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## What are the top 10 physical activity research questions in schizophrenia?

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## **Abstract**

*Purpose:* Research has only recently started to consider the applicability of physical activity (PA) for people with schizophrenia. Although there is increasing evidence for the benefits of physical activity, this population remains generally physically inactive and sedentary. The aim of the current study is to highlight 10 pertinent physical activity research questions in people with schizophrenia.

*Method:* The International Organization of Physical Therapy in Mental Health (IOPTMH) executed a consultation of its National Organizations (n=13) to identify the most salient questions relevant to guide clinical practice on physical activity in people with schizophrenia.

*Results:* We identified the following 10 questions: (1) What are the benefits of physical activity for people with schizophrenia? (2) What are the mechanisms of the physical activity effects in people with schizophrenia? (3) What are the most prominent safety issues for physical activity prescription in people with schizophrenia? (4) What is the most optimal physical activity prescription for people with schizophrenia? (5) What are the key barriers for engaging people with schizophrenia in physical activity? (6) What are the most effective motivational interventions for physical activity adoption and maintenance in people with schizophrenia? (7) How do we translate physical activity research into clinical and community practice? (8) How can we ensure integration of physical therapists within the multidisciplinary mental health treatment team? (9) How can we prevent sedentary behavior in people with schizophrenia? (10) What is the most appropriate physical activity assessment method in clinical practice?

*Conclusions:* Addressing these questions is critical for developing evidence-based approaches for promoting and sustaining an active lifestyle in people with schizophrenia. Ultimately, achieving this will improve the quality of life of this population

**Keywords:** Exercise; Physical Activity; Psychosis; Schizophrenia

## **Introduction**

People with schizophrenia have dramatically higher levels of morbidity and mortality than the general population [1]. A recent meta-analysis [2] demonstrated that mortality rates are approximately two to three times higher than those of the general population equating to a gap in life expectancy of 10 to 20 years [3]. Of particular concern is the fact that the gap in premature mortality is widening and people with schizophrenia are widely regarded as being among the most deprived [4]. The underlying causes for the increased risk of premature mortality are complex and multi-factorial, however, it is known that natural causes contribute more to the increased risk of premature mortality than accidents or suicide [5]. For example, the most prevalent physical comorbidities contributing to the increased risk of premature mortality are cardio-metabolic [6, 7] and respiratory diseases [8]. Although genetic factors [9] and shared pathophysiological mechanisms [10] contribute significantly to the high risk profile, unhealthy life style habits such as smoking [11], poor diet [12], and high levels of sedentary behavior and low levels of physical activity [13] play the most prominent role. Furthermore, antipsychotic medication that is often the mainstay of treatment [14], may improve psychiatric symptoms but in turn, predispose the individual to increased cardiovascular risk and metabolic abnormalities [15, 16].

The benefits of physical activity are substantial and the literature is unequivocal regarding the preventative effect on cardiovascular disease in the general population [17]. However, only in the past two decades has research started to consider the importance of physical activity in people with schizophrenia. In the last 15 years a number of systematic reviews and meta-analyses [18-26] have demonstrated that including physical activity has a range of benefits and should form a central part of the multidisciplinary treatment of schizophrenia. Despite this, very few people with schizophrenia meet recommended physical activity guidelines and are significantly more sedentary [27]. People with schizophrenia

experience a range of unique challenges in adopting and maintaining an active lifestyle [28, 29] and guidance is needed to help direct future research and clinicians facilitating physical activity programs within clinical practice. The International Organization of Physical Therapists in Mental Health (IOPTMH) [30] set out to summarize, appraise and strengthen the direction of physical activity endeavors in this population. We aimed to describe the 10 most pertinent research questions relating to physical activity and schizophrenia, while providing answers to the most pressing issues facing clinicians today.

