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Highlights

- This review identified 4 studies examining the longitudinal relationships between physical activity and risk for psychosis
- Crude analyses reveal that physical activity may be prospectively associated with a decreased risk of incident psychosis.
- Analyses including 2 studies that adjusted the effects for confounding factors did not find protective effects of PA on incident psychosis/schizophrenia.
- It is unclear if PA is associated with future psychosis/schizophrenia risk and future robust longitudinal studies are required to clarify this potential relationship.

Does physical activity reduce the risk of psychosis? A systematic review and meta-analysis of prospective studies

Luisa Leonie Brokmeier[1], Joseph Firth[2,3,4], Davy Vancampfort[5,6], Lee Smith[7], Jeroen Deenik[8,9], Simon Rosenbaum[10,11], Brendon Stubbs[12,13,] Felipe Barreto Schuch[14]

1 University of Konstanz, Konstanz, Germany;

2 NICM Health Research Institute, Western Sydney University, Westmead, Australia

3 Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

4 Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia

5 KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium

6 University Psychiatric Centre KU Leuven, Kortenberg, Belgium

7 The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

8 GGz Centraal, Utrechtseweg 266, 3818 EW Amersfoort, The Netherlands

9 School for Mental Health and Neuroscience Maastricht University, Minderbroedersberg 4-6, 6211 LK Maastricht, The Netherlands

10 School of Psychiatry, University of New South Wales, Sydney, Australia

11 Black Dog Institute, Sydney, Australia

12 Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK;

13 Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

14 Department of Sports Methods and Techniques, Federal University of Santa Maria, Santa Maria, Brazil.

Corresponding author: Felipe Barreto Schuch
Federal University of Santa Maria (UFSM),
Av. Roraima, 1000, Camobi
Santa Maria, Rio Grande do Sul, BR.
Tel: +55 55 33818877; Fax: +55 55 33818877.
E-mail address: felipe.schuch@ufsm.br

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 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 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 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.

Conflict of Interest

All authors declare that they have no conflicts of interest.

