The efficacy, mechanisms and implementation of physical activity as an adjunctive treatment in mental disorders: a meta-review of outcomes, neurobiology and key determinants

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Research examining physical activity interventions for mental disorders has grown exponentially in the past decade. At this critical juncture, there is a need to synthesize the best evidence to guide researchers, clinicians and people with lived experience. This meta-review aimed to systematically identify and comprehensively evaluate the current evidence about: a) the efficacy of physical activity interventions on mental, cognitive and physical outcomes for individuals with mental disorders; b) the potential neurobiological, psychosocial and behavioral mechanisms underlying the observed effects; and c) the barriers and facilitators for individuals to successfully engage in these interventions. Our systematic search identified 13 meta-analyses of high methodological quality (i.e., A Measurement Tool to Assess Systematic Reviews, AMSTAR score ≥8) assessing outcomes of physical activity as an adjunctive treatment, which included 256 randomized clinical trials (RCTs) and 12,233 individuals. Large effect sizes were found for adjunctive physical activity interventions in improving attention in children and adolescents with attention-deficit/hyperactivity disorder (ADHD); reducing depressive symptoms in children, adolescents and adults with depressive disorders; and reducing body mass index in adults with schizophrenia. Moderate effect sizes were found for reductions of hyperactivity, impulsivity and anxiety, and improvements of executive and social functioning in children and adolescents with ADHD; reduction of anxiety symptoms in adults with anxiety disorders; improved physical and psychological quality of life and cardiovascular fitness in adults with depressive disorders; improved daily living skills, overall quality of life and cardiorespiratory fitness in adults with schizophrenia; reduction of depressive symptoms in older people with depressive disorders; and improvements in cognition and functional mobility in older people with dementia. There is, to date, no meta-analytic evidence for physical activity as a first-line treatment for people with a mental disorder. Five meta-analyses, including 89 RCTs and 4,575 individuals, investigated potential underlying mechanisms. There is a very preliminary evidence for an effect of physical activity on circulating levels of kynurenine, growth hormone, tumor necrosis factor-alpha and brain-derived neurotrophic factor in people with major depressive disorder. No meta-analytic evidence could be found for psychosocial or behavioral mechanisms. Based on 15 umbrella or systematic reviews, covering 432 studies and 48 guidelines, six implementation strategies, along with the most evidence-based behavioral change techniques to support them, were identified. Recommendations to support implementation research in this area were finally formulated.

Key words: Physical activity, exercise, ADHD, anxiety disorders, depression, schizophrenia, dementia, lifestyle physical activity, aerobic exercise, strength training, implementation

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Mental disorders represent an increasingly significant source of burden on global health, posing substantial challenges to health care systems worldwide[1]. Traditional treatment modalities, including pharmacotherapies and psychotherapies, often fall short in leading to comprehensive and sustainable recovery[2], particularly when considering their limitations in addressing the increased risk of chronic physical problems in individuals living with a mental disorder or, in the case of some medications, their potential to induce adverse somatic side effects[3-10].

In response to these challenges, there is a growing interest in adjunctive approaches. Among these, physical activity has emerged as a particularly promising intervention, in particular when viewed through the lens of a "biopsychosocial model" for treating mental disorders. At the biological level, research has suggested that physical activity can modulate various neurotransmitter systems, reduce inflammatory cytokines, and even promote neurogenesis – all of which are also implicated in the pathophysiology of mental disorders[11-13]. At the psychological level, engaging in physical activity can improve affective states, providing a sense of accomplishment on completion, and enhancing self-esteem and self-efficacy over time[14,15]. At the social level, physical activity can provide opportunities for engaging in meaningful interactions and social settings, which is critical for achieving recovery and maintaining well-being[16].

While much of the evidence supporting these biopsychosocial benefits of physical activity has so far been derived from studies in the general population, a rapidly growing body of literature suggests similar effects in psychiatric populations[17-19]. This multifaceted impact suggests that integrating physical activity into treatment plans may provide a valuable adjunct to conventional therapies, promoting not only emotional and psychological well-being, but also better physical health outcomes and improved physical functioning.

Physical activity has been defined as any bodily movement produced by skeletal muscles that results in energy expenditure[20]. Recently, this narrow biomedical perspective has evolved to encompass a more holistic understanding, defining physical activity as people moving, acting and performing within culturally specific spaces and contexts[21]. Exercise, in turn, is recognized as a specific subset of physical activity that is planned, structured and repetitive[20].

To date, several studies have been conducted on the mental and physical health benefits of physical activity and exercise for individual mental disorders. This meta-review aims to provide a comprehensive and systematic evaluation of the available evidence on physical activity as an adjunctive and/or first-line treatment in people living with a mental disorder.

We specifically focus on three types of physical activity: lifestyle physical activity, aerobic exercise, and resistance or strength training. Lifestyle physical activity encompasses everyday activities in which individuals engage as part of their daily routines, such as walking, cycling as a commuting activity, gardening, and household chores, contributing to overall energy expenditure without the need for structured programs[22]. Aerobic exercise involves rhythmic, repetitive movements that increase the heart rate and improve cardiovascular fitness, such as running or cycling on a cycle ergometer[21]. Resistance or strength training involves exercises that induce muscle contraction against resistance, thereby enhancing muscle strength, endurance, and overall functional capacity. This includes activities such as weightlifting, bodyweight exercises, and resistance band workouts[21]. To date, no evidence synthesis has clearly outlined the differential effects of these distinct forms of physical activity across different mental disorders.

We examined the mental, cognitive and physical health outcomes associated with interventions based on these three types of physical activity for the most common mental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, anxiety disorders, depressive disorders, dementia, psychotic disorders, and substance use disorders. Additionally, we explored the potential mechanisms through which physical activity may exert its effects, considering the meta-analytic evidence on possible neurobiological, psychosocial and behavioral pathways.

We also reviewed evidence-based techniques for increasing the uptake and engagement with physical activity among people receiving mental health care. Ultimately, physical activity can only improve outcomes if it is implemented in real-world settings[23]. The current research-to-practice gap highlights the importance of addressing the key determinants that impact individual participation in physical activity interventions. Such determinants span individual (e.g., knowledge and skills of patients and providers), social (e.g., social support and reinforcement), and environmental (e.g., availability of resources) factors[24-26].

