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## **Exploring the Therapeutic Role of Physical Activity in Psychotic Disorders: Cognitive, Somatic, and Mental Health Impacts**

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## **ABSTRACT**

### **Introduction and Purpose:**

Psychotic disorders, such as schizophrenia, significantly affect both physical and mental health, often leading to a reduced quality of life. These conditions are commonly associated with somatic symptoms, fatigue, and impaired psychosocial functioning. This review aims to explore the impact of physical activity on psychotic disorders, focusing on its effects on somatic symptoms, fatigue, and overall well-being, while examining the underlying mechanisms and its potential as an adjunctive therapy.

### **Material and Methods:**

This systematic review was based on a comprehensive search of peer-reviewed literature in PubMed, covering studies published between 2020 and 2024. Studies eligible for inclusion were observational research, clinical trials, and meta-analyses that examined the role of physical activity in alleviating somatic symptoms, reducing fatigue, and improving overall well-being in individuals with psychotic disorders.

**Results:**

The literature review indicates that physical activity has the potential to improve somatic symptoms, reduce fatigue, and enhance overall well-being in individuals with psychotic disorders. Exercise interventions, particularly aerobic and resistance training, seem to benefit both positive and negative symptoms of psychosis, with notable improvements in cognitive function. Further research is necessary to determine the optimal exercise parameters.

**Conclusions:**

This review underscores the significant therapeutic potential of physical activity in alleviating somatic symptoms and improving the overall quality of life in individuals with psychotic disorders. Studies should investigate the neurobiological mechanisms behind the beneficial effects of physical activity in psychosis, such as stress responses and neuroplasticity. Integrating physical activity into standard treatment regimens could significantly improve patient outcomes in this population.

**Keywords:** schizophrenia, psychotic disorders, physical activity, psychosocial well-being, cognitive functioning, mental health, yoga

**Introduction**

Psychotic disorders, such as schizophrenia, have a profound impact on individuals' physical and mental health, often leading to a significant decline in overall quality of life. These disorders are frequently associated with somatic symptoms, profound fatigue, and diminished psychosocial functioning. The diagnostic and therapeutic complexity of psychotic disorders arises from overlapping symptom domains, such as intrusive thoughts, obsessive-compulsive-like phenomena, and subjective sensory anomalies, which complicate diagnosis and treatment [1]. Regular exercise has been shown to be a critical intervention for addressing cognitive dysfunction, improving quality of life, and alleviating psychiatric symptoms in schizophrenia. Exercise not only alleviates somatic complaints and reduces fatigue but also enhances mood and overall well-being. As an adjunctive therapy, it complements pharmacological treatments, addressing the negative side effects of antipsychotic medications [2]. Despite the growing body of evidence supporting these benefits, the underlying mechanisms and optimal exercise interventions remain areas of ongoing investigation. Exploring the role of physical activity in

mitigating these challenges provides critical insights into enhancing patient outcomes and informs evidence-based therapeutic strategies for schizophrenia.

Schizophrenia, one of the most severe and debilitating psychotic disorders, is characterized by a combination of positive symptoms, such as hallucinations, delusions, and thought disorders, and negative symptoms, including social withdrawal, lack of motivation, and cognitive impairments. Cognitive dysfunction, particularly in the domain of executive functioning, significantly impacts daily life and social interactions. People with schizophrenia are at 2–3 times the risk of early mortality compared to the general population, underscoring the severity and challenges in managing the disorder. This increased mortality risk is compounded by comorbid conditions, for example obsessive-compulsive disorder (OCD), where poor insight has been linked to a higher prevalence of schizotypal personality disorder. These findings highlight the complex interplay between psychotic disorders and other psychiatric conditions, further complicating the clinical management of patients with schizophrenia and related disorders [1, 3, 4]. The chronic, relapsing nature of schizophrenia, characterized by frequent recurrences and long-term disability, poses substantial challenges for both patients and their families.