## **Methods**

All the National organizations (n=13; Belgium, Denmark, Finland, Iceland, Japan, Norway, The Netherlands, Spain, South-Africa, Sweden, Switzerland, Turkey, United Kingdom) of the IOPMTH, an official subgroup of the World Confederation of Physical Therapy and representing more than 1100 physical therapists [30], were invited to provide a list of the 5 leading physical activity research questions. The National Boards of the National organizations were requested to consult their own members and to ask what are the most pertinent research questions that they believe most researchers and clinicians should consider as critical. In stage 1, each National organization was asked to answer the question “What are the five most important research questions for the next 10 years in the area of physical activity in people with schizophrenia?” Each National organization put forward five research questions which they believed were priorities in the area. They also provided a brief description of each question and reasons why they believed the issue to be a priority. All National organizations received the most recent systematic reviews on the topic [25, 26]. In the second stage, 4 different researchers from 4 different continents with at least 10 years of clinical and/or research experience (MP, CP, JC, TY) distilled a list with the 15 most reported research questions. To this end the 4 investigators reviewed all research questions that were provided by each National organization, with common issues combined into a single question. In a third stage 3 researchers (DV, SR, BS), all with at least 50 publications in the areas of physical activity, exercise, and rehabilitation of people with severe mental illness reviewed and discussed these questions until a consensus was reached on the top 10 questions. The 3 researchers were requested to “review the research questions put forward in stages 1 and 2 and rate how important they believe each issue is for global research in physical activity in schizophrenia”. The 3 experts rated each research issue independently using a 5-point Likert scale (5 = very important, 4 = important, 3 = moderately important, 2 = of little importance and

1 = unimportant). The three study investigators then short-listed the research questions to 10 according to those with highest mean Likert scale ratings.

## **Results**

All 13 National organizations completed stage 1. Collectively this provided a total of 65 questions. After excluding overlapping questions, 22 questions remained, and the 15 most reported ones were carried forward to stage 3. From stage 3, the mean Likert-scale ratings were used to determine the top 10 research questions. The mean Likert-scale ratings of the top 10 questions ranged from 3.4 to 5.0, with exactly 11 of 15 questions having a median rating of >4.0 (“important”). The mean Likert-scale ratings of the top 10 questions ranged from 3.9 to 5.0.

The top 10 questions are listed in Table 1. The numerical order does not reflect the relative importance of the questions. Questions are organized by topics such that the first three reflect consequences of physical activity prescription, the following five reflect processes for promoting physical activity, and the last two reflect issues of sedentary behavior and physical activity measurement. In the discussion, we provide a brief background and rationale for the top 10 questions and elaborate with reference to the appropriate literature.

[Insert Table 1 about here]

## **Discussion of the top 10 research questions**

*What are the benefits of physical activity for people with schizophrenia?*

A number of systematic reviews and meta-analyses have found that exercise is beneficial for people with schizophrenia. For instance, Rosenbaum et al. [25] demonstrated that exercise significantly reduces psychiatric symptoms of schizophrenia with a large effect size (standardized mean difference=1.0). The effect of exercise on body mass index and cardio-metabolic markers is equivocal [26] and requires more high quality research. In the same way, future research is needed to investigate whether brain health in people with schizophrenia is activity-dependent [24]. Recent systematic reviews of qualitative research considering the lived experience of patients have demonstrated that engaging in physical activity can improve confidence, reduce feelings of isolation and have a number of other important positive influences on bio-psychosocial outcomes [31, 32]. Moreover, future research should explore the effects of physical activity interventions on other clinically relevant outcomes including inflammatory markers [10], pain [33], osteoporosis [34] and the risk for falls and fractures [35]. Finally, the effect of physical activity in youth experiencing their first episode psychosis is distinctly lacking [36] and requires further investigation.

*What are the mechanisms of the physical activity effects in people with schizophrenia?*

Mechanisms explaining the beneficial effects of physical activity in people with schizophrenia are not yet understood. At present, the plausible mechanisms for change in positive and negative symptoms through physical activity and exercise fall into one of two broad testable hypotheses [22-26]: (a) biochemical changes such as increased levels of neurotransmitters (e.g. endorphins or serotonin) and which could be tested in schizophrenia-like animal models, and (b) psychological changes such as social support, sense of autonomy, improved perceptions of competence, enhanced body image, self-efficacy and distraction.

