**Exercise as medicine for mental and substance use disorders: a meta-review of the benefits for neuropsychiatric and cognitive outcomes**

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**Abstract**

**Background**

Exercise may improve neuropsychiatric and cognitive symptoms in people with mental disorders, but the totality of the evidence is unclear. We conducted a meta-review of exercise in (1) serious mental illness ( schizophrenia spectrum, bipolar disorder and major depression (MDD)); (2) anxiety and stress disorders; (3) alcohol and substance use disorders; (4) eating disorders (anorexia nervosa bulimia nervosa, binge eating disorders, and (5) other mental disorders (including ADHD, pre/post-natal depression).

**Methods**

Systematic searches of major databases from inception until 1/10/2018 were undertaken to identify meta-analyses of randomised control trials (RCTs) of exercise in people with clinically diagnosed mental disorders. In the absence of available meta-analyses for a mental disorder, we identified systematic reviews of exercise interventions in people with elevated mental health symptoms that included non-RCTs. Meta-analysis quality was assessed with the AMSTAR/+.

**Results**

Overall, we identified 27 systematic reviews (including 16 meta-analyses representing 152 RCTs). Among those with MDD, we found consistent evidence (meta-analyses=8) that exercise reduced depression in children, adults and older adults. Evidence also indicates that exercise was more effective than control conditions in reducing anxiety symptoms (meta-analyses=3), and as an adjunctive treatment for reducing positive and negative symptoms of schizophrenia (meta-analyses=2). Regarding neurocognitive effects, exercise improved global cognition in schizophrenia (meta-analyses=1), children with ADHD (meta-analyses=1), but not in MDD (meta-analyses=1). Among those with elevated symptoms, positive mental health benefits were observed for exercise in people with pre/post-natal depression, anorexia nervosa/bulimia nervosa, binge eating disorder, post-traumatic stress disorder and alcohol use disorders/substance use disorders. Adverse events were sparsely reported.

**Conclusion**

Our panoramic meta-overview suggests that exercise can be an effective adjunctive treatment for improving symptoms across a broad range of mental disorders.

**Key points:**

* Across 27 reviews of various conditions, it was found that exercise reduces depression in children, adults and older adults, and is more effective than control conditions for reducing anxiety symptoms and for reducing positive and negative symptoms of schizophrenia
* There is also encouraging evidence for exercise in bipolar disorder, eating disorders and ADHD
* Results are promising and can be used as impetus to implement exercise programming into clinical practice
1. **Introduction**

In the general population, robust evidence indicates that physical activity (PA; any bodily movement that increases energy expenditure[1]) contributes to healthy ageing [2], improves sleep [3,4], and preserves cognition across the lifespan [5-7]. Moreover, PA can positively influence neurogenesis in key areas of the brain [8-12]. For instance, longitudinal research [7,13] and randomised controlled trials (RCTs) [8,14] have demonstrated that PA can promote hippocampal neurogenesis in healthy and clinical populations. PA has also been positively associated with psychological wellbeing in children, adults and older adults [15-17]. Research has also demonstrated that PA can confer protection against the emergence of mental disorders. For example, higher levels of PA are consistently associated with a reduced risk of depression [18,19], anxiety and stress-related disorders [20,21].

Exercise is a subset of the PA spectrum and is defined as a planned, structured, form of PA with the objective to improve or maintain physical fitness*1*. Whilst there is promising evidence that light intensity/free living physical activity has beneficial preventive effects in the general population (e.g.[22]), most treatment guidelines to date still focus solely on moderate to vigorous exercise (including resistance training) [23, 24].

Over the past 20 years there has been a growing interest in the evidence and implementation of exercise as an adjunctive treatment among people with severe mental illnesses such as schizophrenia, bipolar disorder, major depressive disorder (MDD) and other mental illnesses such as pre/post-natal depression, anxiety and stress disorders, eating disorders (e.g. anorexia nervosa , bulimia nervosa, binge eating disorder, and alcohol and substance use disorders (alcohol use disorders and substance use disorders). In addition to the potential to help address the poor physical health and associated premature mortality in people with mental disorders [25-31], there is increasing recognition that exercise may have important effects on psychiatric symptoms [32-34] and neurocognitive functioning [32], across many conditions, thus potentially acting as a transdiagnostic treatment for mental disorders. This is important; whilst the pharmacological [35,36] and psychotherapeutic approaches [37,38] are helpful for many, they do not result in full remission in all patients. Furthermore, even those who respond well to traditional treatments, some continue to experience residual symptoms, and/or a risk of future relapse [35,36,38]. Additionally, a broad spectrum of mental disorders are associated with cognitive dysfunction, for which current treatments are limited [39-43]. Thus, novel adjunctive treatments which improve mental health outcomes, while also targeting cognitive dysfunction, would provide a very promising approach for improving long-term outcomes across a range of mental disorders. Exercise may be well positioned to address this gap and act as a non-stigmatising intervention that can complement standard pharmacological and psychological interventions.

A plethora of systematic reviews and meta-analyses have synthesised the primary evidence for the potential for exercise to improve mental health symptoms across mental disorders. Consequently, international evidence-based recommendations for exercise in people with specific mental disorders have been developed and endorsed by key international organisations (e.g. [44,45]). Despite this rapid expansion of meta-analytic evidence on exercise interventions for improving mental and cognitive outcomes in individual classes of mental disorders, no existing research has examined the potential efficacy of exercise as a transdiagnostic intervention across all classes of mental illness. Furthermore, there is little systematic examination of the evidence for aerobic, resistance and combined exercise modalities, which precludes translation into practice and policy. Moreover, the quality of these meta-analyses and the included trials has not been comprehensively evaluated, which is an indispensable step before more rigorous exercise recommendations are made. To address this gap within the literature, we set out to summarise and compare the existing top-tier evidence from the most recent/largest, published meta-analyses of RCTs of exercise interventions targeting mental health and cognitive outcomes in people with mental illness. In the absence of a meta-analysis for a specific mental disorder, we identified systematic reviews of exercise in people with elevated mental health symptoms that included non-RCTs to provide a narrative synthesis.

