**Effect of Physical Exercise on Sleep Quality in Elderly Adults: A Systematic Review with a Meta-Analysis of Controlled and Randomized Studies**

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**Abstract:** Introduction: Aging is directly related to sleep problems. Primary insomnia has a negative impact on the lives of elderly adults, altering cognitive and metabolic functions. Physical activity is positively related to improvement in sleep quality. The objective of this systematic review was to analyze the effects of physical activity programs in healthy elderly individuals aged 60 years or older, using the Pittsburgh Sleep Quality Index (PSQI) as a tool. Methods: The search was performed in the PubMed and Scielo databases, July 2021. Only randomized clinical trials that evaluated the role of physical exercise in the sleep quality of elderly patients were selected by two independent reviewers. Results: The result of the PSQI analysis showed that compared with the control condition, the exercise intervention was beneficial for the groups with insomnia (SMD: −0.59; 95% CI: −0.70 to −0.49; p < 0.00001; \( I^2 = 53\% \)) and without insomnia (SMD: −0.61; 95% CI: −0.75 to −0.47; p < 0.00001; \( I^2 = 73\% \)) and for the two groups combined (SMD: −0.57; 95% CI: −0.61 to −0.53; p = 0.0002; \( I^2 = 53\% \)) and without insomnia (SMD: −0.61; 95% CI: −0.75 to −0.47; p < 0.00001; \( I^2 = 73\% \)) and for the two groups combined (SMD: −0.59; 95% CI: −0.70 to −0.49; p < 0.00001; \( I^2 = 68\% \)). Conclusion: The systematic and continuous practice of physical exercise significantly improves perceived sleep quality in elderly individuals. Therefore, physical activities can be used as a tool to prevent sleep disorders and improve health in general. Future studies may clarify the comparison between aerobic and resistance exercises, evaluate the dose–response relationship and include more participants.

**Keywords:** physical exercise; elderly; aging; sleep; sleep wake disorders; circadian rhythm

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**1. Introduction**

The increased longevity of the world’s population is related to changes in sleep patterns [1]. These changes serve as a tool for assessing the quality of life and are directly linked to some organic issues, such as physical and mental health, well-being and general vitality [2]. Many studies show that changes in sleep patterns have a negative impact on cognitive function and quality of life [3].

Aging can be characterized as a time-dependent process of losing organic functions, and the brain is not spared. Sleep, dependent on several pathways and mechanisms, also has its full functioning altered [4]. The ability to initiate and maintain sleep is compromised, and the electroencephalogram shows less deep sleep. These changes may be associated with reduced white matter density, reduced gray matter volume in some regions, diminishment in functional synapses and impact on the production and degradation of neurotransmitters and neuropeptides [4,5].
Middle age is directly related to an increased prevalence of common sleep problems, such as insomnia [6]. Sleep patterns change with aging. The duration of the more superficial phases of sleep increases, while the durations of deep and Rapid Eye Movement (REM) sleep decrease. For this reason, sleep is less restorative for elderly adults, and they are more vulnerable to being awakened by external stimuli [7]. The production of melatonin, an important regulator of sleep, is decreased in the elderly [8].

The association between insomnia and decreased quality of life is most notable in elderly adults [7]. Sleep disorders affect metabolism, causing weight gain between early adulthood and old age and simultaneously promoting metabolic and immunological disorganization and the resulting emergence of some diseases, such as hypertension, diabetes mellitus, cancer and depression [8].

Sleep disorders are underdiagnosed and undertreated, and more than half of the individuals affected do not receive any type of treatment to resolve the condition [9]. The approach to insomnia in elderly adults is usually complex and multifactorial. In addition to primary insomnia, adverse effects of drugs, psychiatric diseases and other comorbidities can be direct or aggravating causes. Conventional treatment consists of mitigating secondary causes, cognitive-behavioral therapy and medications. However, the risk of treatment failure is still high, and the main drug treatments cause side effects such as dizziness, memory loss, falls, daytime sleepiness and disinhibition [10]. There are less expensive and effective ways to treat this problem that can be added to conventional treatment.

The performance of physical exercise is a positive step toward changes in lifestyle and may comprise a nonpharmacological treatment for sleep disorders and their organic consequences [11]. One way to evaluate sleep quality is using the Pittsburgh Sleep Quality Index (PSQI). This index evaluates sleep quality through a standardized questionnaire consisting of 19 items grouped into 7 components based on sleep in the past month and is able to differentiate between those who sleep well and those who sleep poorly [12].

