

Sports Therapy for Schizophrenia Psychoses: from the Idea to the Guideline

Sporttherapie bei schizophrenen Psychosen: Von der Idee bis zur Leitlinie



Authors

Peter Falkai^{1, 2}, Rebecca Schwaiger¹, Andrea Schmitt^{1, 3}, Lukas Röhl¹, Isabel Maurus¹

Affiliations

- 1 Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich, Germany
- 2 Max Planck Institute of Psychiatry, Munich, Germany
- 3 Laboratory of Neurosciences (LIM-27), Institute of Psychiatry, University of São Paulo (USP), São Paulo, Brazil

Key words

Schizophrenia, sports, endurance training, treatment guidelines, therapy

Schlüsselwörter

Schizophrenie, Sport, Ausdauertraining, Behandlungsleitlinien, Therapie

Bibliography

Gesundheitswesen 2023; 85 (Suppl. 3): 212–217

DOI 10.1055/a-2129-7421

ISSN 0949-7013

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Prof. Dr. Dr. h.c. Peter Falkai
Department of Psychiatry and Psychotherapy
LMU University Hospital, LMU Munich
Nussbaumstrasse 7
80336 Munich
Germany
peter.falkai@med.uni-muenchen.de



Deutsche Version unter:
<https://doi.org/10.1055/a-2129-7421>

ABSTRACT

Schizophrenia psychoses can be treated much better today due to the introduction of antipsychotics about 70 years ago in conjunction with the implementation of specific psychotherapies. However, current treatment options are still limited in the area of negative symptoms and disease-associated cognitive deficits. In the last 15 years, randomised controlled trials (RCTs) have been able to show that physical training and especially endurance training could represent a comprehensive complementary treatment approach and could lead to a significant improvement in positive, but especially also in negative symptoms and cognitive deficits. As a result, sports therapy for schizophrenia psychoses has found its way not only into the national treatment guidelines of the German Society for Psychiatry, Psychotherapy, Psychosomatics and Neurology (DGPPN), but also into European recommendations such as those of the European Psychiatric Association (EPA). With the introduction of the “Living guideline” format (here an update takes place at least once a year), a broader implementation in health care will be easier in the future. Based on a narrative review, this paper describes the process of implementing sports therapy for schizophrenia psychoses from its beginnings to its incorporation into guidelines and can be applied analogously to other forms of therapy.

ZUSAMMENFASSUNG

Schizophrene Psychosen sind aufgrund der Einführung von Antipsychotika vor ca. 70 Jahren in Verbindung mit der Implementierung spezifischer Psychotherapien heute deutlich besser behandelbar. Im Bereich der Negativsymptomatik und krankheitsassoziierten kognitiven Defiziten sind die aktuellen Behandlungsmöglichkeiten jedoch weiter limitiert. In den letzten 15 Jahren konnten randomisiert kontrollierte Studien (RCTs) zeigen, dass körperliches Training und insbesondere Ausdauertraining einen umfassenden ergänzenden Behandlungsansatz darstellen könnte und zu einer signifikanten Verbesserung der Positiv-, aber insbesondere auch der Negativsymptomatik und von kognitiven Defiziten zu führen vermag. In der Folge hat Sporttherapie bei schizophrenen Psychosen

Eingang in die nationale Behandlungsleitlinie der Deutschen Gesellschaft für Psychiatrie, Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), aber auch in europäische Empfehlungen, wie der European Psychiatric Association (EPA) Einzug gehalten. Im nächsten Schritt muss eine breite Implementierung in die Versorgung erfolgen, was mit der Einführung des „Living guideline“ Formats (hier erfolgt mindestens einmal

jährlich eine Aktualisierung) besser als bisher möglich sein wird. Die vorliegende Arbeit bildet, basierend auf einem narrativen Review, den Prozess der Implementierung von Sporttherapie bei schizophrenen Psychosen von ihren Anfängen bis zur Verankerung in Leitlinien ab und kann analog für andere Therapieformen gelten.