1. **Methods**
	1. **Searches**

Four independent pairs of authors searched MEDLINE/PubMed, PsycINFO and EMBASE from inception to 1/10/2018, for systematic reviews with meta-analyses of randomised controlled trials (RCTs) investigating exercise interventions (defined below) across a range of mental disorders.

Separate searches were undertaken for each mental disorder categorisation using the following standard terms: (exercise or aerobic exercise or physical activity or resistance training) and (systematic review or meta-analysis or meta\*or meta-analytic review) and; 1) (schizophrenia or psychosis or psychotic or major depression or depression or bipolar disorder or serious mental illness or serious mental disorder), or 2) (anxiety disorder or generalised anxiety disorder (GAD) or post-traumatic stress disorder (PTSD) or obsessive compulsive disorder (OCD) or panic disorder), or 3) (alcohol use disorder or alcohol addiction or substance use disorder or smoking or cigarette or drug addiction or addiction\*) or 4) eating disorders (eating disorder or anorexia\* or bulimia\* or binge eating disorder) and others (ADHD or attention deficit hyperactivity disorder or pre/post-natal depression). Reference lists of included articles were searched.

**2.2 Inclusion criteria**

We included meta-analyses of RCTs investigating any type of exercise in the following conditions: 1) serious mental illness (including schizophrenia spectrum, bipolar disorder and MDD); 2) anxiety and stress disorders (e.g. PTSD, OCD, GAD); 3) alcohol use disorders and substance use disorders, 4) eating disorders (anorexia nervosa, bulimia nervosa, binge eating disorder) and other mental disorders, including attention deficit disorder (ADHD), pre/post-natal depression). Only meta-analyses including people with mental illnesses diagnosed through structured clinical diagnoses (e.g. DSM [46], ICD [47] criteria) were initially included. Meta-analyses that included people with mental illness/substance use disorders and mental health symptoms were only included if over 80% of the studies had a diagnosed mental illness. If this was not possible, we attempted to extract information on any subgroup meta-analysis results for those with confirmed mental illness. We included studies with data on young people, adults and older adults.

Exercise was defined activity that is *planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness [1]*. Within this definition, we included aerobic exercise (including brisk walking), high-intensity exercise, resistance training, mixed exercise (i.e. aerobic and resistance exercise). We did not include mind-body interventions such as yoga, tai chi and Pilates as the therapeutic benefit of these interventions is theoretically derived from components separate to the exercise itself [48,49]. We excluded low intensity physical activity interventions (e.g. light walking, stretching) given the current focus of moderate-vigorous intensity exercise in current treatment guidelines [23,24]. If we encountered meta-analyses with exercise and mind-body interventions or low intensity PA, we included these if over 80% of the RCTs utilised exercise. We included meta-analyses that considered exercise studies used as monotherapy, or in combination with other types of treatment, e.g. psychotropic medication, psychological interventions.

Where no meta-analyses of exercise RCTs existed for a particular mental disorder, and thus no effect sizes could be extracted, we identified the most recent systematic review meeting the above criteria, and summarised the main findings for exercise intervention (as defined above) in samples with clinical diagnoses of the disorder or those with elevated symptoms captured through validated tools.

**2.3 Primary outcomes**

Primary outcomes were changes in psychiatric symptoms which characterise the target disorders, e.g. positive/negative symptoms in schizophrenia; depressive symptoms in MDD, anxiety levels in anxiety/stress disorders.

**2.4 Secondary outcomes**

We also examined changes in secondary outcomes reported in meta-analyses of RCTs; such as comorbid psychiatric symptoms (e.g. depression in schizophrenia), neurocognitive function or associated changes in brain function or connectivity.

**2.5 Data extraction**

Data extraction was undertaken by four pairs of authors. The information extracted included the number of studies included, the number of participants in each arm, participant demographics, length of follow-up, details of the exercise intervention, statistical analyses conducted, effect size information, heterogeneity (e.g. Cochran's Q and the I2% [50,51]), publication bias (e.g. Egger's regression test [52]) and any meta-regression and subgroup analyses conducted. We did not undertake any additional analyses of the original statistical analyses.

**2.6 Risk of bias (quality) assessment**

For meta-analyses of RCTs among people with structured diagnoses, two independent authors assessed the quality of the systematic reviews and meta-analyses using the AMSTAR and AMSTAR+ tool [53-55]. The AMSTAR is a reliable and valid tool to capture the methodological quality of meta-analyses but does not capture key quality indicators of the meta-analysed trials. Thus, in accordance with previous meta-reviews [25,56] we used the AMSTAR+ which has six additional items on the content validity of included meta-analyses with scores ranging from 0-8 (>4 indicating high quality).

**2.7 Strategy for data synthesis**

Due to the anticipated scale and heterogeneity of the literature, we summarised the results for each mental illness category using a best evidence synthesis and provided a summary of effect sizes reported across the meta-analyses. In the absence of meta-analyses of RCTs in those with structured diagnoses, we included systematic reviews with or without meta-analyses including people with mental disorders classified by validated symptom measures or other primary study designs.

1. **Results**

The initial searches identified 4,089 de-duplicated hits, of which 269 full text screens were reviewed. Following the full text screening, a total of 27 articles were included. This included 16 meta-analyses of 152 RCTs in people with clinical disorders[33,34,57-70] and 11 further systematic reviews in people with elevated symptoms and areas not covered by the existing meta-analyses[71-81]. The search results including reasons for exclusion are displayed in figure 1. A full list of excluded articles is available on request.

Insert figure 1 here

**3.1 Evidence from meta-analyses of RCTs in mental disorders**

The key findings from each of the meta-analyses of RCTs among people with mental disorders categorised according to structured clinical diagnoses are summarised in table 1. The results with regards to each condition are presented below.