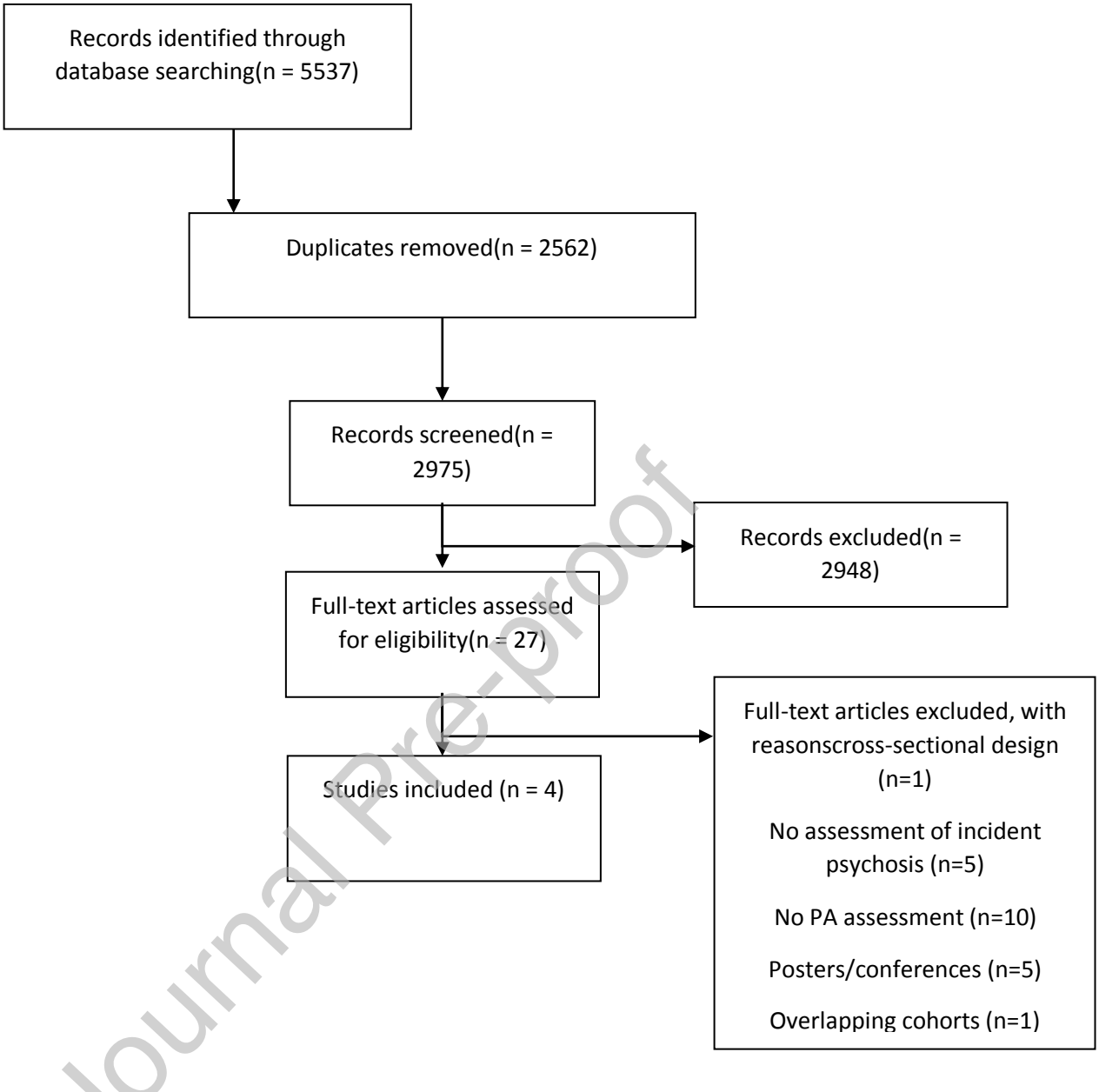

Figure 1. Flowchart of study selection

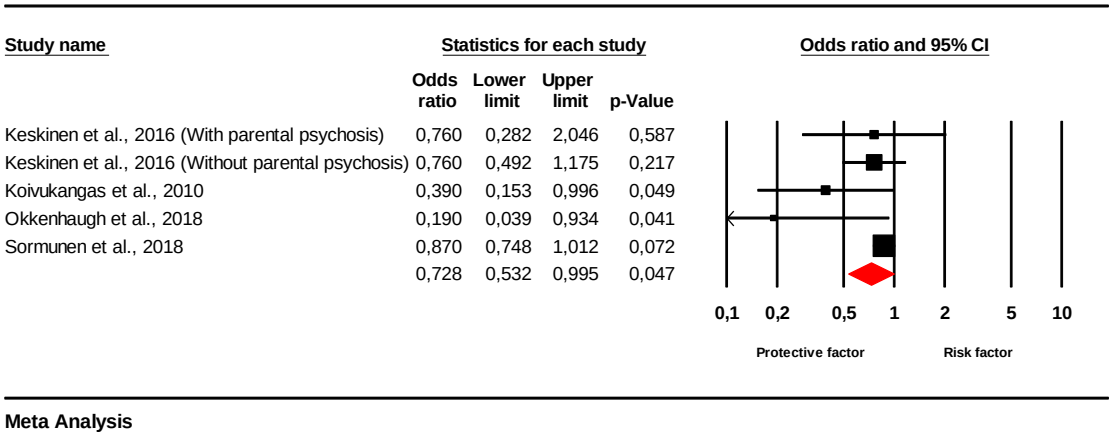

Figure 2. Forest Plot of Studies Examining the Association Between Physical Activity and Incident Psychosis/Schizophrenia. Crude Odds Ratio

