

Exercise as a complementary therapy for depression: a systematic review and meta-analysis of randomized controlled trials and bioinformatics exploration gene network model .

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Research article

Keywords: Depression, exercise, pharmacological, treatment, dose-response

Posted Date: June 10th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-24600/v1>

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Abstract

Background The effect of pharmacological treatment (PT), exercise treatment (ET), and both in depressive symptoms remains a matter of debate.

The present study aimed to clarify (1) the effect of ET as a monotherapy or complementary treatment of pharmacological therapy; (2) changes in the dose-response for different exercise prescription characteristics; and 3) hypothesizing about the gene network model of exercise effects on depression.

Methods We sought Randomized Controlled Trials (RCT) addressing the effects of exercise on depressive patients, published in peer-reviewed journals between 2003-2019 in Scopus, Cochrane, Pubmed/Medline, ISI Web of Knowledge and APA PsycNET databases. Standardized mean difference (SMD) was calculated considering the mean difference on depression scales (pre and post-intervention) and pooled standard deviation for each intention-to-treat in each study. For the gene network model of exercise on depression an *in silico* analyses were used.

Results We found 1,165 articles and selected 15 studies to this meta-analysis. RCTs with different ET and PT prescriptions were examined using the delta (pre and post-intervention) of a validated depression scale compared to the control group in different treatment conditions.

Standardized mean differences and confidence intervals (SMD, 95% CI) were found for ET with or without PT group (-0.45, -0.62 to -0.29), ET and PT group (-0.70, -1.00 to -0.40), and only ET group (-0.39, -0.57 to -0.21). The subgroup analyses showed a moderate and large SMD in favour of resistance training (-0.67, -1.22 to -0.12), aerobic exercise 60-80% of maximum heart rate intensity (-0.56, -0.89 to -0.23), 20 to 30 minutes (-0.59, -0.88 to -0.31) or 45 to 60 minutes (-0.55, -0.81 to -0.29) duration per session, and seven times per week (-0.75, -1.30 to -0.20).

Conclusion ET plus PT showed a better effect on reducing depressive symptoms, and the exercise prescription that shows the best dose-response in subgroup analyses can be the target for ET in depression. Also, the genes network model can withstand the effect of exercise in the depressive symptoms decrease according to an interaction between BDNF and inflammation. More well-designed studies are needed to confirm our findings.

Highlights

- Exercise is an effective coadjuvant therapy for depression.
- Long exercise protocols seem more effective than adherence and benefit elderly the most.
- Gene network model showed biomarkers modulated by exercise.

1. Background

Major depressive disorder (MDD) is a worldwide mental health concern leading to severe morbidity and increased mortality risk [1]. Patients with depression have a twentyfold greater risk of suicide compared to the general population [2]. Several countries have conducted epidemiological surveys, and the high prevalence and persistence of MDD confirm that this is a worldwide disorder of utmost importance [3]. The years lived with disability (YLDs) per 1000 people with depression disease are more than five times higher than the existing global mean burden of disease estimates [4].

Regardless of the research growth during the last decade, no major advances have occurred in the treatment of depression [5]. Although pharmacological therapy (PT) is the current gold standard for the treatment of depression, this treatment may need a combination of therapies such as antidepressants, antipsychotics, electroconvulsive therapy and psychotherapy [6]. Thus, more investment is required to search for effective adjuvant therapies to enhance the treatment of depressive disorders. In recent years, systematic reviews and meta-analyses evidenced that physical activity and exercise have been improving depressive symptoms and benefit physical and mental health. Therefore, clinical guidelines have included exercise as a possible first-line intervention to the treatment of depressive symptoms [7].

Current reviews have been showing different methodologies and results when investigating the evidence that exercise treatment (ET) has a beneficial effect on reducing depressive symptoms [8-10]. Ekkekakis [11] suggests a carefully scrutiny on several grounds in these design-studies, hence aiming to eliminate these biases. Due to the potential inappropriate selection criteria applied, results could lead to misleading interpretations. Other reviews were published to set a consensual exercise prescription and recommend essential variables in the treatment of patients with depression [12-14].

Although these reviews have been helpful, there is an incomplete understanding of the effect of ET with and without PT in the depression treatment. While the impact of exercise interventions among subjects with depression has been explored, the optimal dose that might prove useful remains non-consensual. Also, studies with bioinformatics analyses [15] in an attempt to elucidate gene network models and

biomarkers involved in the depression treatment with exercise are still lacking. Hypothetically, this analysis could be a reliable and straightforward form to study how exercise could decrease depressive symptoms. Different from the traditional published meta-analyses, the current study was structured with a robust methodological criterion to select and analyse the effect of ET with or without PT and bioinformatics data in depressive symptoms and exercise. Therefore, the current study intended to elucidate (1) the effect of ET with and without PT for depression; (2) changes in the dose-response of different exercise prescriptions, intervention and control group characteristics, and 3) a hypothesis about the gene network model *in silico* analyses to clarify how exercise could reduce depressive symptoms.

2. Methods

The registration of this systematic review and meta-analysis has been approved in the International Prospective Register of Systematic Reviews (PROSPERO) with the protocol number CRD42019122638. We followed the PICOS strategy [16] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement [17]. The recommendations of the Cochrane Collaboration [18] were used as a complementary guide.

2.1 Eligibility criteria

The acronym PICOS was primarily established to retrieve studies, as follow: depressive patients (P - participants), exercise (I - intervention), control group (C - comparison), depressive symptoms amelioration (O - outcome) and randomized controlled trials (RCTs) (S - study design).

2.1.1 Types of studies

RCTs conducted between 2003-2019 were selected, whether exercise was beneficial or not in the treatment of depression. To reduce the risk of bias, conference proceedings and unpublished studies were not used [19], and no restrictions on the language of the studies were applied.

2.1.2 Participants

Males and females aged 18 and over (with no upper age limit) with clinical depression as defined by the Diagnostic or Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria or other validated depression scale. Depression encompassing a co-morbid illness such as diabetes (insulin-dependent), cancer, multiple sclerosis, cardiovascular disease and mixed psychiatric diagnosis was not included.

2.1.3 Interventions

Intervention group had as ET aerobic or resistance training programs or a combination of both, in addition to PT, or not. In control group, we analysed interventions, such as pharmacotherapy, psychotherapy, another exercise program or no intervention (placebo or wait-list control). Considering exercise parameters, we included studies in accordance with the following data criteria: minutes per session, duration of intervention (week), frequency (days per week), adherence (percentage of finishers) and the amount of energy expended and measured in kilocalories per week (Kcal/week), or the percentage of maximum heart rate ($\%HR_{max}$), or the percentage of heart rate reserve ($\%HRR$), or the percentage of maximal oxygen uptake (VO_{2max}), or the percentage of maximal oxygen uptake reserve ($VO_{2reserve}$), or metabolic equivalent (METs).

