# The Role of Physical Activity in Opioid Substitution Therapy: A Systematic Review of Interventional and Observational Studies

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## ABSTRACT

**BACKGROUND:** Use of physical activity in the treatment and follow-up of people receiving opioid substitution therapy is an understudied area of research. Therefore, the objective of this systematic review was to synthesize the currently available research on the role of physical activity in opioid substitution therapy and proper adaptions for the group.

**METHODS:** A systematic search was performed on PsycINFO, EMBASE, MEDLINE, CINAHL, and Web of Science until September 2021 (PROSPERO-reg.no: CRD42020109873). The inclusion criteria were studies involving physical activity interventions for opioid substitution patients. Reference lists of relevant studies were screened to identify additional relevant studies. Data extracted were compiled into tables and descriptively presented.

**RESULTS:** The search yielded 2105 unique records. A total of 10 studies were included, whose methodological quality ranged from satisfactory to very good. Study quality was assessed using a 7-/8-point quality score. The agreement between the reviewers, assessed with Cohen's kappa, was 0.91. Overall, the results suggest that physical activity increases physical fitness of patients in opioid substitution therapy and decreases substance use. The minority of studies in this field are of high quality with sufficient power.

**CONCLUSIONS:** The findings of this systematic review suggest beneficial effects of physical activity on physical fitness, substance use, and mental health for patients in opioid substitution therapy. Although the findings are quite consistent across studies, high-quality studies and sufficiently powered clinical trials are needed to confirm and validate the findings and to conclude on the degree of impact.

**KEYWORDS:** Opioid maintenance treatment, exercise, medication-assisted treatment

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## Background

People who use opioids represent about 40% of the estimated 1.5 million people receiving treatment for illicit drug use in the European Union (including Norway and Turkey) in 2017.[1] Individuals with an opioid dependence not only are at high risk for premature death due to overdose,[2,3] but also frequently experience physical and mental health problems.[4,5] Opioid dependence contributes to a large proportion of life years lost due to substance use disorder (SUD).[4,6]

Despite the substantial effect of opioid substitution therapy (OST) that reduces the number of life-years lost due to opioid dependence by several years,[7] high morbidity and mortality remain. Further, a high dropout rate from OST has been found in several settings: Almost half the people in OST dropped out of treatment at 12 months.[8] In order to deal with opioid dependence, it is important to develop primary and adjunctive treatments that are obtainable, affordable, and effective.[9]

Physical activity (PA) and its physiological health benefits are well-established.[10,11] In this article, PA is defined as any bodily movement that increases energy expenditure as opposed to exercise which is planned, structured, repetitive, and intentional PA intended to improve or maintain physical fitness.[12] PA has also been found to improve physical and mental health outcomes for people with mental illness, anxiety and

stress disorders, and eating disorders.[13,14] It addresses physical health as well as cognitive functioning and can constitute an adjunct treatment that complements standard pharmacological and psychological interventions.

The Salem Program, in the 1970 seconds, was one of the first to combine PA and treatment of alcohol dependence.[15] In 1972, a study examined the effect of jogging in hospitalized individuals with alcohol dependence and found improvements in physical status, sleep pattern, and self-esteem compared to age-matched controls.[16] Another study, a randomized controlled trial (RCT) that examined a group of 60 male heavy social drinkers, found that after 8 weeks a group that had been assigned to an exercise intervention had reduced alcohol consumption compared to a pharmacologically treated group and a control group that did not receive any treatment.[17] Based on these and other studies, it was concluded that PA in alcohol use disorder treatment could provide positive results on fitness, strength, anxiety, depression, self-esteem, and prevention of relapse if adherence to the program was high and the program itself was of sufficient quality and duration.[18]

The role of exercise interventions and knowledge on suitable adaptions for people with SUDs beyond alcohol dependence has been less clear. PA may have concomitant therapeutic effects related to both the aforementioned approaches to treat opioid use disorder (OUD) due to its influence on comorbid conditions[19,20] including effects on depression, anxiety, posttraumatic stress disorder, as well as cardiovascular and respiratory diseases,[21-26] which are common among patients with SUD.[27,28] However, there is a lack of broad systematic reviews summarizing and synthesizing the effects of PA interventions and necessary adaptations in the context of OST.[29] Some individual studies have been conducted that may indicate some effects, but it is still uncertain what the overall picture looks like.

Existing systematic reviews[30-32] have included studies with a focus on alcohol, substance use, and smoking in the same analyses, as well as studies with a focus on prevention, harm reduction, and treatment. They all concluded that exercise has shown promising results and has great potential as an effective adjunctive treatment for SUD. In the present review, we explicitly focus on studies on PA in the treatment of OUD, that is, treatment for people with opioid dependence, such as heroin or prescription opioids. Although some previous systematic reviews[26,33,34] that cover OST have been published, these have included interventional studies exclusively, resulting in few studies. They showed that exercise interventions have the potential to improve health and wellness features for people in OST. The reviews have also suggested that there is a need for studies with more standardized interventions and stronger methodology. To date, one systematic review deals specifically with individuals in OST.[33] That review includes 3 interventional studies. Two other systematic reviews on populations with SUD address OST.[26,34] Both include the same 3 interventional studies. Observational studies could add important knowledge on the situation and the need for adaptions of approaches, and an assessment of both experimental and observational evidence from these 2 types of studies may be particularly insightful. Interventional studies often recruit selected populations that are not representative of the population affected by the condition of interest. Formulating inclusion and exclusion criteria to identify a homogeneous group of participants based on complex comorbidities can prove difficult. Exclusion criteria such as a history of psychotic disorder or current psychotic symptoms, an eating disorder, and suicidality limit the number of potential participants in the target group. Thus, the applicability of such data to more general populations is unsure. Observational studies can help address these gaps. They are necessary to describe the disease burden and the health care needs.[35,36] The integration of observational studies can provide further information on patient groups who may have been excluded from interventional studies.

