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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Aerobic exercise training and obstructive sleep apnea: dose-response meta-analyses

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Abstract

Purpose Several studies have shown that aerobic exercise training improves obstructive sleep apnea (OSA) severity. However, a dose-response relationship has never been shown. This study aimed to quantify any dose-response relationships between time spent per week in aerobic exercise and key sleep apnea outcomes.

Methods Randomized controlled trials (RCT) were selected from literature search studying the effects of supervised aerobic exercise training on patients with OSA. Dose-response meta-analyses were performed, where the 'dose' was the total weekly duration of aerobic exercise training. Primary outcomes were apnea hypopnea index (AHI), cardiorespiratory fitness (maximum oxygen consumption or VO_2peak) and Epworth Sleepiness Scale (ESS).

Results Analysis of data from 11 RCTs showed a non-linear dose-response relationship between the total weekly duration of aerobic exercise training and mean differences in AHI. Maximum effects on AHI (-10.92 (95%CIs: -15.57; -6.27)) were observed when the weekly duration of aerobic exercise reached 100 min/week. Similar non-linear dose-response trend was observed in the mean differences in VO_2peak. Studies in which aerobic exercise training lasted ≥ 12 weeks showed greater proportional changes in mean AHI differences with maximal effects reaching a peak at ~ 70 min/week of aerobic exercise training. ESS and total weekly duration of aerobic exercise training showed a linear dose-response relationship based on 4 RCTs.

Conclusions Based on these analyses, aerobic exercise training of 70–100 min/week over 3 or 5 days a week should be recommended as adjunctive treatment for patients with OSA.

Keywords Dose-response meta-analysis · Aerobic exercise · Cardiorespiratory fitness

Introduction

Continuous positive airway pressure (CPAP) and mandibular advancement devices have been mostly used in the treatment of obstructive sleep apnea (OSA) [1, 2]. The field is, however, continuously making progress with newer treatment options being explored based on the different phenotypes and endotypes of OSA [3]. There is now a range of options that can be considered in the personalized/precision care approach for OSA— options such as pharmacological treatment with atomoxetine-oxybutynin combination [4] to surgical procedures like the implantable device for hypoglossal nerve stimulation therapy [5].

However, just as with other chronic cardiometabolic diseases, lifestyle modification including physical activity and weight loss would remain central to the overall management of patients with OSA, especially in those who are overweight [6]. Several clinical trials exploring the effects

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of weight loss through lifestyle modifications in those who are overweight and have OSA, have consistently shown significant improvements in the severity of OSA and functional outcomes [7, 8]. In terms of dose-response relationship a recent study found that even a < 5% weight loss was sufficient for small but statistically significant improvement in OSA severity, and those who achieved a ≥ 10% weight loss exhibited the greatest benefits [9].

Patients with OSA also generally have lower physical activity levels as compared to those without [10] and unlike the guidelines on the optimal duration of aerobic exercise for various other cardiometabolic diseases [11, 12], there are currently no guidelines on the optimal duration of aerobic exercise training for patients with OSA. This formed the basis for this study which primarily aimed to determine if a dose-response relationship exists between the total weekly duration of aerobic exercise training and improvement in OSA severity, cardiorespiratory fitness, and subjective daytime sleepiness.

Methods

This study was conducted in accordance with the *Preferred Reporting Items for a Systematic Review and Meta-analysis* (PRISMA) reported in (Table S1). The protocol was registered in OSF (https://doi.org/10.17605/OSF.IO/4EKVD). PubMed, Scopus and Web of Science databases were searched (independently by three authors) from inception to March 21st, 2024 (search words in Table S2). Inclusion criteria was based on *PI(E)COS* format, where population (*P*) of interest comprised of adult research participants with primarily OSA who were studied for the effects of supervised aerobic exercise training (the intervention (*I*)) and compared to control (*C*) participants who received usual care or engaged in activities like stretching but not in aerobic or non-aerobic (resistance) training. The primary outcomes (*O*) of interest were mean differences in apnea hypopnea index (AHI) based on polysomnogram (PSG) or home sleep apnea tests (an objective index of OSA severity), maximal oxygen consumption (VO_2peak) (a measure of cardiorespiratory fitness) and Epworth Sleepiness Scale (ESS) score (ESS assesses subjective daytime sleepiness on a scale of 0 to 24; scores ≥ 11indicating excessive daytime sleepiness). Other (secondary) outcomes were explored post-hoc (described in Results). The study design (*S*) considered for inclusion was the randomized controlled trial (RCT) design. Studies were excluded if they studied short term effects of aerobic exercise training (< 4 weeks) or if they studied a combination of interventions in conjunction with aerobic exercise training, e.g., dietary modification or CPAP, which would not allow for isolating the effects of aerobic exercise training on the outcomes. Studies were also excluded if the data for outcomes of interest presented in median and ranges was detected to have significant skewness not allowing for calculation of means and standard deviations (SD) [13, 14].

Disagreement on any study selection or study quality was resolved by consensus. The reasons for the exclusion of studies are explained in Table S3. The studies were assessed for study quality/risk of bias (using RoB-2 tool) [15], as reported in Figure S1. Extracted data included baseline characteristics of the included participants, aerobic exercise parameters (i.e., duration of the intervention, frequency and intensity) and change scores of outcomes for each study arm according to Cochrane methodological guidelines [16].