2.1.4 Outcomes

Pre and post-intervention scores of validated depression-rating scales were analysed. Studies that measured outcomes immediately before and after a single exercise session were not included.

2.1.5 Information sources

We conducted searches on PubMed/MedLine, Scopus, ISI Web of Knowledge, Cochrane Trials and APA PsycNET databases. No filters were used to search any of the databases to conduct the broadest search and reduce the risk of bias [19].

2.1.6 Search

Medical Subject Headings (MeSH) and search-indexed descriptors were used to refine data search [20]. Three thematic word groups with MeSH terms were used to conduct the searches. Within each group, the terms were combined using the Boolean operator OR and interaction between sets using the operator AND to form a phrase. Searches were conducted in April 2019 using the following terms: ("depressive disorder" or "unipolar depression" or "major depressive disorder") AND ("exercise" or "exercise programs") AND ("clinical trial" or "randomized controlled trial").

2.1.7 Study selection and data collection process

Studies were screened and data independently extracted by two researchers. Another researcher was requested to confirm the eligibility of the identified studies. Identified studies were tabulated on a worksheet (Microsoft Corporation, Redmond, USA) to confirm if they met the eligibility criteria. All their titles and abstracts were screened and the full-text articles were assessed for potential inclusion by the main investigator. Studies were included in the qualitative synthesis after the exclusion of a comprehensive text review. We identified all studies that presented a high risk of bias for the finish –selection process and finally, we included all quality studies into a quantitative synthesis to perform the meta-analysis.

2.1.8 Appraisal of methodological quality

The quality of the selected studies was appraised using the Delphi-list [21]. We analysed randomized controlled trials (RCT) through: randomization, allocation concealment, baseline comparability, eligibility criteria, blinding, descriptive measures for the primary outcome and intention-to-treat analysis [22]. In this study, except double-blinding, which is not applicable within the framework of trials involving physical exercises, all these features were taken into account by the qualifying examination. Two researchers independently calculated an overall quality score of the Delphi items that scored positive and discussed them to achieve consensus. Studies selected did exhibit weaknesses concerning some criteria and these deficiencies were taken into consideration and explained in the results and discussion sections.

2.2 Data selection

We selected the following characteristics in all studies: 1) total number and age of each group; 2) depression-rating scales used to the diagnosis; 3) type of intervention and other exercise parameters mentioned in the section 2.1.3; 4) pre (M1) and post (M2) intervention depression-rating scales scores (n, means and standard deviation) to calculate the effect size (ES) of intervention and control groups. The mean difference (MD = M2-M1) and the pooled standard deviation ($SD_{pooled} = \sqrt{(SD_{M2}^2 (n_{M2}-1) + SD_{M1}^2 (n_{M1}-1)) / (n_{M2} + n_{M1} - 2)}$) of each group in all studies were calculated to ES analyses [23]. Regarding pre-selected articles that did not present the necessary data in the text, values were requested to the authors by e-mail.

2.3 Risk of bias

The risk of bias was assessed using qualitative analysis for each included study, and each risk of bias item presented on the Delphi-list. This scale provides a quality assessment of RCT studies, and the high quality is defined as achieving over 50% of the maximum attainable score, meaning five or more criteria met on the Delphi-list [21]. To analyse the risk of publication bias, we used funnel plot visual inspection. The risk among studies was assessed using the results of heterogeneity within the forest plot. Heterogeneity was measured using the T^2 , X^2 , and I^2 tests. In the T^2 test, $T^2 > 1$ suggests the presence of substantial statistical heterogeneity. If the X^2 value is statistically significant ($p < 0.05$), there is also evidence of heterogeneity. In the I^2 test analysis, the percentage of the variance attributed to the heterogeneity of the study ranges from low ($25\% < I^2 < 50\%$) to moderate ($50\% < I^2 < 75\%$) to high ($I^2 > 75\%$) [19].

2.4 Summary measures

Analyses were performed considering two different groups, experimental and control. The main analysis was related to the additional effect of ET with or without PT for depression. Also, we included the effect of subgroup analyses among different exercise prescriptions, intervention, and control group characteristics encompassed in the selected studies. Control group data were replicated and compared with the different intervention groups in their studies to comparison analysis in this meta-analysis. For multiple comparison groups in the same study, control group had the sample divided based on the number of groups that existed for comparison [24]. This was to maintain control group correct sample size and allocate the right weight to groups with more subjects.

Standardized mean difference (SMD) was calculated considering the mean difference on depression scales (pre and post-intervention) and pooled standard deviation for each intention-to-treat in each study. This outcome was reported on different validated scales. Consequently, the SMD in this review was calculated based on the random-effect model with 95% confidence intervals (CI: 95%), including the assumption of heterogeneity of the studies and their participants. Analyses of forest and funnel plots were performed using the Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

2.5 The Gene Network Model *in silico* analyses

The GeneCards database (<https://www.genecards.org>) was used to explore proteins-related genes associated with exercise and depression.

Keywords “exercise” OR “physical activity” AND “major depression” were inserted into database to identify genes associated with the subject. GeneCards organizes genes search according to a qualitative score. A score above 10 is acceptable to indicate the gene is known to be

functional (see <https://www.genecards.org/Guide/GeneCard>). To increase the power of the analysis, genes with score 30 or above were retrieved from GeneCards as follows: interleukin 6 (IL-6, score 42.60), tumour necrosis factor (TNF, score 42.44), solute carrier family 6 member 4 (SLC6A4, score 40.72), 5-hydroxytryptamine receptor 2A (HTR2A, score 37.06), tryptophan hydroxylase 2 (TPH2, score 36.12), insulin (INS, score 35.63), brain-derived neurotrophic factor (BDNF, score 32.05) and apolipoprotein E (APOE, score 30.53). Genes aforementioned were inserted into the String database (<https://string-db.org>), which permits exploring genes and their encoded protein interactions as a network. String uses data mining to find published articles which have investigated direct or indirectly targeted protein interactions in different species. According to the interactions found, we can suppose that exercise could result similar interactions, independently of the results from meta-analysis. Our interaction exploration was performed considering *Homo Sapiens* as the studied specie.

3. Results

3.1 Study selection and characteristics

A total of 1,165 articles was found (PubMed = 235; Cochrane = 334; Scopus = 438; ISI Web of Knowledge = 133; APA PsycNET = 25). After applying the exclusion criteria for eligibility, a total of 17 studies were subjected to a qualitative analysis. After this, 15 studies were included, and two studies were excluded from the meta-analysis. Figure 1 shows the screening flow used in the study selection.

