**Does physical activity reduce the risk of psychosis? A systematic review and**

**meta-analysis of prospective studies**

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**Abstract**

Longitudinal prospective cohorts have suggested that physical activity (PA) may be a protective factor against psychosis and schizophrenia. However, no meta-analysis has been conducted. The study aims to To examine the prospective relationship between PA and incident psychosis/schizophrenia. Major databases were searched from inception to July 2019 for prospective studies that calculated the odds ratio (OR) or the adjusted odds ratio (AOR) of incident psychosis/schizophrenia in people with higher PA against people with lower PA. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS). A random-effects meta-analysis was conducted, for OR and AOR, separately. Across 4 cohorts (N=30,025, median males=50%, median follow-up=32 years), people with high self-reported PA (versus low PA) were at reduced odds of developing psychosis/schizophrenia (OR=0.73, 95%CI 0.532 to 0.995, p=0.047). Analysis including only 2 cohorts presenting AOR were not statistically significant (AOR=0.59, 95%CI 0.253 to 1.383, p=0.226). Overall study quality was moderate high (mean NOS=7.,0). The literature on the topic is scarce, whilst crude analysis suggests that PA may be a protective factor against the emergence of psychosis/schizophrenia, but when adjusting for covariates, the association is no longer significant. Further studies with objective physical activity and adjustment for confounders are needed.

**Introduction**

Psychotic disorders, such as schizophrenia, schizoaffective disorder, and delusions disorders, are a heterogeneous group of psychiatric diagnoses with common clinical features (e.g: abnormal thinking and perception), along with overlapping neurobiological dysfunctions and genetic risk factors (Reininghaus et al., 2013). Although schizophrenia is a low prevalent disorder (global age-standardized prevalence of about to 0.28%), it is associated with marked functional impairments (Charlson et al., 2018). For example, schizophrenia contributes 13.4 million years of life lived with disability globally (Charlson et al., 2018). Also, it is associated with increased risk of physical health comorbidities and reduced life expectancy (Firth et al., 2019; Vancampfort et al., 2016; Vancampfort et al., 2015; Walker et al., 2015).

In spite of the advances in mapping the neurobiological and genetic factors associated with psychosis/schizophrenia, etiologic factors are not fully understood (Radua et al., 2018). For example, family history of psychosis is associated with an increased risk of incident psychosis, however, it does not fully explain the likelihood of incident psychosis/schizophrenia (Miettunen et al., 2019). There is evidence supporting that environmental risk factors, such as childhood adversities, cannabis use, history of obstetric complications, adverse events during adulthood, and serum folate level potentially increase the risk of incident psychosis/schizophrenia (Belbasis et al., 2018). Also, emerging evidence further suggests that other environmental factors, such as having higher levels of perceived social support and living in a cohesive neighborhood, are associated with lower rates of incident psychosis/schizophrenia (Riches et al., 2019).

Large scale studies have found that physical activity (PA), is protective against incident mental disorders such as depression (Schuch et al., 2018) and anxiety (Schuch et al., 2019). However, whether PA is related to psychotic disorders remains to be established. There is a substantial body of evidence demonstrating the association between PA and schizophrenia and psychosis, suggesting that the protective effects of PA can be extended to this group. First, there is a wealth of cross-sectional evidence suggesting that PA is inversely associated with the presence of psychotic symptoms (Stubbs et al., 2017; Stubbs et al., 2018), and that people with psychotic disorders have decreased PA levels (Firth et al., 2017; Stubbs et al., 2016; Vancampfort et al., 2017a), reduced cardiorespiratory fitness (Vancampfort et al., 2017b) and spend more time engaged in sedentary behavior (Vancampfort et al., 2017a) in comparison to the general population. However, these data are from cross-sectional studies, which does not allow to establish causal relationships. Second, clinical trials have demonstrated beneficial effects from PA interventions on psychotic symptoms, particularly following structured forms of PA, i.e. exercise in people with psychosis (Firth et al., 2015; Veerman et al., 2017). Lastly, there is biological plausibility since the onset of psychotic disorders is associated with impairments in brain function and structure (Kuo and Pogue-Geile, 2019; Mizutani et al., 2019) and exercise has been shown to have neuroprotective effects (Firth et al., 2018).