Cardio-metabolic and neurochemical pathways between skeletal muscle, the spinal cord, and the brain offer plausible, testable mechanisms that might help explain the effects of physical exercise on brain health. Previous research [37, 38] suggested that aerobic fitness improvements following exercise might be a testable mechanism. Kimhy et al. [39] showed recently that the increased production of brain-derived neurotrophic growth factors (BDNF) following aerobic fitness improvements probably plays a particular role. More interventional and longitudinal exploration of the underlying mechanisms for brain health improvements in patients with schizophrenia following a physical exercise program is needed. For example, future research could investigate whether physical activity reduces the inflammatory status of the brain, by increasing levels of the anti-inflammatory cytokine interleukin-10.

*What are the most prominent safety issues for physical activity prescription in people with schizophrenia?*

Questions about safety of physical activity participation are a critical issue in any chronic disease population including people with schizophrenia who are known to be at risk for somatic co-morbidities [1]. There is increasing evidence from randomized controlled trials (RCTs) reporting that there are no adverse events following physical activity programs [40]. However, RCTs are not always ideal sources to make conclusions regarding the safety of interventions. First, almost all RCTs to date have been selective in the recruitment of participants, excluding high-risk patients with somatic co-morbidities. Second, comprehensive adverse event reporting is limited in the published literature. The biased populations and limited information on adverse events pose a challenge to documenting the safety of physical activity for people with schizophrenia. Longitudinal, observational studies are needed that systematically report adverse events and target higher-risk patients with schizophrenia rather than excluding them. Finally, the most appropriate safety screening and medical clearance

approach for physical activity in clinical and community settings for people with schizophrenia remains a topic for future research. Nevertheless, when supervised by appropriately trained exercise professionals (physical therapists or exercise physiologists) physical activity does appear to be safe in this population.

*What is the optimal physical activity prescription for people with schizophrenia?*

Although a number of physical activity programs have established efficacy in people with schizophrenia, the optimal physical activity prescription for people with schizophrenia is not yet fully established. To date, the majority of studies have compared a single physical activity intervention to no physical activity at all (i.e., usual care, wait list). As a result, the current physical activity recommendations for people with schizophrenia provide generalized recommendations that people with schizophrenia should avoid inactivity and / or follow the IOPTMH guidelines for aerobic and strength based exercise [41]. Several authors have commented that physical activity is not a one-size-fits-all intervention [42, 43] and that the focus should not be on the most ideal general dose-response (i.e., efficacy), but rather on how individuals with schizophrenia can include physical activity within their daily lives (i.e., effectiveness). On the other hand, our survey shows that there is a call from clinicians worldwide to research in greater detail what the most ideal physical activity prescription may be, while considering that a perfect physical activity prescription does not exist. To determine the most ideal physical activity prescription for people with schizophrenia, “second-generation” studies are needed that directly compare physical activity prescriptions with each other. The main components of a physical activity prescription are the frequency, intensity, type, and time, or the FITT-principle. Each of these components can be manipulated to determine its effects on a given schizophrenia outcome.

The intensity of physical activity is one important component that can be manipulated. There is a growing interest in examining the role of vigorous-intensity activity or higher-intensity interval training [44]. The safety and efficacy of high-intensity interval training compared to a standard continuous aerobic exercise prescription or comparing different physical activity intensities using a fixed physical activity volume (i.e., time to achieve the same energy expenditure) is to date yet to be reported in schizophrenia.

In terms of the type of physical activity, several studies have compared yoga with structured aerobic physical activity (i.e. aerobic exercise) [45-47]. However, in all these yoga-studies a brief supervised period was followed by a longer unsupervised study period (with lack of adherence data) making it difficult to compare similar physical activity volumes. With increased interest in other types of physical activity, such as Qigong, Tai Chi [48], and outside adventure activities (including canoeing, kayaking, rock climbing, high and low ropes courses) [49], additional research is warranted.