The method introduced by Crippa and Orsini [17] was used to calculate mean differences and corresponding standard errors of change in AHI in the intervention group relative to the control group in each trial. The method requires dose (minutes/week) of aerobic exercise in each study arm, the mean and its corresponding SD of change of each outcome in each study, and the number of participants in each study. This data was extracted on the working sheets of Comprehensive Meta-analysis (CMA version 2.2.064; Biostat, Englewood, N.J. U.S.A) to get uniform measures of changes as change scores. The "dose" in this meta-analysis was the time in aerobic exercise spent per week by participants and this excluded any pre-workout/warm-up or post-workout/cool-down exercises. For studies in which the frequency (sessions per week) or the duration (minutes per session) of intervention progressed during the study, the duration of exercise in each week was calculated first and then averaged over the follow-up period to estimate the average duration of aerobic exercise (minutes/week) in each study.

Trial-specific results were pooled using a 'one-stage random-effects model' and dose-response curves were constructed in Stata-13 based on the methodology by Crippa and Orsini [17]. Dose-response curves characterize the relative efficacy of the dose under investigation using the placebo effect as referent (i.e. the relative efficacy for the placebo is zero by definition). Linear and nonlinear dose-response curves were plotted using restricted maximum likelihood estimation [18] using Stata packages "*drmeta*" and "*drmeta_graph*". Nonlinear curves were reported (restricted cubic spline model graph) if the Wald test for departure from linearity was significant at $p < 0.1$. Data were fitted with a weighted mixed-effects model restricted cubic splines for 'dose' (exercise— minutes/week) with three knots located at percentiles (10th, 50th, and 90th) of its distribution [19]. The 50% effective dose (ED50) and 95% effective dose (ED95) were also calculated [17]. Linear dose-response curves were reported if the Wald test was

not significant. Conventional direct pairwise meta-analyses were also conducted, and results presented as forest plots.

Additionally, trial-sequential analyses were conducted using TSA program version 0.9.5.10 Beta (www.ctu.dk/tsa) for AHI and ESS outcomes only. Trial sequential analysis tests the credibility of the ascertained results by combining both an estimation of information size (a cumulative sample size of included trials) with an adjusted threshold of statistical significance for the cumulative meta-analysis. Meta-analysis monitoring boundaries (Trial Sequential Monitoring Boundaries) and the required-information-size (RIS) were quantified, with diversity-adjusted information size or D^2 and adjusted 95% confidence intervals (CI). Diversity adjustment was performed according to an overall type I error of 5%, and power of 90%.

Heterogeneity was assessed with I^2 statistics [20, 21]. I^2 greater than 50% was considered to indicate substantial heterogeneity [21]. A funnel plot to assess funnel plot asymmetry was constructed reporting p-values for asymmetry (for Eggers test of intercept) [22]. Risk of bias and study quality assessment are provided in supplement (Figure S1).

Results

A total of 11 RCTs from 12 publications [23–34] (there were two publications [26, 27] from an RCT) were included in this meta-analysis. There were 217 participants who underwent supervised moderate to high intensity aerobic exercise training and 218 participants who formed the control population. Baseline characteristics of the study population as well as details of the aerobic exercise are reported in Table 1. Figure S2 shows the study selection process.

Dose-response meta-analysis of 11 studies [23–26, 28–34] showed a non-linear dose-response relationship between the total weekly duration of aerobic exercise and AHI mean difference. There was a proportional change in the AHI mean difference with the increase in the duration of aerobic exercise up to 100 min/week (mean difference = -10.92 (95%CIs: -15.57; -6.27)), with no remarkable change in effect estimate at higher duration of exercise ($p_{dose-response}<$ 0.001, $p_{Wald-test}$ = 0.03, Fig. 1, Table S2). The ED50 was 26.5 min/week and the ED95 was 71 min/week. The curve (Fig. 1) peaks at 100 min/week and indicates that additional effects of exercise become trivial compared to those at 100 min/week. Pairwise meta-analysis showed that the pooled mean difference in AHI was − 9.90 (95%CIs: -14.26; -5.53), $p<0.001$, $I^2=74\%$ (Figure S3). Trial sequential analysis for mean AHI difference showed that the last line of Z-score curve crossed the conventional monitoring, the trial sequential monitoring and the RIS boundaries (Figure S4). This analysis yielded a similar pooled mean difference − 9.91 (95%CIs: -14.25; -5.56), $p<0.0001$, I^2 74%, as that computed with pairwise meta-analysis.

Restricting the analysis to only the studies [23, 24, 26, 28, 29, 31–34] where aerobic exercise training lasted ≥ 12 weeks showed the same non-linear dose-response relationship but with a greater proportional change in the AHI mean difference compared to the analysis including all studies ($p_{dose-response}<$ 0.0001, $p_{Wald-test}=<0.0001$). Maximum effects were seen ~ 70 min/week where the AHI mean difference was − 15.94 (95%CIs: -23.72; -8.15) and the curve appeared to flatten after 70 min/week (Fig. 2 and Table S5). The ED50 was 20.5 min/week and the ED95 was 52.5 min/week. Corresponding pairwise meta-analysis of studies where the duration of aerobic exercise lasted ≥ 12 weeks showed mean AHI difference of -9.75 (95%CIs: -14.70; -4.80) $p<0.001$, $I^2=78\%$ (Figure S5). Corresponding trial sequential analysis for mean AHI difference from these studies [23, 24, 26–29, 31–34] showed that the line of Z-score curve crossed the conventional monitoring, the trial sequential monitoring and the RIS boundaries (Figure S6) and a pooled mean AHI difference of -9.68 (95%CIs: -13.59; -5.77; $p<0.0001$, I^2 76%), confirming the results of the pairwise meta-analysis.