In addition to its psychological impact, schizophrenia is often linked to various comorbid conditions, including metabolic syndrome, induced by long-term use of antipsychotic medications. Issues such as weight gain, diabetes, and cardiovascular diseases complicate the clinical management of schizophrenia, prompting a search for effective non-pharmacological interventions [2, 4]. Recent studies emphasize the benefits of alternative therapies, such as horticultural therapy and physical activity, which improve both positive and negative symptoms of schizophrenia, promote physical health, and enhance social functioning without the side effects associated with conventional treatments [3, 4].

This review consolidates the existing evidence on the impact of physical activity on psychotic disorders, focusing on the identification of specific exercise types and intensities that help alleviate somatic symptoms, reduce fatigue, and improve overall well-being in individuals with schizophrenia and related conditions. The findings aim to guide the development of targeted therapeutic strategies and interventions to enhance both physical and mental health outcomes for those affected by psychotic disorders.

## **Physical Exercise as Part of Therapy in Psychotic Disorders**

### **Exercise and Cognitive Function in Psychotic Disorders**

The neurocognitive benefits of exercise in schizophrenia have been increasingly studied, with robust evidence supporting its efficacy in improving cognitive function. Previous studies have consistently shown that exercise can have a positive impact on both the positive and negative symptoms of psychotic disorders, though the exact mechanisms remain under investigation. A meta-analysis of various trials demonstrated that exercise significantly enhances global cognition in individuals with schizophrenia [5]. Notably, improvements were observed in social cognition, attention/vigilance, and working memory, though no significant effects were found for processing speed, verbal memory, or reasoning. Aerobic activity has proven to be an effective adjunct to standard schizophrenia treatment, particularly when supervised by professionals. Furthermore, combining aerobic activity with cognitive remediation therapy (CRT) did not yield additional benefits over CRT alone, likely due to variability in intervention types. Given that exercise also improves physical health, such as cardiorespiratory and metabolic fitness, its inclusion in therapeutic programs for schizophrenia is strongly recommended. These findings support the integration of physical activity into therapeutic programs aimed at improving cognitive and overall functioning in individuals with psychotic disorders, particularly schizophrenia. Future research should continue exploring the optimal exercise regimens, duration, and intensity to maximize cognitive benefits while tailoring interventions to individual patient characteristics.

A recent systematic review and meta-analysis evaluated the efficacy and safety of exercise and physical activity in psychotic disorders, specifically comparing exercise interventions to usual care in a hospital setting. This study investigated the impact of exercise on psychotic symptoms and associated side effects [6]. This meta-analysis included several randomized controlled trials (RCTs), involving numerous participants, and focused on both aerobic exercise and mind-body interventions such as yoga. The results revealed that aerobic exercise was more effective than usual care in reducing the severity of both positive and negative psychotic symptoms. Yoga, however, did not produce significant benefits in comparison to usual care. Although the effects of exercise were statistically significant, the clinical relevance of these improvements remains uncertain, and further research is needed to confirm the potential clinical benefits of exercise interventions in psychosis treatment. Psychotic disorders, including schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder, are global health

concerns that affect millions of individuals worldwide. Schizophrenia, for instance, affects approximately 24 million people globally, people with this type of disorder have from 10 to 15 years reduced life expectancy. These disorders are characterized by a range of symptoms, including positive symptoms (hallucinations, delusions), negative symptoms (alogia, avolition), and neurocognitive impairments (attention, memory, executive function). The burden of these disorders is not only psychological but also physical, as patients often experience comorbidities such as metabolic syndrome and cardiovascular diseases, largely due to the side effects of antipsychotic medications [2,3,6].

