Physical exercise as an intervention in people at clinical high-risk for psychosis: A narrative review

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Abstract

The concept of clinical high risk for psychosis has favored research in the neurobiology of the stages prior to psychosis, as well as in preventive interventions. This group is made up of young people with: (1) psychotic symptoms of less intensity or less frequency during a brief time or having genetic history of psychotic disorders associated to a significant deterioration in functioning. The few existing interventions for this population have a low level of evidence. Physical activity and exercise have been shown to be part of the therapy for multiple psychiatric disorders, while a sedentary lifestyle would be a factor that favors psychosis. Indeed, people in clinical high risk for psychosis present a worse physical condition associated with a greater sedentary lifestyle and unhealthy habits. It has been proposed that exercise generates a positive biological effect on the hippocampus and surrounding areas, regions that would be involved in the pathophysiology of psychosis. Some experimental studies have shown a decrease in psychotic symptoms in patients with clinical high risk for psychosis who have followed physical exercise guidelines, as well as morphofunctional changes in brain structures. Although there are barriers to the implementation of this intervention, it is safe and feasible. It is necessary to conduct a greater number of experimental studies on a larger scale to measure its efficacy, generating scientific evidence that will eventually allow physical exercise to be included in clinical practice guidelines as a systematic recommendation for clinical high risk for psychosis.

Main messages

- People at clinical high risk for psychosis have an increased risk of negative psychiatric outcomes.
- Interventions available for this group are scarce and may be associated with negative physical and psychological outcomes.
- Physical exercise is a safe and well-tolerated intervention for people at clinical high risk for psychosis. However, its research is in its early stages; most evidence comes from research on schizophrenia.
- We suggest considering it as an intervention alongside those recommended by clinical practice guidelines.

Introduction

The prediction of clinical conditions in psychiatry has been a subject of great analysis since the second half of the twentieth century since it would allow for preventive interventions, modifying the course of the disease. In the field of psychosis, some constructs have been developed that allow for achieving this purpose. The most developed are the core symptom approach [1] and the ultra-high risk for psychosis [2]. In this sense, similar terms can be found in the literature, such as ultra-high risk and at-risk mental state, which in this review will be grouped under the concept of "clinical high risk for psychosis".

Individuals at high risk for psychosis would present distinctive neurobiological features. Luna et al. [3] conducted a systematic review with a meta-analysis of neuroimaging studies to determine structural and functional brain alterations in participants at clinical high risk for psychosis. They found smaller volumes of gray matter in the gyrus rectus, superior frontal gyrus, and hypoactivation of the frontal gyrus. On the other hand, participants with a genetic risk of schizophrenia exhibited a volumetric decrease of gray matter in the gyrus rectus, right cerebellum, and left amygdala. Other studies have shown increased dopaminergic signaling in the midbrain and striatum [4], while several investigations have reported hippocampal alterations. Among these alterations, morphological modifications in the gray matter [5], increased blood flow [6], and metabolism have been reported, which would lead to dopaminergic dysfunction in the striatum [7,8], a central finding in psychosis.

Physical activity (movements generated by the musculoskeletal system that involve energy expenditure) and physical exercise (structured activities intended to maintain or improve physical fitness) are essential for a healthy lifestyle [9] and have been tested as part of psychotic disorder treatment [10]. From a preventive approach, Sormunen et al. [11] presented a population-based cohort study, which indicated that low levels of physical activity between 9 and 18 years of age independently predicted the development of non-affective psychosis (relative risk of 1.26 [1,5]), thus advocating that physical activity and exercise should be an integral component of psychosis prevention programs. Likewise, a study of psychosis incidence in a Finnish cohort of participants with parents with psychosis verified that physical exercise every two days could decrease the development of psychosis by about 20% [12].

Based on findings from experimental studies, it has been proposed that physical exercise has a morphofunctional effect on the hippocampus [13], a structure implicated in the pathophysiology of clinical high risk for psychosis [14]. Therefore, it seems a biologically plausible intervention for people at clinical high risk for psychosis, especially considering that the scientific evidence is inconclusive regarding the use of antipsychotics [15]. Although these psychotropic drugs could reduce attenuated psychotic symptoms, their effect has not been systematically tested [16]. In parallel, their adverse cardiometabolic and general physical effects are well known. Recommendations made by clinical practice guidelines for other psychological, social, and dietary interventions have variable yet generally low levels of recommendation [17].