VO_2peak data was reported in 'ml/kg/min' units in 7 studies [23–25, 30, 32–34] and in 'ml/min' in one study [31]. Dose-response meta-analysis of 7 studies [23–25, 30, 32–34] for VO_2peak data (reported in ml/kg/min) showed a non-linear dose-response relationship between the total weekly duration of aerobic exercise and VO_2peak mean difference. There was a proportional change in the VO_2peak mean difference with the increase in the duration of aerobic exercise up to 90 to 100 min/week, and no significantly greater effects after that with higher duration of aerobic exercise ($p_{dose-response}<$ 0.001, $p_{Wald-test}$ = 0.007, Fig. 3, Table S6). From this analysis, assuming maximum effects on VO_2peak mean difference reaching 4.73 ml/kg/min, the calculated ED50 was 30 min/week and the calculated ED95 was 85 min/week. Pairwise meta-analysis for standardized mean VO_2peak difference from 8 studies [23–25, 30–34] showed pooled estimate of 0.82 (95%CIs: 0.34; 1.30), $p=<0.001$, $I^2=74\%$ (Figure S7).

Data on ESS from four studies was meta-analyzed [25, 27, 31, 32]. Dose-response meta-analysis showed a linear relationship (Fig. 4) between the total weekly duration of aerobic exercise and mean ESS difference across the range of 0–200 min/week of exercise. The coefficient for slope was − 0.02 (95%CIs: -0.04; -0.007), ($p_{dose-response}$ = 0.006; $p_{Wald-test}$ = 0.34). Direct pairwise meta-analysis showed pooled mean ESS difference of -3.87 (95%CIs: -5.55; -2.18), $p=<0.01$, $I^2=0\%$ (Figure S8). Trial sequential analysis for mean ESS difference showed that the line of Z-score curve crossed the conventional monitoring and RIS boundaries

Table 1 Baseline characteristics of study population

Study	*N* (ITT population)	Duration (weeks)	Age	Gender (females%)	Baseline AHI	Baseline ESS	Aerobic exercise intervention* and control
Kline 2011 [26]	Exercise training: 23 Control: 16	12	Exercise training: 47.6 (1.3) Control: 45.9 (2.2)	Exercise training: 44% Control: 44%	Exercise training: 32 (5.6) Control: 24.4 (5.6)	Exercise training: 11 (0.5) Control: 7.3 (0.9)	**Exercise**: 150 min/week of aerobic exercise (treadmill, elliptical trainer, or recumbent bicycle), performed at 60% of HR reserve, spread across 4 days/week for 12 weeks. Sessions were supervised by staff trained in exercise physiology. **Control**: Low-intensity exercises designed to increase whole-body flexibility.
Sengul 2011 [31]	Exercise: 10 Control: 10	12	Exercise: 54.4 (6.5) Control: 48 (7.4)	Exercise: 0% Control: 0%	Exercise: 15.19 (5.4) Control: 17.92 (6.4)	Exercise: 8.2 (6.14) Control: 3.42 (5.07)	**Exercise**: Aerobic exercise (treadmill, bicycle ergometer) performed at 60–70% of VO_2 peak for 60–90 min/session on 3 days/week for 12 weeks. All exercise sessions were supervised by a single physiotherapist. **Control**: No treatment
Servantes 2012 [33]	Exercise: 17 Control: 11	12	Exercise: 51.7 (9.8) Control: 53 (8.1)	Exercise: 53% Control: 55%	Exercise: 25.2 (24.7) Control: 22.8 (17.4)		**Exercise**: Aerobic exercise group (included in this meta-analysis) received 30–45 min of aerobic exercise each session, performed at a heart rate corresponding to the anaerobic threshold for 12 weeks (3 sessions/week for weeks 1–8, 4 sessions/week for weeks 9–12). First three sessions were supervised by a physiotherapist and a cardiologist; remaining 12 weeks of sessions were home-based. **Control**: No intervention
Desplan 2014 [25]	Exercise: 13 Control: 13	4	Between 35 and 70 years	N/A	Exercise: 40.6 ± 19.4 Control: 39.8 ± 19.2	Exercise: 13.6 (4.5) Control: 8.0 (5.7)	**Exercise**: 1 session per day; 6 sessions per week during a 4-week period of exercise training. The aerobic exercise part of the session was 45 min of cycle ergometer endurance training, supervised by a professional. No restrictive diet was used. **Control**: Standard health education
Mendelson 2016 [30]	Exercise: 22 Control: 22	4	Exercise: 63.8 (8.0) Control: 59.6 (11.8)	Exercise: 6% Control: 18%	Exercise: 31.1(12.9) Control: 28.1(13.5)	N/A	**Exercise**: 30 min of moderate intensity walking per day, 5 days per week. Walking distance of ~ 1.6–2.0 km (on a track or treadmill) at 60% of VO_2peak. Participants attended the Cardiac Rehabilitation Centre for supervised exercise training three times per week and for the other 2 days performed the exercise at home monitored by a pedometer **Control**: Participants maintained their usual level of activity
Servantes 2018 [32]	Exercise: 17 Control: 18	12	Exercise: 51 (9) Control: 57 (8)	Exercise: 56% Control: 37%	Exercise: 28 (17) Control: 29 (17)	Exercise: 11(3) Control: 9 (6)	**Exercise**: Aerobic training (treadmill and cycle-ergometer) 30 min in the first month and 45 min in the last 2 months and there were three sessions per week on nonconsecutive days for 3 months. Exercise intensity was monitored based on anaerobic threshold. Participants exercised in a fitness center and were supervised by a physiotherapist and a cardiologist. **Control**: No exercise or other treatment

