Participation in physical activity is associated with reduced nocturnal hypoxaemia in males

David Stevens¹,², Sarah Appleton¹, Yohannes Melaku ³, Sean Martin³, Robert Adams¹,⁴ and Gary Wittert⁵,⁶, on behalf of the MAILES investigators

Affiliations: ¹Sleep Health, Flinders Health and Medical Research Institute, Flinders University, Adelaide, SA, Australia. ²Centre for Nutritional and Gastrointestinal Diseases, South Australian Health & Medical Research Institute, Adelaide, SA, Australia. ³Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia. ⁴Respiratory and Sleep Services, Southern Adelaide Local Health Network, SA, Adelaide, Australia. ⁵Freemasons Centre for Male Health and Health and Wellbeing, The University of Adelaide, and the South Australian Health and Medical Research Institute, SA, Australia.

Correspondence: David Stevens, Sleep Health, Flinders Health and Medical Research Institute, Flinders University, Bedford Park, Adelaide, South Australia 5001, Australia. E-mail: david.stevens@flinders.edu.au

ABSTRACT Moderate to vigorous physical activity (MVPA) interventions reduce the severity of obstructive sleep apnoea (OSA); however, little epidemiological research exists to confirm these findings.

789 participants from the population-based Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study underwent polysomnography. MVPA was assessed using the Active Australia questionnaire, which was completed when participants were first recruited to the MAILES study (2002–2006), and again in 2010. Multinomial logistic regressions established odds ratio between OSA severity categories with MVPA, whilst adjusted linear models determined associations between OSA metrics with MVPA.

Cross-sectionally, each hour of MVPA was associated with reduced severity of mean oxygen desaturation (unstandardised $\beta$ (B)=−0.002, p=0.043) and reduced time below 90% oxygen saturation (B=−0.03, p=0.034).

Longitudinally, each hour increase in MVPA was associated with a 4% reduction in the odds of severe OSA and less severe mean oxygen desaturation (B=−0.003, p=0.014), time below 90% oxygen saturation (B=−0.02, p=0.02), and mean duration of apnoeas (B=−0.004, p=0.016).

MVPA is associated with reduced hypoxaemia in a cohort of community dwelling males, approximately half of whom had untreated OSA. As nocturnal intermittent hypoxaemia is associated with cardiometabolic disorders, MVPA may offer protection for patients with OSA.

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This study provides epidemiological evidence that moderate to vigorous physical activity is associated with less severe OSA-induced hypoxaemia. This result suggests that MVPA should be actively implemented in treatment regimens for people with OSA. https://bit.ly/3a9asiZ

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Introduction

Obstructive sleep apnoea (OSA) is the recurrent reduction (hypopnoea), or complete cessation (apnoea), of airflow during sleep, resulting in intermittent hypoxaemia and arousals from sleep. OSA severity is clinically assessed by the number of apnoeas and hypopnoeas that occur each hour (apnoea/hypopnoea index (AHI)). Severe OSA (AHI≥30), in particular is associated with increased risk of coronary heart disease and stroke [1], type 2 diabetes [2], and all-cause mortality [3, 4]. Recent cohort studies indicate that, whilst 10% of the population have been diagnosed with OSA, roughly 50% of sample populations had undiagnosed OSA [5, 6], with 26–50% of men and up to 25% women experiencing moderate-to-severe OSA.

The current standard treatment for OSA is continuous positive airway pressure (CPAP). In the majority of patients with OSA, varying anatomical and physiological traits causes the upper airway to be collapsible above atmospheric pressure once conscious control of the upper airway is absent during sleep [7]. As the name implies, CPAP continuously delivers positively pressured air to prevent the upper airway from narrowing or collapsing.