Some authors point out that people at clinical high risk for psychosis have worse physical conditions than the general population [18–20], related to higher smoking rates, sedentary lifestyles, alcohol consumption, and poor nutrition [21–23]. A cross-sectional study by Deighton et al. [24] compared healthy controls (n = 40) with people at clinical high risk for psychosis (n = 40), verifying that the group at clinical high risk for psychosis presented lower levels of participation in physical activities inside and outside the home, less frequent physical training and with lower intensities.

Although it is recognized at the clinical level that physical activity and exercise are positive interventions for health in general, in psychiatry, it has not been incorporated as a systematic prescription [25]. In the case of people at high risk for psychosis, a retrospective study found that, in a specialized early detection program for youth at ultra-high risk for psychosis, less than 10% of clinical records contained anthropometric and physical exercise variables [26]. Similarly, a systematic review describing interventions delivered in 51 clinical services for patients at high risk for psychosis showed that only 37.8% offered interventions associated with physical health [27].

In this article, we describe and analyze the studies conducted regarding physical activity and exercise in people at high risk for psychosis from an observational and experimental perspective. Aspects concerning their effectiveness, feasibility, and neurobiological evidence are included, beginning with a review of the construct of clinical high risk for psychosis (Box 1).

Box 1.

MEDLINE/PubMed was searched for primary articles. Search terms, "ultra-high risk", "at-risk mental state", "clinical high risk", "exercise", "physical exercise", and "physical activity", and their combinations were used. "AND" and "OR" were used as Boolean operators. We selected publications in English and Spanish available until April 2023 that analyzed physical exercise as a possible intervention in people at clinical high risk for psychosis, contemplating primary observational, experimental studies, and systematic reviews with meta-analytic intent. Studies in animal models were excluded. For the inclusion of clinical practice guidelines, we searched MEDLINE/PubMed and the web pages of the main psychosis societies according to the criteria of the authors of the article.

Results

Development of the clinical high risk for psychosis construct

In 1932, Wilhelm Mayer-Gross introduced the concept of "prodrome" in schizophrenia [28]. Later, in his work "Incipient Schizophrenia, an intent of analysis of the delirium form," published in 1958, Klaus Conrad described the initial symptomatology of 107 men diagnosed with schizophrenia who were in a post-World War II lazaretto [29]. However, these were patients in whom the formal onset of the disease had already occurred, thus escaping the idea of a clinical high risk for psychosis. In the 1980s, Gerd Huber and the Bonn School developed the perspective of basic symptoms as they approached the "basic" neurobiological substrate. From cohort studies, they identified a series of subtle non-psychotic alterations, observed up to 10 years before the first psychotic episode, affecting the volitional, affective, cognitive, discursive, and motor spheres [1]. In the 1990s, McGorry's group developed the concept of "ultra-high risk for psychosis" at the Early Psychosis Prevention and Intervention Centre (Melbourne), aiming to provide timely intervention at the origin of psychosis [2]. It differs from the classic "ultra-high risk for psychosis" approach in that it includes individuals with certain clinical features, not just those with a genetic history of psychotic disorders. Ultra-high risk for psychosis is diagnosed in people between 14 and 30 years of age who have not had previous frank psychotic episodes and who show:

1) Attenuated psychotic symptoms: subthreshold psychotic symptoms during the last year. That is, less severe and less frequent than in a frank psychotic episode, with a 24% two-year risk of transition to psychosis.
2) Intermittent psychotic symptoms: frank psychotic symptoms for less than one week and with spontaneous remission, with a 38% two-year risk of transition to psychosis.
3) Risk factors: trait (first-degree relative with psychotic disorder or diagnosis of schizotypal personality disorder) and state (deterioration syndrome, i.e., significant deterioration in functioning in the last year); with 8% two-year risk of transition to psychosis [30].