Table 1 (continued)

Study	*N* (ITT population)	Duration (weeks)	Age	Gender (females%)	Baseline AHI	Baseline ESS	Aerobic exercise intervention* and control
Yang 2018 [34]	Exercise: 35 Control: 35	12	Exercise: 46.3 (6.4) Control: 48.6 (7.2)	Exercise: 31% Control: 31%	Exercise: 20.2 (7.5) Control: 19.5 (6.1)	N/A	**Exercise**: 30 min exercise on a bicycle ergometer until VO_2AT. Exercise sessions were supervised by a cardiologist and a nurse **Control**: Maintained previous lifestyle
Berger 2019 [24]	Exercise: 48 Control: 48	36	Exercise: 62 (60-64) Control: 62 (60-65)	Exercise: 33% Control: 42%	Exercise: 21.9 (19.5-24.2) Control: 21.0 (18.9-23.1)	N/A	**Exercise**: 40 min of combined resistance and aerobic exercises (Nordic walking, gymnastics, and aquagym) at AT, three times/week for 9 months, supervised by an adapted physical activity instructor **Control**: Standard diet and physical activity advice
Lin 2020 [28]	Exercise: 10 Control: 10	12	Exercise: 49.5 (9.7) Control: 52.7 (4.6)	Exercise: 38% Control: 28.5%	Exercise: 47.0 (19.4) Control: 35.8 (17.5)	N/A	**Exercise**: 30-min aerobic resistance exercise with multi-joint exercises involving major muscle groups of trunk and lower extremities. Sessions were hospital based physical therapy, and each session instructed by the same physical therapist. **Control**: Participants waited for 12 weeks for intended treatment
Araujo 2021 [23]	Exercise: 22 Control: 22	40 (3.9)	Exercise: 50 (6) Control: 54 (8)	Exercise: 62.5% Control: 33%	Exercise: 44 (31) Control: 45 (27)	N/A	**Exercise**: 72 exercise sessions at a frequency of 3 days/week. Each exercise session had 40 min of aerobic exercise on a cycle ergometer (in the first month for 30 min). The intensity of aerobic exercise was determined by the corresponding HR of the AT and respiratory compensation point (detected from the cardiorespiratory capacity test) **Control**: Participants were asked to maintain their physical activity habits
Lins-Filho 2024 [29]	Exercise: 13 Control: 13	12	Exercise: 51.2 (2.5) Exercise: 57.0 (2.1)	N/A	Exercise: 33.9 (1.8) Exercise: 35.3 (1.3)	N/A	**Exercise**: Each session was five cycles of 4 min walking or running at 90–95% of HR_{max} interspersed by 3 min of walking at 50–55% of HR_{max}, totaling 35 min. Each session was conducted three times per week for 12weeks. Sessions were supervised by an exercise instructor (P.C) **Control**: Stretching activities twice per week

*Details of the protocol for exercise training are provided excluding the warm-up and cool-down phases and any other non-aerobic exercises; min indicates minutes; HR indicates heart rate; HRmax indicates maximum heart rate; VO_2 indicates peak oxygen consumption; AT indicates anaerobic threshold; P.C indicates that this information was based on personal communication with the author of the study

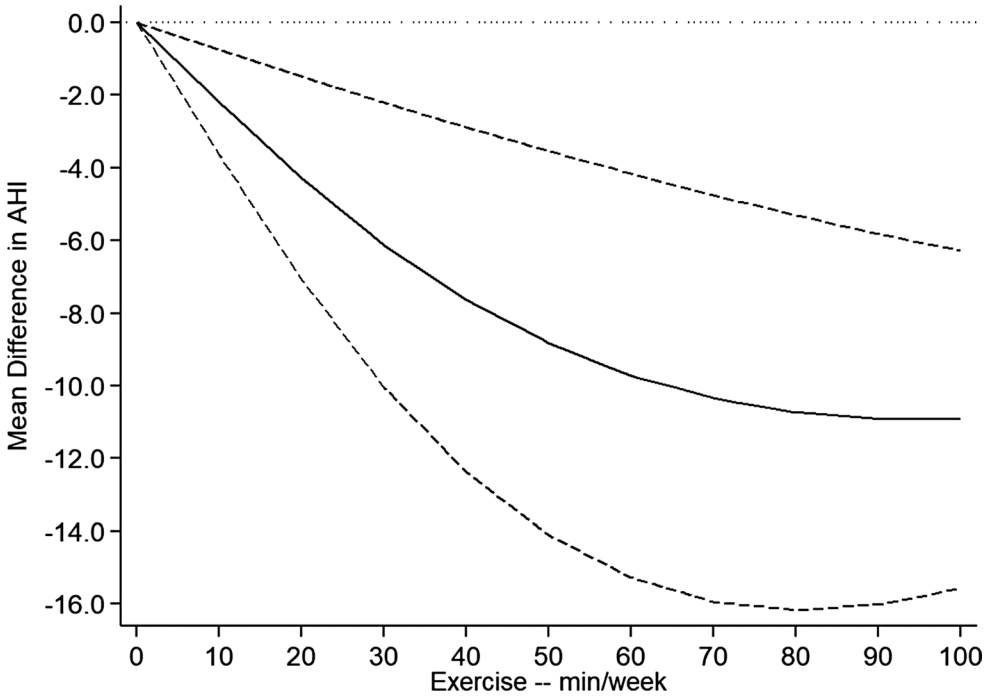

Fig. 1 Dose-response curve for the effects of aerobic exercise on mean differences in apnea-hypopnea index. Solid and dotted lines represent the restricted maximum likelihood estimates and 95% CIs, respectively. AHI indicates apnea hypopnea index. X-axis indicates the "dose" which is aerobic exercise training in minutes/week