Previous reviews have discussed the protective role of PA against incident (the development of) psychosis/schizophrenia (Douglas L. Noordsy et al., 2018). However, to the best of our knowledge, no meta-analysis has evaluated and summarized these preventative effects. The aim of the present study was to comprehensively review and summarize the literature on prospective cohort studies investigating the role of PA as a protective factor against incident psychosis/schizophrenia. The understanding of the protective effect against incident psychosis allows the understanding of how PA can reduce the risk of someone to develop psychosis/schizophrenia.

**Methods**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al., 2009) and the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) statement, following an a priori established, unpublished protocol (available upon request).

*Inclusion criteria*

Eligibility of studies was assessed according to the following criteria: (1) Used a prospective study design with at least one-year period of follow-up duration; (2) PA was defined as "any bodily movement produced by skeletal muscles that result in energy expenditure", matching the definition of Caspersen et al. (1985). In this context, any PA characteristics assessed using self-reported questionnaires, interviews or using objective measures (e.g.: pedometers, accelerometers) were accepted. Therefore, PA assessment via school grades in Physical Education or via cardiorespiratory fitness was not regarded as being in line with this definition. (3) PA was assessed at baseline. (4) Evaluated the longitudinal, prospective associations between PA and schizophrenia or psychosis. Having psychosis/schizophrenia was defined through a diagnosis by a psychiatrist found in medical records, by screening tools assessing psychotic symptoms or schizophrenia, or by other validated instruments to assess psychotic symptoms or schizophrenic according to the DSM (American Psychiatric Association, 2013) or ICD criteria (World Health Organisation, 1993), and (5), excluded people with psychosis or schizophrenia at baseline from analysis. Studies were excluded if (1) did not use original data (e.g.: reviews, commentaries, editorials), (2) were written in languages other than English, German, Portuguese, Spanish, or French.

*Information sources and searches*

Databases PubMed, Embase, Web of Science, PsycINFO, and SPORTDiscus were searched from inception until on 29th of July 2019. Additionally, clinicaltrials.com was scanned for any ongoing or unpublished studies. The following keywords were used, adapted to each database: (physical activity OR exercise OR fitness OR sport\*) AND (schizophren\* OR psychosi\* OR psychotic disorder OR prodromal symptoms) AND (prospective OR longitudinal OR cohort OR association OR risk OR risk factor OR protect\* OR prevent\* OR follow-up OR onset OR causal\*). Reference lists of the articles considered for a second screening were manually searched, as well as the references of a meta-analysis on the protective effects of exercise on depression (Schuch et al., 2018). The full strategy used in each electronic database can be seen in supplementary materials 1.

*Study selection*

After removing duplicates, two authors (LB, FS) independently screened titles and abstracts of all articles retrieved from the search. Then, potentially eligible studies were reviewed in detail. Disagreements were solved by discussion until consensus was reached. Missing data and additional information were requested from authors via e-mail when necessary. If unsuccessful, the online-network *researchgate.net* was used to contact the authors. Authors who did not respond were sent reminder emails after one and again after two weeks of first contact.

*Data extraction*

Descriptive data on the number of subjects, age at baseline, follow-up time, country, assessment method of PA, and psychosis/schizophrenia assessment and incidence were gathered. The main results expressed in odds ratio (OR) were extracted together with 95% confident intervals (CI). Whenever a study reported results using Relative Risks (RR), or Hazard Ratio (HR), the authors were contacted, and the results reported in OR were solicited. Covariates used for adjusting the analysis (for studies presenting adjusted OR) were also extracted.