Whilst CPAP is effective at reducing the AHI to near negligible levels, compliance, defined as at least 4 h of use per night for 70% of the nights, has historically been poor. Rotenburg et al. [8] showed that for each year over a 20-year period (1994–2015), up to 40% of CPAP users were "non-compliant". Furthermore, recent large randomised controlled trials have demonstrated that CPAP does not reduce the chances of a secondary cardiovascular or cerebrovascular event [9], nor improve glycaemic control of type 2 diabetes [10].

In contrast, of moderate to vigorous intensity physical activity (MVPA) decreases the risk of secondary cardiovascular and cerebrovascular events [11, 12], as well as glycaemic control of type 2 diabetes [13]. Importantly, short-term MVPA intervention studies significantly reduce AHI (for reviews, see Edwards et al. [14] and Medelson et al. [15]). MVPA is effective at reducing BMI through reductions in adiposity, which is a modifiable risk factor for OSA [16], whereas CPAP has very little effect on BMI or weight distribution [17]. A recent cohort study showed more time spent undertaking MVPA was associated with decreased prevalence of self-reported diagnosis of OSA but could not provide data on OSA severity [18]. Likewise, another cohort study showed more time spent undertaking MVPA was associated with reduced odds of polysomnography measured moderate to severe OSA [19]. Their models, however, only adjusted for age and BMI, and no other known important determinants of OSA [19].

Therefore, the aim of this study was to determine the cross-sectional associations between MVPA and the presence and severity of OSA, and the associations between changes in MVPA over time and the presence and severity of OSA, whilst adjusting for known determinants of OSA.

Materials and methods

Participants

Data for this study was collected as part of the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study and has been described in detail previously [20]. Briefly, the MAILES cohort was a combination of two existing cohorts (the North West Adelaide Health Study, and the Florey Adelaide Male Aging Study). These cohorts consisted of randomly selected community-dwelling men living in Adelaide, SA, Australia (2002–2006), recruited using the same sampling frame and methodology. Recruitment occurred by random selection of phone numbers from the electronic telephone directory. Participants who were willing to be involved underwent computer-assisted telephone interviews, answered detailed questions regarding biographical, sociodemographic, co-morbidities and lifestyle risk factors. Participants also underwent a clinical assessment including anthropometry, sphygmomanometer and a fasting blood sample.

The study was approved by both the North West Adelaide Health Service (approval number 201005) and the Royal Adelaide Hospital institutional ethics committee (approval number 02305H). All participants gave written informed consent, with consent collected for each new data collection stage.

Polysomnography

In 2010, a computer assisted telephone interview (n=1629) identified 1445 participants without a previous diagnosis of OSA by polysomnography (PSG). These men were invited by to participate in an in-home PSG (Embletta X100; Embla Systems, Thornton, CO, USA) with 1087 (75.2%) agreeing. By the conclusion of the study period, 861 PSGs had been attempted, including repeated PSGs due to initial failure.

The PSG measured electroencephalography (EEG), electrooculography, chin electromyography, nasal pressure, thoracic and abdominal effort, peripheral pulse oximetry and body position. Trained staff visited study participants in their homes to set-up the sleep study, as well as record height and weight measurements. A single experienced PSG technician, who was blinded to all other survey and biomedical
data, performed manual scoring of PSGs according to 2007 American Academy of Sleep Medicine (alternate criteria [21], which is recommended for use in prospective epidemiological studies. Studies were considered acceptable with 3.5 h of sleep and 5.5 h of total recorded study time. Hypopnoeas were a 50% or more reduction in airflow coupled with either: 1) at least a 3% oxygen desaturation, or 2) an EEG arousal. Apnoeas were a 10-s cessation of airflow. OSA severity was categorised as: mild (AHI 10–19 events·h\(^{-1}\)), moderate (AHI 20–29 events·h\(^{-1}\)) and severe (AHI >30 events·h\(^{-1}\)). The cut-offs for classification were chosen because RUEHLAND et al. [22] showed that an AHI of 5 events·h\(^{-1}\) used to define sleep disordered breathing scored by the “recommended” American Academy of Sleep Medicine (AASM) criteria is equivalent to an AHI of 10 events·h\(^{-1}\) of sleep using the alternate AASM definition.

