Research Report

Effects of Six-Month Aerobic Exercise Intervention on Sleep in Healthy Older Adults in the Brain in Motion Study: A Pilot Study

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Abstract

Background: Sleep disturbances have been shown to be associated with the presence of the apolipoprotein (APOE) e4 allele, the well-known genetic risk factor for late-onset sporadic Alzheimer’s disease (AD).

Objective: This study quantifies the effects of a six-month aerobic exercise intervention on objective and subjective sleep quality in middle-aged to older individuals including those at increased genetic risk for late-onset sporadic Alzheimer’s disease (AD), who carry the apolipoprotein (APOE) e4 risk allele.

Methods: 199 sedentary men and women without significant cognitive impairments were enrolled in the Brain in Motion study, a quasi-experimental single group pre-test/post-test study with no control group. Participants completed a six-month aerobic exercise intervention and consented to genetic testing. Genotyping of APOE confirmed that 54 individuals were carriers of the e4 allele. Participants’ subjective quality of sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI) pre- and post-intervention. A convenience sample of participants (n = 29, APOE e4+ = 7) consented to undergo two nights of in-home polysomnography (PSG) pre- and post intervention. Sleep architecture and respiratory variables were assessed.

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Results: The six-month aerobic exercise intervention significantly improved participants’ total PSQI score, sleep efficiency, and sleep latency in the full sample (n = 199). PSG results showed that total sleep time and sleep onset latency significantly improved over the course of the exercise intervention only in individuals who carried the APOE ε4 allele. These results are, however, exploratory and need to be carefully interpreted due to the rather small number of APOE ε4+ in the PSG subgroup.

Conclusions: The six-month aerobic exercise intervention significantly improved participants’ sleep quality with beneficial effects on PSG shown in individuals at increased genetic risk for late-onset sporadic AD.

Keywords: Alzheimer’s disease, APOE ε4, dementia, polysomnography

INTRODUCTION

The number of Canadians living with dementia is projected to double by 2031 [1]. There are currently no disease-modifying pharmacological therapies for Alzheimer’s disease (AD), the most common cause of dementia among older individuals. The available pharmacological agents provide symptomatic benefit and have not been shown to address underlying disease processes [2–4]. Despite a large investment, drug development for AD has been marked by repeated failures [2–4]. This has led to a shift in prevention trials from targeting individuals already showing early cognitive symptoms, to interventions trials on individuals not yet showing symptom but who are at increased risk of AD [5].

Recent research has examined a possible link between changes in sleep quality and the development of AD pathology, particularly amyloid-β deposition. One potential mechanism that could result in increased amyloid-β deposition is the reduced activity of the glymphatic system when sleep is fragmented [6–8]. This system is involved in the clearance of metabolic waste products including amyloid-β from the brain. This clearance takes place at a faster rate during sleep [8]. Reduced slow wave sleep (SWS), which typically occurs in older age has been considered as another potential mechanism through which sleep disruption influences the development of the pathological features of AD [9]. Improving sleep quality may be a strategy to delay the onset of AD and slow its progression [10].

The presence of the apolipoprotein (APOE) ε4 allele is a well-known genetic risk factor for late-onset sporadic AD [11], although the underlying mechanisms for this association are unsettled in the research literature [12, 13]. The presence of this allele in older adults has also been associated with reduced sleep quality [14, 15]. In a previous study [14], we examined the relationship between the quality of sleep and the presence of the APOE ε4 allele.

Compared to non-carriers, individuals with the ε4 allele had lower sleep efficiency (expressed as the ratio of total sleep time to the total time in bed), reduced total sleep time, and increased wakefulness after sleep onset (WASO) on polysomnography (PSG) but did not score differently on subjective (i.e., self-reported) measures of sleep. These results are consistent with previous literature showing the effects of the ε4 allele on sleep architecture [16–20].

