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Effect of exercise on sleep quality and insomnia in middle-aged women: A systematic review and meta-analysis of randomized controlled trials

Short title: Exercise and sleep in middle-aged women

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Highlights

- In middle-aged women, low-moderate levels of programmed exercise for 12-16 weeks had a positive effect on sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI), when compared with controls.
- In a subgroup analysis, moderate levels of programmed exercise (aerobic exercise) had a positive effect on sleep quality measured by the Pittsburgh Sleep Quality Index , while low levels of physical activity (yoga) did not have a significant effect.
- There was a non-significant reduction in the severity of insomnia measured with the Insomnia Severity Index score compared with controls.

Abstract

Objective: We assessed the effects of programmed exercise (PE) on sleep quality and insomnia in middle-aged women (MAW).

Methods: Searches were conducted in five databases from inception through December 15, 2016 for randomized controlled trials (RCTs) evaluating the effects of PE versus a non-exercising control condition on sleep quality, sleep disturbance and/or insomnia in MAW. Interventions had to last at least 8 weeks. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) and insomnia with the Insomnia Severity Index (ISI). Random effects models were used for meta-analyses. The effects on outcomes were expressed as mean differences (MDs) and their 95% confidence intervals (CI).

Results: Five publications reported data from four RCTs on PE effects during 12-16 weeks on sleep quality (n=4 studies reporting PSQI results) and/or insomnia (n=3 studies reporting ISI results), including 660 MAW. Low-moderate levels of exercise significantly lowered the PSQI score (MD=-1.34; 95% CI -2.67, 0.00; p=0.05)

compared with controls. In a subgroup analysis, moderate PE (aerobic exercise) had a positive effect on sleep quality (PSQI score MD=-1.85; 95% CI -3.62, -0.07; p=0.04), while low levels of physical activity (yoga) did not have a significant effect (MD-0.46, 95% CI -1.79, 0.88, p=0.50). In three studies (two studies of yoga, one study of aerobic exercise), there was a non-significant reduction in the severity of insomnia measured with the ISI score (MD -1.44, 95% CI -3.28, 0.44, p=0.13) compared with controls. Heterogeneity of effects among studies was moderate to high.

Conclusion: In middle-aged women, programmed exercise improved sleep quality but had no significant effect on the severity of insomnia.

Keywords: Exercise; Insomnia; Insomnia Severity Index; Middle-aged women; Pittsburgh Sleep Quality Index; Yoga

1. Introduction

Sleep disturbance (insomnia) is quite frequent in the general population, being more prevalent among women [1,2]. Insomnia is not an inherent part of aging, but rather due to multimorbidity, polypharmacy, and socio and laboral factors [3,4]. A 40% to 55% of middle-aged (peri- and postmenopausal) women may show some degree of sleep disturbance according to the menopause status, co-morbid conditions, use of psychiatric and concomitant treatments, lifestyle, chronic life events, intimate partner violence and other partner factors, sociodemographic characteristics, and sleep assessment methods [1,3,5-9]. In addition, poor sleep quality and insomnia are associated, with different magnitudes of the associations, to increased morbidity and mortality in postmenopausal women [10-12]. Despite its importance, insomnia and sleep disorders are under recognized and undertreated. On the other hand, chronic insomnia drug therapy (when used for long periods of time) has several side effects, produces cognitive deficits, and even increases mortality [13-16].

Polysomnography (PSG) has been considered a standard tool to evaluate sleep quality and sleep-related disorders. However, its value remains controversial in assessing insomnia and PSG is not recommended in the evaluation of transient or chronic insomnia [17,18]. Actigraphy data collection has been also used, although it seems that subjective symptoms are more important to assess sleep quality and insomnia [19]. Sleep logs and sleep inventories are simple instruments keeping track of details about sleep or extensive questionnaires providing information about sleep patterns and alterations, respectively. Several of these clinical questionnaires are commonly used including the Pittsburgh Sleep Quality Index (PSQI) to assess global quality of sleep [8,20], and the Insomnia Severity Index (ISI) to assess insomnia [6,21].

Exercise has been proposed as non-pharmacological alternative to improve sleep quality since there is an inverse relation between sedentarism and quality of life [22]. Exercise has been reported to improve insomnia, anxiety, reduce sleep latency and medication use [23,24]. However, the effect of physical activity or exercise on sleep quality and insomnia is controversial in observational studies of middle-aged women. Therefore, we carried out a systematic review and meta-analysis of randomized control trials (RCTs) to assess the effect of short-term exercise programs on the quality of sleep and insomnia.

