A systematic review and meta-analysis of exercise interventions in schizophrenia patients

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Background. The typically poor outcomes of schizophrenia could be improved through interventions that reduce cardiometabolic risk, negative symptoms and cognitive deficits; aspects of the illness which often go untreated. The present review and meta-analysis aimed to establish the effectiveness of exercise for improving both physical and mental health outcomes in schizophrenia patients.

Method. We conducted a systematic literature search to identify all studies that examined the physical or mental effects of exercise interventions in non-affective psychotic disorders. Of 1581 references, 20 eligible studies were identified. Data on study design, sample characteristics, outcomes and feasibility were extracted from all studies and systematically reviewed. Meta-analyses were also conducted on the physical and mental health outcomes of randomized controlled trials.

Results. Exercise interventions had no significant effect on body mass index, but can improve physical fitness and other cardiometabolic risk factors. Psychiatric symptoms were significantly reduced by interventions using around 90 min of moderate-to-vigorous exercise per week (standardized mean difference: 0.72, 95% confidence interval −1.14 to −0.29). This amount of exercise was also reported to significantly improve functioning, co-morbid disorders and neurocognition.

Conclusions. Interventions that implement a sufficient dose of exercise, in supervised or group settings, can be feasible and effective interventions for schizophrenia.

Introduction

Schizophrenia is a common disorder with high personal, social and economic impact. Most people with schizophrenia are unemployed, supported by benefits and require high levels of health and social care (Knapp et al. 2004; Schizophrenia Commission, 2012). In the UK, the direct and indirect costs of the illness reach an estimated £55 000 per person per year (Mangalore & Knapp, 2007), higher than cancer.

Although anti-psychotic medication is effective for positive psychotic symptoms, usually within the first few months of treatment (Crespo-Facorro et al. 2006; Malla et al. 2006), it is of less benefit for negative symptoms and cognitive deficits (Erhart et al. 2006; Kirkpatrick et al. 2006; Goldberg et al. 2007).

Unfortunately, it is these features that cause most disability (Green, 1996; Albert et al. 2011; Rabinowitz et al. 2012). This has been recognized by researchers and clinicians, and the National Institute for Health and Care Excellence (NICE; previously National Institute for Health and Clinical Excellence) guidelines for schizophrenia now recommended the use of adjunctive psychosocial interventions to facilitate complete and sustained recovery (National Institute for Health and Clinical Excellence, 2010). Cognitive–behavioural therapy, family therapy and skills training may reduce negative and cognitive symptoms, improve functioning and reduce long-term disability (Bustillo et al. 2001; Kern et al. 2009). However, these interventions tend to be costly and access is poor (Schizophrenia Commission, 2012). Thus, new low-cost and accessible treatments that decrease negative symptoms, reduce cognitive deficits and promote functional recovery are needed.

In addition to its lack of efficacy for negative and cognitive symptoms, anti-psychotic treatment is also
associated with the ‘metabolic syndrome’ (Hert et al. 2009), a cluster of co-occurring risk factors for diabetes and cardiovascular disease such as obesity, high blood pressure and hyperglycaemia (Alberti et al. 2005). At the onset of psychotic illnesses, the prevalence of these risk factors is no different from that in the general population (Foley & Morley, 2011). However, over the first few years of taking antipsychotics, the incidence of the metabolic syndrome increases fivefold (De Hert et al. 2008) and body weight increases by up to 15 kg (Alvarez-Jiménez et al. 2008a). This decline in physical health continues over time, and reduces the life expectancy of people with schizophrenia by 15–20 years (Hennekens et al. 2005; Laursen, 2011).

There are therefore two pressing issues in the management of schizophrenia: the need to develop feasible interventions for negative symptoms and cognitive dysfunction, and the need to reduce physical health inequalities. Exercise is one possible candidate that could meet both of these needs. For instance, exercise can reduce symptoms in clinical depression (Cooney et al. 2013) and improve cognitive functioning in neurological disorders (Angevaren et al. 2008; Smith et al. 2010). The National Institute for Health and Care Excellence (2014) now recommends using physical activity and dietary advice to improve the physical health of people with schizophrenia, based on their recent systematic review. However, the National Institute for Health and Care Excellence (2014) review focused on behavioural interventions to promote healthy lifestyles, but did not evaluate the impact of directly administered exercise in schizophrenia. Furthermore, effects of physical activity on psychiatric symptoms were not considered.

Therefore, the effectiveness of exercise as a treatment for schizophrenia still needs to be established. A Cochrane review was conducted in 2010, but could not reach any strong conclusions due to the small number of trials (n = 3) (Gorzynski & Faulkner, 2010). Since then, many more trials have taken place. However, the currently available evidence has yet to be reviewed in full.

We conducted a systematic review and meta-analysis to provide a comprehensive summary of all exercise trials in schizophrenia, and to quantify effects on both physical and mental health. Physical outcomes include metabolic risk and physical fitness. Mental health outcomes include positive and negative symptoms, psychosocial functioning, co-morbid disorders and neurocognitive dysfunction. The feasibility of different exercise treatments will also be assessed by comparing adherence and attrition across trials. This has been overlooked in previous reviews but is a crucial factor for determining the clinical applicability of exercise in schizophrenia and informing future trial design.

Method

Eligibility criteria

Only original English-language, peer-reviewed research articles were included in the present review. Studies comprised entirely of participants with any non-affective psychotic disorder were considered, with no restrictions placed on the severity or duration of illness. However, studies published prior to 1994 were excluded to increase diagnostic homogeneity, since this is when the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases (ICD)-10 came into use. First-episode psychosis (FEP) studies were also eligible regardless of formal diagnostic status of participants since, in these early stages, diagnoses are often changed or postponed until temporal criteria are fulfilled (Schwartz et al. 2000).

Eligible studies must have reported the effect of exercise on at least one quantitative measure of physical or mental health. Within health research, ‘exercise’ is defined as any structured and repetitive physical activity that has an objective of improving or maintaining physical fitness (Caspersen et al. 1985). Any intervention using physical activity matching this description was considered, regardless of trial design. Interventions that only used yoga, muscular relaxation or adventure activities were excluded, since their effects are theoretically derived from factors distinct from exercise. Multi-modal programmes that incorporated exercise within a broader lifestyle or psychosocial intervention were also excluded, as the effects of exercise alone cannot be determined.

