Journal of Psychiatric Research 184 (2025) 91–101

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Exercise as a transdiagnostic intervention for improving mental health: An umbrella review

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ARTICLE INFO

Keywords:
Transdiagnostic intervention
Physical exercise
Schizophrenia
Depression

ABSTRACT

Exercise is beneficial for mental health in general, but no review has systematically assessed its potential transdiagnostic nature, i.e. whether it is beneficial across specific disorders. We performed a systematic umbrella review of meta-analyses of randomized controlled trials (RCTs) of exercise in participants with mental disorders defined according to the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of

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https://doi.org/10.1016/j.jpsychires.2025.02.024
Received 9 June 2024; Received in revised form 8 February 2025; Accepted 15 February 2025
Available online 18 February 2025

Anxiety
ADHD

Mental Disorders (DSM), assessing exercise's transdiagnostic nature with TRANSD criteria, including eight meta-analyses (six included in the TRANSD meta-analysis), encompassing 99 RCTs (n = 5,656) across 11 disorders. Moderate/vigorous aerobic exercise was an effective transdiagnostic intervention for disease-specific primary symptoms across 11 disorders (recurrent depressive disorder, social phobia, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, brief psychotic disorder, schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder, attention-deficit/hyperactivity disorder) and four spectra (depressive disorders, anxiety disorders, schizophrenia-spectrum disorders, neurodevelopmental disorders) with a medium effect size (SMD = −0.67, 95%CI = −0.84, -0.50). Moderate/vigorous aerobic exercise also improved cognition across two disorders (schizophrenia, attention-deficit/hyperactivity disorder) and two spectra (schizophrenia-spectrum disorders, neurodevelopmental disorders), with a large effect size (SMD = 0.92, 95%CI = 0.52, 1.33). According to TRANSD criteria, moderate/vigorous aerobic exercise is a transdiagnostic intervention to improve disease-specific primary symptoms of 11 mental disorders, and cognition in two mental disorders.

1. Introduction

Physical activity is defined as any voluntary bodily movement produced by skeletal muscles that requires energy expenditure (Caspersen et al., 1985). Physical inactivity, defined as not meeting the international physical activity recommendation of 150 min of moderate aerobic exercise or 75 min of vigorous aerobic exercise per week for adults, or a combination of both at the same level, is recognized as a global issue that impacts human health and requires global action (Kohl et al., 2012). The Global Burden of Disease (GBD) study has ranked physical inactivity as the fifth leading cause of disease burden and as one of the top modifiable risk factors for physical illness along with tobacco smoking and unhealthy diet (Lim et al., 2012). Several somatic diseases associated with physical inactivity in prospective observational studies include cardiovascular disease, thromboembolic stroke, hypertension, type 2 diabetes mellitus, osteoporosis, obesity, colon cancer, breast cancer, anxiety and depression (Kesaniemi et al., 2001)

People with mental disorders (e.g. depressive disorders, bipolar disorder, schizophrenia-spectrum disorders) are at higher risk of worse physical health compared to the general population (Correll et al., 2017; Firth et al., 2019). This health disparity may be partially attributable to the combined effects of physical inactivity and excessive sedentary behaviour (Vancampfort et al., 2017), which can contribute together with other causes to an increased risk of chronic diseases, including diabetes, metabolic syndrome and cardiovascular disease (Vancampfort et al., 2015, 2016; Correll et al., 2017; Firth et al., 2019).

Given the aforementioned, increasing levels of physical activity and more precisely of exercise, defined as a planned, structured form of physical activity with the objective to improve or maintain physical fitness (Caspersen et al., 1985; Stubbs et al., 2018; Ashdown-Franks et al., 2020) can improve both physical and mental health of people with mental disorders (Stubbs et al., 2018; Firth et al., 2019). The European Psychiatry Association has published guidance on the role of exercise to improve physical and mental health in people with severe mental disorders (Stubbs et al., 2018). Moreover, a more recent umbrella review pooling data from 16 meta-analyses representing 152 randomized controlled trials (RCTs) demonstrated that exercise can also be effective beyond schizophrenia, bipolar disorder, and major depressive disorder, in treating symptoms of anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD) (Ashdown-Franks et al., 2020).

Although this evidence supports the broad beneficial effect of exercise in people with mental disorders, it is not clear whether exercise represents a transdiagnostic construct that can improve outcomes across several mental disorders. Determining a transdiagnostic construct can impact clinical knowledge, for example supporting the development of exercise protocols that can improve outcomes across several mental disorders and patient groups, thereby facilitating its translation in clinical practice, at lower costs (i.e. aerobic exercise for different mental disorders minimizes personnel training costs). Until recently, the notion of a transdiagnostic construct per se has been poorly operationalised and applied. Most studies have adopted unclear and often incoherent definitions, with heterogeneous and flawed methodological designs (Fusar-Poli, 2019b). For example, several studies that acknowledge the word "transdiagnostic" in their title, paradoxically did not formulate any diagnosis of mental disorders at all, or confused symptoms with disorders, or blended together primary and comorbid mental disorders (Fusar-Poli et al., 2019a). To overcome these empirical limitations, a recent evidence-based review has developed a set of empirical "TRANSD" recommendations (Fusar-Poli et al., 2019a). TRANSD recommendations aim to improve the methodological and reporting quality of transdiagnostic research and can be applied to both original studies or meta-research (Fusar-Poli et al., 2019a, 2019b; Solmi et al., 2020). The TRANSD criteria recommend transparency of definition of included participants, the a priori definition of study design, explicit appraisal of the conceptual transdiagnostic framework, clear reporting of lists of diagnoses and spectra across which transdiagnosticity is going to be shown, quantitative approach to compare transdiagnostic vs diagnosis-specific constructs, and verification of generalizability of results outside of individual samples (these criteria are outlined in more detail in the methods section) (Fusar-Poli et al., 2019a).

The principal aim of the current study was to leverage TRANSD recommendations to test whether exercise interventions could be a transdiagnostic intervention that can improve disease-specific primary symptoms across several mental disorders (e.g. psychotic symptoms in schizophrenia, depressive symptoms in depressive disorders, inattention and hyperactivity in ADHD). The secondary aims were to test whether exercise is a transdiagnostic intervention that could improve cognitive symptoms and quality of life across different mental disorders according to TRANSD recommendations.