**3.1.1 Major depression**

Eight meta-analyses examined effects of exercise in MDD [57-64]. The frequency, intensity, type and time of exercise varied considerably across the RCTs in the systematic reviews and invariably included a combination of aerobic with or without resistance training exercises. The mean AMSTAR and AMSTAR+ scores were 9.71 (range 7-11), 1.71 (range 1-4) respectively.

*Adolescents and youth*

One meta-analysis [58] (AMSTAR=7 and AMSTAR+=1) reported effects of exercise interventions across four RCTs of adolescent clinical samples with depression (mean age 16 years, 33% inpatients, n intervention=99, n control=84). The results showed that aerobic and resistance exercise delivered over a median of seven weeks (30-90 minutes, three times a week) had a moderately positive effect on symptoms of depression compared to control conditions including treatment as usual (TAU), stretching and instruction on health topics (SMD =-0.43, 95% CI -0.84 to -0.02, p=0.04, I²=44%). Another meta-analysis [57] (AMSTAR=10, AMSTAR+=2) which included adolescents and young adults with a clinical diagnosis of depression across four RCTs (n=100) and found exercise had a large effect on reducing depressive symptoms (SMD = −0.95, 95% CI −1.37 to −0.53 p<0.00001, I2=0%). Control conditions included no treatment, wait-list and attention/activity placebo controls (i.e. stretching/flexibility, relaxation, physical education, very light activity and unguided group meetings).

*Adults*

Four meta-analyses of RCTs investigated the benefits of exercise for depressive symptoms in adults with MDD [60-63]. Information at a meta-analysis level regarding details of other treatments in the intervention groups (e.g. antidepressant medication, psychological therapy) were scant. The Cochrane review [62] (AMSTAR=11, AMSTAR+=2) included 23 RCTs of people with MDD and found that exercise reduced depressive symptoms (SMD = -0.57, 95%CI -0.81 to -0.32, n=450, I²=67%). No further subgroup analyses were available for the MDD only group.

Schuch et al. [60], (AMSTAR=10, AMSTAR+=1) conducted a meta-analysis of aerobic or resistance exercise interventions for MDD and found that exercise had a large effect on improving depressive symptoms across 9 RCTs (SMD = 1.139, 95% CI 0.464 to 1.814, p<0.0001, I²%=88.54) with a fail-safe number of studies to nullify the result of 123. Results found large significant benefits when exercise interventions were supervised by qualified exercise professionals (SMD= 1.537, 95% CI 0.514 to 2.599, p=0.003, I²%=91.61). However, the benefits of exercise were only evident in low quality studies (SMD= 1.176, 95% ci, 0.244 to 2.109, p=0.013 I²%=87.64). In that meta-analysis, 4 RCTs reported that 100% of intervention participants and controls were taking antidepressants, while 3 RCTs reported a portion of participations in both groups taking antidepressants.

Another meta-analysis [61] (AMSTAR=10, AMSTAR+=1) included 23 RCTs (n=977) with clinical depression (2 with treatment resistant depression & 4 with dysthymia), most included aerobic (N=16) or resistance exercise (N=4). Overall, exercise was effective in reducing depressive symptoms (g=-0.68, 95% CI -0.92 to-0.44, p=0.001, I²=68%). Effects were small, but still significant, after adjusting for publication bias (g=-0.38, 95% CI-0.62 to -0.13; fail-safe number 463). The benefits of exercise were evident in trials that reported blinding of outcomes (g= -0.4, 95% CI-0.7 to -0.11, RCTs=10, n=600) and an ITT analysis (g=-0.67, 95% CI-0.9 to -0.44, RCTs= 12, n= 643). However, across six RCTs with 461 participants that had blinded group allocation, blinded outcome assessments, and ITT analysis, a small, heterogeneous but non-significant effect was evident (g=-0.26, 95% CI -0.61 to 0.08, p=0.14, I2=68%). Aerobic exercise resulted in similar outcomes versus other active treatments including psychological treatment (g=-0.22, 95% CI -0.65 to 0.21, RCTs=3, n=79, I²=0%) and antidepressants (g= -0.08, 95%-0.33 to 0.18, RCTs=3, n=236, I2=0%).

In a trial sequential meta-analysis [63] (AMSTAR=10, AMSTAR+=1), exercise was more effective than control conditions across 35 RCTs (SMD=-0.66, 95% CI-0.86 to -0.46, I²=81%). The benefits of exercise were evident in 31 RCTs deemed “high risk” of bias (SMD= -0.75, 95% CI-0.98 to -0.52, n=1968, I²=81%). However, no difference was noted when comparing exercise versus other active interventions (including other forms of exercise) across four RCTs rated “high quality” (SMD=-0.11, 95% CI-0.41 to 0.18, n=530, I²=62%). Three RCTs reported adverse events and no difference in the exercise or control interventions. 4 studies reported co-treatments; 2 used exercise in combination with sertraline, 1 used ECT and exercise and 1 used CBT and PA promotion along with exercise. Control conditions included meditation, occupational therapy, waitlist, TAU, health education, sertraline, flexibility, placebo medication, stretching/relaxation, attention control, sertraline, behavioural activation.

Brondino et al. [64], (AMSTAR=10, AMSTAR+=4) investigated the potential benefits of exercise for cognitive symptoms in MDD. Across several subgroup analyses exercise did not improve speed of processing; attention/vigilance; working memory; verbal learning and memory and reasoning and problem-solving. However, in a subgroup analysis that excluded mind-body interventions and included only exercise RCTs (four trials), the exercise improved visual learning and memory (g= 0.241, 95% 0.005 to 0.478, I²=68%,). Control conditions included wait list, CBT, sertraline, placebo, relaxation training, stretching, health education.