Although the effects of yoga on psychotic symptoms were less pronounced in some studies, its role in promoting relaxation, reducing stress, and improving mindfulness could be beneficial for managing the psychosocial aspects of the disorder. In clinical practice, physical activity should be integrated into treatment regimens as an adjunct to pharmacotherapy, with careful consideration of the type, intensity, and duration of exercises based on individual patient needs and clinical context. Recent studies from 2024 suggest that yoga interventions can have a beneficial impact on managing both positive and negative symptoms of psychotic disorders, as well as improving the quality of life [7]. These studies indicate that yoga, particularly with longer durations of intervention, leads to moderate reductions in positive symptoms, such as hallucinations and delusions, with passive interventions showing more significant effects. Yoga also appears to alleviate negative symptoms, including social withdrawal and apathy, with more pronounced improvements in patients with more severe baseline symptoms. Additionally, these studies report improvements in overall quality of life, with benefits observed in both active and passive yoga approaches. These findings highlight the potential of yoga as a valuable adjunctive therapy in psychotic disorders, although further research is necessary to refine intervention strategies for optimal outcomes.

### Medication and Physical Activity as Synergistic Benefits for Schizophrenia Treatment

While antipsychotic medications remain the cornerstone of treatment for reducing positive symptoms in patients with schizophrenia, they often do not fully address negative symptoms, cognitive impairments, or the physical health problems associated with the disorder [2]. Furthermore, these medications may have significant side effects, including weight gain, metabolic disturbances, and increased risk of cardiovascular events. As such, there is an increasing recognition of the importance of adjunctive therapies to address these challenges.

Physical activity has been identified as an effective intervention, providing numerous potential benefits with few side effects. The physiological changes resulting from exercise are also associated with enhanced cognitive performance [2,5].

The mechanisms through which physical exercise may influence psychotic symptoms are multifaceted. One proposed mechanism is the improvement of neuroplasticity, which plays a crucial role in reversing cognitive deficits often observed in psychotic disorders. Regular physical activity has been shown to increase brain-derived neurotrophic factor (BDNF) levels, a key molecule that promotes synaptic plasticity and supports brain cell survival. This enhancement of neuroplasticity may contribute to the restoration of cognitive function, particularly in patients experiencing negative symptoms and cognitive impairments.

Additionally, physical activity may have direct effects on the dopaminergic and serotonergic systems, which are implicated in the pathophysiology of psychosis. Aerobic exercise, in particular, has been shown to reduce inflammation and oxidative stress—factors increasingly recognized as contributing to the onset and progression of psychotic disorders. This neurochemical modulation may complement pharmacological interventions, especially in light of the metabolic side effects commonly associated with antipsychotic medications.

Moreover, exercise induces both structural and functional changes in the brain. Neuroimaging studies have demonstrated that physical activity can increase hippocampal volume, a region often affected in psychotic disorders [8]. These structural changes are associated with improved cognitive function, emotional regulation, and overall brain connectivity. Exercise also enhances functional connectivity between the hippocampus and other regions involved in cognitive control and emotion regulation, which may be disrupted in individuals with schizophrenia.

By improving neuroplasticity, reducing inflammation, and promoting structural brain changes, physical activity offers a promising adjunctive therapy to antipsychotic medication. Additionally, exercise can mitigate common side effects of antipsychotics, such as fatigue, poor sleep quality, and metabolic disturbances. These benefits may lead to improved adherence to psychiatric treatments and a reduction in the frequency of psychotic episodes. Ultimately, physical activity may contribute to enhanced quality of life for patients, making it an important component of holistic treatment strategies for psychotic disorders [5].