Search strategy

An electronic database search of Ovid MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted on 1 November 2013 (with an updated search on 6 April 2014) using the following keyword search terms: ‘exercise’ or ‘physical activity’ or ‘sport’ or ‘aerobic training’ or ‘anaerobic training’ or ‘endurance training’ or ‘resistance training’ or ‘walking’ or ‘muscle strengthening’ and ‘psychotic’ or ‘psychosis’ or ‘psychoses’ or ‘schizo’ and ‘intervention’ or ‘treatment’ or ‘trial’ or ‘program’. The reference lists of retrieved articles were searched to identify any additional papers.

Study selection and data extraction

Two reviewers (J.F. and J.C.) independently screened articles for eligibility; disagreements were resolved through discussion. A systematic tool was developed, and quantitative data from each study were extracted and categorized into the following domains:
P1: metabolic health – body composition and cardio-metabolic risk factors;
P2: physical fitness – cardiorespiratory fitness and physical capacities;
M1: psychiatric symptoms – positive, negative and general symptoms;
M2: functioning and disability – quality of life (QoL), socio-occupational functioning and overall illness severity;
M3: co-morbid disorders – specific or subscale measures of depression/anxiety;
M4: neurocognitive effects – brain structure and neurocognitive functioning.

Secondary data on sample characteristics, study design, exercise details, adherence and attrition were also extracted to examine factors that may alter the effectiveness or feasibility of exercise.

**Meta-analysis**

Meta-analyses were conducted to examine effects on body mass index (BMI) and psychiatric symptoms, as these were the most commonly reported physical and mental health outcomes. Although single-arm studies, non-randomized trials and randomized controlled trials (RCTs) were all included within the review, only RCTs were used in the meta-analyses (to increase the validity of findings).

All analyses were performed in Review Manager 5, the recommended meta-analytic software of the Cochrane Collaboration (Higgins & Green, 2008). The risk of bias for each RCT was also assessed using the Cochrane’s Collaboration respective tool (Higgins et al. 2011). This examines six different aspects of trial methodology that could potentially introduce bias; summaries are presented in the Appendix (Figs A1 and A2). To quantify the amount of variation in studies’ effect estimates due to heterogeneity, the $I^2$ test was used. These values can be described as small (0–25%), medium (25–50%) or large (>50%). Due to the considerable variation across exercise studies, a random-effects model (based on the method of DerSimonian & Laird, 1986) was applied throughout. This accounts for variation through providing conservative estimates adjusted in relation to the extent of heterogeneity.

When pooling outcomes data across studies, effects on BMI were calculated by pooling mean differences. Standardized mean difference (SMDs) was used for psychiatric symptoms, to allow for integration of various assessment measures. In both cases, effects were calculated by comparing change in the exercise condition with change in the control condition(s). In studies with more than two conditions, all data from non-exercise conditions were pooled into a single comparator group (Higgins & Green, 2008).

**Results**

The database search returned 2275 results, providing 1581 unique citations after duplicates were removed. A further 1521 articles were excluded at the title–abstract stage. For the remaining 60, the full paper was sought. Of these, 20, reporting data from 17 different trials, met full eligibility criteria and were included in the review. Searching the reference lists of eligible studies did not identify any additional eligible studies. The full study selection process is shown in Fig. 1.

We could not evaluate publication bias using the Cochrane test for funnel plot asymmetry, since fewer than 10 studies were included in each analysis (Higgins et al. 2011). To address publication bias, we applied our initial search terms to four ‘grey literature’ databases (MetaRegistry of Controlled Trials, Index to Thesis, Health Management Information Consortium and OpenGrey). The search returned 227 results, although 203 articles were removed by screening titles and deleting duplicates (including those from the main search). For the remaining 14 studies, all available details were examined and trial protocols were sought. This information revealed that all of these would be excluded from our review due to an ineligible sample ($n=1$), ineligible intervention ($n=8$) or both ($n=5$). Therefore, there is no evidence of existing unpublished trials that would influence our results.

**Study characteristics**

Across all 17 trials, the total number of participants with non-affective psychotic disorders was 659. The median age was 33 years (range = 25–52 years). The median illness duration was 10 years. Only one study used a FEP sample (less than 5 years illness duration).

Of the trials, four implemented exercise as a physical activity control for assessing the effects of yoga (Duraiswamy et al. 2007; Behere et al. 2011; Varambally et al. 2012; Manjunath et al. 2013). The 13 other trials investigated the benefits of exercise, with primary outcomes of physical health ($n=5$), mental health ($n=5$) or both ($n=3$). Of the trials, 10 described themselves as pilots, with five stating their primary objective as assessing the feasibility of exercise (Archie et al. 2003; Marzolini et al. 2009; Dodd et al. 2011; Abdel-Baki et al. 2013; Bredin et al. 2013).

International physical activity guidelines structure their recommendations around time spent exercising at a moderate or vigorous intensity per week (World Health Organization, 2010; Garber et al. 2011). Therefore, we recorded the amount of moderate or vigorous exercise applied by each exercise intervention per week, in order to provide an approximate measure of exercise quantity across studies. 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 (World Health Organization, 2010; Garber et al. 2011). In all, 15 trials specified some moderate-to-vigorous intensity exercise. The median amount was 75 min per week (mean 72 min, range 25–160 min).

Of the trials, 11 were RCTs. Risk of bias assessments are presented in the Appendix (Figs A1 and A2). To summarize, nine used adequate random sequence generation, six had allocation concealment procedures, six stated that assessors were blinded to intervention status and eight may have been affected by attrition or reporting bias. As only one study used an intention-to-treat analysis, our analyses were based on per-protocol outcome data. Due to the very limited number of randomized trials, all RCTs were included in our analyses, regardless of their bias assessment.

