Impact of Physical Exercise on Substance Use Disorders: A Meta-Analysis

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Abstract

Objective: The goal of this meta-analysis was to examine whether long-term physical exercise could be a potential effective treatment for substance use disorders (SUD).

Methods: The PubMed, Web of Science, Elsevier, CNKI and China Info were searched for randomized controlled trials (RCT) studies in regards to the effects of physical exercise on SUD between the years 1990 and 2013. Four main outcome measures including abstinence rate, withdrawal symptoms, anxiety, and depression were evaluated.

Results: Twenty-two studies were integrated in the meta-analysis. The results indicated that physical exercise can effectively increase the abstinence rate (OR = 1.69 (95% CI: 1.44, 1.99), z = 6.33, p<0.001), ease withdrawal symptoms (SMD = −1.24 (95% CI: −2.46, −0.02), z = −2, p<0.05), and reduce anxiety (SMD = −0.31 (95% CI: −0.45, −0.16), z = −4.12, p<0.001) and depression (SMD = −0.47 (95% CI: −0.80, −0.14), z = −2.76, p<0.01). The physical exercise can more ease the depression symptoms on alcohol and illicit drug abusers than nicotine abusers, and more improve the abstinence rate on illicit drug abusers than the others. Similar treatment effects were found in three categories: exercise intensity, types of exercise, and follow-up periods.

Conclusions: The moderate and high-intensity aerobic exercises, designed according to the Guidelines of American College of Sports Medicine, and the mind-body exercises can be an effective and persistent treatment for those with SUD.

Introduction

Substance abuse, such as alcohol, nicotine, and illicit drugs, is one of the largest public health issues in the world. Figures from the World Health Organization (WHO) show that 25 million people die from alcohol abuse each year, and at least 15.3 million people have substance use disorders (SUD). Moreover, 120 countries have reported cases of HIV infection in drug addicts [1]. Substance abuse also increases the risk of spreading HIV and is an overall detriment to society, family, and individuals [2–4]. Currently, one of the most commonly used treatments for substance addiction is drug replacement therapy, using substances such as methadone or buprenorphine. Both methadone and buprenorphine are long-acting opioid agonists and used to treat opioid addiction, such as heroin, by reducing and/or eliminating the use of substances, relieving craving behavior, suppressing abstinence symptoms, and decreasing substance abuse-associated infective diseases transmission [5,6]. However, like all opioids, both methadone and buprenorphine have risk of addiction and often have potential of drug-drug interactions [7]. Opioid substitutes are also linked to diabetes, nicotine addiction, and premature death [8–10]. Therefore, there is a strong interest in finding alternative treatments for SUD.

In general, physical exercise is characterized as a planned, organized, and repeated body movement that aims to promote or maintain physical fitness [11–13]. The most common physical exercises include aerobics (brisk walking and running) and mind-body exercises (Tai Chi Quan, Qigong, and Yoga). Compared to methadone and buprenorphine drug-replacement therapies, physical exercise has been recognized as a potential add-on treatment for SUD. For example, studies showed that subjects with regular physical exercise showed lower rates of SUD compared to people with less exercise [14], and regular physical exercise in adolescence provided a preventive effect on alcohol and illicit drug use in adulthood [15]. Furthermore, exercise training caused a significant reduction in daily use and craving for cannabis in marijuana-dependent adults [16], and enhanced the healing effect on SUD [17–19]. The positive effects of physical exercise on SUD have also been confirmed in animal experiments. For example, wheel-running can ease withdrawal behavior in mice with...
morphine-addiction [20], while voluntary treadmill exercise [21,22] and mandatory treadmill exercise [23] can reduce cocaine, morphine, nicotine, and alcohol intake in various mouse models [22,24,25].

However, some contradictory findings were reported, such as exercise providing no significant effects on substance abusers. For example, one study reported that a 3-week regimen of aerobic exercise and strength training failed to increase the abstinence rate of alcohol abusers [26], and another study found that a 10-week physical exercise program caused no change in the abstinence rate of smokers or relief for emotional symptoms related to smoking [27]. As there is no clear answer for these controversial findings, more comprehensive analyses of physical exercise, such as the intensity and duration of exercise applied, are needed.

In the past two years, a number of articles reviewed whether physical exercise could be considered as a potential method for treating SUD [13,18,28–35]. These articles included preclinical and clinical literature of physical exercise-induced protective effects on the different transitional phases of SUD. These include the initiation of drug use, the progression from use to addiction, the drug withdrawal and relapse period [29] in alcohol, nicotine and illicit drug use disorders [32], and the improvement of mood and overall life quality of those with SUD [13]. A few articles also reviewed the relationship between various types of physical exercises as promising complementary therapies for SUD [33,34]. To further understand the relationship between physical exercise intervention and SUD, several statistical review articles have analyzed the effects of acute exercise on nicotine addiction. For example, Usher et al. found that physical exercise can effectively intervene in symptoms related to smoking (RR: 0.97–4.96) using meta-analyses on thirteen [36] and fifteen [37] original research articles, while others reported similar results using analyses of individual participant data (IPD) or the systematic review method [38]. Together, these studies provide the support for using physical exercise as a treatment for SUD. However, there is a shortage of important evidence in previously published meta-analyses of physical exercise as treatments in SUD, such as the effect of mind-body exercise or chronic physical exercise on substance addiction with one or polydrugs, as well as a systematic evaluation of randomized controlled trials (RCT). A recent study reported that Yoga, a typical mind-body exercise, may improve mood status and quality of life for women undergoing detoxification for heroin dependence [39]. In addition, subjects who are addicted to more than one drug often develop more complicated symptoms related to the synergistic effect of drug-drug interaction on brain structures and functions [40]. It is known that acute exercise produces different effects on brain function, such as cognition, than long-term routing exercises, which can lead to improvement of object recognition memory and reduction of perceived stress [41]. Indeed, both acute and chronic aerobic exercises have been extensively used to treat SUD. The changes induced by acute exercise can be viewed as a transitory modulation of the arousal physiology [42], while effects of chronic physical exercise are generally explained by structural and durable changes in the organism, such as angiogenesis [43] and neurogenesis [44]. All of these may help to explain the contradictory findings on exercise intervention in SUD.