The global recommended level of PA for adults is moderate-intensity aerobic PA for at least 150 minutes per week or at least 75 minutes of vigorous-intensity aerobic PA throughout a week.[11] Physical inactivity is more common in countries of high income than in those of low income.[37] This can be explained by more sedentary occupations and regular use of motorized transportation.[37,38] People enrolled in OST are seldom employed and often cannot afford to travel by car. Instead, they often walk or bike to pick up their medicine or in their constant pursuit of drugs/money. Yet, the aforementioned recommendations should rather be considered aspirations for people with OUD due to barriers that can pose an obstacle to PA. They may have health and life concerns that disrupt clinical study participation.[39]

In this context, we therefore aim to systematically review studies on the role and adaptions of PA for people receiving OST, which constitute the largest subgroup of patients with an illicit SUD in the European Union.[1]

## Methods

This article aimed to identify all relevant interventional and observational studies on PA in OST. A study protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[40] and pre-registered within the international prospective register of systematic reviews (PROSPERO; registration number: CRD42020109873). The PRISMA 2020 Checklist can be found in Supplemental Table S1.

### *Information sources and search strategy*

The electronic databases PsycINFO, EMBASE, MEDLINE, CINAHL, and Web of Science were searched in September 2020 for studies investigating any form of PA as a therapeutic intervention strategy in OST. A supplementary search was conducted on September 1, 2021. The key search terms were

**Table 1.** Inclusion and exclusion criteria.

| |
|---|
| *Inclusion criteria* |
| Population: Adults enrolled in OST |
| Exposure: Exercise-based intervention or status of physical activity level |
| Comparators for the interventional studies: Not receiving a similar exercise-based intervention |
| Outcomes for the interventional studies: Changes in physical function, mental health, and perceived health |
| Outcomes for the observational studies: Status of physical activity, mental health, and perceived health |
| Study design: interventional (randomized controlled trials, controlled clinical trials) or observational (prospective or cross-sectional) studies conducted in any setting (inpatients or outpatients) |
| Language: English, German, Norwegian, Swedish, Danish |
| Publication status: Published articles indexed in PsycINFO, Medline, Embase, CINAHL, and |
| Web of Science |
| *Exclusion criteria* |
| Animal studies/cell studies |
| Studies not including patients enrolled in OST |
| Non-quantitative studies |

connected (and brought together with the Boolean expression OR and then combined with Boolean AND) to 1 of 2 categories: OST and PA, as follows:

1. Exposure terms: physical activity, physical fitness, physical endurance, exercise, aerobic fitness, aerobic capacity, motor activity, motor control, cardiovascular fitness, cardiovascular capacity, muscle strength, muscular strength
2. Population terms: methadone, opioid, opiate, buprenorphine, naloxone, naltrexone, maintenance, substitution, replacement

For a more detailed description of the search string, see Supplemental Table S2.

The search strategy was adapted for each database according to its specific parameters. The search was not restricted by language or study design. Grey literature searches were performed to warrant maximum coverage of the subject area. The grey literature strategy covered searches on Google, Google Scholar, and Open Grey. The extraction process was conducted following the PRISMA methodology and used the Participants, Intervention, Comparison, Outcome, and Study Design (PICOS) strategy.

### *Study eligibility and selection process*

After duplicates were removed, 2 authors (SEA and EF) independently screened the titles and abstracts of all retrieved references against the inclusion and exclusion criteria (see Table 1). The full texts of potentially relevant papers were then individually examined by the same 2 authors. A senior researcher (LTF) resolved discrepancies and confirmed the relevance of all included papers. Articles were considered eligible for this systematic review if they included PA level measures or an exercise-based intervention in people receiving OST for OUD. Regarding outcome measures, we focus on physical and mental health, as well as perceived health.

Using Clarivate Analytics EndNote X9, full-text articles were screened and inclusion/exclusion was agreed upon through discussions. Studies with inadequate control strategies, such as small samples, were included in the review to present a comprehensive overview of the empirical status of this field. The reference lists of papers retrieved from the original search were manually inspected for additional references. The full details of the search are detailed in Figure 1.

### *Data extraction, risk of bias assessment, and data synthesis*

Two review authors (SEA and EF) independently extracted data from the search results and performed a quality/risk of bias assessment of the included articles. Since the present review included studies with different research designs, quality assessment/risk of bias tools for the specific study designs were used. The Evidence Project Risk of Bias Tool[41] assesses the risk of bias across both randomized and non-randomized study designs and is therefore applicable to interventions that include a range of study designs. The Newcastle-Ottawa Scale[42] was designed to evaluate bias based on selection, comparability, and assessment of the outcome or exposure. As the effectiveness of

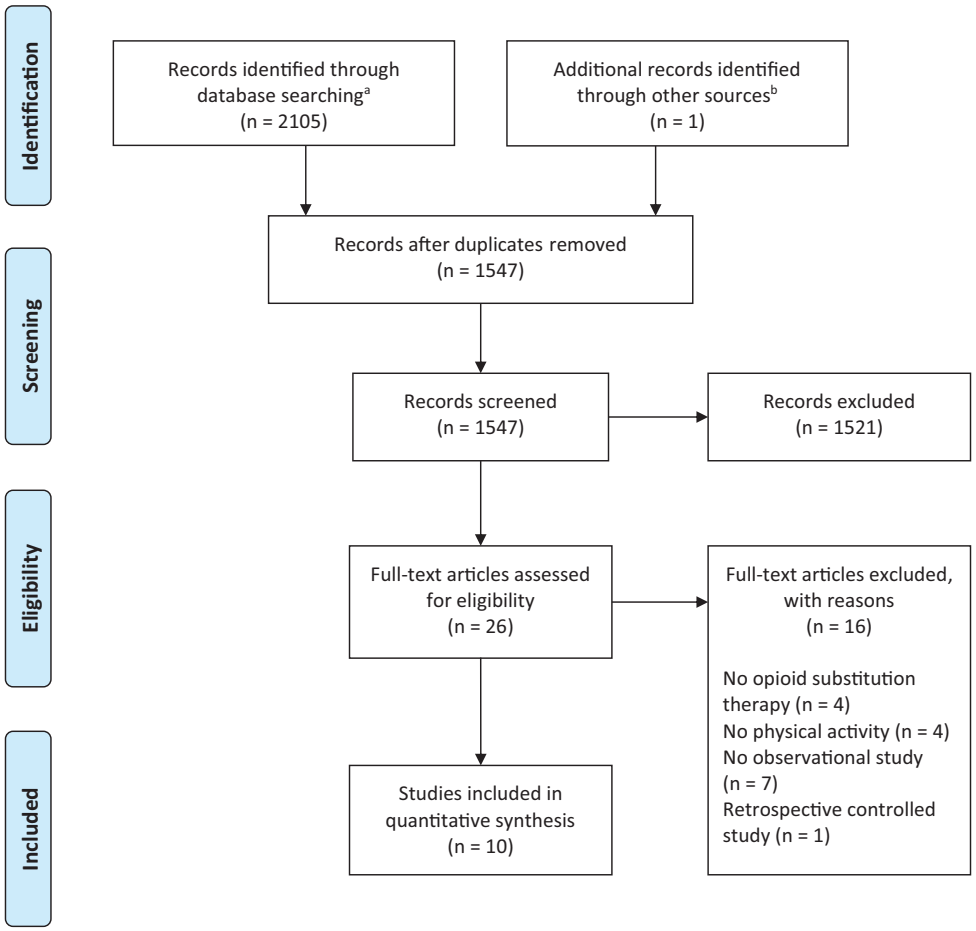


**Figure 1.** PRISMA flow diagram of search and selection of studies.
[a]Records identified from PsycINFO, EMBASE, MEDLINE, CINAHL, and Web of Science.
[b]Records identified from screening references of included articles.