Previous meta-analyses suggest that elderly people who exercise constantly have better sleep quality and less insomnia compared to elderly people who do not regularly exercise [13,14]. This article aims to perform an updated meta-analysis to survey the effects of physical activity programs on the quality of sleep in healthy elderly individuals aged 60 years or older, using the PSQI as a tool.

2. Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria for systematic reviews [15,16]. The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with ID number 271071.

2.1. Eligibility Criteria

The inclusion criteria for this study were as follows: (1) studies characterized as randomized clinical trials; (2) studies that included individuals aged 60 years or older; (3) clinical trials that included physical exercise as an intervention; (4) any year of publication; and (5) only studies that evaluated the outcome using the PSQI questionnaire for sleep quality. Clinical trials were excluded if they had the following characteristics: (1) participants had comorbidities or systemic diseases (diabetes, hypertension, dementia, etc.), with the exception of primary insomnia; (2) interventions targeting specific comorbidities (such as respiratory therapy, physical therapy for osteoarthritis, etc.); and (3) publication language other than English.

2.2. Data Source and Search Strategies

Studies with the potential to be included in this review were obtained by searching electronic databases. During the search, the PubMed and SciELO databases were consulted; the first was searched up to 21 June 2021, and the second was searched up to 9 July 2021. The descriptors “aged”, “exercise”, and “sleep” were combined using the Boolean operator
AND. Duplicate articles were removed manually. In PubMed, the filter for obtaining randomized clinical trials was used.

A total of 4653 articles were identified using the descriptors. After duplicate articles were removed, 4620 articles remained. By limiting the study to randomized clinical trials, 689 articles were obtained. Subsequently, 17 articles were considered eligible according to the inclusion criteria. Finally, 12 articles were included in the meta-analysis, and among these, 3 included at least two intervention arms [17–19]. Each intervention arm and the specific exercise used is described in Table 1.

2.3. Selection of Clinical Trials

Two independent reviewers (MH and VP) reviewed the clinical trials to verify whether they met the eligibility criteria. The results that they obtained were reviewed by another reviewer (VLS), and disagreements regarding the inclusion of a clinical trial were resolved by discussion.

2.4. Data Collection

Relevant data were collected by two reviewers (JP, JVM) and reviewed by another author (OA). A standardized table was created using an Excel spreadsheet, as described in the Cochrane Handbook for Systematic Reviews of Interventions. The collected data were the characteristics of the participants involved (age, sex and health conditions), the characteristics of the intervention (type of exercise, intensity, frequency and duration) and outcome data on sleep quality (sample size and the postintervention PSQI scores of the control and exercise groups).

We used articles that reported the PSQI scores as means and standard deviations. We contacted the authors of studies that presented insufficient data in their reviews. After this contact, clinical trials that still presented insufficient data or did not meet the necessary standard were excluded from this review.

The dropout values of the control and exercise groups were compared to assess the adverse effects of physical exercise.
Table 1. Characteristics of the included studies.