Physical health outcomes (Table 1)

P1: markers of metabolic health

Of the 11 trials assessing physical health, 10 observed significant improvement from exercise in at least one measure. Body weight (or BMI) was the most common measure of physical health. This was examined in nine studies, four of which were RCTs. The pooled mean difference from the RCTs (Beebe et al. 2005; Marzolini et al. 2009; Battaglia et al. 2013; Scheewe et al. 2013a) was calculated using the random-effects model, and it was found that exercise did not significantly reduce BMI across 80 participants [mean difference = −0.98 kg/m²; 95% confidence interval (CI) −3.17 to 1.22 kg/m²] (Fig. 2).

Six non-randomized trials also reported body weight/BMI. Two studies observed a significant reduction in body weight from group training programmes (Dodd et al. 2011; Bredin et al. 2013). Two other studies, using solitary exercise, observed clinically significant improvements among the few participants who attended exercise sessions, but experienced very high attrition (Archie et al. 2003; Abdel-Baki et al. 2013). Two further studies, using high-intensity interval training (Heggelund et al. 2011) and maximal strength training (Heggelund et al. 2012), observed no change in body weight.

Findings were inconsistent for several other measures of metabolic health. This was the case both within and between studies. For example, Bredin et al. (2013) and Abdel-Baki et al. (2013) reported substantial decreases in waist circumference, while others observed no change (Marzolini et al. 2009; Scheewe
<table>
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<tr>
<th>Study</th>
<th>Primary outcomes</th>
<th>Patient group</th>
<th>Mean age, years</th>
<th>Duration of illness, years</th>
<th>Study arms</th>
<th>RCT, yes/no</th>
<th>Key findings</th>
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</table>
| Abdel-Baki et al. (2013)     | Feasibility of exercise, and effects on metabolic health/fitness                 | FEP           | 25             | About 3.6                | No         | No          | Participants completing the programme had: P1: reduced body weight (1 kg), WC (4.3 cm*) and resting heart rate (8.6 bpm*)  
P2: improved CV fitness (↑ 38%* in \( V_{O2max} \))  
M2: no change in psychosocial functioning (GAF, SOFAS) or illness severity (CGI-S) |
| Acil et al. (2008)           | Effects on QoL and psychotic symptoms                                           | SZ            | 30             | About 10                 | Yes        | Yes         | Only changes from baseline were reported. TAU group showed no significant change  
M1: exercise decreased positive and negative symptoms (↓ 38%* SAPS, ↓ 41% SANS*)  
M2: exercise improved mental and physical QoL (↑ 14%* in WHO-QOL-BREF mental and physical subscales) and overall mental health (↓ 40% BSI*)  
M3: exercise improved in BSI subscale anxiety, but had no effect on depression |
| Archie et al. (2003)         | Adherence to unsupervised exercise                                               | SZ            | 27             | N/R                       | No         | No          | P1: participants gained a mean of 2 kg over the intervention period. However, the one who adhered to recommended exercise significantly reduced body weight (−15 kg)  
P1: soccer training decreased body weight/BMI more than TAU control (Δ5.4%*)  
P2: soccer training improved functional exercise capability (30 m* sprint)  
M2: soccer training improved QoL more than TAU control (↑ 10.6%* SF-12) |
| Battaglia et al. (2013)      | Effects on fitness and QoL                                                      | SZ            | 36             | N/R                       | Yes        | Yes         | P1: treadmill walking reduced body fat (3.7%* v. 0.02% control)  
P1: treadmill walking reduced body weight (3.7%* v. 0.02% control)  
P2: treadmill walking improved CV fitness (↑ 11%**, walking distance, v. 4% control)  
M1: treadmill walking reduced psychotic symptom severity compared with TAU (Δ19%**, PANSS total) |
| Beebe et al. (2005)          | Effects of yoga on facial emotion recognition                                   | SZ            | 52             | N/R                       | Yes        | Yes         | Note: yoga showed significantly greater effects than exercise (NFP) in all measures  
M1: no change in psychotic symptoms in NFP or waitlist control (PANSS) |
<p>| Behere et al. (2011)         |                                                                                   | SZ            | 32             | About 10                 | Yes        | Yes         |                                                                                      |</p>
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<th>Study</th>
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<th>Patient group</th>
<th>Mean age, years</th>
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<th>RCT, yes/no</th>
<th>Key findings</th>
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<tbody>
<tr>
<td>Bredin et al. (2013)</td>
<td>The risk of CV disease in SZ, and feasibility of exercise for reducing this</td>
<td>SZ</td>
<td>31</td>
<td>N/R</td>
<td>Aerobic–resistance training (n = 13)</td>
<td>No</td>
<td>M2: no significant change in social functioning in NFP or waitlist control (SOFs)</td>
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<td>No control</td>
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<td>Before-and-after comparisons showed: (\downarrow 3) kg**, WC (\downarrow 6.6) cm** and blood pressure</td>
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<td>No</td>
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<td>P1: reduction in weight (\downarrow) WC (\downarrow) and blood pressure</td>
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<td>No</td>
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<td>P2: improvement in CV fitness (\uparrow 12%)** (\uparrow) time to exhaustion, (\uparrow) power</td>
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<td>No</td>
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<td>M1: reduction in psychotic symptom severity (\downarrow 15.8) PANSS total</td>
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<tr>
<td>Dodd et al. (2011)</td>
<td>Feasibility of exercise, and effects on body weight</td>
<td>SZ-AF</td>
<td>46</td>
<td>&gt;10</td>
<td>Group aerobic programme (n = 8)</td>
<td>No</td>
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<td>Duraiswamy et al. (2007)</td>
<td>Efficacy of yoga as an adjunctive treatment for reducing psychiatric symptoms</td>
<td>SZ</td>
<td>32</td>
<td>About 7</td>
<td>Yoga (n = 31)</td>
<td>Yes</td>
<td>M1: NFP reduced positive and negative psychotic symptoms from baseline (\downarrow 24) PANSS-P, (\downarrow 18) SANS, (\downarrow 21) PANSS-N, (\downarrow 6) PANSS total</td>
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<td>NFP (n = 30)</td>
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<td>Yes</td>