an intervention was not measured, this tool is suitable for the evaluation of cross-sectional studies. By using these 2 tools, the quality of the included studies could be assessed in a reliable manner, taking into account differences in research designs. The level of agreement between the 2 authors in terms of risk of bias assessment was calculated and reported in terms of Cohen's kappa score.[43]

Due to an insufficient number of articles that overlapped on exposure and outcome, the data were deemed unsuitable for a meta-analytic approach. Our discussion covers all articles, including those with a high risk of bias or small sample size. The results are presented in a descriptive narrative summary including important information about study populations, design and study procedures, as well as synthesized patterns across studies.

## Results

The initial search yielded 2105 records. Following the exclusion of duplicates and non-eligible records, we retrieved 26 articles for full-text screening. Ten studies met the inclusion criteria. The 2 researchers (SEA and EF) rated each study on study quality/risk of bias and achieved high inter-rater reliability. For the Evidence Project risk of bias tool, Cohen's kappa was 0.91, and for the Newcastle-Ottawa Scale, it was 1.00, suggesting almost perfect agreement.[44]

In the 10 articles, 1215 participants were included. In Table 2, we summarize the extracted data and study characteristics. The search of the grey literature did not yield any additional articles. The studies were carried out predominantly in high-income countries. Seven studies were conducted in the United States,[45-51] one in Spain,[52] one in Switzerland,[53] and one in Lebanon.[54] All studies included adults over 18 years of age and both sexes.

We found some common characteristics between the included articles using the Newcastle-Ottawa Scale for cross-sectional studies and the Evidence Project risk of bias tool assessing interventional studies. In the interventional studies, a maximum score of 8 stands for "good quality"[41] (Supplemental Table S3). The study by Abrantes et al scored 3/8[51] and the one by Pérez-Moreno et al scored 5/8.[52] The studies by Colledge et al,[53] Shaffer et al,[48] and Uebelacker et al[50] scored 6/8. The pilot study by Cutter et al scored 7/8 on the quality assessment.[47] One of the common limitations was the lack of random selection of participants for assessment.[48,50-53] One study did not report data, thus excluding the evaluation on this

**Table 2.** Summary of the included records.

| STUDY | DESIGN AND QUALITY | POPULATION | INTERVENTION AND CONTROL PROCEDURES | OUTCOME VARIABLES | SUBSTANCE USE | MENTAL HEALTH | PHYSICAL ACTIVITY/ FITNESS | OTHER FINDINGS |
|---|---|---|---|---|---|---|---|---|
| Abrantes et al,[51] USA | Pre-post feasibility study, single-arm pilot trial<br><br>Quality: 3/8 | N = 26<br>27% men<br>Individuals in methadone maintenance treatment<br>Age<br>Total: 41.2 (11.0) | I: 12 wk, peer-led group discussion (one weekly session of 20-30 min), walking sessions (one weekly session of 30 min), and use of activity tracker<br>C: None<br>Trained peer-facilitators<br>Intensity: NR | Substance use:<br>TLFB: Timeline Followback questionnaire<br>Mental health:<br>CES-D: Center for Epidemiologic Studies Depression Scale Revised,<br>GAD-7: General Anxiety Disorder-7,<br>PANAS: The Positive and Negative Affect Scale<br>Physical activity/ fitness:<br>Self-Report Physical Activity,<br>Objectively Measured Physical Activity (accelerometer)<br>Others:<br>CSQ: Client Satisfaction Questionnaire,<br>Exercise Benefits and Barriers Scale,<br>PACES: Physical Activity Enjoyment Scale,<br>SAFTEE: Systematic Assessment of Treatment-Emergent Events | Small-to-moderate effects for decreases in illicit opioid use and cocaine use. | No changes in depression, anxiety, and negative affect. Increase in positive affect from baseline to end of treatment. | Small-to-moderate effect sizes for increases in PA. Intervention adherence: 63% of sessions completed<br>Intervention dropout: 19% | High levels of satisfaction with the intervention. Small-to-moderate effects for increases in PA enjoyment and perceived benefits of PA, as well as decreases in perceived barriers to engaging in PA. Reasons for non-adherence were health-related issues, substance use relapse, becoming homeless, relationship issues, court-mandated appearances, loss of transportation, and conflict in trying to get a new job. Disruptions in smartphone access/data plans was also a barrier. Positive feedback on the use of the Fitbit. Group walks in nearby parks were experienced positively. |
| Colledge et al,[53] Switzerland | Randomized, controlled single-blinded pilot trial<br>Quality: 6/8 | N = 24 (13 + 11)<br>63% men<br>Individuals in heroin-assisted treatment<br><br>Age<br>I: 42.7 (6.5)<br>C: 45.8 (4.2) | I: 12 wk, 2 sessions per week (duration unspecified), moderate to vigorous PA (incl. climbing, badminton, strength training, boxing, dance), and walking<br>C: Non-exercise activities<br>Trained study personnel with a background in sports education<br>Intensity: NR | Substance use:<br>TLFB: Timeline Followback questionnaire<br>Mental health:<br>ADS: Allgemeine Depressionsskala–Kurz,<br>ISI: Insomnia Severity Index,<br>BSC: Brief Self Control Scale,<br>PSS: Perceived Stress Scale<br>Physical activity/ fitness:<br>IPAQ-SF, Handgrip strength<br>Others:<br>SF-36: Short Form Health Survey,<br>Blood pressure | No significant effects of time, group, or time by group. | A large effect size for the exercise group was observed for limitations in usual activities because of emotional problems. | The exercise group increased its daily exercise levels significantly.<br>Compliance:<br>I: 38% compliant (⩾80% of sessions completed), 54% semi-compliant (between 20% and 80% of sessions completed), 8% non-compliant<br>C: 46% non-compliant | The exercise group scored significantly better than the comparison group across all time points including baseline on physical functioning and limitations in usual activities due to physical problems. The exercise program was designed using patient feedback, allowing patients to choose the type and intensity of activity they engaged in. |

