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Original article

EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH)

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ABSTRACT

Physical activity (PA) may be therapeutic for people with severe mental illness (SMI) who generally have low PA and experience numerous life style-related medical complications. We conducted a meta-review of PA interventions and their impact on health outcomes for people with SMI, including schizophrenia-spectrum disorders, major depressive disorder (MDD) and bipolar disorder. We searched major electronic databases until January 2018 for systematic reviews with/without meta-analysis that investigated PA for any SMI. We rated the quality of studies with the AMSTAR tool, grading the quality of evidence, and identifying gaps, future research needs and clinical practice recommendations. For MDD, consistent evidence indicated that PA can improve depressive symptoms versus control conditions, with effects comparable to those of antidepressants and psychotherapy. PA can also improve cardiorespiratory fitness and quality of life in people with MDD, although the impact on physical health outcomes was limited. There were no differences in adverse events versus control conditions. For MDD, larger effect sizes were seen when PA was delivered at moderate-vigorous intensity and supervised by an exercise specialist. For schizophrenia-spectrum disorders, evidence indicates that aerobic PA can reduce psychiatric symptoms, improves cognition and various

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subdomains, cardiorespiratory fitness, whilst evidence for the impact on anthropometric measures was inconsistent. There was a paucity of studies investigating PA in bipolar disorder, precluding any definitive recommendations. No cost effectiveness analyses in any SMI condition were identified. We make multiple recommendations to fill existing research gaps and increase the use of PA in routine clinical care aimed at improving psychiatric and medical outcomes.

1. Introduction

1.1. Serious mental illness, physical co-morbidity and premature mortality

Severe mental illnesses (SMI), defined as schizophrenia-spectrum disorders, bipolar disorder (BD) and major depressive disorder (MDD), are leading causes of years lived with global disability and are of considerable public health importance [1]. In addition to the impact of the mental health symptoms and reduced daily life functioning, people with SMI are at increased risk of premature mortality by between 10–20 years compared to age- and sex-matched controls [2–5]. While suicide accounts for a concerning portion of the early mortality [6,7], there is increasing recognition that physical disorders account for approximately 70% of these premature deaths [3,8]. Of notable concern, cardiovascular and metabolic diseases appear to greatly increase the risk of early death in those with SMI [9], which is of particular importance, given the high prevalence of these diseases in SMI [9–11]. People with SMI are also at increased risk of various other physical comorbidities, such as respiratory disease [12,13], poor bone health [14] and physical multimorbidity [15]. Moreover, people with SMI typically experience pronounced cognitive impairment, which often worsens over time [16–18] and for which treatment approaches remain limited [19,20].

Current treatment for mental health symptoms and functioning largely revolves around psychotropic medication [21,22] and/or psychotherapeutic interventions [23–25]. Whilst both of these dominant approaches, alone and in combination, have demonstrated treatment efficacy on mental health symptoms [26], their impact on the rising physical health burden in this population is limited, and psychotropic medication may even have an adverse relationship with cardiometabolic/physical health [8,9]. In addition, antipsychotic medication has been associated with reduced grey matter volume in people with schizophrenia [27] while psychotherapeutic interventions appear to have limited efficacy for cognitive impairment in this population [28].

1.2. Established benefits of physical activity in the general population

In the general population, there is evidence that physical activity is equally effective as frontline pharmacological interventions, such as statins and beta-blockers, in preventing cardiovascular disease mortality [29]. Moreover, there is consistent evidence that physical activity and exercise can decrease the risk of developing cardiovascular and metabolic disease [30–32] and reduce inflammatory parameters, such as C-reactive protein [33,34], which are commonly raised in people with SMI [35]. Conversely, higher levels of sedentary behaviour (characterized by an energy expenditure $\leq$1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture during waking hours [36]) are independently associated with an increased risk of diabetes, cardiovascular disease and premature mortality [37]. In the general population, there is also evidence that lower levels of cardiorespiratory fitness are a more accurate determinant of premature death than body mass index (BMI) [38]. Moreover, there is evidence that aerobic exercise is effective in improving cognitive function in the general population [39–43] including potentially increasing hippocampal volume [44]. In addition, a recent global meta-analysis has demonstrated that higher levels of PA confers protection from the development of depressive symptoms and MDD [45].

1.3. Low levels of physical activity and fitness

Despite the aforementioned, there is evidence to suggest that less than half of people with SMI (schizophrenia [46], bipolar disorder [47] and major depression [48] [49]) meet recommended physical activity levels of 150 min of moderate-vigorous physical activity per week [50]. Moreover, each of these populations engage in remarkably high levels of sedentary behaviour [46 [48] and have low levels of cardiorespiratory fitness [51]. People with SMI experience, a number of barriers from engaging in physical activity exist, such as side effects of medications, complications from obesity/poor physical health [52,53], lack of resources/professional support [54], various motivational factors [55], which calls for targeted interventions in this highly sedentary population [56–58].

2. Aims

The overall aims of this meta-review and position statement were as follows: First, to establish the benefits of physical activity / exercise across all categories of severe mental illness (SMI), using top-tier evidence from published systematic reviews and meta-analyses. Second, examine how the benefits of physical activity may differ across specific SMIs, including schizophrenia-spectrum disorders, BD and MDD. Finally, to use these findings to provide guidance for clinical practice, policy and future research.

3. Methods

3.1. Guidance development process

This guidance paper was performed in accordance with the PRISMA guidelines [59] following a pre-determined, published protocol (PROSPERO registration CRD42017068292). Moreover, the current guidance was conducted in accordance with the European Psychiatric Association (EPA) guidelines framework and wherever possible, adopted guidance based on the findings from systematic reviews and meta-analyses [60].

3.2. Searches and study selection

Two independent authors searched from inception to 15th January 2018 Medline/ Pubmed, PsychInfo, EMBASE and the Cochrane database for systematic reviews (with and without meta-analyses) of studies investigating physical activity/ exercise among people with SMI, schizophrenia-spectrum disorders, BD or MDD. The search terms included (exercise or aerobic exercise or physical activity or resistance training) and (schizophrenia or

psychosis or psychotic or major depression or depression or bipolar disorder or serious mental illness or serious mental disorder). The reference lists of included articles were also hand-searched.

3.3. Type of studies eligible for inclusion

We followed the European Psychiatric Association manual for identifying and conducting this review and evidence was considered in a hierarchical approach, going from systematic reviews to the highest level of meta-analyses. In the absence of these two data sources for particular outcomes, we sought to identify newer randomised/controlled trials.

The specific inclusion criteria were: 1) systematic reviews (with or without meta-analyses) that synthesised randomised, controlled clinical trials or randomised control trials (RCTs) or controlled clinical trials (CCTs); 2) physical activity/ exercise interventions, including aerobic, high intensity and resistance exercise as monotherapy or in conjunction with other treatment options, including psychotropic medication or psychological therapies; 3) systematic reviews of PA, which included people with pooled SMI or schizophrenia-spectrum disorders, BD or MDD, confirmed through validated assessment measures (e.g. Diagnostic and Statistical Manual of Mental Disorders [61](DSM), International Classification of Diseases [62] (ICD) criteria), in any setting; 4) systematic reviews, which included a non-active/ non-exercise control group (e.g., does not include physical activity). We excluded mind-body physical activity interventions, such as yoga and tai-chi, since these activities are presumed to exert beneficial effects on mental health through additional factors distinct from the physical activity itself.

3.4. Definition of exercise and physical activity

We included systematic reviews investigating the benefits of exercise or physical activity in people with SMI. Exercise was defined as "*planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness*." [63]. Within this definition, we included aerobic exercise, high intensity exercise, resistance exercise and mixed exercise (i.e., aerobic and resistance exercise). Physical activity was defined as "*any bodily movement produced by skeletal muscles that results in energy expenditure*" [63]. We considered exercise/physical activity studies used as monotherapy or in combination with other types of treatment, e.g., psychotropic medication or psychological interventions.

3.5. Outcomes

As indicated in the EPA guidelines manual [60], as a first choice in the hierarchy of evidence, we drew evidence from systematic reviews of exercise/ physical activity interventions, including meta-analyses and/ or RCTs/ CCTs that considered the outcomes listed below. In accordance with our published protocol, we included data from the largest and/or most recent paper investigating each type of PA and each outcome in any population.

3.5.1. Primary outcomes

The primary outcomes focused on changes in the severity of symptoms, which characterise the included psychiatric disorders. For example, positive and negative symptoms in people with schizophrenia-spectrum disorders; and depressive symptoms in people with MDD or BD.

3.5.2. Secondary outcomes

We were interested in a range of secondary outcomes, including:

- Physical health factors, e.g., cardiovascular or metabolic parameter changes, anthropometric measures (e.g., BMI, waist circumference) or body composition measures (e.g., amount of intra-abdominal and cardiac adipose tissue).
- Cardiorespiratory fitness (expressed as percentage maximal or peak oxygen uptake), muscular fitness.
- Increasing physical activity levels or decreasing sedentary behaviour.
- Biomarkers, e.g., HbA1C, C-reactive protein, brain derived neurotrophic factor (BDNF), interleukin-6.
- Cognitive functioning, e.g. performance in neuropsychological tests
- Brain structure and connectivity, e.g., determined through magnetic resonance imaging or diffusor tension imaging changes.
- Quality of life and functioning.
- Dropout rates and predictors from physical activity interventions.
- Adverse events (e.g., injuries sustained from PA)
- Economic evaluations.

3.6. Data extraction

Data extraction was conducted by two authors and reviewed by a third author. We extracted data from systematic reviews and meta-analyses of RCTs/ CCTs investigating exercise interventions, including:

Number of studies included, number of participants in each arm, participant demographics, length of follow-up, details of the exercise intervention, statistical analyses conducted, effect size information, heterogeneity, publication bias and details of any meta regression and subgroup analyses.

Where a systematic review was not available for an outcome, we narratively summarized information from newer RCTs/ CCTs in the manuscript text, noting the study design, sample size, description of the intervention and control group, intervention effect and any harms and dropout rates.

3.7. Quality assessment and grading of evidence

Two independent authors assessed the quality of systematic reviews and meta-analyses with the AMSTAR tool [64,65]. In addition, we assessed the quality of evidence using the SIGN (2011) recommendations as indicated by the EPA guidelines [60] and in accordance with a recent published EPA guidelines on psychotherapy for depression [24]. Specifically, each included study was graded from 1++ (highest quality) to 4 (lowest quality) (see Table 1). Based on the quality of evidence, we graded recommendations according to best practice (Table 2).

4. Results

4.1. Search results and included studies

The initial database searches acquired 2722 hits and 2081 were reviewed at the abstract level. Subsequently, we reviewed 145 full texts, and 125 were excluded with reasons (see Fig. 1). Overall, 20 systematic reviews and meta-analyses were included in this guidelines document, which included studies that provided effect sizes for the benefit of exercise for SMI [51] (N = 1), schizophrenia-spectrum disorders [67–73] (N = 7), BD [74,75](N = 2) and MDD [76–85] (N = 10).

Details of the included systematic reviews representing participants, interventions, outcomes, main results, considerations, AMSTAR scores and level of evidence scores are

Table 1
Grading of evidence in accordance with SIGN (2011 (and adapted from [24]).

Grade	Description
1 ++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1−[a]	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2 ++	High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−[a]	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Nonanalytic studies, e.g. case reports, case series
4	Expert opinion

Table 2
Grading of recommendations, modified from the SIGN (2011) and adopted from [66].