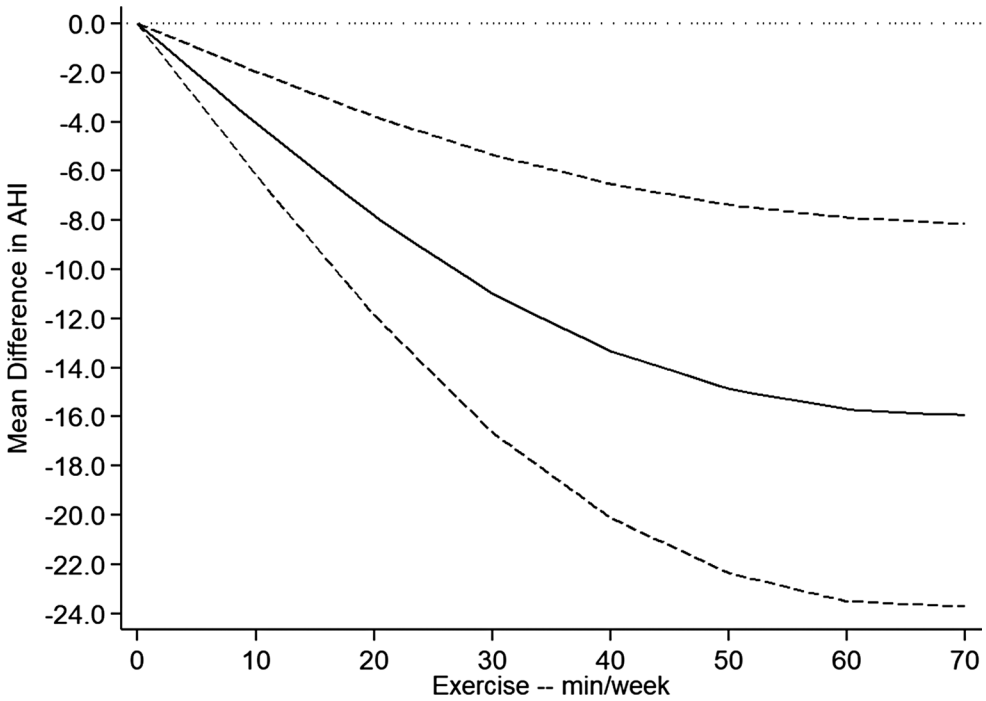

Fig. 2 Dose-response curve for the effects of ≥ 12 weeks aerobic exercise on mean differences in apnea-hypopnea index. Solid and dotted lines represent the restricted maximum likelihood estimates and 95% CIs, respectively. AHI indicates apnea hypopnea index. X-axis indicates the "dose" which is aerobic exercise training in minutes/week

(Figure S9) and this analysis showed a similar pooled mean ESS difference as that obtained with pairwise meta-analysis (trial sequential analysis pooled mean ESS difference = -3.83 (95%CIs: -5.46; -2.20), p = < 0.0001, $I^2 = 0\%$.

From the studies included in the meta-analysis for AHI mean difference, *post-hoc* exploratory meta-analyses for other outcomes were also conducted. Two RCTs [25, 27] reported data on Pittsburgh sleep quality index (PSQI) and Short Form-36 (SF-36). Pooled mean differences in PSQI and the vitality subcomponent score of SF-36 were − 1.94 (95CIs: -3.56; -0.32), $p = 0.02$, $I^2 = 0\%$, and 26.17 (95%CIs: 1.18; 51.16), $p = 0.04$, $I^2 = 84\%$, respectively (Figure S10 and S11).

PSG follow-up data was available from a few studies and pooled in separate meta-analyses. Data on oxygen desaturation index was meta-analyzed from six studies [23–26, 28, 34] and the mean difference was − 3.55 (95%CIs: -6.28; -0.82), $p = 0.01$, $I^2 = 2\%$ (Figure S12). Sleep efficiency (total