2. Methods

2.1. Data sources and searches

A comprehensive literature search was performed using PubMed-Medline, Web of Sciences and the Cochrane Library from database inception through December 10, 2016. The database searches were performed independently by three authors (JARA; DJRC and EMC). The following combination terms was used: "peri-menopausal" or

"perimenopausal" or "pre-menopausal" or "premenopausal" or "postmenopausal" or "post-menopausal". The Boolean operator "AND" was used to combine these descriptors with: "sleep" or "insomnia" or "sleep disturbance" and "exercise" or "physical activity" or "training" or "yoga" or "sport".

2.2. Inclusion and exclusion criteria

The following specific inclusion criteria were considered: (1) RCTs examining the effect of programmed regular physical activity or exercise lasting at least 8 weeks on a self-reported of sleep quality tool using the Pittsburgh Sleep Quality Index (PSQI) and/or insomnia severity using the Insomnia Severity Index (ISI); (2) the presence of a control group; (3) based on physical activity in late pre-, peri- and/or postmenopausal women; (4) studies in English language; (5) Studies provided information of outcomes both at baseline and follow-up.

Studies were excluded if: (1) used a sample population with pathologies or if they were young premenopausal women; (2) were observational studies; (3) did not provide or specify numerical data on the specified tools; (4) examined acute effects of interventions; (5) people with pathologies and testing with food supplements, nutritional or pharmacological aids; (6) studies examining atypical sleep regimens, such as studies with shift workers or utilizing experimentally-induced insomnia; (7) studies of populations with medical and psychiatric conditions other than sleep disturbance.

2.3. Outcomes

Outcomes were the PSQI and the ISI. The self-reported PSQI assesses quality of sleep during the previous weeks and includes nine items describing seven sleep components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep

disturbance, use of sleep medications, and daytime dysfunction. Each item can be scored from 0 (no difficulty or absent) to 3 (severe difficulty), and results are summed providing a global PSQI score from 0 to 21. A global PSQI score of 5 or higher is indicative of poor sleep quality [8,20].

The self-applicable ISI is a tool that assesses perceived severity of insomnia during the previous weeks and includes seven questions in relation with the satisfaction experienced, the degree of functional impairment during the day, perception of decline and the concerns related to the sleep problem. Each item is rated on a Likert scale (from zero to four) to set a score from zero to 28. The higher scores indicate very severe insomnia, and a cutoff point of ten has been proposed as optimal for detecting cases of insomnia in the population. A global ISI score of 8 or higher correspond to some degree of insomnia, being moderate insomnia with score 15-21 and severe insomnia with score 22-28 [6,21].

2.4. Study selection and data extraction

Retrieved articles were reviewed independently by three authors (JARA; DJRC and EMC), to choose potentially relevant articles; all disagreements on inclusion/exclusion were discussed and resolved by consensus. References of potentially relevant articles were also searched to find additional studies, and authors of selected studies were contacted for non-reported information. Three reviewers (JARA; DJRC and EMC) independently extracted data from included studies. The following information was extracted: site and country of the study, type of exercise, number of women included, menopause status, age, body mass index (BMI), clinical characteristics, and hormone therapy. The information about characteristics of exercise programs included exercise

intensity, frequency (sessions/week), session length (minutes/week), study duration in weeks, total number of sessions and the baseline mean PSQI and ISI scores.

2.5. Risk of bias assessment (study quality)

The methodological quality of selected RCTs was assessed with the Cochrane risk of bias tool (Higgins et al 2011) [25]. This tool evaluates the following aspects: randomness of the allocation sequence (selection bias); concealment of the allocation sequence (selection bias); blinding of participants and personnel and blinding to outcome assessment (performance and detection bias, respectively); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and any other biases. For each RCT, each item was described as having either a low risk of bias, a high risk of bias, or an unclear risk of bias. RCTs with high risk of bias for items of randomization or blinding were considered being a high risk of bias. Risk of bias was assessed independently by two authors (J.A.R.A. and E.M.C.) using the Cochrane risk of bias tool [25].

2.6. Data Synthesis and Statistical Analysis

Our systematic review and meta-analysis follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al 19 2009) [26]. A random effects meta-analysis was conducted to determine summary effect of physical activity on quality of sleep (PSQI score) and insomnia (ISI score). Effects on outcomes between exercise and control arms were expressed as mean differences (MDs) and their 95% confidence intervals (CI). Differences within arms were calculated as MDs between the follow-up and baseline times. If enough

information was available, we planned to perform subgroup analyses by comparing yoga intervention versus more intense exercise types.