Grade	Description
A	At least one meta-analysis, systematic review, or other study rated at low risk of bias
B	A body of evidence including studies rated as 2, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as I or II
C	A body of evidence including studies rated as II–III, directly applicable to the target population and demonstrating overall consistency of results.
D	Good practice point recommended good practice based on the clinical experience of the Guidance development group and arrived at through consensus

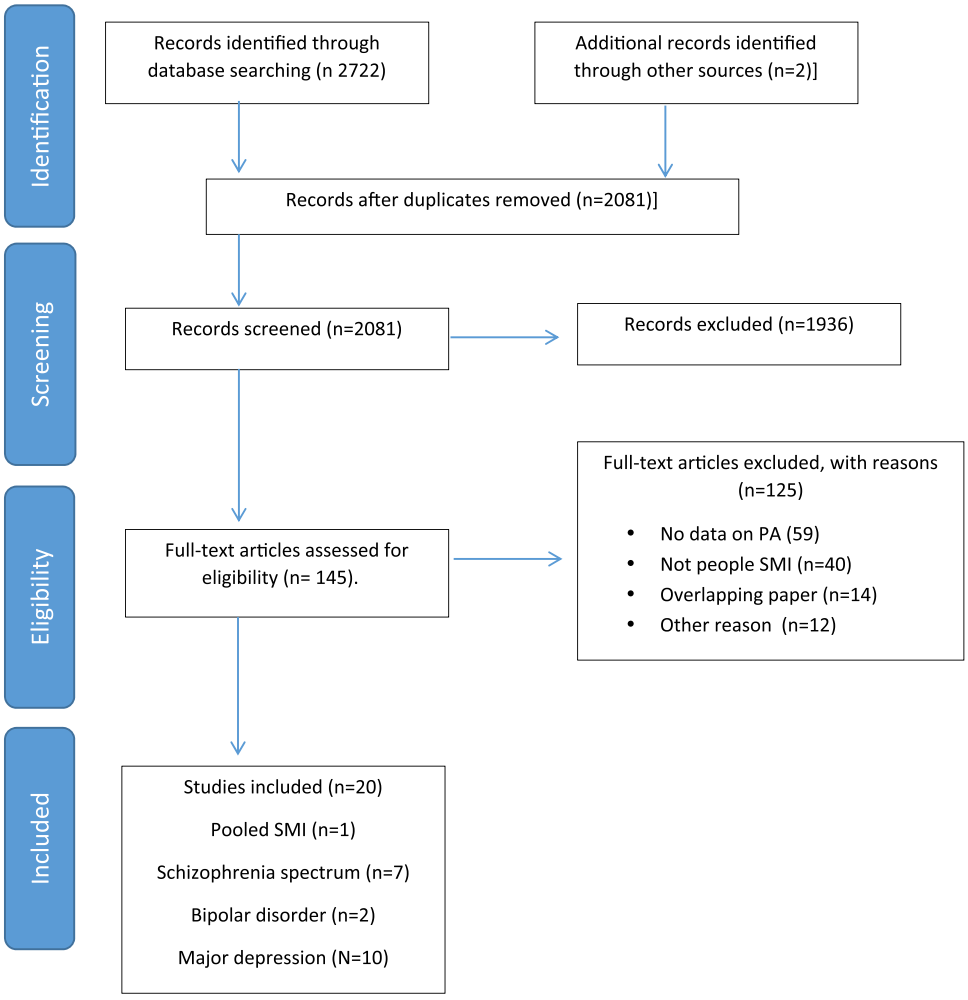

Fig. 1. PRISMA flow-chart.

summarized in Table 3 for schizophrenia-spectrum disorders and mixed SMI participants, and in Table 4 for MDD and BD participants. Details of the results are described below for each population group.

4.2. Pooled SMI

One meta-analysis provided non-overlapping data on exercise for people with pooled SMI [51,86]. It was demonstrated that aerobic exercise improved fitness in pre and post-test studies among people with schizophrenia-spectrum disorders and MDD (Hedges' g = 0.33, 95% CI 0.21–0.45, p = 0.001, 13 studies) [51] (AMSTAR 7, evidence level -1). Improvements in fitness were not accompanied by improvements in BMI. Meta regression showed that higher (vs, low or moderate) intensity interventions and those delivered by qualified professional predicted better outcomes. In 5 RCTs, exercise improved fitness versus control (Hedges' g = 0.43, 95% CI 0.10–0.76, p = 0.01; n = 109).

4.3. Dropout, adverse events and economic evaluations of exercise interventions in pooled SMI

No information was reported on dropout rates, adverse events or economic evaluations in people with SMI.

4.4. Schizophrenia-spectrum disorders

In total, 7 systematic reviews and meta-analyses reported the benefits of exercise for schizophrenia-spectrum disorders [67–73]. There was broad variation in the frequency, intensity, type and time of the interventions across the included systematic reviews and meta-analyses (Table 3). The mean AMSTAR score for the included reviews was 6 (range 4–10).

A summary of the main results for exercise interventions in schizophrenia are presented in Table 5. In a meta-analysis of 8 RCTs [68] (AMSTAR 5, evidence level -1) and 659 patients with schizophrenia-spectrum disorders, exercise reduced total psychiatric symptoms when interventions used at least 90 min of moderate-to-vigorous physical activity (MVPA) per week (SMD: 0.72, 95% confidence interval −1.14 to −0.29). Ninety minutes of MVPA was also associated with reduced positive (SMDs -0.54, 95% CI -0.95 to -0.13) and negative symptoms (SMD-0.44, 95% CI -0.78 to -0.09). Pooled data from four RCTs found that exercise had no significant effect on reducing BMI (MD: -0.98 kg/m2; 95% CI -3.17 to 1.22 kg/m2, N = 4). Narrative findings regarding the influence of exercise on additional cardiometabolic parameters, such as waist circumference, high density lipoprotein levels and triglycerides, were inconsistent. Data from a narrative synthesis across 3 RCTs found that exercise also improved quality of life in people with schizophrenia-spectrum disorders. The key consideration from this systematic review was that optimal effects of exercise interventions are derived when people achieve over 90 min of MVPA per week.

A meta-analysis from 10 studies [67] (AMSTAR 5, evidence level -1) including a sample of 186 in the intervention and 199 in the control group, found that exercise improved global cognition (g = 0.33, 95% CI = 0.13–0.53, P = .001). Meta-regression analyses indicated that greater improvements in global cognition were moderated by greater amounts of weekly exercise and when interventions were delivered by exercise professionals (e.g., physiotherapists, BSc level qualified exercise scientists). Sub-group analyses found that exercise improved cognitive domains of working memory (g = 0.39, P = .024, N = 7, n = 282), social cognition (g = 0.71, P = .002, N = 3, n = 81), and attention/vigilance (g = 0.66, P = .005, N = 3, n = 104). A systematic review of 14 trials [69] investigated the pro-cognitive mechanisms of exercise in schizophrenia-spectrum disorders (AMSTAR 4, evidence level -1). The review suggested that exercise may increase brain volume, although there was a lack of consistency regarding which regions. One region that has been implicated is the hippocampus [87] although a meta-analysis of four studies did not support this hypothesis [44]. This review [69] also found inconsistent evidence for an effect of exercise on BDNF levels, which is consistent with a meta-analysis [72] (AMSTAR 10, evidence level -1) also finding that exercise did not influence BDNF levels. Thus, whilst there seems reasonable evidence that exercise does improve cognition in schizophrenia-spectrum disorders [67], the underlying mechanisms are not yet clear.

A recent systematic narrative review [88] investigated the influence of strength training on outcomes in schizophrenia-spectrum disorders (AMSTAR 4, evidence level -1). Across 6 studies (3 RCTs) the authors found tentative evidence that strength training over time can improve muscle strength, walking performance and reduce psychopathology symptoms. This systematic review was complimented by another systematic review [71] (AMSTAR 7, evidence level -1) that found evidence that combined aerobic and strength training (7 RCTs) may improve strength, symptoms of schizophrenia and mental health, but not cardiovascular fitness.

A narrative systematic review [70] across 10 intervention studies (5 RCTs) (AMSTAR 5, evidence level -1) found that in those with schizophrenia-spectrum disorders, walking may reduce weight, BMI and body fat in the short-term. The authors noted that walking appeared to be safe, although the evidence was noted to be of medium-high risk of bias in the included studies.

Finally, a meta-analysis of seven studies (3 RCTs) [73] (AMSTAR 8, evidence level -1) found that over a 12 week exercise intervention, aerobic exercise improved cardiorespiratory fitness versus control conditions (g = 0.41, 95% = CI 0.05 to 0.82, P = 0.028).

4.5. Dropout, adverse events and economic evaluations of exercise interventions in schizophrenia-spectrum disorders

A meta-analysis of 19 RCTs and 594 schizophrenia-spectrum disorder patients [89] demonstrated that 26.7% [95% confidence interval (CI) = 19.7%–35.0%] of patients dropped out of interventions, more than double reported in non-active control interventions (odds ratio = 2.15, 95% CI = 1.29–3.58, P = .003). Factors influencing lower dropout in meta-regression analyses included supervision from a recognized exercise professional and including a motivational component.

Surprisingly, very little information is available on the potential harms or adverse events from exercise in schizophrenia-spectrum disorder patients. Specifically, the following papers did not report harms [67–69,71,72,88]. Only one study [70] reported potential harms and found that walking was not associated with adverse events in schizophrenia-spectrum disorders.

To the best of our knowledge, there have been no studies with an economic evaluation of the cost and value of delivering exercise interventions in schizophrenia-spectrum disorders.

4.6. Major depression

In total 10 systematic reviews and meta-analyses reported the benefits of exercise for MDD [76–85]. The mean AMSTAR score for the included reviews was 9.1 (range 3–10). Full details of the included systematic reviews are summarized in Table 4.

A summary of the effects of exercise in MDD are reported in Table 5. In a comprehensive Cochrane review [83] including exercise trials, the authors found that exercise was effective in reducing depressive symptoms versus control conditions (Hedge's g=-0.68, 95% CI -0.92 to -0.44, p = 0.001, I^2 = 67.99, k = 23) (AMSTAR

Table 3
Characteristics and results of systematic reviews and meta-analyses including studies comparing effects of PA with a control group in Schizophrenia and mixed SMI participants.