Finally, through this comprehensive meta-review, we provide evidence-based recommendations to guide future implementation efforts, inform clinical practice, drive future research, and contribute to the development of effective physical activity interventions that can enhance the well-being of individuals living with a mental disorder.

METHODS

Searches

Two authors (DV and ADW) independently searched Medline/PubMed, PsycArticles and EMBASE, from their respective inception dates until August 22, 2024, without language restrictions.

For all searches, we used the following terms: ("meta-analysis" OR "systematic review") AND ("alcohol" OR "Alzheimer" OR "attention deficit hyperactivity disorder" OR "ADHD" OR "anxiety" OR "autism" OR "dementia" OR "depression" OR "depressive" OR "illicit drugs" OR "psychosis" OR "psychotic" OR "severe mental illness" OR "schizophrenia" OR "substance") AND ("physical activity" OR "exercise*" OR "resistance" OR "strength"). For investigating the efficacy of physical activity interventions and the potential underlying mechanisms, we added the terms ("randomized controlled trial" OR "RCT"). Narrative reviews, methodology articles, and papers focusing on assessment tools were excluded.

To explore potential neurobiological, psychosocial and behavioral mechanisms, we also added the terms ("brain" OR "brain structure" OR "brain function" OR "brain plasticity" OR neurogenesis OR neurotransmitter OR BDNF OR biomarker OR "growth factors" OR "stress" OR immunology OR neuroimmunology OR neurons OR glia OR vasculature OR IGF1 OR VEGF OR hormones OR peptides OR metabolism OR imaging OR neuromodulation OR volumetry OR endorphin OR monoamine OR dopamine OR noradrenaline OR norepinephrine OR serotonin OR opioid OR social OR self-perception OR self-efficacy OR self-confidence OR confidence OR competence OR "perceived ability" OR relatedness OR belong* OR autonomy OR choice OR "basic needs satisfaction" OR "psychological needs" OR mastery OR mood OR emotion OR sleep OR nature OR greenspace OR "natural environment").

To explore the key determinants that impact individual participation in physical activity interventions, we added the terms (barriers OR impediment* OR obstacle* OR hurdle* OR hindrance* OR challenge* OR facilitat* OR enabler* OR implement* OR determinants OR "implementation evaluation" OR "process evaluation" OR process* OR "qualitative evaluation" OR "qualitative study" OR "qualitative research" OR qualitative OR "mixed method*" OR perspectives OR experienc* OR translat*).

Inclusion criteria

Inclusion criteria for the meta-analyses investigating physical activity outcomes were organized in accordance with the Patient, Interventions, Comparisons, Outcomes and Setting/study design (PICOS) reporting structure (see also supplementary information). We focused on mental, cognitive and physical health outcomes in children, adolescents, adults and older adults with primary diagnoses (based on DSM/ICD criteria/requirements) of ADHD, autism spectrum disorder, anxiety disorders, depressive disorders, dementia, psychotic disorders, and substance use disorders.

We included meta-analyses of high methodological quality (i.e., A Measurement Tool to Assess Systematic Reviews, AMSTAR[27]

score ≥8) informed by a systematic review of RCTs examining physical activity (i.e., lifestyle physical activity, aerobic exercise, or resistance/strength training) as an adjunctive and/or first-line intervention in any health care setting. Meta-analyses meeting the inclusion criteria were removed if there was a more recent meta-analysis with a larger sample and more than 75% overlapping trials. Yoga, tai chi, qigong and other holistic movement practices were excluded due to their inherently multifactorial nature, complicating the isolation of specific effects of the physical activity component on mental health outcomes. Comparisons were made with relevant control conditions (e.g., placebo, treatment as usual/usual care, waiting list, or no treatment).

Inclusion criteria for the meta-analyses investigating potential neurobiological, psychosocial and behavioral mechanisms, and for the umbrella reviews or meta-analyses exploring barriers and facilitators to implementing physical activity, were organized in accordance with the Sample, Phenomenon of Interest, Design, Evaluation, Research type (SPIDER) reporting structure (see also supplementary information).

Data extraction, outcomes, and data synthesis

To evaluate the efficacy of physical activity interventions, we extracted effect size data with 95% confidence intervals (CIs) for all relevant outcomes, as well as the number of participants in the intervention and control arms. Data for effect sizes of continuous outcomes were extracted or recalculated as standardized mean difference (SMD) using comprehensive meta-analysis (CMA, Biostat, version 3). An SMD is regarded as negligible if it is <0.2, small if it is between 0.2 and <0.5, moderate if it is between 0.5 and 0.8, and large if it is >0.8[28].

We also gathered evidence-based FITT (Frequency, Intensity, Time and Type) recommendations regarding the optimal frequency (number of sessions per week), intensity (light, moderate, vigorous), type (aerobic vs. strength training vs. lifestyle physical activity), and time/duration (expressed as minutes for a single session and number of weeks for the entire duration) of physical activity interventions, when available based on sensitivity analyses.

The potential mechanisms underlying the effects of physical activity were summarized according to age group (i.e., children and adolescents, adults, and older adults) and organized following the conceptual framework of Lubans et al[29] in three categories, i.e., neurobiological, psychosocial and behavioral.

We extracted the main individual, social and environmental factors or intervention components that impact individual participation in physical activity interventions within mental health care settings. We defined facilitators as factors that favor, facilitate or help people to engage in physical activity, and barriers as factors that hinder, limit or prevent people from engaging in physical activity. Barriers and facilitators at individual, social and environmental levels were used to develop theoretically informed and evidence-based implementation strategies, composed of behavior change techniques. To this end, we used the Behavior Change Techniques taxonomy[30] and followed the recommendations by Proctor et al[31].