We evaluated statistical heterogeneity using the Cochran chi-square, the I^2 statistic, and the between-study variance using the tau-square (Tau^2) (Higgins 2003, 2008) [27,28]. I^2 values of 30-60% represented a moderate level of heterogeneity. A p value <0.1 for the chi-square was defined as indicating the presence of heterogeneity; a $Tau^2 > 1$ suggests the presence of substantial statistical heterogeneity. Publication bias was considered with the funnel plot and tested with the Egger test of funnel plot asymmetry if a minimum of 10 studies were available, and $p \leq 0.05$ was considered to be statistically significant (Egger et al 1997) [29].

For statistical analyses we used the Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, UK) [30] and Comprehensive Meta-analysis software (Version 2; Biostat, Englewood, NJ, USA).

3. Results

3.1. General Characteristics of Studies

After the evaluation of 246 abstracts from primary sources, 221 were excluded; 25 were assessed as full texts. From these, 20 studies were excluded (Figure 1). Thus, 5 RCTs (n = 660 women) were included [31-35]. Two studies reported different exercise programs, yoga and aerobic activity, compared, to the same control group [33,34]. All studies were published between 2007 and 2016, were conducted in both developing (Brazil and Iran) [31,35] and developed countries (3 in the US) [32-34], and had sample sizes in the range of 30 to 249 women [31,33].

Mean age (SD) range from 48.6 (3.5) and 55.8 (3.6), most postmenopausal, with sedentarism or low physical activity and hot flashes (Table 1). BMI range from 26.8 (3.9) kg/m² [34] to 30.4 (7.8) kg/m² [32], one study included women with BMI <30 kg/m² [31], and another does not report BMI [35] (Table 1). Exercise program duration ranged from 12 to 16 weeks and clinical characteristics are displayed in Tables 1 and 2. Four studies reported PSQI [32-35], and three studies reported ISI results [31,33,34]. Baseline sleep quality PSQI scores ranged from 5.5 (3.0) [32] to 13.0 (1.6) [35], which correspond to a mild to moderate poor quality of sleep. Baseline insomnia severity ISI scores ranged from 11.5 (5.7) [34] to 15.2 (4.6) [31], which correspond to a moderate degree of insomnia (Table 2).

3.2. Risk-of-bias assessment

Risk-of-bias assessment is shown in Figure 2. Overall, the risk of bias was high in all studies due to lack of blinding of participants and personnel. However, this issue cannot be omitted since the peculiarity of the intervention (exercise versus no exercise) and should be considered in perspective.

3.3. Meta-analyses

In four studies [32-35], programmed low-moderate exercise (n = 354 women) decreased PSQI scores (MD = -1.34; 95% CI = -2.67, 0.00; p = 0.05) when compared to controls (n = 396 women) (Figure 3). Moderate programmed exercise (aerobic exercise, 3 studies, n = 198 women) had favorable effect on the PSQI scores (MD = -1.85; 95% CI -3.62, -0.07; p = 0.04) as compared to controls (n = 226 women). Low physical activity (yoga, 2 studies, 156 women) did not have significant effect on the PSQI scores (MD = -0.46, 95% CI -1.79, 0.88, p = 0.50) as compared to controls (n = 170 women). In three

studies (two studies of yoga, one study of aerobic exercise, $n = 194$ women), there was a non-significant reduction in the ISI score (MD = -1.44, 95% CI -3.28, 0.44, $p = 0.13$) as compared to controls ($n = 275$ women) [31,33,34] (Figure 4).

Heterogeneity of effects was moderate to high among studies with a broad range of I^2 : for PSQI total population 68%, ranging from 0% for yoga to 73% for aerobic exercise; and for ISI 0%.

4. Discussion

Our study reports for the first time that exercise for 12-16 weeks significantly improved sleep quality in middle aged women. We also found that programmed exercise does not change insomnia severity. Risk of bias was high in all studies, related to lack of blinding to participants or personnel. Heterogeneity of effects was moderate to high across studies.

A previous meta-analysis of 38 polysomnographic studies without information about age and gender examined the effect of acute exercise on adult sleep, reporting moderate effect sizes on slow-wave sleep, rapid eye movement (REM) sleep, REM latency and total sleep time. In this particular study sleep moderators were exercise duration and time of day, concluding that quantitative analysis was inconsistent with previous narrative reviews. It seems that population included were majority good sleepers [36]. Our study was based in a subjective assessment rather than on polysomnography, and middle-aged women showed PSQI to different degrees of low quality of sleep. Buysse et al [20] proposed that a total PSQI score ≥ 5 defines poor sleepers, with a sensitivity of 89.6% and a specificity of 86.5%. Sleep quality in middle-aged women has been related with hot flashes severity and frequency that might reduce

the PSQI valued to assess sleep quality. However, the PSQI tool does need different scoring adjustments in clinical practice in middle-aged women [37]. In our meta-analysis, programmed low (yoga) or moderate physical activity (aerobic exercise) improved sleep quality, although the effect seems only related to moderate physical activity intensity since the benefit was only significant with aerobic exercise and not with yoga. However, yoga has been recommended as a behavioral intervention to reduce hot flashes [38], that indirectly may contribute to a better sleep. However, our meta-analysis did not support such assumption. On the other hand, aerobic exercise and yoga intervention, for three months in middle-aged women, were not associated with statistically significant changes on sleep-related actigraphy measures [39].