*Meta-analysis*

A random-effects meta-analysis was used to investigate the relationship between baseline PA and incident psychosis/schizophrenia. First, data were pooled across all studies comparing incident psychosis/schizophrenia in the highest PA levels group (the group of greater frequency, intensity, volume, energy expenditure or other measures of PA participation, from each study, as defined by the authors) versus the lowest PA level group (reference group). Whenever the reference group was inverted, the OR value was inverted. Analysis for adjusted odds ratio (AOR) and crude OR were conducted separately. For the AOR, estimates were pooled using the model with the greatest number of covariates presented by the authors. The Q and I2 statistic were used to assess and to quantify the heterogeneity, respectively. Scores of <25%, 25-50% and >50% indicated low, moderate and high heterogeneity, respectively (Higgins et al., 2003). All analyses were performed using Comprehensive Meta-Analysis software (version 3).

*Risk of bias and quality assessment*

The risk of bias was assessed using the Newcastle Ottawa Scale (NOS). The NOS has three domains: 1) selection of participants comprises four items regarding the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of the study was not present at baseline assessment, 2) The second domain, comparability, evaluates the adjustment for potential confounding factors in the analyses, and 3) outcome, has three items concerning quality of outcome assessment, length of follow-up, and completion rate of follow-up. For each item, one point can be achieved, except for the comparability item (two points are possible for more controlling factors). The maximum score of the NOS is 9 (highest quality) and we assigned scores of 0–3, 4–6 and 7–9 for the low, moderate and high quality of studies, respectively, according to previous references (Schuch et al., 2018; Schuch et al., 2019).

**Results**

*Search results*

The initial search yielded 5537 references. After removing duplicates, 2975 studies were considered on the abstract/title level. Of these, 27 studies were then read at the full-text stage and four met the criteria for inclusion in the quantitative analysis (Keskinen et al., 2016; Koivukangas et al., 2010; Okkenhaug et al., 2018; Sormunen et al., 2017). The flowchart detailing the number of studies excluded at each step with reasons can be seen in Figure 1.

Insert Figure 1 here

*Studies details*

A total of 30,025 participants were included at the baseline assessments in the studies. All studies assessed PA levels in children, adolescents or young adults, with the age at baseline ranging from 9 to 18 years old. Two studies reported the proportion of women at baseline (ranging from 49% to 52%) (ranging from 49% to 52%, Keskinen et al., 2016; Koivukangas et al., 2010), whilst two studies did not indicate sex distribution (Okkenhaug et al., 2018; Sormunen et al., 2017). The follow-up period ranged from 4 to 32 years. Three studies were conducted in Finland (Keskinen et al., 2016; Koivukangas et al., 2010; Sormunen et al., 2017), and one in Norway (Okkenhaug et al., 2018). All studies performed the diagnostic assessments of psychosis/schizophrenia using data from national/regional registers (Keskinen et al., 2016; Koivukangas et al., 2010; Okkenhaug et al., 2018; Sormunen et al., 2017). All studies assessed PA using self-reported PA questionnaires. However, only one study tested the validity of the PA measure against objective measures (accelerometers and pedometers) (Sormunen et al., 2017), and only one performed test-retest reliability using the intraclass correlation coefficient (ICC=0.83) (Koivukangas et al., 2010). Details of the included studies can be found in table 1.

Insert Table 1 here

*Meta-analysis*

A meta-analysis pooling five effects from four unique studies (Keskinen et al., 2016; Koivukangas et al., 2010; Okkenhaug et al., 2018; Sormunen et al., 2017) presenting crude OR suggests that higher PA levels is longitudinally associated with decreased risk of incident psychosis/schizophrenia of about 27%. The analysis had low heterogeneity (I2=36.93 Q-value=6.34, p=0.17, Tau=0.21). The forest plot can be seen in Figure 2. The studies had, on average (mean=7, standard deviation=1), a low risk of bias. The full assessment of all domains is presented in supplementary table 1.

Insert Figure 2 here

Data pooled from two unique studies (Koivukangas et al., 2010; Sormunen et al., 2017) using analysis adjusted for covariates, however, found no significant protective effects of PA on incident psychosis/schizophrenia. The adjusted analysis was found to have moderate heterogeneity (I2=54.71, Q-value=2.20, p=0.13, Tau=0.50). The forest plot can be seen in Figure 3.