*(continued)*

**Table 2.** (Continued)

| STUDY | DESIGN AND QUALITY | POPULATION | INTERVENTION AND CONTROL PROCEDURES | OUTCOME VARIABLES | SUBSTANCE USE | MENTAL HEALTH | PHYSICAL ACTIVITY/ FITNESS | OTHER FINDINGS |
|---|---|---|---|---|---|---|---|---|
| Cutter et al,[47] USA | Randomized, controlled pilot trial<br>Quality: 7/8 | N = 29 (15 + 14)<br>41% men<br>Individuals in methadone maintenance treatment<br>Age<br>Total: 43.4 (8.5)<br>I: 42.8 (8.7)<br>C: 44.0 (8.5) | 8 wk, 5 weekly sessions of 20-25 min/session<br>I: PA (aerobic, strength, balance, and yoga) through video game (Wii Fit Plus)<br>C: Sedentary video game (Wii)<br>Intensity: i1 (55%-72% HR) | Substance use:<br>Weekly Substance Use Inventory, Urine toxicology screens<br>Mental health:<br>PSS: Perceived Stress Scale, LOT-R: Life Orientation Test–Revised, BSI-18: Brief Symptom Inventory-18, BLSS: Brief Life Satisfaction Scale<br>Physical activity/ fitness:<br>MET: Metabolic equivalent of task, IPAQ-L, kcal<br>Others:<br>Acceptability | Both groups reduced drug use; no differences between groups. | Both groups improved optimism and perceived stress, without differences between groups. No significant differences in global psychiatric symptoms or life satisfaction. | Individuals in Active Game Play reported significantly higher levels of overall moderate or vigorous PA outside the Wii Fit Plus sessions based on the IPAQ-L than those in Sedentary Game Play.<br>Intervention adherence: 63% of sessions completed<br>Intervention dropout: 7% | High overall acceptability in both groups.<br>Wii Fit Plus: novel, low-cost, transportable, feasible, and acceptable intervention.<br>High patient satisfaction and interest. |
| Pérez-Moreno et al,[52] Spain | Randomized, controlled single-blinded trial<br>Quality: 5/8 | N = 19 (9 + 10)<br>100% men<br>Individuals in methadone maintenance program<br>Age<br>I: 37 (3)<br>C: 37 (2)<br>Range: 30-55 y | I: 4 mo, 3 weekly sessions of 90 min/ session, warm-up, resistance and aerobic training, cool-down<br>C: Standard therapy<br>Supervised by the same experienced investigator<br>Intensity: i2 (72-82% HR) | Substance use:<br>Methadone dosage<br>Mental health:<br>QOL: Quality of life global scale<br>Physical activity/ fitness:<br>Heart rate (HR), knee-extensor 6-RM, bench press 6-RM, body mass, muscle mass<br>Others:<br>Hemoglobin, leukocyte, platelet count, CD4 lymphocytes | No difference at baseline between the 2 groups.<br>Decreased required methadone dosage in both groups after intervention. | QOL significantly increased in the training group after the intervention period, no change was observed in controls. | The intervention group showed significant improvement in peak completed workload, peak heart rate, and rate of HR decrease at 1 min, as well as in both bench press and knee-extensor 6-RM tests.<br>Intervention adherence: 71% of sessions completed<br>Intervention dropout: 36% | The mean levels of CD4 lymphocytes and the mean estimated muscle mass of the training group significantly increased after training compared with baseline levels, whereas no change was found in controls. |
| Shaffer et al[48] USA | Randomized, controlled trial<br>Quality: 6/8 | N = 59 (29 + 30)<br>59% men<br>Individuals in methadone treatment<br>Age<br>Total: 35.9<br>I: 36.3<br>C: 35.5<br>Range: 23-46 year | I: 5 mo of yoga, 75 min/session, 1 session per week<br>C: Psychotherapy (weekly 50-75 min)<br>Certified yoga instructor<br>Intensity: i1 (55%-72% HR) | Substance use:<br>ASI: Addiction Severity Index<br>Mental health:<br>SCL-90-R<br>Physical activity/ fitness:<br>Others: | Longer treatment was positively correlated with reduced drug use.<br>No significant differences in any variable between the 2 groups. | No statistically significant changes in both groups.<br>No significant differences between the 2 treatments. | Not reported<br>Intervention adherence: Mean attendance 37% of the sessions<br>Intervention dropout: 28% | Lack of staff acceptance of the intervention.<br>Transfers from intervention to control group were due to episodic or chronic medical conditions. |

*(continued)*

**Table 2.** (Continued)

| STUDY | DESIGN AND QUALITY | POPULATION | INTERVENTION AND CONTROL PROCEDURES | OUTCOME VARIABLES | SUBSTANCE USE | MENTAL HEALTH | PHYSICAL ACTIVITY/ FITNESS | OTHER FINDINGS |
|---|---|---|---|---|---|---|---|---|
| Uebelacker et al,[50] USA | Randomized, controlled blinded pilot trial<br>Quality: 6/8<br>Registered at clinicaltrials.gov: NCT03022890. | N = 40 (20 + 20)<br>43% men<br>Individuals in opioid maintenance therapy<br>Age<br>Total: 43<br>I: 43 (10.7)<br>C: 44 (10.8) | 12 wk, 1 h/session, 1 session per week<br>I: Yoga<br>C: Health education (HE)<br>Registered yoga teachers and HE teachers<br>Intensity: i1 (55%-72% HR) | Substance use:<br>Mental health:<br>Mood and pain (sadness, anxiety, irritability, fatigue, and pain)<br>Physical activity/ fitness:<br>IPAQ<br>Others:<br>BPI-I: Brief Pain Inventory–Pain Interference Scale, SAFTEE: Systematic Assessment of Treatment-Emergent Events - General Inquiry, CEQ: Credibility Expectancy Questionnaire, CSQ-8: Client Satisfaction Questionnaire | Not reported | Participant mood improved pre-class to post-class, with greater decreases in anxiety and pain for those in the yoga group. | 50% of participants in yoga and 65% of participants in HE attended at least 6 of 12 possible classes.<br>61% in the yoga group reported practicing yoga at home.<br>Intervention adherence: 50% of sessions completed<br>Intervention dropout: 10% | Participants practiced yoga at home, but class attendance was lower than desired.<br>Acceptable levels of satisfaction with the program.<br>Familiarity with the OST clinic may be important for helping participants feel comfortable attending class. |
| Beitel et al,[45] USA | Cross-sectional<br>Quality: Satisfactory | N = 303 (81 + 222)<br>61% men<br>Individuals in methadone maintenance treatment<br>Age<br>Total: 33.4 (10.4)<br>I: 33.9 (9.8)<br>C: 33.3 (10.6) | I: SA, sufficiently active (at least 150 min moderate or vigorous PA weekly)<br>C: IA, insufficiently active (<150 min moderate or vigorous PA weekly) | Substance use:<br>Mental health:<br>BASIS-24: Behavior and Symptom Identification Scale-24<br>Physical activity/ fitness:<br>MVPA: Weekly levels of moderate-to-vigorous PA<br>Others:<br>BPI: Brief Pain Inventory | Not reported | Intervention group: significantly lower levels of depression, emotional liability, and overall psychiatric distress. | 27% met recommended PA levels, 71% reported no min of moderate or vigorous PA in the last week. | Intervention group: lower levels of current pain intensity and pain interference, and higher levels of pain control.<br>Participants with chronic pain who met the recommended levels of weekly PA reported higher levels of pain control.<br>Female participants were more likely than male participants to report interest in exercise group participation. |