Different scales have been used to diagnose these three groups. It is assumed that some patients may present a first psychotic episode without having gone through the ultra-high risk and that, likewise, many will enter the ultra-high risk group without culminating in a formal diagnosis of schizophrenia. Estimating the conversion rate to psychosis in different ultra-high-risk populations is inconsistent. A risk of about 20-fold of developing psychosis has been suggested when compared to the general population. Still, most people at clinical high risk for psychosis will not develop a psychotic disorder, strictly speaking [31]. A systematic review with meta-analysis incorporating 27 studies (n = 2500 participants at clinical high risk for psychosis) using different scales concluded a risk of transition to psychosis progressing from 18% at 6-month follow-up to 36% at three years [32].

In 2013, the Diagnostic and Statistical Manual of Mental Disorders, in its fifth version [33], incorporated the "attenuated psychosis syndrome" in the section "Other specified psychotic disorder" of the chapter "Spectrum of schizophrenia and other psychotic disorders", similar to the attenuated psychotic symptoms of ultra-high risk, but without specifying the age of occurrence. This reduces specificity in the prediction of a psychotic disorder. This diagnostic category was retained in its 2022 revised version [34].

Although the ultra-high risk approach to psychosis is the most widespread in the current literature, approaches have been studied that weight this perspective with that of the Bonn School and others that also consider neurophysiological and neurocognitive markers, which would potentially provide a more accurate prediction [35,36].

Evidence of physical activity and exercise on patients at clinical high risk for psychosis in primary studies

Damme et al. [18] designed a randomized clinical trial to measure the effects of physical exercise (n = 17) compared to no intervention (n = 15) in people at clinical high risk for psychosis; none of the participants received antipsychotics. The intervention contemplated a protocol of high-intensity interval exercise, considering one minute of higher-intensity exercise every 10 minutes, reaching 30 minutes twice a week for three months. The group with physical exercise showed improved physical condition, cognitive performance, and decreased psychotic symptomatology. In conjunction, it was verified that this

group maintained stable hippocampal volumes and greater connectivity in the structure. In contrast, the group that did not receive the intervention exhibited a 3.5% decrease in hippocampal volume. Along the same lines, another open-label pilot randomized clinical trial conducted by Dean et al. [37] randomized 12 participants with clinical high risk for psychosis to moderate (twice a week at 65% of maximal aerobic capacity or "maximum oxygen consumption" for a total of 24 sessions) or vigorous (three times a week at 85% of maximal aerobic capacity in for a total of 36 sessions) physical exercise for 15 to 30 minutes. Only nine participants completed the intervention, so the data analysis combined both interventions. The results found an improvement in social functioning (small to moderate effect size), positive (moderate to large effect size), and negative (small to moderate effect size) symptomatology. The intervention significantly affected all neurocognitive dimensions (working memory, verbal and visual learning, processing speed, attention, and reasoning) but not social cognition. In contrast to the group of Damme et al. [18], the researchers did not observe changes in hippocampal volume. Still, they corroborated increased functional connectivity between the left hippocampus and bilateral occipital cortex.

At the neurobiological level, the effects of physical exercise on hippocampal neurogenesis are relevant since it has been a structure consistently involved in the pathophysiology of psychosis [38]. Mittal et al. [22] conducted a cross-sectional study in people at clinical high risk for psychosis, concluding that low levels of physical exercise had a moderate and positive correlation with lower right (r = 0.44) and left (r = 0.51) parahippocampal gyrus volumes, but not with hippocampal volume. The authors concluded that physical exercise is associated with medial temporal lobe "health".

Clinical practice guidelines for clinical high risk for psychosis are very scarce [17,39–41]. The inclusion of physical exercise as part of therapy is summarized in Table 1.

Barriers and possibilities of the intervention

From the findings observed in people with schizophrenia, some psychological mechanisms that would explain the effect of physical exercise in people at clinical high risk for psychosis are the impact on behavioral activation, self-esteem, and motivation [43,44]. Deighton et al. [24] reported that people at clinical high risk for psychosis have significantly lower physical performance than healthy controls. Strikingly, but in line with what was reported for patients with schizophrenia, according to these results, physical exercise levels were not related to symptomatology or functioning but rather to barriers related to self-perception. Sormunen et al. [11] added that psychomotor difficulties could be associated with low physical activity levels in people with premorbid phases of psychosis. Additional methodological complexity is related to the particularities of the population under study since it has been reported that subjective measures of physical fitness (self-report) do not necessarily reflect what is shown by objective measures, such as body mass index and maximal aerobic capacity, making the study of

Table 1. Inclusion of physical exercise in clinical practice guidelines for clinical high risk psychosis.