2. Materials and methods

2.1. The systematic search

We undertook a systematic search in PubMed and PsycINFO from inception to September 30th, 2024 using the following search key: [exercise or aerobic exercise or (physical activity) or (resistance training)] and (systematic or meta-analysis) and (schizophrenia or psychosis or psychotic or depression or bipolar or (mental illness) or (mental disorder) or anxiety or GAD or post-traumatic or PTSD or obsessive-compulsive or OCD or panic or alcohol or addiction or substance or smoking or cigarette or drug or (eating disorder) or anorexia or bulimia or binge or ADHD or (attention-deficit) or hyperactivity or (post-partum) or (perinatal) or autism or neurodevelopmental). This umbrella review complied to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009; Moher et al., 2009) (Supplementary materials - Table S1), and followed pre-published TRANSD recommendations for the assessment of transdiagnosticity (Fusar-Poli et al., 2019a).

2.2. Transdiagnostic definition

We adhered to TRANSD reporting recommendations. Rationale and

conceptual framework of TRANSD recommendations have been detailed in two previous publications (Fusar-Poli et al., 2019a, 2019b) and implemented in one publication on the transdiagnostic properties of aripiprazole (Solmi et al., 2020) and in another publication examining risk and protective factors for mental disorders beyond genetics (Arango et al., 2021). Thus, only the specific definitions and applications of such recommendations are described below. TRANSD research recommendations include empirical approaches to evaluate a putative transdiagnostic construct across six domains. The first TRANSD recommendation ("Transparency") is to have a transparent definition according to gold standards (the International Classification of Diseases (ICD), or the Diagnostic and Statistical Manual of Mental Disorders (DSM), or other), including specific diagnoses, diagnostic codes, primary vs secondary diagnoses, and diagnostic assessment interviews. Second, ("Report") the primary outcome of the study, the study design, and the definition of the transdiagnostic construct should be reported in the abstract and main text. Third, ("Appraise") the conceptual framework/approach of the transdiagnostic approach should be appraised. The simplest transdiagnostic approach is defined as "across-diagnoses" and compares different ICD/DSM categorical diagnoses against each other, to test their diagnostic boundaries and cross-cutting features. The across-diagnoses model can include one diagnostic spectrum, multiple diagnostic spectra and/or non-clinical samples, including also healthy individuals. Diagnostic spectra are defined according to the ICD diagnostic blocks: organic, including symptomatic mental disorders; mental and behavioural disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood (affective) disorders; neurotic, stress-related and somatoform disorders; behavioural syndromes associated with physiological disturbances and physical factors; disorders of adult personality and behaviour; mental retardation; disorders of psychological development; behavioural and emotional disorders with onset usually occurring in childhood and adolescence; and unspecified mental disorders. A more elaborate approach, termed "beyond-diagnoses", considers standard ICD/DSM diagnostic information but aims to define new diagnostic-like constructs, for example, based on biotypes or clinical types, and then test the relatedness of these newly defined constructs against the gold standard. Fourth, ("Numerate") the diagnostic categories, diagnostic spectra, and non-clinical samples in which the transdiagnostic construct is being tested and then validated should be indicated. Fifth, ("Show") the degree of improvement of the transdiagnostic approach should be shown against the specific diagnostic approach through specific comparative analyses (that can include superiority or non-inferiority hypotheses). Sixth, ("Demonstrate") the generalizability of the transdiagnostic construct should be demonstrated through external validation studies (Fusar-Poli et al., 2019a).

The full-set of TRANSD criteria is also available on the left side of Table 1, while our approach to meet TRANSD recommendations is reported below and in the right part of Table 1.

1. *Transparent definition of the gold standard, diagnostic types, codes, interviews and primary vs secondary diagnoses.* We only included RCTs in patients with depressive disorder, anxiety disorders, schizophrenia-spectrum disorders, and ADHD according to DSM or ICD, any version and reported the specific diagnostic types and codes. RCTs had to include primary and not secondary/comorbid disorders.
2. *Report the primary outcome, study design, construct.* We only included the largest meta-analyses of RCTs administering exercise. Exercise could be aerobic or resistance training (Howley, 2001). We excluded mind-body interventions, such as tai-chi, yoga, or Pilates, as they are not consistently defined as exercise (Brinsley et al., 2021), and low-intensity movement/stretching interventions, as the physiological mechanisms which could underlie any benefit of these interventions may be distinct from the exercise itself (Imboden et al., 2020). Primary outcome was random effect pooled standardized mean difference (SMD) of physical exercise vs control intervention on disease-specific primary symptoms of each given disease. These were defined as: depressive symptoms in depressive disorders, anxiety symptoms in anxiety disorder, positive and negative symptoms considered separately in schizophrenia-spectrum disorders, and inattention and hyperactivity in ADHD. Secondary outcomes were SMD of cognition (defined as a score in validated tests) and quality of life.
3. *Appraise the conceptual framework.* Exercise as a transdiagnostic intervention across diagnoses, across spectra.
4. *Numerate the diagnostic categories, spectra and non-clinical samples.* Diagnostic categories and spectra and non-clinical samples included in the present study will be listed in the results table.
5. *Show the degree of improvement of transdiagnostic vs diagnostic-specific approaches.* Each individual disorder will be compared with the others pooled together, by means of subgroup meta-analysis.
6. *Demonstrate the generalizability.* We reported whether physical exercise was effective on primary and secondary outcomes in at least two independent RCTs in each included meta-analysis.

Table 1
TRANSD recommendations testing exercise as a transdiagnostic intervention across mental disorders (Fusar-Poli et al., 2019a; 2019b). **Note.** ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders; RCTs, randomized controlled trials; ADHD, attention-deficit/hyperactivity disorder.