Insert Figure 3 here

**Discussion**

To the best of our knowledge, this is the first study to summarize the evidence on PA as a protective or risk factor for incident psychosis/schizophrenia. With a low risk of bias, the crude analysis revealed that higher PA levels are associated with a 27% decreased risk of incident psychosis/schizophrenia. However, after pooling effects from two studies that adjusted for potential confounding factors such as age, sex, parents’ mental disorders, and BMI, the protective effect of PA dissipated. This preliminary suggests that PA may not be related to the onset of psychosis/schizophrenia and the unadjusted results may be explained by confounding factors.

Although following the adjusted analysis we did not find significant protective effects, there are some aspects that should be considered. First, the analysis only included two studies. Second, one of the studies did not exclude participants with prodromal symptoms at baseline (Koivukangas et al., 2010). This study, although has excluded caseness from baseline, might have included participants in the at-risk mental state phase who are at increased risk of developing schizophrenia and it is not possible to account fully for this. There is evidence that people at risk for psychosis/schizophrenia are also in increased risk of presenting cardiometabolic risk factors, social isolation and low physical activity (Carney et al., 2016). Therefore, they are more likely be encouraged to be more active to preserve their physical health. Third, the incidence of schizophrenia was, as expected, low in the two studies included in the adjusted analysis (0.5% and 1.8%) (Koivukangas et al., 2010; Sormunen et al., 2017), which may reduce the power of the analysis. Therefore, it is not possible to discard this hypothesis. More cohort studies are necessary to clarify if there is a potential relationship between physical activity and the risk of psychosis/schizophrenia.

There are some possible explanations as to how PA may exert a protective effect against psychosis and schizophrenia, such as structural brain changes or increases in neurogenesis. First, psychosis and schizophrenia are associated with abnormalities in brain function and structure (Kuo and Pogue-Geile, 2019). For example, an increased volume of intracranial (+2.8%), lateral (+8.7%) and third (+14.1%) ventricles was found in people with schizophrenia compared to healthy controls (Kuo and Pogue-Geile, 2019). PA, on the other hand, promotes brain plasticity in certain regions (Firth et al., 2018), potentially protecting those at increased risk to develop the disorder. Second, people with schizophrenia, and even at risk for schizophrenia, have decreased brain-derived neurotrophic factor (BDNF) serum levels, a marker of neuronal regeneration and plasticity (Green et al., 2011; Heitz et al., 2018). PA, in turn, can increase BDNF serum levels in healthy people (Szuhany et al., 2015). Some preliminary evidence suggests PA exerts similar beneficial effects in those at risk for psychosis/schizophrenia (Dean et al., 2017). Lastly, people with later development of schizophrenia present poorer motor performance in childhood (Stochl et al., 2019). Poor motor performance, in turn, is associated with PA avoidance and reduced PA levels (Jaakkola et al., 2019). Thus, increasing PA levels results in an increase of motor performance, and consequently, at a lesser risk of incident psychosis/schizophrenia.

The present study has some limitations. First, people with lower PA levels may have other risk factors for psychosis/schizophrenia, such as poor diet, use of tobacco, and other clinical comorbidities (Firth et al., 2019). Second, all the studies included used self-reported instruments for assessing PA levels, being more susceptible to recall bias, particularly in individuals with psychotic disorders(Firth et al., 2017b). Also, the studies evaluated different parameters of PA (frequency (Keskinen et al., 2016; Okkenhaug et al., 2018), volume (Koivukangas et al., 2010), or a composure measure including frequency, volume and intensity (Sormunen et al., 2017)), and there are not enough studies to explore the role of each variable individually on the protective effects of PA. On the other hand, there is no heterogeneity in the crude analysis, suggesting that the effects do not vary across the different forms of assessing PA. Third, all of the data presented came from Finland or Norway. Therefore, generalization to other countries, and particularly low and middle income regions, is limited.

**Conclusion**

PA may be a protective factor against the emergence of psychosis/schizophrenia. However, when adjusting for covariates and limited to only two studies, the association is dissipated. The literature on the topic is still in its infancy and more studies are needed to reach a stronger statement.

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