Possibilities and limits of the treatment of schizophrenia psychoses

Recovery capacity

Schizophrenia psychoses are clinically characterized by both so-called positive and negative symptomatology [1]. Positive symptomatology is reflected in disturbances of thinking (e. g., experience of persecution), perception (e. g., auditory hallucinations such as commenting voices), and ego disturbances (e. g., other persons can perceive one's own thoughts), and are readily treatable in 50–70% of affected individuals by administration of antipsychotics in combination with specific psychotherapies (primarily cognitive behavioral therapy and metacognitive training) [2]. Negative symptomatology, on the other hand, is defined as a deficit in drive and social interaction, as well as a reduced ability to feel emotions [3]. It is usually accompanied by a disturbance in cognition, characterized by an impaired ability to perceive and store information at an adequate rate. In particular, this results in dysfunction of verbal memory, learning ability, and attention [4]. Negative symptoms and cognitive disturbances are currently not sufficiently treatable by antipsychotics or specific psychotherapies [5, 6] and lead to a significant restriction in the area of a lifestyle in which professional and private goals are usually difficult to achieve [7, 8]. Consequently, the recovery rate for this group of disorders is only 15–20%, i. e. 80% of those affected cannot lead a life unaffected by the disorder [9].

Comorbidity and mortality

People with schizophrenia psychoses have a 10–15 years reduced life expectancy [10–13]. This is not primarily explained by an increased suicide rate, but by a lifestyle that results in a significantly increased cardiovascular risk profile. For example, people with schizophrenia have a diet very high in fat and carbohydrates, are predominantly physically inactive, smoke, and also drink more alcohol than the average population [14, 15]. In addition, psychotropic drugs contribute to increased weight gain and dyslipidemia. These factors result in increased prevalences of type2 diabetes mellitus [16, 17], obesity [18], hypertension, dyslipidemia, and metabolic syndrome [19], which in turn accounts for the increased rates of coronary heart disease, heart failure, and cerebrovascular disease in people with schizophrenia [20].

Ultimately, to improve the prognosis of people with schizophrenia psychoses, both the burden of disease from persistent symptoms and the increased mortality from cardiovascular disease must be reduced [21]. Since new developments in the field of psychopharmacotherapy over the past 20 years have not yielded resound-

ing success in these areas, it is of great importance to develop and establish further therapies that improve symptom areas in which standard procedures have not been sufficiently effective to date. In this context, methods that are able to reduce negative symptoms and cognitive deficits in particular, while at the same time having a positive influence on lifestyle factors and the associated somatic diseases, are considered ideal. Sports interventions are a promising treatment option, as will be shown in the following.

Evidence for the effectiveness of exercise therapy in schizophrenia psychoses

Influence on psychological symptoms

In a first controlled three-arm study [22] of our research group, it was shown that a three-month cycle ergometer training with three training sessions of 30 minutes per week was able to lead to a reduction of negative symptoms and cognitive impairments. In a follow-up study [23, 24], we were also able to demonstrate that the additional combination of three months of bicycle ergometer training with cognitive training produced better effects for functional capacity (measured with the Global Assessment of Functioning (GAF), the Social Assessment Scale (SAS)) and cognitive performance compared to the control condition (table soccer). This provided evidence that the use of larger muscle groups in the intervention, as opposed to more coordinative movement patterns in the control condition table soccer, was necessary to achieve a positive impact on psychopathology and cognition. In a subsequent multicentre study conducted by our group, a clear positive effect of aerobic exercise on positive, negative, and cognitive symptomatology was found in a total sample of 180 patients with schizophrenia psychoses [25, under review].

Subsequently, several other randomized controlled trials were conducted, and their effects were summarized in a meta-analysis by Firth et al. In this, sports intervention was found to improve general cognitive performance, working memory, and attention in people with schizophrenia [26]. Further meta-analyses have demonstrated reductions in negative and positive symptoms, depressive symptoms [27–31], and increases in quality of life and level of functioning in everyday life [27, 32–35].