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<td>Note: yoga resulted in significantly more improvement than NFP across all measures</td>
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<td>M1: NFP reduced positive and negative psychotic symptoms from baseline (\downarrow 24) PANSS-P, (\downarrow 18) SANS, (\downarrow 21) PANSS-N, (\downarrow 6) PANSS total</td>
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<td>M2: NFP improved socio-occupational functioning from baseline (\downarrow 23) SOFS</td>
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<td>M3: NFP reduced depression from baseline (\downarrow 21) SOFS</td>
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<td>Pajonk et al. (2010), Falkai et al. (2013)</td>
<td>Effects of exercise on fitness, symptoms, cognition and hippocampal volume</td>
<td>SZ</td>
<td>35</td>
<td>About 10.4</td>
<td>Aerobic exercise (n = 13)</td>
<td>Yes</td>
<td>P2: exercise improved fitness more than table football (\Delta 10)% power, (\Delta 8) (\Delta VO_{2\text{max}})</td>
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<td>Table football (n = 11)</td>
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<td>M1: exercise reduced psychotic symptoms more than table football (\Delta 22)% PANSS</td>
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<td>M4: exercise increased verbal STM (\uparrow 34)% and hippocampal volume (\uparrow 12)% more than table football. Increases in brain volume correlated with fitness (r = 0.83)</td>
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<td>Gholipour et al. (2012)</td>
<td>Effect of exercise and behavioural</td>
<td>SZ</td>
<td>41</td>
<td>N/R</td>
<td>Exercise (n = 15)</td>
<td>Yes</td>
<td>M1: exercise reduced negative symptoms more than TAU (\downarrow 30) SANS*. However, there was a greater effect from behavioural therapy (\downarrow 47) SANS*</td>
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<td>Behavioural</td>
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<td>Heggelund et al. (2011)</td>
<td>Effects of HIT on walking ability and CV risk factors</td>
<td>SZ/SZ-AF</td>
<td>34</td>
<td>About 8.7</td>
<td>HIT (n = 16) Computer games control (n = 9)</td>
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<td>DD</td>
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<td>No: P1: HIT improved HDL-cholesterol. No significant changes in weight/BMI</td>
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<td>P2: HIT improved CV fitness (↑ 12% VO$_2$<em>) and walking efficiency (↑ 12% E-net</em>)</td>
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<td>M1: no significant change in psychotic symptom severity (PANSS)</td>
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<td>M2: no significant change in QoL (SF-36)</td>
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<td>M3: no significant change in depression (CGSS)</td>
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<td>Heggelund et al. (2012)</td>
<td>Effect of strength training on gait deficits</td>
<td>SZ/SZ-AF</td>
<td>38</td>
<td>About 14</td>
<td>Strength training (n = 7) Computer games control (n = 9)</td>
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<td>DD</td>
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<td>No: P1: no significant change in body weight/BMI</td>
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<td>P2: strength training increased strength (↑ 38%), walking efficiency (↑ 3.4% E-net*)</td>
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<td>M1: no significant change in psychotic symptoms (PANSS)</td>
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<td>M2: no significant change in QoL (SF-36)</td>
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<tr>
<td>Manjunath et al. (2013)</td>
<td>Efficacy of yoga as an adjunctive treatment for reducing psychiatric symptoms</td>
<td>SZ</td>
<td>32</td>
<td>About 9</td>
<td>Yoga (n = 44) Exercise (n = 44)</td>
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<td>Yes: P1: yoga resulted in significantly more improvement than exercise in all measures</td>
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<td>M1: exercise reduced positive and negative symptoms from baseline (↓ 51% PANSS)</td>
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<td>M2: exercise reduced overall mental illness from baseline (↓ 35%* CGI-S)</td>
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<td>M3: exercise reduced depression from baseline (↓ 56%* HAMD)</td>
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<td>Marzolini et al. (2009)</td>
<td>Feasibility of using aerobic–resistance training for fitness and overall mental health</td>
<td>SZ/SZ-AF</td>
<td>45</td>
<td>N/R</td>
<td>Aerobic-resistance training (n = 7) TAU control (n = 6)</td>
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<td>Yes: P1: aerobic–resistance had no significant effect on BMI or WC</td>
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<td></td>
<td>P2: aerobic–resistance increased fitness (Δ13%* walk test) and strength (↑ 21%*)</td>
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<td></td>
<td>M2: aerobic–resistance improved overall mental health from baseline (15%* MHI)</td>
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<td>M3: aerobic–resistance improved depression (25% MHI subscale). This change was non-significant, but increased fitness did correlate with reduced depression (r = 0.9*)</td>
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<td></td>
<td>In comparison with occupational therapy:</td>
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<td></td>
<td></td>
<td>P1: exercise decreased triglycerides (↓ 13.5%) but had no effect on BMI, HDL or WC</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2: exercise increased CV fitness (Δ13%* peak work rate, Δ9% VO$_2$max)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Primary outcomes</td>
<td>Patient group</td>
<td>Mean age, years</td>
<td>Duration of illness, years</td>
<td>Study arms</td>
<td>RCT, yes/no)</td>
<td>Key findings</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Varambally et al. (2012)</td>
<td>Efficacy of yoga as an adjunctive treatment for reducing psychiatric symptoms</td>
<td>SZ</td>
<td>33</td>
<td>About 10</td>
<td>Yoga (n = 47) NFP (n = 37) Waitlist (n = 36)</td>
<td>Yes</td>
<td>M1: exercise reduced psychotic symptoms ((\downarrow 20.7% v. \uparrow 3.3%) PANSS&lt;sup&gt;<em>&lt;/sup&gt;)&lt;br&gt;M2: exercise reduced ‘need of care’ ((\downarrow 22% v. \downarrow 4%) CAN&lt;sup&gt;</em>&lt;/sup&gt;)&lt;br&gt;M3: exercise reduced depression ((\downarrow 36.6% v. \downarrow 4.4%) MADRS&lt;sup&gt;<em>&lt;/sup&gt;)&lt;br&gt;M4: there were no significant changes in brain volume. However, changes in brain volume correlated significantly with increased CV fitness Note: yoga produced greater improvement than exercise across all measures M1: NFP had no effect on psychotic symptoms in comparison with waitlist control ((\downarrow 13% v. \downarrow 9%) PANSS total)&lt;br&gt;M2: NFP improved socio-occupational functioning (17%</em> SOFS v. 9% control)</td>
</tr>
</tbody>
</table>