TRANSD recommendation	Application to the current study
1 Transparent definition of the gold standard (ICD, DSM, other), including specific diagnostic types, official codes, primary vs. secondary diagnoses, diagnostic assessment interviews.	Gold standard: ICD-DSM defined mental disorders Diagnostic types: specified Diagnostic codes: specified Primary vs secondary: specified
2 Report the primary outcome of the study, the study design and the definition of the transdiagnostic construct, in the abstract and main text.	Primary outcome: disease-specific primary symptoms in each mental disorder Study design: meta-analyses of RCTs Transdiagnostic construct exercise defined as moderate-to-vigorous physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness. We considered aerobic and resistance exercise.
3 Appraise the conceptual framework/approach of the transdiagnostic approach: across-diagnoses, beyond-diagnoses, other (explain).	Transdiagnostic type: across diagnoses, across spectra.
4 Numerate the diagnostic categories, spectra and non-clinical samples in which the transdiagnostic construct is being tested and then validated.	Number of spectra: depressive disorders, anxiety disorders, schizophrenia-spectrum disorders, ADHD. Number of diagnoses: 11 Non-clinical samples: none
5 Show the degree of improvement of the transdiagnostic approach against the specific diagnostic approach through specific comparative analyses.	Subgroup meta-analysis, each disorder compared with the others pooled together.
6 Demonstrate the generalizability of the transdiagnostic construct through external validation studies.	At-least two independent RCTs in each meta-analysis showing exercise is effective on primary outcome.

2.3. Statistical analysis

We recalculated those meta-analyses that had applied a fixed-effects model, applying a random-effects model due to the anticipated heterogeneity across different studies included in each eligible meta-analysis (Riley et al., 2011). We also recalculated those meta-analyses that included studies with designs other than RCT, after excluding the studies with non-RCT designs, and those reporting a non-standardized effect size (e.g., mean difference). Random-effects pooled SMD (other effect sizes were transformed to SMD) (Chinn, 2000) for each outcome were

computed, for aerobic and resistance exercise separately. If a meta-analysis did not compute specific effect sizes for aerobic or resistance exercise, we recalculated it pooling RCTs based on aerobic, or resistance exercise. To test the fifth TRANSD criterion, subgroup random-effects meta-analyses were conducted, leaving one disorder out at once, according to the number of mental disorders included in the original report. We conducted these analyses with R – metafor package (Viechtbauer, 2010).

2.4. Methodological quality appraisal

Quality of included meta-analyses was assessed with A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) (Shea et al., 2017). Quality was categorized into high, moderate, low, very low, according to criteria provided at https://amstar.ca/Amstar_Checklist.php.

3. Results

3.1. Search results

Out of 9,699 initial hits, we assessed the full text of 98 meta-analyses and finally included eight in people with clinical mental disorders, with 99 RCTs, including 5,656 subjects in total (2,834 intervention and 2,822 control). Interventions were aerobic, and resistance exercise, and control conditions included no treatment and waiting list and activity placebo controls (i.e. stretching, relaxation, physical education). The whole study selection process is reported in Fig. 1. Characteristics and results of included meta-analyses (Cerrillo-Urbina et al., 2015; Brondino et al., 2017; Krogh et al., 2017; Ramos-Sanchez et al., 2021; Sun et al., 2022; Yu et al., 2022; Lak et al., 2024; Yang et al., 2024) have been reported in Table 2, where we also indicate what meta-analyses were not included in TRANSD assessment because of non-significant results within diagnoses. Meta-analyses excluded with reason are reported in Supplementary materials (Table S2).

3.2. Aerobic exercise as transdiagnostic construct to improve primary symptoms across mental disorders

Results according to TRANSD recommendations are reported in Table 3 and visualized in Figs. 2 and 3.

Four meta-analyses were included to assess the effect of aerobic exercise on disease-specific symptoms with 53 RCTs (n intervention = 1,397, n control = 1,332) (Cerrillo-Urbina et al., 2015; Ramos-Sanchez et al., 2021; Yu et al., 2022; Yang et al., 2024) The mean duration of the interventions was 10 weeks; the mean duration of sessions was 45 min, with an average frequency of three times per week. Aerobic exercise was a transdiagnostic intervention for disease-specific primary symptoms of depressive disorders, anxiety disorders, schizophrenia-spectrum disorders, and ADHD, according to TRANSD recommendations. Included were disorders defined with a transparent definition (DSM-IV, DSM-5 or ICD-10) (TRANSD criterion 1). Disease-specific primary symptoms for depressive disorders, anxiety disorders, schizophrenia-spectrum disorders, and ADHD were the primary outcome, across meta-analyses of RCTs, administering aerobic exercise vs control group (TRANSD criterion 2). Transdiagnostic type was across diagnoses, across several spectra (TRANSD criterion 3). Aerobic exercise was an effective transdiagnostic intervention across 11 diagnoses (as above) and across four spectra (depressive disorders, anxiety disorders, schizophrenia-spectrum disorders, and neurodevelopmental disorders) (TRANSD criterion 4). The magnitude of effect size across 11 pooled