| Study (Year) Location | Population Condition | Sample Size (n) E/C | Sex (Male, %) | Age Mean (SD) | Intervention Group | Control Group | Duration (Weeks) | Results * |
|----------------------|----------------------|---------------------|--------------|--------------|--------------------|---------------|------------------|-----------|
| Almazán [20] (2019) Spain | Healthy postmenopausal woman | E: 55 C: 55 | E: 0% C: 0% | E: 69.98 (7.8) C: 66.8 (10.1) | Pilates (1 h, 2 times a week) | No intervention | 12 | E > C ** |
| Baker [17] (2020) USA SSSH | Healthy older adults | E: 20 C: 20 | 76% | E: 68.2 (6.7) C: 67.6 (6.9) | SSSH (1 h, 2 times a week) | No intervention | 8 | E > C |
| Baker [17] (2020) USA Walk | Healthy older adults | E: 20 C: 20 | 76% | E: 68.6 (8.7) C: 67.6 (6.9) | Walking (1 h, 2 times a week) | No intervention | 8 | E > C |
| Chen [21] (2009) Taiwan | Healthy older adults | E: 62 C: 66 | E: 83.87% C: 62.12% | E: 70.5 (7.9) C: 73.0 (8.3) | Baduanjin exercise (30 min, 3 times a week) | No intervention | 24 (6 months) | E > C |
| Chen [22] (2012) Taiwan | Healthy older adults | E: 27 C: 28 | E: 37% C: 32.1% | E: 71.0 (5.7) C: 71.8 (6.7) | Baduanjin exercise (45 min, 5 times a week) | Usual lifestyle behavior | 12 | E > C |
| Fan [23] (2020) China | Healthy older adults with PSQI ≥ 5 and insomnia | E: 67 C: 72 | E: 17.9% C: 30.6% | E: 70.3 (5.7) C: 71.8 (6.7) | Baduanjin exercise (45 min, 5 times a week) | Usual lifestyle behavior | 24 | E > C |
| Garcia [18] (2021) Spain HIIT | Healthy older adults | E: 28 C: 27 | E: 37.8% C: 47.1% | E: 68.2 (3.0) C: 68.5 (6.3) | HIIT (1 h/day, 2 times a week) | Daily activities | 12 | E > C |
| Garcia [18] (2021) Spain MIIT | Healthy older adults | E: 27 C: 27 | E: 41.2% C: 47.1% | E: 68.7 (6.0) C: 68.5 (6.3) | MIIT (1 h/day, 2 times a week) | Daily activities | 12 | No significant difference |
| Hosseini [24] (2011) Iran | Healthy older adults | E: 31 C: 31 | E: 51.6% C: 45.1% | E: 68.7 (5.5) C: 69.4 (5.3) | Tai chi (5–25 min, 3 times a week) | No intervention | 12 | E > C |
| Hsiao [25] (2018) Taiwan | Healthy older adults | E: 106 C: 114 | E: 17.7% C: 25.2% | E: 74.6 (6.0) C: 73.9 (5.4) | Healthy Beat Acupunch (40 min, 3 times a week) | Daily activities | 52 (12 months) | E > C |
| Karimi [26] (2016) Iran | Older adults with primary insomnia | E: 23 C: 23 | E: 100% C: 100% | E: 66.8 (3.8) C: 67.5 (4.3) | Walking (30 min, 3 times a week) | Usual lifestyle behavior | 8 | E > C |
| Nguyen [27] (2012) Vietnam | Healthy older adults | E: 48 C: 48 | E: 50% C: 50% | E: 69.3 (5.3) C: 68.7 (4.9) | Tai chi (1 h/day, 2 times a week) | Daily activities | 26 (6 months) | E > C |
| Schega [28] (2013) Germany | Healthy older adults | E: 17 C: 17 | E: 30.76% C: 30.76% | E: 63.7 (3.4) C: 63.6 (3.2) | Hypoxia and resistance training (45 min protocol, 3 times a week) | Placebo air mixture | 6 | E > C |
| Su [19] (2021) China Conventional exercise | Older adults with insomnia | E: 105 C: 100 | E: 20% C: 20% | E: 67.3 (5.7) C: 68.0 (8.2) | Brisk walking and muscle-strengthening exercises (1 h/day, 3 times a week) | No intervention | 12 | E > C |
| Su [19] (2021) China Tai chi | Older adults with insomnia | E: 105 C: 100 | E: 20% C: 20% | E: 67.3 (5.7) C: 68.0 (8.2) | Tai chi (1 h/day, 3 times a week) | No intervention | 12 | E > C |

Exercise group (E); control group (C); Pittsburgh Sleep Quality Index (PSQI); high-intensity interval training program (HIIT); moderate-intensity interval training program (MIIT); Stay Strong, Stay Healthy training program (SSSSH) * Numerical results are presented in Figure 3 ** E > C was considered when p < 0.05.
2.5. Assessment of Risk of Bias

Two authors (VLB and JVZ) independently investigated the risk of bias in each group. Differences in opinion regarding the evaluation of each study were discussed between these authors until they reached a consensus. The risk of bias was measured using the Cochrane Risk of Bias Assessment Tool [29] and is reported in Figure 1.

![Figure 1](https://example.com/figure1.png)

Figure 1. (A) Risk of bias for each RCT included low risk of bias (+), high risk of bias (−) and unclear risk of bias (?). (B) Bar chart comparing the risk of bias percentage for each included RCT.

2.6. Data Analysis

The main outcome evaluated was the PSQI measurement of sleep quality. The analysis was performed using RevMan 5 Software (available for free from the website https://training.cochrane.org/online-learning/ accessed on 10 October 2021), which was used to generate a forest plot in which the participants were divided into groups with and without complaints of insomnia. The treatment effect was calculated using the standardized mean difference (SMD) and the 95% confidence interval for the post-intervention PSQI values of the control and exercise groups.