The aim of this meta-analysis is to verify the treatment effects of chronic physical exercise on various SUD by analyzing the current RCT studies. The abstinence rate, withdrawal symptoms, anxiety levels, and depression levels are included in this meta-analysis as outcomes of treatment. Furthermore, we also included the analyses of exercise intensities, exercise types, and lasting effects of physical exercise on SUD. Lastly, we performed sub-group analyses to provide details of potential optimal physical exercise therapies for specific drug addictions.

**Methods**

This meta-analysis followed the PRISMA guidelines [45] for conducting and reporting systematic reviews.

**Search strategy**

We conducted a search for relevant literature in the following electronic databases: PubMed, Web of Science, Elsevier, China National Knowledge Infrastructure (CNKI), and China Info. The key search words included exercise, physical activity, qigong, tai chi, yoga, heroin, morphine, opioid, opiate, cocaine, methadone, marijuana, cannabis, alcohol, drinker, cigarette, smoke, nicotine, drug abuse, drug dependence, and substance use. The search was limited to Chinese and English literature studying adults (≥18 years old) published from January 1990 to August 2013.

**Study selection and quality assessment**

During reviewing relevant papers, data extraction and analysis complied in accordance to the following standards: (1) The selected papers were studying physical exercise intervention’s effect on drug abuse, excluding preventive studies. (2) All research use RCT. (3) Objects of the study were adults over 18 years old who were assessed as alcohol, nicotine, and illicit drug abusers through the DSM-III(R)/IV. (4) Excluding the studies on acute exercise, we selected results from chronic physical exercise experimental studies. (5) The primary outcome measures in the study included the rate of abstinence from drug addiction, withdrawal symptoms, the level of depression, and anxiety. (6) The baseline of the primary outcome measures in the study and descriptive statistical data after intervention must be obtainable.

The Delphi List Criteria was used to [46] assess the quality of each literature included in the meta-analysis. Our literature evaluation criteria included: randomness of grouping, concealment of treatment allocation, homogeneity of baseline data, clarity of various standards, viability of using the blind method for outcome measurement, assessment tools for the main outcome, and intent treatment analysis. In the current research, items 6 and 7 in the Delphi List are not integrated in the assessment. When measuring the effect of physical exercise on SUD, treatment providers need to guide and monitor patients to execute physical exercise intervention, making a blind method impossible.

**Data extraction and statistical analysis**

We used an Excel spreadsheet to extract the data from the integrated literature. The data included information of participants, intervention of experimental and control groups, types of drug addiction, and primary outcome measurements. We conducted a meta-analysis through the meta package in R software (R 3.0.1 version) [47]. We used the odd ratio (OR) to assess the abstinence rate under two different conditions. Due to different follow-up intervals, we defined follow-up periods of 1–3 months, 4–7 months, and ≥8 months as short, middle, and long term, respectively. We evaluated the treatment effect by measuring abstinence rates at the end of physical exercise and throughout different follow-up periods, and then conducted a sub-group analysis based on different follow-up phases. We also employed the standardized mean difference (SMD) to assess withdrawal symptoms, depression, and anxiety after physical exercise intervention. The confidence interval was set at 95%. A p value less than 0.05 is referred to the level of statistical significance. We used $Q$-test and $I^2$-test to assess heterogeneity. If the p value in $Q$-test was less than 0.05
or if the $I^2$ index in $I^2$-test was more than 50%, the data was judged to achieve heterogeneity [48,49]. If there was heterogeneity, the random effects model was chosen in the meta-analysis; otherwise, the fixed effects model was used. Given the heterogeneity in the study, we rendered sensitivity analysis. We employed the funnel plot visual, Egger’s test, and false safe number ($N_{fs0.05}$) to assess publication bias in the meta-analysis including more than ten papers [50]. In addition, we performed sub-group analysis according to certain characteristics of participants in the studies (physical exercise intensity, physical exercise type, addictive type, and follow-up period).

Authors WYQ and WYY completed the screening of the literature, data extraction, quality analysis, and statistical analysis process independently. Meetings were held regularly to minimize the risk of error in each link. In case of conflicts between two authors in any process, the final decision was made by another author.