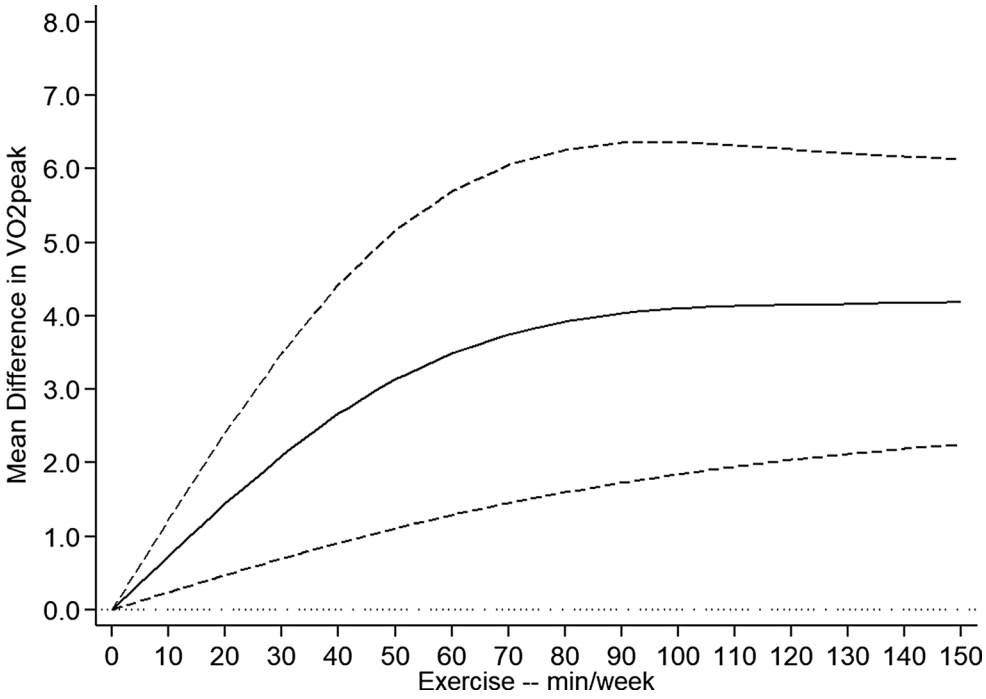

Fig. 3 Dose-response curve for the effects of aerobic exercise on mean VO_2 peak differences. Solid and dotted lines represent the restricted maximum likelihood estimates and 95% CIs, respectively. VO_2 peak is the maximum oxygen consumption. X-axis indicates the "dose" which is aerobic exercise training in minutes/week

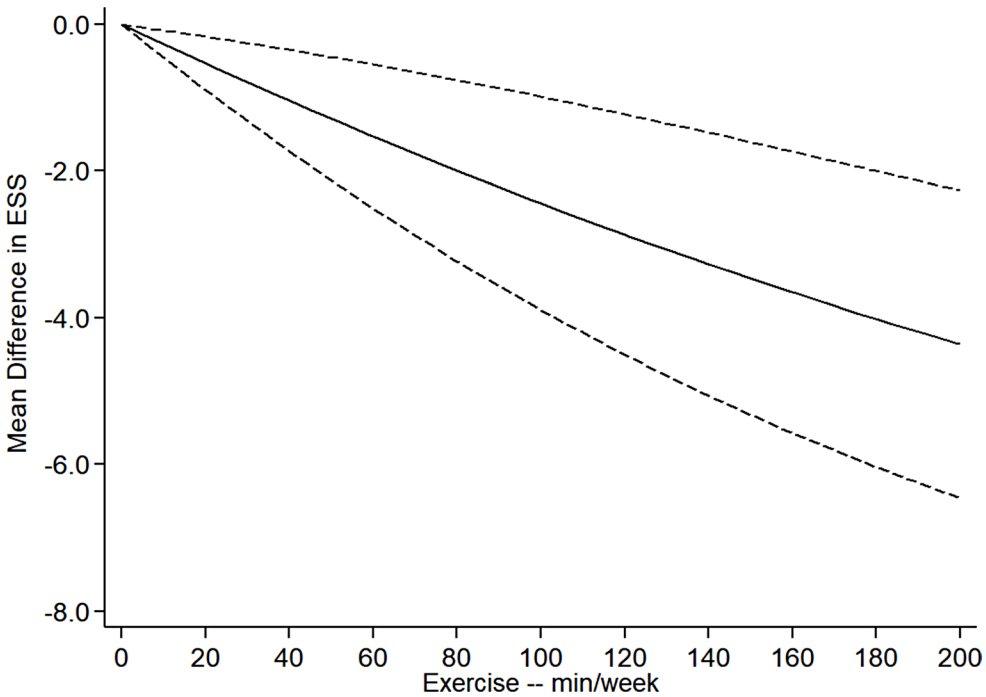

Fig. 4 Dose-response curve for the effects of aerobic exercise on mean differences in Epworth Sleepiness Scale scores. Solid and dotted lines represent the restricted maximum likelihood estimates and 95% CIs, respectively. ESS indicates Epworth Sleepiness Scale score. X-axis indicates the 'dose' which is aerobic exercise training in minutes/week

sleep time/total recording time in %) data from five studies [26, 30–33] showed mean difference in sleep efficiency of 3.88% (95%CIs: 0.39%; 7.38%), $p=0.03$, $I^2=0\%$ (Figure S13). PSG-recorded minimum oxygen saturation from 6 studies [23, 24, 26, 30, 32, 34] showed a mean difference of 1.19% (95CIs: -1.63%; 4.02%), $p=0.41$, $I^2=67\%$ (Figure S14). Based on data from 3 studies [26, 30, 32], the mean difference in stage 3 sleep was 0.68% (95%CIs: -3.29%; 4.65%), $p=0.74$, $I^2=44\%$ (Figure S15) and based on data from 7 studies [23, 25, 26, 28, 30–32] mean difference in total sleep time was 10.81 min (95%CIs: -4.19 min; 25.81 min), $p=0.16$, $I^2=0\%$ (Figure S16).