Clinical practice guideline	Country	Physical activity and exercise intervention	Intervention description
Canadian Treatment Guidelines for Individuals at Clinical High risk for psychosis [17]	Canada	No proposal	No proposal
[a]*Australian Clinical Guidelines for Early Psychosis* [39]	Australia	Counseling on physical exercise in clinical examination is recommended, as well as education about physical exercise as an intervention when initiating antipsychotic treatment.	No proposal
[b]*Implementing the Early Intervention in Psychosis Access and Waiting Time Standard: Guidance* [42]	United Kingdom	A physical exercise program should be offered to people with psychosis, especially if they use antipsychotics (no specific recommendations for people at clinical high risk for psychosis).	No proposal
[a]*International Clinical Practice Guidelines for Early Psychosis* [40]	International	No proposal	No proposal
EPA Guidance on the Early Intervention in Clinical High Risk States of Psychoses [41]	International	No proposal	No proposal

[a]These clinical practice guidelines are focused on the early stages of psychosis and not on persons at clinical high risk for psychosis. [b]These clinical practice guidelines are focused on the early stages of psychosis and not on people at clinical high risk for psychosis but indicate that their recommendations are relevant for this group.
Source: Prepared by the authors.

barriers even more complex. Damme et al. [19] reported that this discrepancy is possibly explained by some clinical features of people at clinical high risk for psychosis that distort the self-perception of physical fitness, such as psychotic experiences.

Likewise, the motivational dimension is reduced compared to healthy controls. Accordingly, Newberry et al. [20], based on the results of a cross-sectional study (51 at clinical high risk for psychosis and 37 healthy controls), highlight that the decrease in the frequency of physical exercise is related to motivational barriers. Therefore, the available evidence suggests that the main barriers to establishing physical exercise from the participants' point of view are psychomotor difficulties, altered perception of their physical state, and lack of motivation.

Firth et al. [21] made a series of recommendations to improve the adherence and success of physical exercise prescriptions in people at clinical high risk for psychosis. They point out that flexible and individualized guidelines should be indicated, considering the patient's preferences; also, the intervention's physical, psychological and cognitive benefits can be obtained with multiple modalities, such as group sports, resistance training, and aerobic exercises. The prescription should be made by physical exercise professionals rather than mental health professionals since it has been shown that involving professionals in this area leads to greater adherence and better results. Finally, prolonged planning should be contemplated, as long-term benefits are associated with sustained physical exercise [45] (Table 2).

Discussion

Diagnosing patients at clinical high risk for psychosis is challenging, as the symptomatology considered by the construct is variable and not always straightforward. This paradigm has been criticized for including many false positives, mainly people with substance use disorders, depression, and anxiety disorders with psychotic experiences [46]. Also, the transition to a psychotic disorder varies between studies, so establishing a prognosis with a given patient is complex. Despite this, it is a construct that has given significant predictive value to a specific field of psychiatry, comparable to that of disciplines such as cardiology and neurology, especially when combined with other sociodemographic variables [47]. Regardless of being able to offer a definite diagnosis to a patient, the clinical decision on the therapy of patients at clinical high risk for psychosis is a controversial area. Still, physical exercise seems an indication to consider.

Physical exercise, a nonspecific resource that promotes overall mental health, emerges as a plausible alternative in people with clinical high risk for psychosis from the point of view of its feasibility and tolerability proven in pilot clinical trials [18,37]. Although interventions are recommended by clinical practice guidelines, such as antipsychotics, their adverse effects and the associated subjective burden question their use, limiting the number of available interventions.