Time or duration can also be manipulated in physical activity studies. Additional studies exploring the effects of manipulating different components of the physical activity prescription will assist in determining their impact on specific outcomes and will hopefully refine the current general physical activity recommendations for people with schizophrenia.

*What are the key barriers for engaging people with schizophrenia in physical activity?*

Although there is established evidence for the benefits of physical activity participation only a small percentage of people with schizophrenia are meeting the recommended levels of physical activity [27]. Behavioral theories such as socio-ecological models are useful in attempting to understand specific barriers to physical activity participation. Socio-ecological models posit that multiple factors including intrapersonal (e.g. demographic, biological, psychological, cognitive, emotional), interpersonal / cultural (e.g. social support), physical

environment (e.g. distance to facilities, low program cost, enjoyable scenery, neighborhood safety and the presence of sidewalks) and policy (e.g. laws, rules, regulations, codes) all influence health behavior [50]. Previous systematic reviews and multi-center studies in people with schizophrenia [51-53] have already demonstrated that significant correlates are found in six of the seven categories (excluding policy level) supporting the hypothesis that in people with schizophrenia, physical participation is a complex behavior determined by several factors. In particular the presence of negative symptoms, pain, cardio-metabolic comorbidity, side-effects of antipsychotic medication, lack of knowledge on cardiovascular disease risk factors, no belief in the health benefits of physical activity, a lower self-efficacy and social isolation are negatively correlated with physical activity participation. A recent synthesis of qualitative research also reinforced the importance of many of these barriers to physical activity [28]. The current evidence is however, mainly based on cross-sectional studies, highlighting the need for longitudinal and interventional designs to better understand these relationships. If the ultimate purpose of physical activity research is to inform and motivate policy changes that will improve the mental and physical health of people with schizophrenia, merely documenting the relation of intrapersonal, interpersonal / cultural, physical environment and policy variables to physical activity behavior is insufficient. Environmental and policy change research is needed and should include assessments of broader health outcomes, such as changes in prevalence of chronic comorbidities, physical activity service utilization, as well as the economic costs and benefits of proposed policy changes.

*What are the most effective motivational interventions for physical activity adoption and maintenance in people with schizophrenia?*

It is essential to determine the most effective interventions for assisting people with schizophrenia to increase their physical activity levels. Several behavioral change studies

have demonstrated significant effects on physical activity participation. These interventions have ranged from less intensive interventions using pedometers [54, 55] to more intensive multicomponent behavioral support [56-58]. Nevertheless, the long-term effects of such interventions have not been well documented. Effective technologies for changing physical activity behavior in other clinical populations are understudied and warrant further research. Findings from a recent review suggest that online physical activity interventions may have positive effects on depression symptoms, but the size of the effects and mechanism of change remain unclear [59]. Further research is needed to explore the efficacy and acceptability of online physical activity interventions for people with schizophrenia. Next to this, there is a need to construct interventions targeting the underpinning psychological mediators of behavior change that may result in physical activity interventions being more effective [60]. Incorporating mediator analyses into future research will help confirm if any action, or conceptual theory links exist between theoretical frameworks and desired behavioral goals. Current evidence suggests that behavior change theories used in the general population, such as the self-determination theory [61] and the transtheoretical model of change [62] appear to be suitable for application among individuals with schizophrenia [63-66]. Large-scale effectiveness trials in real-world settings and comparative effectiveness studies of motivational strategies are urgently needed. The implementation of evidence-based behavior change interventions is a critical step in achieving the goals of better quality, improved outcomes, and reduced costs of care for this vulnerable population

*How do we translate physical activity research into clinical and community practice?*

