the cortisol (Carneiro et al., 2016 and Fernandes et al., 2022; N=59), IL-6 (Euteneuer et al., 2017; Fernandes et al., 2022 and Hennings et al., 2013; N=190), IL-10 (Euteneuer et al., 2017 and Fernandes et al., 2022; N=104), TNF-α (Fernandes et al., 2022 and Imboden et al., 2021; N=82), kynurenine (Hennings et al., 2013 and Millischer et al., 2017 N=115) and brain-derived neurotrophic factor (BDNF) (Imboden et al., 2021; Kerling et al., 2017; Krogh et al., 2014 and Schuch et al., 2014 N=189). Meta-analysis showed that exercise

training improved circulating levels of depression-related biomarkers (SMD: 0.31; 95%CI: 0.11, 0.51; n=946 participants). Exercise training promoted a superior increase in the circulating levels of BDNF (SMD: 0.44; 95%CI: 0.15, 0.73) and kynurenine (SMD: 0.29; 95%CI: 0.04, 0.54) compared to the changes observed in the control group (Figure 2). The Begg-Mazumdar Kendall's Tau (p=0.511) and the Egger tests did not indicate publication bias in our findings (p=0.729) (Supplementary Figure 1).

3.4. Depressive symptoms

Depressive symptoms were most assessed by Beck Depression Inventory - BDI (Beck et al., 1961) (Euteneuer et al., 2017; Hennings et al., 2013 and Kerling et al., 2017), Hamilton Depression Rating Scale - HDRS (Hamiltom et al., 1960) (Fernandes et al., 2022; Imboden et al., 2021 and Schuch et al., 2014), and Montgomery-Asberg Depression Rating Scale - MADRS (Montgomery & Åsberg, 1979) (Kerling et al., 2017 and Millischer et al., 2017). Four studies (Carneiro et al., 2016; Carneiro et al., 2016b; Krogh et al., 2014 and Rethorst et al., 2014) did not provide data about depressive symptoms. As shown in Figure 3, exercise decreased depressive symptoms in adults with major depressive disorder at higher levels than in the control group (SMD: -0.76; 95%CI: -1.13, -0.40). No publication bias was detected in this analysis (Supplementary Figure 1).

3.5. Subgroup analysis

Subgroup analyses showed that the sample's age and sex and the weekly volume of exercise showed a null or small effect on exercise's beneficial response on circulating biomarkers levels, as shown in Table 2. Chronic exercise performed at moderate intensity, with supervised exercise sessions, and those performed in Europe significantly positively affected biomarkers.

3.6. Meta-regression

As illustrated in Table 3, the crude analysis showed that interventions conducted in the European continent were more effective in increasing circulating biomarkers in people with depression. However, such association was lost after multivariate analysis. Similarly, a higher proportion of women in the study's sample was

associated with a reduced effect of exercise intervention in univariate analysis. However, this association was lost in the final adjusted model. Figure 4 illustrates the association between the SMD of change in biomarkers and the SMD of change in depressive symptoms between exercise and control groups. Our findings indicated that the reduction in depressive symptoms induced by exercise training was associated with improving circulating biomarkers in adults with depression (β=-0.41; 95%CI: -0.80, -0.06; p=0.021). The multivariate model included sex and age of participants, volume, type, the intensity of exercise intervention, whether sessions were supervised, and the continent in which the study was performed. This model explained 100% of the heterogeneity in the included studies. Figure 5 showed a negative correlation between changes in major depressive symptoms and changes in circulating biomarkers, stratified by the most prevalent biomarkers: IL-6, kynurenine, and BDNF.

3.7. Pre and post-intervention analysis

We also performed a meta-analysis considering baseline and post-intervention data from the exercise groups only (Supplementary Figures 2, 3, and 4). In this sub-analysis, chronic exercise interventions improved circulating BDNF (SMD: 0.54; 95%CI: 0.00, 0.68; p=0.049). No effect of exercise intervention was observed in other biomarkers. In addition, exercise reduced depressive symptoms (SMD: -1.57, 95%CI: -1.97, -1.18). As observed in the previous analysis, improving circulating biomarkers was associated with improvement in depressive symptoms (β: -0.06; 95%CI: -0.11, -0.01, p=0.040).

4. Discussion

In this systematic review with meta-analysis, we identified that exercise increased circulating levels of kynurenine and BDNF in adults with major depressive disorder. We also showed that the exercise-induced improvement in circulating biomarkers is associated with a decrease in depressive symptoms. Our findings confirmed the anti-depressant effect of exercise and provided clinically meaningful insights into the potential pathway exercise triggers to promote such positive effects.

The beneficial effect of exercise on people with depression has been documented (Schuch et al., 2016; De Sousa et al., 2021) and can be used as part of the treatment of people with major depressive disorder (Lee et al., 2021). Lee and collaborators (2021) showed a moderate effect of exercise combined with usual treatment (i.e., pharmacotherapy and psychotherapy) when compared with usual treatment alone (SMD = -0.62). In our study, we showed that exercise could reduce depressive symptoms in adults with major depressive disorder. The exact mechanisms by which exercise can promote such antidepressant effects are uncertain. However, recent evidence revealed that exercise-induced skeletal muscle contraction could promote the release of myokines (e.g., irisin and cathepsin B) and the expression of kynurenine aminotransferase (Pedersen, 2019). These biomarkers' increased circulating levels and activities are associated with improved cognitive function and reduced depressive symptoms (Pedersen, 2019).