This review shows 17 studies selected that met the quality assessment score based on the Delphi-list (Table 1). Regarding the RCT studies evaluated, scores ranged between 3 and 7 points (mean = 5.5 points). Two studies [25, 26] scored 3, indicating unsatisfactory quality, and therefore, were excluded.

Table 1 - Evaluation of the methodological quality of the RCT studies by the Delphi-list.

Randomized Clinical Trials	Was a method of randomization performed?	Was the treatment allocation concealed?	Were the groups similar at baseline regarding the most important prognostic indicators?	Were the eligibility criteria specified?	Was the outcome assessor-blinded?	Was the care provider blinded?	Was the patient blinded?	Were point estimates and measures of variability presented for the primary outcome measures?	Did the analysis include an intention-to-treat analysis?	Quality score
Buschert, Prochazka [27]	Y	Y	N	Y	?	?	?	Y	Y	5
Carneiro, Fonseca [28]	Y	Y	Y	Y	N	N	N	Y	Y	6
de la Cerda, Cervello [26]	N	N	N	Y	N	N	N	Y	Y	3#
Cheung and Lee [29]	Y	Y	Y	Y	Y	N	N	Y	Y	7
Dunn, Trivedi [30]	Y	Y	Y	Y	?	Y	N	Y	Y	7
Hallgren, Kraepelien [31]	Y	Y	?	Y	?	?	?	Y	Y	5
Hoffman, Blumenthal [32]	Y	?	?	Y	Y	Y	?	Y	Y	6
Kerling, Tegtbur [33]	Y	Y	Y	Y	?	?	?	Y	Y	6
Knubben, Reischies [34]	Y	Y	?	Y	?	?	N	Y	Y	5
Krogh, Videbech [35]	Y	Y	?	Y	Y	Y	?	Y	Y	7
Legrand and Neff [36]	Y	Y	Y	Y	?	?	?	Y	Y	6
Belvederi Murri, Amore [37]	Y	Y	?	Y	?	?	?	Y	Y	5
Olson, Brush [38]	Y	Y	Y	Y	?	?	?	Y	Y	6
Roy, Govindan [39]	Y	N	Y	Y	N	N	N	Y	Y	5
Schuch, Vasconcelos-Moreno [25]	Y	?	?	Y	?	?	?	N	Y	3#
Siqueira, Valiengo [40]	Y	Y	Y	Y	?	Y	?	Y	Y	7
Strom, Uckelstam [41]	Y	Y	?	Y	?	?	?	Y	Y	5

Y: yes; N: no; ?: Don't know; #: excluded

3.2 Summary of studies

The 15 studies included in the meta-analysis provided a total sample size of 1,532 individuals, with a mean age 44 years, which ranged from 21 to 75 years. The mean percentage of females' sample was 66.5% and varied between 30 and 100%. Investigations occurred in different countries, expanding different personal characteristics in the present study. Co-morbidities were not found among the participants. In all selected articles, interventions with aerobic, resistance training, or a combination of both, and validated depression-scales were used, and other characteristics of the studies are described in Table 2.

Table 2 - Characteristics of selected studies.

RCT study	Groups	N	Sex, F %	Age, years	Main outcome	Pre-intervention outcome	Post-intervention outcome	Intervention	Minutes per session	Time of intervention, week	Frequency, day/week	Intensity	Adherence
Buschert, Prochazka [27]	Control group	15	66.67	47.47 (8.47)	HDRS-7	9.67 ± 4.21	6.44 ± 3.43	TAU + occupational or art therapy	30	3 to 4	2 to 3	not reported	not reported
	Intervention group	15	60	47.27 (6.84)	HDRS-7	11.00 ± 3.42	7.20 ± 3.88	Endurance training	30	3 to 4	2 to 3	> 85% HRmax	not reported
Carneiro, Fonseca [28]	Control group	10	not reported	47.80 (15.05)	BDI-II	46.10 ± 11.52	49.40 ± 16.72	TAU	-	-	-	-	not reported
	Intervention group	9	not reported	52.78 (7.66)	BDI-II	45.56 ± 9.65	34.89 ± 10.56	Warm-up, aerobics and cool-down.	45-50	16	3	Average number of 4 months was 65%, 73%, 74% and 76% HRmax, respectively	not reported
Cheung and Lee [29]	Control group	17	70.6	48.1 (10.8)	HDRS-17	19.40 ± 3.60	14.50 ± 5.30	TAU	-	-	-	-	not reported
	Intervention group	17	88.2	47.4 (11.2)	HDRS-17	18.5 ± 3.20	9.80 ± 5.60	TAU + 1x/week aerobic session under supervision; at least 2x/week aerobic session home training	60	12	3x/w at least	> 60% HRmax	52%, 82.2%, and 38.9%
Dunn, Trivedi [30]	Control group	13	62	34.5 (7.3)	HDRS-17	20.50 ± 2.40	14.00 ± 4.90	Stretching exercise	15 to 20	12	3	not reported	42%
	Intervention LD/3 group	16	81	35.8 (6.1)	HDRS-17	19.30 ± 2.60	11.70 ± 5.80	Aerobic LD, 3 days per week	> 20	12	3	7 kcal/kg/week, low dose	78%
	Intervention LD/5 group	18	72	37.7 (5.1)	HDRS-17	19.20 ± 2.30	12.80 ± 5.00	Aerobic LD, 5 days per week	> 20	12	5	7 kcal/kg/week, low dose	78%
	Intervention PHD/3 group	17	76	33.2 (6.7)	HDRS-17	19.10 ± 1.80	9.00 ± 3.60	Aerobic PHD, 3 days per week	> 20	12	3	17.5 kcal/kg/week; public health dose	65%
	Intervention PHD/5 group	16	81	37.9(6.3)	HDRS-17	19.10 ± 2.20	10.00 ± 5.50	Aerobic PHD, 5 days per week	> 20	12	5	17.5 kcal/kg/week; public health dose	65%
Hallgren, Kraepelien [31]	Control group	232	not reported to each group	not reported to each group	MADRS	20.90 ± 7.50	13.80 ± 8.90	TAU and counselling with a CBT	not reported	12	not reported	not reported	30%
	Exercise intervention group	249	not reported to each group	not reported to each group	MADRS	22.20 ± 6.80	11.30 ± 7.90	Randomized with three conditions: yoga, or aerobics, or aerobics + strength + balance class	60	12	3	light, moderate, and vigorous exercise	33%
Hoffman, Blumenthal [32]	Placebo	49	77.5	51.2 (7.8)	HDRS-17	17.20 ± 4.30	11.00 ± 7.00	Placebo pill	-	-	-	-	86%
	Supervised exercise	51	76.5	51.0 (7.0)	HDRS-17	16.40 ± 3.70	9.20 ± 6.10	Aerobic exercise (treadmill)	not reported	16	3	70 - 85% of their HRR	60.6%
	Home-based	53	73.6	52.8 (7.7)	HDRS-17	17.30 ± 4.60	10.20 ± 6.70	Aerobic exercise	not reported	16	3	70 - 85% of their HRR	60.6%