Student’s t-test for independent variables was performed to investigate possible significant differences in the dropout percentage between the control group and the exercise group. Possible publication bias was investigated using visual inspection of the funnel plot and Egger’s test [30,31].

The heterogeneity among the studies was evaluated using the I² test. High heterogeneity among the studies is indicated by an I² > 50%. A sensitivity analysis was performed to evaluate the contribution of each study to the heterogeneity. One article was removed at a time, including those with a higher risk of bias.

The statistical power of this meta-analysis was assessed using the Meta Power Calculator software (available for free on https://jtiebel.shinyapps.io/MetaPowerCalculator/ accessed on 31 March 2022). A study is deemed to be large powered if it has a statistical
power of 0.8, considering a significance level, $\alpha$, of 0.05 [32,33]. Finally, the quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [34].

3. Results

3.1. Article Selection and Bias Analysis

Of a total of 4653 studies, 17 met the inclusion criteria, and 12 randomized clinical trials were analyzed. The study selection process is shown in Figure 2. Five of the 17 initially eligible studies were excluded from the present review: two studies presented insufficient data because they did not provide postintervention PSQI scores [35,36], and three articles did not include necessary data, including one that did not provide PSQI data [37], one that did not present a specific physical exercise intervention [38] and one that did not include a control group that did not receive an intervention because it compared two forms of exercise [39].

Three out of twelve studies analyzed had two intervention groups. As a way of simplifying the visualization of the results, we choose to divide these studies into two. For this reason, Table 1 and Figures 1, 3 and 4 show 15 studies in their outputs. The divided studies are Siu et al., 2021 (Exe and Tai), Baker et al., 2020 (SSSH and Walk), García et al., 2021 (HIIT and MIIT), and its features are explained in the next section.

The risk of bias was evaluated using the Cochrane Risk of Bias Tool 2 (RoB 2), and the result is shown in Figure 1. Figure 1A summarizes the risk of bias in each study. Figure 1B shows the risk of bias of all of the RCTs included in the study in a table that presents the reviewers’ assessments. All of the studies had a high risk of bias, and the domains with the highest risk of bias were “performance bias” and “other bias”.

Figure 2. PRISMA flow diagram of the selected studies. Randomized controlled trials (RCTs).
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training (MIIT) and Stay Strong and Stay Healthy (SSSH) program exercises, which included
other comorbidities.

749 were included in the control groups. The study participants included men and women,
there were 1482 participants, of whom 733 were included in the intervention groups and

Funnel plot showing publication bias for depression.

Figure 3. Forest plot showing the standardized mean difference in PSQI scores between the exercise
group and the control group.

Figure 4. Funnel plot showing publication bias for depression.

3.2. Study Characteristics

The main characteristics of the included studies are summarized in Table 1. The studies
had a minimum duration of 6 weeks and a maximum duration of 52 weeks (1 year). In total,
there were 1482 participants, of whom 733 were included in the intervention groups and
749 were included in the control groups. The study participants included men and women,
elderly individuals, individuals with or without sleep disorders and individuals without
other comorbidities.

The intervention protocols included walking, resistance exercise (Exe), yoga, tai chi
(Tai), Baduanjin, Pilates, high-intensity interval training (HIIT), medium-intensity interval
training (MIIT) and Stay Strong and Stay Healthy (SSSH) program exercises, which included
gymnastics, flexibility and balance exercises.
3.3. Effect of Physical Exercise on Sleep Quality

The outcome of interest of this review and meta-analysis was the effect of physical exercise on the sleep quality of elderly individuals, based on the postexposure PSQI score of the control and exercise groups. The graph in Figure 3 shows the SMD, and the left (negative) side of the graph favors the exercise group. This is because the lower the PSQI score is, the higher the sleep quality. As Figure 3 shows, physical exercise alone was able to improve sleep quality in patients with and without complaints of insomnia. An effect in favor of intervention for all groups was identified in the meta-analysis. For patients with insomnia, a significant decrease in the PSQI score was found in the exercise group (SMD: $-0.57; 95\%\ CI: -0.73$ to $-0.4; p < 0.00001; I^2 = 53\%$); for patients without insomnia, there was also a significant decrease in the PSQI score in the exercise group compared to the control group (SMD: $-0.61; 95\%\ CI: -0.75$ to $-0.47; p < 0.00001; I^2 = 73\%$). For the two groups combined, a significant reduction in the PSQI score was obtained in the exercise group compared to the control group (SMD: $-0.59; 95\%\ CI: -0.70$ to $-0.49; p < 0.00001, I^2 = 68\%$). The observed heterogeneity, a measure of the inconsistency of the results of the studies, was substantial in both subgroups and the two groups combined ($I^2 = 53\%$ with insomnia, $I^2 = 73\%$ without insomnia and $I^2 = 68\%$ combined).