Exercise increased circulating kynurenine in adults with major depressive disorder, and such improvement was associated with reduced depressive symptoms. Kynurenine is a neurotrophin produced as a metabolic of tryptophan. Tryptophan is metabolized to kynurenine through the 2,3-dioxygenase and indoleamine 2,3-dioxygenase enzymes (Stone et al., 2012). In the central nervous system, the kynurenine can be converted to 3-hydroxyanthranilic acid through anthranilic acid or 3-hydroxykynurenine and posteriorly into quinolinic acid in the microglia. The oxidative stress and the excitotoxic effects of quinolinic acid are associated with neurotoxicity and neurodegenerative process, ultimately leading to mental disorders, including major depressive disorder (Stone & Darlington, 2002). On the other hand, exercise can promote an increase in kynurenine aminotransferase enzyme expression, altering the peripheral metabolism of kynurenine for the production of kynurenic acid (Cervenka et al., 2017). This enzyme converts the kynurenine into neuroprotective kynurenic acid. Thereby, there is a reduction of neurotoxic kynurenine in the CNS, leading to a reduction in depressive symptoms (Pedersen, 2019). Quinolinic acid and kynurenic acid are frequently found unbalanced in people with mental disorders like depression and schizophrenia (Müller & Schwarz, 2007). Another meta-analysis (Lim et al., 2021) assessed the effects of exercise on the kynurenine pathway and psychological outcomes. The authors analyzed six studies

and verified that exercise significantly benefited the kynurenine pathway and psychological outcomes in domains of somatization, anxiety, and depression, corroborating our findings.

BDNF is a neurotrophin involved in neural plasticity regulation of synaptic activity, cell survival, hippocampal function, and the learning process (Wrann et al., 2013). Low circulating levels of BDNF are associated with affective/emotional dysregulation, like in depressive disorders. As for kynurenine, our meta-analysis demonstrated that increased BDNF promoted by exercise was associated with decreased depressive symptoms. In previous systematic reviews with meta-analysis, the authors identified that resting concentrations of peripheral blood BDNF were higher after chronic exercise intervention, including in people with depression (Dinoff et al., 2016; Feter et al., 2019). Furthermore, there is a relation between PGC1-α/FNDC5/BDNF pathway and physical exercise that can lead to changes in depressive symptoms. The irisin is a myokine secreted by skeletal muscle after exercise stimulation, which is processed from the type I membrane protein encoded by the FNDC5 gene (Boström et al., 2012). Physical exercise upregulates the expression of peroxisome proliferator-stimulated by receptor-gamma coactivator-1 alpha (PGC-1α) in skeletal muscle cells. Subsequently, the FNDC5 is produced, and its cleavage results in irisin production (Norheim et al., 2014). In turn, the irisin, mediated by PGC-1α, crosses the blood-brain barrier, increasing the BDNF expression in the brain (Wrann et al., 2013).

Although our findings were limited by the small number of studies evaluating the effect of exercise on IL-6 levels, we showed that changes in this myokine were associated with reducing depressive symptoms. The previous meta-analysis revealed that circulating levels of IL-6 were positively associated with depression (Liu et al., 2012).

Myokines such as IL-6 are small proteins secreted from muscle tissue from muscle contraction (Gleeson et al., 2011). The IL-6 has up to a 100-fold increase in circulating levels in response to exercise and declines in the post-exercise period (Pedersen, 2019). This increase induces an anti-inflammatory IL-10 and TNF-α increase in production (Pedersen & Mark, 2008). There is no evidence that inflammation is the cause (Dantzer et al., 2008) or consequence of depression (Berk

et al., 2013), but it is known that some pro- and anti-inflammatory biomarkers are involved in this process (Mac et al., 2021).

Limitations

The present study has numerous limitations that need to be acknowledged. First, light-intensity activities performed by control groups of the included studies varied (e.g., relaxation, stretching, psychotherapy, or passive control only). Second, we could not stratify our findings by the type of medication used by participants due to a lack of reporting on whether participants were under medication use, classes, and doses of medication. Third, only a few studies provided required data on other biomarkers (e.g., TNF-α and IL-10) besides BNDF and kynurenine. Fourth, because of the limited number of studies available for each variable, we could not determine the influence of exercise characteristics on changes in outcomes.

In conclusion, exercise improved circulating levels of depression-related biomarkers, especially kynurenine and BDNF, in adults with major depressive disorder. The exercise-induced improvement in the circulating levels of BDNF, kynurenine, and IL-6 was associated with reduced depressive symptoms in adults with major depressive disorder. Future clinical trials are warranted to examine the effect of different exercise modalities on other biomarkers.

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Figure. 1. PRISMA flowchart of search process.

Figure. 2. Forest plot on the effect of exercise training compared to control group in several biomarkers in adults with major depressive disorder.

Figure. 3. Forest plot on the effect of exercise training compared to control group in depressive symptoms in adults with major depressive disorder.

Figure. 4. Correlation between the standardized mean difference (SMD) of the changes (post-intervention minus baseline) in the circulating levels of biomarker and depressive symptoms of exercise and control groups. Grey area indicates 95% confidence interval. The size of each bubble represents the weight of the study in the meta-analysis.

Figure. 5. Correlation between the standardized mean difference (SMD) of the changes (post-intervention minus baseline) in the circulating levels of interleukine-6, kynurenine, and brain-derived neurotrophic factor (BDNF) and depressive symptoms of exercise and control groups. Model adjusted for sex and age of participants, intensity, and type of exercise training.

Table 1. The summary with the main characteristics of the included studies.