### Impact of Exercise on Clinical High-Risk Psychosis

A recent study published in 2022 examined the impact of exercise on individuals at Clinical High Risk for Psychosis (CHR-p), a group characterized by lower fitness levels and



hippocampal abnormalities linked to clinical symptoms [9]. Given that exercise promotes hippocampal neurogenesis, the study hypothesized that physical activity could alleviate these deficits and improve cognitive and clinical outcomes. The study assessed participants' fitness, cognitive performance, clinical symptoms, and brain structure before and after the intervention. The results showed that the exercise intervention was well-tolerated, with participants demonstrating improvements in physical fitness, cognitive function, and a reduction in psychotic symptoms compared to the waitlist group. Additionally, the exercise group maintained stable hippocampal volumes, while the waitlist group experienced a decrease. Enhanced hippocampal connectivity was also observed in the exercise group. These findings suggest that high-intensity exercise could serve as an effective therapeutic tool for individuals at risk of psychosis, contributing to improvements in physical health, symptom reduction, and brain function, particularly regarding hippocampal health.

#### Suicide Risk in Psychotic Disorders: The Role of Physical Activity

Suicide rates among individuals with psychotic disorders, including schizophrenia, are notably higher compared to the general population. Suicidal ideation, attempts, and completions represent significant concerns in managing these patients. Research indicates that individuals with psychosis face a range of risk factors for suicide, such as functional impairments, substance use comorbidities, and psychological distress. While physical activity has been associated with reduced suicide attempts in individuals with mental disorders, its influence on suicidal ideation and suicide deaths remains inconclusive. Further studies are needed to clarify the relationship between exercise and suicidal behaviors in psychotic disorders [10].

#### Summary: Exercise in Psychotic Disorder Treatment

Physical activity offers promising adjunctive benefits for managing psychotic symptoms and should be considered in treatment regimens for psychotic disorders. While its effects on negative and cognitive symptoms may be modest, exercise can contribute significantly to overall patient outcomes. Negative symptoms, such as avolition, alogia, and diminished emotional expression, represent a core and enduring feature of psychotic disorders, particularly schizophrenia, and are often the earliest to emerge [11]. These findings align with previous reviews that have emphasized the benefits of exercise for individuals with schizophrenia and related psychotic disorders, showing improvements in depression, negative symptoms, and

cognitive deficits. However, integrating exercise into treatment programs, particularly in hospital settings, may present logistical challenges. In parallel, family interventions and cognitive behavioral therapy (CBT) have shown consistent results and are considered priorities in treatment plans for schizophrenia [12]. Together, these findings support the inclusion of physical activity as an adjunct to pharmacotherapy, potentially enhancing treatment effectiveness. Continued research is essential to further refine these therapeutic approaches and optimize patient outcomes.

### **Physical Activity as a Preventive Measure for Psychotic Episodes and Improvement of Quality of Life in Psychosis**

#### Physical Activity in Psychosis Prevention and Mental Health Improvement

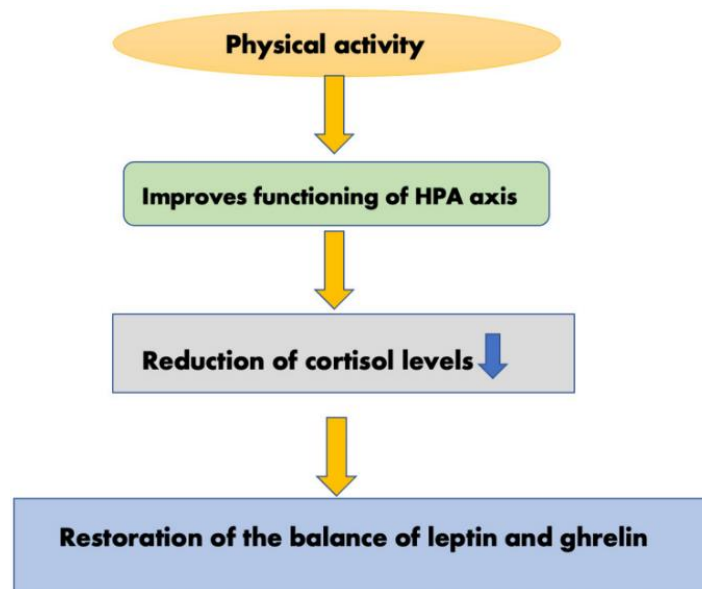
Schizophrenia is often characterized by recurrent episodes of psychosis, which significantly impair quality of life. While antipsychotic medications are crucial for relapse prevention, their adverse effects can reduce adherence and negatively impact patient well-being. Consequently, psychosocial interventions, including physical activity, have gained increasing attention as adjunctive strategies to pharmacological treatments, offering potential benefits in preventing psychotic episodes and enhancing both daily functioning and mental health outcomes.