3.4. Publication Bias, Sensitivity Analysis, Statistical Power and Quality of Evidence

The visual inspection of the funnel plot (Figure 4) and the regression test for graph asymmetry (Egger’s test) did not suggest publication bias ($z = -0.575, df = 15, p = 0.565$).

The results of the sensitivity analysis did not show significant differences between the groups. This analysis was performed by excluding each study individually, including those most vulnerable to bias. It is possible that the substantial heterogeneity presented arose from the lack of uniformity among the interventions, which involved different types of exercises and different durations.

Statistical power calculation indicated large power (0.9989), considering the prominent heterogeneity. Highly powered meta-analyses increase the chance that a statistically significant finding reflects a true effect [32].

The use of the GRADE approach indicated that the estimates of this study show a low quality of evidence (⊕⊕⊖⊖). The high risk of bias and the heterogeneity among studies contribute to this.

3.5. Difference in Dropout between Groups

The number of volunteers who discontinued the protocol was slightly higher in the exercise group than in the control group. A student’s t-test for independent variables did not reveal significant differences in the percentage of dropouts between the control group and the exercise group ($p = 0.369$).

4. Discussion
4.1. This Work

A total of 12 studies were reviewed, all of which were randomized clinical trials in which the effects of physical exercise on healthy adults over 60 years of age were analyzed to assess the impacts on sleep quality. The studies had a varied number of patients, and with the exception of one arm of one study [18], all showed that physical activity had a favorable effect on sleep compared to the control condition. There was a significant positive effect of exercise on sleep quality in the exercise group compared to the control group, as measured using the PSQI. However, there was no significant difference in the improvement of sleep quality between the group with insomnia and the group without insomnia.

One of the goals of the meta-analysis methodology is to increase statistical power by summing the sample sizes of individual studies [33]. Despite the high heterogeneity of the studies, the number of studies analyzed, their mean sample sizes and their effect sizes were able to generate high statistical power for this meta-analysis.
Although the statistical analysis did not find a significant difference in the mean dropout rate between the intervention and control groups, it is noteworthy that adherence to physical exercise is not easily achieved in clinical practice. In any case, it is interesting to note that the low dropout rate of the exercise group indicates that the intervention itself is achievable in clinical practice as a treatment for sleep disorders in the elderly.

The results are consistent with those of Banno et al. [13], who suggested in 2018 that exercise can improve sleep quality. Rubio-Arias [40] et al., in a study evaluating middle-aged women, found different results according to the exercise protocol applied: while there was no significant improvement in groups that performed low-intensity exercise (yoga), groups that engaged in moderate exercise (aerobic exercise) showed improvement in sleep quality. Xie et al. [41], in a systematic review of 22 randomized clinical trials that included adults over 18 years of age, showed that overall, both classical exercises (walking, cycling) and mind–body exercises (yoga) improved sleep quality to the same degree.

The mechanisms by which exercise affects sleep are still widely discussed. Hughes et al. [42] reported that exercise improves the circadian cycle in mice through VIP and GABA signaling on clock cells. The effect of exercise on melatonin secretion is controversial, with some studies showing that exercise increased melatonin secretion in the short term [43] and others showing that nocturnal exercise decreased [44] or did not affect the secretion of this hormone [45]. According to Uchida et al. [46], exercise causes increased secretion of brain-derived neurotrophic factor (BDNF) and growth hormone. However, as the same authors also emphasized, the effects of these exercise-related changes need further study.

Sleep quality can be positively impacted through the release of molecules secreted from myocytes and adipocytes in response to exercise [47,48]. Changes in leptin and ghrelin levels are associated with sleep disorders, and physical exercise modulates their levels [49]. Exercise increases the muscle expression of BDNF, Irisin, IL-6 and TNF-α. These substances have circadian behavior and, in animal experiments, change the depth of slow-wave sleep and the total sleep duration [47]. According to Abd El-Kader, IL-6 and TNF-α levels significantly reduce after aerobic training [50].