**Results**

**Included trials**

Based on the selection criteria, we derived 22 out of 3683 studies for meta-analysis. The flow diagram of identification, screening and the inclusion of studies was shown (see Figure 1). One doctoral dissertation was selected [26], and the original data of one study was provided by contacting the author [51]. Five papers from 22 studies investigated the treatment effects of physical exercise on illicit drug abusers [39,51–54], eleven on nicotine abusers [27,55–64], three on alcohol abusers [26,65,66], and four on polydrug abusers of alcohol, nicotine, and illicit drugs [26,67–69]. Table 1 shows the specific characteristics of the included studies. Among all the studies, abstinence rate was regarded as the primary outcome measure with four reporting only the abstinence rate or abstinence population after physical exercise intervention [52,53,64,67]. Other papers reported abstinence conditions immediately after intervention and in different follow-up periods. Moreover, five papers reported withdrawal symptoms [51–54,57], seven papers described changes in anxiety levels before and after physical exercise intervention [26,27,39,53,54,63,65,66,69], and nine present variety in depression levels before and after physical exercise intervention [26,27,39,53,54,63,65,66,69].

**Methodological Quality of Included Studies**

Delphi List Criteria, which assesses the quality of RCT methodology [46], was used for quality assessment of all studies. Scores of quality ranged from 4 to 7 (see Table 2), which indicated
| Article          | Substance                        | Group    | N   | Age      | Gender | Race                  | Physical Exercise                                                                 | Outcome measure                  |
|------------------|----------------------------------|----------|-----|----------|--------|-----------------------|----------------------------------------------------------------------------------|----------------------------------|
| Burling (1992)   | Illicit drug, alcohol            | Exp      | 34  | 38.8     | F      | 50% Black; 41% Caucasian | Softball                                                                         | Abstinent rate^{a}                |
|                  |                                  | Ctrl     | 61  | NR       | NR     | NR                    | No Exercise                                                                      | NR                               |
| Marcus (1995)    | Nicotine                         | Exp      | 10  | 39       | F      | NR                    | Walking, rowing, cycle ergometry                                                 | Abstinent rate^{a}                |
|                  |                                  | Ctrl     | 10  | 36       | F      | NR                    | Education meeting                                                               | NR                               |
| Donaghy (1997)   | Alcoholic, alcohol               | Exp      | 80  | 41.3     | F      | NR                    | Aerobic exercise, strengthening                                                  | NR                               |
|                  |                                  | Ctrl     | 78  | 41.7     | F      | NR                    | Breathing                                                                        | NR                               |
| Martin (1997)    | Nicotine, alcohol, illicit drug  | Exp      | 72  | 40.5     | F      | 90.4% Caucasian        | Walking                                                                          | NR                               |
|                  |                                  | Ctrl     | 70  | 41.5     | F      | 95.7% Caucasian        | Standard treatment                                                               | NR                               |
| Marcus (1999)    | Nicotine                         | Exp      | 134 | 40.7     | F      | NR                    | Walking, rowing, cycle ergometry                                                 | NR                               |
|                  |                                  | Ctrl     | 147 | 39.7     | F      | NR                    | Education meeting                                                               | NR                               |
| Huang (2000a)    | Heroin                           | Exp      | 60  | NR       | F      | 30% Asia, Chinese      | Jogging                                                                          | 40–70% VO_{2\text{max}}          |
|                  |                                  | Ctrl     | 60  | NR       | F      | 33% Asia, Chinese      | Daily life                                                                       | 7–8 Borg^{c}                     |
| Huang (2000b)    | Heroin                           | Exp      | 60  | 27.0     | F      | 30% Asia, Chinese      | Brisk walking                                                                    | 50–60% VO_{2\text{max}}          |
|                  |                                  | Ctrl     | 50  | 28.2     | F      | 27% Asia, Chinese      | Daily life                                                                       | 9–10 Borg^{c}                     |
| Li (2002)        | Heroin                           | Exp      | 34  | 33.3     | M      | Asia, Chinese          | Qi Gong                                                                          | NR                               |
|                  |                                  | Ctrl     | 26  | 31.7     | M      | Asia, Chinese          | NR                                                                               | NR                               |
| Utshera (2003)   | Nicotine                         | Exp      | 154 | 41.5     | F      | 87.9% Caucasian        | ‘Life-style’ or more structured exercise                                         | 40% HR max                       |
|                  |                                  | Ctrl     | 145 | 44.4     | F      | 87.9% Caucasian        | Health education                                                                  | NR                               |
| Marcus (2005)    | Nicotine                         | Exp      | 109 | 42.5     | F      | 82.5% Caucasian; 6.9% Black | Aerobic training                                                                | 50–69% HR max                    |
|                  |                                  | Ctrl     | 145 | 44.4     | F      | 87.9% Caucasian        | Health education                                                                  | NR                               |