Quality assessment of included studies

Included meta-analyses investigating physical activity outcomes were assessed using AMSTAR[27] (range: 0-11, with a score of 8 or higher indicating "high quality"). We also assessed the content validity of included trials, using a set of five additional quality items, each ranging between 0 and 1 or 2 (AMSTAR Plus Content)[3]. The item regarding double blindness of the design was removed, as it cannot be realized in physical activity trials. The AMSTAR Plus Content score ranges from 0 to 7, with a score of 4 or higher indicating "high quality".

RESULTS

Evidence on physical activity outcomes for people with a mental disorder

The search resulted in 4,299 hits. After removing duplicates and irrelevant abstracts, a total of 147 full texts were screened. Thirteen meta-analyses of randomized controlled trials[32-44], encompassing 256 RCTs and 12,233 participants, were included (see Figure 1 and supplementary information). All of them investigated physical activity as an adjunctive intervention. There was no meta-analysis investigating physical activity as a first-line treatment in people with a mental disorder.

The AMSTAR score ranged from 8 to 11, and the AMSTAR+ score from 0 to 5. The most common methodological shortcomings of individual RCTs were the small sample size and the lack of intention-to-treat analyses (see also supplementary information).

In meta-analyses concerning children and adolescents, large effect sizes were found for adjunctive aerobic exercise in improving attention among individuals with ADHD (SMD=0.84, 95% CI: 0.48 -1.20), and for adjunctive combined aerobic exercise and strength training in reducing depressive symptoms among those with a depressive disorder (SMD=–1.14, 95% CI: –1.88 to –0.40) (see Table 1).

Moderate effect sizes were found for adjunctive aerobic exercise in reducing hyperactivity (SMD=–0.56, 95% CI: –1.08 to –0.04), impulsivity (SMD=–0.56, 95% CI: –1.08 to –0.04) and anxiety (SMD=–0.66, 95% CI: –1.18 to –0.13), and in improving executive (SMD=0.58, 95% CI: 0.15-1.00) and social (SMD=0.59, 95% CI: 0.03-1.16) functioning among individuals with ADHD (see Table 1). A small effect size was observed for adjunctive aerobic exercise alone (i.e., without strength training) in reducing depressive symptoms among children and adolescents with a depressive disorder (SMD=–0.32, 95% CI: –0.59 to –0.05) (see Table 1).

In meta-analyses concerning adults (all ages), large effect sizes were observed for adjunctive aerobic exercise (SMD=–1.16, 95% CI: –1.46 to –0.85) and strength training (SMD=–1.04, 95% CI: –1.87 to –0.22) in reducing depressive symptoms among people with a depressive disorder, and for adjunctive aerobic exercise in reducing body mass index (SMD=–1.69, 95% CI: –3.26 to –0.11) in people with schizophrenia (see Table 2).

Moderate adjunctive effects of aerobic exercise were found in reducing anxiety symptoms among people with anxiety disorders

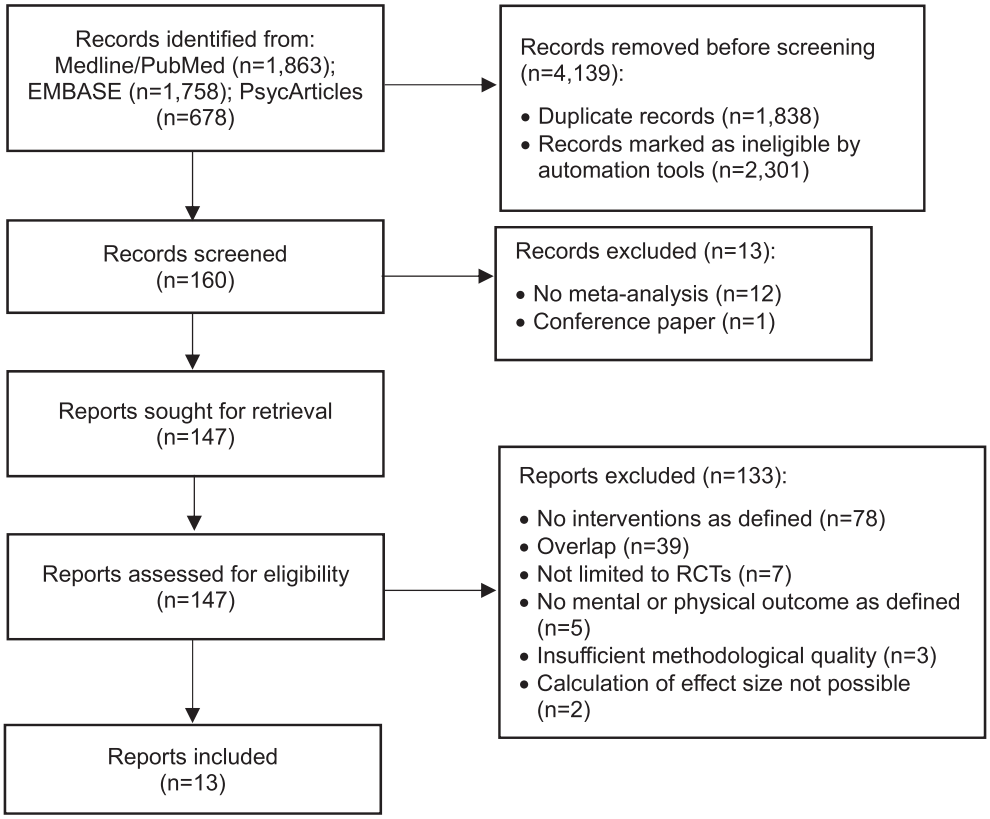

Figure 1 Flow diagram of included and excluded reports on physical activity outcomes in people with a mental disorder. RCT – randomized controlled trial.