Study	Type of review and Sample included	Sample size PA: C:	Physical activity/ exercise intervention	Control group	Outcome measures	Main results	Considerations	AMSTAR	Evidence level
Firth et al., 2015	Meta-analysis 20 studies 11 RCTs Schizophrenia diagnosed through the Diagnostic and Statistical Manual of mental Disorders or the International Classification of Diseases-9 or 10. No data regarding the stage/phase of schizophrenia	659 patients (total)	Mean duration: not reported. Frequency: median amount was 75 min per week (mean 72 min, range 25–160 min. Intensity: 15 studies specified some moderate to-vigorous intensity exercise Types of exercise: Moderate-to vigorous exercise constitutes activities such as jogging cycling, sports or resistance training, while stretching, warm-ups or self-paced walking are classified as low intensity.	Various control groups: National Fitness Corps Programme, waitlist, Occupational therapy, Computer games, exercise, behavioural therapy, table football.	Metabolic health (body composition and cardiometabolic risk factors); physical fitness (cardiorespiratory fitness and physical capacities); psychiatric symptoms (positive, negative and general symptoms); functioning and disability (quality of life), socio-occupational functioning and overall illness severity); co-morbid disorders (specific or subscale measures of depression/ anxiety); neurocognitive effects (brain structure and neurocognitive functioning).	Exercise interventions had no significant effect on body mass index (MD 0.98 kg/m2; 95% CI -3.17 to 1.22 kg/m2, N = 4) Exercise improved physical fitness. Findings for cardiometabolic risk factors were inconsistent. Total symptoms were not reduced by exercise in 8 RCTs (SMD = -0.16, 95% CI -0.51 to 0.18). However, excluding active controls and including studies that employed 90 min of moderate-to-vigorous exercise per week found exercise reduced total symptoms (SMD: 0.72, 95% confidence interval −1.14 to −0.29). 90 minutes MVPA reduced positive (SMDs -0.54, 95% CI -0.95 to -0.13) and negative symptoms (SMD-0.44, 95% CI -0.78 to -0.09). This amount of exercise was also reported to significantly improve functioning, co-morbid disorders and neurocognition. Two RCTs, which both used 120 min of moderate-to-vigorous exercise per week, reported significant improvements in quality of life and disability, whilst lower amounts did not lead to any significant results.	Interventions that implement a sufficient dose of exercise, in supervised or group settings, can be feasible and effective interventions for schizophrenia.	5	1-
Firth et al., 2017 (Cognitive function)	Meta-analysis Ten studies Seven RCTs No specific criteria used for the diagnosis of schizophrenia. 92.1% had schizophrenia/ schizoaffective disorder and 7.9% had other nonaffective psychotic disorders.	PA: 186 C: 199	Mean duration: 12.2 weeks Frequency: 2.9 sessions per week (range = 2–4 sessions) of 20–60 minutes in duration Intensity: supervised (yoga teacher, physical trainer, sport scientist). Types of exercise: aerobic (aerobic machines such as cycle ergometers/ treadmills (N = 5), bodyweight exercises (N = 3), interactive video games (N = 2), and free-weights	Various control groups: waitlist, treatment as usual, table football, occupational therapy, cognitive remediation in three studies.	Cognitive function (verbal acquisition, retention, forward digit span, backward digit span, Wisconsin card Sorting, verbal and visuospatial short term memory, Trail-making task, spatial span, verbal learning, global intelligence quotient, global cognition, social cognition, working memory, processing speed, attention/vigilance)	Exercise significantly improved global cognition (g = 0.33, 95% CI = 0.13–0.53, P = .001). Meta-regression analyses indicated that greater amounts of exercise are associated with larger improvements in global cognition. Interventions which were supervised by physical activity professionals were also more effective (g = 0.47, P < .001). Exercise significantly improved the cognitive domains of working memory (g = 0.39, P = .024, N = 7, n = 282), social cognition (g = 0.71, P = .002, N = 3, n = 81), and attention/vigilance (g = 0.66, P = .005, N = 3, n = 104). Effects on processing speed, verbal memory, visual memory and reasoning and	This meta-analysis provides evidence that exercise can improve cognitive functioning among people with schizophrenia, particularly from interventions using higher dosages of exercise. Given the challenges in improving cognition, and the wider health benefits of exercise, a greater focus on providing supervised exercise to people with schizophrenia is needed.	5	1-

Table 3 (*Continued*)

Study	Type of review and Sample included	Sample size PA: C:	Physical activity/ exercise intervention	Control group	Outcome measures	Main results	Considerations	AMSTAR	Evidence level
			(N = 2), although 3 also incorporated resistance based (muscle strengthening) training			problem solving were not significant.			
Firth et al., 2017 (brain structures)	Systematic review 16 studies for 14 independent trials Nine RCTs At least 80% had received a clinical diagnosis of a non-affective psychotic disorder (such as schizophrenia) or were being treated for first-episode psychosis. 370 with long-term schizophrenia/ schizoaffective disorder (11 studies) and 53 with first-episode psychosis (three studies).	PA: 247 C: 176	Duration: 12 weeks (eight studies), with others lasting 6months (two studies), 10 weeks (two studies), 8 weeks (one study) or 20 weeks (one study). Frequency: 2.9 sessions per week (range = 2–4 sessions) of 20–60 minutes in duration Intensity: supervised (yoga teacher, physical trainer, sport scientist). Types of exercise: moderate aerobic training alone, combined aerobic and resistance training, low-intensity exercise with some aerobic activity, high intensity interval training, or bodyweight workout videos; two of the studies embedded exercise within broader 'lifestyle programs' for encouraging healthy habits and two combined exercise with cognitive remediation	Other control conditions included occupational therapy, tai-chi, table football, yoga, video games, or usual treatment	Seven studies used neuroimaging techniques to assess the effects of exercise in schizophrenia, and seven others used blood/salivary biomarkers to assess physiological response to exercise interventions.	Imaging studies collectively indicated that exercise can increase brain volume in people with schizophrenia, although the regions which responded to exercise varied across studies. Several studies found significant increases from exercise along with positive correlations between BDNF and cognitive enhancements (indicating a mechanistic link), although other studies did not observe this relationship.	The cognitive benefits of exercise in schizophrenia may be due to exercise stimulating neurogenesis, perhaps by up-regulating BDNF, although current evidence is insufficient to draw definitive conclusions.	4	1-

			therapy, but controlled for this in the comparator condition.						
Keller-Varady et al., 2017	Systematic review Six studies Three RCTs. Only two studies reported on the effects of isolated ST. Schizophrenia spectrum disorders. Schizophrenia diagnosed through the Diagnostic and Statistical Manual of mental Disorders or the International Classification of Diseases-9 or 10.	Overall: 187	Mean duration: 14 weeks Frequency: two (four studies) or three (3 studies) weekly. Intensity: different study by study. Types of exercise: muscle strength.	Computer game (Tetris); lower amount of muscle strength; occupational Therapy; stretching, dancing and recreational Activity; usual care.	Psychopathology (PANSS), quality of life, depressive symptoms, BDNF serum levels.	Strength training with a single exercise did not improve psychopathology, but walking performance. Strength training for several large muscle groups significantly improved muscle strength and psychopathology	To date, no treatment recommendations can be made for ST. Consistent with recommendations for healthy people combined strength and endurance training can be recommended for schizophrenia.	4	1-
Martin et al., 2017	Systematic review Seven RCTs Adults with a confirmed diagnosis (DSM-IV or DSMV) of schizophrenia with no limit to duration since diagnosis, including first episode psychosis. All the RCTs excluded first episode psychosis.	PA: 193 C: 182	Mean duration: 18 weeks Frequency: 20 to 60 min and resistance training volume varied significantly with many variables unreported. Intensity: Intensity was prescribed by percentage of one repetition maximum (% 1RM), predicted RM and the Rate of Perceived Exertion scale, equivalent intensities in all studies were between 50 and 85% 1RM. Types of exercise: aerobic and resistance.	Two utilised a passive control where the participants performed treatment as usual over the full length of the study. An active control group was used in four studies such as occupational therapy, the same intervention program with a restriction to intensity, sets and reps.	Strength, cardiovascular fitness, mental health variables.	Combined exercise was found to improve strength, symptoms of schizophrenia and overall mental health. Though improvements in cardiovascular fitness were not statistically significant they were still clinically meaningful.	Combined exercise for individuals with schizophrenia is effective at improving strength and mental health variables	7	1-
Sanada et al., 2016	Meta-analysis The review included seven RCTs with non-pharmacological strategies, three RCTs used physical activity as exercises.	PA: 65 C: 54	Mean duration: 10.7 weeks Frequency: not reported. Intensity: not reported Types of exercise: hatha yoga, aerobic exercise,	Treatment as usual, day-care programs, routine activities.	BDNF	No significant effect of exercise on serum BDNF levels	Despite insufficient evidence to draw a firm conclusion, the results suggest that use of non-pharmacological therapies as adjunctive treatments,	10	1-

Table 3 (*Continued*)

Study	Type of review and Sample included	Sample size PA: C:	Physical activity/ exercise intervention	Control group	Outcome measures	Main results	Considerations	AMSTAR	Evidence level
	Diagnostic criteria not declared.		combined exercise.				specifically non-exercise interventions, may affect positively serum or plasma BDNF in patients with schizophrenia.		
Soundy et al., 2014	Systematic review Ten studies Five RCTs Schizophrenia diagnosed through the Diagnostic and Statistical Manual of mental Disorders or the International Classification of Diseases-9 or 10.	339 total. Not available by intervention	Mean duration: 19 weeks Frequency: 1-5 times weekly. Intensity: A variety of intervention strategies were undertaken that included behavioural components that supplemented the walking intervention. Types of exercise: walking.	Waitlist, normal care.	Primary: mean change in weight (kg) or BMI. Secondary: adherence, mood, quality of life, cardiovascular risk, hypertension, indices of cholesterol and other specific psychological inventories e.g. the Brief Psychiatric Rating Scale; the Scale for the Assessment of Negative Symptoms ; and the Hamilton Depression Rating Scale.	There is some evidence to suggest walking interventions may benefit an individual's weight, specifically resulting in small reduction in body mass index or body fat in the short term. Evidence for other health outcomes was limited but no adverse events were reported and walking appears to be safe.	No harmful effects were reported and small, short-term weight reduction was identified. However, the results may not be clinically meaningful and should be viewed with caution due to the medium-to-high risk of bias	5	1-
Vancampfort et al., 2015	Meta-analysis Seven studies Three RCTs Schizophrenia diagnosed through the Diagnostic and Statistical Manual of mental Disorders or the International Classification of Diseases-9 or 10.	PA: 77 C: 48	Mean duration: 12 weeks Frequency: 5 studies reported an activity 3 times weekly and 2 two times. Intensity: depending on VO2 and heart rate, various study by study. Types of exercise: mixed (aerobic, resistance, both).	All non-aerobic interventions, usual-care or wait-list controls.	Cardiorespiratory fitness or peak oxygen uptake	Engaging in exercise improves cardiorespiratory fitness in people with schizophrenia (g = 0.40, 95% CI = 0.16–0.64, p = 0.001, N = 7, n = 77). Data from four controlled studies demonstrated that exercise (n = 53) significantly improves cardiorespiratory fitness compared to control groups (n = 48) (g = 0.43, 95% CI = 0.05–0.82, p = 0.028).	Aerobic exercise results in significant improvements in cardiorespiratory fitness.	8	1-
Vancampfort et al 2017	Meta-analysis 13 interventions studies 5 RCTs DSM schizophrenia and major depression	13 intervention studies 255 total 5 RCTs 109 total	Aerobic exercise interventions over mean 14 weeks. Varying type and weekly amount.	In RCTs non active interventions	Cardiorespiratory fitness	In pre and post-test analyses, exercise improved fitness (Hedges' g = 0.33, 95 % CI 0.21–0.45, p = 0.001). Meta regression showed that higher (v low or moderate) intensity interventions and those delivered by qualified professional predicted better outcomes. In 5 RCTs exercise improved fitness versus control (Hedges' g = 0.43, 95 % CI 0.10–0.76, p = 0.01; n = 109).	Small number of control conditions	7	−1

Key: BDNF = Brain-derived neurotrophic factor, C = control, CI = confidence intervals, DSM = Diagnostic and Statistical Manual of mental Disorders, PA = physical activity, RCT = randomized controlled trial, SMD = standardized mean difference.

Table 4
Characteristics and results of systematic reviews and meta-analyses including studies comparing effects of PA with a control group in major depression and bipolar disorder.