The efficacy of physical activity interventions in people with schizophrenia is well established when tested in scientific settings with research staff trained in exercise prescription. There have been, to date, few effectiveness trials for people with schizophrenia in community

settings and hence, less is known about how to translate this information into “real-world” settings. Until recently, community mental health centers have neglected lifestyle promotion as a core service for their patients [67], so dissemination of information regarding physical activity benefits and physical activity behavior change interventions to clinicians is essential. A physical activity intervention algorithm, e.g. as the one proposed by the IOPTMH [41] might assist clinicians and researchers. However, such algorithms should be validated. Algorithms need to be adaptable and updated when new evidence regarding optimal physical activity type, dose, timing, and enablers of response becomes available. Another essential element for maximizing translation is the interaction between patients and health care providers. Researchers should explore what patients in clinical and community settings want from their care providers regarding physical activity counseling and which resources are required to facilitate engagement. This kind of qualitative research could inform clinicians and researchers to develop a physical activity counseling model and tool kit for physical activity promotion through patient-health care provider interactions. Such an approach might bridge the transition between rehabilitation and physical activity promotion in the wider community. Once physical activity interventions have demonstrated efficacy through RCTs, their effectiveness should also be tested in real world settings so that their viability and efficaciousness can be determined outside the artificial RCT paradigm. This is an important step to ensuring that interventions are feasible and translatable into everyday clinical practice.

*How can we ensure integration of physical therapists within the multidisciplinary mental health treatment team?*

Integration of clinicians with expertise in exercise prescription (e.g. physiotherapists and exercise physiologists) and training in psychopathology, as members of the multidisciplinary mental health team (MDT) is important to ensure people with schizophrenia have adequate

access to physical activity interventions [68, 69]. One way to ensure integration is through education of the existing mental health workforce. There is a clear need for the development of education modules outlining the role of physical activity in the treatment of schizophrenia to be delivered to members of the MDT including e.g. psychiatrists, psychologists, mental health nurses, occupational therapists and social workers. Furthermore, it is imperative that students studying physical therapy receive training in psychopathology. While this is commonplace in some countries (e.g., Belgium and Norway), it is often neglected in others [30]. In addition, the increasing evidence base should increase the credibility and priority of physical activity in the clinical care of people with schizophrenia.

#### *How can we prevent sedentary behavior in people with schizophrenia?*

Sedentary behavior refers to activities that do not increase energy expenditure substantially above the resting level and includes activities such as sitting, lying down, watching television, and other forms of screen-based entertainment [70]. There is a growing body of evidence demonstrating that sedentary behavior, independent of physical activity, is a distinct risk factor for multiple adverse health outcomes. Interest in the potential health risk of sedentary behavior in people with schizophrenia is growing [13, 71, 72]. The current evidence is conflicting, for example, while Vancampfort et al. [13] found an association between greater time spent sitting and a higher body mass index, Janney et al. [72] did not find such association. In the general population, there is undeniable, rigorous evidence that sedentary behavior is, independent of physical activity associated with cardiovascular disease mortality [Hazard ratio (HR)=1.179, 95%CI=1.106 to 1.257), cardiovascular disease incidence (HR=1.143, 95%CI= 1.002 to 1.729), cancer mortality (HR=1.173, 95%CI=1.108 to 1.242)], cancer incidence (HR=1.130, 95%CI=1.053 to 1.213), and type 2 diabetes incidence (HR=1.910, 95%CI=1.642 to 2.222) [73]. Next to this, sedentary behavior is associated with

risk of depression. The summary relative risk (RR) of depression for the highest versus non-occasional/occasional sedentary behaviour is 1.25 (95%CI=1.16-1.35,  $I^2=50.7\%$ ). The pooled RRs of depression for sedentary behaviour are 1.31 (95%CI=1.16- 1.48) in cross-sectional studies and 1.14 (95%CI=1.06-1.21) in longitudinal studies. In subgroup analysis by different types of sedentary behaviour, the pooled RRs of depression are 1.13 (95%CI=1.06-1.21) for long-time TV viewing and 1.22 (95%CI=1.10-1.34) for prolonged computer or internet use [74]. However, given the limited number of published studies to date and the mixed and conflicting results among people with schizophrenia, it is difficult to draw conclusions regarding associations of sedentary time and health outcomes in this population. Inconsistent relationships between sedentary time and health outcomes might be due to: (a) self-reported [13] versus objective sedentary time [72], (b) the assessment of global time spent sedentary (sitting, and lying down) versus sitting time only assessments (e.g., highly variable responses), or (c) the heterogeneous samples recruited, e.g. the age range in the study of Janney et al. [72] was 18-70yrs. Future studies should therefore obtain objective assessments of both total sedentary time (accelerometers) as well as the specific behavior of sitting (inclinometers). Along with objective measures, an understanding of how sedentary behavior changes across the disease is currently lacking. The associations between sedentary time and physical health outcomes such as the long-term risk for cardio-metabolic diseases, cardiorespiratory fitness, muscular strength, relapse and risk for premature mortality remain unknown and currently limited to cross sectional data. Determining the unique contribution of sedentary time to these health outcomes is essential in order to define treatment priorities and to refine the current health recommendations and clinical practice guidelines. Since people with schizophrenia are typically very sedentary [13, 71, 72], there is a need to increase incremental daily physical activities, with the ultimate aim of reaching physical activity