	exercise				(outside)								
Kerling, Tegtbur [33]	Control group	20	30	40.9 (11.9)	BDI-II and MADRS	28.30 ± 11.20; 24.50 ± 10.30	15.90 ± 12.50; 16.40 ± 9.40	TAU + CBT + workout supervised in the morning	20	6	7	light	not reported
	Intervention group	22	45	44.2 (8.5)	BDI-II and MADRS	29.40 ± 10.90; 23.50 ± 8.70	13.40 ± 13.20; 11.80 ± 10.40	CBT + Aerobic workout	45	6	3	moderate intensity with incremental exercise	90%
Knubben, Reischies [34]	Control group	18	55.55	50 (13)	CES-D	39.20 ± 8.50	31.80 ± 11.20	Low-intensity stretching	30	10 days	daily	not reported	not reported
	Intervention group	20	55.00	49 (13)	CES-D	37.60 ± 12.90	22.40 ± 10.00	Interval training on treadmill	30	10 days	daily	80% HRmax	not reported
Krogh, Videbech [35]	Control group	59	62.7	43.4 (11.2)	HDRS-17 and BDI-II	18.60 ± 4.00; 35.50 ± 8.40	10.50 ± 6.40; 21.20 ± 15.10	Social interaction and contact with health care professionals in an aerobic exercise group.	45	9	3	not reported	not reported
	Intervention group	56	71.4	39.7 (11.3)	HDRS-17 and BDI-II	19.20 ± 4.70; 35.70 ± 7.00	11.30 ± 6.60; 21.70 ± 13.90	Aerobic exercise on a stationary cycle ergometer	45	9	3	4 week 65% HRR at least, progressing to 70% and 80% in 3 and 4 months	66%
Legrand and Neff [36]	Control group	10	70	49.1 (16.5)	BDI-II	35.70 ± 6.70	29.70 ± 12.30	TAU	-	-	-	-	not reported
	Aerobic group	14	64.3	45.3 (10.6)	BDI-II	36.10 ± 5.90	18.50 ± 6.0	Daily brisk walking or jogging	30	10 days	daily	65-75% HRmax	80%
Belvederi Murri, Amore [37]	Control group	42	76	75.6 (5.6)	HDRS-17	20.40 ± 3.40	11.70 ± 5.90	TAU	-	-	-	-	26%
	Sertraline plus non-progressive activity group	37	68	75.0 (6.3)	HDRS-17	20.10 ± 3.20	8.50 ± 4.50	TAU + Strength, balance, respiration and motor coordination	60	24	3	70% HRmax non-progressive intensity	70%
	Sertraline plus progressive activity group	42	69	75.0 (6.2)	HDRS-17	19.80 ± 2.60	7.10 ± 4.20	TAU + Warm-up, cycling, and cool-down	60	24	3	Start with 60% HRmax for progressive intensity	70%
Olson, Brush [38]	Control group	15	not reported to each group	21.2 (2.2)	BDI-II	24.30 ± 11.90	20.00 ± 12.00	Stretching targeting major muscle groups	30-45	8	3	not reported	not reported
	Intervention group	15	not reported to each group	21.0 (1.9)	BDI-II	24.50 ± 11.50	10.00 ± 10.00	Aerobic continuous steady-state exercise	45	8	3	40-65% of HRR	not reported
Roy, Govindan [39]	Control group	20	100	32.9 (8.53)	HDRS-17	16.55 ± 4.14	13.85 ± 3.16	TAU	-	-	-	-	100%
	Intervention group	20	100	31.1 (8.88)	HDRS-17	19.30 ± 4.83	15.00 ± 4.93	Video Assisted Structured Aerobic Exercise Program	20	10 days	daily	moderate to low intensity	100%
Siqueira, Valiengo [40]	Control group	28	71	37.86 (9.85)	HDRS-17 and BDI	20.42 ± 2.99; 33.92 ± 9.64	12.64 ± 5.74; 20.50 ± 10.21	TAU	-	-	-	-	not reported

Exercise intervention	29	72.4	39.76 (11.60)	HDRS-17 and BDI	19.21 ± 3.14; 29.51 ± 9.46	11.38 ± 3.94; 18.39 ± 9.00	Continuous and intermittent aerobic activity	not reported	4	4	Initially set up at 60% of VO _{2max} and progressively increased up to 85% of VO _{2max} by the endpoint.	<90%	
Strom, Uckelstam [41]	Control group	24	83.3	49.6 (8.7)	MADRS and BDI-II	23.92 ± 3.87; 28.25 ± 7.08	20.38 ± 7.87; 24.04 ± 6.86	Wait list	-	-	-	-	
	Intervention group	24	83.3	48.8 (12.7)	MADRS and BDI-II	23.54 ± 4.39; 26.92 ± 9.30	15.71 ± 7.54; 17.88 ± 11.30	Aerobic self-help program administered through an Internet-based system.	not reported	9	3	not reported	not reported

Abbreviations:

N = Total number of participants included in the study. Age = mean (standard deviation). Sex, F% = female percentual in the sample.

Main outcome: MADRS = Montgomery-Asberg Depression Rating Scale. BDI = Beck Depression Inventory. CES-D = Centre for Epidemiologic Studies Depression Scale. HDRS = Hamilton Depression Rating Scale.

Intervention: TAU = Usual care. CBT = Cognitive behaviour therapy. LD = Low dose. PHD = Public health dose.

Intensity: HRmax = Maximum heart rate. HRR = Heart rate reserve. Kcal/kg/week = Energy expended and measured in kilocalories per week. VO_{2max} = Maximal oxygen consumption.

Adherence: percentage of finishers.

3.3 Standardized mean difference (SMD)

One study [30] presented four different intervention groups relative to the intensity and volume of exercise prescribed, which were included separately in the comparisons; two studies [32, 37], which showed two different intervention groups associated with the presence of supervision or not and to the type of exercise, have also been included separately to ES analyses. SMD analyses in studies with more than one intervention group had the number of participants in the control group divided by the number of groups that existed for comparison in these studies. However, twelve studies [27-29, 31, 33-36, 38-41] showed just one intervention group to compare. To interpret SMD we used the scale suggested by Cohen [23]: > 0.30 small; > 0.50 moderate; > 0.80 large.