RCT, Randomized controlled trial; FEP, first-episode psychosis; P1, metabolic health; \(\downarrow\), decrease; WC, waist circumference; bpm, beats per min; P2, physical fitness; CV, cardiovascular; \(\uparrow\), increase; \(V_{\text{O}_2\text{max}}\), maximal oxygen consumption; M2, functioning and disability; GAF, Global Assessment of Functioning; SOFAS, Social Occupational Functioning Assessment Scale; CGI-S, Clinical Global Impressions Severity; QoL, quality of life; SZ, schizophrenia; TAU, treatment as usual; M1, psychiatric symptoms; SAPS, Scale for Assessment of Positive Symptoms; SANS, Scale for Assessment of Negative Symptoms; WHQ-QOL-BREF, World Health Organization Quality of Life Abbreviated; BSI, Brief Symptom Inventory; M3, co-morbid disorders; SZ-AF, schiz-affective disorder; N/R, not reported; BMI, body mass index; SF-12, Short Form Health Survey – 12 items; PANSS, Positive and Negative Syndrome Scale; NFP, National Fitness Corps Programme; SOFS, Socio-Occupational Functioning Scale; PANSS-P, Positive and Negative Syndrome Scale, positive symptoms scale; PANSS-N, Positive and Negative Syndrome Scale, negative symptoms scale; PANSS-G, Positive and Negative Syndrome Scale; general scale; M4, neurocognitive effects; STM, short-term memory; HIT, high-intensity training; DD, delusional disorder; HDL, high-density lipoprotein; E-Net, net efficiency of walking; SF-36, Short Form Health Survey – 36 items; CGSS, Calgary Depression Scale for Schizophrenia; HAMD, Hamilton Depression Rating Scale; MHI, Mental Health Inventory; SZ-P, schizophrreniform disorder; CAN, Camberwell Assessment of Need; MADRS, Montgomery–Åsberg Depression Rating Scale.<br><sup>*</sup> \(p < 0.05\); ** reported as ‘clinically significant’ improvement.
et al. 2013a). Heggelund et al. (2011) reported improvement in high-density lipoprotein (HDL) levels with no change in triglycerides, while Scheewe et al. (2013a) reported the opposite of this (i.e. improved triglycerides with no change in HDL).

P2: physical fitness

Seven studies used VO2max as an assessment of fitness (Pajonk et al. 2010; Dodd et al. 2011; Heggelund et al. 2011, 2012; Abdel-Baki et al. 2013; Bredin et al. 2013; Scheewe et al. 2013a), which measures maximal oxygen consumption and reflects overall aerobic capacity. Three studies reported clinically significant increases in VO2max (Dodd et al. 2011; Heggelund et al. 2011; Abdel-Baki et al. 2013), defined as sufficient to reduce cardiovascular disease risk by 15%, and mortality by 20% (Myers et al. 2004; Kodama et al. 2009). These improvements occurred in as little as 8 weeks. Eight studies reported other fitness outcomes: seven of these observed significant increases in running/walking capacities (Beebe et al. 2005; Heggelund et al. 2011, 2012; Battaglia et al. 2013) and power output/ strength (Marzolini et al. 2009; Heggelund et al. 2012; Bredin et al. 2013; Scheewe et al. 2013a).

Mental health outcomes (Table 1)

M1: psychiatric symptoms

Of the trials, 16 provided data for effects on mental health. The most commonly assessed mental health outcome was total change in positive and negative symptoms. For the eight RCTs examining total symptoms scores (357 participants), the pooled SMD was calculated, and showed no significant effect of exercise (SMD = −0.16, 95% CI −0.51 to 0.18) (Fig. 3). There was also substantial heterogeneity between studies (I2 = 54%). However, four of these eight trials implemented exercise only as a ‘physical activity control’ for yoga (Duraiswamy et al. 2007; Behere et al. 2011; Varambally et al. 2012; Manjunath et al. 2013) and their exercise interventions consisted almost entirely of low-intensity exercise such as walking, stretches and postures.

Therefore, a sensitivity analysis was performed to exclude these interventions, and thus investigate the effects of moderate-to-vigorous exercise on psychiatric symptoms (by only including interventions that used >30 min of moderate-to-vigorous exercise per week). Four trials remained, which implemented an average of 90 min per week (range = 75–120 min) (Beebe et al. 2005; Acil et al. 2008; Pajonk et al. 2010; Scheewe et al. 2013a). These showed a strong effect of exercise on total psychiatric symptoms (SMD = −0.72, 95% CI −1.14 to −0.29) (Fig. 3). Furthermore, no heterogeneity was found amongst these trials (I2 = 0%). Further analyses were carried out to determine the effect of moderate-to-vigorous exercise on separate scales of positive and negative symptoms. Both positive and negative symptoms were significantly reduced by moderate-to-vigorous exercise, with pooled SMDs of −0.54 (95% CI −0.95 to −0.13) and −0.44 (95% CI −0.78 to −0.09), respectively (Fig. 3).

Meta-analytic techniques were not applied to the other mental health outcomes (i.e. functioning, co-morbid disorders and neurocognition), as no common measures were used across the RCTs. Instead, effects in each domain were systematically reviewed (see Table 1 and summarized below.

M2: functioning and disability

Functioning and QoL were assessed in seven trials. Two RCTs, which both used 120 min of moderate-to-vigorous exercise per week, reported significant improvements in QoL (Battaglia et al. 2013) and functional disability (Scheewe et al. 2013a). Two RCTs which used low-intensity exercise as an active control for yoga observed increases in social functioning from baseline, although this improvement was significantly less than in the comparator condition (Duraiswamy et al. 2007; Varambally et al. 2012). Two non-randomized trials also assessed QoL, but observed no significant change (Heggelund et al. 2011, 2012).