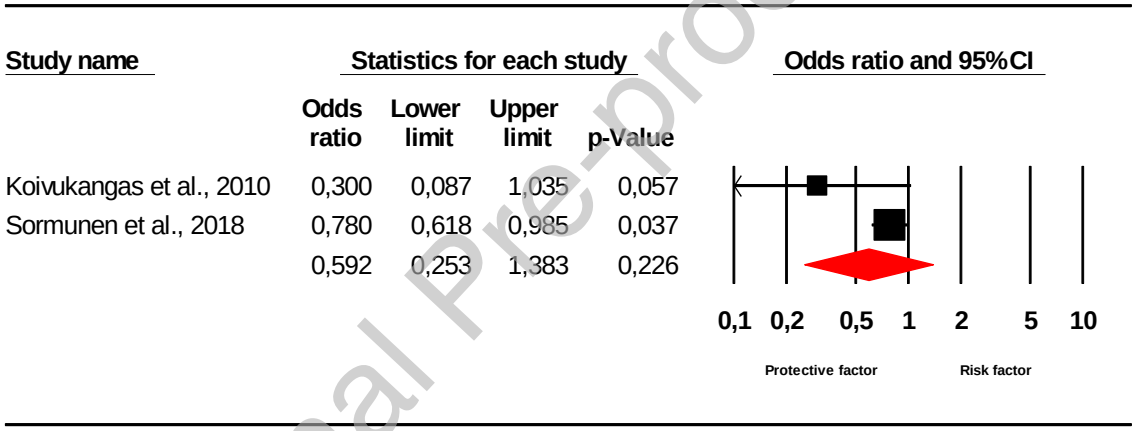

Figure 3. Forest Plot of Studies Examining the Association Between Physical Activity and Incident Psychosis/Schizophrenia. Adjusted Odds Ratio

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). In spite of the advances in mapping the neurobiological and genetic factors associated with psychosis, etiologic factors are not fully understood (Radua et al., 2018). For example, although familial history of psychosis is a consistent risk factor, it does not fully explain the likelihood of incident psychosis (Miettunen et al., 2019). There are evidences supporting the notion that childhood

adversities, cannabis use, history of obstetric complications, adverse events during adulthood, and serum folate level potentially increase the risk of psychosis (Belbasis et al., 2018). Emerging evidence further suggests that other factors such as having higher levels of perceived social support and living in a cohesive neighborhood, reduces the risk of psychosis (Riches et al., 2019).

Large scale studies have found that physical activity (PA), defined as any bodily movement produced by skeletal muscles that requires energy expenditure (Caspersen et al., 1985) is protective against other 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. A wealth of cross-sectional evidence suggests that PA is inversely associated with the presence of psychotic symptoms (Stubbs et al., 2017; Stubbs et al., 2018). In addition, people with psychotic disorders have decreased PA levels (Firth et al., 2017b; 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. In addition, clinical trials have demonstrated beneficial effects from PA interventions on symptoms of psychosis, particularly following structured forms of PA, i.e. exercise (Firth et al., 2015; Veerman et al., 2017). Exercise also improves cardiorespiratory fitness, cognition and quality of life in people with schizophrenia (Firth et al., 2017a; Vancampfort et al., 2014; Vancampfort et al., 2015a). Moreover, whereas the onset of psychotic disorders is associated with impairments in brain function and structure (Kuo and Pogue-Geile, 2019; Mizutani et al., 2019), exercise has been shown to have neuroprotective effects (Firth et al., 2018). Therefore, it is biologically possible that PA can be prospectively associated with a decreased risk of incident psychosis/schizophrenia.

To the best of our knowledge, no meta-analysis has evaluated and summarized the effects of PA on incident psychosis/schizophrenia. 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 for incident 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 results in energy expenditure", matching the definition of Caspersen et al. (1985). In this context, intensity and frequency of PA should be assessed, using self-reported questionnaires, interviews or using objective measures (e.g.: pedometers, accelerometers). 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 was evaluated. 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 the DSM (American Psychiatric Association, 2013) or ICD criteria (World Health Organisation, 1993), and (5), have 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 mails after one and again after two weeks of first contact.

Data extraction

Descriptive data on the number of subjects, age at baseline, and follow-up time, country, assessment method of PA, and schizophrenia. 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 was 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 measure 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 I^2 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%)(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 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 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 (OR=0.72, 95% CI 0.532 to 0.995, p=0.047). The analysis had low heterogeneity (I^2=36.93 Q-value=6.34, p=0.17, Tau=0.21). The forest plot can be seen in Figure 2.