The 2017 Canadian Treatment Guidelines for Individuals at Clinical High Risk of Psychosis [17], based on the National Institute for Health and Care Excellence (NICE, United Kingdom) and European Psychiatric Association [17] guidelines, suggests the inclusion of cognitive behavioral therapy and low-dose second-generation antipsychotics in patients at clinical high risk for psychosis, with a grade of recommendation D, namely evidence provided by case reports or series and expert opinion. Although the guideline does not suggest physical exercise as part of the interventions, it recommends actions to prevent the development or persistence of functional deficits, among which we believe exercise can be inserted. The exclusion of physical exercise from the few recommendations is probably related to the lack of research on the subject. Indeed, in this review, only two randomized clinical trials analyzed the intervention. Among the available clinical guidelines that specifically addressed the clinical high-risk stages for psychosis, only two were found [17,41], but none mentioned physical exercise as a feasible possibility to implement. However, physical exercise is an intervention that deserves study and implementation due to the large amount of evidence verifying its efficacy in other mental disorders (e.g., affective and traumatic disorders) and, more closely, in the schizophrenia spectrum.

The results of Mittal et al. [22] should be evaluated with caution since causality cannot be established due to the study's design. They report a significant correlation between low physical activity and lower parahippocampal volume. The authors did not verify that the level of physical activity correlated significantly with hippocampal volumes. Hinney et al. [14] performed a meta-analysis to compare the right and left hippocampal volume of persons at clinical high risk for psychosis who developed psychosis with those who did not, without finding that the volume of this structure was a biomarker related to the risk of transition. It is also important to note that the existence of hippocampal neurogenesis in adult humans is still a matter of debate. It has been questioned at the level of immunohistochemical studies, which point to a volumetric increase at the expense of glial cells [48].

Although a large proportion of people at clinical high risk for psychosis will not develop a psychotic disorder, only a minority of this group will be free of any psychiatric disorder during their lifetime [21], i.e., they are at increased risk of developing a range of psychiatric conditions, including affective and anxiety disorders. Considering that, it could be theorized that physical exercise as a nonspecific intervention has a positive impact regardless of the subsequent development of psychosis, so its systematic incorporation within intervention plans would be beneficial in therapeutics and eventually in prevention [49]. Its inclusion can be parallel to the prescription of antipsychotic drugs, as recommended by some clinical practice guidelines.

Even though all the included studies share the substantial concepts of clinical high risk for psychosis, that is, young people with psychotic symptoms of recent onset and limited time, who eventually may also present a genetic risk, but who do not meet the criteria of a psychotic disorder, there is some heterogeneity

Table 2. Summary of primary clinical studies analyzing the relationship between physical exercise and clinical and neurobiological variables in people at clinical high risk for psychosis.

Study (country)	Design	Participants	Intervention	Clinical outcomes	Neurobiological outcomes
22 (United States) [22]	Observational	29 participants with clinical high risk for psychosis and 27 healthy controls	No intervention	Participants with clinical high risk for psychosis showed more sedentary lifestyles	Participants with clinical high risk for psychosis showed a lower medial temporal volume, with a moderate correlation with physical exercise
24 (Canada) [24]	Observational	40 participants with clinical high risk for psychosis and 40 healthy controls	No intervention	Participants with clinical high risk for psychosis exhibited lower levels of outdoor activities and physical training, unrelated to clinical symptoms or functioning. This group showed greater barriers to physical exercise related to self-perception.	Not explored
37 (United States) [37]	Experimental (randomized clinical trial)	12 participants with clinical high risk for psychosis	Moderate (24 sessions) or vigorous (36 sessions) physical exercise	Improvement in social functioning, psychotic symptomatology, and neurocognition	Increased functional connectivity between the hippocampus and occipital cortex
20 (United States) [20]	Observational	51 participants with clinical high risk for psychosis, and 37 healthy controls	No intervention	Participants with clinical high risk for psychosis exhibited less physical activity and more motivation-related barriers to its execution. A negative correlation existed between perceived physical fitness and negative symptomatology and disorganization	Not explored
19 (United States) [19]	Observational	40 participants with clinical high risk for psychosis and 40 healthy controls	No intervention	Participants with clinical high risk for psychosis showed a higher body mass index and lower maximal aerobic capacity	Not explored
18 (United States) [18]	Experimental (randomized clinical trial)	32 participants at clinical high risk for psychosis	High-intensity physical exercise twice a week for three months	The intervention group exhibited an improvement in cognitive performance and a decrease in psychotic symptomatology	Preservation of hippocampal volume and increase in its connectivity.

Source: Prepared by the authors, based on references [18–20,22,24,37].

explained by the different criteria used, which difficult their comparison. Also, very few randomized clinical trials have been conducted, which is the design of choice for studying an intervention, considering small sample sizes.