It has been suggested that exercise reduce vasomotor menopausal symptoms (hot flashes and night sweats), although a meta-analysis of five RCTs did not find enough evidence when compared with hormone therapy or yoga [40]. Improvement of sleep quality has been reported after 6 months of an unsupervised aerobic training intervention in middle-aged women, including reduction of hot-flashes at the end of the 6-month study [19]. In our meta-analysis the benefit of aerobic exercise on sleep quality was significantly evident as determined by the subjective evaluation provided by the PSQI, aside of undetermined effects on vasomotor symptoms. The present meta-analysis also assessed subjective insomnia severity using the validated ISI. In postmenopausal women, the mean ISI score increases in magnitude with the frequency a severity of hot flashes, and hot flashes characteristics were also associated with nighttime wakefulness and number of wake episodes and not with total sleep time, sleep efficiency or sleep latency [41]. The three available RCTs include two studies using yoga intervention and one about aerobic exercise. The effect of physical activity on insomnia severity, ISI score, was not significantly different from as compared to women

who have their current ordinary physical activity. Insomnia is a complex condition due to multiple factors (co-morbid conditions and medical treatments, negative life events and family problems, social factors, work conditions, and other factor that may not be neutralized by exercise [1-3]. However, the analysis synthesis was based only in three studies: two using yoga as exercise (and controls doing the usual physical activity) and the third doing aerobic exercise. Further studies are needed, including new approaches to assess more intense forms of exercise, confounding factors and specific quantitative endpoints, including polysomnography since insomnia may be related to disruption of sleep circuitry and secondary to modern lifestyle.

Sleep alterations have been associated with metabolic and clinical changes that may increase cardiovascular risk, especially since the reduction of menopause hormone therapy [10,42,43]. Recent meta-analyses reported that short sleep duration and some symptoms of insomnia are associated with higher incidence of hypertension [43], cardiovascular events [44], and cardiovascular-related mortality [45]. In adults, early-morning awakening and combined symptoms of insomnia increased the risk of hypertension for short sleep duration, for sleep continuity disturbance, for early morning awakening and for combined insomnia symptoms [43]. Capuccio et al [44] reported that short duration of sleep, in both male and female, is associated with increased relative risk of developing or dying of coronary heart disease, stroke, but not total cardiovascular disease while long duration of sleep is also associated with a significant higher risk of coronary heart disease, stroke, and total cardiovascular disease, with no evidence of publication bias. Finally, Sofi et al [45] reported that insomnia causes an increased risk of developing or dying of cardiovascular disease. These results combining adults, both men and women, pointed out the insomnia importance for the general health and the need to identify insomnia very early and to design effective

preventive measures. Our results suggest that moderate short duration exercise did not have any significant effect to reduce insomnia.

We acknowledge several limitations on this meta-analysis which are related in part to the available RCTs, including (i) the small number of studies; (ii) the lack of systematic information about the menopause-related symptoms separating peri- and postmenopausal women; (iii) the lack of studies using more intense physical activity to assess a possible physical activity dose response; (iv) the lack of objective measures such as sleep duration, concomitant snoring or sleep apnea-hypopnea syndrome, muscle strength changes and/or cardiorespiratory outcomes. Observational studies suggested that yoga and aerobic exercise have no effect on moderate vasomotor symptoms [46]. Other observational studies indicated that postmenopause and snoring are related with higher PSQI scores (worse quality of sleep) while sleep duration was inversely associated with PSQI score independently metabolic and lifestyle factors [42]. Insomnia prevalence also varied with ethnicity and obesity status that may contribute to heterogeneity [47].

The current evidence on sleep quality insomnia in middle-aged women should be interpreted with caution due to small number of studies and should be implemented to design more elaborated studies to get the best recommendations which might improve quality of life. New information is needed before give a final recommendation about yoga effect on sleep and insomnia. In addition, we found that the available evidence have high risk of bias and a moderate to high heterogeneity of effects due to low quality of available RCTs. Further studies, of better quality, assessing exercise intensity and longer duration approaches are needed before give final recommendations.