Among the sports that have therapeutic application in people with schizophrenia, **endurance training** has been the best studied to date. This form of exercise is considered by the American College of Sports Medicine (ACSM) to be any movement that uses large muscle groups, can be sustained continuously, and has a rhythmic nature [36]. In two meta-analyses [26, 37], endurance exercise was

shown to improve general cognitive functioning in people with schizophrenia, as well as memory domain-specific improvements in working memory, social cognition, and attention. These findings were confirmed in a recently published meta-analysis by Shimada et al. [37]. In contrast, two other meta-analyses could not replicate the effect on cognition [38] or on positive symptomatology, respectively [39].

In contrast, a combination of **strength and endurance training** appears to lead to greater reductions in schizophrenia-specific symptomatology and increased improvements in physical fitness than either type of training separately in people with schizophrenia [29, 40]. However, even this meta-analytic finding has not gone unchallenged in the literature to date [39], so further, carefully designed and ideally multicenter studies are needed to bring clarity to this part of the research. Furthermore, strength training may also contribute to the prevention of physical diseases, as it is known that muscle strength is inversely associated with long-term mortality risk in the general population [41].

Yoga combines movement and body awareness techniques [42, 43]. Vancampfort and colleagues were able to show in a systematic review that yoga leads to an improvement in psychopathology and quality of life in people with schizophrenia [44], which was confirmed by the work of Dauwan et al. [27]. However, two meta-analyses were unable to confirm these findings [45, 46], so further studies should also be conducted to clarify the evidence base.

In summary, although studies are still mixed, sports interventions can lead to further improvements in cognition and psychopathology in people with schizophrenia as an add-on therapy to pharmacotherapy and psychotherapy, which are also reflected in an increase in quality of life and an increased level of functioning in everyday life. Sport thus represents an important therapeutic approach, particularly for areas such as negative symptomatology and cognition, which can only be inadequately addressed with previous standard therapy methods.

Influence on physical fitness

As already described, people with schizophrenia suffer from a significantly increased morbidity and mortality due to cardiovascular diseases, the first of which is often a significant weight gain of those affected. Considering the effect of preventive measures on weight gain, this is usually only slightly achieved by switching antipsychotics, whereas it is highest by lifestyle modification measures, and here in particular by performing regular endurance training [47]. Programs that aim to reduce obesity, for example in people with a BMI above 25 kg/m², are successful if they integrate not only the topic of exercise but other domains of lifestyle modification [48]. A meta-analysis of 13 studies showed that BMI can be reduced by endurance training combined with strength training in people with schizophrenia [29]. Maximal oxygen uptake (VO_{2max}) is also an indicator of cardiovascular fitness and can be improved by exercise interventions [49, 50]. A meta-analysis across seven studies in people with schizophrenia identified an increase of 2.87 ml/kg/min on average [49] with exercise intervention. Improvements in cardiovascular fitness are of great predictive value, as evidenced by the fact that an increase in maximal oxygen uptake of 3.5 ml/kg/min in the general population reduces the risk of all-cause mortality and

cardiovascular disease by 13–15% [51, 52]. In addition, a trend toward reduction in triglycerides has been noted [29]. Thus, exercise is able to reduce the cardiovascular risk profile at multiple levels.

Lifestyle modification with the goal of better physical health is a longer-term process that receives special attention under the “Implementation” paragraph.

Effect of sports therapy on the brain

With the evidence of clinically relevant changes under sports therapy in people with schizophrenia, it is reasonable to assume that brain structural changes can also be found in these patients as a result of the intervention. In the three-arm clinical study by Pajonk et al. [22] mentioned above, we found not only an effect on negative symptomatology and cognition in the intervention arm, but also bilateral increases in hippocampal volume. Although there is evidence for this in healthy humans [53] and also animal experiments in mice [54, 55], the finding could not be substantiated in a follow-up study by our own research group [23, 24] and also by other research groups [56–58]. However, we were subsequently able to show that a significant increase in volume under exercise was not found for the total volume of the hippocampus, but for its subregion CA4, which was associated with an activation of regenerative genetic pathways in the Polygenic Risk Score (PRS), especially for synaptic plasticity [59]. Using the cell-specific PRS, an association was found between volume increase in CA4 and risk genes for oligodendrocyte progenitor cell maturation [60]. This is interesting in that we demonstrated a significant reduction in oligodendrocyte number in schizophrenia psychosis in two independent post-mortem samples in the CA4 subsegment [61–63], which could be a consequence of insufficient maturation of oligodendrocyte progenitor cells. These and other findings suggest that disruption of myelin-associated plasticity may be the basis for cognitive dysfunction in schizophrenia [64].