(SMD=–0.66, 95% CI: –1.06 to –0.26); in improving overall quality of life in people with schizophrenia (SMD=0.60, 95% CI: 0.08-1.11); and in improving cardiorespiratory fitness both in people with a depressive disorder (SMD=0.64, 95% CI: 0.32-0.96) and in those with schizophrenia (SMD=0.68, 95% CI: 0.34-1.01). Moderate adjunctive effects of aerobic exercise on physical (SMD=0.53, 95% CI:

Table 1 Meta-analytic evidence on outcomes of physical activity as adjunctive treatment in children and adolescents with a mental disorder

	Outcomes	Intervention	N. trials	N. participants	SMD (95% CI)	Effect size interpretation	AMSTAR	AMSTAR+
ADHD								
Cerrillo-Urbina et al[32]	Attention	AE	5	72	0.84 (0.48-1.20)	Large	10/11	2/7
	Hyperactivity	AE	2	29	–0.56 (–1.08 to –0.04)	Moderate	10/11	2/7
	Impulsivity	AE	2	29	–0.56 (–1.08 to –0.04)	Moderate	10/11	2/7
	Anxiety	AE	2	28	–0.66 (–1.18 to –0.13)	Moderate	10/11	2/7
	Executive functioning	AE	3	49	0.58 (0.15-1.00)	Moderate	10/11	2/7
	Social functioning	AE	2	26	0.59 (0.03-1.16)	Moderate	10/11	2/7
Depressive disorders								
Zhang et al[33]	Depressive symptoms	AE	6	231	–0.32 (–0.59 to –0.05)	Small	10/11	0/7
	Depressive symptoms	AE+ST	7	202	–1.14 (–1.88 to –0.40)	Large	10/11	0/7

ADHD – attention-deficit/hyperactivity disorder, AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content

0.22-0.84) and psychological (SMD=0.54, 95% CI: 0.22-0.86) quality of life were observed in individuals with a depressive disorder. A moderate adjunctive effect on daily living skills (SMD=0.65, 95% CI: 0.07-1.22) was also found for aerobic exercise and/or strength training in people with schizophrenia (see Table 2).

Small adjunctive effects were found for strength training in reducing anxiety symptoms (SMD=–0.37, 95% CI: –0.80 to –0.06). Small effect sizes were also observed for adjunctive aerobic exercise and/or strength training in reducing negative symptoms (SMD= –0.24, 95% CI: –0.43 to –0.06), and in improving social (SMD=0.41, 95% CI: 0.08-0.74) and global (SMD=0.41, 95% CI: 0.12-0.70) functioning in individuals with schizophrenia (see Table 2).

In meta-analyses focusing on older adults, moderate adjunctive effects were observed for both aerobic exercise (SMD=–0.73, 95% CI: –1.07 to –0.39) and strength training (SMD=–0.68, 95% CI: –1.00 to –0.36) in reducing depressive symptoms among individuals with a depressive disorder. Moderate adjunctive improvements were also found with strength training for cognition (SMD=0.74, 95% CI: 0.22-1.26) and functional mobility (Time Up Go test) (SMD=0.74, 95% CI: 0.17-1.31) in people with dementia (see Table 3).

No meta-analyses of high methodological quality investigating the efficacy of physical activity using RCTs only were found for autism spectrum disorder and substance use disorders.

Available FITT recommendations in children and adolescents suggest that combined aerobic exercise and strength training yields greater effects on depressive symptoms than aerobic exercise alone, with group exercise further enhancing these benefits. Engaging in exercise for twelve or more weeks is recommended, with individual sessions lasting between 20 and 60 min. A frequency of

Table 2 Meta-analytic evidence on outcomes of physical activity as adjunctive treatment in adults (all ages) with a mental disorder

	Outcomes	Intervention	N. trials	N. participants	SMD (95% CI)	Effect size interpretation	AMSTAR	AMSTAR+
Anxiety disorders								
Ramos-Sanchez et al[34]	Anxiety symptoms	AE and/or ST	13	731	–0.42 (–0.68 to –0.18)	Small	10/11	2/7
	Anxiety symptoms	AE	8	-	–0.66 (–1.06 to –0.26)	Moderate	10/11	1/7
	Anxiety symptoms	ST	4	-	–0.37 (–0.80 to –0.06)	Small	10/11	1/7
	Anxiety symptoms	AE+ST	3	-	–0.12 (–0.34 to 0.10)	NS	10/11	1/7
Depressive disorders								
Heissel et al[35]	Depressive symptoms	AE	30	1218	–1.16 (–1.46 to –0.85)	Large	11/11	3/7
	Depressive symptoms	ST	7	245	–1.04 (–1.87 to –0.22)	Large	11/11	1/7
	Depressive symptoms	AE+ST	10	1195	–0.46 (–0.80 to –0.11)	Small	11/11	5/7
Schuch et al[36]	Physical QoL	AE+ST	5	175	0.53 (0.22-0.84)	Moderate	9/11	1/7
	Psychological QoL	AE+ST	5	175	0.54 (0.22-0.86)	Moderate	9/11	1/7
	Social QoL	AE+ST	3	110	0.29 (–0.13 to 0.71)	Not significant	9/11	1/7
	Environmental QoL	AE+ST	3	110	0.37 (–0.12 to 0.85)	Not significant	9/11	1/7
	Overall QoL	AE+ST	3	104	0.39 (0.05-0.74)	Small	9/11	1/7
Stubbs et al[37]	Cardiorespiratory fitness	AE	8	498	0.64 (0.32–0.96)	Moderate	8/11	1/7
Schizophrenia								
Sabe et al[38]	Negative symptoms	AE and/or ST	17	953	–0.24 (–0.43 to –0.06)	Small	8/11	3/7
	Positive symptoms	AE and/or ST	16	935	–0.18 (–0.34 to –0.02)	Negligible	8/11	3/7
Korman et al[39]	Global functioning	AE and/or ST	17	734	0.41 (0.12–0.70)	Small	10/11	2/7
	Social functioning	AE and/or ST	5	191	0.41 (0.08–0.74)	Small	10/11	1/7
	Daily living skills	AE and/or ST	3	111	0.65 (0.07–1.22)	Moderate	10/11	1/7
Fernandez-Abascal et al[40]	Body mass index	AE	4	141	–1.69 (–3.26 to –0.11)	Large	9/11	0/7
	Overall QoL	AE	3	113	0.60 (0.08–1.11)	Moderate	9/11	1/7
	Cardiorespiratory fitness	AE	3	192	0.68 (0.34–1.01)	Moderate	9/11	1/7