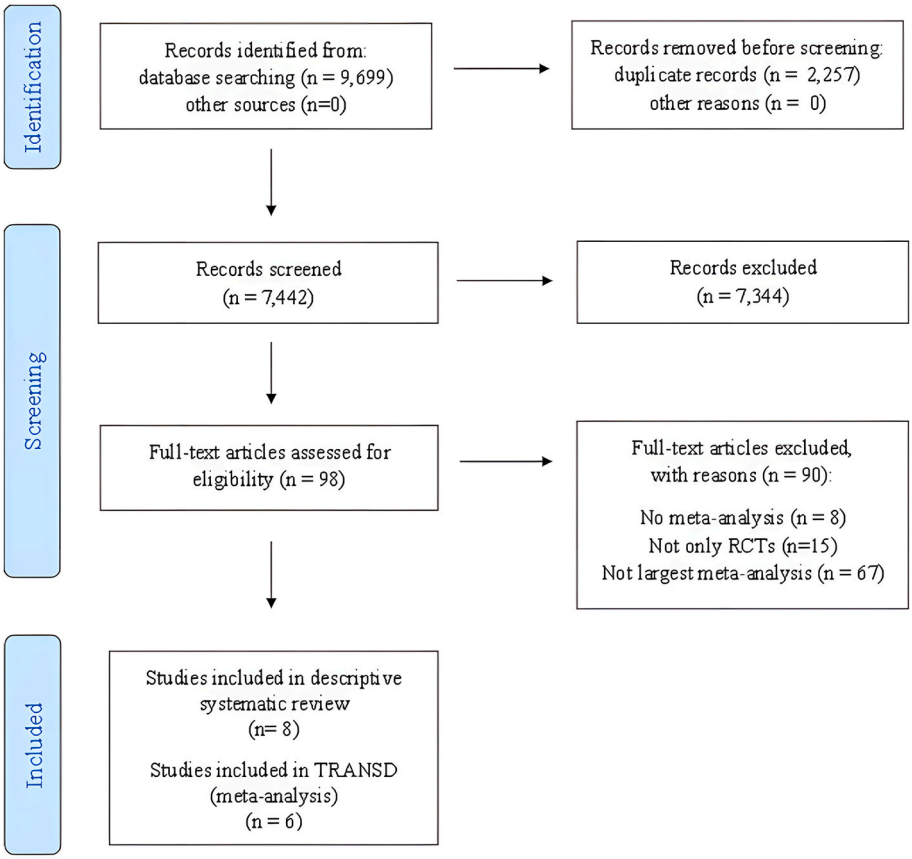

Fig. 1. PRISMA flow-chart of study selection.

Table 2
Characteristics of included meta-analyses. **Note**. MA, meta-analyses; NMA, network meta-analyses.

Author, year (MA/NMA)	Disorder	Exercise type	Trial duration weeks (median, range)	Outcomes	k exercise/NMA-MA	n NMA/MA (exercise/control)	n/% Industry sponsored	AMSTAR2 quality
Yang et al. (2024)	Schizophrenia-spectrum disorders	Aerobic exercise	12 weeks (8–16 weeks)	Disease-specific symptoms	10	569 (282/287)	0 (0%)	Moderate quality
Yu et al. (2022)	Major depressive disorder	Aerobic exercise	10 weeks (2–24 weeks)	Disease-specific symptoms	30	1695 (875/820)	0 (0%)	Moderate quality
Ramos-Sanchez et al. (2021)	Anxiety and stress disorders	Aerobic exercise	10 weeks (4–12 weeks)	Disease-specific symptoms	8	323 (168/155)	0 (0%)	High quality
Cerrillo-Urbina et al. (2015)	ADHD	Aerobic exercise	5 weeks (1–10 weeks)	Disease-specific symptoms	5	142 (72/70)	0 (0%)	Moderate quality
Lak et al. (2024)	Schizophrenia-spectrum disorders	Aerobic exercise	12 weeks (4–24 weeks)	Cognition	18	790 (384/406)	0 (0%)	Moderate quality
Brondino et al. (2017)	Major depressive disorder	Aerobic exercise	12 weeks (4–16 weeks)	Cognition[a]	8	687 (313/374)	0 (0%)	Moderate quality
Sun et al. (2022)	ADHD	Aerobic exercise	9 weeks (8–12 weeks)	Cognition	4	130 (67/63)	0 (0%)	Moderate quality
Yang et al. (2024)	Schizophrenia-spectrum disorders	Aerobic exercise	12 weeks (10–16 weeks)	Quality of life	5	221 (110/111)	0 (0%)	Moderate quality
Krogh et al. (2017)	Major depressive disorder	Aerobic exercise	12 weeks (2–16 weeks)	Quality of life[a]	6	494 (249/245)	0 (0%)	High quality
Yang et al. (2024)	Schizophrenia-spectrum disorders	Resistance training	20 weeks (12–24 weeks)	Disease-specific symptoms[a]	3	127 (63/64)	0 (0%)	Moderate quality
Krogh et al. (2017)	Major depressive disorder	Resistance training	12 weeks (8–32 weeks)	Disease-specific symptoms[a]	5	426 (225/201)	0 (0%)	High quality
Ramos-Sanchez et al. (2021)	Anxiety and stress disorder	Resistance training	3 weeks (no range)	Disease-specific symptoms	2	52 (26/26)	0 (0%)	High quality

[a] No statistically significant benefit and not included in TRANSD assessment.

disorders was moderate (SMD = −0.67, 95%CI = −0.84, -0.50, p < 0.0001) (TRANSD criterion 3), and no significant difference emerged in subgroup meta-analyses (subgroup meta-analyses p values ranged from 0.64 to 0.99) (TRANSD criterion 5). Efficacy of aerobic exercise was replicated in at least two different RCTs in all disorders (TRANSD criterion 6).

3.3. Aerobic exercise as transdiagnostic construct to improve cognition across mental disorders

Results according to TRANSD recommendations are reported in Table 3 and visualized in Figs. 4 and 5.

Regarding cognition, two meta-analyses were included on aerobic exercise with 22 RCTs (n intervention = 451, n control = 469) (Sun et al., 2022; Lak et al., 2024). The mean duration of the interventions was 11 weeks; the mean duration of sessions was 55 min, with an average frequency of three times per week. The aerobic exercise proved to be a transdiagnostic intervention for cognition of schizophrenia-spectrum disorders and ADHD, according to TRANSD recommendations. Included were disorders defined with a transparent definition (DSM-IV, DSM-5 or ICD-10) (TRANSD criterion 1). Improvements in cognition of schizophrenia-spectrum disorders and ADHD were the secondary outcome, across meta-analyses of RCTs, administering aerobic exercise vs control group (TRANSD criterion 2). Transdiagnostic type was across diagnoses, across several spectra (TRANSD criterion 3). Aerobic exercise was an effective transdiagnostic intervention, across two diagnoses and across two spectra (schizophrenia-spectrum disorders and neurodevelopmental disorders) (TRANSD criterion 4). The magnitude of effect size across two pooled disorders was large (SMD = 0.92, 95%CI = 0.52, 1.33, p < 0.0001) (TRANSD criterion 3), and no difference emerged across disorders (p = 0.63) (TRANSD criterion 5). Efficacy of aerobic exercise was replicated in at least two different RCTs in all disorders (TRANSD criterion 6).