Exercise has been associated with improvements in general well-being, body weight and metabolism, cerebrovascular reserve, cognitive performance, and brain health (hippocampal volume and functional connectivity) [21–27]. Further, physical activity has been associated with improved sleep quality, particularly sleep efficiency, sleep latency and depth [28–30], possibly due to stimulation of the serotoninergic pathway [31]. Wilckens and colleagues [32] examined the role of sleep efficiency in mediating the effects of physical activity on cognitive functioning. They reported that improved sleep efficiency modulated the relationship between physical activity and improved cognitive performance. In another study [33], independent relationships between both physical activity (PA) and sleep efficiency and improvements in cognitive performance were found. Altogether, this evidence supports the hypothesis that aerobic exercise, partly by improving sleep quality, promotes better cognitive function and reduces the risk of developing sporadic late-onset AD.

In the current study, we examined the effects of a six-month aerobic exercise intervention on sleep quality in healthy middle-aged and older participants as an ancillary study of the larger Brain in Motion study [34], a quasi-experimental single group pre-test/post-test study with no control group on the effects of aerobic exercise on cerebral blood flow and cognition. Our primary objective was to determine whether six-months of aerobic exercise improved overall sleep quality and sleep efficiency as determined by both subjective (self-reports) and objective
(PSG) measures of sleep. As a secondary objective, we assessed if individuals who carried the risk allele APOE e4 showed differential effects with exercise on sleep quality compared to non-carriers. Specifically, we hypothesize that individuals carrying at least one e4 allele (APOE e4+) would show greater improvements in sleep quality as compared to non-carriers.

METHODS

Participants

Two hundred and sixty-five sedentary middle-aged to older participants of either sex (mean age (SD) 65.2 (6.4) years; 141 (53.2%) females) without significant cognitive impairment (mean Montreal Cognitive Assessment (MoCA) [35] score (SD) 27.2 (1.6)) were enrolled in the Brain in Motion study, a quasi-experimental single group pre-test/post-test study with no control group [34]. A total of 203 individuals completed the exercise intervention with 62 dropouts (mainly due to changes in their medical conditions). Of the 203 who completed the intervention, 199 consented to genetic testing and their data are reported in this manuscript.

Participants were volunteers recruited through word-of-mouth, social media, posters and newspaper advertisements. Ethics approval was obtained by the University of Calgary Conjoint Health Research Ethics Board (CHREB: REB 14–2284) and the study was done in agreement with the Helsinki Declaration of 1975. Participants provided informed written consent prior to enrollment and a separate written consent for genetic testing. For further details, please see Tyndall et al. [34].

APOE genotyping

Genomic DNA was extracted from buffy coats obtained from whole blood samples (Gentra Puregene Blood Kit; Qiagen, Venlo, Netherlands). Samples underwent PCR amplification followed by Sanger sequencing (Big Dye v1.1 Cycle Sequencing Kit; Applied Biosystems, Foster City, CA) on ABI 3130XL Genetic Analyzer (Applied Biosystems). Mutation Surveyor DNA Variant Analysis software (Soft Genetics, LLC; State College, PA) was identified APOE e2, e3, and e4 alleles by manually combining the alleles from the single nucleotide polymorphisms NM_000041.2:c.388T>C (p.(Cys130Arg); rs429358) and c.526C>T (p.(Arg176Cys); rs7414). Individuals who carried the e3/e4, e2/e4, and e4/e4 allele combinations were classified as APOE e4+, while individuals who carried the other allele combinations (e2/e2, e2/e3, e3/e3) were classified as APOE e4− (detailed breakdown of the APOE alleles is reported in Table 1). The e2/e4 allele combination has been shown to have protective effects [36] however we included the e2/e4 carriers in the APOE e4+ group because of a recent meta-analysis of clinical and autopsy-based studies on sporadic late onset AD reporting higher risk of AD in individuals with one copy of the e4 allele (e2/e4, OR 2.6; e3/e4, OR 3.2) or two copies (e4/e4, OR 14.9) among Caucasian subjects [37].

One hundred and ninety-nine participants (mean age (SD) = 65.00 (6.00) years; mean years of formal education (SD) = 15.8 (2.5) years; mean MoCA (SD) = 27.5 (1.4), BMI (SD) = 27 (4) kg·m⁻²; 103 (51.8%) females) completed the exercise intervention, had complete PSQI data, and underwent genetic testing. Fifty-four individuals were APOE e4+ (mean age (SD) = 64.5 (5.9) years; mean years of formal education (SD) = 16.0 (2.3) years; mean MoCA (SD) = 27.5 (1.4); 24 (44.4 %) females).