Author/Year/ Country	Sample size (n)	Mean age (years)	Type of exercise	Exercise intensity	Weekly volume (days)	Total weekly intervention (weeks)	Biomarkers	Depressive symptoms measure
Carneiro et al., 2016 - Portugal	Exercise: 9 Control: 10	Exercise: 52.8 Control: 47.8	Aerobic	Moderate	3	16	**Dopamine** ↔ exercise ↓ control **Noradrenaline** ↑exercise ↑control **Adrenaline** ↑exercise; ↔ control **Serotonin** ↓exercise ↑control **Cortisol** ↓exercise ↓ control	Data were not collected
Carneiro et al., 2016b - Portugal	Exercise: 7 Control: 7	Exercise: 55.0 Control: 47.9	Aerobic	Moderate	3	16	**Erythrócite (S-COMT)** ↑exercise; ↑control	Authors did not provide data
Euteneuer, et al, 2017 - Germany	Exercise: 36 Control: 30	Exercise: 36.9 Control: 37.9	Aerobic	Moderate	4	16	**CRP** ↔ exercise ↑control **IL-6** ↑exercise ↓ control **IL-10** ↑exercise ↓ control **Leukocytes** ↑exercise ↓ control **Limphocytes** ↑exercise ↓ control **Neutrophilis** ↑exercise ↓ control **Monocytes** ↓exercise ↓ control **Total T cells** ↑exercise ↓ control	**BDI-I** ↓exercise ↓ control

							T helper cells ↑exercise ↑control **Cytotoxic T cells** ↑exercise ↓ control **Regulatory T cells** ↑exercise ↑control **B cells** ↑exercise ↓ control **NK cells** ↑exercise ↑control	
Fernandes et al, 2022 - Brazil	Exercise: 32 Control: 25	Exercise: 43.5 Control: 38.6	Aerobic intermitent	High	4	4	**IL-1β** ↑exercise ↓ control **IL-6** ↓ exercise ↓ control **IL-8** ↓ exercise ↓ control **IL-10** ↓ exercise ↓ control **IL-12** ↓ exercise;↔ control **TNF** ↓ exercise;↓ control **Cortisol** ↓ exercise ↓ control	**HDRS** ↓ exercise ↓ control
Hennings et al, 2013 - Germany	Exercise: 38 Control: 48	Exercise: 32.1 Control: 36.4	Aerobic	Moderate	5	4	**IL-6** ↓ exercise ↓ control **Neopterin** ↑exercise ↓ control **Tryptofhan** ↓ exercise ↓ control **Kynurenine** ↓ exercise ↓ control	**BDI-I** ↓ exercise ↓ control
Imboden et al,, 2021 - Switzerland	Exercise: 22 Control: 20	Exercise: 41.3 Control: 38.3	Aerobic	Moderate	3	6	**BDNF** ↑exercise↑control **TNF**	**HDRS** ↓ exercise ↓ control

							↔ exercise ↓ control	
Kerling et al., 2017 - Germany	Exercise: 22 Control: 20	Exercise: 44.2 Control: 40.9	Aerobic	Moderate	3	6	**BDNF** ↑exercise ↓ control	**BDI-II** ↓ exercise ↓ control **MADRS** ↓ exercise ↓ control
Krogh et al., 2014 - Denmark	Exercise: 41 Control: 38	Exercise:38.9 Control: 43.8	Aerobic	Moderate	3	12	**BDNF** ↑exercise ↓ control **VEGF** ↓ exercise ↓ control **IGF-1** ↓ exercise ↓ control	Authors did not provide data
Millischer et al., 2017 - Sweden	Exercise 1: 37 Exercise 2: 40 Control: 40	Exercise 1: 46,7 Exercise 2: 44.0 Control: 42.0	Aerobic	Moderate (exercise 1) and Vigorous (exercise 2)	3	12	**Kynurenine** ↑exercise 1 ↑ exercise 2 ↔ control **KYNA** ↑exercise 1 ↔ exercise 2 ↔ control	**MADRS** ↓ exercise 1 ↓ exercise 2 ↓ control
Rethorst et al, 2014 – United States	Exercise1: 53 Exercise2: 52	Exercise 1: 49.2 Exercise 2: 46.8	Aerobic	Self-selected; Exercise 1: Waste 4KKW (kcal per kg per week); Exercise 2: Waste 16KKW	Changed each week	‘12	**IFN-γ** ↑exercise 1 ↑exercise 2 **IL-1β** ↑exercise 1 ↑exercise 2 **IL-6** ↓ exercise 1 ↑exercise 2 **TNF-α** ↓ exercise 1 ↔ exercise 2	Authors did not provide data
Schuch et al., 2014 - Brazil	Exercise: 15 Control: 11	Exercise: 42.8 Control: 42.5	Aerobic	Moderate-high	3	3	**BDNF** ↑exercise↑control **TBARS** ↓ exercise 1 ↑exercise 2	**HDRS** ↓ exercise 1 ↓ exercise 2
Toups et al.,	Exercise 1: 52	Exercise: 46.1	Aerobic	Moderate	Exercise	12	**BDNF**	**IDS-C**

2011 – United States	Exercise 2: 52	Exercise: 49.2			1: Waste 16KKW; Exercise 2 Waste 4KKW		↔ exercise 1 ↑exercise 2	↓ exercise 1 ↓ exercise 2 **IDS-SR** ↓ exercise 1 ↓ exercise 2

Table 2. Effect of exercise training on biomarkers in adults with major depressive disorder according to sample and exercise program characteristics.