*Older adults*

One meta-analysis [59] (AMSTAR=10, AMSTAR+=1) included two RCTs of older people with MDD or dysthymia and found the effects of exercise on symptoms of depression fell short of statistical significance. (SMD=-1.883, 95%CI 0.44 to -4.21, p=0.11, I²=93.06%). However, the pooled data including older people with depressive symptoms found that aerobic exercise improved depressive symptoms (SMD = -0.90, 95%CI -0.29 to -1.51, RCTs=8, n intervention=138, n control=129).

**3.1.2 Anxiety and stress-related disorders**

Overall, three meta-analyses investigated the benefits of exercise in anxiety and stress-related disorders [65-67]. All systematic reviews were in adults and information at a meta-analysis level on additional treatments among participants (e.g. medication) was sparse. The frequency, intensity, type and time of exercise varied considerably across the RCTs. Overall, the mean AMSTAR and AMSTAR+ scores were 6.66 (range 5-9) and 3, (range 1-3) respectively.

Stubbs et al. [65], (AMSTAR=6, AMSTAR+=1) conducted a meta-analysis of exercise in six RCTs (n=262, mean 34.74 years) including panic disorder (N=2), GAD (N=1), PTSD (N=2) and a further RCT that included people with either GAD, PD or social phobia. All but one RCT used aerobic exercise compared to non-active control conditions. Exercise reduced anxiety symptoms at the trial end point (SMD=−0.581, 95%CI −1.0 to −0.76, p=0.02, I²=66%). Of the included RCTs, only 1 used exercise as a monotherapy, while another study reported 20% of participants and 20% of controls taking antidepressants. Information on other treatments in the other studies was not detailed.

An earlier meta-analysis [66] (AMSTAR=5, AMSTAR+=2) investigated the potential benefit of exercise versus non-active and active (antidepressant medication, non-aerobic exercise) in seven RCTs of 407 people with anxiety disorders. There was no benefit of aerobic exercise when compared to both treatment as usual or other active treatments for anxiety symptoms (SMD = 0.12, 95%CI −0.33 to 0.58, p = 0.60), although compared to wait-list or placebo aerobic exercise was effective (SMD = 1.42, 95%CI: 0.80–2.04, p=0.001, RCTs=2). No difference was noted when stratified according to anxiety disorder type, when exercise was compared to pharmacotherapy (SMD = −0.28, 95%CI: −0.76 to 0.20, p = 0.25, RCTs=2) or versus CBT (ES = −0.70, 95%CI: 0.03 to 1.38, RCT=1).

Aylett et al. [67], (2018, AMSTAR=9, AMSTAR+=3) meta-analysed four RCTs of people with anxiety disorders in primary care and found that exercise reduced anxiety symptoms (SMD= −0.32, 95% CI -0.62 to − 0.01). 2 studies used psychological therapy as co-treatments in both the intervention and control groups. Control groups included a non-active waiting list and a non-active control group taking placebos.

**3.1.3 Schizophrenia Spectrum/ Serious Mental Illness**

Three meta-analyses investigated the benefits of exercise in schizophrenia spectrum disorders [33,34,69], whilst one investigated the benefits of exercise in people with serious mental illness [70]. All of the systematic reviews were in adults. The frequency, intensity, type and time of exercise varied considerably across the RCTs in the meta-analyses. The AMSTAR and AMSTAR+ scores were all rated as 5 and 3 respectively.

One meta-analysis [34] (AMSTAR=5, AMSTAR+=3) included eleven RCTs of exercise in schizophrenia spectrum disorders (mean 33 years (range = 25–52 years, median illness duration 10 years)). Exercise interventions varied but only interventions delivered at over 90 minutes of MVPA per week improved total symptoms (SMD = -0.72, 95% CI-1.14 to-0.29), positive symptoms (SMD -0.54, 95% CI -0.95 to -0.13) and negative symptoms (SMD=-0.44, 95% CI -0.78 to-0.09). In that meta-analysis, control conditions included TAU, behavioural therapy, table football, computer games, occupational therapy and waitlist. Similar findings were evident for these outcomes in another meta-analysis [80] (AMSTAR=5, AMSTAR+=3) but no effect was found for depressive symptoms from aerobic exercise across five RCTs. A meta-analysis of seven RCTs [33] (AMSTAR=5, AMSTAR+=3) of aerobic exercise and 292 people with schizophrenia spectrum disorder found that exercise improved global cognition versus control conditions which included table football alone (N=1), occupational therapy (N=1) and TAU (N=5), (g= 0.412, 95% 0.19 to 0.64, p<.001). Three interventions combined exercise with cognitive remediation.

An older meta-analysis [70](AMSTAR=4, AMSTAR+=2) among people with serious mental illness (schizophrenia spectrum and bipolar disorder) included suggested that exercise did not improve anxiety and depression scores combined (SWD=-0.26, 95% CI-0.91 to 0.39, RCT=3, n= 94, I²=49%). Six of the 8 studies used TAU for their control condition.

**3.1.4 ADHD**

One meta-analysis[68] (AMSTAR=8, AMSTAR+=2) examined five trials of aerobic exercise versus usual care or education in children (mean age 11 years) diagnosed with ADHD. Overall exercise improved multiple outcomes including attention (SMD= 0.84, 95% CI 0.48 to 1.20, I2=0%), hyperactivity (SMD= 0.56, 95% CI 0.04 to 1.08, RCTs= 2, n=62, I²=0%), impulsivity (SMD= 0.56, 0.04 to 1.08, RCTs=2, n=62, I²=0%), anxiety symptoms (SMD= 0.66, 95% CI 0.13 to 1.18, RCTs =2, n=64, I2=0%), executive function (SMD= 0.58, 95% CI 0.15 to 1.00, RCTs=3, n=102, I²=8%) and social disorders (SMD= 0.59, 95% CI 0.03 to 1.16, RCTs=2, n= 53, I²=0%).