In conclusion, programmed exercise with a moderate physical activity improved sleep quality and should be encouraged in middle-aged women. This effect should be

added to other positive changes in middle-aged women such as metabolic improvements, muscle and neuromuscular coordination to prevent falls, and prevention of sarcopenia and frailty. However, insomnia deserve a special medical approach and meticulous management to fight against different its causes, complications and to prevent long term health risks. A relevant implication of this meta-analysis is the future need to develop more detailed studies and more targeted interventions. At the same time, more precise exercise-related endpoints should be evaluated such cardiovascular endpoints, diet and glucose-related markers.

Contributors

FR-PL, AVH and JAR-A designed the study.

JAR-A, DJR-C and EM-C did the literature searches and designed the data-extraction form.

JAR-A, DJR-C, EM-C and FRP-L selected studies.

JAR-A, DJR-C and EM-C extracted the data.

JAR-A did statistical analyses.

FRP-L and AVH supervised the study.

All authors read and approved the submitted version.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev.* 2002; 6:97-111.
2. Cunnington D, Junge MF, Fernando AT. Insomnia: prevalence, consequences and effective treatment. *Med J Aust.* 2013;199(8):S36-40.
3. Morin CM, Drake CL, Harvey AG, Krystal AD, Manber R, Riemann D, Spiegelhalder K. Insomnia disorder. *Nat Rev Dis Primers.* 2015 Sep 3;1:15026.
4. Miner B, Kryger MH. Sleep in the Aging Population. *Sleep Med Clin.* 2017;12(1):31-38.
5. Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Ehrlich K. Night sweats, sleep disturbance, and depression associated with diminished libido in late menopausal transition and early postmenopause: baseline data from the Herbal Alternatives for Menopause Trial (HALT). *Am J Obstet Gynecol.* 2007;196(6):593.e1-7; discussion 593.e7.
6. Arakane M, Castillo C, Rosero MF, Peñafiel R, Pérez-López FR, Chedraui P. Factors relating to insomnia during the menopausal transition as evaluated by the Insomnia Severity Index. *Maturitas.* 2011;69(2):157-61.
7. Cuadros JL, Fernández-Alonso AM, Cuadros-Celorrio AM, Fernández-LuzónN, Guadix-Peinado MJ, del Cid-Martín N, Chedraui P, Pérez-López FR; MenopAuse Risk Assessment (MARIA) Research Group. Perceived stress, insomnia and related factors in women around the menopause. *Maturitas.* 2012;72(4):367-72.
8. Monterrosa-Castro A, Marrugo-Flórez M, Romero-Pérez I, Fernández-Alonso AM, Chedraui P, Pérez-López FR. Assessment of sleep quality and correlates in a large cohort of Colombian women around menopause. *Menopause.* 2013;20(4):464-9.
9. Ornat L, Martínez-Dearth R, Chedraui P, Pérez-López FR. Assessment of subjective sleep disturbance and related factors during female mid-life with the Jenkins Sleep Scale. *Maturitas.* 2014;77(4):344-50.
10. Pérez-López FR, Chedraui P, Gilbert JJ, Pérez-Roncero G. Cardiovascular risk in menopausal women and prevalent related co-morbid conditions: facing the post-Women's Health Initiative era. *Fertil Steril.* 2009;92(4):1171-86.
11. Maness DL, Khan M. Nonpharmacologic Management of Chronic Insomnia. *Am Fam Physician.* 2015;92(12):1058-64.
12. Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. *Chest.* 2017 Jan 30. pii: S0012-3692(17)30134-4. doi: 10.1016/j.chest.2017.01.026. [Epub ahead of print] Review. PubMed PMID: 28153671.