Beyond the hippocampus, a few other brain regions have been investigated for possible plastic effects of exercise training. For example, there was an increase in the thickness of the cortex in the anterior cingulate [65], an increase in the volume of the left hemisphere [66], and an improvement in the integrity of the white matter [67]. In our own large multicenter study, we demonstrated a positive effect on cortex thickness, gyrification as a measure of atrophy, and centrally important functional networks [68, 69]. In summary, aerobic exercise has an effect on brain structure and function, and according to our closer findings, a subgroup of 40% of patients in particular are able to benefit and thus also show a proplastic effect [70], which explains the heterogeneity in the literature.

Embedding in guidelines and implementation

In its **guideline on the management of physical health in adults with severe mental illness**, the World Health Organization points out that exercise interventions can have a positive effect on cardiovascular risk factors, such as a reduction in obesity and an improvement in blood glucose levels, where appropriate [71].

In the current **S3 guideline schizophrenia of the German Society of Psychiatry, Psychosomatics, Psychotherapy and Neurology** [72], exercise interventions such as physiotherapy or interventions with a psychotherapeutic approach, are assigned recom-

mendation grade B, which is a so-called “should recommendation” [72]. A strong recommendation could not be assigned due to the current inconsistent study situation. Sports interventions such as aerobic endurance training, yoga, or strength training have a recommendation grade of PPP (clinical consensus point), which means that there is agreement by clinical experience but further scientific studies are needed [72]. Due to the current insufficient number of studies, a stronger recommendation for sports therapies cannot be given at present. In previous meta-analyses, different clinical studies were considered together, but previous individual studies were mostly monocentric in design and were characterized by a small number of cases and short observation periods [72]. To address this and generate robust evidence, future studies should be multicenter in design, include an adequate number of participants, and use sufficient observation periods of up to one year based on the current state of studies [70]. In addition, future meta-analyses should consider different sports interventions such as endurance training, strength training, or yoga separately as well as in combination to provide clear recommendations [72]. **The European Psychiatric Association (EPA) Guidance Paper** for the Treatment of Negative Symptomatology currently gives exercise therapy for people with schizophrenia a “should-recommend” (recommendation grade B) [73] building on the above literature.

Looking at the current treatment reality compared to these guideline recommendations, currently people with schizophrenia receive physiotherapy mainly exclusively in the inpatient setting, which is qualitatively and quantitatively behind endurance training three times a week for 30–50 minutes each time for three months. What needs to be changed in order to provide patients with sports therapy as an add-on that would significantly improve both their mental and physical health:

- At least one **multicenter study** is needed that convincingly demonstrates the positive effect of sports therapy for people with schizophrenia.
- Further **implementation studies** must be carried out that allow as many people with schizophrenia as possible to receive regular sports therapy and create more offers for this target group, which requires personal guidance and supervision in the group. This is possible in particular through the use of qualified personnel (sports therapists, physiotherapists), for example, within the framework of the specialization “Psychiatry, Psychosomatics, Addiction” of the German Association for Health Sports and Sports Therapy (DVGS). For this purpose, according to proven evidence, an additional digital health application via app could prove helpful, which, however, includes adequate personal guidance and accompaniment and allows the formation of a digital motivational group as well as regular “motivational follow-up”.
- An **incentive** needs to be created that makes it attractive for both interdisciplinary therapists and individuals across settings to become part of a sports therapy network and remain in one over the long term.
- Large-scale studies would enable the **identification of responders** vs. non-responders, and thus sports therapy could be offered to precisely these subgroups in the future (keyword: precision psychiatry).

Contributor’s Statement

None

Conflict of Interest

RS, AS, LR, and IM have no conflict of interest. PF is co-editor of the German (DGPPN) schizophrenia treatment guidelines and co-author of the WFSBP schizophrenia treatment guidelines; he serves on advisory boards and receives lecture honoraria from Boehringer-Ingelheim, Janssen, Lundbeck, Otsuka, Recordati, and Richter.