targets. Walking is one strategy that has potential and may assist in helping particularly sedentary patients to start to live more active lifestyles [75].

*What is the most appropriate physical activity assessment method?*

There are concerns that symptoms of schizophrenia might influence the psychometric properties of common physical activity measures, thereby undermining the validity of score interpretation [76]. For example, cognitive impairment in memory is common in schizophrenia and might influence recall with self-report questionnaires and compliance with wearing accelerometers. Accelerometers provide objective measurement of physical activity and are particularly useful for measuring light intensity physical activities, which may be interspersed throughout the day, and thus more difficult to recall accurately than moderate to vigorous physical activity. In most mental health care settings clinicians are unlikely to have access to these devices. Interviews and questionnaires are, in contrast, cheaper and easier to use but often prone to systematic errors because of poor recall, in particular in people with schizophrenia [76]. Valid physical activity instruments that accurately capture sedentary behaviors and physical activity in people with schizophrenia have not been developed to date. One of the most important challenges in physical activity research in people with schizophrenia is producing a low cost, easy to use, reliable and valid physical activity questionnaire that captures sedentary behaviors and physical activities. Such a reliable and valid questionnaire is necessary for standardization across studies and clinical practices that occur worldwide and would permit meaningful comparisons of values, for example between diseases stages.

## **Limitations**

Our 10 research questions should be considered in the light of some methodological limitations of the survey executed. First of all, we did not use a systematic approach such as a thematic analysis [77] in order to select our questions. Secondly, patients were not consulted in this study. Patients are more and more regarded as stakeholders in the quest to improve the quality of their care. Patients should therefore be involved as well in setting a research agenda. In a next stage, the current top 10 research questions should therefore be discussed with patient organizations. Finally, no systematic review of the literature was executed in order to start to respond the most pressing physical activity questions researchers and clinicians working with people with schizophrenia are facing today.

## **Conclusions**

There is increasing evidence of the significant benefits of physical activity in people with schizophrenia, yet this population is overwhelmingly inactive and sedentary. In this article, the IOPTMH proposed 10 prominent research questions for the field of physical activity and schizophrenia. The IOPTMH believes that these questions are critical for informing our understanding of the short-term and long-term benefits of physical activity in people with schizophrenia and for developing approaches for promoting and sustaining an active lifestyle. Future research that addresses these questions may greatly improve the quality of life and daily life functioning of people living with this chronic disease.

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**Table 1.** Top 10 research questions for physical activity research in schizophrenia

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1. What are the benefits of physical activity for people with schizophrenia?
  2. What are the mechanisms of the physical activity effects in people with schizophrenia?
  3. What are the most prominent safety issues for physical activity prescription in people with schizophrenia?
  4. What is the most optimal physical activity prescription for people with schizophrenia?
  5. What are the key barriers for engaging people with schizophrenia in physical activity?
  6. What are the most effective motivational interventions for physical activity adoption and maintenance in people with schizophrenia?
  7. How do we translate physical activity research into clinical and community practice?
  8. How can we ensure integration of physical therapists within the multidisciplinary mental health treatment team?
  9. How can we prevent sedentary behavior in people with schizophrenia?
  10. What is the most appropriate physical activity assessment method in clinical practice?
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