3.4. Aerobic exercise as transdiagnostic construct to improve quality of life across mental disorders

Regarding quality of life, two meta-analyses had data on aerobic exercise with 11 RCTs (n intervention = 359, n control = 356) (Krogh et al., 2017; Yang et al., 2024). The mean duration of the interventions was 12 weeks; the mean duration of sessions was 55 min, with an average frequency of three times per week. Aerobic exercise did not prove to be a transdiagnostic intervention for quality of life of schizophrenia-spectrum disorders and depressive disorders, according to TRANSD recommendations.

3.5. Resistance training as transdiagnostic intervention to improve primary symptoms, cognition and quality of life across mental disorders

Three meta-analyses had data on the effect of resistance training on disease-specific symptoms with 10 RCTs (n intervention = 314, n control = 291) (Krogh et al., 2017; Ramos-Sanchez et al., 2021; Yang et al., 2024) The mean duration of the interventions was 14 weeks and ranged from 3 to 32 weeks. Resistance training did not prove to be a transdiagnostic intervention for disease-specific primary symptoms of schizophrenia-spectrum disorders, depressive disorders, and anxiety disorders, according to TRANSD recommendations.

There were no meta-analyses to assess the effects of resistance exercise for cognition or quality of life in mental illness.

3.6. Quality of included meta-analyses

To assess the quality of the meta-analyses (MA) and network meta-analyses (NMA), we used AMSTAR 2. According to AMSTAR 2, six out of eight had moderate quality; two had high quality (Supplementary materials - Table S3).

Table 3
TRANSD criteria on aerobic exercise for mental disorders. **Note**. SMD, standardized mean difference.

TRANSD criteria		Aerobic exercise	
Domain	Subdomain	Mental disorder disease-specific primary symptoms	Overall cognition
(T) Transparent definition	Gold standard	DSM-IV, DSM-5, ICD-10	DSM-IV, DSM-5, ICD-10
	Diagnostic types	Schizophrenia-spectrum disorders, Major depressive disorder, Anxiety and stress disorders, ADHD	Schizophrenia-spectrum disorders, ADHD
	Diagnostic codes	F20, F20.81, F22, F23, F25, F33, F40.1, F41.0, F41.1, F43.1, F90.2	F20, F90.2
	Primary or secondary diagnoses	RCTs targeting primary conditions	
(R) Report	Primary outcome	Reduction in disease-specific primary symptoms	Global cognition
	Study design	Meta-analyses of RCT administering exercise in subjects with mental disorder	
	Transdiagnostic construct	Aerobic exercise	
(A) Appraise the conceptual framework	Transdiagnostic type	Across diagnoses, across several spectra	
(N) Numerate the diagnostic categories, spectra, non-clinical samples	Number of diagnoses	11	2
	Number of spectra	4	2
	Non-clinical sample	not included	not included
(S) Show the degree of improvement	Diagnostic-specific ES	1 Schizophrenia. Positive symptoms. SMD = −0.41, 95%CI = −0.81, -0.01. Negative symptoms. SMD = −0.60, 95%CI = −1.01, -0.2. 2 Major depressive disorder. Depressive symptoms. SMD = −0.98, 95%CI = −1.50, -0.46. 3. Anxiety disorders. Anxiety symptoms. SMD = −0.66, 95%CI = −1.06, -0.26. 4 ADHD. Inattention. SMD = −0.84, 95%CI = −1.20, -0.48. Hyperactivity. SMD = −0.56, 95%CI = −1.08, -0.04.	1. Schizophrenia. Global cognition. SMD = 0.88, 95%CI = 0.46, 1.31. 2. ADHD. Executive Function. SMD = 1.34, 95%CI = 0.01, 2.68.
	Transdiagnostic ES	SMD = −0.67, 95%CI = −0.84, -0.50, z = −7.60, p < 0.0001	SMD = 0.92, 95%CI = 0.52, 1.33, z = 4.46, p < 0.0001
	Transdiagnostic vs diagnostic-specific ES	p = 0.82 (schizophrenia vs others) p = 0.64 (depressive disorders vs others) p = 0.93 (anxiety disorders vs others) p = 0.99 (ADHD vs others)	p = 0.63 (schizophrenia vs ADHD)
(D) Demonstrate the generalizability	Results replicated across at least 2 independent RCTs	Aerobic exercise is effective on disease-specific primary symptoms in 8 different RCTs.	Aerobic exercise is effective on overall cognition in 4 different RCTs.
TRANSD criteria met		yes	yes

4. Discussion

Results of the present study show that moderate/vigorous aerobic exercise can be considered a transdiagnostic intervention which improves disease-specific primary symptoms across four spectra (anxiety disorders, depressive disorders, schizophrenia-spectrum disorders, neurodevelopmental disorders) and 11 mental disorders according to TRANSD criteria. Moderate/vigorous aerobic exercise can also be considered as a transdiagnostic intervention improving cognition across two spectra (schizophrenia-spectrum disorders and neurodevelopmental disorders) and two mental disorders according to TRANSD criteria. Aerobic exercise was not a transdiagnostic intervention to improve quality of life in people with schizophrenia-spectrum disorders and depressive disorders, but this outcome was much less studied. Resistance training was also less studied and thus more research is required to further understand its potential transdiagnostic benefits.

The transdiagnostic nature of aerobic intervention may be related to the biochemical pathways underlying the effects of physical exercise on mental health. Although those pathways have not yet been fully elucidated, there is evidence that physical exercise reduces oxidative stress, promoting the balance with the antioxidant system in mental disorders (Schuch et al., 2014; Fisher et al., 2020). Moreover, growing findings highlight a correlation between major psychiatric conditions and an upregulated inflammatory status, reporting shared or disease-specific altered biomarkers (Yuan et al., 2019). In human and animal studies, physical exercise seems to increase immune cell activity and favor an anti-inflammatory response, which benefits neurotransmitter metabolism and neuroendocrine functions (Meyer-Lindemann et al., 2023). The same positive impact is also emerging in relation to mental disorders (Ren and Xiao, 2023). Furthermore, physical exercise appears to elevate the expression of Brain-Derived Neurotrophic Factor (BDNF) (Fernández-Rodríguez et al., 2022), which is essential in synaptic plasticity and neural signal transmission and is often decreased in mental disorders (Autry and Monteggia, 2012). Interestingly, antidepressants also seem to favor the concentration of peripheral BDNF, but with a longer timescale of administration to stimulate similar biochemical changes and with non-negligible side effects (Jemni et al., 2023).