	Interventions	Participants	SMD (95%CI)	p-value	I^2 (%)	p-value
Type of training						
Aerobic	13	777	0.33 (0.11, 0.54)	0.004	56.6	0.005
Other	1	86	0.13 (-0.29, 0.56)	0.541	-	-
Intensity						
Moderate	8	507	0.44 (0.18, 0.72)	0.001	56.0	0.002
Moderate-to-high	6	356	0.11 (-0.16, 0.38)	0.428	38.0	0.153
Weekly volume						
≤150 minutes	5	291	0.35 (0.02, 0.68)	0.038	50.3	0.073
>150 minutes	9	570	0.28 (0.01, 0.55)	0.040	60.8	0.009
Supervision						
No	4	304	0.41 (-0.04, 0.87)	0.076	74.4	0.008
Yes	10	559	0.26 (0.03, 0.49)	0.023	21.2	0.248
Continent						
Europe	10	656	0.41 (0.21, 0.62)	<0.001	45.3	0.051
American	4	197	-0.06 (-0.40, -0.29)	0.753	29.4	0.236
Sex, % female						
> 50%	9	605	0.56 (0.25, 0.86)	<0.001	30.6	0.217
≤50%	5	256	0.19 (-0.04, 0.42)	0.099	49.1	0.039
Age, years						
≤ 40	6	388	0.38 (0.04, 0.71)	0.028	62.6	0.020
> 40	8	475	0.26 (-0.00, 0.52)	0.053	51.3	0.037

Table 3. Meta-regression on the association between exercise training and biomarkers in adults with major depressive disorder.

	k	Coefficient (95%CI)	Adjusted R^2 (%)	I^2 (%)	P-value	tau^2
Univariate						
Intensity	14	0.09 (-0.12, 0.29)	-10.9	48.1	0.419	0.06
Sex, % female	14	-0.49 (-0.81, -0.18)	86.7	10.2	0.002	0.01
Biomarker	14	0.06 (-0.06, 0.19)	-3.3	46.5	0.337	0.06
Type of exercise	14	0.08 (-0.43, 0.26)	-17.4	49.1	0.639	0.07
Age, years	14	-0.23 (-0.61, 0.14)	1.3	45.3	0.224	0.06
Volume	14	-0.01 (-0.42, 0.40)	18.9	50.0	0.980	0.07
Supervision	14	0.09 (-0.12, 0.29)	-10.9	48.1	0.419	0.06
Continent	14	0.45 (0.07, 0.82)	56.3	27.1	0.019	0.03
Δ depression symptoms	14	-0.18 (-0.53, 0.17)	-1.3	36.5	0.320	0.04
Multivariate						
Multivariate	14		100.0	0.0	0.049	0.00
Intensity		0.31 (-0.23, 0.84)				
Sex, % female		-0.31 (-0.79, 0.17)				
Biomarker		**0.15 (0.01, 0.30)**				
Type of exercise		-0.24 (-0.60, 0.12)				
Age, years		-0.41 (-1.05, 0.23)				
Volume		0.73 (-0.48, 1.94)				
Supervision		0.17 (-0.22, 0.57)				
Continent		0.44 (-0.61, 1.49)				
Δ depression symptoms		**-0.41 (-0.76, -0.06)**				

Bold values indicate p<0.05 in the adjusted model.

CRediT authorship contribution statement: Larissa L da Cunha: Conceptualization, Methodology, Writing – original draft. **Natan Feter:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision. **Ricardo Alt:** Methodology, Writing – review & editing. **Airton J Rombaldi**: Writing – review & editing, Supervision.