13. Bierman EJ, Comijs HC, Gundy CM, Sonnenberg C, Jonker C, Beekman AT. The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or indifferent. *Int J Geriatr Psychiatry*. 2007;22(12):1194–200.
14. Davidson JR. Insomnia treatment options for women. *Obstet Gynecol Clin North Am*. 2009;36(4):831-46.
15. Mallon L, Broman JE, Hetta J. Is usage of hypnotics associated with mortality? *Sleep Med*. 2009;10(3):279-86.
16. López de Castro F, Fernández Rodríguez O, Mareque Ortega MA, Fernández Agüero L. [Therapeutic approach to insomnia]. *Semergen*. 2012;38(4):233-40.
17. Littner M, Hirshkowitz M, Kramer M, et al. Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for using polysomnography to evaluate insomnia: an update. *Sleep*. 2003;26:754–60.
18. Feige B, Baglioni C, Spiegelhalder K, Hirscher V, Nissen C, Riemann D. The microstructure of sleep in primary insomnia: an overview and extension. *Int J Psychophysiol*. 2013;89(2):171-80.
18. Youngstedt S. Exercise effects on sleep. *Clinical Journal of Sport Medicine* 2005;24:355–65.
19. Mansikkamäki K, Raitanen J, Nygård CH, Heinonen R, Mikkola T, Eija Tomás, Luoto R. Sleep quality and aerobic training among menopausal women--a randomized controlled trial. *Maturitas*. 2012;72(4):339-45.
20. Buysse DJ, Reynolds CHF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
21. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297–307.
22. Youngstedt SD, Kline CE. Epidemiology of exercise and sleep. *Sleep Biol Rhythms*. 2006;4:215–221.
23. Buman MP, King AC. Exercise as a treatment to enhance sleep. *Am J Lifestyle Med*. 2010;4:500–514.
24. Reid KJ, Baron KG, Lu B, Naylor E, Wolfe L, Zee PC. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Med*. 2010; 11(9):934-40.
25. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

26. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
28. Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008;37:1158-60.
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;315:629-34.
30. Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.
31. Afonso RF, Hachul H, Kozasa EH, Oliveira Dde S, Goto V, Rodrigues D, Tufik S, Leite JR. Yoga decreases insomnia in postmenopausal women: a randomized clinical trial. *Menopause*. 2012;19:186-93
32. Elavsky S, McAuley E. Lack of perceived sleep improvement after 4-month structured exercise programs. *Menopause*. 2007;14(3 Pt 1):535-40.
33. Newton KM, Reed SD, Guthrie KA, Sherman KJ, Booth-LaForce C, Caan B, Sternfeld B, Carpenter JS, Learman LA, Freeman EW, Cohen LS, Joffe H, Anderson GL, Larson JC, Hunt JR, Ensrud KE, LaCroix AZ. Efficacy of yoga for vasomotor symptoms: a randomized controlled trial. *Menopause*. 2014;21(4):339-46.
34. Sternfeld B, Guthrie KA, Ensrud KE, LaCroix AZ, Larson JC, Dunn AL, Anderson GL, Seguin RA, Carpenter JS, Newton KM, Reed SD, Freeman EW, Cohen LS, Joffe H, Roberts M, Caan BJ. Efficacy of exercise for menopausal symptoms: a randomized controlled trial. *Menopause*. 2014;21(4):330-8.
35. Tadayon M, Abedi P, Farshadbakht F. Impact of pedometer-based walking on menopausal women's sleep quality: a randomized controlled trial. *Climacteric*. 2016;19(4):364-8.
36. Youngstedt SD, O'Connor PJ, Dishman RK. The effects of acute exercise on sleep: a quantitative synthesis. *Sleep*. 1997;20(3):203-14.
37. Otte JL, Rand KL, Landis CA, Paudel ML, Newton KM, Woods N, Carpenter JS. Confirmatory factor analysis of the Pittsburgh Sleep Quality Index in women with hot flashes. *Menopause*. 2015;22(11):1190-6.
38. Avis NE, Legault C, Russell G, Weaver K, Danhauer SC. Pilot study of integral yoga for menopausal hot flashes. *Menopause*. 2014;21(8):846-54.
39. Buchanan DT, Landis CA, Hohensee C, Guthrie KA, Otte JL, Paudel M, Anderson GL, Caan B, Freeman EW, Joffe H, LaCroix AZ, Newton KM, Reed SD, Ensrud KE. Effects

- of Yoga and Aerobic Exercise on Actigraphic Sleep Parameters in Menopausal Women with Hot Flashes. *J Clin Sleep Med*. 2017;13(1):11-18.
40. Daley A, Stokes-Lampard H, Thomas A, MacArthur C. Exercise for vasomotor menopausal symptoms. *Cochrane Database Syst Rev*. 2014;(11):CD006108.
41. Ensrud KE, Stone KL, Blackwell TL, Sawaya GF, Tagliaferri M, Diem SJ, Grady D. Frequency and severity of hot flashes and sleep disturbance in postmenopausal women with hot flashes. *Menopause*. 2009;16(2):286-92.
42. Hung HC, Yang YC, Ou HY, Wu JS, Lu FH, Chang CJ. The association between self-reported sleep quality and metabolic syndrome. *PLoS One*. 2013;8(1):e54304.
43. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertens Res*. 2013;36(11):985-95.
44. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J*. 2011;32(12):1484-92.
45. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol*. 2014;21(1):57-64.
46. Guthrie KA, LaCroix AZ, Ensrud KE, Joffe H, Newton KM, Reed SD, Caan B, Carpenter JS, Cohen LS, Freeman EW, Larson JC, Manson JE, Rexrode K, Skaar TC, Sternfeld B, Anderson GL. Pooled Analysis of Six Pharmacologic and Nonpharmacologic Interventions for Vasomotor Symptoms. *Obstet Gynecol*. 2015;126(2):413-22.
47. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcántara C, Jackson CL, Williams MA, Redline S. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep*. 2015;38(6):877-88.