Non-specific measures of overall illness severity were applied in three RCTs (Acil et al. 2008; Marzolini et al. 2009; Manjunath et al. 2013). All
reported improvement following their exercise interventions, but did not find changes to significantly exceed control conditions.

**M3: co-morbid disorders**

Three trials used specific measures of depression (Heggelund et al. 2011; Manjunath et al. 2013; Scheewe et al. 2013a). Scheewe et al. (2013a) reported 120 min per week of aerobic–resistance exercise reduced depression significantly more than the occupational therapy control. The other two trials, both using ≥75 min per week, observed no significant benefits of exercise (Heggelund et al. 2011; Manjunath et al. 2013). Three trials also observed exercise to reduce
Table 2. Exercise intervention details and feasibility

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary of exercise sessions</th>
<th>Sessions per week</th>
<th>Moderate-to-vigorous exercise per week</th>
<th>Duration, weeks</th>
<th>Exercise setting</th>
<th>Attrition in exercise condition, % (n/n)</th>
<th>Average attendance, % completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Baki et al. (2013)</td>
<td>Supervised aerobic interval training. 5 min warm-up. 10 × 30 s running intervals (with 90 s of walking between each), 5 min cool-down</td>
<td>2</td>
<td>40 min: 80–95% of HR max running, 50–65% of HR max walking</td>
<td>14</td>
<td>Solitary Supervised</td>
<td>36 (9/25)</td>
<td>48</td>
</tr>
<tr>
<td>Acil et al. (2008)</td>
<td>Home-based aerobic exercise plan. 10 min stretching. 25 min aerobic work-out with heart rate feedback. 5 min cool down/stretches</td>
<td>3</td>
<td>75 min: HR monitoring used, but target HR was not specified</td>
<td>10</td>
<td>Solitary Unsupervised</td>
<td>0 (0/15)</td>
<td>N/R</td>
</tr>
<tr>
<td>Archie et al. (2003)</td>
<td>Gym access. Provided access to an exercise facility (swimming, weights, aerobics, etc.) and recommended regular attendance</td>
<td>3</td>
<td>Not specified: recommended 3 × 30 min sessions per week</td>
<td>24</td>
<td>Solitary Unsupervised</td>
<td>90 (9/10)</td>
<td>30</td>
</tr>
<tr>
<td>Battaglia et al. (2013)</td>
<td>Soccer training. Sessions totalled 2 h including warm-up, social time, etc. 60 min of each session was active training, consisting of football matches and skills training</td>
<td>2</td>
<td>120 min: 50–85% of maximal HR during training period</td>
<td>12</td>
<td>Group Supervised</td>
<td>17 (2/12)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Beebe et al. (2005)</td>
<td>Treadmill walking programme. 10 min stretching. 30 min treadmill walking at a target HR</td>
<td>3</td>
<td>90 min: target HR set at baseline</td>
<td>16</td>
<td>Group Supervised</td>
<td>33 (2/6)</td>
<td>43–91</td>
</tr>
<tr>
<td>Behere et al. (2011)</td>
<td>National Fitness Corps Programme. 10 min walking. 5 min self-paced jogging. 45 min of postures. Supervised by a yoga instructor 5 days per week for 1 month, then continued alone</td>
<td>5</td>
<td>25 min: HR monitoring not used, but jogging is often ‘moderate exercise’</td>
<td>16</td>
<td>Solitary Unsupervised</td>
<td>45 (14/31)</td>
<td>N/R</td>
</tr>
<tr>
<td>Bredin et al. (2013)</td>
<td>Supervised aerobics or resistance programme. 10 min warm-up. Then either (i) 30 min of bicycle, treadmill and elliptical training or (ii) 8–10 resistance exercises for major muscle groups. 10 min cool down</td>
<td>3</td>
<td>90 min: aerobic; target HR increased weekly. Resistance; 50–70% of 1 RM</td>
<td>12</td>
<td>Group Supervised</td>
<td>31 (4/13)</td>
<td>81</td>
</tr>
<tr>
<td>Dodd et al. (2011)</td>
<td>Group aerobic programme. 2–3 people, 30 min circuit of gym exercises conducted by an expert, suited to each person’s abilities/preferences</td>
<td>2</td>
<td>60 min: 65–75% of HR max</td>
<td>24</td>
<td>Group Supervised</td>
<td>0 (0/8)</td>
<td>73</td>
</tr>
<tr>
<td>Pajonk et al. (2010)</td>
<td>Group aerobic sessions. Groups of 2–4 participants cycling on stationary bikes</td>
<td>3</td>
<td>90 min: Target HR determined at baseline</td>
<td>12</td>
<td>Group Supervised</td>
<td>38 (5/13)</td>
<td>85</td>
</tr>
<tr>
<td>Study</td>
<td>Summary of exercise sessions</td>
<td>Sessions per week</td>
<td>Moderate-to-vigorous exercise per week</td>
<td>Duration, weeks</td>
<td>Exercise setting</td>
<td>Attrition in exercise condition, % (n/n)</td>
<td>Average attendance, % completers</td>
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<tr>
<td>Gholipour et al.</td>
<td>Therapeutic exercise sessions. 2 h sessions delivered to in-patients three times per week</td>
<td>3</td>
<td>Not specified: up to 360 min</td>
<td>16</td>
<td>N/R</td>
<td>(0/15)</td>
<td>N/R</td>
</tr>
<tr>
<td>Heggelund et al. (2011)</td>
<td>High intensity interval training. Four bouts of 4 min running with 3 min walking intervals</td>
<td>3</td>
<td>75 min: 85–95% of max HR for running, 70% for walking</td>
<td>8</td>
<td>Supervised</td>
<td>25 (4/16)</td>
<td>85</td>
</tr>
<tr>
<td>Heggelund et al. (2012)</td>
<td>Maximal strength training. 5 min treadmill walking. Four sets of four repetitions in a leg press machine with 3 min breaks between each set</td>
<td>3</td>
<td>&lt;60 min: 70% of max HR walking. 16 repetitions at 85–90% 1 RM</td>
<td>8</td>
<td>Supervised</td>
<td>17 (1/7)</td>
<td>85</td>
</tr>
<tr>
<td>Manjunath et al.</td>
<td>National Fitness Corps Programme. See Behere et al. (2011). Supervised for 2 weeks, then continued alone</td>
<td>5</td>
<td>25 min: see Behere et al. (2011)</td>
<td>6</td>
<td>Solitary Unsupervised</td>
<td>43 (19/44)</td>
<td>N/R</td>
</tr>
<tr>
<td>Marzolini et al.</td>
<td>Group aerobics and weights training at a leisure centre. 10 min warm up, 20 min of resistance training, 60 min of aerobic training, 5 min cool-down</td>
<td>2</td>
<td>160 min: 60% of 1 RM for resistance. 60-80% of HR reserve for aerobic</td>
<td>12</td>
<td>Group Supervised</td>
<td>(0/7)</td>
<td>72</td>
</tr>
<tr>
<td>Scheewe et al.</td>
<td>Combined aerobic and resistance training. 40 min aerobic training plus 20 min resistance exercise</td>
<td>2</td>
<td>120 min: 45-75% of HR reserve</td>
<td>24</td>
<td>Solitary Supervised</td>
<td>42 (13/31)</td>
<td>79</td>
</tr>
<tr>
<td>Varambally et al.</td>
<td>National Fitness Corps Programme. See Behere et al. (2011). Supervised for 1 month, then continued alone</td>
<td>5</td>
<td>25 min: see Behere et al. (2011)</td>
<td>16</td>
<td>Solitary Unsupervised</td>
<td>41 (22/37)</td>
<td>N/R</td>
</tr>
</tbody>
</table>