^{a} Abstinent rate; ^{b} HR max; ^{c} VO_{2\text{max}}; ^{d} Borg; ^{e} SAS; SDS; ^{f} MPSS
| Article                  | Substance | Group | N  | Age   | Gender | Race                  | Physical Exercise                        | Outcome measure                        |
|-------------------------|-----------|-------|----|-------|--------|-----------------------|------------------------------------------|-----------------------------------------|
| Vedamurthachar (2006)   | Alcohol   | Ctrl  | 108| 43.0  | F      | 82.5%Caucasian; 6.9%Black | Health education                         | NR                                      |
|                         |           | Exp   | 30 | 35.6  | M      | NR       | Sudarshana Kriya Yoga | NR                                      |
| Sareen (2007)           | Alcohol   | Ctrl  | 30 | 37.7  | M      | NR       | No intervention       | NR                                      |
|                         |           | Exp   | 26 | 50    | 14%F  | NR       | Iyengar Yoga         | NR                                      |
| Prapavessis (2007) [59] | Nicotine  | Ctrl  | 66 | 38.2  | NR    | NR       | Cognitive behavior therapy | NR                                      |
|                         |           | Exp   | 76 | 37.9  | F     | NR       | Walking, rowing, cycle ergometry | 60–75% HR max |
| Vedamurthachar (2006)   | Alcohol   | Ctrl  | 30 | 35.6  | M      | NR       | Usual care            | NR                                      |
|                         |           | Exp   | 26 | 50    | 14%F  | NR       | Walking, rowing, cycle ergometry | 60–75% HR max |
| Prapavessis (2007) [59] | Nicotine  | Ctrl  | 66 | 38.2  | NR    | NR       | Cognitive behavior therapy | NR                                      |
|                         |           | Exp   | 154| 41.5  | 53%F  | 87.9%Caucasian | ‘Life-style’ or more structured exercise | 40% HR max |
| Kinnunen (2008) [61]    | Nicotine  | Ctrl  | 145| 44.4  | 53%F  | 87.9%Caucasian | Health education               | NR                                      |
|                         |           | Exp   | 92 | 38.3  | F     | 81.5%Caucasian | Treadmill                  | 60–80% HR max |
| Vickers (2009) [27]     | Nicotine  | Ctrl  | 30 | 41.8  | F     | 86.7%Caucasian | Sensory control               | NR                                      |
|                         |           | Exp   | 30 | 41.8  | F     | 86.7%Caucasian | Sensory control               | NR                                      |
| Williams (2010) [62]    | Nicotine  | Ctrl  | 30 | 40.9  | F     | 97%Caucasian | Health counseling            | NR                                      |
|                         |           | Exp   | 29 | 41.5  | F     | 83.3%Caucasian | Treadmill                  | 60–75% HR max |
| Li (2013) [54]          | Heroin    | Ctrl  | 16 | 29.6  | F     | Asia/Chinese | Tai Chi                     | NR                                      |
|                         |           | Exp   | 17 | 30.3  | F     | Asia/Chinese | Tai Chi                     | NR                                      |
| Whiteley (2012) [64]    | Nicotine  | Ctrl  | 164| 42.9  | F     | NR       | Wellness session           | NR                                      |
|                         |           | Exp   | 166| 44.1  | F     | NR       | Wellness session           | NR                                      |
| Smelson (2013) [69]     | Cocaine, alcohol | Ctrl | 16 | 29.6  | F     | Asia/Chinese | Daily life                 | NR                                      |
|                         |           | Exp   | 51 | 30.6  | 4%F  | 60%Caucasian; 35%Black | Qi Gong                         | NR                                      |

Abbreviations:
- NR: Not reported
- HR: Heart rate
- STAI: State-Trait Anxiety Inventory
- CESD: Center for Epidemiologic Studies–Depression Scale
- HRSD: Hamilton Rating Scale for Depression
- BDI: Beck Depression Inventory
- POMS: Profile of Mood States
that the bias of the study was relatively low. Some authors did not clearly report the experimental information such as whether the assessment of outcome adopted the blind method, or if sufficient concealment was made in the allocation of participants.

**Effect of physical exercise on abstinence rate**

We conducted a meta-analysis of the abstinence rate for SUD at the end of the physical exercise treatment, the short-term (≤3 months), middle-term (4–7 months) and long-term (≥8 months) follow-up periods after the intervention. The Q test (Q(31) = 36.64, $p = 0.22$) and $I^2$ test ($I^2 = 15.4\%$) revealed no heterogeneity in any of the studies. The meta-analysis of the fixed effects model shows that physical exercise can significantly increase the abstinence rate in subjects with SUD (OR = 1.69 (95% CI: 1.44, 1.99), $z = 6.33, p < 0.001$) (see Figure 2). There was no evidence of publication bias upon using Egger’s test ($z = 1.02, p = 0.31$) and a false safe number ($N_{FAS} = 351$). Table 3 shows the result of sub-group analysis indicating the effect of physical exercise intervention on the abstinence rate in various follow-up periods having no significant differences. The effect of physical exercise intensity and type of physical exercise on abstinence rate is not significantly different. However, there is strong evidence indicating the special effect of physical exercise on various addictive drugs. The treatment effect of physical exercise on drug abusers is better than its effect on alcohol and nicotine abusers (see Table 3).

**Effect of physical exercise on withdrawal symptoms**

We conducted a meta-analysis on withdrawal symptoms in drug abusers after physical exercise intervention. The Q test (Q(4) = 151.4, $p < 0.001$) and $I^2$ test ($I^2 = 97.4\%$) showed heterogeneity in the included studies. We chose the random effects model in meta-analysis and the result indicates that exercise can significantly reduce withdrawal symptoms of SUD (SMD = −1.24 (95% CI: −2.46, −0.02), $z = −2.06, p < 0.05$) (see Figure 3). The sub-group analysis finds that different types of physical exercise affect withdrawal symptoms of SUD differently (see Table 3).