Most of the included studies in this review analyze the associations between physical exercise and clinical and psychological characteristics in people at clinical high risk for psychosis from an observational point of view since only two experimental studies tested physical exercise as an intervention. Only three of the included studies investigated the neurobiological impact in this group using functional neuroimaging techniques. We recommend the execution of clinical trials with larger sample sizes that analyze the effect of physical activity and exercise on the symptomatology of patients at clinical high risk for

psychosis with longer follow-up periods, evaluating outcomes such as conversion to psychosis and specific effects on the brain regions of interest, i.e., those involved in the pathophysiology of psychosis. Simultaneously, prospective cohort studies should be established to evaluate the effect of exposure to physical activity and exercise on the transition to psychosis in the mid and long-term considering the studied population's different intervention modalities and characteristics. Basic research has pointed out the neuroplastic susceptibility of the hippocampus to physical exercise, as well as its participation in the pathophysiology of psychosis in studies with people with schizophrenia.

Implications for clinical practice

Based on clinical evidence, physical exercise is an intervention that is well tolerated, feasible, and does not require a significant economic investment in people at high risk for psychosis, where it has been associated with an improvement in physical fitness, cognitive and social performance, self-esteem and motivation, as well as with a decrease in positive and negative symptomatology. Moreover, the intervention has been associated with increased hippocampal functional connectivity. The experimental studies included in this review tested aerobic-type physical exercises, with a frequency of about three times per week with a maximum duration of 30 minutes for each session. Based on these results, we suggest that aerobic physical exercise, in conditions of frequency and duration similar to those studied, may be indicated in conjunction with the interventions recommended by clinical practice guidelines as a therapeutic alternative within the scarce sum of interventions available for people at clinical high risk for psychosis.

Notes

Contributor roles

All authors contributed to the planning and writing of the original manuscript. MAr and MAb prepared the Introduction, Development of the clinical high risk for psychosis construct, and Evidence of physical activity and exercise on patients at clinical high risk for psychosis in primary studies. MAr, MAb, HP, and RN performed Table 1, Barriers and possibilities of the intervention, and Discussion.

Conflictos de intereses

The authors completed the ICMJE conflict of interest statement and declared that they received no funds for the realization of this article; they have no financial relationships with organizations that may have an interest in the published article in the last three years and have no other relationships or activities that may influence the publication of the article. Forms can be requested by contacting the corresponding author.

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Ethics

This study did not require evaluation by an ethical-scientific committee since it worked on secondary sources.

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Ejercicio físico como intervención en personas en alto riesgo clínico de psicosis: revisión narrativa

Resumen

El constructo de alto riesgo clínico de psicosis ha favorecido la investigación en la neurobiología de los estadios previos a la psicosis, así como también en intervenciones preventivas. Se trata de personas jóvenes que presentan síntomas psicóticos de menor intensidad o de menor frecuencia en un tiempo determinado, o bien tienen antecedentes genéticos de trastornos psicóticos sumados a un deterioro significativo del funcionamiento. Las escasas intervenciones existentes para esta población cuentan con un bajo nivel de evidencia. La actividad y el ejercicio físico han demostrado ser parte de la terapia de múltiples trastornos psiquiátricos, mientras que el sedentarismo sería un factor favorecedor de la psicosis. Efectivamente, las personas en alto riesgo clínico de psicosis presentan un peor estado físico asociado a mayor sedentarismo y hábitos de vida poco saludables. Se ha propuesto que el ejercicio genera un efecto biológico positivo sobre el hipocampo y las áreas circundantes, regiones que estarían involucradas en la fisiopatología de la psicosis. Algunos estudios experimentales han mostrado una disminución en la sintomatología psicótica en pacientes en alto riesgo clínico de psicosis que han seguido pautas de ejercicio físico. También dan cuenta de cambios morfofuncionales en estructuras cerebrales. Si bien existen barreras para la implementación de esta intervención, se trata de una intervención segura y factible. Es necesario realizar una mayor cantidad de estudios experimentales de una escala mayor para medir su eficacia, generando evidencia científica que permita eventualmente integrar el ejercicio físico a las guías de práctica clínica como una recomendación sistemática.