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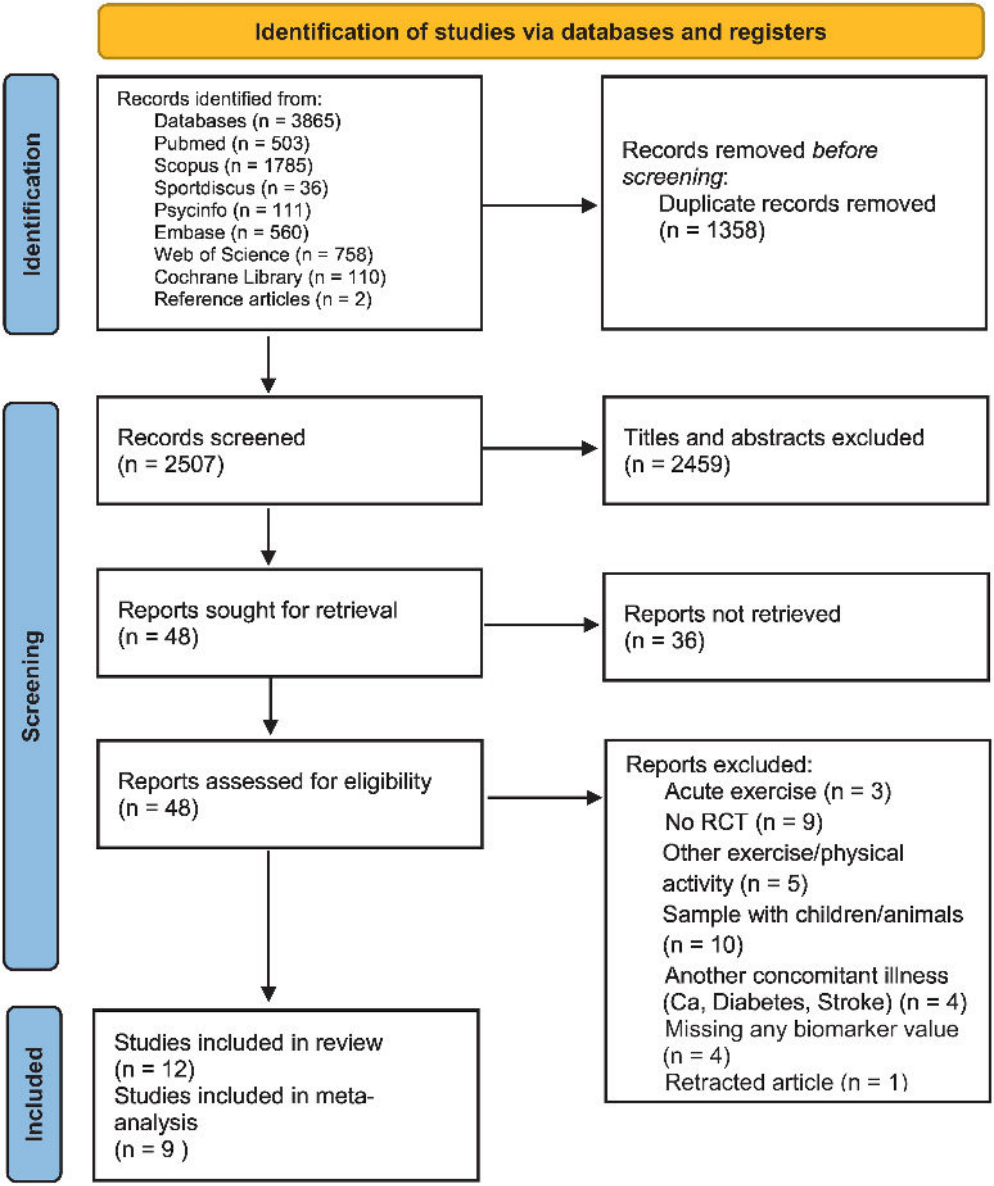
Conflict of Interest

All authors declare that they have no conflicts of interest.

Highlights

- Moderate-intensity, supervised exercise training improved biomarkers levels
- Exercise increases BDNF and kynurenine levels in adults with MDD
- Exercise-induced changes in BDNF, KYN, and IL-6 correlated with lower depressive symptoms.
- Interventions with other types of exercise training in adults with MDD are required.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Identification
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Pubmed (n = 503)
Scopus (n = 1785)
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Psycinfo (n = 111)
Embase (n = 560)
Web of Science (n = 758)
Cochrane Library (n = 110)
Reference articles (n = 2)
Records removed *before screening*:
Duplicate records removed (n = 1358)
Screening
Records screened (n = 2507)
Titles and abstracts excluded (n = 2459)
Reports sought for retrieval (n = 48)
Reports not retrieved (n = 36)
Reports assessed for eligibility (n = 48)
Reports excluded:
Acute exercise (n = 3)
No RCT (n = 9)
Other exercise/physical activity (n = 5)
Sample with children/animals (n = 10)
Another concomitant illness (Ca, Diabetes, Stroke) (n = 4)
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Retracted article (n = 1)
Included
Studies included in review (n = 12)
Studies included in meta-analysis (n = 9)