**Effect of physical exercise on anxiety levels in subjects with SUD**

We employed a meta-analysis on anxiety levels in subjects with SUD after physical exercise intervention. No evidence of heterogeneity was found based on the result of the Q test (Q(6) = 4.17, $p = 0.65$) and $I^2$ test ($I^2 = 0\%$). The meta-analysis of the fixed effects model showed that physical exercise can significantly attenuate anxiety symptoms in subjects with SUD (SMD = −0.31 (95% CI: −0.45, −0.16), $z = −4.11, p < 0.001$) (see Figure 4). The sub-group analysis finds that different types of physical exercise do not have significantly different effects on anxiety symptoms of addicts, and physical exercise does not differently influence the anxiety symptoms of all kinds of SUD (see Table 3).

**Effect of physical exercise on depression levels in subjects with SUD**

We conducted a meta-analysis on the depression level in SUD after physical exercise intervention. There was moderate heterogeneity exhibited in the studies demonstrated by the Q test (Q(8) = 31.99, $p < 0.001$) and $I^2$ test ($I^2 = 75\%$). The random effects model meta-analysis showed that physical exercise can significantly relieve depression symptoms in SUD (SMD = −0.47 (95% CI: −0.80, −0.14), $z = −2.76, p < 0.01$) (see Figure 5). The sub-group analysis indicated that the effect of physical exercise on the

| Substance Group | N | Gender | Race | Outcome measure | Artic...
| Study          | Randomization* | Similar at baseline*b | Criteria specified*c | Assessor blinded*d | Allocation concealment*e | Variability outcome*f | ITA*g | Total score |
|---------------|----------------|-----------------------|----------------------|-------------------|--------------------------|-----------------------|-------|-------------|
| Burling (1992) [67] | Unknown        | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Marcus (1995) [55]   | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Donaghy (1997) [26]  | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Martin (1997) [60]  | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | NO    | 5           |
| Marcus (1999) [56]  | YES            | YES                   | YES                  | Yes               | YES                      | YES                   | YES   | 6           |
| Huang (2000a) [52]  | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | NO    | 5           |
| Huang (2000b) [53]  | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 6           |
| Li (2002) [51]       | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Ussher (2003) [57]   | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Marcus (2005) [58]  | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Char (2006) [65]     | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 6           |
| Sareen (2007) [66]   | YES            | YES                   | YES                  | NO                | Unknown                  | YES                   | YES   | 5           |
| Prapavessis (2007) [59] | YES        | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 6           |
| Ussher (2007) [60]   | YES            | YES                   | YES                  | YES               | YES                      | YES                   | YES   | 7           |
| Kinnunen (2008) [61] | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | NO    | 5           |
| Vickers (2009) [27]  | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | NO    | 5           |
| Williams (2010) [62] | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | NO    | 4           |
| Bock (2012) [63]     | YES            | YES                   | YES                  | Unknown           | YES                      | YES                   | YES   | 5           |
| Whiteley (2012) [64] | YES            | YES                   | Unknown             | YES               | YES                      | YES                   | YES   | 6           |
depression symptoms of SUD is not significantly different. However, physical exercise does have a significant relief effect on depression symptoms in alcohol and illicit drug abusers (see Table 3).

Discussion

Summary of main results

Based on our knowledge, our statistical review of physical exercise in SUD is the first meta-analysis article on the treatment effects of chronic physical exercise on alcohol, nicotine, and illicit drugs in human studies. Our meta-analysis assesses the effects of various forms of physical exercises on SUD in the following four aspects: abstinence rate, withdrawal symptoms, anxiety, and depression level. Compared to the treatment effects on alcohol and nicotine abusers, chronic physical exercises can better increase the abstinence rate in illicit drugs abusers. Meanwhile, physical exercise (aerobic exercise and mind-body exercise) can effectively attenuate withdrawal symptoms and ease anxiety symptoms in alcohol, nicotine and illicit drug addictions, while physical exercise-induced improvement of depression symptoms was only observed in illicit drug abusers. Furthermore, there are no significant differences in exercise-induced treatment on SUD between exercise types (aerobics vs. mind-body exercise), nor among different levels of physical exercise intensities (low, moderate, and high intensity). Overall, physical exercise can effectively assist abusers with withdrawing from addictive drugs. The result of this meta-analysis is not only consistent with the previous meta-analysis results from a single acute physical exercise treatment for SUD [38,70], but it also complies with the result of several review articles [18,29,32].

Specificity of physical exercise on different addictive drugs. There are three types of addictive substances included in this analysis. They are alcohol, nicotine, and illicit drugs that induce strong dependence in human beings and could result in abuse. Since the different addictive mechanisms of these three substances may be involved, we performed sub-group analyses on each addictive substance independently. Indeed, we found that exercise affects the abstinence rate of illicit drugs more than that of alcohol and nicotine abuse. The possible cause for this result may be the difference in addictive mechanisms for each of the three addictive substances. For example, opioid drugs (morphine, heroin, etc.) take effect through β-endorphin neurotransmitters activating the μ and δ opium receptors [71]. Alcohol takes effect through promoting the reaction of the GABAA receptor [72] and increasing stimulation to the dopamine and opiate receptor [73,74]. Nicotine takes effect through acetylcholine neurotransmitters activating the α2β4nACh receptor [75–77].