A few studies analyzed anthropometrics post-intervention. Pairwise meta-analyses showed mean difference in body mass index (BMI) of -1.10 kg/m^2 (95%CIs: -2.21 kg/m^2; 0.02 kg/m^2), $p=0.05$, $I^2=8\%$ from 5 studies [23–25, 31, 34] (Figure S17), mean difference in neck circumference of -1.09 cm (95%CIs: -2.19 cm; 0.01 cm), $p=0.05$, $I^2=16\%$

from 5 studies [25, 26, 30, 31, 34] (Figure S18), and mean difference in body fat percentage of -2.26% (95%CIs: -4.82%; 0.30%) $p = 0.08$, $I^2 = 0\%$, from 2 studies [26, 31] (Figure S19).

Data on lung functions reported in a few studies was also meta-analyzed. Maximum expiratory pressure and maximum inspiratory pressure data pooled from 3 studies [26, 28, 31] showed mean differences of 13.77 (95%CIs: -13.61; 41.15), $p = 0.32$, $I^2 = 59\%$, and 26.65 (95%CIs: -17.11; 70.41), $p = 0.23$, $I^2 = 79\%$, respectively (Figure S20). Standardized mean differences in forced expiratory volume in 1 s and forced vital capacity from 2 studies [26, 31] pooled were, -0.04 (95CIs: -0.54; 0.47), $p = 0.88$, $I^2 = 0\%$, and -0.19 (95%CIs: -0.69; 0.32), $p = 0.47$, $I^2 = 0\%$, respectively (Figure S21).

Visual inspection of funnel plot for AHI meta-analysis did not show plot asymmetry (Figure S22). Based on Egger's test of intercept, the intercept (B0) was at -0.32 (95%CIs: -2.95, 1.95), p (1-tailed) = 0.32, which indicated no publication bias.

Discussion

To our knowledge this is the first dose-response meta-analysis and trial sequential analysis of studies on the effects of supervised moderate to high intensity aerobic exercise training in patients with OSA. Results from these analyses show significant dose-response relationships between the duration of aerobic exercise and mean differences in AHI, VO_2peak and ESS. The dose-response effects for mean AHI differences were most pronounced when restricting the analysis to studies where the duration of aerobic exercise training was ≥ 12 weeks. Trial sequential analyses for AHI and ESS indicated that the observed effects from pairwise meta-analyses on AHI and ESS were conclusive and the evidence sufficient to conclude that aerobic exercise has statistically significant effects on AHI and ESS.

AHI effect-size estimates from the pairwise meta-analyses are modest in terms of the magnitude of effect size when compared to what has been shown earlier for CPAP and mandibular advancement device [35]. Nevertheless, from an epidemiological standpoint, these are significant findings, especially since these effects seem to be driven primarily by improvement in aerobic fitness with only slight decrease in BMI and do not factor in other active lifestyle interventions like dietary weight loss, which could have synergistic effects in patients with OSA. Beneficial effects of aerobic exercise training extend beyond those of improvements in OSA severity and daytime sleepiness. The 2018 *Physical Activity Guidelines for Americans*, recommend that adults should engage in at least 150 min of moderate intensity aerobic physical activity or at least 75 min of vigorous intensity aerobic physical activity each week, or an equivalent combination of both [36]. In a recent study with a large nationally representative sample of US adults, those who engaged in aerobic activities consistent with the recommended *Physical Activity Guidelines for Americans* showed a 29% reduced risk of all-cause mortality compared to those not meeting the guidelines recommended physical activity [37]. The beneficial effects on mortality risk were largely comparable between those who engaged in ≥ 150 min/week of light to moderate intensity exercise or ≥ 75 min/week of vigorous intensity exercise [37]. Considering the health risks of untreated OSA, and the generally low PAP adherence, there are strong rationales for recommending exercise training for individuals with OSA.

Accordingly, findings from these dose-response meta-analyses can be helpful to determine the optimal duration of aerobic exercise that should be recommended for those with OSA. Overall, the maximum effects on AHI (-10.92 (95%CIs: -15.57; -6.27) occurred with 100 min/week of aerobic exercise. This equates to 20 min/day of aerobic exercise 5 days a week. However, restricting the dose-response meta-analysis to studies in which aerobic exercise training lasted ≥ 12 weeks, AHI mean differences were even greater (-15.94 (95%CIs: -23.72; -8.15)) and with only 70 min/week of aerobic exercise. It is logical to assume that if aerobic exercise training can be maintained long-term one can expect sustained if not more clinically significant benefits in AHI. Aerobic exercise training for 70 min/week equates to 14 min/day of aerobic exercise 5 days a week and this excludes pre-workout warm-up and post-workout cool down exercises. Aerobic exercise training for 14–20 min a day for 5 days a week could be a time-efficient strategy for most patients with OSA with no medical contraindications otherwise for exercising and for those with no access to sophisticated training programs or resistance-training equipment. In this context, the World Health Organization guidelines [38] are noteworthy which recommend 150–300 min/week of moderate-intensity aerobic exercise for those who have hypertension and recommends 30–60 min/day of moderate aerobic physical activity at least 5 days a week for otherwise healthy adults.