HR, Heart rate; max, maximum; N/R, not reported; 1 RM, one repetition maximum.
depression/anxiety subscales within broader mental health assessments (Duraiswamy et al. 2007; Acil et al. 2008; Marzolini et al. 2009), although only in relation to baseline scores (rather than control conditions).

**M4: brain structure and neurocognitive functioning**

Two studies examined effects of exercise on brain volume. Only Pajonk et al. (2010) observed a significant main effect, as exercise increased hippocampal volume by 12% (significantly more than the table-football control). Both Pajonk et al. (2010) and Scheewe et al. (2013a) found that increased physical fitness was significantly correlated with increases in brain volume. Pajonk et al. (2010) also examined cognition, and found that exercise improved verbal short-term memory by 34% ($p<0.05$).

**Different exercise types**

Tables 1 and 2 reveal that significant improvements in mental health (in any domain) were only observed from interventions which used some form of aerobic exercise; with cycling (Pajonk et al. 2010), treadmill walking (Beebe et al. 2005) and sports training (Battaglia et al. 2013) all proving beneficial. However, some aerobic interventions had no effect on mental health, perhaps due to the relatively low dose applied (less than 90 min per week) (e.g. Dodd et al. 2011; Heggelund et al. 2011).

All three studies that incorporated aerobic with resistance training methods observed significant improvements in overall mental health (Marzolini et al. 2009; Bredin et al. 2013; Scheewe et al. 2013a). No studies used traditional resistance training alone, so the relative effectiveness of aerobic versus resistance components cannot be determined. It should also be noted that three ‘high-intensity’ training interventions, involving short bursts of strenuous physical activity, had no effect on symptoms or functioning, despite improving physical strength/fitness (Heggelund et al. 2011, 2012; Abdel-Baki et al. 2013).

**Feasibility of exercise (Table 2)**

All trials reported drop-out rates. Total attrition was 32.5% (118/362 participants). Attrition from group exercise was 22% (13/59 participants). However, attrition from solitary exercise, which mostly involved exercising alone after a briefly supervised introductory period, was almost double this, at 43% (96/223 participants). Adherence rate (i.e. attendance of exercise sessions) was reported in 10 studies. Group exercise adherence was substantially higher than solitary training interventions (78.8% vs. 55%).

Another factor affecting exercise adherence was supervision. Across nine supervised trials, participant attendance averaged 77% (range = 48–85%). Only one unsupervised intervention monitored adherence effectively; by recording participants’ gym attendance after providing them with a free membership, a gym induction session and an advised exercise programme to complete by themselves three times per week (Archie et al. 2003). Total adherence to the training routine was only 30%.

**Discussion**

This review aimed to capture all relevant studies of exercise in schizophrenia and related psychotic disorders by including single-arm trials, non-randomized trials and RCTs to provide a complete picture of the research. A total of 17 trials were reviewed in full and outcomes were categorized into six domains of physical and mental health. We found that exercise can improve cardiometabolic risk, functional disability, psychiatric symptoms, co-morbid disorders and neurocognition in schizophrenia (Table 1). Meta-analytic techniques were also applied to the most commonly reported outcomes for physical and mental health. Although there was no change in BMI, moderate-to-vigorous exercise was found to significantly improve positive and negative symptoms.

**Exercise and physical health in schizophrenia**

Reduction in body weight and BMI was not consistently found following exercise interventions. A more realistic goal may be the attenuation of expected weight gain, to which FEP patients are particularly susceptible (Alvarez-Jiménez et al. 2008a). Thus, the finding of no weight gain after 14 weeks of exercise in FEP (Abdel-Baki et al. 2013), along with a significant reduction in waist circumference (~4.3 cm), is noteworthy. Waist circumference may in fact be a more appropriate target than BMI for future exercise studies, especially if resistance training is included; reductions in body fat co-occurring with increases in muscle can improve overall body composition, while leaving BMI unchanged. Additionally, waist circumference is more useful than BMI for assessing cardiometabolic health (Janssen et al. 2004).