Experimental procedures

Participants completed four testing sessions including one just before the start of the six-month exercise intervention (taken as the baseline assessment for this report) and one at the end. At each session, participants were asked to complete the Pittsburgh Sleep Quality Index (PSQI) [38], a retrospective self-report measure assessing their quality of sleep during the month preceding the study. Scores for the seven components of the PSQI were computed and represented 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5) sleep disturbance; 6) sleep medications; and, 7) daytime dysfunction. The component scores were then summed to produce a global score (range 0 to 21). Lower scores indicate better sleep with global scores.

| Allele Combinations | n   |
|---------------------|-----|
| e3/e3              | 123 |
| e3/e4              |     |
| e2/e2              | 1   |
| e2/e3              | 4   |
| e2/e4              | 21  |
| e3/e4              | 45  |
| TOT                | 199 |

Detailed breakdown of the APOE alleles in N = 199 individuals
Participants also completed the Epworth Sleepiness Scale (ESS) [39] at each session, which measures individuals’ general level of daytime sleepiness. In this study, we only report pre- and post-intervention data for participants that 1) completed the exercise intervention, 2) provided pre/post PSQI data, and 3) consented to genetic testing.

**In-home polysomnography (PSG)**

A convenience sample of participants (n = 29, APOE e4+ = 7) consented to undergo two nights of unattended PSG recordings in their home, which were done just prior to six-month exercise intervention and immediately after its conclusion. This was a convenience sample and post-hoc evaluations revealed matching pre-intervention characteristics to the full sample (i.e., mean age (SD) = 65.00 (5.00) years; mean years of formal education (SD) = 16.7 (3.09) years; mean MoCA = 27.5 (1.4); BMI (SD) = 26.4 (3.8) kg·m⁻²; 17 (58.6%) females). We used the Embletta MPR PG (Natus Medical Inc., Pleasanton, CA) and an ST1 proxy unit. Each participant was instrumented by a trained technician in his/her home. Respiratory data were obtained through finger pulse oximetry and respiratory effort through inductive plethysmography. Airflow was measured by using nasal pressure and an oro-nasal thermistor. Participants were also instrumented with standard one-lead ECG. Body position was derived using the gravity sensors in the Embletta unit. Electrode placement for the EEG followed the standard 10–20 system. Data were scored by an experienced registered polysomnographic technologist (J.K.R.). The following variables were extracted: 1) total sleep time; 2) total recording time; 3) sleep efficiency; 4) sleep onset latency; 5) REM onset latency; and, 6) number of awakenings. The number of minutes spent in each sleep stage (Awake, N1, N2, N3, REM) was also computed together with respiratory variables (including oximetry) that were then used to compute the apnea/hypopnea index (AHI). Apneas and hypopneas were defined according to the revised American Academy of Sleep Medicine guidelines [40].

**Six-month aerobic exercise intervention**

Participants were enrolled in a supervised six-month aerobic exercise training program held three days per week at the Fitness Centre in the Faculty of Kinesiology at the University of Calgary. Each session included a five-minute warm up, aerobic exercise and a five-minute cool down with stretching. Exercise prescriptions followed the American College of Sports Medicine guidelines [41]. As participants progressed through the program, the duration of exercise between warm up and cool down increased from 20 to 40 minutes. In the case of aerobic exercise, the intensity was determined based on individual VO₂max. The intensity increased from 30–45% maximum heart rate reserve (HRR) to 60–70%. For further details, see Tyndall et al. [34].