3.3.1 Main analyses

The forest plot of different treatments for depression in Figure 2 shows the global data with a small ES (SMD = -0.45, CI95% = -0.62 to -0.29, P < 0.00001; T² = 0.04, X² = 0.08, I² = 33%), and two subgroup analyses: exercise and pharmacological treatment (SMD = -0.70 [moderate], CI95% = -1.00 to -0.40, P < 0.00001; T² = 0.00, X² = 0.41, I² = 0%), and only exercise treatment (SMD = -0.39 [small], CI95% = -0.57 to -0.21, P < 0.0001; T² = 0.04, X² = 0.11, I² = 31%). The overall and subgroup analyses in different treatments for depression (ET and PT or only ET) have not shown heterogeneity among studies, with a trivial percentage of the variance. A visual analysis of the funnel plot in Figure 2 shows a symmetrical plot in the absence of publication bias.

3.3.2 Subgroup analyses

Forest and funnel plot of different characteristic analyses are displayed in the supplementary data, and Table 3 presents all of the subgroup SMD analyses with heterogeneity.

Global data in each feature of the selected studies showed: a small ES on exercise type (SMD = -0.45, CI95% = -0.59 to -0.31, P < 0.00001; T² = 0.02, X² = 0.10, I² = 30%), and methods for intensity control (SMD = -0.42, CI95% = -0.63 to -0.22, P < 0.0001; T² = 0.05, X² = 0.10, I² = 33%), exercise frequency per week (SMD = -0.45, CI95% = -0.62 to -0.29, P < 0.00001; T² = 0.04, X² = 0.08, I² = 33%), intervention time (SMD = -0.47, CI95% = -0.64 to -0.30, P < 0.00001; T² = 0.04, X² = 0.07, I² = 35%), intervention adherence (SMD = -0.41, CI95% = -0.61 to -0.22, P < 0.0001; T² = 0.05, X² = 0.05, I² = 41%), age-range intervention (SMD = -0.46, CI95% = -0.65 to -0.27, P < 0.00001; T² = 0.06, X² = 0.06, I² = 35%), control group characteristics (SMD = -0.39, CI95% = -0.59 to -0.21, P < 0.0001; T² = 0.04, X² = 0.11, I² = 31%), and a moderate ES on exercise duration per session (SMD = -0.56, CI95% = -0.74 to -0.37, P < 0.00001; T² = 0.04, X² = 0.10, I² = 32%). The overall analysis in different characteristics on the treatment for depression has not exhibited heterogeneity among studies, except on the intervention adherence. A visual analysis of the

funnel plot in supplementary data did not show an asymmetrical plot, and also studies outside the pseudo-cone (CI 95%), proving the absence of publication bias.

Table 3 shows that in favour of ET, with or without PT, the subgroup analysis on the treatment for depression has displayed : a small ES for two and three sessions ($p < 0.00001$), intervention time between one to nine weeks ($p = 0.006$), 50 to 70% of intervention adherence ($p = 0.0002$), different age-range groups intervention at 30 to 60 years old ($p = 0.002$) and 20 to 50 years old ($p = 0.02$), when compared to an active control group with stretching and light exercise ($p = 0.03$); a moderate ES on resistance training ($p = 0.02$), moderate exercise intensity (60 to 80%) controlled by MHR ($p = 0.0008$), different exercise duration per session at 45 to 60 min ($p < 0.0001$) and 20 to 30 min ($p < 0.0001$), intervention time for more than 20 weeks ($p < 0.00001$), when compared to a control group with usual treatment use ($p = 0.0007$); a large ES for seven sessions ($p = 0.008$), and intervention with people aged 60 years or more ($p < 0.0001$). The heterogeneity between studies in subgroup analysis was not exhibited, except on the moderate intensity exercise (60 to 80%), exercise duration time for 45 to 60 min, intervention time between one to nine weeks, and intervention adherence between 50 to 70%.

Table 3 - Subgroup meta-analysis.

Subgroups	Number of RCTs	Meta-analysis			Heterogeneity		
		SMD [effect size]	95% CI	P-value	T ² (> 1)	X ² (< 0.05)	I ² (%)
Exercise type							
Aerobic training	15	-0.44 [small]	-0.61, -0.27	< 0.00001	0.004	0.07	35%
Resistance training	1	-0.67 [moderate]	-1.22, -0.12	0.02	NA	NA	NA
Aerobic and resistance training	1	-0.49 [small]	-0.67, -0.31	< 0.00001	NA	NA	NA
Methods for intensity control							
60 to 80% of HRmax	8	-0.56 [moderate]	-0.89, -0.23	0.0008	0.12	0.03	54%
40 to 85% HRR	2	-0.31 [small]	-0.68, -0.06	0.10	0.03	0.25	28%
Kcal / kg / week	1	-0.48 [small]	-1.10, 0.15	0.14	0.00	0.59	0%
60 to 85% of VO ₂ max	1	-0.01 [trivial]	-0.53, 0.51	0.96	NA	NA	NA
Exercise duration per session							
45 to 60 minutes	7	-0.55 [moderate]	-0.81, -0.29	< 0.0001	0.07	0.03	54%
20 to 30 minutes	6	-0.59 [moderate]	-0.88, -0.31	< 0.0001	0.00	0.45	0%
Exercise frequency per week							
2 and 3 sessions	11	-0.45 [small]	-0.63, -0.27	< 0.00001	0.04	0.10	35%
4 and 5 sessions	2	-0.08 [trivial];	-0.53, 0.36	0.72	0.00	0.69	0%
7 sessions	3	-0.75 [large]	-1.30, -0.20	0.008	0.10	0.17	43%
Intervention time							
1 to 9 weeks	8	-0.42 [small]	-0.73, -0.12	0.006	0.10	0.04	52%
20 weeks or more	6	-0.51 [moderate]	-0.68, -0.34	< 0.00001	0.01	0.35	10%
Intervention adherence							
50 to 70%	6	-0.45 [small]	-0.68, -0.21	0.0002	0.06	0.04	50%
> 70%	5	-0.35 [small]	-0.72, 0.03	0.07	0.07	0.20	31%
Intervention on age-range							
> 60 years old	1	-0.83 [large]	-1.22, -0.44	< 0.0001	0.00	0.42	0%
30 to 60 years old	9	-0.41 [small]	-0.67, -0.16	0.002	0.07	0.06	44%
20 to 50 years old	4	-0.35 [small]	-0.66, -0.04	0.02	0.00	0.48	0%
Control group characteristics							
Wait list	2	-0.26 [trivial]	-0.78, 0.26	0.32	0.06	0.18	43%
Placebo pill	1	-0.17 [trivial]	-0.51, 0.17	0.32	0.00	0.93	0%
Stretching and light exercise	4	-0.42 [small]	-0.81, -0.04	0.03	0.09	0.17	34%
Usual treatment	5	-0.56 [moderate]	-0.89, -0.24	0.0007	0.05	0.18	37%