Recent studies highlight the positive effects of structured physical activity on the psychological and physical health of individuals with schizophrenia. These benefits include reduced relapse rates, improved mood, cognitive function, and social engagement [12]. Programs combining physical exercise with cognitive-behavioral therapy (CBT) or psychoeducation have demonstrated particular efficacy. Moreover, physical activity aids in stress management, mitigates negative symptoms, and enhances overall physical health, which is often compromised in individuals with psychotic disorders [11].

For individuals identified as being at Clinical High Risk (CHR) for psychosis, physical activity shows promise as a preventive intervention. This stage represents a critical period for implementing early interventions that may delay or prevent the onset of full-threshold psychosis [9,13]. By improving hypothalamus-pituitary-adrenal (HPA) axis functioning, physical activity helps regulate stress responses, alleviating co-occurring symptoms of anxiety and depression commonly observed in CHR individuals.

Beyond psychological benefits, physical activity also addresses medical comorbidities prevalent in psychotic disorders, such as cardiovascular disease and obesity, particularly in

patients undergoing antipsychotic treatment [2,14]. Regular exercise enhances sleep quality, physical fitness, and overall health. Thus, incorporating structured physical activity into early intervention strategies during the CHR stage not only supports mental and somatic health but also offers a sustainable approach to reducing the long-term burden of psychotic disorders.



**Fig 1. The effects of physical activity on the HPA (hypothalamus-pituitary-adrenal) axis [14].**

#### Antipsychotic Drugs or Physical Activity in Relapse Prevention – Which is Better?

Antipsychotic maintenance therapy plays a key role in preventing relapse in patients with schizophrenia, with numerous studies confirming its ability to reduce relapse rates over time. While the evidence for quality of life improvement is less conclusive, research generally indicates that antipsychotic drugs may also positively influence the quality of life. Seven studies, employing various quality-of-life rating scales like the Self-report Quality of Life Scale (SQLS), Schizophrenia Quality of Life Scale (S-QoL), and EuroQOL Visual Analog Scale (EQ5D-VAS), found mixed results. Four studies showed significant improvements, while three reported no significant changes [15]. Despite the variability, the overall aggregated data suggest that antipsychotic treatment has a statistically significant positive effect on quality of life, challenging the common concern that medication side effects would worsen it. However, the

limitations of small sample sizes and diverse measurement tools point to the need for further research, particularly studies focusing on quality of life during stable periods of treatment rather than post-relapse recovery. Physical activity has been studied as an alternative - aerobic exercises, such as walking, running, and cycling, and anaerobic exercises, like weightlifting and yoga. The benefits of physical activity are well-documented in enhancing overall fitness, including improved cardiovascular health, weight management, and mental well-being [2]. Several studies suggest that exercise not only supports physical health but also promotes mental resilience by reducing symptoms of depression and anxiety, which are often present in patients with schizophrenia. While exercise may not directly prevent relapse in the same way as antipsychotic medications, its potential to improve physical and mental well-being positions it as a valuable adjunctive therapy in relapse prevention. Regular physical activity can help manage weight and improve the quality of life for individuals with schizophrenia [16]. In comparing the two approaches, the choice between antipsychotic drugs and physical activity for relapse prevention depends on individual patient needs. While antipsychotics are effective in directly reducing relapse rates, the holistic benefits of physical activity—improving both physical fitness and mental health—should not be underestimated. Future research should explore how combining both treatments could provide optimal outcomes in preventing relapse, enhancing quality of life, and supporting long-term well-being in patients with schizophrenia.