**Statistical analysis**

Data were analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM, Armonk, NY, USA). Pre-intervention descriptive statistics are reported in Tables 2 and 3; Paired samples t-tests were used to compare pre- and post- measurements for continuous variables and descriptive statistics are reported in Tables 4 and 5. Categorical variables were examined with the McNemar Chi-squared for repeated measures. Further, stratified analyses for genetic status were conducted. All analyses were two-tailed and
statistical significance was set at $p < 0.05$, Bonferroni-Holm correction for multiple comparisons was used [42]. We performed four tests for the PSQI in the full sample ($n = 199$) looking at PSQI total score, sleep efficiency, duration, and sleep latency. According to the Bonferroni-Holm method [42] $\alpha = 0.05/(4-1+1) = 0.0125$ for the smallest $p$ value, $\alpha = 0.05/(4-2+1) = 0.0167$ for the second smallest, $\alpha = 0.05/(4-3+1) = 0.025$ for the third and $\alpha = 0.05/(4-4+1) = 0.05$ for the last. In the PSG, we examined similar characteristics of sleep quality and performed three tests looking at total sleep time, sleep efficiency, and sleep latency. Similarly, as per the Bonferroni-Holm method [42] $\alpha = 0.05/(3-1+1) = 0.016$ for the smallest $p$ value, $\alpha = 0.05/(2-2+1) = 0.025$ for the second smallest, $\alpha = 0.05/(3-3+1) = 0.05$ for the last.

RESULTS

Subjective sleep measures

One-hundred and eleven participants (55.7%) out of 199 reported global scores on the PSQI $\geq 5$ indicating poor sleep quality at pre-intervention. This percentage decreased to 46.7% (93/199, 9% decrease,) at post-intervention. Statistically significant but modest (6.9%) improvements in global PSQI scores between pre- (mean (SD) = 5.8 (3.1)) and post-intervention (mean (SD) = 5.4 (3)), $t_{198} = 3.166$, $p = 0.002$, Cohen’s $d_z = 0.22$; see Fig. 1A) were found. Statistically significant but likewise modest (3.4%) improvements were found in sleep efficiency (pre-intervention mean (SD) = 85.1 (10.2) versus post-intervention mean (SD) = 88 (12), $t_{195} = -3.845$, $p < 0.001$, Cohen’s $d_z = 0.27$; see Fig. 1B). Sleep latency also showed a statistically significant decrease of 14.1% post-intervention (pre-intervention mean (SD) = 19 (17) minutes versus post-intervention mean (SD) = 16.3 (15.1) minutes), $t_{190} = 2.596$, $p = 0.010$, Cohen’s $d_z = 0.18$; see Fig. 1C). No statistically significant changes were found in sleep duration ($p = 0.154$). Among the four categorical components statistically significant differences ($p = 0.012$) were only found for the subjective sleep quality component. Sixty percent of participants reported very good sleep quality after the intervention compared to 51.3% before. Changes in sleep quality were not related to changes in body mass index. There were no statistically significant changes in daytime sleepiness as measured by the ESS ($p = 0.442$).

The analysis of pre-intervention characteristics revealed no statistically significant differences in global PSQI score, sleep efficiency, sleep latency and sleep durations between $APOE \ e_4$ carriers and non-carriers (see Table 2). Over the course of the exercise intervention, statistically significant differences in global PSQI scores were only
Fig. 1. Effects of six-months aerobic exercise on subjective sleep measures (PSQI). Panel A illustrates the total Pittsburgh Sleep Quality Index (PSQI) in the overall sample (n = 199) between pre-intervention scores [Mean (SD) = 5.8 (3.1)] and post-intervention scores [Mean (SD) = 5.4 (3)]. We note a significant decrease in the total PSQI score, reflecting an 6.9% improvement in sleep quality. Panel B illustrates sleep efficiency in the overall sample (n = 199) between pre-intervention [Mean (SD) = 85.1 (10.2)] and the end of the exercise intervention [Mean (SD) = 88 (12)]. We note a significant 3.4% increase in sleep efficiency in the overall sample. Panel C illustrates a 14.1% decrease in sleep latency in the overall sample (n = 199) before (pre-intervention) [Mean (SD) = 19 (17) minutes] and after (post-intervention) six-months of aerobic exercise intervention [Mean (SD) = 16.3 (15.1) minutes]. Bars represent Means and Standard Error; ∗p < 0.5; ∗∗p < 0.01; ∗∗∗p < 0.001.