Physical exercise intensity for effectively treating drug abuse. The sub-group analysis indicated no significant difference in the abstinence rate among low-, moderate-, and high-intensity long-term physical exercise. It is mean that all three exercise intensities induce similar levels of abstinence rate reduction in alcohol, nicotine and illicit drug abusers. Correspondingly, non-RCT studies presented that long-term treadmill exercise at moderate-intensity (55–69% HR max) can effectively ease the craving for cannabis [16] and increase abstinence rate of other drugs in SUD [17]. And non-RCT studies also show that high- and moderate-intensity long-term physical exercise can significantly treat alcohol abuse. A pilot study on the treatment effects of aerobics on alcohol abusers [78] reported that 35 minutes of moderate- (HR = 50–60% VO2max) to high-intensity (HR = 80–90% VO2max) physical exercise for six weeks, can significantly reduce depression symptoms in alcohol abusers.
Another cross-over design study showed that moderate-intensity fast walking can significantly enhance self-management techniques in alcohol abusers [79,80]. The results of the above-mentioned study further proved the findings of our meta-analysis. While the mechanisms underlying these results remain unclear, moderate- and high-intensity aerobic exercises have significant effects on SUD. Mind-body exercises are included as low-intensity physical exercise in this meta-analysis. Due to the different nature of mind-body exercises compared to classical running and walking, we have included the analyses of mind-body exercises in SUD independently in the sections below.

**Persistency of treatment effects of physical exercise on SUD.** To investigate the long lasting effects of exercise on SUD, we conducted a sub-group analysis to evaluate the treatment effects of physical exercise in different follow-up periods. As shown in Table 3, there is no significant difference in exercise-induced reduction of the abstinence rate among the different follow-up periods, suggesting that physical exercise leaves a long lasting treatment effect on SUD. The results of two meta-analyses [36,37]

| Study               | Experimental Events Total | Control Events Total | Odds Ratio | OR  | 95%-CI W(fixed) |
|---------------------|---------------------------|----------------------|------------|-----|-----------------|
| Burling,1992 short  | 21                        | 34                   | 34         | 82  | 2.28 [1.01; 5.17]| 3.4% |
| Marcus,1995 end     | 3                         | 10                   | 1          | 10  | 3.86 [0.33; 45.57]| 0.3% |
| Marcus,1995 long    | 3                         | 10                   | 1          | 10  | 3.86 [0.33; 45.57]| 0.3% |
| Donaghy,1997 middle | 10                        | 20                   | 8          | 21  | 1.62 [0.47; 5.63]| 1.7% |
| Donaghy,1997 short  | 11                        | 35                   | 9          | 29  | 1.02 [0.35; 2.95]| 3.0% |
| Martin,1997 end     | 19                        | 72                   | 22         | 70  | 3.24 [1.62; 6.45]| 4.0% |
| Martin,1997 middle  | 21                        | 72                   | 15         | 70  | 1.51 [0.70; 3.24]| 4.7% |
| Martin,1997 long    | 19                        | 72                   | 18         | 70  | 1.04 [0.49; 2.19]| 5.9% |
| Marcus,1999 end     | 26                        | 134                  | 15         | 147 | 2.12 [1.07; 4.20]| 5.1% |
| Marcus,1999 short   | 22                        | 134                  | 12         | 147 | 2.21 [1.05; 4.66]| 4.2% |
| Marcus,1999 long    | 16                        | 134                  | 8          | 147 | 2.36 [0.97; 5.70]| 3.0% |
| Huang,2000a long    | 15                        | 38                   | 4          | 51  | 7.66 [2.28; 25.71]| 0.9% |
| Huang,2000b long    | 27                        | 60                   | 6          | 50  | 6.00 [2.22; 16.20]| 1.6% |
| Ussher,2003 end     | 73                        | 154                  | 63         | 145 | 1.17 [0.74; 1.85]| 15.0% |
| Marcus,2005 end     | 16                        | 109                  | 12         | 108 | 1.38 [0.62; 3.07]| 4.5% |
| Marcus,2005 short   | 8                         | 109                  | 4          | 108 | 2.06 [0.60; 7.05]| 1.6% |
| Marcus,2005 long    | 1                         | 109                  | 1          | 108 | 0.99 [0.06; 16.04]| 0.4% |
| Prapavessis,2007 end| 17                        | 49                   | 16         | 59  | 1.43 [0.63; 3.25]| 4.2% |
| Prapavessis,2007 short| 7                         | 20                   | 9          | 33  | 1.44 [0.43; 4.75]| 1.9% |
| Prapavessis,2007 long| 3                         | 9                    | 4          | 15  | 1.38 [0.23; 8.30]| 0.9% |
| Ussher,2007 long    | 14                        | 154                  | 18         | 145 | 0.71 [0.34; 1.48]| 7.4% |
| Kinnunen,2008 end   | 22                        | 92                   | 5          | 34  | 1.85 [0.64; 5.36]| 2.4% |
| Kinnunen,2008 long  | 9                         | 92                   | 2          | 34  | 1.73 [0.36; 8.47]| 1.2% |
| Vickers,2009 end    | 3                         | 19                   | 4          | 20  | 0.75 [0.14; 3.90]| 1.4% |
| Williams,2010 end   | 10                        | 29                   | 5          | 30  | 2.63 [0.77; 9.99]| 1.4% |
| Williams,2010 short| 6                         | 29                   | 4          | 30  | 1.70 [0.42; 6.77]| 1.4% |
| Bock,2012 end       | 15                        | 32                   | 4          | 23  | 4.19 [1.16; 15.11]| 1.1% |
| Bock,2012 short     | 7                         | 32                   | 2          | 23  | 2.94 [0.55; 15.70]| 0.8% |
| Bock,2012 middle    | 7                         | 32                   | 3          | 23  | 1.87 [0.43; 8.16]| 1.2% |
| Whiteley,2012 end   | 23                        | 166                  | 23         | 164 | 0.99 [0.53; 1.84]| 8.8% |
| Whiteley,2012 short | 12                        | 166                  | 9          | 164 | 1.34 [0.55; 3.28]| 3.7% |
| Whiteley,2012 middle| 10                        | 166                  | 6          | 164 | 1.69 [0.60; 4.76]| 2.5% |