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 (AOR=0.59, 95% CI 0.253 to 1.383, p=0.226). Low heterogeneity was found (I^2=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

Study quality

The studies had, on average (mean=6.7, standard deviation=1.50), a moderate risk of bias. Full assessment of all domains is presented in supplementary table 1.

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. 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.

Some caution, however, is necessary when interpreting this data due to the limited sample size, number of studies (particularly in the adjusted analyses) and reliance on self-reported PA.

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, it may have included participants at 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. In fact, people with mental illnesses have higher risk of cardiometabolic diseases (Correll et al., 2017; Vancampfort et al., 2016; Vancampfort et al., 2015b), which can be partially attributed to their lower PA levels and higher amount of time spent in sedentary behavior (Correll et al., 2017; Vancampfort et al., 2016; Vancampfort et al., 2015b). 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 variation in 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). Second, it is well known that 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). Exercise, on the other hand, may promote brain plasticity in certain regions (Firth et al., 2018), and it is possible that PA may help to protect those at increased risk to develop the disorder. 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). Another potential explanation is associated with poor motor development in people with schizophrenia. Some evidence suggests that 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).

The present study has some limitations. First, the data presented came from two high income countries (Finland and Norway). Therefore, generalization to other countries is limited. 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). Third, 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).

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 in the topic is still in its infancy and more studies are needed to reach a stronger statement.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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Table 1. Description of studies

Study	Cohort	Country	Baseline sample size (% women)	Age at baseline	Follow-up	Psychosis/Schizophrenia definition	Psychosis/ schizophrenia Incidence	PA measure	PA unit	Covariates included in adjusted model
Keskinen et al., 2016	The Northern Finland 1966 Birth Cohort (NFBC)	Finland	n=10458 (49.2% women)	14 years	32 years	Non-organic psychosis (i.e. ICD-8: 295–299; ICD-9: 295, 2961E, 2962E, 2963E, 2964E, 2967, 297–299; ICD-10: F20, F22-F29) in database medical registers	3.1%	SRQ on PA and sport participation. Questionnaires applied at 1980 (validation unclear)	Frequency (weekly frequency)	-
Koivukangas et al., 2010	The Northern Finland 1986 Birth Cohort (NFBC)	Finland	n=6987 (51.8% women)	15-16 years	4 years	Non-organic psychosis (ICD-10 codes F20–F33 except non-psychotic mood disorders in database medical	0.5%	SRQ on PA on hours per week spent on brisk PA Physical inactivity = Less	Volume (hours per week)	Socioeconomic status, family structure,

						registers.		than one hour of MVPA per week (test-retest intraclass correlation coefficient = 0.83)		gender, and father and mother PA
Okkenhaugh et al., 2018	North Troendelag Health Study (Young - HUNT1 Study)	Norway	N=8984 (% women unclear)	16 years	?	Schizophrenia (F.20.0–F.20.9 of the ICD-10 categories)	0.16%	SRQ on hours and days spent in PA or exercise past week (validation unclear)	Frequency (days per week)	-
Sormunen et al,. 2017	Cardiovascular Risk of Young Finns	Finland	n=3596 (% women unclear)	9-18 years	32 years	Schizophrenia (DSM-IV 295) and all non-affective psychoses (DSM-IV 295, 297, 298) in database medical registers	1.8%	SRQ on PA (validated against accelerometers and pedometers)	Composed (an index composed by PA Frequency, Intensity and Volume/Time)	Gender, age, BMI, PAI, birth weight, and non-preterm birth. Mother's mental disorders

Key: BMI=Body Mass Index, DSM= Diagnostic and Statistical Manual of Mental Disorders, ICD=International Classification of Disease, MVPA=Moderate to Vigorous Physical Activity, PA=Physical Activity, PAI=Physical Activity Index, PDI=Peters Delusional Inventory, SRQ=Self-reported questionnaire.