While more research is needed on the biological mechanisms underlying the transdiagnostic efficacy of aerobic exercise, our study's results present interesting implications that may be immediately applied to the clinical context. First, given the high burden and low resources generally affecting the implementation of effective modern interventions in public health systems worldwide (Márquez-Calderón et al., 2014; Marquez and Saxena, 2016; Mnookin et al., 2016), exercise programs should be implemented in mental health care services, and their cost-efficacy should be tested (Hatziandreu et al., 1988; Sevick et al., 2000; Czosnek et al., 2020). Moreover, by demonstrating its transdiagnostic properties, exercise's cost-effectiveness can be improved, targeting a wider range of people with different mental disorders, with no need for different programs if all are effective for different mental disorders. In addition, although physical exercise should always be delivered by professionals to maximize efficacy and minimize drop-out rates according to previous evidence and recommendations (Stubbs et al., 2016, 2018), group settings are viable, sustainable, cost-effective options outside of mental health systems (Alhambra-Borrás et al., 2019). Therefore, after adequate training, people with mental disorders can be supported to autonomously exercise in community-based settings with regular follow-up by exercise professionals. Moreover, exercise can reduce social isolation, when done in the context of group activities or team sports, hence having the

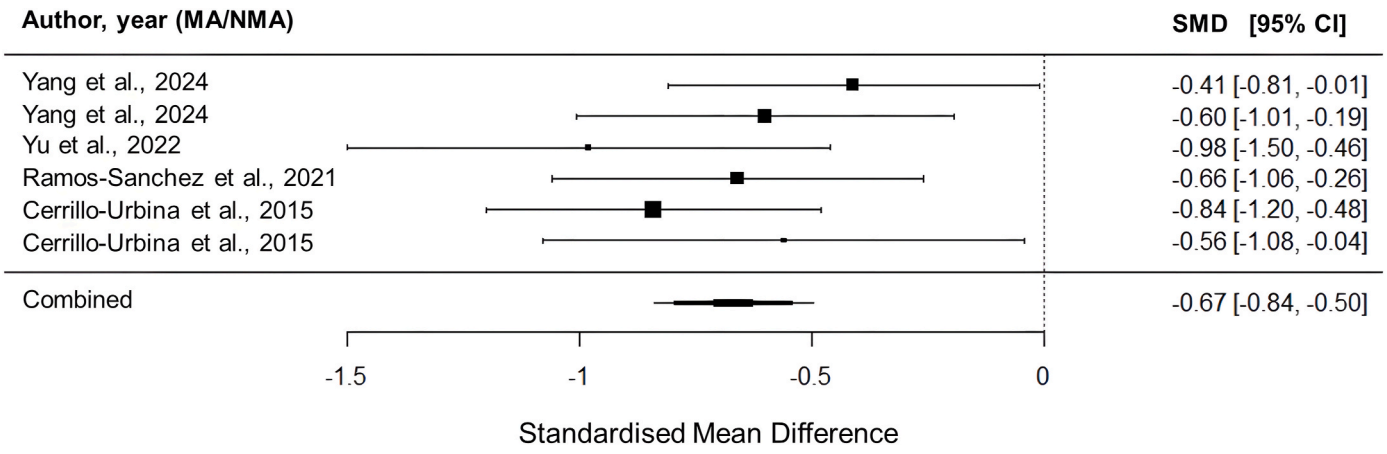

Fig. 2. Forest plot for the TRANSD effect of aerobic exercise on disease-specific primary symptoms. **Note.** MA = Meta-analysis, NMA = Network meta-analysis.

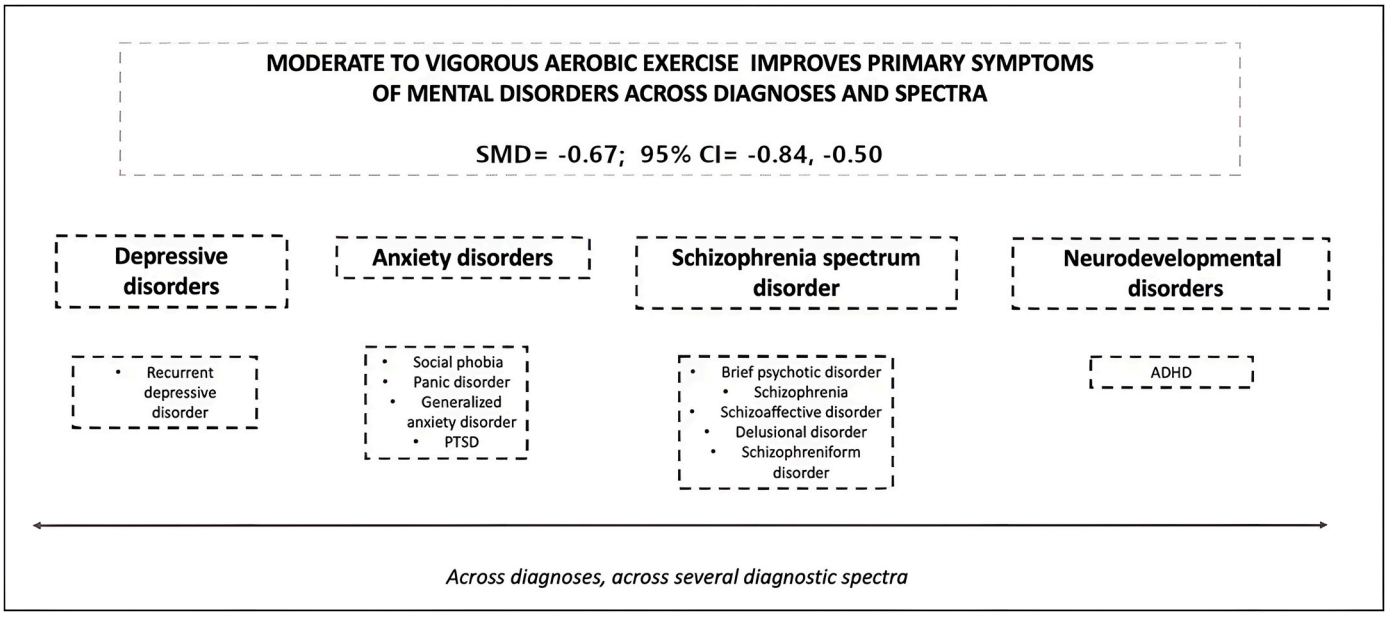

Fig. 3. Exercise as a transdiagnostic intervention to improve disease-specific primary symptoms across eleven disorders and four spectra according to TRANSD criteria.