Physical fitness is also more important than body weight for protecting against cardiometabolic diseases (Fogelholm 2010; McNamee et al. 2013). Among the 11 studies measuring cardiovascular fitness and/or exercise capacity, 10 reported significant improvement from exercise. While the prevalence of cardiometabolic diseases is elevated in established schizophrenia (Hennekens et al. 2005; Vancampfort et al. 2013), this
Exercise and psychiatric symptoms

Eight RCTs were included in our meta-analysis of total symptom scores (Fig. 3). This found no effect of exercise. However, after excluding trials that used only very low-intensity exercise, we found that moderate-to-vigorous exercise significantly improved total symptom scores, along with the scores of both the positive and negative symptom subscales. Meta-analytic techniques were not applied to other domains of mental health due to the paucity of common measures across studies. Instead, effects of exercise in each mental health domain (detailed in Table 1) were systematically reviewed, and considered alongside the intervention characteristics in Table 2, in order to elucidate which factors may determine effectiveness. Aerobic exercise was a component in all interventions that improved mental health. However, some effective interventions also included resistance training, while several low-dose aerobic interventions had no effect (e.g. Dodd et al. 2011; Heggelund et al. 2011). In all, there was no clearly superior modality of exercise for improving mental health in psychotic disorders.

Rather, it was dose of exercise that seemed to determine effectiveness. Interventions using at least 90 min per week of any moderate-to-vigorous exercise, such as aerobic/resistance gym sessions (Marzolini et al. 2009; Bredin et al. 2013; Scheewe et al. 2013a), football practice (Battaglia et al. 2013) or stationary bike training (Pajonk et al. 2010), proved beneficial across all domains of mental health assessed, including psychiatric symptoms, functional disability and cognition. On the other hand, all interventions that failed to improve mental health beyond control conditions had used lower amounts, through either quick burst, maximal-effort training (Heggelund et al. 2012; Abdel-Baki et al. 2013), low-intensity interventions (acting as a control for yoga), or simply shorter durations of endurance exercise (Dodd et al. 2011; Heggelund et al. 2011). This is consistent with research in depression, which shows that benefits are most reliably observed from interventions that implement 90 min per week of any aerobic exercise, provided it is at least moderately intense (Perraton et al. 2010). A recent review commissioned by ‘Exercise and Sports Science Australia’ also concluded that interventions which use at least 90 min per week of moderate-to-vigorous exercise, regardless of modality, can be effective for a range of mental health problems (Morgan et al. 2013).

Using exercise to improve outcomes of schizophrenia

Our review found that exercise can significantly improve both positive and negative symptoms (even when measured independently) and verbal short-term memory. Thus exercise could target aspects of schizophrenia that are resistant to conventional treatments. Indeed, exercise may be particularly effective in these areas, as correlational research shows that physical activity and fitness levels bear especially strong relationships with negative and cognitive symptoms (Vancampfort et al. 2012a, b, c).

The only study of exercise in FEP to date primarily examined physical health (Abdel-Baki et al. 2013). Although single-item scales of mental health were included, the study had no control condition. Therefore, the effects of exercise in early psychosis have yet to be explored. Using exercise to treat negative and cognitive symptoms during FEP could facilitate long-term recovery, as early improvements in these areas reduce the likelihood of enduring symptoms and functional disability (de Haan et al. 2003; Alvarez-Jiménez et al. 2012; Galderisi et al. 2013).

Exercise may also attenuate the neurological deterioration associated with psychotic disorders (Pajonk et al. 2010). Since the neurological deficits present in schizophrenia occur mostly in the first few years after onset (Andreasen et al. 2011; McIntosh et al. 2011), implementing exercise during this ‘critical period’ (McGowan et al. 2008) may limit neurological deterioration, or prevent it from occurring. Future trials should explore both the immediate and long-term benefits of implementing exercise in the early stages of psychosis, as along with these theoretical benefits, a recent longitudinal study has also observed that greater amounts of physical activity during FEP predict better functional outcomes (Lee et al. 2013).

Feasibility of exercise in psychotic disorders

The average attendance of exercise sessions in final-sample participants was 72%. Supervised interventions and group exercise resulted in substantially higher attendance and retention than unsupervised or solitary exercise. Therefore, offering supervised exercise in a group setting could maximise adherence.

The dropout rate across all participants was only 32.5% (118/362). This compares favourably with exercise interventions in the general population and antipsychotic medication trials, both of which have drop-out rates of around 50% (Dishman 1991; Robison & Rogers, 1994; Martin et al. 2006). Furthermore, in the Schizophrenia Commission (2012) report, exercise ranked as the third...
most desirable intervention (ahead of family therapy, art, self-help and others). Thus, exercise is a feasible and highly valued intervention for schizophrenia.

Limitations and future research

One limitation of this review is that we focused entirely on studies that administered exercise as the sole component of the intervention. Therefore, broader ‘healthyliving’ programmes were excluded. This prevented us from evaluating how exercise can work in synergy with other health behaviours, such as diet. Although we found no effect on BMI, other reviews have found that exercise does stimulate weight loss in schizophrenia when used alongside dietary advice (National Institute for Health and Care Excellence, 2014), while interventions that focus solely on diet or physical activity alone are unsuccessful for reducing body weight (Bonfio et al. 2012; Fernández-San-Martín et al. 2014).

Another limitation is that patients with schizophrenia who opt in to exercise interventions could be an atypical subgroup. If this is the case, the observed effects may not generalize across the whole population. Our findings were also based on outcome data from participants who completed the exercise interventions. This may also skew results, favouring individuals who fully engage with exercise. Indeed, the single study that did compare per-protocol and intention-to-treat analyses found that significant improvements in fitness, psychiatric symptoms and overall functioning only occurred in participants who attended ≥50% of exercise sessions (Scheewe et al. 2013a).

Since improvements in mental health appear to depend upon the dose of exercise applied, rather than the modality, interventions could be tailored around patient preferences, so that they can readily achieve 90 min of moderate-to-vigorous exercise per week. Participation could also be maximized through use of groups and supervision. Future research should aim to establish the efficacy of exercise for psychotic disorders using large-scale RCTs, especially in early psychosis. Furthermore, there is a need to explore how effective and engaging interventions can be implemented in clinical practice.

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Declaration of Interest

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References


Appendix

Fig. A1. Cochrane ‘risk of bias’ assessment: across trials.

Fig. A2. Cochrane ‘risk of bias’ assessment: within trials.