The PSG provided the following OSA variables; AHI (events·h\(^{-1}\)), mean duration of apnoeas and hypopnoeas (seconds), AHI during rapid eye movement sleep (REM AHI), mean oxygen desaturation (%), and percent of time spent below 90% oxygen saturation (T\(_{90\%}\)). Participants were removed if their oxygen saturation was deemed of poor quality, determined by either; having an AHI <10 events·h\(^{-1}\) but had >20% of the night below T\(_{90\%}\) or spent more than 20% of the night below T\(_{90\%}\) yet had no time below 80% oxygen saturation.

**Physical activity questionnaire**

Physical activity was measured by the Active Australia Survey [23]. During initial recruitment (2002–2006), participants completed the 1999 version of the questionnaire (then called the National Physical Activity Survey), which asked for the amount of time spent, in minutes, undertaking walking, moderated physical activity, and vigorous physical activity, over the past two weeks [24]. In 2010, participants completed an updated version of the questionnaire [23], which assessed activity over the previous week instead of the past two weeks (herein referred to as MVPA-2010).

To synthesise the results from both questionnaires, the values recorded during baseline by the National Physical Activity Survey were halved. Furthermore, vigorous physical activity levels in both questionnaires was given twice the weight of both walking and moderate vigorous physical activity, as per guidelines for both versions of the questionnaire [23, 24]. Thus, the MVPA levels for both questionnaires was the addition of the adjusted vigorous values with the unadjusted moderate and walking values. Longitudinal changes in MVPA levels were calculated by subtracting the baseline MVPA (2002–2006) from the 2010 MVPA assessment (herein referred to as MVPA-Δ).

To increase interpretability of the MVPA values, both MVPA-2010 and MVPA-Δ were converted to hours per week. Participants who reported more than 56 h·week\(^{-1}\) for the MVPA-2010 (i.e. more than 8 h·day\(^{-1}\), which allows those in active professions, such as the construction industry, to be included in the analysis), or more than 56 h·week\(^{-1}\) of change in MVPA-Δ were excluded, as these values were considered unrealistic, suggesting the participant answered the question incorrectly.

**Statistical analysis**

Multinomial logistic regressions and linear models were used in this analysis, both of which adjusted for confounders. Confounders were determined by examining known or suspected determinants of both AHI and T\(_{90\%}\) in univariate models. Covariates with a p<0.1 for both AHI and T\(_{90\%}\) were included in all analyses. The following variables were included as confounders: age, BMI, study group, income, testosterone (log transformed), inflammation using C-reactive protein (log-transformed), diabetes, cardiovascular disease, hypertension and smoking status. Additionally, for MVPA-Δ, we also adjusted for baseline MVPA levels in hours. Details on collection methods of the known or suspected confounders, as well as results for the univariate analyses, are in the online supplementary material (Supplement S1).

Multinomial logistic regression analysis was used to determine the likelihood of the dependent variable, the OSA severity category associated with MVPA-2010 and MVPA-Δ. For the linear regression models, the continuous dependent variables were AHI, REM AHI, mean oxygen desaturation, T\(_{90\%}\) and mean duration of apnoeas and hypopnoeas. These metrics were all normalised by log transformation, however, to increase interpretability of the level of change in OSA/hypoxaemia metric associated with an hour change in MVPA-2010 and MVPA-Δ, the regression coefficients were exponentially transformed. A further analysis is presented in the supplementary material (Supplement S2), which examines differences in OSA indices between participants who increased, and those who decreased, MVPA by at least five hours (300 min) between baseline and 2010.