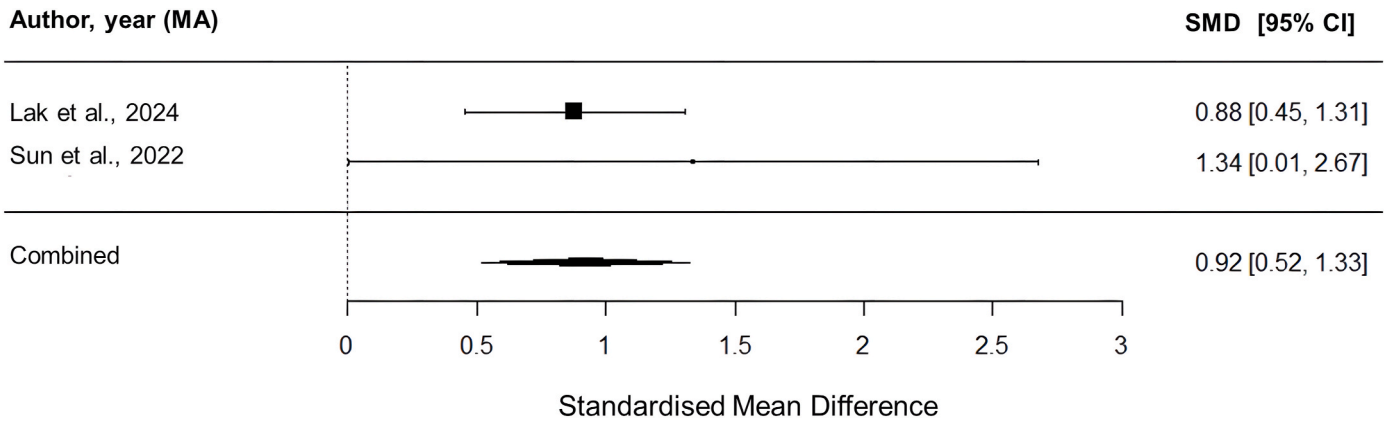

Fig. 4. Forest plot for the TRANSD effect of aerobic exercise on cognition. **Note.** MA = Meta-analysis.

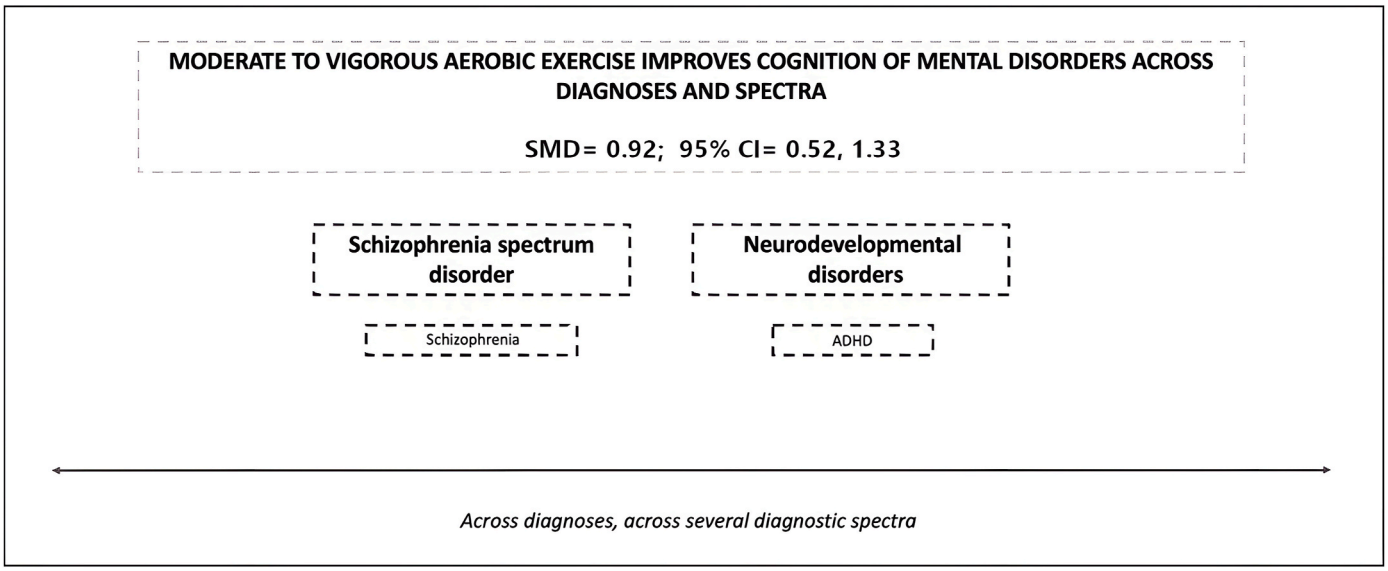

Fig. 5. Exercise as a transdiagnostic intervention to improve cognition across two disorders and two spectra according to TRANSD criteria.

potential to reduce loneliness and social withdrawal (Vancampfort et al., 2019). Given that exercise has been shown to be effective in improving primary symptoms across 11 disorders, and cognition in two disorders, moderate/vigorous aerobic exercise should be recommended in clinical guidelines.