HRmax = Maximum heart rate; HRR = Heart rate reserve; Kcal / kg / week = Energy expended and measured in kilocalories per week; VO₂max = Maximal oxygen consumption; RCTs = Randomized clinical trials; SMD = Standard mean deviation; 95% CI = confidence interval; Heterogeneity: T² = Tau > 1; X² = Chi-value (p < 0.05); I² = percentage of the variance; NA = Not applied, heterogeneity analyses with one subgroup selected;

3.4 The gene network model in *silico* analyses

Specific and non-specific (unknown) significant interactions (PPI Enrichment p-value <0.01) [15] among all genes were found in the network (Figure 4). Interactions were explored when specified edges were clearly shown, and the combined score reached 0.4 or above, determined as medium confidence (see String Statistics Section on <https://string-db.org>). Two genes (TPH2 and SLC6A4) have not met the criteria above and were excluded from the analysis. Therefore, the following genes remained significant (PPI Enrichment p-value <0.03) in the model: BDNF, HTR2A, APOE, IL6, INS, and TNF (Figure 5). The combined score of each interaction is shown in Table 4.

Table 4 - Specified interactions and confidence score of the gene network model

Interaction	Type of interaction	Direction of interaction	Combined score
HTR2A / BDNF	Unknown transcriptional regulation	Unidirectional	0.80
APOE / BDNF	Unknow transcriptional negative regulation	Unidirectional	0.81
IL-6 / BDNF	Unknown transcriptional regulation	Unidirectional	0.81
TNF / BDNF	Unknown transcriptional negative regulation	Unidirectional	0.80
IL-6 / APOE	Reaction and catalysis	Bidirectional	0.96
INS / IL-6	Unknown transcriptional regulation	Bidirectional	0.94
TNF / IL-6	Negative regulation and inhibition	Unidirectional	0.98
APOE / INS	Binding	Unidirectional	0.84

4. Discussion

This study aimed to review the effect of additional ET, with or without PT, on the depression treatment. Moreover, its objective was to investigate subgroups in the selected studies to compare different exercise prescription, intervention, and control group characteristics, which could influence ET response. Finally, explore the hypothesis about the gene network model *in silico* analyses to explain how exercise could reduce depressive symptoms. After these analyses, results presented a moderate SMD on the additional effect of ET on PT for depression. Subgroup analyses showed that the moderate intensity, in 20 to 60-minute sessions preferably every day, could be the ideal exercise prescription in depressive treatment. Interventions prescribed 20 weeks or more with 50 to 70% of adherence may show a better result. When analysing based age-range studies, we found that ET can trigger a better result in older adults. Our gene network model also indicates that ET can be useful in decreasing depressive symptoms due to BDNF and inflammation interaction pathway, and regulation of HTR2A and APOE.

4.1 Meta-analysis evidence

This is the first review that confirms that exercise provides a vital add-on effect on PT for depression, according to the [Gourgouvelis, Yielder \[42\]](#) trial. It is not new that exercise training programs can be considered a treatment for depression and that PT is the gold-standard. However, antidepressants also promote a more rapid initial therapeutic response than exercise [\[43\]](#). Considering this, it is adequate that ET and PT working together show a better result in the depression treatment.

There are preferences and growing evidence for using aerobic exercise in moderate-intensity to treat depression, as recent systematic reviews have shown [\[8, 12, 14\]](#). Although, it is already clear that resistance training can produce a similar positive neurophysiological alteration by reducing depressive symptoms [\[44\]](#). Even though one study, our review showed that resistance training could be a good alternative for the treatment. Based on the overload principle of training (progression), the exercise under a minimum intensity or threshold will not induce sufficiently the body to result in important neurophysiological adaptations for depression treatment [\[45\]](#). In the initial program stage, a self-selected comfortable exercise intensity seems to be the better option to induce intrinsic exercise motivation and adherence [\[10\]](#). We sustain that exercise intensity should be pleasurable, but it should also be gradually increased to guarantee a minimum level required to induce a training effect. Despite the diversity of tools to assess prescribed intensity (i.e., HR_{max} , HRR, Kcal/kg/week, VO_{2max} , and the Borg scale), it is yet premature to provide recommendations concerning what is the better to control exercise intensity. In relation to the volume of prescribed exercise, other reviews [\[12-14\]](#) argue a reduced volume in the session duration and frequency when compared with our results. Utilizing the principle of progression again, we understand that the target in the volume prescription needs to follow our findings, which show a better response for both 20 to 30 min and 45 to 60 min every day. In the depression treatment, it does not matter if the patients are training for 20 or 60 minutes if they do it [\[46\]](#).

Regarding ET duration, past reviews reported positive outcomes after at least 8 or 9 weeks [\[12, 14\]](#). However, based on the chronic neurobiological effects of exercise in depression, a regular exercise intervention is critical for satisfactory treatment response [\[47\]](#). Corroborating that, our results show a better response for treatment of interventions equal to or more than 20 weeks. Intensity control contributes to the adherence in exercise intervention [\[10\]](#). Notwithstanding, in the study by [Callaghan, Khalil \[48\]](#), the preferred intensity group only showed 66% of adherence. As well, when we observed data from studies where the preferred intensity was not prescribed but showed a significant reduction in depressive symptomatology, three studies [\[49-51\]](#) presented high rates of adherence (80-100%). To our understanding, adherence rate is an essential factor for ET, although it resulted in a small effect in the present review. Adherence could be achieved not only by the most convenient intensity, but also with other strategies of intervention (e.g., knowledge of subjects' daily and leisure activities, exercise supervised and preferences about the context) [\[46\]](#).

It is essential to report that the effectiveness of pharmacological treatment in depression is not substantially affected by age [52]. According to a recent meta-analysis [53], exercise improves the response and can be considered as a routine tool in the management of depression in older adults. Nonetheless, Mura and Carta [54] have noticed the difficulty to establish the real effectiveness of exercise on depressive symptoms in elderly. However, the same author suggested that physical activity combined with antidepressants might be a beneficial strategy in treating late-life depression. The large ES showed in the older adult group in the current review can be related to the benefits that exercise promotes in other chronic diseases usually common in the elderly. Decreasing the symptoms of these comorbidities can result in a better socio-economic situation and positively impact on the quality of life of these depressive older adults [55].