All statistical analyses were calculated in R (v3.1.0, R Foundation for Statistical Computing, Vienna, Austria), and utilised the “LSR” and “NNET” packages. All models were assessed for linearity and homoscedasticity (residual versus fitted plots and scale-location plots), normal distribution of residuals (Q-Q plot), and influential values (Cooks D>0.5). A p-value <0.05 was considered significant. Figures were created in Prism (GraphPad Software, San Diego, CA, USA).
Results

Participants

Figure 1 illustrates the derivation of the final analysis set; 34 participants were excluded due to inadequate OSA data, whilst an additional 25 participants were removed from the T90% analysis due to potential signal quality issues. Nine participants were excluded for reporting more than 56 h·week\(^{-1}\) of MVPA, whilst a further four were excluded for reporting a change or more than 56 h·week\(^{-1}\). This resulted in the analysis of 789 participants, whose characteristics are outlined in table 1. One participant was excluded from the analysis for mean oxygen desaturation due to be an influential value according to the Cook’s D of 0.5.

Associations between MVPA-2010 with OSA severity categories and nocturnal hypoxaemia metrics

Multinomial logistic regressions indicated that each hour of MVPA was associated with modest but nonsignificant reduced odds for both mild OSA (OR 0.976, 95% CI 0.95–1.01; p=0.11) and severe OSA (OR=0.96, 95% CI 0.91–1.01; p=0.09), and a small, nonsignificant increased odds of moderate OSA (OR=1.01, 95% CI 0.98–1.04; p=0.54).

Forest plots derived from adjusted linear regressions examining cross-sectional associations between MVPA and OSA metrics are shown in figure 2. More time spent undertaking MVPA-2010 was associated with reduced mean oxygen desaturation (unstandardised \(\beta\) \(B\)=−0.002, p=0.043) and reduced T90% \(B=−0.03, p=0.034\). No significant associations occurred with AHI \(b=−0.01, p=0.15\), REM AHI \(B=−0.005, p=0.59\), or the duration of apnoeas \(B=−0.001, p=0.38\) and hypopnoeas \(B=−0.001, p=0.58\).

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**FIGURE 1** Consort diagram showing number, and reasons, for exclusion from analysis. MAILES: Men Androgen Inflammation Lifestyle Environment and Stress; FAMAS: Florey Adelaide Men’s Aging Study; NWAHS: North West Adelaide Health Study; OSA: obstructive sleep apnea; MVPA: moderate to vigorous physical activity.
A sensitivity analysis (not included) indicates that when participants with pulse oximetry irregularities were included in the linear regressions, no differences in associations between MVPA-2010 and OSA indices occurred.

**Associations between MVPA-Δ with OSA severity categories and nocturnal hypoxaemia metrics**

Multinomial logistic regressions indicated that each hour increase in MVPA-Δ was associated with a small, nonsignificant reduced odds of mild OSA (OR 0.980, 95% CI 0.96–1.01; p=0.12), no change in odds of moderate OSA (OR 1.00, 95% CI 0.97–1.03; p=0.89) and a moderate, significant reduced odds of severe OSA (OR 0.960, 95% CI 0.93–0.99; p=0.03).

Forest plots derived from adjusted linear regressions examining associations between MVPA-Δ and OSA metrics are shown in figure 3. There were significant inverse associations between MVPA-Δ and mean oxygen desaturation (B=−0.003, p=0.014), T90% (B=−0.02, p=0.02), and mean duration of apnoeas (B=−0.004, p=0.016). No significant associations occurred with AHI (B=−0.008, p=0.17), REM AHI (B=0.001, p=0.88) or duration of hypopneas (B=−0.001, p=0.27). For interpretability, the change in each metric per hour of MVPA-2010 is shown in table 2.

A sensitivity analysis (not included) indicates that when participants with pulse oximetry irregularities were included in the linear regressions, T90% was no longer associated with MVPA-Δ (B=−0.015, p=0.07). No other changes in associations occurred.