Second, diagnostic changes are frequent across mental disorders (Fusar-Poli et al., 2014), because they reflect the evolving nature of these conditions, in particular, for adolescents and young patients. Symptoms in early stages of mental disorders can be heterogeneous, diagnoses can frequently be hard to define, and clinical pictures in adolescents and young adults can have sudden modifications. In this context, making a definitive and correct diagnosis from the very early presentation of disorders can be challenging, and even more so at the first presentation of symptoms. For instance, clinical high-risk symptoms of psychosis often include depressed mood, and vice versa mood disorders are also often associated with psychotic symptoms (Yung and McGorry, 1996; Addington, 2003; Mishara and Fusar-Poli, 2013; Walker et al., 2013; Fusar-Poli et al., 2014; Rutigliano et al., 2016). Since exercise works across different disorders according to the present findings, it should be considered in preventive services where a definitive diagnosis is often not feasible, given the benefits across several mental disorders that are often comorbid with clinical high risk for psychosis (CHR-P) (Fusar-Poli et al., 2013; Schuch et al., 2018, 2019). Whilst no clear evidence has shown that exercise is effective in preventing transition to psychosis (Stubbs et al., 2018; Brokmeier et al., 2020), exercise would still be effective in treating comorbid mental disorders and symptoms in people at risk for psychosis, as well as positive symptoms of psychosis. Importantly, to date no intervention has shown to be the best strategy to prevent psychosis, according to two recent network meta-analyses (Fusar-Poli et al., 2019c), hence no gold-standard intervention to avoid the onset of psychosis has yet been identified. Also, beyond transition to psychosis, several further outcomes are important when treating subjects with CHR-P state. These include functioning at follow-up, number of admissions after psychosis onset, number of compulsory admissions after psychosis onset, among others (Fusar-Poli et al., 2013), on which exercise has the potential to show efficacy, given its transdiagnostic action on mood, anxiety, psychotic symptoms and cognition. Hence, by means of one intervention, a heterogeneous set of symptoms can be improved.

Third, according to the present data, exercise should also be considered among those interventions to be delivered in early intervention settings, if one or more of the 11 diagnoses across which exercise is transdiagnostic are comorbid with clinical high risk for psychosis or other first episode serious mental health conditions. Given the markedly detrimental effects many psychopharmacological agents can have on meta bolic status and on weight in drug-naïve subjects, in particular (Correll et al., 2010; Krause et al., 2018), exercise is indicated not only as a possible monotherapy for individuals with positive symptoms but can improve mental health as well as physical health in subjects exposed to pharmacological treatment due to higher severity of disorders (Schuch et al., 2015).

Fourth, the preliminary positive effect on cognition is particularly interesting and promising, given the role of cognitive functioning on psychosocial functioning across mental disorders. For instance, it has been shown that cognition plays a central role and is highly connected with psychosocial functioning in patients suffering from schizophrenia (Galderisi et al., 2018). Cognition poorly responds to standard psychopharmacologic treatments. Pending replication, exercise might improve cognition across schizophrenia-spectrum disorders and ADHD, and such therapeutic action could be more relevant provided the transdiagnostic nature of the exercise shown here. While few agents have been shown to be effective on cognition in specific disorders (i.e. vortioxetine in depression) (McIntyre et al., 2014) and only few are in current development (Correll et al., 2023), such agents may not play any role in disease-specific primary symptoms of other conditions (e.g. positive symptoms in schizophrenia).

The present work has several strengths, including being the first study to apply TRANSD criteria to a non-pharmacological intervention (Solmi et al., 2020). Second, it may have immediate and substantial clinical implications, either in preventive services, early intervention services, or general psychiatry services, but most of all moderate/vigorous aerobic exercise should become a mainstream add-on treatment for the eleven mental disorders considered here. Third, results are based on 99 RCTs across eight meta-analyses, including over 5, 600 subjects. Nonetheless, results should be interpreted in light of certain limitations. First, this umbrella review relies on published data, and it does not look into individual patient data. Hence, findings of this umbrella review mainly rely on the quality of individual studies included in each meta-analysis. Second, insufficient data were available for the effects of exercise on quality of life and functioning. Third, similarly, insufficient data were available on the effects of resistance training. Fourth, it should be noted that mental disorders may manifest differently depending on age. The meta-analyses on schizophrenia-spectrum disorders, depressive disorders, and anxiety

disorders included in the present work are mainly based on studies with mean participant ages between 35 and 50 years, unlike the meta-analyses on ADHD, whose participants were children/adolescents. Therefore, it is desirable that the transdiagnostic effect of aerobic exercise could be further explored in the future, especially with respect to age groups that have been less represented so far. Finally, safety outcomes were not considered in the present meta-review. However, according to previous umbrella reviews, very few data are available on safety of exercise in literature (Stubbs et al., 2018; Czosnek et al., 2019; Ashdown-Franks et al., 2020).

In conclusion, moderate/vigorous aerobic exercise is a transdiagnostic intervention for disease-specific primary symptoms across four spectra and 11 mental disorders, according to TRANSD criteria. However, more evidence is needed for effect on quality of life and functioning, and on resistance training. Given the transdiagnostic nature of exercise and low risks and its desirable adaptation to the diagnostic uncertainties in early stages of mental disorders, exercise should be offered and implemented in all (prevention) mental health services.

CRediT authorship contribution statement

Marco Solmi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Ilaria Basadonne:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Luca Bodini:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Simon Rosenbaum:** Writing – review & editing, Writing – original draft, Methodology. **Felipe B. Schuch:** Writing – review & editing, Writing – original draft, Methodology. **Lee Smith:** Writing – review & editing, Writing – original draft, Methodology. **Brendon Stubbs:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Joseph Firth:** Writing – review & editing, Writing – original draft, Methodology. **Davy Vancampfort:** Writing – review & editing, Writing – original draft, Methodology. **Garcia Ashdown-Franks:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Andre F. Carvalho:** Writing – review & editing, Writing – original draft, Methodology. **Joaquim Radua:** Writing – review & editing, Writing – original draft, Methodology. **Laura Fusar-Poli:** Writing – review & editing, Writing – original draft, Methodology. **Christoph U. Correll:** Writing – review & editing, Writing – original draft, Methodology. **Paolo Fusar-Poli:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

Marco Solmi received honoraria from Angelini, Lundbeck. Paolo Fusar-Poli has received research fees from Lundbeck and honoraria from Lundbeck, Angelini, Menarini and Boehringer Ingelheim outside the current study. Christoph U.Correll has been a consultant and/or advisor to or has received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma. Other authors have no conflict of interest.

Acknowledgment

IB, LFP and PFP were supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.02.024.

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