Study	Type of review and Sample included	Sample size PA: C:	Physical activity/ exercise intervention	Control group	Outcome measures	Main results	Considerations	AMSTAR	Evidence level
De Souza Moura et al, 2015	Systematic review 13 studies (all randomized) Depression, 85% mild to moderate depression, 15% moderate to severe depression Diagnosis: DSM, ICD, and/or depression rating scale	PA: 908 C: 662	Mean duration of intervention 149 weeks (range 8-32). Frequency: mean days/week 3,5 (range 2-5). Intensity controlled in 12 studies, and supervised in 10. Types of exercise: incentive to practice (k = 1), strength (k = 1), aerobic and strength (2), aerobic and stretching (k = 4), aerobic only (k = 5). Time: mean duration of session 488 min (range 20-90 min).	AD, PLC, non-exercise group. Six out 13 studies included medication in control group (3/6 sertraline).	Depressive symptoms, cardiorespiratory fitness, blood glucose, body fat percentage.	Primary outcomes: exercise effective in reducing depressive symptoms (k = 9, 8 AE vs control – 1 AnE vs control), and reduced use of antidepressants (k = 1, AE vs control). Exercise had no effect on depressive symptoms compared with control group (k = 4, 2 AE vs control, AE + AnE vs REL, AE vs AD) Secondary outcomes: No change in cognitive functions (k = 1, AE vs control), improvement in anxiety (k = 1, AE vs control), increased oxygen uptake (k = 1, AE + AnE vs control), decreased blood glucose (k = 1, AE + AnE vs control) decreased body fat percentage (k = 1, AE vs control), global impression and functioning (k = 1, AE vs control).	There is still disagreement regarding the effect of exercise compared to the use of antidepressants in symptomatology and cognitive function in depression, this suggests that there is no consensus on the correct intensity of aerobic exercise as to achieve the best dose-response, with intensities high to moderate or moderate to mild.	4	1-
Brondino et al, 2017	Systematic review and meta-analysis 8 studies (all RCTs assessing cognitive function in MDD – results from 3 excluded because M-B intervention) Major depressive disorder Diagnosis: DSM or ICD, and depression rating scales	PA: 359 C: 251	Mean duration of intervention: 106 weeks (range 4-16). Frequency: sessions/ week range 1-3. Intensity: aerobic 70-80% HR (k = 1), till 80% HR (k = 1), till 89% HR (k = 1); anaerobic till 75% of max strength (k = 1), moderate intensity (climbing k = 1). Types of exercise: 3 aerobic, 2 anaerobic. Time: mean duration of session 95 min (range 30-270).	Waiting list, sertraline, placebo, health education, relaxation or stretching.	Depressive symptoms, global cognitive function and individual cognitive domains	Primary outcomes: Pooled effect size for cognitive domains calculated with meta-analysis does not show any efficacy of exercise on specific and global cognitive function, with no heterogeneity (Hedge's g = 0,075, SE 0,082, p = 0,36, I^2 = 0%, k = 8).	Meta-analysis showed no effect of PA (included M-B) on cognition in MDD. However included RCTs considered cognitive domains as secondary outcome, while this SR/MA assesses effects of PA on cognition in MDD. Almost no report on primary outcome (depressive symptoms).	10	1-
Thomson et al, 2015	Systematic review 13 (12 excluded since not describing any intervention or not having any control group) Severe mental illness (schizophrenia, schioaffective disorder, BD, MDD) Diagnosis: NA	Overall 291	Duration of intervention: mean 18 months (k = 1) Frequency: NA Intensity: NA Type: group exercise (k = 1) Time: NA	Non-intervention group (k = 1)	Weight.	Primary outcomes: not reported. Secondary outcomes: exercise decreased weight more than non-intervention group (k = 1).	One study eligible in the whole systematic review.	4	1-
Souza de Sà Filho et al, 2015	Systematic Review 4 studies (2 excluded due to no control group) BD Diagnosis: ICD or DSM	PA: 137 C: 85	Duration of intervention: mean 162 months (range 8.5-24). Frequency: mean sessions/week 3. Intensity: moderate effort or free. Type: AE.	Non exercise, or control group	Depressive, general symptoms, global impression, functioning, anxiety, stress.	Primary outcome: improvement in depressive symptoms (k = 1, AE vs non-exercise, ES = 1,4). Secondary outcome: improvement in stress (k = 1, AE vs non-exercise, ES 0,8), anxiety (k = 1, AE vs non-exercise, ES = 0,7), but not in functioning, general	Only two studies compared intervention vs control group.	3	1-

Table 4 (*Continued*)

Study	Type of review and Sample included	Sample size PA: C:	Physical activity/ exercise intervention	Control group	Outcome measures	Main results	Considerations	AMSTAR	Evidence level
			Time: mean session duration 35 min (range 30-40).			symptoms (k = 1, AE vs control), or global impression (k = 1, AE vs non-exercise.			
Stubbs et al, 2016	Systematic review and meta-analysis 7 studies (8 interventions, all RCTs) MDD Diagnosis: DSM or depressive symptom rating scale	PA: 293 C: 205	Duration of intervention: mean 1175 weeks (range 6-16). Frequency: Intensity: light to moderate (k = 1), moderate (k = 4), intense (k = 1) Type: AE (k = 6), supervised (k = 6) by professionals (k = 4), group (k = 4). Time: NA	Control group	Cardiorespiratory fitness.	Primary outcomes: exercise improves CRF (Hedge's = 0.64, 95%CI 0.32–0.96, p = 0.001, I^2 = 67%, k = 8), with higher baseline depressive symptoms predicting lower CRF increase. Exercise improved CRF in diagnosis made according to DSM (Hedge's = 0.407, 95%CI 0.18–0.63, p < 0.001, I^2 = 0%, k = 5)or depressive symptoms rating scales (Hedge's = 1.209, 95%CI 0.82–1.6, p < 0.001, I^2 = 65%, k = 3), in high (Hedge's = 0.595, 95%CI 0.18–1.00, p = 0.004, I^2 = 67%, k = 5) and low quality (Hedge's = 0.747, 95%CI 0.16–1.33, p = 0.01, I^2 = 69%, k = 3) studies, in outpatients (Hedge's = 0.681, 95%CI 0.32–1.04, p < 0.001, I^2 = 71%, k = 7) not in inpatients (k = 1). Mean increase in relative predicted VO2 max or VO2 peak was 3.05 ml/kg/min (95%CI 1.33–4.78, p = 0.001, k = 8).	Exercise improves CRF, in particular in mild depression.	10	1+
Schuch et al, 2016 (older adults)	Systematic review and meta-analysis 8 studies (all RCTs) Depression Diagnosis: DSM, ICD or depressive symptoms rating scales	PA: 138 C: 129	Duration of intervention: mean 11.1 weeks (range 8-16). Frequency: NA Intensity: intense (k = 2), moderate (k = 3) Type: AE (k = 3), resistance (k = 3), mixed (k = 2), supervised (k = 7) by exercise porofessionals (k = 3) Time: NA	Non active control group	Depressive symptoms.	Primary outcome: improvement in depressive symptoms (SMD = -0.90, 95%CI 0.28-1.51, p = 0.004, I^2 = 81.63, p = 0.001, k = 8), in particular in diagnosis made according to symptoms (SMD=-0,56, 95% CI -0,97 to -0.14, p = 0.008, I^2 = 61, k = 6) not to DSM (k = 2), in outpatients (SMD=-1.037, 95% CI -1.74 to -0.37, p = 0.002, I^2 = 82.3, k = 7) not in nursing home(k = 1), in samples without clinical comorbidities (SMD=-1.25, 95% CI -1.87 to -0.62, p < 0.001, I^2 = 74.1, k = 6) not with comorbidities (k = 2), in interventions combining AE and AnE (SMD=-0.92, 95% CI -1.43 to -0.41, p < 0.001, I^2 = 0, k = 2) not singularly AE (k = 3) or AnE (k = 3), in moderate (p = 0.02, k = 1) not vigorous (k = 3) intensity, in group exercise(SMD=-0.97, 95% CI -1.71 to -0.24, p = 0.009, I^2 = 84.35, k = 6) not in individual (k = 2), and in both supervised (SMD=-0.86, 95% CI -1.66 to –0.07, p = 0.032, I^2 = 85.1, k = 6) and unsupervised (p = 0.003, k = 1) formats. Secondary outcomes: not reported.	All studies had low quality (high risk of bias).	10	1-
Schuch et al, 2016 (exercise	Systematic review and meta-analysis 25 studies (all RCTs)	PA: 757 C: 730	Duration of intervention: NA. Frequency: NA	Non active control group.	Depressive symptoms.	Primary outcome: exercise had a large and significant effect on depression (SMD	4 studies of high quality, the others of low quality with high risk of bias.	10	1+

general, adjusted for publication bias)	Depression Diagnosis: DSM, ICD or depressive symptoms rating scales		Intensity: vigorous (k = 8), light to moderate or moderate (k = 9). Type: AE (k = 19), resistance (k = 3), mixed (k = 3), group (k = 13), individual (k = 8), supervised (k = 20), by exercise professionals (k = 11). Time: NA.			adjusted for publication bias = 1.11, 95% CI 0.79-1.43, k = 25) with a failsafe number of 1057. Exercise was effective in both diagnosis made according to DSM (SMD = 1.14, 95% CI 0.46-1.81, $p < 0.001$, $I^2 = 88.5$, k = 9) or depressive symptoms (SMD = 0.801, 95% CI 0.49-1.11, $p < 0.001$, $I^2 = 68.5$, k = 14), high (SMD = 0.882, 95% CI 0.221-1.544, p = 0.009, $I^2 = 90.1$, k = 4) and low (SMD = 1.033, 95% CI 0.66-1.41, $p < 0.001$, $I^2 = 79.2$, k = 21) quality studies, outpatients (SMD = 1.123, 95% CI 0.77-1.47, $p < 0.001$, $I^2 = 84.6$, k = 21) and inpatients (SMD = 0.553, 95% CI 0.167-0.938, p = 0.005, $I^2 = 0$, k = 3), not in nursing home (k = 1), was effective in moderate(SMD = 1.33, 95% CI 0.46-2.197, p = 0.003, $I^2 = 83.4$, k = 6) and vigorous (SMD = 1.342, 95% CI 0.437-2.246, p = 0.004, $I^2 = 91.1$, k = 7), not in light intensity (k = 3), was effective in aerobic exercise (SMD = 1.045, 95% CI 0.653-1.437, $p < 0.001$, $I^2 = 80.97$, k = 19) and mixed (SMD = 0.659, 95% CI 0.248-1.069, p = 0.002, $I^2 = 48.4$, k = 3), not in resistance only (k = 3), was effective in both group (SMD = 0.924, 95% CI 0.51-1.34, $p < 0.001$, $I^2 = 76.1$, k = 13) and individual (SMD = 1.531, 95% CI 0.775-2.29, $p < 0.001$, $I^2 = 90.4$, k = 8) exercise, in supervised (SMD = 0.906, 95% CI 0.05-1.27, $p < 0.001$, $I^2 = 80.3$, k = 18) not in non-supervised (k = 5), with both professional (SMD = 1.261, 95% CI 0.55-1.97, $p < 0.001$, $I^2 = 87.2$, k = 11) or non professional supervision (SMD = 1.094, 95% CI 0.45-1.73, $p < 0.001$, $I^2 = 16.1$, k = 6), in samples without comorbidities (SMD = 1.142, 95% CI 0.81-1.47, $p < 0.001$, $I^2 = 82.6$, k = 22) not in those with comorbidities (k = 3), and regardless the type of publication. Most adjusted analyses suggested publication bias led to an underestimated SMD. Larger effects were found for interventions in MDD, utilising aerobic exercise, at moderate and vigorous intensities, in a supervised and unsupervised format. In MDD, larger effects were found for moderate intensity, aerobic exercise, and interventions supervised by exercise professionals. Secondary outcomes: not reported.			
Krogh et al 2017	Systematic review with trial sequential meta-analysis Diagnosis of MDD according to DSM/ICD	PA: 2498 C:2630	Details of exercise intervention not described.	Active and non-active control groups	Depressive symptoms	In the main analysis exercise improved depressive symptoms SMD − 0.66 (95% CI − 0.86 to −0.46; $p < 0.001$). PA reduces remission RR 0.78, (95% CI 0.68 to 0.90; p = 0.0008).	Main results in agreement with earlier data. However, caution should be given when interpreting the pooling of 4 “high quality” studies, since	10	−1

Table 4 (*Continued*)