QoL – quality of life, AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content

Table 3 Meta-analytic evidence on outcomes of physical activity as adjunctive treatment in older adults with a mental disorder

	Outcomes	Intervention	N. trials	N. participants	SMD (95% CI)	Effect size interpretation	AMSTAR	AMSTAR+
Dementia								
Li et al[41]	Functional mobility (TUG)	AE	2	105	0.78 (–0.53 to 2.09)	Not significant	9/11	0/7
	Functional mobility (TUG)	ST	2	53	0.74 (0.17-1.31)	Moderate	9/11	1/7
Mendes et al[43]	Quality of life	AE and/or ST	5	661	0.10 (–0.14 to 0.34)	Not significant	8/11	2/7
Zhou et al[42]	Cognitive function	AE	12	795	0.74 (0.22-1.26)	Moderate	8/11	2/7
Depressive disorders								
Tang et al[44]	Depressive symptoms	AE	9	646	–0.73 (–1.07 to –0.39)	Moderate	10/11	1/7
	Depressive symptoms	ST	11	397	–0.68 (–1.00 to –0.36)	Moderate	10/11	0/7
	Depressive symptoms	AE+ST	11	825	–0.21 (–0.52 to 0.11)	Not significant	10/11	2/7

TUG – Time Up Go test, AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content

three or more sessions per week is most beneficial, as well as maintaining at least a moderate intensity during workouts[33]. In adults, FITT recommendations are inconsistent, with only supervised exercise consistently demonstrating larger effects than unsupervised exercise[34-36] (see also supplementary information).

Evidence on potential mechanisms for physical activity effects in people with a mental disorder

The search resulted in 7,282 hits. After removing duplicates and irrelevant abstracts, 29 full texts were screened. Twenty-four studies were excluded (see supplementary information). Five meta-analyses[45-49], covering 89 trials and 4,575 participants, were included. Based on the AMSTAR score, three included meta-analyses were of high methodological quality. The most common methodological problem of individual RCTs was the small sample size (see also supplementary information).

Acute bouts of physical activity produced a large effect size for increased circulating levels of atrial natriuretic peptide, and a moderate effect size for increased growth hormone levels, in people with major depressive disorder (see Table 4). For chronic physical activity, small significant effect sizes were found for increased circulating levels of tumor necrosis factor-alpha (TNF-α), kynurenine, and brain-derived neurotrophic factor (BDNF) in adults with major depressive disorder (see Table 5).

No meta-analytic evidence could be found for psychosocial or behavioral mechanisms.

Table 4 Meta-analytic evidence on neurobiological effects of acute bouts of physical activity in adults with a mental disorder

	Intervention	N. trials	N. participants	Biomarker	SMD (95% CI)	p	Effect size interpretation	AMSTAR	AMSTAR+
Major depressive disorder									
Guimarães et al[45]	AE, ST	3	110	TNF-α	0.29 (–0.54 to 1.13)	0.49	Not significant	9/11	0/7
		4	140	IL-6	0.73 (–0.41 to 1.87)	0.21	Not significant		0/7
		2	74	IL-8	0.51 (–0.25 to 1.26)	0.19	Not significant		0/7
		4	140	IL-10	0.04 (–0.07 to 0.16)	0.46	Not significant		0/7
Schuch et al[46]	AE	2	150	Atrial natriuretic peptide (↑)	1.22 (0.59-1.85)	<0.001	Large	5/11	2/7
		2	161	Cortisol	–0.01 (–0.23 to 0.21)	0.90	Not significant		2/7
		2	161	Growth hormone (↑)	0.78 (0.55–1.01)	<0.001	Moderate		2/7
		2	161	Prolactin	0.19 (–0.03 to 0.41)	0.09	Not significant		2/7

AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content, TNF-α – tumor necrosis factor alpha, IL – interleukin

Table 5 Meta-analytic evidence on neurobiological effects of chronic physical activity in adults and older adults with a mental disorder

	Intervention	N. trials	N. participants	Biomarker	SMD (95% CI)	p	Effect size interpretation	AMSTAR	AMSTAR+
Major depressive disorder in adults									
Guimarães et al[45]	AE, ST	3	175	IL-1β	0.24 (–0.06 to 0.53)	0.11	Not significant	9/11	1/7
		5	427	IL-6	0.08 (–0.44 to 0.60)	0.77	Not significant		1/7
		4	217	TNF-α (↑)	0.29 (0.03-0.55)	0.03	Small		1/7
da Cunha et al[47]	AE, ST	3	123	IL-10	0.24 (–0.72 to 1.21)	NA	Not significant	9/11	0/7
		4	149	BDNF (↑)	0.44 (0.15-0.73)	NA	Small		0/7
		3	243	Kynurenine (↑)	0.29 (0.04-0.54)	NA	Small		0/7
Schuch et al[46]	AE, ST	2	129	Cortisol	–0.17 (–0.52 to 0.18)	0.34	Not significant	5/11	0/7
		2	116	Prolactin	–0.13 (–0.50 to 0.23)	0.73	Not significant		0/7
Dementia in older adults									
Kress et al[49]	AE, ST	3	139	Total hippocampal volume	0.18 (–0.16 to 0.51)	0.30	Not significant	5/11	1/7
Huang et al[48]	AE	2	98	TNF-α	–0.47 (–1.05 to 0.11)	-	Not significant	8/11	0/7

AE – aerobic exercise, ST – strength training, SMD – standardized mean difference, AMSTAR – A Measurement Tool to Assess Systematic Reviews, AMSTAR+ – AMSTAR Plus Content, TNF-α – tumor necrosis factor alpha, IL – interleukin, NA – not available

Evidence on barriers and facilitators for individuals to successfully engage in physical activity interventions within mental health care settings

The search resulted in 18,031 hits. After removing duplicates and irrelevant abstracts, 24 full texts were screened. Nine studies were excluded (see supplementary information). Fifteen umbrella reviews or systematic reviews[50-64], covering 432 studies and 48 guidelines, were selected. Four reviews focused on children and adolescents, ten on adults and one on older adults. The AMSTAR score ranged from 3 to 11. Eleven reviews had an AMSTAR score of 8 or higher, indicating that they were of high methodological quality (see also supplementary information). All evidence was based on studies from high- and middle-income countries.