Figure Captions

Figure 1. Flow diagram of study selection. RCTs: Randomized controlled trials. PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia severity index.

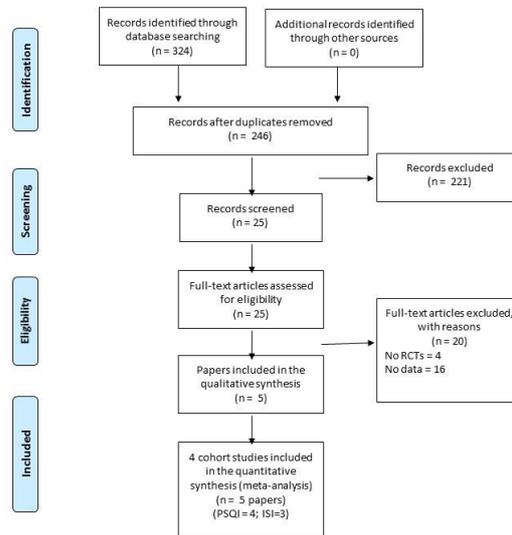


Figure 2. Assessment of risk of bias in included RCT's

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alonso 2012	●	●	●	●	●	●	●
Elavsky 2007	●	●	●	●	●	●	●
Newson 2014	●	●	●	●	●	●	●
Sternfeld 2014	●	●	●	●	●	●	●
Tadavon 2016	●	●	●	●	●	●	●

Figure 3. Association between physical activity and sleep quality. Upper figure: Overall effect; Lower figure: Subgroup by type of physical activity. Squares represent the MD for each trial. Diamonds represent the pooled MD across trials. AA: aerobic activity.

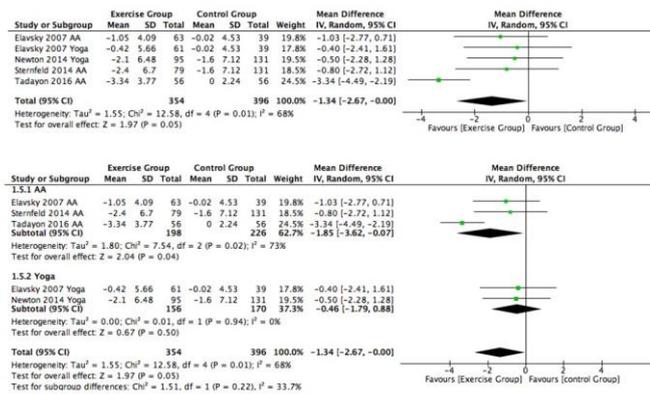


Figure 4. Association between physical activity and insomnia severity. Squares represent the MD for each trial. The diamond represents the pooled MD across trials. AA: aerobic activity.

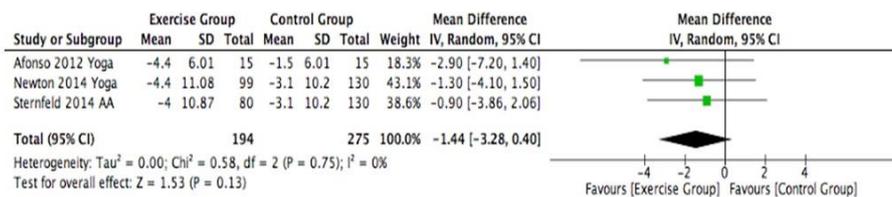


Table 1. Main characteristics of included studies in the meta-analysis.

Study, year [reference]	Site of study, country	Exercise	n	Menopause Status (%)	Age, years (SD)	BMI, kg/m ² (SD)	Clinical characteristics, hormone therapy/other
Afonso RF, 2014 [31]	Sao Paulo, Brazil	Yoga	15	Amenorrhea 1 year	Range: 50-65	<30	Women with an apnea-hypopnea index < 15, and who had a diagnosis of insomnia by a specialist based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. A daily dose of 500 mg of calcium was received by all women.
		CG	15	Amenorrhea 1 year	Range: 50-65	<30	
Elavsky S, 2007 [32]	Illinois, US	Yoga	61	PreM: 13.1%; EPerM: 29.5%; LPerM: 29.5%; EPM: 11.5%; LPM: 16.4%	50.0 (3.7)	29.8 (6.8)	Sedentary or low-active middle-aged women who had no history of surgical menopause and had not used hormone therapy for at least 6 months. There was no inclusion criterion for perceived sleep quality, and baseline analyses revealed that overall sleep quality was poor in the sample (mean PSGI = 6.2, SD = 3.5), with 88% of the sample scoring above the cutoff point for poor sleepers. No hormone therapy for at least 6
				PreM: 19.0%; EPerM: 27.0%; LPerM: 12.7%; EPM: 12.7%; LPM: 28.6%	50.5 (3.4)	30.4 (7.8)	
				PreM: 20.5%; EPerM: 25.6%; LPerM: 12.7%; EPM: 12.7%; LPM: 28.6%	48.6 (3.5)	28.1(5.9)	