**Fixed effect model**

- 2392
- 2334

Heterogeneity: I-squared=15.4%, tau-squared=0.0426, p=0.2234

**Figure 2. The forest plot about the effect of physical exercise on abstinence rate.** The abstinence rate of past physical exercise treat, and differences follow-up periods were used odds ratio analysis.

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Table 3. Sub-group analysis results.

| Sample size | N of studies | Meta-analytic effect size | Heterogeneity |
|-------------|--------------|---------------------------|---------------|
| (Exp/Ctrl)  | SMD/OR(95%-CI) | Q(d.f.) | p | I² | Q |

### Abstinence rate

#### Intensity type

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| low  | 96/69       | 3            | 2.96(1.29,6.83) | 1.91(2) | 0.3841 | 0% | 0.66 |
| moderate | 1193/1244   | 19           | 1.62(1.32,1.98) | 36.8% | 28.49 |
| high | 1103/1021   | 10           | 1.71(1.28,2.29) | 0% | 5.47 |

#### Physical exercise type

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| aerobic Ex | 2296/2265 | 29 | 1.65(1.40,1.95) | 1.82(1) | 0.177 | 17.9% | 34.10 |
| mind-body Ex | 96/69 | 3 | 2.96(1.29,6.83) | 0% | 0.66 |

#### Follow-up period

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| end | 865/810 | 11 | 1.60(1.26,2.02) | 0.57(3) | 0.9027 | 23.8% | 13.12 |
| short-term | 559/616 | 8 | 1.79(1.25,2.56) | 0% | 2.65 |
| middle-term | 290/278 | 4 | 1.62(0.96,2.71) | 0% | 0.07 |
| long-term | 678/630 | 9 | 1.84(1.30,2.59) | 60.9% | 20.45 |

#### Addict type

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| alcohol | 271/260 | 5 | 1.65(1.42,2.39) | 11.51(2) | 0.0032** | 33.1% | 5.98 |
| illicit drug | 132/183 | 3 | 4.13(2.39,7.14) | 0% | 3.56 |
| nicotine | 1989/1891 | 24 | 1.51(1.24,1.83) | 0% | 16.40 |

### Withdrawal symptoms

#### Physical exercise type

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| aerobic Ex | 274/255 | 3 | −1.67(−3.51,0.17) | 0.71 (1) | 0.399 | 98.5% | 2.59 |
| mind-body Ex | 51/42 | 2 | −0.61(−2.25,1.03) | 0% | 1.30 |

#### Anxiety

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| alcohol | 61/55 | 2 | −0.21(−0.58,0.16) | 1.03(2) | 0.5975 | 37.9% | 1.61 |
| illicit drug | 145/126 | 3 | −0.40(−0.64,−0.16) | 0% | 1.41 |
| nicotine | 186/168 | 2 | −0.26(−0.47,−0.05) | 0% | 0.13 |

#### Depression

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| aerobic Ex | 249/224 | 3 | −0.23(−0.47,−0.11) | 0.06(1) | 0.8065 | 21.1% | 2.54 |
| mind-body Ex | 143/125 | 4 | −0.33(−0.57,−0.09) | 0% | 1.57 |

### Physical exercise type

| Type | Sample Size | N of studies | SMD/OR(95%-CI) | p | I² | Q |
|------|-------------|--------------|----------------|---|----|---|
| aerobic Ex | 132/117 | 3 | −0.43(−0.84,−0.03) | 0.04(1) | 0.838 | 59.4% | 4.93 |
| mind-body Ex | 186/175 | 6 | −0.50(−1.00,−0.01) | 0% | 27.03 |
studies have also shown obvious treatment effects in 3 and 12 months follow-up periods. These results are likely due to the long lasting effect of physical exercise on changes in brain structure and function. For instance, studies showed that physical exercise can regulate the gene transcription of endogenous opioid brain-derived neurotrophic factor (BDNF) by activating the cyclic AMP response element-binding (CREB) protein [81] and synaptic plasticity [82,83], which is critical for rehabilitation for patients with SUD via promoting repair of drug-induced neuronal damage [84] and improving corresponding brain functions [85]. This neuronal structural change induced by exercises might contribute a long lasting effect on SUD.