The most reported facilitators were having access to a structured/supervised physical activity program (n=5), having a social support network (n=4), access to physical activity facilities (n=3), having the autonomy to choose (n=2), experiencing enjoyment (n=2), and trained staff (n=2).

The most reported barriers were the presence of a physical comorbidity (n=6), low self-efficacy (n=5), lack of social support (n=4), financial constraints (n=3), poorly trained staff (n=2), safety issues (n=2), sensory or behavioral dysregulation (n=2), lack of knowledge by patients about physical activity (n=2), side effects of medication (n=2), and lack of time (n=2).

The identified facilitators and barriers were used to develop six theoretically informed implementation strategies, composed of behavior change techniques[29]. These strategies were: a) enhance access to physical activity facilities and opportunities; b) provide trained and engaged staff to facilitate interventions; c) ensure a psychologically and physically safe environment; d) develop tailored interventions; e) foster autonomous motivation, and f) facilitate a resilient social support network (see Table 6).

Most evidence was available for fostering autonomous motivation. Twelve included reviews[50,51,53-55,57-60,62-64] referred to this topic. Fostering commitment to behavior change, providing reg-

Table 6 Evidence-based implementation strategies for physical activity in mental health settings (with behavioral change techniques supporting them)

1. Enhance access to physical activity facilities and opportunities (ensure that physical spaces are designed to encourage activity; add necessary equipment or objects that facilitate physical activity).
2. Provide trained and engaged staff to facilitate interventions (equip staff with motivational interviewing and cognitive behavioral principles to provide general social support; train staff to serve as credible sources for promoting physical activity, ensuring that they can guide participants effectively).
3. Ensure a psychologically and physically safe environment (use social and emotional support to enhance safety; eliminate discomfort or barriers to participation; create a physically and socially supportive environment for physical activity; ensure access to objects that promote physical activity).
4. Develop tailored interventions (set behavior and outcome goals tailored to individual needs; plan concrete actions to meet these goals; encourage self-monitoring to track progress; provide general support and instructional guidance; ensure that staff are seen as credible sources).
5. Foster autonomous motivation (foster commitment to behavior change; provide regular feedback on behaviors and outcomes; offer general and emotional social support to motivate participants; educate participants on the health benefits of physical activity; reinforce identity changes that result from behavior change).
6. Facilitate a resilient social support network (establish a network of social support, including practical, emotional and general support; create social environments that encourage ongoing physical activity).

ular feedback on behaviors and outcomes, offering general and emotional social support to motivate participants, educating participants on the health benefits of physical activity, and reinforcing identity changes that result from behavior change were the main supporting behavioral change techniques (see Table 6).

Evidence for developing tailored interventions was based on data from eleven reviews[51-53,56,57-60,62-64]. Setting behavior and outcome goals tailored to individual needs, planning concrete actions to meet these goals, encouraging self-monitoring to track progress, providing general support and instructional guidance, and ensuring that staff are seen as credible sources were the main supporting behavioral change techniques (see Table 6).

Next, most evidence was found for ensuring a psychologically and physically safe environment, which could be derived from ten reviews[50,53,54,56,58-61,63,64], and for facilitating a resilient social support network, which was reported in eight reviews[53-56,58,62,63,64]. Finally, providing trained and engaged staff to facilitate interventions[53-55,62,63], and enhancing access to physical activity facilities and opportunities[52-54,56,64] were considered important in five reviews each. The main supporting behavioral change techniques relevant to these latter four strategies are listed in Table 6.

DISCUSSION

This meta-review systematically and comprehensively evaluated current evidence on the efficacy of physical activity for individuals living with a mental disorder. The preliminary evidence concerning possible neurobiological effects of physical activity in these individuals was also summarized. We additionally identified within the existing scientific literature the barriers and facilitators for people living with a mental disorder to participate in physical activity interventions in real-world settings, and used this evidence to develop six theoretically informed implementation strategies.

The available meta-analytic literature clearly demonstrates that physical activity is a transdiagnostic efficacious adjunctive intervention. Large effect sizes were found for the adjunctive effects of aerobic exercise in improving attention in ADHD, and of combined aerobic exercise and strength training in reducing depressive symptoms in children and adolescents with depressive disorders. Similarly, large adjunctive effects were seen for aerobic exercise and strength training in adults with a depressive disorder, and for aerobic exercise in reducing body mass index in people with schizophrenia. Moderate adjunctive effects were observed in reducing hyperactivity, impulsivity and anxiety, and in improving executive and social functioning among children and adolescents with ADHD. Adults with anxiety disorders benefited from moderate adjunctive reductions of anxiety symptoms through aerobic exercise. Moderate adjunctive effects were also found in improving daily living skills and overall quality of life in people with schizophrenia, physical and psychological quality of life in individuals with a depressive disorder, and cardiorespiratory fitness in people with schizophrenia or a depressive disorder. Similarly, moderate adjunctive effects were observed in reducing depressive symptoms among older adults with a depressive disorder, and in improving cognition and functional mobility in older adults with dementia.

Of interest, meta-analytic evidence of high methodological quality investigating the efficacy of aerobic exercise and/or strength training only using RCTs is currently lacking for children and adolescents with autism spectrum disorder, and for adolescents and adults with substance use disorders. Besides this, while our current findings are based on meta-analyses of high methodological quality, the evidence base itself is not limited to trials of high methodological quality. Thus, it could be further strengthened through larger trials with greater power and using intention-to-treat analyses.

Important for clinicians is that there is currently no meta-analytic evidence base for physical activity as a first-line intervention in people living with a mental disorder. The existing evidence for physical activity as a first-line treatment is, to date, limited to only one RCT[65] in people with a depressive and/or anxiety disorder. This RCT reported that remission rates were similar following 16 weeks of at least twice weekly running therapy as a first-line treatment versus treatment with escitalopram or sertraline. Only running therapy and not pharmacotherapy had a significant beneficial effect on cardiometabolic parameters[65]. Rigorous, large-scale randomized controlled trials are, therefore, needed to ascertain the efficacy of physical activity as a first-line treatment in people with mental disorders.