Effect size estimates on ESS are generally consistent with what was observed in a previously published network comparative meta-analysis which showed ESS effect size estimate from aerobic exercise greater than that of CPAP or mandibular advancement device, though these comparisons did not reach statistical significance [35]. A growing body of evidence shows that aerobic exercise training induces beneficial effects on vigilance and cognitive functions [39, 40] and an improvement of the information processing speed, measured by a reduction in reaction time on attentional

tasks [41]. The key physiological factors driving that link, however, are still a matter of scientific debate. A number of studies have examined changes in brain structure and function, as it relates to selective aspects of cognition, with aerobic exercise training. This includes evidence that aerobic exercise training leads to increase in the volume of a number of frontal and temporal gray matter and white matter regions [42, 43] and also evidence indicating increase in the hippocampal volume [44, 45]. From studies showing that aerobic exercise training leads to increase in cerebral blood flow [46] to others indicating cellular links such as increase in brain-derived neurotrophic factor [47] (in hippocampus and cerebral cortex and considered to play a central role in learning, memory and executive function), there is ample evidence to support that aerobic exercise can improve daytime sleepiness.

Aside from the analyses on AHI and ESS, most other analyses should be considered exploratory, or hypothesis-generating given the limited number of studies in each analysis. None of the studies included in the meta-analysis showed significant improvements in PSG-measured sleep efficiency but the effect size estimate pooled from these studies was statistically significant. There are, however, limitations in assessing sleep efficiency based on a single night PSG. Several other studies have shown that aerobic exercise improved insomnia symptoms as well as sleep efficiency based on either sleep diaries or multiple nights actigraphy recordings [48–50].

None of the other analyses in specific, the mean differences in stage 3 sleep, as well as in BMI, neck circumference, body fat percentage or lung functions showed a statistically significant difference. Therefore, none of these seem to explain the changes in AHI from aerobic exercise training. The underlying mechanisms of how aerobic exercise training exerts protective effects on OSA severity are not entirely clear with different theories and mechanisms postulated. One of these relates to the effects of aerobic exercise training on increasing stage 3 sleep [51] which is believed to protective in OSA [52, 53]. Another possible explanation is that aerobic exercise training may reduce the overnight rostral body fluid shift [54–57]. This is based on experimental observations of overnight changes in neck and calf circumferences of patients with OSA that indicate an overnight rostral body fluid shift [30, 55]. Except for one study [30], the other studies [25, 26, 31, 34] in the meta-analysis on neck circumference did not measure overnight neck circumference change. Therefore, the non-significant change in neck circumference observed in this meta-analysis does not as such disprove the overnight rostral body fluid shift hypothesis. There has also been some interest in respiratory muscles strength exercise training and whether increasing the strength of inspiratory or expiratory muscles improves upper airway patency. A recent meta-analysis did not find significant effects on AHI in participants with OSA who received training for respiratory muscles by breathing through an adjustable valve against a specific resistance [58].

The dose-response curves for AHI and VO_2peak, although in opposite directions, appear similar in shape and findings. The magnitude of change and the proportionality of change in VO_2peak seems to be correlated with that of AHI based on these dose-response curves. Both show maximal effects at 100 min/week of aerobic exercise— the former on AHI, and the latter on VO_2peak. This suggests that the effects on AHI from aerobic exercise training are directly or indirectly a function of the improvement in cardiorespiratory fitness itself.

Findings from the dose-response meta-analyses presented here are consistent with those from similar analyses on the effects of aerobic exercise training on blood pressure in individuals with hypertension [59] and on HbA_{1C} in individuals with type 2 diabetes mellitus [60]. Aerobic exercise training in individuals with hypertension resulted in a non-linear dose-dependent reduction in systolic and diastolic blood pressure with the greatest effects at 150 min/week of aerobic exercise training [59], and in those with type 2 diabetes mellitus, levels of HbA_{1C} decreased proportionally with aerobic exercise training with the greatest effects at 100 min/week of aerobic exercise training [60].

It has been hypothesized that the effects of aerobic exercise on glycemic control are possibly mediated through multiple pathways— improved insulin sensitivity in the muscles, improved blood flow to tissues, weight loss, decrease in inflammatory cytokines and reduction in visceral fat [61]. However, there is no clear understanding of the exact underlying causal links or mechanistic pathways between improvements in VO_2peak and in improvements in HbA_{1C} or for that matter, in blood pressure in those with hypertension. Nevertheless, it is a finding that has been observed in several studies. As noted in this meta-analysis, the relationship between improvements in VO_2peak and improvement in AHI is akin to that of VO_2peak with blood pressure and HbA_{1C}. Given the apparent link between VO2peak and AHI, possibly causal, and considering the variety of sleep apnea phenotypes and endotypes, it is likely that the protective effects of aerobic exercise against sleep apnea are not mediated by a single mechanistic pathway but involve several different pathways.

There are some limitations to this meta-analysis that warrant consideration. Firstly, the analyses on mean AHI reduction showed high statistical heterogeneity. Clinical heterogeneity of the diverse population could explain some of this. However, due to the limited number of studies, it was not possible to conduct further sub-group analyses

to explore sources of heterogeneity. Additionally, most of the exploratory analyses, though with low heterogeneity in pooled estimates, contained a limited number of studies compared to the AHI meta-analysis, which limits the generalizability of these findings. Though most exercise training protocols were designed to be moderate-to-high intensity, these protocols varied across the included studies in terms of the frequency and duration, and details about intervention adherence were not uniformly reported.

Overall, in conclusion, the dose-response meta-analyses show significant beneficial effects of aerobic exercise in patients with OSA. Based on these analyses, for patients with OSA with no limitations to exercising otherwise, we recommend 70–100 min of moderate to high intensity aerobic exercise per week, spread over 3 to 5 days per week, in addition to standard treatment (such as CPAP or mandibular advancement device). More sustained effects are likely to be reached in patients after 3 months of regular aerobic exercise.

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