References

- [1] Weber S, Scott JG, Chatterton ML. Healthcare costs and resource use associated with negative symptoms of schizophrenia: A systematic literature review. *Schizophr Res* 2022; 241: 251–259. DOI: 10.1016/j.schres.2022.01.051
- [2] Leucht S, Leucht C, Huhn M et al. Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: Systematic Review, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors. *Am J Psychiatry* 2017; 174: 927–942. DOI: 10.1176/appi.ajp.2017.16121358
- [3] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet* 2016; 388: 86–97. DOI: 10.1016/S0140-6736(15)01121-6
- [4] Saykin AJ, Shtasel DL, Gur RE et al. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* 1994; 51: 124–131. DOI: 10.1001/archpsyc.1994.03950020048005
- [5] Erhart SM, Marder SR, Carpenter WT. Treatment of schizophrenia negative symptoms: future prospects. *Schizophr Bull* 2006; 32: 234–237. DOI: 10.1093/schbul/sbj055
- [6] Fusar-Poli P, Papanastasiou E, Stahl D et al. Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. *Schizophr Bull* 2015; 41: 892–899. DOI: 10.1093/schbul/sbu170
- [7] Rabinowitz J, Levine SZ, Garibaldi G et al. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. *Schizophr Res* 2012; 137: 147–150. DOI: 10.1016/j.schres.2012.01.015
- [8] Tseng P-T, Zeng B-S, Hung C-M et al. Assessment of Noninvasive Brain Stimulation Interventions for Negative Symptoms of Schizophrenia: A Systematic Review and Network Meta-analysis. *JAMA Psychiatry* 2022; 79: 770–779. DOI: 10.1001/jamapsychiatry.2022.1513
- [9] Häfner H, der Heiden W. an. Course and Outcome of Schizophrenia 2003; 101–141. DOI: 10.1002/9780470987353.ch8
- [10] Crump C, Winkleby MA, Sundquist K et al. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry* 2013; 170: 324–333. DOI: 10.1176/appi.ajp.2012.12050599
- [11] Hennekens CH, Hennekens AR, Hollar D et al. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005; 150: 1115–1121. DOI: 10.1016/j.ahj.2005.02.007
- [12] Osby U, Correia N, Brandt L et al. Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. *BMJ* 2000; 321: 483–484. DOI: 10.1136/bmj.321.7259.483
- [13] Tiihonen J, Lönnqvist J, Wahlbeck K et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; 374: 620–627. DOI: 10.1016/S0140-6736(09)60742-X