Sensitivity analyses suggested that combined aerobic exercise and strength training yields greater effects on depressive symptoms than aerobic exercise alone in children and adolescents. Additionally, exercising in a group setting has been shown to enhance these benefits, indicating the importance of social aspects of physical activity as a critical component of mental health improvement. To maximize the effects on depressive symptoms, engagement in twelve or more weeks of regular exercise is recommended. Optimal single-session durations range from 20 to 60 min. Furthermore, frequency plays a crucial role, with three or more sessions per week associated with the most significant improvements in mood. Finally, maintaining at least a moderate intensity during these sessions seems to be important for achieving the largest effects.

In adults living with a mental disorder, the existing evidence regarding the optimal frequency, intensity, type and duration of physical activity interventions remains inconsistent, making it challenging to formulate clear clinical guidelines. However, one consistent finding across the literature is that supervised exercise yields more significant benefits compared to unsupervised exercise. This suggests that the presence of a qualified facilitator can enhance motivation and foster a supportive environment, ultimately leading to improved outcomes.

Although our meta-review clearly shows that physical activity should be considered as an evidence-based adjunctive treatment modality, in routine care only a small proportion of people receiving mental health care are asked about their physical activity levels[66] and offered related interventions[67]. Future research should focus on how to close this translation gap, including at the health care policy level, where resource decisions and clinical priorities are determined.

One of the reasons for the above gap might be that clinical practice guidelines do not usually consider the adjunctive value of

physical activity, with only a few exceptions[68-70]. Only recently the World Federation of Societies for Biological Psychiatry[26] and the European Psychiatric Association[71] have published guidance documents concluding that physical activity should be used as an adjunctive treatment modality to improve psychotic symptoms and cognition in adults with schizophrenia, and depressive symptoms in adults with a depressive disorder. These guidelines recommend that patients living with a severe mental disorder aim to achieve a minimum of 150 min of moderate-to-vigorous intensity physical activity per week to improve mental health. It is important to note, however, that also lower levels of physical activity have been shown to confer mental health benefits[72]. Given that previous high-quality studies have shown beneficial effects of both light- and high-intensity exercise on mental health outcomes, future research should explore the dose-response relationship (considering frequency, intensity, type and time) in more detail, and its implications for clinical practice.

Future meta-analytic research could also focus on the efficacy of lifestyle physical activity counseling, i.e. integrating physical activity in daily life, as meta-analyses of RCTs investigating the efficacy of this counseling are currently lacking. In this respect, recent research in the general population[73-75] underscores the importance of distinguishing between various domains of physical activity (i.e., leisure time, commuting, occupational activity, and domestic physical activity), exploring their respective impacts on mental health. Evidence suggests that leisure time physical activity is particularly beneficial for mental well-being, often yielding greater psychological benefits compared to activities performed in other contexts. Mental health benefits of leisure time physical activity may stem from its association with increased social interaction and opportunities for enjoyment[76]. A nuanced understanding of how different types of lifestyle physical activity influence mental health in people living with a mental disorder will be essential for developing effective clinical interventions and public health strategies.

It has also been recommended to assess lifestyle from a 24-hour perspective[77,78]. This approach highlights the importance of considering time spent being physically active, sedentary and asleep, since each of these components influences overall health. For children and adolescents, guidelines recommend at least 60 min of moderate-to-vigorous physical activity daily, no more than two hours of recreational screen time, and sufficient sleep (9-11 hours for children, 8-10 hours for adolescents), as this balance positively impacts mental health by reducing anxiety and depression, and improving emotional regulation[77,78]. In adults, the recommendation is 150-300 min of moderate-intensity aerobic activity weekly, along with breaking up sedentary time and ensuring 7-9 hours of quality sleep, as these habits lower the risk of anxiety, depression, and cognitive decline[77,78]. Future research should investigate the impact of complying with the 24-hour guideline in people living with a mental disorder.

Further research should also explore which patients will benefit most from physical activity. There may be subgroups with certain neurobiological characteristics who respond better. Therefore, it is important to know how physical activity works, and to identify potential neurobiological, psychological and behavioral pathways. Overall, we found that the meta-analytic evidence on the neurobiological effects of physical activity in people with mental disorders is very preliminary, and limited to adults with major depressive disorder. Larger studies are obviously needed.

We found some evidence that chronic exercise stimulates the kynurenine pathway, which involves the breakdown of tryptophan, an amino acid crucial for serotonin production. Regular exercise increases the metabolism of tryptophan into kynurenine, leading to the production of metabolites, such as kynurenic acid, that can protect brain function[79]. A meta-analysis in people with age-related diseases[80] also found that structured physical activity had a significant concomitant effect on kynurenine pathway metabolite levels and psychological outcomes, reinforcing the current meta-analytic findings.

Meta-analytic evidence was also available showing a small effect of chronic exercise in promoting an increase of TNF-α. Of note, this increase was observed in adults with depression, but not in older adults with dementia. It has been hypothesized that the intensity of the intervention might play a role[81], with only higher intensity exercise, which is less suitable for older adults, resulting in increases of TNF-α levels. Chronic exercise-induced increases in TNF-α might play a beneficial role in regulating immune function and metabolic health by promoting a balance between pro-inflammatory and anti-inflammatory responses[82].

Effects on the hypothalamic-pituitary-adrenal (HPA) axis activity were inconsistent, with no physical activity-induced changes of cortisol levels in people with a major depressive disorder, but a large acute effect on natriuretic peptides. These peptides play a role in inhibiting HPA axis activity, but they are also a diagnostic and prognostic biomarker of cardiovascular diseases[83].

Our meta-review suggests that physical activity has a moderate acute, but not chronic, effect on growth hormone levels in people with major depressive disorder. Growth hormone regulates several important physiological functions in the brain, including neural plasticity[84]. We also found evidence of small effects of physical activity in increasing BDNF circulating levels.