Figure 1

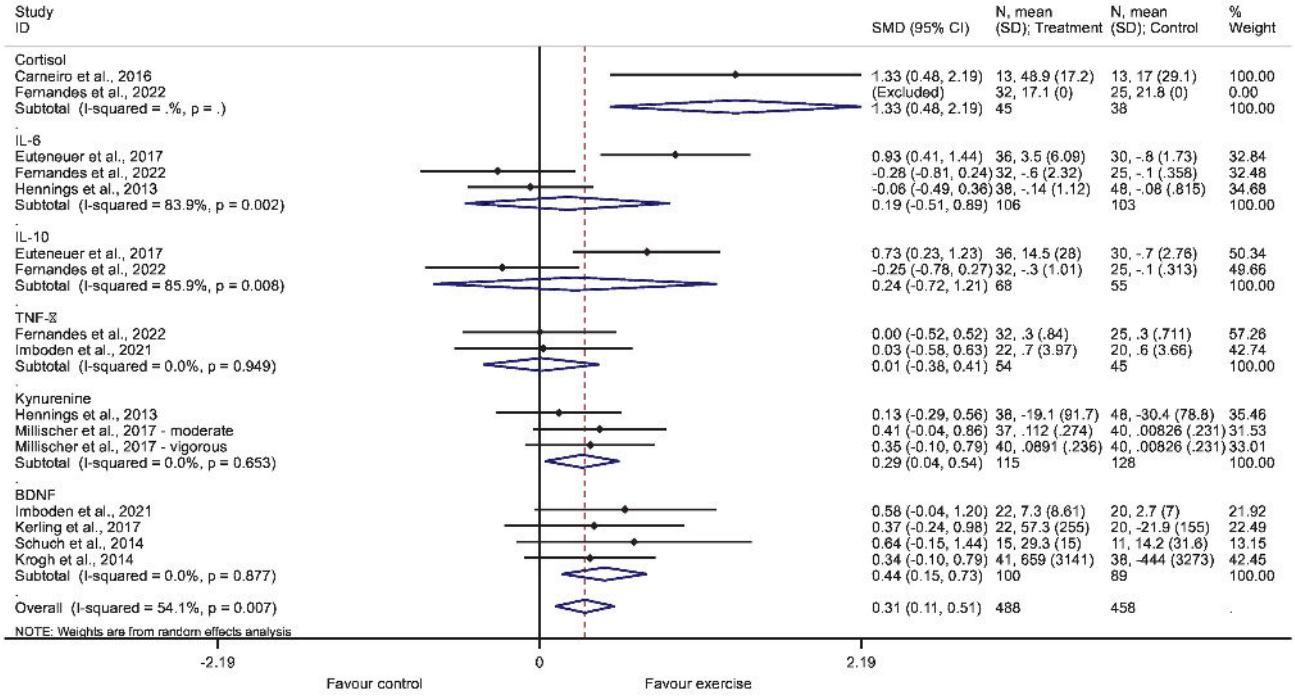
Study ID
SMD (95% CI)
N, mean (SD); Treatment
N, mean (SD); Control
% Weight
Cortisol
Carneiro et al., 2016 1.33 (0.48, 2.19) 13, 48.9 (17.2) 13, 17 (29.1) 100.00
Fernandes et al., 2022 (Excluded) 32, 17.1 (0) 25, 21.8 (0) 0.00
Subtotal (I-squared = .%, p = .) 1.33 (0.48, 2.19) 45 38 100.00
IL-6
Euteneuer et al., 2017 0.93 (0.41, 1.44) 36, 3.5 (6.09) 30, -.8 (1.73) 32.84
Fernandes et al., 2022 -0.28 (-0.81, 0.24) 32, -.6 (2.32) 25, -.1 (.358) 32.48
Hennings et al., 2013 -0.06 (-0.49, 0.36) 38, -.14 (1.12) 48, -.08 (.815) 34.68
Subtotal (I-squared = 83.9%, p = 0.002) 0.19 (-0.51, 0.89) 106 103 100.00
IL-10
Euteneuer et al., 2017 0.73 (0.23, 1.23) 36, 14.5 (28) 30, -.7 (2.76) 50.34
Fernandes et al., 2022 -0.25 (-0.78, 0.27) 32, -.3 (1.01) 25, -.1 (.313) 49.66
Subtotal (I-squared = 85.9%, p = 0.008) 0.24 (-0.72, 1.21) 68 55 100.00
TNF-α
Fernandes et al., 2022 0.00 (-0.52, 0.52) 32, .3 (.84) 25, .3 (.711) 57.26
Imboden et al., 2021 0.03 (-0.58, 0.63) 22, .7 (3.97) 20, .6 (3.66) 42.74
Subtotal (I-squared = 0.0%, p = 0.949) 0.01 (-0.38, 0.41) 54 45 100.00
Kynurenine
Hennings et al., 2013 0.13 (-0.29, 0.56) 38, -19.1 (91.7) 48, -30.4 (78.8) 35.46
Millischer et al., 2017 - moderate 0.41 (-0.04, 0.86) 37, .112 (.274) 40, .00826 (.231) 31.53
Millischer et al., 2017 - vigorous 0.35 (-0.10, 0.79) 40, .0891 (.236) 40, .00826 (.231) 33.01
Subtotal (I-squared = 0.0%, p = 0.653) 0.29 (0.04, 0.54) 115 128 100.00
BDNF
Imboden et al., 2021 0.58 (-0.04, 1.20) 22, 7.3 (8.61) 20, 2.7 (7) 21.92
Kerling et al., 2017 0.37 (-0.24, 0.98) 22, 57.3 (255) 20, -21.9 (155) 22.49
Schuch et al., 2014 0.64 (-0.15, 1.44) 15, 29.3 (15) 11, 14.2 (31.6) 13.15
Krogh et al., 2014 0.34 (-0.10, 0.79) 41, 659 (3141) 38, -444 (3273) 42.45
Subtotal (I-squared = 0.0%, p = 0.877) 0.44 (0.15, 0.73) 100 89 100.00
Overall (I-squared = 54.1%, p = 0.007) 0.31 (0.11, 0.51) 488 458
NOTE: Weights are from random effects analysis
-2.19
0
2.19
Favour control
Favour exercise