- [14] Coustals N, Martelli C, Brunet-Lecomte M et al. Chronic smoking and cognition in patients with schizophrenia: A meta-analysis. *Schizophr Res* 2020; 222: 113–121. DOI: 10.1016/j.schres.2020.03.071
- [15] Firth J, Siddiqi N, Koyanagi A et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry* 2019; 6: 675–712. DOI: 10.1016/S2215-0366(19)30132-4
- [16] Mitchell AJ, Vancampfort D, de Herdt A et al. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull* 2013; 39: 295–305. DOI: 10.1093/schbul/sbs082
- [17] Stubbs B, Vancampfort D, de Hert M et al. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. *Acta Psychiatr Scand* 2015; 132: 144–157. DOI: 10.1111/acps.12439
- [18] Smith E, Singh R, Lee J et al. Adiposity in schizophrenia: A systematic review and meta-analysis. *Acta Psychiatr Scand* 2021; 144: 524–536. DOI: 10.1111/acps.13365
- [19] de Hert M, Schreurs V, Vancampfort D et al. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry* 2009; 8: 15–22. DOI: 10.1002/j.2051-5545.2009.tb00199.x
- [20] Correll CU, Solmi M, Veronese N et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 2017; 16: 163–180. DOI: 10.1002/wps.20420
- [21] Yusuf S, Joseph P, Rangarajan S et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020; 395: 795–808. DOI: 10.1016/S0140-6736(19)32008-2
- [22] Pajonk F-G, Wobrock T, Gruber O et al. Hippocampal plasticity in response to exercise in schizophrenia. *Arch Gen Psychiatry* 2010; 67: 133–143. DOI: 10.1001/archgenpsychiatry.2009.193
- [23] Malchow B, Keller K, Hasan A et al. Effects of Endurance Training Combined With Cognitive Remediation on Everyday Functioning, Symptoms, and Cognition in Multipisode Schizophrenia Patients. *Schizophr Bull* 2015; 41: 847–858. DOI: 10.1093/schbul/sbv020
- [24] Malchow B, Keeser D, Keller K et al. Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. *Schizophr Res* 2016; 173: 182–191. DOI: 10.1016/j.schres.2015.01.005
- [25] Maurus I, Roell L, Lembeck M et al. Exercise as an Add-on Treatment in Individuals with Schizophrenia: Results from a Large Multicentre Randomized Controlled Trial. *Psychiatry and Clinical Neurosciences* submitted
- [26] Firth J, Stubbs B, Rosenbaum S et al. Aerobic Exercise Improves Cognitive Functioning in People With Schizophrenia: A Systematic Review and Meta-Analysis. *Schizophr Bull* 2017; 43: 546–556. DOI: 10.1093/schbul/sbw115
- [27] Dauwan M, Begemann MJH, Heringa SM et al. Exercise Improves Clinical Symptoms, Quality of Life, Global Functioning, and Depression in Schizophrenia: A Systematic Review and Meta-analysis. *Schizophr Bull* 2016; 42: 588–599. DOI: 10.1093/schbul/sbv164
- [28] Kim M, Lee Y, Kang H. Effects of Exercise on Positive Symptoms, Negative Symptoms, and Depression in Patients with Schizophrenia: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2023; 20. DOI: 10.3390/ijerph20043719
- [29] Vera-García E, Mayoral-Cleries F, Vancampfort D et al. A systematic review of the benefits of physical therapy within a multidisciplinary care approach for people with schizophrenia: An update. *Psychiatry Res* 2015; 229: 828–839. DOI: 10.1016/j.psychres.2015.07.083
- [30] Firth J, Cotter J, Elliott R et al. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychol Med* 2015; 45: 1343–1361. DOI: 10.1017/S0033291714003110