*(continued)*

**Table 2.** (Continued)

| STUDY | DESIGN AND QUALITY | POPULATION | INTERVENTION AND CONTROL PROCEDURES | OUTCOME VARIABLES | SUBSTANCE USE | MENTAL HEALTH | PHYSICAL ACTIVITY/ FITNESS | OTHER FINDINGS |
|---|---|---|---|---|---|---|---|---|
| Caviness et al,[46] USA<br>Stein et al,[49] USA | Cross-sectional[46,49]<br><br>Quality: Very good[46,49]<br>Registered at clinicaltrials.gov: NCT00790569.[46] | N = 303 (117 + 186)[46]/ 315 (121 + 194)[49]<br>50% men[46,49]<br>Individuals in methadone maintenance treatment[46,49]<br>Age<br>Total: 39.7 (9.6)[46]/39.9 (9.6)[49] | I: sufficiently active (moderate PA for at least 30 min per day on 5 or more days a week, or vigorous-intensity activities for at least 20 min per day on 3 or more days a week)<br>C: insufficiently active | Substance use: Smoking via time line follow-back[46]<br>Mental health: CES-D: Center for Epidemiologic Studies Depression Scale[49]<br>Physical activity/ fitness: IPAQ-SF,[46,49]<br>BMI: Body Mass Index[46]<br>Others: Barriers to exercise (18-item scale),[46] Motives for Physical Activity Measure[46]<br>SF-12: Short-Form Health Survey[49] | Those who met guidelines for weekly PA were significantly more likely than those who were less active to report a reduced likelihood of relapse as a benefit of exercise.[46] | Those with higher levels of PA were significantly more likely to report that exercise reduced anxiety.[46]<br>Depression was significantly and positively related to sitting time.[49]<br>Depression scores were inversely associated with SF-12 physical function scores.[49] | 38% met weekly recommendations for PA, nearly 25% reported no PA.<br>Those with higher levels of PA were significantly more likely to report that exercise helped with physical fitness.[46]<br>The effect of time spent sitting did not differ significantly by level of activity.[49] | The most commonly identified barrier to exercise was lack of motivation.[46]<br>The most commonly identified motive for exercise was improvement of health.[46]<br>The likelihood of believing exercise would improve cardiovascular fitness increased significantly as age increased.[46]<br>As age increased, endorsement of barriers related to possible injury, poor health, or physical disabilities increased.[46]<br>Minutes sitting per day was inversely associated with SF-12 physical function scores.[49] |
| Mahboub et al,[54] Lebanon | Cross-sectional<br><br>Quality: Good | N = 97<br><br>97% men<br><br>Individuals in OST<br><br>Age Total: 33.7 (8.2) | I: low, moderate, and high activity levels among OST<br><br>C: none | Substance use: Mental health: PSQI: Pittsburgh Sleep Quality Index<br><br>Physical activity/ fitness: IPAQ-SF, MET, BMI, Body composition<br><br>Others: SGA: Subjective Global Assessment (Nutritional status), Blood pressure, MPR: Multiple Pass Food Recall, CoNKQ: Consumer Oriented Nutrition Knowledge Questionnaire, YFAS: Yale Food Addiction Scale, Blood serum analysis | Not reported | 69% had poor sleep quality. | 71% had a low PA level. | 45% had a food addiction.<br><br>32% of the OST sample reported weight loss.<br><br>73% showed poor knowledge of nutrition. |

Abbreviations: ADS, Allgemeine Depressionsskala; ASI, Addiction Severity Index; BASIS-24, Behavior and Symptom Identification Scale-24; BLSS, Brief Life Satisfaction Scale; BMI, Body Mass Index; BPI, Brief Pain Inventory; BPI-I, Brief Pain Inventory–Pain Interference Scale; BSC, Brief Self Control Scale; BSI-18, Brief Symptom Inventory-18; C, Control group; CEQ, Credibility Expectancy Questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale; CoNKQ, Consumer Oriented Nutrition Knowledge Questionnaire; CSQ, Client Satisfaction Questionnaire; GAD-7, General Anxiety Disorder-7; HE, health education; HR, Heart rate; I, intervention group; IPAQ, International Physical Activity Questionnaire; IPAQ-SF, International Physical Activity Questionnaire Short Form; IPAQ-L, International Physical Activity Questionnaire Long Form; ISI, Insomnia Severity Index; LOT-R, Life Orientation Test–Revised; MET, metabolic equivalent of task; MPR, Multiple Pass Food Recall; MVPA, weekly levels of moderate-to-vigorous physical activity; NR, not rated; OST, opioid substitution therapy; PA, physical activity; PACES, Physical Activity Enjoyment Scale; PANAS, The Positive and Negative Affect Scale; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; QOL, Quality of life global scale; RM, Repetition maximum; SAFTEE, Systematic Assessment of Treatment-Emergent Events; SCL-90-R, Symptom Checklist 90 Revised; SF-12, 12-item Short-Form Health Survey; SF-36, 36-item Short Form Health Survey Questionnaire; SGA, Subjective Global Assessment (Nutritional status); TLFB, Timeline Followback; YFAS, Yale Food Addiction Scale.