Different effects of various forms of physical exercises. In addition to aerobic exercises, mind-body exercises are also acceptable and easy to apply in treatment for drug abuse. The sub-group analysis showed that mind-body exercises and aerobic exercises induce similar beneficial effects on the abstinence rate, withdrawal symptoms, anxiety, and depression levels in subjects with SUD (see Table 3). The outcome from our analysis is consistent with previously published literatures, suggesting that mind-body exercises can also effectively facilitate the treatment of drug addiction [35].

In terms of exercise intensity, some studies have shown that the intensity of Tai Chi Quan is about 52–63% HR max [86], which is similar to low- or moderate-intensity aerobic exercises [87–89]. Meanwhile, Qigong [90] and Yoga [91,92] are also regarded as low- and moderate-intensity physical exercises. Therefore, both mind-body exercise and aerobic exercise show similar beneficial effects on drug addiction when administered at low- or moderate-intensities as shown in Table 3. In addition to exercise intensity, the particular characteristics of mind-body exercise, namely meditation and breathing exercises, may be the key reasons for producing significant exercise effectiveness [93,94].

Physical exercise inducing emotional improvement in SUD. The meta-analysis indicates that physical exercise can effectively ease anxiety and depression symptoms in subjects with SUD. The sub-group analysis shows that physical exercises reduce anxiety symptoms in nicotine, alcohol and illicit drug abusers, while significant exercise-induced improvement on depression symptoms was only found in alcohol and illicit drug abusers (see Table 3). Our findings are consistent with previously published review articles which also found that physical exercise can effectively ease anxiety symptoms in subjects with SUD [29,32,95]. However, we also included three studies that reported that physical exercise did not reduce depression symptoms in nicotine and alcohol abusers [27,63]. As the number of the RCT studies included in our meta-analysis is limited, it is insufficient to make a valid conclusion of whether exercise reduces depression symptoms in subjects with SUD. However, some review articles claim that physical exercise could attenuate depression symptoms in alcohol and nicotine abusers based on non-RCT studies [32,70]. Hence, subsequent studies are needed for further evidence of the effect of exercise on altering depression symptoms in SUD.

Limitations

There are some limitations that need to be considered in the current meta-analysis: (1) Addictive drugs involved in the studies often include participants with polydrug use disorders. Therefore, the specific treatment of exercise on a single drug abuse is difficult to analyze. Because there are insufficient RCT studies on exercise as an intervention for alcohol and drug abuse, the results in the present meta-analysis study may need further investigation. (2) Due to the limitation of available studies, only published RCT studies from 1990 to 2013 were included. There were no
Figure 3. The forest plot about the effect of physical exercise on withdrawal symptoms.

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Figure 4. The forest plot about the effect of physical exercise on anxiety status.

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Figure 5. The forest plot about the effect of physical exercise on depression status.

doi:10.1371/journal.pone.0110728.g005
unpublished papers and dissertations found. These limitations in the literature collection may cause publishing bias. (3) Some papers lack clear explanations on the study information. Such limitation affected the quality of study and the assessment of clinic-relevant data. (4) In the research, some studies comprised of mostly female participants, whereas male participants accounted for only a small part. We were unable to evaluate the differences in gender through a statistical method due to difficulty in obtaining individual data. Accordingly, compared with males, female participants have more difficulty in giving up drug addiction [95]. (5) The main outcome indices in meta-analysis include abstinence rate, withdrawal symptoms, anxiety, and depression levels; the assessment tools in the literature also varied. (6) The included studies have some risk of bias. Lacking of assessor blinding and allocation concealment was the most frequent shortcoming of these studies (See Table 2). Other limitations included the small sample size of two studies [54,55]. Although we adopted some methods (e.g., continuous variable adopts standardization mean difference method) for the assessment, certain biases listed above still exist.

Conclusions

The current meta-analysis provides strong evidence that physical exercise can be an effective adjunct treatment method for abstinence from alcohol, nicotine, and illicit drugs in abusers. Physical exercise not only increases the abstinence rate in subjects with SUD, but also eases withdrawal symptoms, anxiety, and depression symptoms. The treatment effects of physical exercise in these four aspects verify that physical exercise guidance by the American College of Sports Medicine (ACSM) [12] is an effective means for drug abstinence. Additionally, mind-body exercises (including Tai Chi Quan, Qi gong, and Yoga) have similar treatment effects as to aerobic exercise. Although physical exercise has been proven effective in facilitating drug abstinence, its effects on alcohol, nicotine and illicit drug abusers are different. From the results of the meta-analysis, the effects of physical exercise on illicit drugs abusers are significantly greater compared to the others. Given the limitation of materials, these issues require further investigation.

Supporting Information

Checklist S1 PRISMA Checklist.

(DOC)

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Author Contributions

Conceived and designed the experiments: DSW CLZ RL. Performed the experiments: DSW YQW YYW. Analyzed the data: DSW. Contributed reagents/materials/analysis tools: DSW YQW YYW. Wrote the paper: DSW RL YQW.

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