		LPerM: 30.8%; EPM: 12.8%;			months.		
		LPM: 10.3%					
Newton KM, 2014 [33]	NCT01178892	Yoga	107	PM 74.8%; LT 22.4%; EA: 2.8%	54.3 (3.9)	27.1 (4.6)	Effects of exercise training with previously sedentary women. No hormone therapy in the past 2 months. No head-to-head comparisons between yoga and exercise were planned. Eligibility criteria were ≥ 14 vasomotor symptoms/week in each of three consecutive weeks, based on daily diaries. BMI < 37 kg/m ² .
	MsFLASH Indianapolis, Oakland, and Seattle, US	UA	142	PM 81.7%; LT 16.2%; EA: 2.1%	54.2 (3.5)	26.9 (4.6)	
Sternfeld B, 2014 [34]	NCT01178892	AA	106	PM 84.9%; LT 14.2%; EA: 0.9%	55.8 (3.6)	26.8 (3.9)	Effects of exercise training with previously sedentary women. No hormone therapy in the past 2 months. No head-to-head comparisons between yoga and exercise were planned. Eligibility criteria were ≥ 14 vasomotor symptoms/week in each of three consecutive weeks, based on daily diaries. BMI < 37 kg/m ² .
	MsFLASH Indianapolis, Oakland, and Seattle, US	UA	142	PM 81.7%; LT 16.2%; EA: 2.1%	54.2 (3.5)	26.9 (4.6)	
Tadayon M, 2016 [35]		AA	56	Lacking menstrual flow for 1	52.3 (1.6)		No hormone therapy. A 32% reported experiencing mild insomnia, 26% reported moderate insomnia, and 4.5% reported severe insomnia; 37.5% reported experiencing good-quality sleep.
	Ahvaz, Iran	CG	56	year or having a hormone blood test corresponding to postmenopause	52.5 (1.7)	-	

SD: Standard Deviation; BMI: Body mass index; AA: aerobic activity; CG: control group; UA: usual activity; PreM: Premenopause; EperM: Early perimenopausal; LperM: Late perimenopausal; EPM: Early postmenopausal; LPM: Late postmenopausal; PM: Postmenopause; LT: Late transition; EA: Early transition. MsFLASH: Menopause Strategies - Finding Lasting Answers for Symptoms and Health Research Network.

Table 2. Characteristics of exercise programs and outcomes assessment of studies included in meta-analyses.

Study, year publication [reference]	Type of exercise	Exercise intensity (Low, moderate)	Exercise frequency (sessions/week)	Session length (min/week)	Study duration (weeks/study)	Number of sessions/ study	Basal score	Basal score
							PSQI score Mean (SD)	ISI score Mean (SD)
Afonso RF, 2012 [31]	Yoga	Low	2	120	16	32	-	14.1 (4.6)
	CG	-	-	-	-	-	-	15.2 (4.6)
Elavsky S, 2007 [32]	AA	50% - 75% HRR (moderate)	3	120	16	48	6.0 (3.2)	-
	Yoga	Low	2	180	16	32	6.9 (3.9)	-
	CG	-	-	-	-	-	5.5 (3.0)	-
Newton KM, 2014	Yoga	Low		90	12		7.7 (3.0)	11.8 (5.2)
	UA	-					8.4 (3.6)	12.4 (4.8)

[33]									
Sternfeld B, 2014	AA	50% -70% HRR (moderate)	3	150	12	36		7.8 (3.6)	11.5 (5.7)
[34]	UA	-	-	-	-	-		8.4 (3.6)	12.2 (4.8)
Tadayon M, 2016	AA	Low	-	40,000 steps	12	-		12.7 (2.4)	-
[35]	CG	-	-	-	-	-		13.0 (1.6)	-

CG: Control Group; HRR: heart rate reserve; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; AA: aerobic activity; CG: control group; UA: usual activity; HRR: heart rate reserve.