Study	Type of review and Sample included	Sample size PA: C:	Physical activity/ exercise intervention	Control group	Outcome measures	Main results	Considerations	AMSTAR	Evidence level
	35 RCTs in main analysis					In 4 "high quality" studies, which includes active control groups, PA may not be effective SMD − 0.11 (−0.41 to 0.18; p = 0.45). No difference in adverse outcomes in PA and control groups.	these include active control groups and number studies likely too small for reliable outcome for sequential meta analysis.		
Schuch et al, 2016 (quality of life)	Systematic review and meta-analysis 6 studies (all RCTs) Depression Diagnosis: DSM, ICD or depressive symptoms rating scales	PA: 106 C: 92	Duration of intervention: mean 14.5 weeks (range 3-32). Frequency: mean 3.5 session/week Intensity: light to moderate (k = 1) or moderate (k = 2) Type: AE (k = 3), supervised by professionals (k = 5), group exercise (k = 3), individual exercise (k = 1) Time: NA	Non active control group	Quality of life	Primary outcomes: exercise improved quality of life (SMD = 0.39, 95%CI 0.47–0.74, p = 0.002, I^2 = 0.0, k = 5), both physical (SMD = 0.53, 95%CI 0.22–0.84, p = 0.001, I^2 = 00.00, k = 5) and psychological (SMD = 0.53, 95%CI 0.22–0.85, p = 0.001, I^2 = 4.89, k = 5), but not in social (SMD = 0.28, 95%CI -0.13 to 0.71,p = 0.18, I^2 = 13.04, k = 5) or environmental domains (SMD = 0.36, 95%CI -0.12 to 0.85,p = 0.14, I^2 = 30.75, k = 5).	Control group did not improve quality of life in any domain.	10	1-
Kvam et al, 2016	Systematic review and meta-analysis 23 studies MDD Diagnosis: DSM or ICD.	PA: 511 C: 466	Duration of intervention: NA Frequency: NA Intensity:NA Type:NA Time:NA	Placebo, usual care, AD, psychotherapy, alternative interventions, no intervention, WL.	Depressive symptoms.	Primary outcome: improvement in depressive symptoms (Hedge's g=-0.68, 95% CI -0.92 to -0.44, p = 0.001, I^2 = 67.99, k = 23). Exercise was effective in studies with (Hedge's g=-0.4, 95% CI -0.7 to -0.11, p = 0.01, k = 10) or without (Hedge's g=-0.91, 95% CI -1.22 to -0.61, p < 0.001, k = 13) blinded outcome, with (Hedge's g=-0.56, 95% CI -0.87 to -0.25, p < 0.001, k = 12) or without (Hedge's g=-0.8, 95% CI -1.15 to -0.46, p < 0.001, k = 11) intention-to-treat, and in studies comparing exercise with no intervention (Hedge's g=-1.24, 95% CI -1.83 to -0.65, k = 4), usual care (Hedge's g=-0.48, 95% CI -0.8 to -0.16, k = 4), but not compared with psychological intervention (Hedge's g=-0.22, 95% CI -0.65 to 0.21, k = 4), or antidepressant treatment (Hedge's g=-0.08, 95% CI -0.33 to 0.18, k = 3), or exercise + antidepressant vs antidepressants only (Hedge's g=-0.5, 95% CI -1.1 to 0.11, k = 4). The significant results were confirmed when considering only studies with blinded outcome (Hedge's g=-0.4, 95% CI -0.69 to -0.11, p = 0.01, k = 10), but not considering blinded outcome with both allocation concealment, and intentio to treat together (Hedge's g=-	Large MA suggests efficacy of exercise while smaller subgroup MA with high quality studies does not. Overall exercise is effective in improving depressive symptoms, and show no difference compared with antidepressants or psychotherapy. However we suggest it should not replace standard treatment for depression.	10	1+

						0.26, 95% CI -0.61 to 0.08, p = 0.14, k = 6). Also, at follow-up (mean 10.75 month) no significant effect was reported (Hedge's g=-0.22, 95% CI -0.53 to 0.09, p = 0.16, k = 7). Secondary outcome: not reported.			
Silveira et al, 2013	Systematic review and meta-analysis 10 studies(2 studies included exercise in control group) - 4 randomized -12 interventions Depression Diagnosis: DSM or ICD or other interview.	Overall 593 subjects	Duration of intervention: mean 12.7 week (range 2-24) Frequency: mean session / week 3.2 (range 2-5). Intensity: low (k = 2), moderate (k = 2), high (k = 1), intensity controlled (k = 13), intensity supervised (k = 13). Type: AE (k = 12), AnE (k = 3) Time: mean session duration42.7 min (range 20-60).	Psychotherapy, treatment as usual, placebo, AD.	Depressive symptoms, response and remission rates.	Primary outcome: exercise improved depressive symptoms pooling AE and AnE (SMD=-0.61, 95%CI -0.88 to -0.33, I^2 = 75.4%, p < 0.001, k = 18), or AE only (SMD=-0.52, 95%CI -0.79 to -0.25, I^2 = 69%, p = 0.001, k = 14), but only with a trend toward significance for AnE (SMD=-0.96, 95%CI -1.97 to 0.05, I^2 = 88.5%, p = 0.06, k = 4). Exercise increased rates of response (RR = 1.49; 95% CI: 1.10–2.03, p = 0.01, k = 9), but not of remission (RR = 1.14; 95% CI: 0.97–1.35, p = 0.12, k = 12). Moreover, age > 6o years old vs younger samples (p = 0.041), and mild depression samples vs mild to moderate ones (p = 0.007) showed higher efficacy of exercise in meta-regression. Secondary outcomes. Not reported.	No study included severe depression. Exercise seems to be effective in increasing rates of response, not only in decreasing depressive symptoms. Also doses of exercise comparable with public health recommendations improve mild to moderate MDD, while lower dose is comparable to placebo.	7	1-
Cooney et al, 2013	Systematic review and meta-analysis 39 randomised controlled trials Depression Diagnosis: as defined by trial authors	Overall 2326	Duration of intervention: NA Frequency: NA Intensity:NA Type:NA Time:NA	Treatment as usual, pharmacological treatment, psychotherapy, other active treatments, no treatment, placebo.	Depressive symptoms	Primary outcome: exercise improved depressive symptoms compared with no treatment or a control intervention (SMD= -0.62, 95%CI -0.81 to -0.42, I^2 = 63%, k = 35), and the effect was confirmed at long-term follow-up (SMD=-0.33, 95%CI -0.63 to -0.03, k = 8). However when only trials with allocation concealment, intention to treat and blinded outcomes were considered together, no effect of exercise on depression was computed (k = 6). Also, exercise did not make any difference compared with psychological intervention (k = 7), or pharmacological intervention (k = 4) Secondary outcome: exercise was considered acceptable with no increased risk of drop-out compared with control intervention (k = 29).	Exercise is effective in improving depression, with no significant depression compared with AD or psychological intervention.	11	1+

Key: AD = antidepressant treatment, AE = aerobic exercise, AnE = anaerobic exercise, BMI = body mass index, BP = blood pressure, C = control, CL = climbing, CRF: cardiorespiratory fitness; CRP: C-reactive protein, EDU = educational intervention, ES = effect size, M—B = mind-body, MDD = major depressive disorder; NA = not available, PA = physical activity, PLC = placebo, RCT = randomized controlled trial, REL = relaxation, ST = stretching, WT = waiting list.

Table 5
Summary of included systematic review results and quality of the evidence.

Population	Outcome	Results	Level of evidence	Gaps/considerations
Schizophrenia	Psychiatric symptoms	Aerobic exercise delivered over 90 minutes MVPA can reduce total, negative and positive symptoms No evidence for strength training.	−1-	Small number of studies and sample size
Schizophrenia	Body weight, BMI, waist circumference, body fat	Inconsistent evidence	−1-	Very small sample sizes and number of studies
Schizophrenia	Cardiorespiratory fitness	Aerobic exercise increases cardiorespiratory fitness over 12 weeks.	−1-	Small number of RCTs.
Schizophrenia	Cognition and subdomains	Aerobic exercise can improve global cognition, working memory, social cognition and attention/vigilance (10 RCTs). Greater effects seen for higher dose of PA and interventions delivered by exercise professionals	−1-	Small number RCTs. Mechanisms not understood, but evidence does not support hippocampal volume changes or changes in BDNF underlying response.
SMI	Cardiorespiratory fitness	Aerobic exercise can improve cardiorespiratory fitness versus control conditions.	−1-	Interventions of higher intensity, supervised by qualified professionals yield larger effect sizes.
Major depression	Depressive symptoms	Consistent evidence that aerobic exercise is effective versus control conditions post follow up in reducing depressive symptoms. Consistent evidence that exercise has a similar effect versus psychological therapy and antidepressant treatment	1+	Exercise is only effective immediately after follow up. There are too few long term follow up studies to make firm conclusions about the long-term effectiveness of exercise. There are few studies that have directly compared exercise versus psychological or pharmacological interventions.
Major depression	Cardiorespiratory fitness	Exercise is effective at improving cardiorespiratory fitness versus control conditions.	1-	Limited to a few small RCTs with no long term data.
Major depression	Quality of Life	Exercise improves overall QOL, physical and psychological QOL domains. No evidence for other QOL domains.	1-	Limited to a few small RCTs with no long term data.
Major depression	Cognition	Aerobic exercise does not improve global cognition or any subdomain versus control conditions.	1-	Limited to a few small RCTs with no long term data.
Major depression	Anxiety symptoms	No evidence	2+	Limited to one RCT
Major depression	Physical health outcomes	No evidence for body weight, waist circumference, blood glucose, BMI, body fat.	2+	Limited to few/one RCT in each outcome
Bipolar disorder	Mood symptoms	Limited evidence from one RCT that exercise improves depressive symptoms and reduces stress.	2+	Limited to one RCT
Bipolar disorder	Weight	Evidence from one RCT that exercise is more effective than control conditions reducing weight.	2+	Limited to one RCT

Key: MVPA = moderate-vigorous physical activity, BMI = body mass index, PA = physical activity.

11, evidence level 1+). Exercise was effective in studies with (Hedge's g = -0.40, 95% CI = -0.70 to -0.11, P = 0.01, k = 10) or without (Hedge's g=-0.91, 95% CI = -1.22 to -0.61, P < 0.001, k = 13) blinded outcome, with (Hedge's g=-0.56, 95% CI -0.87 to -0.25, p < 0.001, k = 12) or without (Hedge's g =-0.80, 95% CI = -1.15 to -0.46, p < 0.001, k = 11) intention-to-treat, and in studies comparing exercise with no intervention (Hedge's g = -1.24, 95% CI = -1.83 to -0.65, k = 4), and with usual care (Hedge's g = -0.48, 95% CI = -0.8 to -0.16, k = 4). There was no difference in exercise versus psychological interventions (Hedge's g = -0.22, 95% CI -0.65 to 0.21, k = 4), or antidepressant treatment (Hedge's g = -0.08, 95% CI = -0.33 to 0.18, k = 3), indicating exercise demonstrated comparable efficacy versus these established interventions. However, information on symptom severity was not available. Of note, beneficial effects were confirmed when considering only studies with blinded outcomes (Hedge's g = -0.40, 95% CI -0.69 to -0.11, P = 0.01, k = 10), but not when considering blinded outcomes with both adequate allocation concealment and intention-to-treat together (Hedge's g = -0.26, 95% CI = -0.61 to 0.08, P = 0.14, k = 6). Also, at longer follow-up (mean 10.75 month) no significant effect was reported (Hedge's g =-0.22, 95% CI -0.53 to 0.09, P = 0.16, k = 7).