dimension.[47] The quality of the included cross-sectional studies was assessed as satisfactory,[45] good,[54]or very good [46,49]; see Supplemental Table S4 for a more detailed report. Only one of the interventional studies had a sample size of >50.[48] One article[54] reported a power analysis and 4 articles reported effect sizes.[47,50,51,53]

All studies included adults who had opioid substance dependence, often combined with other substances, and enrolled in specialist treatment programs. One study included people attending heroin-assisted treatment[53] and 9 studies included those engaged in methadone maintenance therapy.[45-52,54]

In total, the interventional studies reported low intensity (maximal heart rate 55%-82%) except for Colledge et al,[53] where the intervention was designed to increase the heart rate to moderate/vigorous intensity. One study did not report the intensity of the exercise intervention.[51]

### *Interventional studies*

Six studies[47,48,50-53] were designed as interventional studies, with 197 subjects in total, and examined PA for people receiving OST. The number of participants per study varied between 19[52] and 59[48] participants; 27%[51] to 100%[52] of the participants were male.

Exercise interventions varied considerably between studies. Treatment duration ranged from 8 weeks[47] to 5 months.[48] The exercise sessions lasted from 20 to 90 minutes per week from 1 to 5 sessions. The total duration of the weekly exercise lasted between 50 and 180 minutes.

The exercise intensity scale developed by the Norwegian Olympic Centre[55] was used to classify training intensity (I-zones). Two studies[51,53] did not rate exercise intensity, 3 studies[47,48,50] included exercise interventions with an intensity belonging to intensity zone 1, and one study[52] enforced exercise classified as I-zone 2.

Of the 6 interventional studies, 4 employed control procedures that matched the PA intervention in terms of time, frequency, and duration without a PA element,[47,48,50,53] one included a control arm consisting of treatment as usual,[52] and one did not have control procedures.[51]

All exercise interventions were supervised, mainly by exercise professionals or trained personnel. Exercise training sessions were delivered face to face, except for one[47] who used a computer game platform. Five studies[47,50-53] used measurements for PA. Of these, one[52] reported maximum heart rate and another[51] used accelerometers to measure PA.

The adherence to the exercise interventions also varied between studies: the study[52] with the highest adherence reported 71% completed sessions, the lowest adherence was 37%,[48] one study[50] reported 50% adherence, 2 studies[47,51] reported that 63% of intervention sessions were completed, and one study[53] reported that 38% of the participants missed fewer than 5 of 23 sessions.

In total, 5 interventional studies provided data on dropout from exercise interventions. The dropout rate ranged from 7%[47] to 36%.[52] One study reported 14% dropout after randomization and before the start of the intervention.[53]

### *Observational studies*

Four studies with a cross-sectional design were identified,[45,46,49,54] including a total of 1018 participants, that assessed PA. Aside from these, no other observational study designs were identified. Two of the articles on the cross-sectional studies were mainly based on the same population and study,[46,49] but presented different outcome variables. All cross-sectional studies used the International Physical Activity Questionnaire (IPAQ) to evaluate the level of PA. No study rated exercise intensity or used objective measures such as accelerometers or other outcomes such as $VO_2$max.

### *Substance use*

One interventional article did not report substance consumption as an outcome.[50] Two articles found no differences in substance use between the intervention and control groups.[52,53] In Cutter et al[47] both groups reduced their consumption. Extended treatment was positively correlated with reduced drug use. Interestingly, one cross-sectional study found that those who met the recommended PA guidelines were significantly more likely to report a reduced likelihood of relapse as a benefit of exercise than those less active.[46] Five of the cross-sectional articles found that a decrease in substance use was associated with PA or exercise[46-49,51], two did not report substance consumption as an outcome.[45,54]

### *Mental health*

Five studies reported depression as an outcome: In 3 studies, no differences in mental health were found compared to baseline data[51] or the control group.[48,53] In one study, depression was positively related to inactivity[49] and in another study, a significant reduction compared to the control group was found.[45] Four studies reported anxiety as an outcome.[46,48,50,51] Two found a reduction compared to the control condition (reduced anxiety of 77.8% in the intervention group versus 65.1% in the control group,[46] and a 1.79 point decrease in anxiety from pre- to post-class in the intervention group versus a 1.07 point decrease in the control group[50]); two found no difference to the control group[48] or baseline measurements.[51] Three studies reported stress as an outcome.[45,47,53] Two studies reported a decrease in stress from pre- to posttreatment but found no differences compared to non-exercising controls.[47,53] In one study, the intervention group reported significantly lower levels of psychiatric stress than the control group.[45] Two studies reported dimensions of QOL as outcomes.[47,52] Both found no difference compared to controls. However, one study presented a significantly increased QOL in

the exercise (from a score of 76 to 87 on the global QOL scale) but not in the control group (from 76 to 77) after the intervention.[52] Two studies reported dimensions of sleep.[53,54] In a cross-sectional study, 69% of the subjects reported poor sleep quality[54] whereas non-significant improvements in subjective sleep quality were reported in an RCT.[53]

### *Physical activity/fitness*

All 4 cross-sectional studies investigated PA levels. They report that roughly 30% of the participants met the global recommendations for PA. Additionally, people enrolled in OST scored higher on sedentary behavior than the rest of the population. In Beitel et al[45] 27% reached the recommended PA level. In Caviness et al[46] and Stein et al[49] 38% met the recommendation. The newly published article from Mahboub et al[54] described that 71% had low PA levels.

An overall increase in physical fitness was observed in the exercise intervention groups; although not all interventional studies had a physically active control group. In Colledge et al[53] the participants in the exercise group significantly increased their PA level and handgrip strength. In the Cutter et al study,[47] incorporating Wii fit gameplay, the active gameplay intervention group reported a higher level of moderate and high-intensity PA than the control group during the sessions (35 kcal more). They also reported higher levels of overall moderate-to-vigorous PA outside sessions (9.7 hours per week versus 4.0 hours per week). Pérez-Moreno et al[52] who conducted a randomized clinical trial in prison also reported a significant increase in several aspects of physical fitness, including strength and heart rate. Small-to-moderate effect sizes for increases in PA were also observed in the study by Abrantes et al[51]

### *Other findings and findings on barriers and facilitators of PA*

Two studies[49,53] reported on physical functioning, quantified by the Short-Form Health Survey SF-36[56] and SF-12.[57] In one of them,[53] the exercise group scored significantly better than the comparison group at baseline, during, and after the intervention. In Stein et al[49] the time spent sitting per day was inversely associated with physical functioning. Three studies recounted adverse events.[50-52] No serious event was related to PA or participating in the respective interventions.