Clinical trials that used an active control group, as well as usual treatment, must be carefully analysed because sometimes the results do not show reduced depressive symptoms when both groups are compared [11]. Researches [30, 56] with stretching or yoga and light exercise in an active control group showed a significant reduction in the depressive symptomatology. It is not surprising since a meta-analysis concluded that yoga was an effective adjunct treatment of major psychiatric disorders, particularly depression and anxiety [57]. However, most often, there are improvements when the differences between baseline and post-intervention in each group are assessed, as in our study. When an exercise group is compared to an active control group instead of a passive control group, the differences between the efficacy of exercise and active placebos are much less pronounced. It is expected that doing something is likely to induce higher expectations for improvements than doing nothing [58]. Corroborating our viewpoint, a meta-analysis that investigated the predictors in control groups of exercise RCTs among adults with depression demonstrated that control group responses could negatively influence antidepressant efficacy [59].

4.2 Bioinformatics analysis evidence

Interesting molecular interactions among genes related to BDNF, serotonin receptor (5HT2A), IL-6, INS, APOE, and TNF were identified in our protein-protein network model associated exercise. Literature has shown molecular interactions among these proteins in different conditions. BDNF and 5HT2A/2C agonists interact differently in the brain. While 5HT2A/2C agonists decrease BDNF on the hippocampus, they increase it dramatically in rats' neocortex and parietal cortex [60]. BDNF is also mediated by APOE isoforms. Sen, Nelson [61] demonstrated in a recent study that cultured human astrocytes responded differently when treated with APOE2, APOE3, and APOE4. BDNF was 19% overexpressed in the astrocytes treated with APOE2 and 3, while APOE 4 decreased it 21% on average. Regarding inflammatory markers, IL-6 and TNF are pro-inflammatory cytokines that influence cell insulin uptake, causing insulin resistance [62, 63]. IL-6 and TNF- α are overexpressed in psychiatric disorders [64]. Decreased BDNF, serotonin deficits, APOE4 overexpression, increased pro-inflammatory cytokines and insulin resistance were already investigated as biomarkers of depression [63-67]. Furthermore, depressive patients show an atrophied hippocampus [68], which may be affected by decreased BDNF and increased cortisol. However, all of these biomarkers are modulated by exercise. For instance, IL-6 is reduced in older adults who performed regular exercise (2-5 times, weekly) [69]. In addition, neurotransmitter synthesis and trophic factors secretion (e.g. BDNF) can improve serotonergic, noradrenergic and dopaminergic circuitry through exercise [47, 70]. Hence, results from our gene network model suggest a clinical modulation of depressive symptoms by protein interactions through exercise.

4.3 Limitations

This systematic review has some limitations that must be considered. We included studies only since 2003, and this might have reduced the extent of the search scope. Concerning the missing data, selected studies in this current review do not report some essential data. Therefore, measures should be taken to improve the methodological standard of these RCT studies. Concerning heterogeneity, the random-effect model results in broader confidence intervals around the point estimates. However, it is a more conservative choice for the analysis [18]. Future research studies should evaluate exercise prescription reported in trials according to the application of the principles of exercise training (specificity, progression, overload, reversibility, diminishing returns). Also, studies should evaluate feelings of autonomous motivation in subjects with depression, as they are associated with the adherence and response to the treatment.

5. Conclusion

This study corroborated the additional effect of ET on PT for depression. We found that a long program with regular exercise has more effect on the treatment-response than the adherence percentage, and that ET can benefit older adults than adults and adolescents. Finally, the gene network model analyses involving molecular interactions in depression treatment showed biomarkers modulated by exercise, but this needs to be further explored.

Abbreviations

(DSM-IV)	Diagnostic or Statistical Manual of Mental Disorders, Fourth Edition
%HR _{max}	Percentage of maximum heart rate

%HRR	Percentage of heart rate reserve
APOE	Apolipoprotein E
BDNF	Brain-derived neurotrophic factor
CI	Confidence intervals
ES	Effect size
ET	Exercise treatment
HTR2A	5-hydroxytryptamine receptor 2A
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10 th Revision
IL-6	Interleukin 6
INS	Insulin
Kcal/week	Kilocalories per week
M1	Pre
M2	Post
MDD	Major depressive disorder
MeSH	Medical Subject Headings
METs	Metabolic equivalent
PROSPERO	Prospective Register of Systematic Reviews
PT	Pharmacological treatment
RCT	Randomized Controlled Trials
RevMan	Review Manager
SD _{pooled}	Pooled standard deviation
SLC6A4	Solute carrier family 6 member 4
SMD	Standardized mean differences
TNF	Tumour necrosis factor
TPH2	Tryptophan hydroxylase 2
VO _{2max}	Percentage of maximal oxygen uptake
VO _{2reseve}	Percentage of maximal oxygen uptake reserve
YLDs	Years lived with disability

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Not applicable.

Availability of data and materials

Data access statements, also known as data availability statements, are used in publications to describe where the data directly underpinning the publication can be found and under what conditions they can be accessed.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work is financed by National Funds through FCT - Foundation for Science and Technology under the project UID04045 / 2020. The founders had no intervention in any part of the study.

Author's contributions

Conception & Design; LC, FS, MM, VR, RJ: Data analysis: LC, FS, HM, GA, RJ Interpretation of data; LC, FS, MM, MC, AD, HM, GA, RJ Draft and revising work LC, FS, MM; MC, AD, HM; GA, JR, RJ. ; All authors approved the final version.

Acknowledgments

Renato S. Monteiro-Junior thanks the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) for a Post-doctoral support.

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Figures

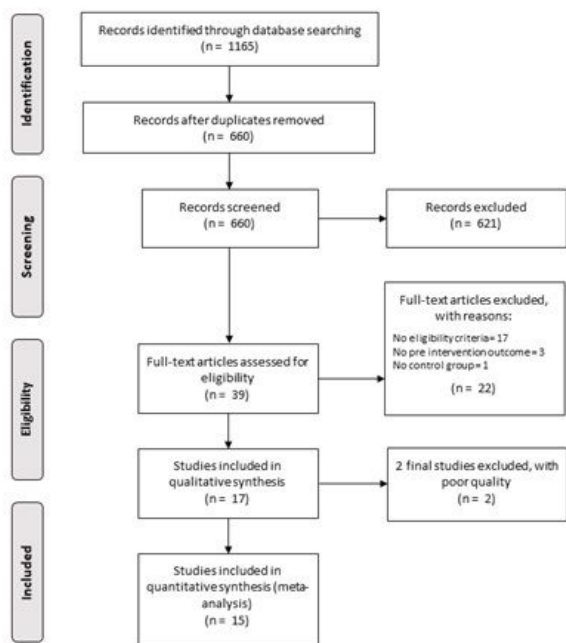


Figure 1

Flow-chart of the selected studies.