- [31] Schuch FB, Vancampfort D, Richards J et al. Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *J Psychiatr Res* 2016; 77: 42–51. DOI: 10.1016/j.jpsychires.2016.02.023
- [32] Ashdown-Franks G, Firth J, Carney R et al. Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes. *Sports Med* 2020; 50: 151–170. DOI: 10.1007/s40279-019-01187-6
- [33] Fernández-Abascal B, Suárez-Pinilla P, Cobo-Corralles C et al. In- and outpatient lifestyle interventions on diet and exercise and their effect on physical and psychological health: a systematic review and meta-analysis of randomised controlled trials in patients with schizophrenia spectrum disorders and first episode of psychosis. *Neurosci Biobehav Rev* 2021; 125: 535–568. DOI: 10.1016/j.neubiorev.2021.01.005
- [34] Vogel JS, van der Gaag M, Slofstra C et al. The effect of mind-body and aerobic exercise on negative symptoms in schizophrenia: A meta-analysis. *Psychiatry Res* 2019; 279: 295–305. DOI: 10.1016/j.psychres.2019.03.012
- [35] Sabe M, Kaiser S, Sentissi O. Physical exercise for negative symptoms of schizophrenia: Systematic review of randomized controlled trials and meta-analysis. *Gen Hosp Psychiatry* 2020; 62: 13–20. DOI: 10.1016/j.genhosppsych.2019.11.002
- [36] Patel H, Alkhawam H, Madanieh R et al. Aerobic vs anaerobic exercise training effects on the cardiovascular system. *World J Cardiol* 2017; 9: 134–138. DOI: 10.4330/wjc.v9.i2.134
- [37] Shimada T, Ito S, Makabe A et al. Aerobic exercise and cognitive functioning in schizophrenia: An updated systematic review and meta-analysis. *Psychiatry Res* 2022; 314: 114656. DOI: 10.1016/j.psychres.2022.114656
- [38] Xu Y, Cai Z, Fang C et al. Impact of aerobic exercise on cognitive function in patients with schizophrenia during daily care: A meta-analysis. *Psychiatry Res* 2022; 312: 114560. DOI: 10.1016/j.psychres.2022.114560
- [39] Bredin SSD, Kaufman KL, Chow MI et al. Effects of Aerobic, Resistance, and Combined Exercise Training on Psychiatric Symptom Severity and Related Health Measures in Adults Living With Schizophrenia: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2021; 8: 753117. DOI: 10.3389/fcvm.2021.753117
- [40] Keller-Varady K, Varady PA, Röh A et al. A systematic review of trials investigating strength training in schizophrenia spectrum disorders. *Schizophr Res* 2018; 192: 64–68. DOI: 10.1016/j.schres.2017.06.008
- [41] Rantanen T, Harris T, Leveille SG et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci* 2000; 55: M168–M173. DOI: 10.1093/gerona/55.3.m168
- [42] Feuerstein G. The yoga tradition: Its history, literature, philosophy and practice. Prescott, Ariz.: Hohm Pr 2008
- [43] Iyengar BKS. Light on yoga: Yoga dipika. 4th ed. New York: Schocken Books; 1995
- [44] Vancampfort D, Vansteelandt K, Scheewe T et al. Yoga in schizophrenia: a systematic review of randomised controlled trials. *Acta Psychiatr Scand* 2012; 126: 12–20. DOI: 10.1111/j.1600-0447.2012.01865.x
- [45] Broderick J, Crumlish N, Waugh A et al. Yoga versus non-standard care for schizophrenia. *Cochrane Database Syst Rev* 2017; 9: CD012052. DOI: 10.1002/14651858.CD012052.pub2
- [46] Cramer H, Lauche R, Klose P et al. Yoga for schizophrenia: a systematic review and meta-analysis. *BMC Psychiatry* 2013; 13: 32. DOI: 10.1186/1471-244X-13-32