Two studies reported low participation rates: In a clinic with about 150 patients, 16% were willing or able to participate.[53] Another study stated a slightly higher percentage of 23%.[47] One interventional study[51] used peer-facilitated PA interventions, one study[53] used study personnel for the execution of the intervention, 3 studies[48,50,52] used external instructors, and one study[47] used video games. Class attendance was lower than desired in one of the studies using an instructor[50] and the other 2 had the highest dropout rates among the intervention groups (36%[52] and 28%[48]). Abrantes et al[51] found that peer-facilitated PA interventions were effective and satisfactory for the participants. They also found that non-adherence was often linked to health-related issues, homelessness, relationship issues, court-mandated appearances, loss of transportation, looking for work, and disruptions in their smartphone access or data plans. Group walks in nearby parks were experienced positively. Moreover, the use of the Fitbit activity tracker was facilitating and motivating. Cutter et al[47] used video games in the intervention and control groups. Participants in both groups showed high acceptability and satisfaction. Colledge et al[53] reported low adherence in the control group which carried out non-exercise group activities. Adherence was high in the intervention group that completed a training program that the participants themselves were able to determine and influence. Shaffer et al[48] reported a dropout rate of 28% and participants who transferred from the yoga intervention to conventional treatment because they wished for a less demanding and active activity. They also found a lack of staff acceptance of the intervention. Participants in the study by Uebelacker et al[50] showed acceptable levels of satisfaction with the yoga program. Moreover, the PA intervention took place at the OST clinic. The familiarity of the setting may be important for helping participants feel comfortable attending sessions. According to Beitel et al[45] female participants were more likely than male participants to report interest in exercise group participation. Caviness et al[46] found that as age increased, there was also an increase in the endorsement of barriers related to possible injury, poor health, or physical disabilities.

## Discussion

This systematic review raises an important topic of health behavior as a treatment for OUD. There is a lack of studies covering PA interventions and activity status, and this current review is distinct from earlier reviews as it includes both interventional and observational studies.

In general, the overall activity status within OUD is low, with an almost non-existing high-intensity exercise load.[45,54] The general findings of the interventional studies show positive indications for effects on physical fitness, substance use, and mental health. These results should be carefully interpreted because of few high-quality studies within this population. However, they are consistent with findings from other SUD populations.[30,31]

In epidemiological research, the most significant health benefits were observed among training programs of greater duration and/or higher intensity.[11] The studies included in this review delved into a wide range of PA with varying results. Thus, existing literature can not provide sufficient information on the importance of type and intensity of activity as this requires many studies where different PA has been carried out with different intensities.

We found that approximately 30% of people in OST met the global recommendations for PA. Thus, they are roughly at

the same level as the general population.[38] This may be because they walk more and spend less time sitting still. Due to their life circumstances, they have a less sedentary lifestyle than the general population. At the same time, they are at increased risk for mental and physical illnesses. We found that the participants often were satisfied with the interventions and that the interventions themselves were not the main reason for low attendance or dropout.[47,50,51] The most common reasons for non-adherence were health-related issues and substance use relapse.[50,51] Furthermore, a high rate of psychosocial stressors, including low income, homelessness, and transportation problems, can influence the level of adherence.[51,58] The result may be that individuals do not have the surplus energy they need to participate. Abrantes et al[51] pointed out that social determinants are important for the execution of an exercise intervention. By having the exercise sessions at the clinic, participants would be spared extra travel and meeting arrangements. Another facilitating factor could be the provision of training gear, sports equipment, food and drink after the sessions, and help with their smartphone cellular data plans.[51,59] The last one is especially relevant if the intervention includes the wearing of a device or using a smartphone app that tracks daily activity. The use of PA monitors is a cost-effective approach that can reach a wider number of participants. They can register PA throughout the day and include exercise and everyday activities.[60] Abrantes et al[51] reported that participants had positive feedback on the use of the Fitbit. Another facilitator for participation is the integration of PA in OST. Colledge et al[53] reasoned that a longer-term program might lead to an increase in participation, due to increased trust and acceptance of an established program. If an intervention is not tailored to the participants, low motivation, low interest in participation, and low adherence can be the consequences.

This was also reflected in the participation rates of the studies. Many of them had small sample sizes. Despite a large number of available patients at the respective recruitment sites, only a few were able and/or willing to participate. Poor overall health or acute health crises have been stated as the main reasons for nonadherence and dropout and are referred to as barriers to PA,[50,51] although the expectation of improved health has a positive influence on participation.[46] Lack of motivation might also prevent participation.[46] Participants who experience exercise as rewarding and enjoyable are less likely to drop out of the program.[60] Staub et al[59] also concluded that treatment must be tailored to the health conditions of the participants. Exercises that are too challenging can entail low levels of motivation and adherence. In a group setting, different physical abilities can lead to bored participants on the one hand and overburdened ones on the other. Thus, exercise interventions have to be effective in promoting patients' health and simultaneously consider the needs of the participants. The study by Colledge et al[53] implemented patient feedback to design the exercise program and reported only 8% non-compliance. In this regard, it is also important to consider the age and gender of the participants. With increasing age, the barriers for PA might increase as a result of deteriorating health conditions.[46] Women may be more apt to take part in group exercise programs than men.[45]