*Insert table 1 here*

**3.2 Evidence for exercise in mental disorders without meta-analyses of RCTs in clinically-diagnosed samples**

We did not find any meta-analyses that focussed on exercise RCTs with clinically diagnosed bipolar disorder, eating disorder, post-traumatic stress disorder, pre/post-natal depression, alcohol use disorders or substance use disorders. Thus, we identified 11 recent systematic reviews that have investigated the benefits of exercise in each condition, including in individuals symptomatic for these disorders (as identified by clinically-validated tools). The summary of this evidence is presented in table 2.

**3.2.1 Bipolar Disorder**

A systematic review examined the association between exercise on bipolar disorder [71] across 31 studies (n=15,587). No RCT was included and most studies were cross-sectional. Exercise was found to be associated with less depressive symptoms and there was a lack of clarity with mania symptoms.

**3.2.2 Eating Disorders**

*Anorexia Nervosa*

Moola et al. [72], conducted a systematic review of exercise in AN across five RCTs, two quasi-experimental studies, two case studies and one qualitative study. Participants (n exercise=91; n control=87) were mostly female (7 males across all studies), with median age of 28 years (range of 11-45). The ten included studies varied in exercise type, with aerobic, anaerobic, and resistance training being used, with varied intensity and the duration lasting between two weeks and twelve months. The authors reported two studies found exercise reduced eating disorder symptoms (e.g. less food preoccupation) following exercise participation. No evidence of eating disorder distress was exacerbated by exercise (Moola et al., 2013). Six studies found psychological wellbeing improved following participation in exercise. A separate systematic review, not included in the main results, reported that supervised exercise did not result in BMI or weight change in four RCTs [82] thus indicating a degree of safety.

*Binge Eating Disorder*

Blanchet et al. [73], examined the effect of exercise on 842 people with binge eating disorder, across eight studies. The age range was 36-51 years, mean BMI was 34 kg/m2, and 84% of participants were women. Various types of exercise were used including home exercise practice, brisk walking and aerobic exercise. Among the RCTs, it was found that number of BE episodes were significantly reduced with exercise compared to other interventions, and a significant decrease in depressive symptoms was also found when accompanied by the treatment of binge eating disorder. 2 studies included co-treatments of CBT, and one study included a dietary group as a control condition, however information regarding the other studies was not provided.

*Bulimia Nervosa*

Vancampfort et al. [74], examined the effects of exercise in bulimia nervosa. One RCT focused on a once weekly, 60 min aerobic exercise program. In 64 women (age range = 18-29 years, BMI = 20.3 kg/m²) exercisers reported 18 months post-intervention significantly less binges and vomiting compared to control interventions that included cognitive behavioural therapy and nutritional counselling. One study involved the use of Basic Body Awareness Therapy as a co-treament. Control conditions included TAU, CBT, nutrition counselling and wait list.

**3.2.3 Post-traumatic stress disorder (PTSD)**

Rosenbaum et al. [75], examined the effect of exercise on PTSD in a systematic review of four RCTs (*n*=200, age range of 34-52 years). Although two of the included studies investigated the impact of yoga, data from two of the pooled trials utilised combined aerobic and resistance, and aerobic only exercises providing promising evidence that exercise can significantly reduce PTSD symptoms, compared to control conditions. Preliminary evidence also suggests that compared to controls, interventions with exercise are significantly more effective at decreasing depressive symptoms in people experiencing PTSD.

* + 1. **Pre/post-natal depression**

A meta-analysis [76] examining the use of exercise in the prevention or treatment of postpartum depression included 17 RCTs (n=1428) which involved aerobic exercise and coaching compared to usual care-non-intervention and active controls. Compared to control conditions, exercise was effective in reducing depressive symptoms (SMD = -0.64, 95% CI=-0.96 to-0.33, p<0.001). Control conditions included TAU, informal social support sessions and health education.

A meta-analysis of 12 RCTs (n exercise=471, n control= 461, TAU) examined the effect of exercise-based interventions on postpartum depressive symptoms[77]. Interventions varied and included both aerobic and resistance training, home based programs and brisk walking programs, and sessions varied from one to five per week. Exercise interventions reduced post-partum depressive symptoms during pregnancy and the postpartum period (SMD=0.41, 95% CI 0.28-0.54).

A final review[78] examining the effect of pre-natal exercise on depression and anxiety during both the pregnancy and the postpartum period included 52 studies (n= 131.406). Interventions ranged from 20-75 minutes per session, from 1-7 days/week, and included aerobic exercise, resistance training and pelvic floor muscle training. Co-treatments included diet, education classes and a smoking cessation program, along with exercise. Evidence from RCTs found that exercise interventions, compared to no exercise, decreased the severity of prenatal depressive symptoms (13 RCTs, n=1076; SMD= -0.38, 95% CI -0.51 to -0.25, I2=10%), and reduced the odds of prenatal depression by 67% (5 RCTs, n=683; OR: 0.33, 95% CI 0.21 to 0.53, I2=0%).

**3.2.5 Alcohol use disorder/any substance use disorder**

Hallgren et al. [79], examined the use of exercise as treatment for alcohol use disorders among 21 studies (*n*=1204 people, 37.8 years, illness duration of 4.4 years). The mean duration of exercise session was 43 minutes (SD=19 mins), and interventions involved aerobic exercise and strength training. While exercise did not reduce daily alcohol consumption or total scores on the Alcohol Use Disorders Identification Test, it reduced depressive symptoms when compared to controls (RCTs =4; SMD=−0.867, p=0.006, I2=63%)

Among individuals with multiple substance use disorders, Colledge et al. [80], examined the effect of anaerobic exercise specifically, in a systematic review of 26 studies (nicotine dependence=12; alcohol dependence=1; illicit drug dependence= 13). The mean sample size was 97, with a mean age of 34.3 years. With the exception of four studies looking at acute exercise bouts, all others examined long-term interventions, with varying levels of intensity. The results of the study were extremely mixed, however some positive effects (not significant) were found for the outcome of abstinence in nicotine dependence. Control conditions included TAU, health education and behavioural modification training.