Fig. 2. Effects of a 6-month aerobic exercise on subjective sleep quality and sleep efficiency in individuals with APOE e4± alleles. Panel A highlights changes before (pre-intervention) [Mean (SD) = 5.8 (3.1)] and after (post-intervention) six-months of aerobic exercise intervention [Mean (SD) = 5.4 (3.0)], in total Pittsburgh Sleep Quality Index (PSQI) in the APOE e4− (light bars, n = 145) group but not in the APOE e4+ (dark bars, n = 54) group. Panel B shows improvements in sleep efficiency in both APOE e4+ (dark bars, n = 54) and APOE e4− (light bars, n = 145) groups, with the APOE e4+ group having the greatest improvement (4.5 %) before (pre-intervention [Mean (SD) = 84.3 (10.7)]) and after (post-intervention) six-months of aerobic exercise intervention [Mean (SD) = 88.1 (14.3)]. Panel C shows a decrease in sleep latency only in the APOE e4− (light bars, n = 145) group from pre-intervention [Mean (SD) = 18.7 (17.5)] to post-intervention [Mean (SD) = 16.6 (16.2)]. Bars represent Means and Standard Error; ∗p < 0.5; ∗∗p < 0.01; ∗∗∗p < 0.001.

found in APOE e4− individuals (pre-intervention mean (SD) = 5.8 (3.1) versus post-intervention mean (SD) = 5.4 (3.0)), t144 = 2.889, p = 0.004, Cohen’s d2 = 0.23; see Fig. 2A) with no significant differences found in the APOE e4+ group (p = 0.181). Statistically significant differences were found in sleep efficiency for both APOE e4+ and APOE e4− participants (pre-intervention APOE e4+ mean (SD) = 84.3 (10.7) versus post-intervention APOE e4+ mean (SD) = 88.1 (14.3)); APOE e4− mean (SD) = 87.6 (11.1); APOE e4+: t53 = −2.390, p = 0.021, 4.5 % change, Cohen’s d2 = 0.32 APOE e4−: t142 = −3.011, p = 0.003, 2.5 % change, Cohen’s d2 = 0.25; see Fig. 2B). Sleep latency decreased only in APOE e4− participants (pre-intervention mean (SD) = 18.7 (17.5) minutes...
Fig. 3. Effects of a 6-month aerobic exercise on objective sleep measures (PSG) in individuals with APOE e4± alleles. Panel A highlights changes in total sleep time before (pre-intervention) [Mean (SD) = 352 (66.7) minutes] and after (post-intervention) six-months of aerobic exercise intervention [Mean (SD) = 406 (44.2) minutes] in the APOE e4+ (dark bars, n = 7) group but not in the APOE e4− (light bars, n = 22) group. Panel B shows changes in sleep efficiency before (pre-intervention) [Mean (SD) = 73.8 (16.9)] and after (post-intervention) [Mean (SD) = 83.2 (11.4)] six-months of aerobic exercise intervention in the APOE e4+ (dark bars, n = 7) group but not in the APOE e4− (light bars, n = 22) group. Panel C shows changes in sleep onset latency before (pre-intervention) [Mean (SD) = 20.8 (25.6)] and after (post-intervention) [Mean (SD) = 16.6 (16.2)] minutes, \( t_{138} = 1.982, p = 0.049, \) Cohen’s \( d_z = 0.16 \) (see Fig. 2C). However, this comparison did not survive the Bonferroni-Holm correction for multiple comparisons \( \alpha = 0.05/(4-3+1) = 0.025 \). No significant changes were found in sleep latency for APOE e4+ or sleep duration for either group.