### **Application of Physical Therapy in Disorders Related to the Development and Early Onset of Psychosis**

#### Application of Physical Therapy in Early-Onset Schizophrenia (EOS) and Childhood-Onset Schizophrenia (COS)

Early-onset schizophrenia (EOS) and childhood-onset schizophrenia (COS) represent a subset of schizophrenia where the onset of symptoms occurs before adulthood. These conditions are associated with a greater risk of severe cognitive deficits, poor social functioning, and treatment resistance compared to adult-onset schizophrenia (AOS). Given the profound impact of schizophrenia on young individuals, it is crucial to adopt early intervention strategies aimed not only at symptom control but also at improving overall quality of life and functional outcomes. In addition to pharmacological treatment, physical activity has emerged as a valuable adjunctive intervention. Regular exercise has been shown to have a positive effect on cognitive functioning, particularly in the areas of attention, memory, and processing speed, which are often impaired

in both EOS and COS [17, 18]. Moreover, exercise can mitigate some of the adverse physical health consequences of the disorder and its treatment, such as obesity and metabolic dysfunction, which are prevalent in this population due to both the illness itself and the antipsychotic medications used. Early intervention is crucial in the management of psychotic disorders, particularly in individuals experiencing their first episode of psychosis (FEP). This critical phase of illness offers a unique opportunity to implement treatments that may alter the course of the disorder, including the integration of physical activity interventions. Research has shown that regular physical exercise can lead to significant improvements in psychiatric symptoms, neurocognitive functioning, and overall physical health, especially when initiated early in the illness trajectory [17]. An exploratory study on the effects of exercise in individuals with FEP revealed promising results. The findings demonstrated significant reductions in both positive and negative symptoms of schizophrenia, particularly negative symptoms. In addition to symptom improvement, participants also showed enhancements in psychosocial functioning, verbal short-term memory, cardiovascular fitness, and processing speed. These improvements were positively correlated with the amount of exercise completed, highlighting the potential of exercise as a valuable adjunctive treatment for individuals experiencing first-episode psychosis. The early stages of psychosis, especially during the first episode, are critical for preventing long-term health complications, such as obesity and metabolic dysfunction, which can result from both the illness and the medications used for treatment. The introduction of physical activity during this phase can mitigate these risks by improving health and fostering lasting healthy habits, potentially reducing the premature mortality often associated with schizophrenia. The available evidence suggests that exercise is a feasible and potentially effective intervention for young individuals at high risk for psychosis [13].

### Psychopharmacology

Clinical trials support the efficacy of atypical antipsychotics such as risperidone, aripiprazole, olanzapine, paliperidone, and lurasidone, along with some traditional neuroleptics like haloperidol and loxapine in treating schizophrenia-spectrum disorders in children and adolescents. In practice, the most commonly prescribed are risperidone, quetiapine, and aripiprazole. The choice of medication is influenced by side effects, patient preferences, clinician experience, and cost. Antipsychotics with established efficacy in pediatric populations are preferred, while those with negative results or limited evidence in early-onset schizophrenia (e.g., asenapine, ziprasidone) should be avoided until further pediatric data becomes available

[19]. Despite the efficacy of antipsychotics, many patients switch medications due to lack of efficacy, side effects, or noncompliance. If insufficient improvement is noted after a 4-6 week trial, an alternative antipsychotic should be considered. Pharmacotherapy requires support from additional methods, such as physical therapy, to enhance treatment outcomes [18].