Figure 2

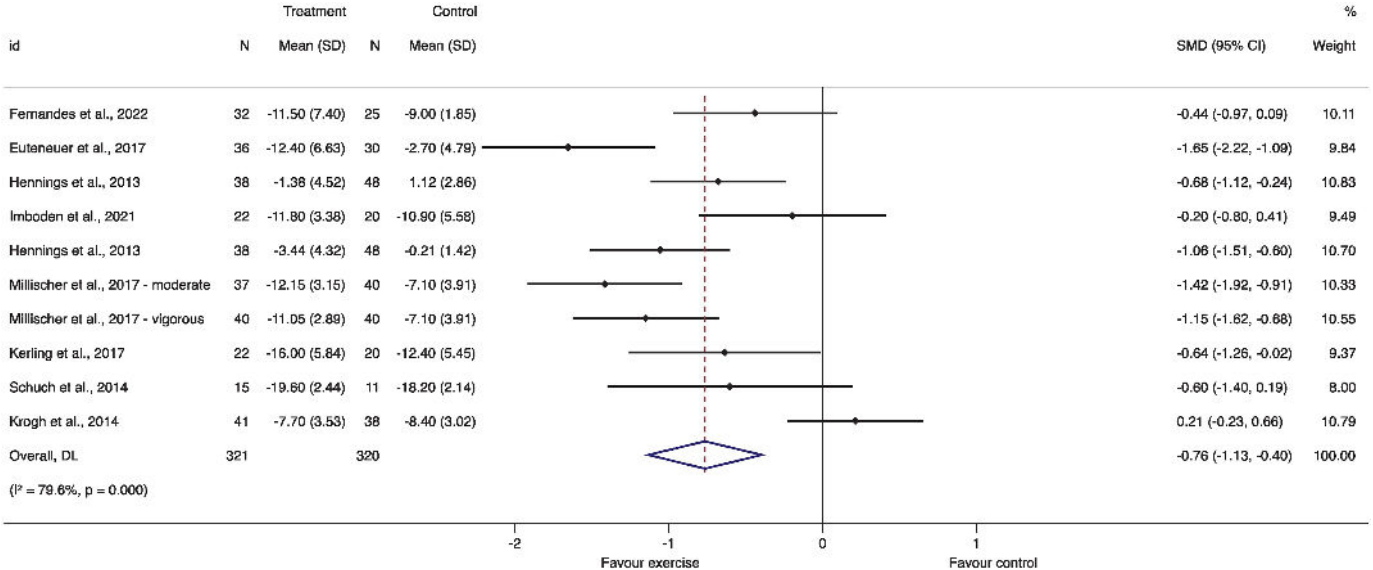
Treatment
Control
%
id
N
Mean (SD)
N
Mean (SD)
SMD (95% CI)
Weight
Fernandes et al., 2022 32 -11.50 (7.40) 25 -9.00 (1.85) -0.44 (-0.97, 0.09) 10.11
Euteneuer et al., 2017 36 -12.40 (6.63) 30 -2.70 (4.79) -1.65 (-2.22, -1.09) 9.84
Hennings et al., 2013 38 -1.38 (4.52) 48 1.12 (2.86) -0.68 (-1.12, -0.24) 10.83
Imboden et al., 2021 22 -11.80 (3.38) 20 -10.90 (5.58) -0.20 (-0.80, 0.41) 9.49
Hennings et al., 2013 38 -3.44 (4.32) 48 -0.21 (1.42) -1.06 (-1.51, -0.60) 10.70
Millischer et al., 2017 - moderate 37 -12.15 (3.15) 40 -7.10 (3.91) -1.42 (-1.92, -0.91) 10.33
Millischer et al., 2017 - vigorous 40 -11.05 (2.89) 40 -7.10 (3.91) -1.15 (-1.62, -0.68) 10.55
Kerling et al., 2017 22 -16.00 (5.84) 20 -12.40 (5.45) -0.64 (-1.26, -0.02) 9.37
Schuch et al., 2014 15 -19.60 (2.44) 11 -18.20 (2.14) -0.60 (-1.40, 0.19) 8.00
Krogh et al., 2014 41 -7.70 (3.53) 38 -8.40 (3.02) 0.21 (-0.23, 0.66) 10.79
Overall, DL 321 320 -0.76 (-1.13, -0.40) 100.00
(I² = 79.6%, p = 0.000)
-2
-1
0
1
Favour exercise
Favour control