In a separate meta-analysis among individuals with substance use disorders, 22 studies were included to examine whether physical exercise could act as a treatment for substance use disorders, with the primary outcome being abstinence rates[81]. Exercises varied from light-vigorous intensity and included aerobic and some mind-body exercises. When individuals of all substance use disorders were grouped together (i.e. nicotine, alcohol, illicit drug users), it was found that exercise effectively increased abstinence rates OR = 1.69 (95% CI: 1.44, 1.99), eased withdrawal symptoms SMD = −1.24 (95% CI: −2.46, −0.02), and reduced symptoms of anxiety SMD = −0.31 (95% CI: −0.45, −0.16) and depression SMD  =  −0.47 (95% CI: −0.80, −0.14).

*Insert table 2 here*

1. **Discussion**

Our meta-review examined the potential benefits of exercise for neuropsychiatric and cognitive symptoms across the spectrum of mental disorders. By combining evidence from 27 different systematic reviews and meta-analyses, we produced a number of novel findings. First, we found relatively consistent evidence across eight meta-analyses [57-64] that structured moderate-to-vigorous intensity exercise can have a positive impact on symptoms of depression as an add-on treatment in adolescents, working age and older adults. Second, there is tentative evidence that moderate-to-vigorous intensity aerobic and resistance training exercise improves mental health symptoms and cognition in people with schizophrenia spectrum disorders [33,34,70]. Third, the data indicate that moderate-to-vigorous intensity aerobic exercise can have a positive impact on multiple outcomes in children with ADHD[68]. Fourth, in people with PTSD (as indicated by validated measures, but without confirmed diagnoses), preliminary evidence suggests that moderate-to-vigorous intensity exercise can reduce symptoms of both PTSD and depression[75]. There is also good evidence that moderate-to-vigorous intensity exercise in the pre- and post-partum period can reduce depressive symptoms and the odds of developing depression [76-78]. Among people with alcohol use disorder, preliminary evidence suggests that moderate-to-vigorous intensity exercise may improve depressive symptoms but does not appear to influence alcohol intake [79], although this evidence was based on three trials. Available evidence indicates that moderate-to-vigorous intensity exercise may improve SUD abstinence rates and anxiety/depressive symptoms across multiple SUDs [80,81]. There is some tentative evidence that supervised exercise may be helpful for people with AN [72] without negatively impacting BMI [82] and may help improve ED symptoms in bulimia nervosa [72] whilst also potentially reducing binge eating disorder symptomology and depressive symptoms and improving psychological wellbeing in binge eating disorders [71]. Finally, limited data from interventions are available to support the use of moderate-to-vigorous intensity exercise in bipolar disorder, although observational data imply exercise can have a positive impact on depressive symptomology. Taken together, our data provide robust evidence for the value of moderate-to-vigorous intensity exercise as a potential transdiagnostic intervention for mental health symptoms across people with mental disorders.

4.1 Potential Mechanisms

Despite the increasing evidence base for the positive effects of exercise on mental health symptoms in people with mental disorders, relatively little has been established in humans about the underlying mechanisms. This lack of clarity is perhaps exemplified by the most densely researched area of exercise and MDD where a recent systematic review [83] found tentative evidence that acute (i.e. a single bout) exercise may exert its antidepressant effect by increasing atrial natriuretic peptide, brain natriuretic peptide, copepetin and growth hormone among people with MDD. The review [83] also found that longer term exercise may exert its antidepressant effect by promoting long-term adaptations of copeptin, thiobarbituric acid reactive species and total mean frequency. A recent acute exercise study[84] and longer term RCT [85] demonstrated that aerobic exercise may exert its effect by increasing brain derived neurotrophic factors (BDNF). However, a preliminary meta-analysis [86] of only 6 RCTs and 176 participants found that longer term changes in BDNF fell short of significance (SMD = 0.43, 95% CI:−0.06–0.92, p = 0.09). Among people with schizophrenia, the potential positive effects on mental health and cognitive symptoms have been suggested to be related to increases in hippocampal volume [87], yet these findings in mental disorders have not been replicated in a recent meta-analysis of RCTs[8]. Nonetheless, neurocognitive improvements following exercise in schizophrenia may again be linked to increased levels of BDNF [32]. However, psychosocial mechanisms also play a pivotal role in the mental health benefits of exercise, such as increased social support and reduced social isolation [88], improved self-esteem [89] and body image [90]. Among people with anxiety and stress disorders a number of theories with modest amounts of data have suggested that increasing self-esteem, adaptations in GABA levels, adaptations in norepinephrine and the serotonin neurotransmitter system may account for the anxiolytic effects [91].

4.2 Exercise and Physical Health

Whilst not the focus of this review, along with the neuropsychiatric benefits, exercise interventions can also play an important role in reducing the physical health inequalities observed in people with mental illness [44]. Specifically, there is a plethora of evidence from the general population that exercise can reduce the risk of cardio-metabolic diseases (such as obesity, diabetes and metabolic syndrome [92,93]). This is particularly relevant to psychiatric populations, as people with mental illness are significantly less active and more sedentary than the general population [94], and this has been identified as a transdiagnostic risk factor for the elevated cardio-metabolic risk [95-97]. Moreover, increased cardio-metabolic dysfunction has been associated with worse mental and cognitive symptoms in those with schizophrenia [98], MDD [99], bipolar disorder [100] and bing eating disorder [101]. Clearly, exercise has considerable potential to act as a transdiagnostic “polypill” across multiple domains (mental, cognitive, physical) and future ambitious well-powered RCTs are required to target these multiple domains affected by people with mental disorders.