More recently, a meta-analysis [81] (AMSTAR 10, evidence level 1+) attempted to address some of the criticisms of the Cochrane review [83], such as the inclusion of a number of in-eligible trials, comparing exercise versus other exercise interventions, and the absence of adjusting for publication bias. The authors [81] found across 25 RCTs (intervention 757, control 730) that exercise versus non-active interventions over a mean of 14 weeks resulted in a large improvements of depressive symptoms (SMD = 1.11, 95% CI % = 0.79–1.43, k = 25) with a failsafe number of 1057. Exercise was effective both when the diagnosis was made according to DSM [61] (SMD = 1.14, 95% CI = 0.46–1.81, P < 0.001, I^2 = 88.5, k = 9) or depressive symptoms (SMD = 0.801, 95% CI = 0.49–1.11, P < 0.001, I^2 = 68.5, k = 14), high (SMD = 0.882, 95% CI = 0.221–1.544, P = 0.009, I^2 = 90.1, k = 4) and low (SMD = 1.033, 95% CI = 0.66–1.41, P < 0.001, I^2 = 79.2, k = 21) quality studies, outpatients (SMD = 1.123, 95% CI = 0.77–1.47, p < 0.001, I2 = 84.6, k = 21) and inpatients (SMD = 0.553, 95% CI = 0.167-0.938, P = 0.005, I^2 = 0, k = 3), but not in a nursing home (k = 1). Exercise was effective at moderate (SMD = 1.33, 95% CI 0.46–2.197, P = 0.003, I^2 = 83.4, k = 6) and vigorous (SMD = 1.342, 95% CI = 0.437–2.246, P = 0.004, I^2 = 91.1, k = 7), but not at light intensity (k = 3), and was effective as aerobic exercise (SMD = 1.045, 95% CI = 0.653–1.437, P < 0.001, I^2 = 80.97). The same author group also reported that exercise was effective in improving depressive symptoms in older adults (SMD = -0.90, 95%CI = 0.28–1.51, P = 0.004, I [2] = 81.63, P = 0.001, k = 8). In addition, a recent meta-analysis [82] (AMSTAR 10, evidence level 1+) confirmed that exercise was effective in reducing depressive symptoms, including those with and without blinded outcomes and with or without intention-to-treat analysis (see Table 4). The authors [82] also confirmed results from the Cochrane review that exercise was as effective as psychological intervention and antidepressant treatment for depressive symptoms (see Table 4). In another review regarding mental health symptoms [84] (AMSTAR 7, evidence level -1), exercise increase response but not remission of MDD (see Table 4). Finally, a trial sequential meta-analysis [85] (AMSTAR 10, evidence level -1) confirmed earlier results that exercise was effective for MDD (SMD − 0.66, 95% CI − 0.86 to −0.46; p < 0.001). Moreover, the authors tentatively suggested that when pooling four RCTs of "high quality" with a trial sequential meta-analysis (two of which were their own studies and concerns have been raised about the inappropriate use of active control groups [90]) that exercise may no longer be effective.

A narrative systematic review [76] (AMSTAR 4, evidence level -1) suggested that exercise did not influence anxiety symptoms, oxygen uptake, blood glucose, body fat or functioning versus control conditions, although all of these outcomes were limited to one study only. A recent meta-analysis of 8 RCTs [77] (AMSTAR 10, evidence level -1) found that aerobic exercise was not effective for global cognition (Hedges' g = 0.07, 95% CI = -0.08 to 0.24, I^2 = 0%) nor for any cognitive subdomains. A meta-analysis of 7 RCTs [78] demonstrated that aerobic exercise over approximately 12 weeks improved cardiorespiratory fitness (Hedge's g = 0.64, 95%CI = 0.32–0.96, P = 0.001, I^2 = 67%, k = 8) (AMSTAR 10, evidence level 1+). Exercise also improved quality of life (QOL) overall (SMD = 0.39, 95%CI = 0.47–0.74, P = 0.002, I^2 = 0.0, k = 5) in addition to physical (SMD = 0.53, 95%CI = 0.22–0.84, P = 0.001, I^2 = 00.00, k = 5) and psychological (SMD = 0.53, 95%CI = 0.22–0.85, P = 0.001, I^2 = 4.89, k = 5) QoL domains. However, no effect was seen in social (SMD = 0.28, 95%CI = -0.13 to 0.71,p = 0.18, I^2 = 13.04, k = 5) or environmental QoL domains (SMD = 0.36, 95%CI = -0.12 to 0.85, P = 0.14, I^2 = 30.75, k = 5).

4.7. Dropout, adverse events and economic evaluations of exercise interventions in major depression

A meta-analysis of 31 RCTs [91] reported that the dropout rate adjusted for publication bias was 17.2% (95%CI = 13.5–21.7) in MDD only. In MDD participants, higher baseline depressive symptoms (β = 0.0409, 95%CI = 0.0809-0.0009, P = 0.04) predicted greater dropout, whilst supervised interventions delivered by physiotherapists (β = -1.2029, 95%CI = -2.0967 to -0.3091, P = 0.008) and exercise physiologists (β = -1.3396, 95%CI = -2.4478 to -0.2313, P = 0.01) were associated with lower dropout. A comparative meta-analysis (N = 29) established dropout was lower in exercise than control conditions (OR = 0.642, 95%CI = 0.43-0.95, P = 0.02).

Information on adverse events was limited in the reported systematic reviews. One review [83] reported that 6 RCTs reported adverse events. These included muscular pain/symptoms, fatigue and increased depressive symptoms, but there was no difference versus those reported in control conditions. Another review confirmed there were no differences in serious or non-serious adverse events versus control conditions [85].

To the best of our knowledge, there have been no economic evaluations of the cost effectiveness of delivering exercise interventions for people with MDD.

4.8. Bipolar disorder

In total, 2 systematic reviews reported the benefits of exercise for BD [74,75]. Both systematic reviews were rated with an AMSTAR score of 4. The evidence was very limited because of the number of eligible studies in BD patients. A summary of the effects of exercise in BD are reported in Table 5. One review identified only two studies that included people with BD, [74] finding some evidence that exercise may improve depressive symptoms and reduce stress, but observing no influence on function, general symptoms or clinical global impression. In the other systematic review, only one study was identified in BD patients, 75] which suggested that exercise decreased body weight more than in the control group.

4.9. Dropout, adverse events and economic evaluations of exercise interventions in bipolar disorder

We found no reports in the included systematic reviews of dropout rates, adverse events or economic evaluations.

4.10. Recommendations

Based on our extensive systematic review of the literature, we have made ten recommendations for future research (where gaps

are evident) and clinical practice based on the degree of evidence and grades in line with the SIGN methodology checklist. In line with the SIGN and previous EPA guidelines, [66] recommendations were graded as A (meta-analysis, systematic review or other level 1 evidence), B (meta-analysis, systematic review or RCT with moderate or high risk of bias), C (large body of evidence from intervention studies, observational data), or D (expert opinion).

5. Research recommendations

5.1. For all SMI groups, more research is needed into the effects of PA interventions during the prodromal and early phase of illness onset (Based on expert opinion, D)

The majority of research on the effect of PA has been conducted in patients with established SMI. However, in the case of physical health outcomes, there is evidence from the general population that using lifestyle changes to prevent deterioration in metabolic health is a more feasible and effective approach than attempting to reverse chronic cardio-metabolic diseases [92]. Research is needed to determine whether exercise interventions in the early stages of SMI likewise have a positive effect on physical and mental health outcomes. Furthermore, research is needed to assess whether using exercise to improve mental health and psychosocial functioning shortly after illness onset may reduce the likelihood of long-term functional disability, or increase the likelihood of achieving a full and sustained recovery. Given this situation, we recommend a greater research emphasis on evaluating PA interventions during the prodromal phase and first/early presentation of SMI.

5.2. To optimize treatment 'reach', research should focus on establishing pragmatic, scalable methods for delivering PA as a treatment for SMI (Based on expert opinion, D)

Research priorities should shift from efficacy studies to pragmatic effectiveness trials. Specifically, there is a need to develop replicable and scalable methods for delivering PA interventions to people with SMI, in a format which is accessible, engaging and effective for large numbers of patients. There is sufficient evidence to indicate that the most effective and engaging interventions will be those that are (i) delivered by qualified exercise professionals (rather than mental health staff), and (ii) delivered at sufficient levels of intensity to significantly improve physical capacities, such as cardiorespiratory fitness. Whilst the evidence is clear that better treatment outcomes and less dropout are achieved across SMI for PA interventions delivered by qualified exercise professionals, the potential benefits of training mental health staff (e.g., psychologists, psychiatric nurses - of whom there are many more) on principles of PA in delivering exercise interventions should be evaluated.

5.3. Controlled trials of exercise for SMI should aim to determine the optimal dose-response of PA needed to treat SMI and should focus on implementation and culture in clinical practice (Based on expert opinion, D)

Whilst there is some evidence from exercise trials in MDD that moderate/high intensity PA is associated with larger effect sizes than low-intensity PA for mental health and cardiorespiratory fitness [81] and for better cognitive outcomes in established schizophrenia [67], more research is specifically required to ascertain the optimum frequency, intensity, time and type of interventions in each SMI, although it is important to note this may vary for each individual based on their preferences and/or illness characteristics. In addition, very few systematic reviews reported adverse events. Future studies should carefully assess any adverse events, particularly in light of any cardiovascular risk and events. This may include screening for cardiovascular risk and appropriately individualizing the optimal frequency and intensity of PA, which has been covered extensively elsewhere [93,94]. Of most importance, future translational research focussing on implementation into clinical practice is urgently required. This should involve determining optimal motivational frameworks and understanding cultures in practice that enable the optimal uptake and maintenance of PA.

5.4. Research examining the effects of interventions to reduce sedentary behaviours and increase PA is needed (Based on expert opinion, D)

Recent meta-analyses have demonstrated that people with SMI are highly sedentary [49]. With increasing evidence that sedentary behaviours have independent adverse effects on somatic health [37], research is needed to investigate if sedentary behaviours can be reduced in this population and tease out the relative importance of reducing sedentary behaviours in the context of structured exercise interventions.

5.5. The underlying neurobiological mechanisms of PA in SMI are inadequately understood and require further investigation (Based on expert opinion, D)

Several tenable theories have been proposed to explain the positive effects of PA in SMI, but the results are unclear. In particular, it is uncertain what 'dose' of exercise is needed to elicit the purported biological mechanisms, and how these interact with the psycho-social benefits of exercise. Future research should explore the underlying mechanisms of PA efficacy in all SMIs.

5.6. Undertake long term and cost-effectiveness analyses of PA interventions (Based on expert opinion, D)

Whilst there is an increasing evidence base on the efficacy of PA for SMI, there is an absence of cost effectiveness studies. Undertaking cost-effectiveness research should be a priority. There are also relatively few long term ($\geq$12 months) trials, although a recent large RCT lasting 12 months demonstrated that PA was as effective as internet-delivered CBT, and both were better than the control group [95].

6. Clinical practice recommendations

6.1. Physical activity should be used as a treatment for mild-moderate depression to improve symptoms and physical fitness (good evidence, A)

There is now an abundance of data demonstrating that as an adjunctive treatment, PA is effective in reducing depressive symptoms in people with MDD. Specifically, based on current evidence, we recommend that intervention consists of 2–3 sessions of supervised aerobic and/or aerobic and resistance training exercise a week of 45–60 minutes duration of moderate intensity. The literature regarding resistance training as a standalone intervention for MDD is limited, but growing. To date, there have been limited direct head-to-head comparisons of different types of exercise interventions (in terms of frequency, intensity, time and type), which precludes definitive conclusions being made about the superiority or better acceptability (or lack thereof) of specific forms of PA, and our current knowledge is derived primarily from interventions comparing "PA" versus non-active interventions. In order to achieve optimal outcomes and less dropouts, the evidence base indicates that physiotherapists/qualified exercise professionals should lead and

supervise PA interventions. However, since qualified exercise professionals are not available in each setting, the efficacy and effectiveness of training other personnel in the principles and delivery of PA requires further study. Finally, there is also good evidence that PA can improve cardiorespiratory fitness in people with depression [78].

6.2. Physical activity should be utilised as an adjunctive treatment for schizophrenia-spectrum disorders, to improve symptoms, cognition and QoL (good evidence, B)

Our review indicates that PA is an effective adjunct to improve symptoms, global cognition and various subdomains, and quality of life in schizophrenia-spectrum disorders. In fact, at least in indirect comparison, the benefits of PA for cognition seem to be comparable to other psychological interventions (e.g., cognitive remediation) and should be a core part of multidisciplinary treatment. The most consistent evidence to date is available for aerobic exercise that meets 150 min of moderate to vigorous PA per week. There are limited data available specifically on resistance training for people with schizophrenia-spectrum disorders and data are inadequate comparing the potential superiority of various forms of PA to each other. Nonetheless, interventions supervised by qualified professionals, with a motivational component result in less dropout.