**Polysomnography**

There were no statistically significant differences in PSG variables over the course of the exercise intervention in the full sample. The analysis of pre-intervention characteristics revealed statistically significant differences at pre-intervention between APOE e4 carriers and non-carriers in total sleep time \( (p = 0.001) \), sleep efficiency \( (p = 0.001) \), and N2 sleep stage \( (p = 0.001) \), see Table 3) with APOE e4 carriers reporting less total sleep time, worse sleep efficiency and less minutes spent in N2 stage of sleep. Over the course of the exercise intervention, stratified analyses revealed statistically significant improvements exclusively in participants who carried the e4 allele. There were statistically significant differences in total sleep time (pre-intervention APOE e4+ mean (SD) = 352 (66.7) minutes versus post-intervention mean (SD) = 406 (44.2) minutes, \( t_6 = -3.880, p = 0.008, \) Cohen’s \( d_z = 1.47 \); see Fig. 3A) and sleep efficiency (pre-intervention APOE e4+ mean (SD) = 73.8 (16.9) versus post-intervention (mean (SD) = 83.2 (11.4)), \( t_6 = 2.615, p = 0.040, \) Cohen’s \( d_z = 0.99; \) see Fig. 3B), however, this comparison did not survive the Bonferroni-Holm correction for multiple comparisons \( \alpha = 0.05/(2-1+1) = 0.025 \). Sleep onset latency in APOE e4+ significantly changed from pre- to post-intervention (pre-intervention APOE e4+ mean (SD) = 20.8 (25.6) versus post-intervention mean (SD) = 15.3 (23.7), \( t_6 = 3.702, p = 0.010, \) Cohen’s \( d_z = 1.38 \); see Fig. 3C). These changes were not related to changes in AHI \( (p = 0.710, p = 0.118, p = 0.353 \) for total sleep time, sleep efficiency and sleep onset latency, respectively).

**DISCUSSION**

We report on the effects of a six-month aerobic exercise intervention on both subjective (PSQI) and objective (PSG) measures of sleep quality in healthy middle-aged and older adults with and without the APOE e4 risk allele. Major findings from the PSQI data for the entire study sample were an improvement in sleep quality reflected by a decrease in overall PSQI scores after the exercise intervention, reduced sleep latency, and increased sleep efficiency. The changes seen in sleep quality were modest in nature though statistically significant. No significant difference in terms of percent change was found between carriers and non-carriers, which is similar to other
samples. These are necessary to replicate our findings in larger quality and perceive it as “normal” [46]. Further study who have grown accustomed to diminished sleep may be especially problematic in an older population than an objective evaluation of the sleep [45]. This individual perception of his/her own sleep rather potential explanation is that the PSQI reflects the who underwent PSG recordings (n = 29). Another possible explanation may be the differences in sample sizes and composition between individuals who completed the PSQI (n = 199) and individuals who underwent PSG recordings (n = 29). Another potential explanation is that the PSQI reflects the individual perception of his/her own sleep rather than an objective evaluation of the sleep [45]. This may be especially problematic in an older population who have grown accustomed to diminished sleep quality and perceive it as “normal” [46]. Further studies are necessary to replicate our findings in larger samples.

This study has several limitations. Neither participants nor investigators were blinded to the intervention. The small sample size, especially for PSG with only seven individuals carrying the risk allele limits the robustness and generalizability of our results. The sample size also limited the choice and power of the statistical analyses. Furthermore, our sample was healthy with an overall good quality of sleep as measured by the PSQI. Although we found a statistically significant positive change in global PSQI scores with the exercise intervention, this change cannot be defined as a clinically meaningful change according to the method discussed by Surman et al. [47]. Moreover, the lack of a control group in the study limits our ability to make firm conclusions about the effect of the exercise intervention. Other factors such as increased socialization may have led to the improvements in general well-being, mood, and sleep. Our results are preliminary and should be interpreted with caution. Future studies are needed to confirm and expand on our findings. We did not collect a familiarization night for PSG and therefore participants scores may reflect the discomfort of sleeping with unfamiliar equipment. Finally, the presence of sleep complaints was not an inclusion criterion. We cannot comment on the potential impact of the exercise intervention on sleep in a population with greater sleep disturbances at baseline.

In our study, aerobic exercise failed to show a clinically meaningful change in the quality of sleep of generally healthy older adults with no sleep complaints at baseline. However, our results could inform the design of future studies targeting older individuals with sleep complaints, a greater degree of comorbidities and/or at higher risk for AD that could shed light on the potential mediating role of improved sleep in understanding the relationship between exercise and cognitive status.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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