4.3 Exercise and Depressive Disorders

To date, most evidence for exercise interventions in psychiatry is for depressive disorders - where there is relative harmony across the seven meta-analyses of RCTs that exercise is an effective add-on treatment to usual care to reduce symptoms of depression in adolescents [57,58], working age [60-63] and older adults [59]. There is also some tentative evidence from comparative meta-analyses that exercise has similar effects to psychotherapy [61] and antidepressant medications [61,62]. However, caution should be taken in the interpretation of these comparisons, due to the small number of participants (typically <300) and trials (<5) in such analyses. A previous Cochrane review [64] found that exercise was not effective in reducing depressive symptoms in a subgroup of “high quality” studies that included subthreshold depression. This Cochrane review [64] was heavily criticised for multiple methodological and selection biases [102] . Subsequent meta-analyses in working age adults [60,61,63] have consistently reported the overall benefits of exercise but reported equivocal data regarding the outcome in “high quality studies”. For instance, Schuch et al. [60] found exercise was effective in high quality RCTs when considering those with MDD and subthreshold depressive symptoms but not in MDD only (although limited to 2 RCTs). Kvam et al [61] and another meta-analysis [103] published after our search date, found that aerobic exercise was more effective than control conditions for depressive symptoms in MDD in RCTs at low risk of bias. However, a further trial-sequential meta-analysis [63] of four “high quality” RCTs which compared exercise versus other active interventions (including physical activity) found no effect. Clearly, whilst there is a consensus of the benefit of exercise for depression, there is a need for larger and better controlled RCTs to be developed in MDD to attempt to match the standards in other areas of psychiatry such as psychological therapy.

For optimal outcomes in MDD, it appears that supervised exercise interventions tailored to the individual have larger effect sizes [60]. A major criticism of the potential benefits of exercise for MDD is the relative short follow up of most studies (<6 months). Whilst the diagnoses of depression were identified through the patient health questionnaire [104], a recent large scale (n=945) study [105] has partly addressed this concern, finding that aerobic exercise was equally as effective as internet delivered CBT and better than usual care after 12 months. Whilst there is some encouraging evidence of the role of resistance training alone in people with depressive symptoms [106], there are very limited data available to date on exercise as a stand-alone intervention in people with MDD. Thus, moderate-to-vigorous intensity aerobic exercise alone or in combination with resistance training [44] over at least 12 weeks and achieving 90 minutes per week appears the optimal mode of delivery of structured exercise. Whilst this is informed by the evidence base in people with MDD, one should note that people should be encouraged to adopt general guidelines of 150 minutes of vigorous PA per week[23,43].

Among people with MDD, one meta-analysis [64] found that aerobic exercise had no main effects on cognitive functioning. However, almost all of the included studies did not set out with the primary objective to influence cognition and no studies included people with cognitive dysfunction at baseline. Whilst there is robust evidence in the general population for the potential of exercise on preserving and improving cognition [11,12,107], future adequately powered, RCTs with the primary objective of improving cognition are needed. Future interventions should also examine the role of resistance training for improving cognition in serious mental illness, since there is a clear association between increased muscular strength and cognition in people with major depression, bipolar disorder and schizophrenia [108,109] and evidence from the general population indicates resistance training can improve cognition [110, 111].

4.4 Exercise and Schizophrenia/Serious Mental Illness

Four meta-analyses investigated exercise in people with schizophrenia/serious mental illness [33,34,80,81]. Whilst the data are encouraging for core psychiatric symptoms [34,69], this finding requires replication in large, controlled trials. Nonetheless, the emerging data suggest that higher intensities of aerobic exercise may produce neuropsychiatric benefits in this population [33,34,80]. For instance, for cognitive outcomes, greater effect sizes were observed by interventions which administered higher doses of exercise (minutes per week) and were delivered by a qualified exercise professional [33]. Similarly, significant effects on positive and negative symptoms were only observed in RCTs which administered at least 90 minutes per week of moderate-to-vigorous intensity exercise (with no symptomatic benefits observed from low-intensity training) [34]. It does appear from the paucity of RCTs available that aerobic exercise does improve depressive symptoms in schizophrenia [69]. Depression is highly comorbid in schizophrenia and treatment options are limited [112], thus future well-powered RCTs are required that specifically include people with schizophrenia and depression to elucidate if exercise can improve depressive symptoms. Among schizophrenia/serious mental illness adverse event reporting at a meta-analytical level is sparse, whilst dropout from exercise interventions appears higher than in control groups [113]. Given the mental health benefits, along with the clear potential for exercise to improve the poor physical health among people with schizophrenia [44], further research should now be dedicated towards establishing feasible and sustainable methods for engaging this population with moderate-to-vigorous intensity exercise training in real-world settings.

4.5 Exercise and Stress Disorders

In those with anxiety and stress disorders, there was evidence that exercise was effective versus non-active interventions in reducing anxiety symptoms [33,34,69]. The RCTs in anxiety and stress disorders to date have included relatively few people and there are a small number of RCTs, clearly emphasising a need for larger scaled RCTs. To date, most RCTs have focussed on aerobic exercise in people with clinical anxiety/stress disorders. However, there is encouraging evidence for the benefits for resistance training for people with elevated symptoms of anxiety [115] and testing resistance training protocols in those with anxiety/stress disorders should be a future priority.

 4.6 Exercise and ADHD

Despite the small number of participants and RCTs, there is also encouraging evidence that aerobic exercise can improve multiple cognitive domains in children with ADHD [68]. Similar positive effects of the benefits of aerobic exercise on cognition, mental health and academic achievement have been observed in children in the general population [5,6,115] . Given the burden of attention, behavioural and cognitive deficits often noted in children with ADHD and concerns about over prescription of medications with side effects [116], exercise could hold promise as an adjunctive treatment and requires testing in robust well-powered RCTs.

* 1. Exercise and mental health symptoms

Among people with mental disorders identified through clinically-validated measures (but in absence of confirmed diagnoses), there is encouraging evidence for improved mental health outcomes across those with PTSD [75], anorexia nervosa [72], bulimia nervosa [74], binge eating disorder [73], alcohol use disorder [79], substance use disorders [80,81] and pre/post-natal depression [76-78]. With the exception of the pre- and post-natal depression reviews [76-78] the sample sizes were relatively small in these areas and future adequately powered RCTs are needed to confirm/refute the encouraging work in these areas. Disappointingly, there is a dearth of evidence from RCTs that can elucidate the potential benefits of exercise for mental health or cognitive symptoms in people with bipolar disorder.