Physical activity can improve sleep by regulating the circadian cycle, which is often altered with aging. Physical exercise can work like a Zeitgeber, adjusting the biological clock [51]. Aging decreases parasympathetic tone, while exercise can modulate vagus nerve activity, increasing parasympathetic tone. This function can be associated with improved sleep quality both by neural mechanism and by altering blood pressure levels and heart rate [52]. Physical exercise impacts not only the circadian fluctuations of cortisol but also the density of receptors for this hormone on brain and muscle tissue, decreasing tissular sensitivity to glucocorticoids and increasing its metabolic degradation rate [53].

4.2. Limitations

Not all of the articles used in this review provided a comparison of scores for each aspect of the PSQI, and it is not possible to provide a more detailed analysis. Furthermore, it should be remembered that the PSQI is a subjective analysis of sleep, which restricts its ability to discriminate among groups [54].

The differences in exercise protocols among the included studies contributed to the high heterogeneity that was observed. In this review, different exercise modalities (aerobic, resistance and “mind and body”, such as tai-chi and yoga) were used, with differences in the number of days per week, intensities, total duration and other factors. It was possible to conclude that the I² values that were obtained were between moderate and high [55]. However, these I² values may have suffered from a size bias in the meta-analysis [56], and such inaccuracy is common in meta-analyses with few studies.

Regarding the risk of considerable bias, in all of the studies, it was impossible to blind the subjects and those who administered the intervention, an issue that is understandably inherent to the type of intervention. The “other bias” and “selective reporting” domains contributed to the increased risk of bias in the paper. The high risk of bias and the prominent heterogeneity of this review contributed to the low level of reliability (GRADE) of the effect
measures found. Theoretically, this implies a certain difficulty in concluding that the interventions adopted in the studies can be implemented in the general population over 60 years of age.

4.3. Future Work

We suggest that future studies may deepen the comparison between aerobic and resistance exercises, compare the elements of the PSQI in addition to the overall score, use objective measures of sleep quality (such as polysomnography parameters), evaluate the dose–response relationship in a more elaborate way and include more participants with a diagnosis of primary insomnia.

5. Conclusions

The results suggest that physical exercise improves sleep quality in both patients with previous complaints of insomnia and patients without previous complaints and has few adverse effects, making it a valuable adjuvant approach in the treatment of elderly patients with complaints of insomnia that may even reduce the number of medications used to sleep. Nevertheless, many of the studies included in the review had a high risk of bias, and they used very different interventions, which compromised the ability to generalize the results. Further studies are needed to investigate a greater number of participants diagnosed with insomnia, compare aerobic and resistance exercises, and use other scores of sleep quality.

Author Contributions: Conceptualization, H.M.d.A.M., M.L.C.D. and V.P.O.S.; methodology, V.L.d.S.S., D.B.C.M., M.P.H., O.A. and V.L.B., validation, data curation and formal analysis, V.P.O.S., M.P.O.S. and H.M.d.A.M.; investigation, M.P.H., O.A. and V.L.B.; writing—original draft preparation, V.P.O.S., D.B.C.M., V.L.d.S.S., Y.L.C., J.V.M., M.P.O.S., J.V.V.O., J.P.d.L.P., M.P.H., O.A. and V.L.B.; writing—review and editing, M.P.O.S., J.V.M., M.P.O.S., J.V.V.O. and J.P.d.L.P.; visualization and supervision, M.L.C.D. and H.M.d.A.M.; project administration, M.P.O.S., V.P.O.S. and H.M.d.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

| Abbr. | Abbreviation                              |
|-------|-------------------------------------------|
| BDNF | Brain-Derived Neurotrophic Factor         |
| GABA | Grading of Recommendations, Assessment, Development and Evaluation |
| HIIT | High-Intensity Interval Training Program  |
| MIIT | Moderate-Intensity Interval Training Program |
| PRISMA| Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROSPERO| Prospective Register of Systematic Reviews |
| PSQI  | Pittsburgh Sleep Quality Index            |
| RCT   | Randomized Controlled Trial               |
| SSSH  | Stay Strong, Stay Healthy training program |
| SMD   | Standardized Mean Difference              |
| RoB 2 | Cochrane Risk of Bias Tool 2             |
| REM   | Rapid eye Movement                        |
| VIP   | Vasoactive intestinal peptide            |

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