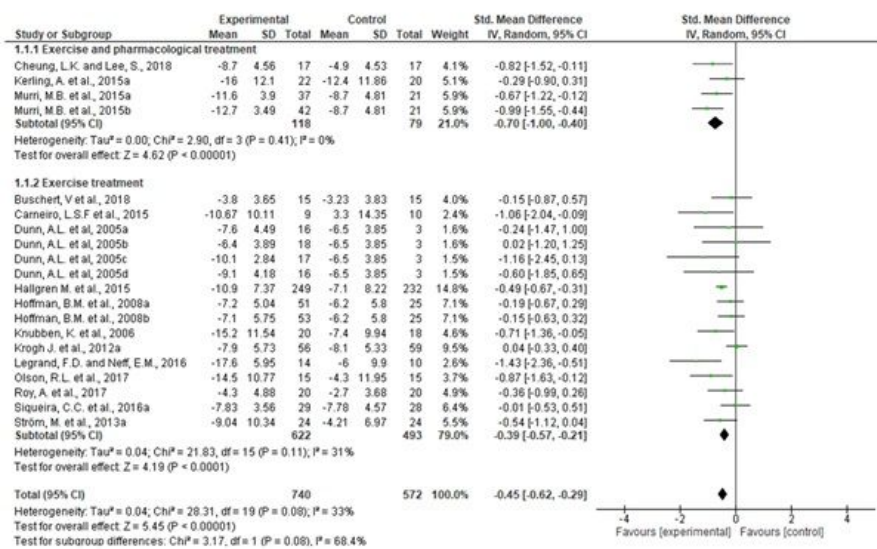


Figure 2

Forest plot.

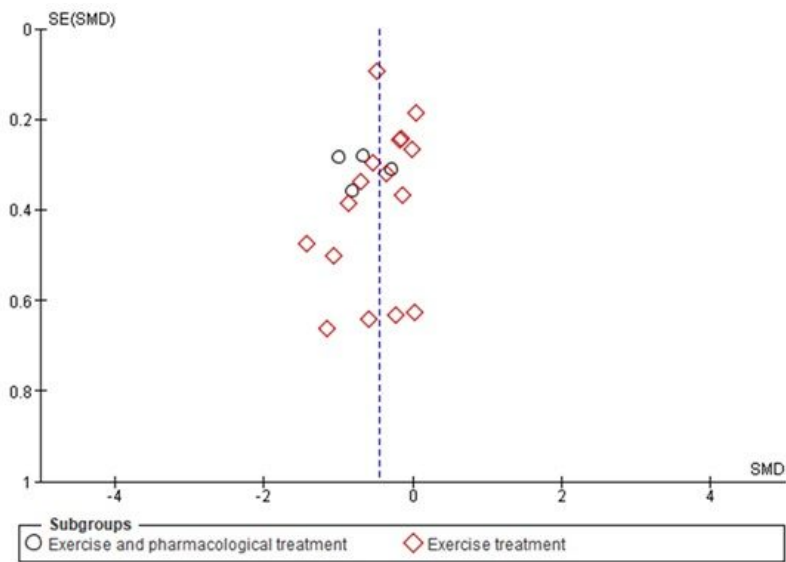


Figure 3

Funnel plot.

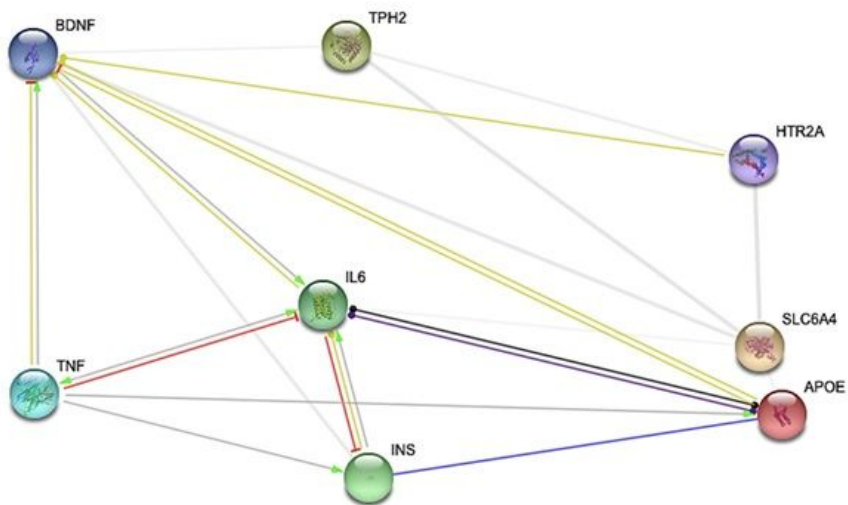


Figure 4

Full network genes interaction. Coloured lines (yellow, blue, red, purple, and black): known interactions; Grey lines: unknown interactions; Arrow: positive action; Dots: unspecified interaction; Dash: negative action.

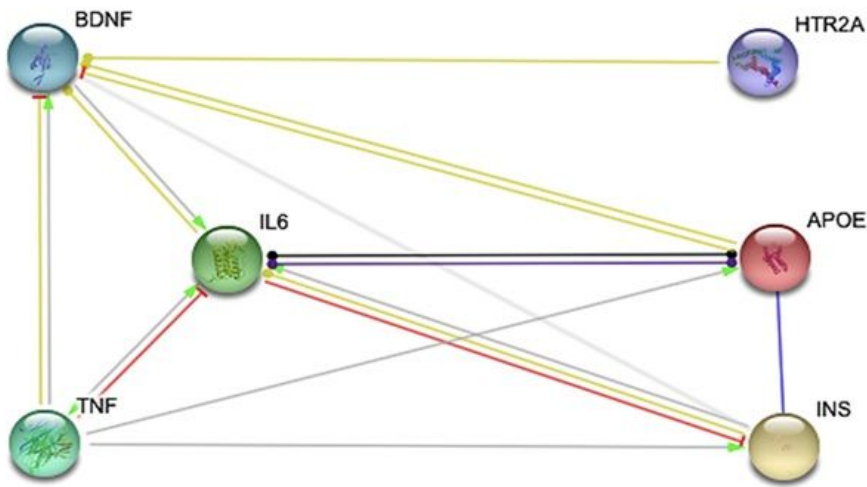


Figure 5

Clear network genes interaction. Yellow line: transcriptional regulation; Red line: inhibition; Black line: reaction; Purple line: catalysis; Blue line: binding; Grey lines: unknown interactions; Arrow: positive action; Dots: unspecified interaction; Dash: negative action.

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