4.8 Strengths and Limitations

Whilst this meta-review provides a comprehensive overview of exercise for all mental and SUDs, a number of limitations prevail. First, there was considerable heterogeneity in the exercise interventions across the included systematic reviews and specific details regarding the frequency, intensity, type and time of exercise were often lacking. This rendered it impossible to make meaningful direct statistical comparisons between different modes of exercise (e.g. resistance versus aerobic exercise) within and across mental disorders. Future research should thus clearly outline exercise protocols using recognised guidelines (e.g.[117]) to maximise the potential translation into clinical practice. Second, for many of the mental disorder categories, the number of RCTs and included participants was small and included unrepresentative samples from the realities of clinical practice. To overcome this, future research could consider examining the benefits of exercise randomised at a service-level. One option to assess this would be using cluster RCTs to randomly allocate clinical services to either exercise interventions (active) or control conditions, and then assess the extent to which integration of exercise interventions within services improves the patient outcomes, compared to usual service provision. Such studies could also be used to assess the cost-effectiveness of delivering exercise interventions within psychiatric care. Another alternative methodological approach is to use multiple baseline or stepped-wedged designs in which individual participants can act as their own control in order to overcome the ethical issues associated with delaying or withholding access to evidence-based exercise interventions. Third, there is a relative paucity of data on the impact of exercise in adolescents and youth with mental disorders. This is particularly relevant given the concerns about adverse outcomes with pharmacotherapy in youth [30, 118]. Fourth, based on the current AMSTAR+ scores publication bias was potentially problematic for the majority of the meta-analyses, potentially overestimating the pooled effect sizes. Fifth, owing the complex nature of the field, there was variation in the calculation & reporting of effect sizes, publication bias, heterogeneity and general reporting. This makes comparison across the field at times challenging and calls for some standardisation in the future. Finally, there is a paucity of data on potential adverse events and cost-effectiveness data from exercise interventions. However, several recent studies have suggested exercise is safe in serious mental illness [44,119]. Future long-term research is required to address this important oversight.

Despite these aforementioned limitations, the field of exercise science has in the space of 20 years made significant strides in establishing itself as an important adjunctive treatment for mental disorders, underpinned by ever increasing robust science. Whilst the focus of exercise in psychiatric multidisciplinary teams has revolved around the need to address the unanimous poor physical health across mental disorders [44], our review adds support to the utilisation of exercise as a treatment for neuropsychiatric symptoms. Beyond MDD, we are not yet at the stage of making evidence-based bespoke recommendations on the optimal clinical delivery of exercise. Thus, psychiatric teams should seek to follow recent exercise guidelines which emphasise the need for people to be supported to achieve 150-300 minutes or 75-150 minutes of moderate or vigorous exercise over each week [24]. Given the unanimous low levels of moderate-vigorous physical activity in mental disorders ([94, 120-122], with the exception of AN [123]) achieving such targets are aspirational. Thus, people should be encouraged to start making small changes to increase their exercise levels, with the support of recognised exercise professionals. In addition, recent guidelines recommend that resistance training be undertaken twice a week [24]. There is encouraging evidence for resistance training in people with elevated mental health symptoms [108-114], but this requires further testing in those with mental disorders. Beyond treatment, there are encouraging data considering the potential for exercise to act as a primary prevention for mental disorders that should be tested further. There are recent large-scale observational [18] and Mendelian randomisation studies [124] suggesting that higher levels of physical activity can confer against the protection against mental disorders. However, this has yet to be tested in experimental studies, and so the key question remains as to whether increasing an individual’s physical activity behaviour can actually prevent the onset of psychiatric conditions. These data have significant implications for public health campaigns targeting physical activity which should ensure that the mental health benefits are appropriately prioritised alongside the physical health benefits.

1. Conclusion

In conclusion, across those with mental disorders, there is promising evidence that exercise has a positive impact on mental health symptoms and tentative evidence for benefits for cognition in schizophrenia spectrum disorders. Consistent evidence that exercise can reduce depressive symptoms in children, adults and older adults with encouraging evidence in anxiety and stress disorders, children with ADHD and people with schizophrenia spectrum. Among people with elevated mental health symptoms, exercise can improve multiple mental health outcomes in those with anorexia nervosa, binge eating disorder, bulimia nervosa, alcohol use disorders, substance use disorders and pre- and post-natal depression, however further research is needed in these conditions. Given these findings, the potential for exercise to act as a transdiagnostic treatment is considerable. Future research should prioritise robust RCTs that can directly inform the design and delivery of exercise interventions across a range of settings (including low resource settings), diagnoses and demographics to ensure the translation of this body of evidence into routine clinical practice.

Data Availability Statement

As this article is a review, the data can be found within each article referenced (see References list below).

**Compliance with Ethical Standards**

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**Conflicts of Interest**

Garcia Ashdown-Franks, Joseph Firth, Rebekah Carney, Andre Carvalho, Mats Hallgren, Ai Koyanagi, Simon Rosenbaum, Felipe Schuch, Lee Smith, Marco Solmi, Davy Vancampfort and Brendon Stubbs declare that they have no conflicts of interest relevant to the content of this review.

**Authors Contributions**

Brendon Stubbs, Joseph Firth and Davy Vancampfort designed the review. Brendon Stubbs, Ai Koyanagi, Mats Hallgren, Joseph Firth, Felipe Schuch, Garcia Ashdown-Franks, Marco Solmi, Simon Rosenbaum and Rebekah Carney conducted the literature searches and extracted the data. Brendon Stubbs, Joseph Firth, Davy Vancampfort and Garcia Ashdown-Franks wrote the paper. All authors provided critical comments, approved the final version and meet the criteria for authorship.

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