- [47] Vancampfort D, Firth J, Correll CU et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry* 2019; 18: 53–66. DOI: 10.1002/wps.20614
- [48] Green CA, Yarborough BJH, Leo MC et al. The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry* 2015; 172: 71–81. DOI: 10.1176/appi.ajp.2014.14020173
- [49] Vancampfort D, Rosenbaum S, Ward PB et al. Exercise improves cardiorespiratory fitness in people with schizophrenia: A systematic review and meta-analysis. *Schizophr Res* 2015; 169: 453–457. DOI: 10.1016/j.schres.2015.09.029
- [50] Curcic D, Stojmenovic T, Djukic-Dejanovic S et al. Positive impact of prescribed physical activity on symptoms of schizophrenia: randomized clinical trial. *Psychiatr Danub* 2017; 29: 459–465. DOI: 10.24869/psyd.2017.459
- [51] Anderson L, Oldridge N, Thompson DR et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. *J Am Coll Cardiol* 2016; 67: 1–12. DOI: 10.1016/j.jacc.2015.10.044
- [52] Kodama S, Saito K, Tanaka S et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009; 301: 2024–2035. DOI: 10.1001/jama.2009.681
- [53] Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiol Aging* 2014; 35: S20–S28. DOI: 10.1016/j.neurobiolaging.2014.03.034
- [54] van Praag H. Neurogenesis and exercise: past and future directions. *Neuromolecular Med* 2008; 10: 128–140. DOI: 10.1007/s12017-008-8028-z
- [55] van Praag H, Shubert T, Zhao C et al. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* 2005; 25: 8680–8685. DOI: 10.1523/JNEUROSCI.1731-05.2005
- [56] Firth J, Stubbs B, Vancampfort D et al. Effect of aerobic exercise on hippocampal volume in humans: A systematic review and meta-analysis. *Neuroimage* 2018; 166: 230–238. DOI: 10.1016/j.neuroimage.2017.11.007
- [57] van der Stouwe ECD, van Busschbach JT, de Vries B et al. Neural correlates of exercise training in individuals with schizophrenia and in healthy individuals: A systematic review. *Neuroimage Clin* 2018; 19: 287–301. DOI: 10.1016/j.nicl.2018.04.018
- [58] Vancampfort D, Probst M, de Hert M et al. Neurobiological effects of physical exercise in schizophrenia: a systematic review. *Disabil Rehabil* 2014; 36: 1749–1754. DOI: 10.3109/09638288.2013.874505
- [59] Papiol S, Popovic D, Keeser D et al. Polygenic risk has an impact on the structural plasticity of hippocampal subfields during aerobic exercise combined with cognitive remediation in multi-episode schizophrenia. *Transl Psychiatry* 2017; 7: e1159. DOI: 10.1038/tp.2017.131
- [60] Papiol S, Keeser D, Hasan A et al. Polygenic burden associated to oligodendrocyte precursor cells and radial glia influences the hippocampal volume changes induced by aerobic exercise in schizophrenia patients. *Transl Psychiatry* 2019; 9: 284. DOI: 10.1038/s41398-019-0618-z
- [61] Falkai P, Malchow B, Wetzstein K et al. Decreased Oligodendrocyte and Neuron Number in Anterior Hippocampal Areas and the Entire Hippocampus in Schizophrenia: A Stereological Postmortem Study. *Schizophr Bull* 2016; 42: S4–S12. DOI: 10.1093/schbul/sbv157
- [62] Schmitt A, Steyskal C, Bernstein H-G et al. Stereologic investigation of the posterior part of the hippocampus in schizophrenia. *Acta Neuropathol* 2009; 117: 395–407. DOI: 10.1007/s00401-008-0430-y
- [63] Schmitt A, Tatsch L, Vollhardt A et al. Decreased Oligodendrocyte Number in Hippocampal Subfield CA4 in Schizophrenia: A Replication Study. *Cells* 2022; 11. DOI: 10.3390/cells11203242
- [64] Falkai P, Rossner MJ, Raabe FJ et al. Disturbed Oligodendroglial Maturation Causes Cognitive Dysfunction in Schizophrenia: A New Hypothesis. *Schizophr Bull* 2023. DOI: 10.1093/schbul/sbad065
- [65] McEwen SC, Jarrahi B, Ventura J et al. A combined exercise and cognitive training intervention induces fronto-cingulate cortical plasticity in first-episode psychosis patients. *Schizophr Res* 2023; 251: 12–21. DOI: 10.1016/j.schres.2022.12.001
- [66] Scheewe TW, van Haren NEM, Sarkisyan G et al. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. *Eur Neuropsychopharmacol* 2013; 23: 675–685. DOI: 10.1016/j.euroneuro.2012.08.008
- [67] Svatkova A, Mandl RCW, Scheewe TW et al. Physical Exercise Keeps the Brain Connected: Biking Increases White Matter Integrity in Patients With Schizophrenia and Healthy Controls. *Schizophr Bull* 2015; 41: 869–878. DOI: 10.1093/schbul/sbv033
- [68] Roell L, Maurus I, Keeser D et al. Association between aerobic fitness and the functional connectome in patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2022; 272: 1253–1272. DOI: 10.1007/s00406-022-01411-x
- [69] Takahashi S, Keeser D, Rauchmann B-S et al. Effect of aerobic exercise on cortical thickness in patients with schizophrenia-A dataset. *Data Brief* 2020; 30: 105517. DOI: 10.1016/j.dib.2020.105517
- [70] Falkai P, Maurus I, Schmitt A et al. Improvement in daily functioning after aerobic exercise training in schizophrenia is sustained after exercise cessation. *Eur Arch Psychiatry Clin Neurosci* 2021; 271: 1201–1203. DOI: 10.1007/s00406-021-01282-8
- [71] World Health Organization. Management of physical health conditions in adults with severe mental disorders: WHO guidelines. Geneva: World Health Organization; 2018
- [72] Gaebel W, Hasan A, Falkai P. S3-Leitlinie Schizophrenie. Springer-Verlag; 2019
- [73] Galderisi S, Kaiser S, Bitter I et al. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur Psychiatry* 2021; 64: e21. DOI: 10.1192/j.eurpsy.2021.13