6.3. Physical activity should be used to improve physical health in people with SMI (Some evidence, C)

Whilst there is an abundance of evidence for PA to prevent the onset of a number of physical diseases (e.g., cardiovascular disease) and to have the potential to improve these conditions in the general population, the evidence base in individual SMIs is mixed, possibly due to poor adherence and the paucity of studies that have targeted this important topic. However, there is some indication that PA can improve cardiovascular disease risk markers in people with SMI. Given the weight of evidence in the general population and some initial data in people with SMI, we advocate that PA forms a core part of preventing and managing poor physical health in people with SMI. Nevertheless, more research should be performed in this area to further strengthen the support for this recommendation.

6.4. People with SMI should be screened for PA habits in primary and secondary care (Based on expert opinion, D)

In light of the evidence of the health benefits of PA, the use of brief PA screening in primary/secondary care in the general population as a health indicator and to manage chronic conditions is common [96,97]. A previous systematic review [98] identified, no specific self-report PA tool has robust psychometric properties and can be advocated for routine use in clinical practice. Nonetheless, given that people with all SMIs are known to engage in low levels of PA and high SB [49] a routine measure of PA to monitor PA habits could prove useful. To the best of our knowledge, only one PA tool, the SIMPAQ [99] has been developed specifically for use to measure PA and SB in clinical practice. Given the above literature, we advocate that people with SMI are screened for PA and advised on increasing activity levels in primary and secondary services. Further research is needed to identify a practical and valid measure that can be used in clinical care.

7. Conclusion

There is now considerable empirical evidence supporting the use of PA interventions in the treatment of MDD and schizophrenia-spectrum disorders. Specifically, our meta-review supports the use of aerobic exercise of moderate-vigorous intensity at a frequency of 2–3 times a week, ideally supervised by qualified professionals and achieving 150 min of MVPA per week in order to improve outcomes in people with MDD and schizophrenia-spectrum disorders. There is also some evidence that a combination of aerobic and resistance training meeting the above frequency, intensity and time criteria can improve outcomes in people with MDD and schizophrenia-spectrum disorders. There is growing interest in the use of resistance training as a standalone PA intervention. However, the literature is equivocal in both MDD and schizophrenia-spectrum disorders. Currently, the evidence for use of PA in patients with BD is promising, but limited by the paucity of studies, and it is therefore not possible to reach any firm conclusions regarding population-specific recommendations above and beyond those aimed at the general population. Across all disorders, there have been limited interventions that have specifically compared various forms of PA versus one another, which again precludes reaching any firm conclusions based on the relative superiority of the different forms of PA, and one should be aware that our knowledge to date is largely drawn from studies comparing PA versus non-active control conditions. The underlying psychobiological mechanisms of the benefits derived from PA are only poorly understood, and further research is needed to elucidate causal relationships between exercise and improvements in the mental and physical domains of people with SMI. Finally, due to absence of data, it is currently unclear whether PA is a cost-effective treatment option, and more work is needed to establish the financial aspects of this mode of treatment compared with conventional approaches, taking into account the various domains of lives of people with SMI that PA can affect.

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Conflict of interest

BS, DV, JF, MH, MS, MG, NV, FK have no conflicts of interest to declare.

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References

[1] Whiteford H.A., Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS ONE 2015;10(2):e0116820.

[2] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72(4):334–41.
[3] Nielsen RE, Uggerby AS, Jensen SOW, McGrath JJ. Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades–a Danish nationwide study from 1980 to 2010. Schizophr Res 2013;146(1-3):22–7.
[4] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76.
[5] Hayes JF, Miles J, Walters K, King M, Osborn DPJ. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand 2015.
[6] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T, Whiteford L, Degenhardt J. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;9904:1575–86.
[7] Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014;13(2):153–60.
[8] Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14(2):119–36.
[9] Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, Thapa-Chhetri N, Fornaro M, Gallicchio D, Collantoni E, Pigato G, Favaro A, Monaco F, Kohler C, Vancampfort D, Ward PB, Gaughran F, Carvalho AF, Stubbs Correll B, M, Solmi N. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017;16(2):163–80.
[10] Vancampfort D, Correll CU, Galling B, Probst M, DeHert M, Ward PB, Rosenbaum S, Gaughran F, Lally J, Stubbs B, Vancampfort CU, Correll B. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 2016;2:166–74.
[11] Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU, Vancampfort B, Stubbs AJ. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 2015;3:339–47.
[12] Partti K, Vasankari T, Kanervisto M, Perälä J, Saarni SI, Jousilahti P, Lönnqvist J, Suvisaari J, Partti T, Vasankari M. Lung function and respiratory diseases in people with psychosis: population-based study. Br J Psychiatry 2015;1:37–45.
[13] Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015;72 (12):1172–81.
[14] Stubbs B, De Hert M, Sepehry AA, Correll CU, Mitchell AJ, Soundy A, Detraux J, Vancampfort D, Stubbs M, De Hert AA. A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia. Acta Psychiatr Scand 2014;130(6):470–86.
[15] Stubbs B, Koyanagi A, Veronese N, Vancampfort D, Solmi M, Gaughran F, Carvalho AF, Lally J, Mitchell AJ, Mugisha J, Correll CU, Stubbs A, Koyanagi N. Physical multimorbidity and psychosis: comprehensive cross sectional analysis including 242,952 people across 48 low- and middle-income countries. BMC Med 2016;1:189.
[16] Metzler S, Dvorsky D, Wyss C, Müller M, Gerstenberg M, Traber-Walker N, Walitza S, Theodoridou A, Rössler W, Heekeren K, Metzler D, Dvorsky C. Changes in neurocognitive functioning during transition to manifest disease: comparison of individuals at risk for schizophrenic and bipolar affective psychoses. Psychol Med 2015;10:2123–34.
[17] Amann B, Gomar JJ, Ortiz-Gil J, McKenna P, Sans-Sansa B, Sarró S, Moro N, Madre M, Landin-Romero R, Vieta E, Goikolea JM, Salvador R, Pomarol-Clotet E, Amann JJ, Gomar J. Executive dysfunction and memory impairment in schizoaffective disorder: a comparison with bipolar disorder, schizophrenia and healthy controlsó[corrected][published erratum appears in PSYCHOL MED 2012 Oct; 42: 2136]. Psychol Med 2012;10:2127–35 2129p.
[18] Elias LR, Miskowiak KW, Vale AM, Köhler CA, Kjærstad HL, Stubbs B, Kessing LV, Vieta E, Maes M, Goldstein BI, Carvalho AF, Elias KW, Miskowiak AM. Cognitive impairment in euthymic pediatric bipolar disorder: a systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2017;4:286–96.
[19] Koster LS, Carbon M, Correll CU. Emerging drugs for schizophrenia: an update. Expert Opin Emerg Drugs 2014;19(4):511–31.
[20] Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr 2014;19(Suppl 1)38–52 quiz 35-37, 53.
[21] Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM, Leucht A, Cipriani L. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;9896:951–62.
[22] Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. JAMA Psychiatry 2017;74(7):675–84.
[23] Turner DT, van der Gaag M, Karyotaki E, Cuijpers P. Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. Am J Psychiatry 2014;171(5):523–38.
[24] Jobst A, Brakemeier EL, Buchheim A, Caspar F, Cuijpers P, Ebmeier KP, Falkai P, Jan van der Gaag R, Gaebel W, Herpertz S, Kurimay T, Sabaß L, Schnell K, Schramm E, Torrent C, Wasserman D, Wiersma J, Padberg Jobst F, EL, Brakemeier A. European Psychiatric Association Guidance on psychotherapy in chronic depression across. Europe Eur Psychiatry 2016;33:18–36.
[25] Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry 2016;15(3):245–58.
[26] Huhn M, Tardy M, Spineli LM, Kissling W, Förstl H, Pitschel-Walz G, Leucht C, Samara M, Dold M, Davis JM, Leucht S, Huhn M, Tardy LM. Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic overview of meta-analyses. JAMA Psychiatry 2014;6:706–15.
[27] Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 2013;37(8):1680–91.
[28] Cella M, Preti A, Edwards C, Dow T, Wykes T. Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis. Clin Psychol Rev 2017;52:43–51.
[29] Naci H, Ioannidis JPA. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. BMJ 2013;347: f5577–f5577.
[30] Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C, Nelson WJ, Rejeski SN. Physical activity and public health in older adults: recommendation from the american college of sports medicine and the American heart association. Med Sci Sports Exerc 2007;8:1435–45.
[31] Sattelmair J, Pertman J, Ding EL, Kohl 3rd HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation 2011;124(7):789–95.
[32] Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A, Haskell IM, Lee RR. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;8:1423–34.
[33] Hayashino Y, Jackson JL, Hirata T, Fukumori N, Nakamura F, Fukuhara S, Tsujii S, Ishii H, Hayashino JL, Jackson T. Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Metab Clin Exp 2014;3:431–40.
[34] Bergström G, Behre CJ, Schmidt C. Moderate intensities of leisure-time physical activity are associated with lower levels of high-sensitivity C-reactive protein in healthy middle-aged men. Angiology 2012;63(6):412–5.
[35] Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctôt KL, Carvalho AF, Kohler TH, Freitas M. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 2017;5:373–87.
[36] Sedentary behaviour research N. letter to the editor: standardized use of the terms' sedentary' and' sedentary behaviours'. Appl Physiol Nutr Metab 2012;37(3):540–2.
[37] Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA, Biswas PI, Oh GE. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015;2:123–32.
[38] Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone / Kodama HK, Saito S. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009;19:2024–35.
[39] Voelcker-Rehage C, Niemann C. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci Biobehav Rev 2013;37(9, Part B):2268–95.
[40] Stubbs B, Chen LJ, Chang CY, Sun WJ, Ku PW. Accelerometer-assessed light physical activity is protective of future cognitive ability: a longitudinal study among community dwelling older adults. Exp Gerontol 2017;91:104–9.
[41] Snowden M, Steinman L, Mochan K, Grodstein F, Prohaska TR, Thurman DJ, Brown DR, Laditka JN, Soares J, Zweiback DJ, Little D, Anderson LA, Snowden L, Steinman K. Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. J Am Geriatr Soc 2011;4:704–16.
[42] Prakash RS, Voss MW, Erickson KI, Kramer AF. Physical activity and cognitive vitality. Annu Rev Psychol 2015;66(1):769–97.
[43] Stanmore E, Stubbs B, Vancampfort D, de Bruin ED, Firth J. The effect of active video games on cognitive functioning in clinical and non-clinical populations: a meta-analysis of randomized controlled trials. Neurosci Biobehav Rev 2017;78:34–43.
[44] Firth J, Stubbs B, Vancampfort D, Schuch F, Lagopoulos J, Rosenbaum S, Ward PB, Firth B, Stubbs D. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. Neuroimage 2018;166:230–8.
[45] Schuch F, Vancampfort, D., Firth., J., Rosenbaum., Ward, PB., Silva, E., Hallgren, Dunn, AL., Deslandes.,A., Fleck MC., Carvalho A.F., Stubbs B., Physical activity and incident depression: A meta-analysis of prospective cohort studies. In. American Journal of Psychiatry In press 1;175 (7): 631-648.
[46] Stubbs B, Firth J, Berry A, Schuch FB, Rosenbaum S, Gaughran F, Veronesse N, Williams J, Craig T, Yung AR, Vancampfort D, Stubbs, Firth JA. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression. Schizophr Res 2016;176(2-3):431–40.

[47] Vancampfort D, Firth J, Schuch F, Rosenbaum S, De Hert M, Mugisha J, Probst M, Stubbs B, Vancampfort J, Firth F. Physical activity and sedentary behavior in people with bipolar disorder. a systematic review and meta-analysis J Affect Disord 2016;201:145–52.