### **Adjunct Therapies: Art Therapy and Other Complementary Techniques**

Art therapy, horticultural therapy, and mindfulness-based interventions (MBIs) are three non-pharmacological approaches that have gained recognition for their potential role as adjunct treatments for schizophrenia. While the evidence for the effectiveness of art therapy in combination with standard pharmacological treatment remains inconclusive, recent systematic reviews have begun to assess its impact on schizophrenia symptoms, rehabilitation, and quality of life. Art therapy shows promise in improving psychosocial functioning, self-esteem, and global health, although variations in its effectiveness may arise depending on factors such as schizophrenia type, severity, and the specific form of therapy used. Subgroup meta-analyses of these treatments offer a more comprehensive understanding of how these therapies influence outcomes, guiding clinical practices and providing valuable evidence for their use [4, 20].

Horticultural therapy, another growing form of complementary treatment, has also demonstrated positive therapeutic effects for individuals with schizophrenia. Research indicates that this form of therapy improves symptoms, rehabilitation outcomes, social functioning, and quality of life, particularly in non-hospital settings. The effectiveness of horticultural therapy is enhanced when conducted outside of hospital environments, demonstrating better therapeutic outcomes compared to those in institutional settings. These findings support the incorporation of therapeutic landscapes in treatment planning and highlight the importance of the setting in optimizing patient outcomes [4]. Mindfulness-based interventions (MBIs), such as Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT), have also shown promise in treating psychosis. Evidence suggests that MBIs can reduce both positive and negative symptoms, improve overall functioning, and decrease hospitalization rates. While further research is necessary, MBIs represent a valuable complementary strategy for enhancing treatment outcomes in individuals with schizophrenia [21]. Together, art therapy, horticultural therapy, and MBIs represent promising adjunctive approaches that, when integrated into treatment plans, could contribute to improved long-term outcomes for individuals with schizophrenia.

## **Postpartum Psychosis Treatment and Physical Activity**

Postpartum psychosis (PP) is a rare but serious psychiatric disorder that can occur shortly after childbirth, often associated with bipolar affective disorder and significant psychological stress. Symptoms include delusions, hallucinations, and disorganized thinking, requiring immediate medical intervention. While pharmacotherapy, including antipsychotics and mood stabilizers like lithium, is central to managing PP, physical activity may play a supportive role. Exercise is known to improve mood, reduce stress, and stabilize emotions, which can aid in recovery [22]. However, there is no direct evidence linking physical activity to the prevention or moderation of postpartum psychosis treatment. Current research on PP treatment outcomes shows that the prognosis is generally positive when intervention begins promptly [22,23]. Most women return to their premorbid functioning within nine months, and a four-year follow-up found that the majority did not experience a recurrence of psychosis outside the postpartum period. Although a first episode of PP tends to have a more favorable prognosis, more research is needed to explore the role of physical activity in managing or preventing this condition.

### **Conclusion**

Physical exercise, particularly aerobic and resistance training, has been increasingly recognized as an important therapeutic adjunct in the treatment of psychotic disorders, including schizophrenia. The evidence supports its role in reducing both positive and negative symptoms, improving cognitive function, and enhancing overall quality of life. Exercise interventions, when incorporated into a comprehensive treatment plan that includes pharmacotherapy and psychotherapy, can lead to significant improvements in patient outcomes.

Moreover, physical activity has proven benefits in preventing psychotic episodes and mitigating their severity, highlighting its role not only in active treatment but also as a preventive measure. The neurobiological mechanisms through which exercise exerts its effects, including the modulation of inflammatory markers, stress responses, and brain-derived neurotrophic factor (BDNF), further underline its potential as a multifaceted therapeutic approach.

In conclusion, physical exercise should be considered as a valuable tool in the therapeutic management of psychotic disorders. By promoting physical health, it simultaneously supports mental well-being, offering a holistic approach to treatment. When used in combination with

pharmacological treatments and other forms of psychotherapy, exercise interventions can significantly enhance both the physical and psychological aspects of recovery. Future research should continue to explore the optimal types, intensities, and durations of exercise interventions to maximize their benefits and refine their application in clinical practice.

## **Disclosures**

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The authors confirm that the data supporting this study are available in the article's references.

### **Conflict of Interest Statement**

No conflicts of interest.



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