Figure 3

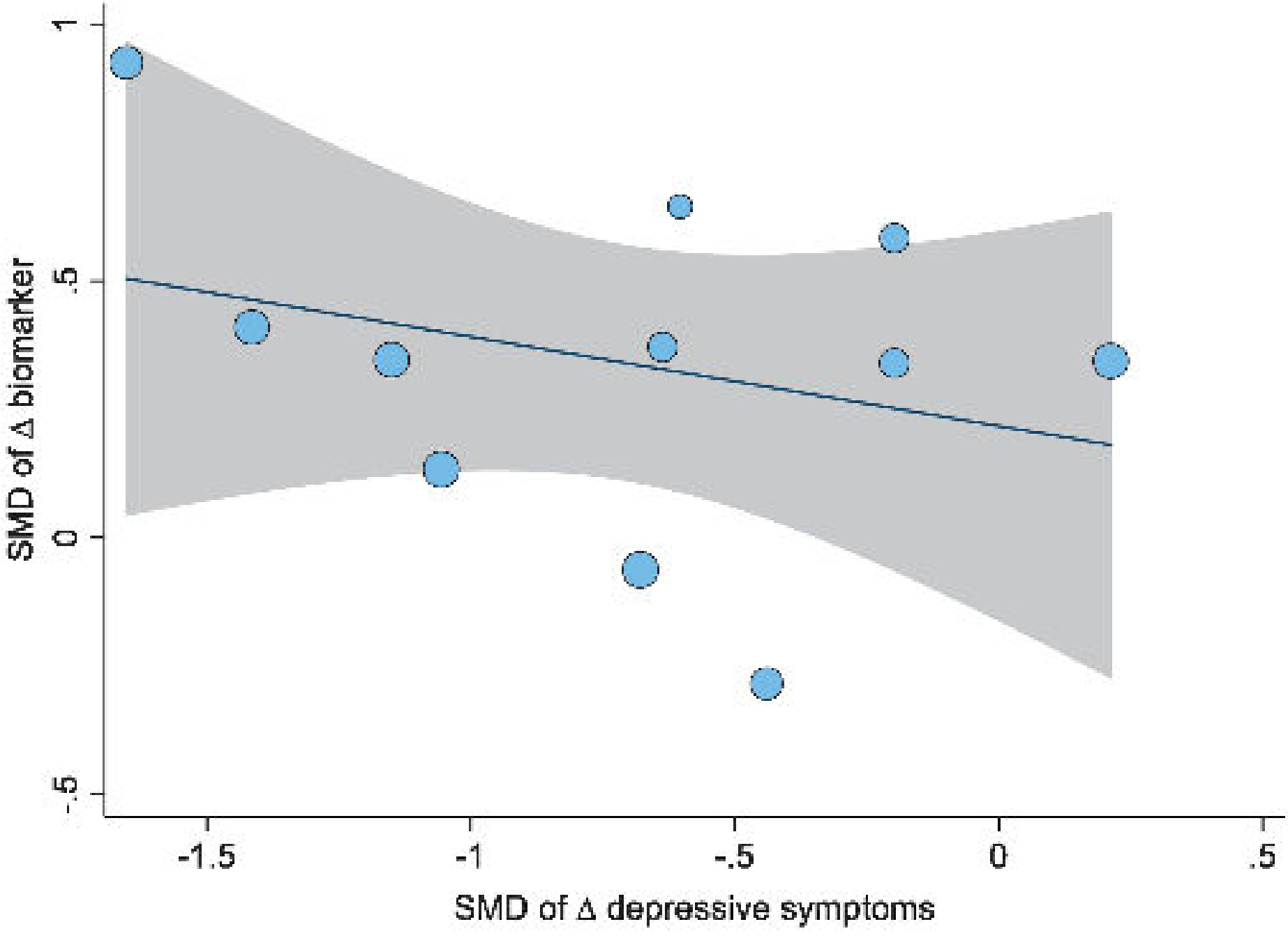

Figure 4

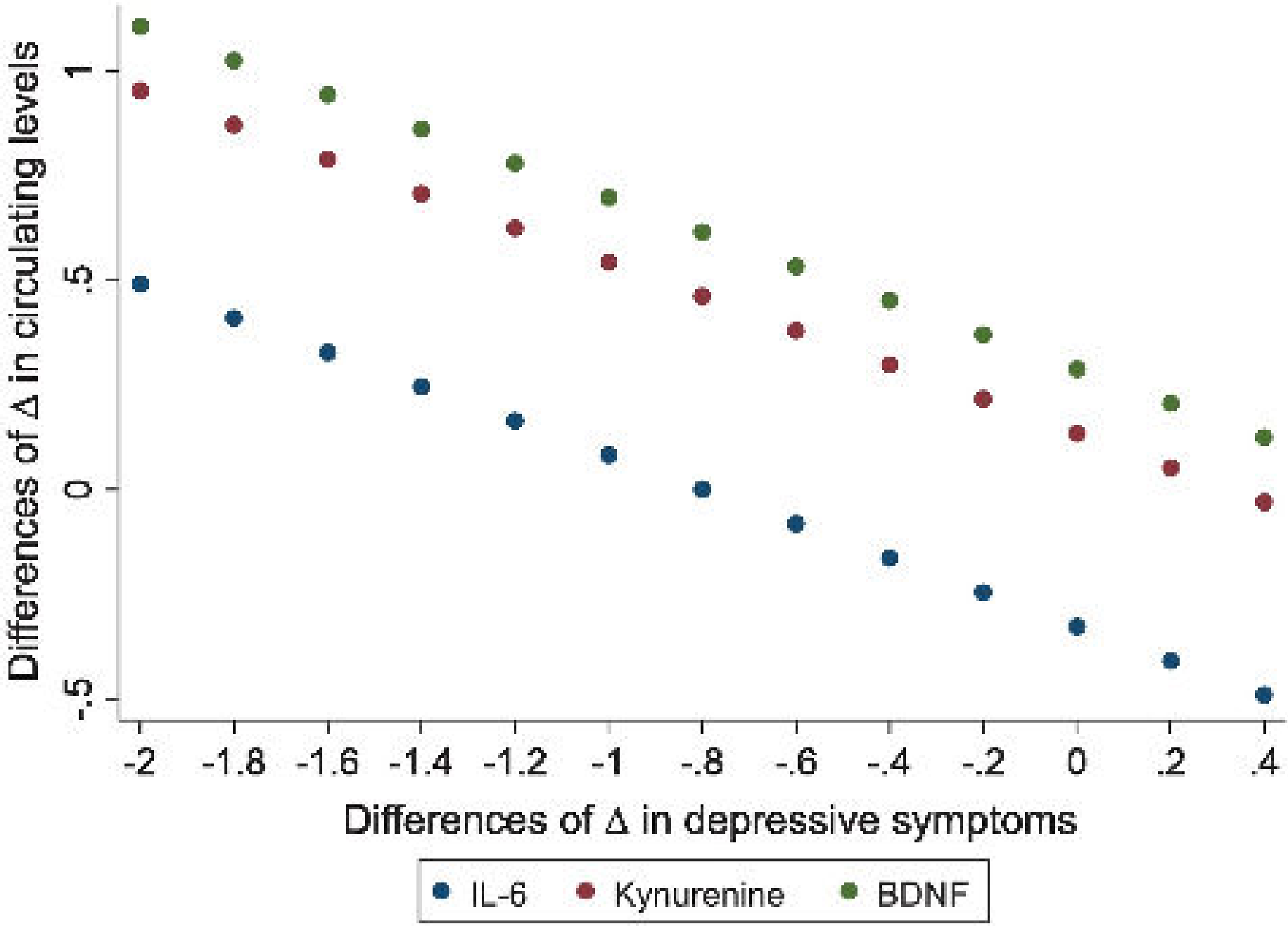
Differences of Δ in circulating levels
-.5
0
.5
1
-2
-1.8
-1.6
-1.4
-1.2
-1
-.8
-.6
-.4
-.2
0
.2
.4
Differences of Δ in depressive symptoms
IL-6
Kynurenine
BDNF

Figure 5