No meta-analytic evidence could be found for psychosocial or behavioral moderators of the benefits of physical activity in people living with a mental disorder. Indeed, most individual trials did not adequately measure or control for psychosocial factors such as social support, motivation, and changes in self-esteem or coping skills, nor for behavioral factors such as individual goal-setting. A recent systematic review[85], in which only three out of 22 included studies were RCTs, did find that the strongest available evidence was for psychosocial mechanisms, including increased self-esteem, self-efficacy and self-concept, but further research is needed to confirm these findings in controlled trials. With regards to behavioral pathways, it has been proposed that better sleep quality might moderate the mental health benefits observed following physical activity[29]. For instance, a previous meta-analysis of RCTs[86] found that physical activity has a large statistically significant effect on sleep quality in those living with a mental disorder.

Research on individual, social and environmental factors, as well as intervention components, that impact individual participation in physical activity interventions within mental health care settings has grown considerably. Based on our meta-review, we were able to derive six implementation strategies, along with the behavioral change techniques to support them. These strategies include enhancing access to physical activity facilities and opportunities; providing trained and engaged staff to facilitate interventions; ensuring a psychologically and physically safe environment; developing tailored interventions; fostering autonomous motivation; and facilitating a resilient support network. The most extensive evidence was available for fostering autonomous motivation, which involves encouraging commitment to behavior change through goal-setting, regular feedback, and education on the health benefits of physical activity, while also reinforcing identity transformations associated with these changes.

Despite the large body of evidence of high methodological quality supporting the efficacy of physical activity interventions on mental and cognitive health in people living with a mental disorder, there is a lack of clinical practice guidelines, including clearly defined referral pathways, to inform the integration of physical activity into routine mental health care. This meta-review highlights that most existing studies have primarily focused on the question "Does it work, and how?", by evaluating efficacy under ideal conditions. Most studies do not reflect real-world circumstances, with resources, staffing and less complex disorder severity of participants that are not representative for everyday contexts[87,88], although there are exceptions[89]. Moreover, efficacy trials are typically conducted in high-resource settings, raising concerns about their ecological validity in low-income countries.

Future research should focus on strengthening evidence for the implementation strategies identified in this meta-review. We need reviews and meta-analyses that incorporate effectiveness studies [90], which allow to capture critical factors that cannot be fully identified under controlled conditions, such as contextual, organizational and systemic determinants. There is, for example, preliminary meta-analytic evidence that being physically active in nature is more beneficial for a range of psychological outcomes than being physically active in an urban environment[91]. Collaboration between researchers investigating physical activity for mental health and urban planners will be essential in the future, because the green and built environment significantly influence physical activity levels in people with a mental disorder, which in turn directly impact mental health outcomes[92], also in low-income countries[93]. Urban planners should help design and modify spaces to promote active lifestyles, ensuring that interventions are context-specific, sustainable and equitable.

To support implementation research in physical activity for mental illness trials, we formulate the following main recommendations:

- Available information on the implementation of interventions should be reported, also in efficacy studies. Fidelity (i.e., the extent to which the intervention was implemented as intended) is a critical element for determining whether (in)effectiveness can be attributed to the intervention itself. Additionally, details such as the strategies used, the context, and any adaptations to the intervention during the study should be reported. This information supports the interpretation of findings in a way that is useful for clinical practice and replication studies.
- For groups/settings with sufficient evidence of efficacy, the next step is to move on to effectiveness studies representing real-world practice. For this, alternative designs should be considered capturing real-world practice within methodologically-sound research, such as stepped-wedge trials and ecological momentary assessments. Preferably this should be done by hybrid designs where the implementation is evaluated in addition to health-related outcomes[94].
- Internationally agreed-upon methods and frameworks for implementation outcomes, determinants and strategies should be used. For outcomes, models such as RE-AIM[95] could be considered. For determinants, including their identification as barriers and facilitators, broad frameworks such as the Consolidated Framework for Implementation Research[96] could be used, or specific models such as the Theoretical Domains Framework[25] or the Capability, Opportunity, and Motivation model (COM-B) [97] for more individual-level behavioral analysis could be adopted. To target barriers, the Expert Recommendations for Implementing Change (ERIC)[98] are recommended. There are also frameworks that incorporate multiple steps and even offer tools that can be used by teams from the design to maintenance of interventions (e.g., iPRISM)[99]. This will also improve consistent terminology within implementation science as well as comparability and transferability between studies.
- Implementation starts with the design of the intervention, by involving key stakeholders relevant to real-world context. Therefore, recognizing and amplifying the contribution of people with lived experience to physical activity and mental health research may also help facilitate translation into practice and ensure that implementation strategies meet the needs of affected individuals and their families. This includes, for example, the co-design and co-delivery of interventions and the shared generation of research priorities[100-102]. Likewise, it is of value to recruit health care practitioners prescribing or supervising physical activity in mental health care settings. Based on frameworks mentioned above, the relevant team of stakeholders can already identify potential barriers, facilitators and needed strategies from the start.
- As indicated, more research on the implementation of physical activity within mental health care settings should be conducted in low-income countries. It can be hypothesized, however, that implementing physical activity interventions in these settings presents additional challenges, due to a shortage of trained facilitators and appropriate facilities, and the lack of environments that are both psychologically and physically safe for physical activity.

In conclusion, this meta-review sought to aggregate the vast but disparate evidence base around physical activity in the treatment of mental disorders. From this, we can show how the efficacy of exercise interventions is well-established across a broad spec-

trum of mental disorders. Alongside this, the preliminary evidence emerging around the neurobiological effects of physical activity in people with mental disorders has been reviewed. Finally, the literature examining the central determinants of uptake and adherence among people living with a mental disorder has become substantial enough to distill the main barriers and facilitators and develop implementation strategies to inform effective integration into care services. Overall, the findings and conclusions from each part of this meta-review may be used to expose critical gaps for future research, produce a case for dedicating further resources towards including physical activity interventions in mental health care, whilst also presenting the most evidence-based strategies available to date for delivering them successfully.

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