[48] Schuch F, Vancampfort D, Firth J, Rosenbaum S, Ward P, Reichert T, Bagatini NC, Bgeginski R, Stubbs B, Schuch D, Vancampfort J. Physical activity and sedentary behavior in people with major depressive disorder: a systematic review and meta-analysis. J Affect Disord 2016;210:139–50.

[49] Vancampfort D, Firth J, Schuch FB, Rosenbaum S, Mugisha J, Hallgren M, Probst M, Ward PB, Gaughran F, De Hert M, Carvalho AF, Stubbs B, Vancampfort J, Firth FB. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. World Psychiatry 2017;3:308–15.

[50] (WHO) WHO. 10 facts on physical activity. In: 2014.

[51] Vancampfort D, Rosenbaum S, Schuch F, Ward PB, Richards J, Mugisha J, Probst M, Stubbs B, Vancampfort S, Rosenbaum F. Cardiorespiratory fitness in severe mental illness: a systematic review and meta-analysis. Sports Med 2016.

[52] Vancampfort D, Correll CU, Probst M, Sienaert P, Wyckaert S, De Herdt A, Knapen J, De Wachter D, De Hert M, Vancampfort CU, Correll M. A review of physical activity correlates in patients with bipolar disorder. J Affect Disord 2013;3:285–91.

[53] Vancampfort D, Knapen J, Probst M, Scheewe T, Remans S, De Hert M. A systematic review of correlates of physical activity in patients with schizophrenia. Acta Psychiatr Scand 2012;125(5):352–62.

[54] Vancampfort D, Stubbs B, Sienaert P, Wyckaert S, De Hert M, Rosenbaum S, Probst M, Vancampfort B, Stubbs P. What are the factors that influence physical activity participation in individuals with depression? A review of physical activity correlates from 59 studies. Psychiatr Danub 2015;3:210–24.

[55] Firth J, Rosenbaum S, Stubbs B, Gorczynski P, Yung AR, Vancampfort D. Motivating factors and barriers towards exercise in severe mental illness: a systematic review and meta-analysis. Psychol Med (Paris) 2016;46(14): 2869–81.

[56] Vancampfort D, Stubbs B, Ward PB, Teasdale S, Rosenbaum S. Integrating physical activity as medicine in the care of people with severe mental illness. Aust N Z J Psychiatry 2015;49(8):681–2.

[57] Vancampfort D, Rosenbaum S, Probst M, Connaughton J, du Plessis C, Yamamoto T, Stubbs B, Vancampfort S, Rosenbaum M. What are the top 10 physical activity research questions in schizophrenia? Disabil Rehabil 2016;22:2235–43.

[58] Vancampfort D, Rosenbaum S, Probst M, Connaughton J, du Plessis C, Yamamoto T, Stubbs B, Vancampfort S, Rosenbaum M. Top 10 research questions to promote physical activity in bipolar disorders: a consensus statement from the International Organization of Physical Therapists in Mental Health. J Affect Disord 2016;195:82–7.

[59] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Clin Trials 2009;6(7):1–6.

[60] Heun R, Gaebel W. The relevance of EPA guidance papers in the framework of the European Psychiatric Association. Eur Psychiatry 2015;30(3):357–9.

[61] Association AP. Diagnostic and statistical manual of mental disorders – DSM-IV-TR. 4th edition American Psychiatric Association; 2000.

[62] World Health organisation. The ICD-10 classification of mental and behavioural disorders – diagnostic criteria for research.. 1993.

[63] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100(2):126–31.

[64] Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M, Shea C, Hamel GA. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009;10:1013–20.

[65] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM, Shea JM, Grimshaw GA. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10–7.

[66] Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, Maric NP, Salokangas RK, Riecher-Rössler A, van der Gaag M, Meneghelli A, Nordentoft M, Marshall M, Morrison A, Raballo A, Klosterkötter J, Ruhrmann Schmidt SF. EPA guidance on the early intervention in clinical high risk states of psychoses. Eur Psychiatry 2015;3:388–404.

[67] Firth J, Stubbs B, Rosenbaum S, Vancampfort D, Malchow B, Schuch F, Elliott R, Nuechterlein KH, Yung Firth AR, Stubbs BS. Aerobic exercise improves cognitive functioning in people with schizophrenia: a systematic review and meta-analysis. Schizophr Bull 2016.

[68] Firth J, Cotter J, Elliott R, French P, Yung AR. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. Psychol Med 2015;45(7):1343–61.

[69] Firth J, Cotter J, Carney R, Yung AR. The pro-cognitive mechanisms of physical exercise in people with schizophrenia. Br J Pharmacol 2017;174(19):3161–72.

[70] Soundy A, Muhamed, A., Stubbs, B., Probst, M., Vancampfort, D. The benefits of walking for individuals with schizophrenia spectrum disorders: A systematic review. In. International Journal of Therapy and Rehabilitation 21 (9), 410-4202014.

[71] Martin H, Beard, S., Clissold, N., Androas, K., Currey, L. Combined aerobic and resistance exercise interventions for individuals with schizophrenia: A systematic review. In. Mental Health and Physical Activity, March, pg 147–1552017.

[72] Sanada K, Zorrilla I, Iwata Y, Bermúdez-Ampudia C, Graff-Guerrero A, Martínez-Cengotitabengoa M, González-Pinto A, Sanada I, Zorrilla Y, wata I. The efficacy of non-pharmacological interventions on brain-derived neurotrophic factor in schizophrenia: a systematic review and meta-analysis. Int J Mol Sci 2016;10:.

[73] Vancampfort D, Rosenbaum S, Ward PB, Stubbs B. Exercise improves cardiorespiratory fitness in people with schizophrenia: a systematic review and meta-analysis. Schizophr Res 2015;169(1-3):453–7.

[74] de Sá Filho AS, de Souza Moura AM, Lamego MK, Ferreira Rocha NB, Paes F, Oliveira AC, Lattari E, Rimes R, Manochio J, Budde H, Wegner M, Mura G, Arias-Carrión O, Cheniaux E, Yuan TF, Nardi AE, Machado de Sa Filho SAM, de Souza Moura MK. Potential therapeutic effects of physical exercise for bipolar disorder CNS. Neurol Disord Drug Targets 2015;10:1255–9.

[75] Thomson D, Turner A, Lauder S, Gigler ME, Berk L, Singh AB, Pasco JA, Berk M, Sylvia L, Thomson A, Turner S. A brief review of exercise, bipolar disorder, and mechanistic pathways. Front Psychol 2015;6:147.

[76] de Souza Moura AM, Lamego MK, Paes F, Ferreira Rocha NB, Simoes-Silva V, Rocha SA, de Sá Filho AS, Rimes R, Manochio J, Budde H, Wegner M, Mura G, Arias-Carrión O, Yuan TF, Nardi AE, Machado S, de Souza Moura MK, Lamego F. Comparison among aerobic exercise and other types of interventions to treat depression: a systematic review. CNS Neurol Disord Drug Targets 2015;9:1171–83.

[77] Brondino N, Rocchetti M, Fusar-Poli L, Codrons E, Correale L, Vandoni M, Barbui C, Politi P, Brondino Rocchetti ML. A systematic review of cognitive effects of exercise in depression. Acta Psychiatr Scand 2017;4:285–95.

[78] Stubbs B, Rosenbaum S, Vancampfort D, Ward PB, Schuch FB. Exercise improves cardiorespiratory fitness in people with depression: a meta-analysis of randomized control trials. J Affect Disord 2016;190:249–53.

[79] Schuch FB, Vancampfort D, Rosenbaum S, Richards J, Ward PB, Stubbs B. Exercise improves physical and psychological quality of life in people with depression: a meta-analysis including the evaluation of control group response. Psychiatry Res 2016;241:47–54.

[80] Schuch FB, Vancampfort D, Rosenbaum S, Richards J, Ward PB, Veronese N, Solmi M, Cadore EL, Stubbs B, Schuch Vancampfort DS. Exercise for depression in older adults: a meta-analysis of randomized controlled trials adjusting for publication bias. Rev Bras Psiquiatr 2016;3:247–54.

[81] Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J Psychiatr Res 2016;77:42–51.

[82] Kvam S, Kleppe CL, Nordhus IH, Hovland A. Exercise as a treatment for depression: a meta-analysis. J Affect Disord 2016;202:67–86.

[83] Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE, Cooney K, Dwan CA. Exercise for depression Cochrane Database. Syst Rev 2013;9:CD004366.

[84] Silveira H, Moraes H, Oliveira N, Coutinho ES, Laks J, Deslandes A. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. Neuropsychobiology 2013;67(2):61–8.

[85] Krogh J, Hjorthoj C, Speyer H, Gluud C, Nordentoft M. Exercise for patients with major depression: a systematic review with meta-analysis and trial sequential analysis. BMJ Open 2017;7(9):e014820.

[86] Rosenbaum S, Tiedemann A, Sherrington C, Curtis J, Ward PB. Physical activity interventions for people with mental illness: a systematic review and meta-analysis. J Clin Psychiatry 2014;75(9):964–74.

[87] Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, Kierer A, Müller S, Oest M, Meyer T, Backens M, Schneider-Axmann T, Thornton AE, Honer WG, Falkai P, Pajonk T, Wobrock O. Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry 2010;2:133–43.

[88] Keller-Varady K, Varady PA, Röh A, Schmitt A, Falkai P, Hasan A, Malchow B, Keller-Varady PA, Varady A. A systematic review of trials investigating strength training in schizophrenia spectrum disorders. Schizophr Res 2018;192:64–8.

[89] Vancampfort D, Rosenbaum S, Schuch FB, Ward PB, Probst M, Stubbs B. Prevalence and predictors of treatment dropout from physical activity interventions in schizophrenia: a meta-analysis. Gen Hosp Psychiatry 2016;39:15–23.

[90] Ekkekakis P. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Ment Health Phys Act 2015;8:21–36.

[91] Stubbs B, Vancampfort D, Rosenbaum S, Ward PB, Richards J, Soundy A, Veronese N, Solmi M, Schuch FB, Stubbs D, Vancampfort S. Dropout from exercise randomized controlled trials among people with depression: a meta-analysis and meta regression. J Affect Disord 2016;190:457–66.

[92] Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159(8):543–51.

[93] Vancampfort D, Rosenbaum S, Probst M, Soundy A, Mitchell AJ, De Hert M, Stubbs Vancampfort Rosenbaum BSM. Promotion of cardiorespiratory fitness in schizophrenia: a clinical overview and meta-analysis. Acta Psychiatr Scand 2015;2:131–43.

[94] De Hert M, Dekker JM, Wood D, Kahl KG, Holt RIG, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry 2009;24(6):412–24.

[95] Hallgren M, Kraepelien M, Öjehagen A, Lindefors N, Zeebari Z, Kaldo V, Forsell Y, Hallgren M, Kraepelien A. Physical exercise and internet-based cognitive behavioural therapy in the treatment of depression: randomised controlled trial. Br J Psychiatry 2015, doi:http://dx.doi.org/10.1192/bjp.bp.114.160101.

[96] Golightly YM, Allen KD, Ambrose KR, Stiller JL, Evenson KR, Voisin C, Hootman JM, Callahan LF, Golightly, KD, Allen KR. Physical activity as a vital sign: a systematic review. Prev Chronic Dis 2017;14:E123.
[97] Carlson SA, Maynard LM, Fulton JE, Hootman JM, Yoon PW. Physical activity advice to manage chronic conditions for adults with arthritis or hypertension, 2007. Prev Med 2009;49(2–3):209–12.
[98] Soundy A, Roskell C, Stubbs B, Vancampfort D. Selection, use and psychometric properties of physical activity measures to assess individuals with severe mental illness: a narrative synthesis. Arch Psychiatr Nurs 2014;28(2):135–51.
[99] Rosenbaum S, Ward PB. The simple physical activity questionnaire. Lancet Psychiatry 2016;3(1):e1.