Administering a structured intervention to persons in OST can be complicated by homelessness, social instability, personal economy, but also overall physical and mental health. Perhaps only the most resourceful patients are recruited due to the nature of interventional studies, and their inclusion and exclusion criteria. Three interventional studies[48,50,53] relied on the health service staff or the principal investigator to decide whether patients should be excluded from the study. They had to infer medical conditions that would make participation difficult or potentially dangerous. In this way, interventional studies are vulnerable to selection bias. Abrantes et al[51] excluded patients with current eating disorders. On the other hand, Mahboub et al[54] found in their observational study that 45% of the participants had a food addiction. People with OUD show an interest in bodily movement if the programs meet their requirements. One review[32] describes the most preferred type of exercise as walking and strength training, and patients would like exercise to be integrated as available in treatment facilities. Involving staff members in the intervention or using a peer-facilitated model could not only be more cost-effective than hiring external instructors but also allow for sustainability of the intervention, as well as raise staff acceptance.[48,51] Shaffer et al[48] reported that the addiction counselors showed a lack of acceptance of the new treatment and seemed to be more interested in the affirmation of established treatment methods. This can lead to poor recruitment and low adherence if the participants do not feel support from their counselors. Peer-facilitated interventions are conceivably the most cost-effective way of integrating PA in OST. Additionally, participants may benefit from being exposed to successful examples of their peers.[60] The self-determination theory identifies relatedness as a basic psychological need necessary to promote motivation.[61] Highprevised relatedness between participants and supervisors may also increase adherence and lower exercise dropout. A prerequisite is that the exercise supervisors receive sufficient training to be competent in the execution of the intervention and to provide constructive feedback. Support and engagement from staff and exercise trainers can be a motivating factor for adherence and participation. Constant reminders of the sessions and confirmation that participants will not be excluded due to some missed sessions are other important factors.[59]

Few studies reported pre and post-data on substance use or symptoms of SUD, such as cravings or abstinence, and thus no meaningful conclusions can be made from this review. Nevertheless, such an important topic should receive more attention in future studies. Exercise interventions show positive mental health outcomes for patients, for example, reducing stress, anxiety, and depression.[45,46,49,50]

Not surprisingly, people who participate in exercise interventions increase their total daily activity level, as well as strength and aerobic fitness. This total increase in physical fitness and activity level was not seen to the same degree in control conditions and, as such, demonstrates the potential of exercise interventions. Instant reward with a relatively low amount and effort is perhaps one of the greatest benefits of exercise as therapy.[62] Although 3 of the interventional studies were designed as pilot studies, their findings are in line with meta-analyses on physical exercise interventions among subjects suffering from various diseases.[31,63,64] PA and exercise show the potential to be an adjunctive therapy for individuals with dependence on opioids to improve health and daily function.

We find a wide range of different outcomes in the included studies, which was also noted in another systematic review on the OST population.[33] As such, there is a need to coordinate a standard in physical function testing, which can increase the use of exercise tests in both research and clinical practice.

Establishing a consensus on physical tests can help close the gap between different medical disciplines and ultimately improve patient treatment. Other medical disciplines could set examples for the input and coordination of similar tests. For instance, many people diagnosed with mental illness or SUD are at increased risk of heart and lung disease. There are other disciplines and professions that could add valuable information to this scope, such as exercise physiologists and physiotherapists.

Notably, a small number of studies were included in the present review. This research field seems thus in its infancy and lacks adequate and proper trials so far. We were unable to conduct a meta-analysis due to the few studies and the heterogeneity between them. The wide range of different methods used to measure and classify PA and the variety of designs made it also difficult to compare studies and perform a meta-analysis.

Another finding was the inconsistency in the measurement and definition of PA in the included studies and the absence of objective measurement of PA. Lack of reporting and description of interventions lowers study quality and increases the degree of bias. The current review highlights the need for researchers in this field to further explore the practice of PA in medication-assisted OUD treatment. A prerequisite for this is the use of appropriate and agreed-upon tools to measure PA to obtain reliable and comparable results. The published research in the area of PA among people in OST is small in quantity and low to moderate in quality. Researchers have tried to systematically analyze PA in SUD treatment before[29,30,33] and have come to the same general conclusion that the research field has to conduct several methodologically comparable studies to reach reliable conclusions. Nonetheless, there has been a rise in interest in this field of study in recent years. Studies should continue to meet higher standards in terms of research design and methodology. In addition, studies with PA should include people with professional exercise competence to design appropriate training interventions.

One limitation of this review is that 2 of the 3 cross-sectional studies had the same study population.[46,49] Another concern that arises due to studies with single-source, self-report, cross-sectional designs is that of common method bias (CMB). CMB occurs when the instrument or measurement method is responsible for variations in responses rather than the actual predispositions of the respondents.[65] Cross-sectional survey study designs are particularly prone to the occurrence of CMB. Other common risks associated with self-reporting are recall and social desirability biases. Only 2 of the 4 cross-sectional studies[46,49] acknowledged potential bias; none of them tested for CMB.

Although the differences between countries can be vast, individuals with an opioid dependence consume a great part of available treatment resources. PA in combination with other types of therapy may effectively reduce withdrawal and abstinence symptoms for OUD.[31] Furthermore, the benefits of PA can have a motivating effect on patients receiving OST.[47]

There are several suppositions as to why PA appears to be effective in the treatment of patients with SUD.[66,67] One key hypothesis is that mastery of one segment of life may "spill over" to other areas.[68,69] The biological monoamine theory states that depression is caused by underactivity of monoamines in the brain, such as dopamine, serotonin, and norepinephrine[18,70] and that exercise increases their levels. The endorphin theory suggests that electrical impulses stimulate the production of endorphins[71] blocking pain messages from reaching the brain. According to the distraction theory, PA provides relief from everyday life hassle[72] whereas the thermogenic theory hypothesis posits that increased temperature through exercise is responsible for mood enhancement.[73] However, none of the theories mentioned above have yet received strong support from empirical data.[66,74,75]

## Conclusions

In conclusion, this systematic review provides insight into the role of physical activity in opioid substitution therapy. We found that increased physical activity positively affects physical fitness, substance use, and mental health in patients with opioid use disorders. These findings are in line with other substance use disorder populations. Furthermore, our findings highlight barriers and facilitators to the implementation of feasible and acceptable PA interventions. PA interventions should meet the needs of individuals enrolled in OST, involve the health service staff, and consider practical aspects that affect the implementation process. This review also showed a lack of standardized interventions and outcomes, a lack of analytical power, and attention to bias in interventional studies on physical activity in opioid substitution therapy. Further research should focus on improving the methodological issues of power and design, but also bridge knowledge into useful adaptions for the group.

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## Author Contributions

SEA coordinated the review and conducted the literature searches. SEA and EF conducted the screenings, extracted the data, and conducted the quality assessments. SEA drafted the manuscript and EF assisted. LTF, SP, AM, and SMD contributed substantially to the conception and design of the review and contributed critical revisions to the manuscript. All authors read, critically reviewed, and approved the final manuscript.

## Availability of Data and Materials

All relevant data are within this paper. If further data are needed, it could be accessed from the first author upon request via e-mail: silvia.eiken.alpers@helse-bergen.no.

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## Supplemental Material

Supplemental material for this article is available online.

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