### TABLE 1 Polysomnographic characteristics of study participants

| Characteristic                              | Value     |
|--------------------------------------------|-----------|
| Age years                                  | 60±17     |
| Body mass index kg·m·⁻²                    | 28.5±5.3  |
| AHİ events·h⁻¹                              | 15.7±15.2 |
| REM AHİ events·h⁻¹                          | 19.0±20.0 |
| Mean oxygen desaturation %                 | 4.2±1.0   |
| T90% %                                     | 3.5±3.4   |
| Mean hypopnoea duration s                  | 23.2±6.0  |
| Mean apnoea duration s                     | 21.3±8.2  |
| MVPA-2010 h                                | 4.5±5.6   |
| MVPA-Δ h                                   | 0.3±4.3   |

Data are presented as median±interquartile range. AHİ: apnoea/hypopnoea index; REM: rapid eye movement; T90%: amount of sleep with oxygen saturation <90%; MVPA: moderate to vigorous physical activity; MVPA-2010: time spent undertaking MVPA during 2010 collection; MVPA-Δ: change in time spent undertaking MVPA from baseline (2002–2006) to 2010.

### FIGURE 2 Cross-sectional associations between moderate to vigorous physical activity (MVPA) in 2010 and obstructive sleep apnea metrics. X-axis indicates log-transformed unstandardised β. Adjustments: age, body mass index, study group (Florey Adelaide Men’s Aging Study versus North West Adelaide Health Study), income, serum testosterone, serum C-reactive protein, cardiovascular disease status, diabetes status, hypertension status. Missing data: MVPA difference: 36; income: 20; testosterone: 66; inflammation: 65; diabetes status: 12; cardiovascular disease status: 14; blood pressure: 26; mean O2 desaturation: 1. AHİ: apnoea/hypopnoea index; REM: rapid eye movement; T90%: amount of sleep with oxygen saturation <90%.

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Discussion

This study highlights spending more time engaged in MVPA was associated with less severe nocturnal hypoxaemia indices, but in cross-sectional analyses was not associated with AHI or REM AHI. The same associations with hypoxaemia indices persisted when we examined the changes in time spent engaging in MVPA from baseline (2002–2006) to 2010, suggesting this is a robust finding. Furthermore, increasing MVPA over time was associated with significantly reduced odds of severe OSA.

The results of this study are consistent with the cross-sectional data of DA SILVA et al. [19], despite this study utilising more stringent adjustments for known confounders of OSA, and the different physical activity questionnaires used. Importantly, to our knowledge, this is the first study to examine associations of longitudinal changes in MVPA on OSA metrics. Thus, this study adds further evidence highlighting the potential benefits of MVPA in reducing the severity of OSA [14, 15].

A novel finding of this study was the significant association between increasing the amount of time undertaking MVPA between baseline and 2010 and shorter mean duration of apnoeas, along with the nonsignificant association with shorter mean duration of hypopnoeas. This is clinically important, as longer duration of apnoeas and hypopnoeas are associated with increased prevalence and severity of hypertension [25–27], and increased prevalence of cardiovascular disease [28]. The reductions in apnoea duration, but not hypopnoea duration, may provide a mechanism as to why increased MVPA over time may improve hypoxaemia. Yet, as MVPA-2010 was not associated with either apnoea or hypopnoea mean duration but was associated with improved hypoxaemia indices, changed in MVPA must affect other contributors to OSA and hypoxaemia severity.

| TABLE 2 Percentage change in obstructive sleep apnoea (OSA) metrics for each hour increase in MVPA-2010 and MVPA-Δ |
|-----------------------------------------------|
| OSA index                                   | MVPA-2010 | MVPA-Δ |
|-----------------------------------------------|
| AH events-h⁻¹                               | −0.5      | −0.6   |
| REM AH events-h⁻¹                            | −0.1      | −0.1   |
| Mean oxygen desaturation %                   | −0.2²     | −0.3²  |
| T90% %                                      | −2.0²     | −1.5²  |
| Mean hypopnoea duration s                    | −0.06     | −0.1   |
| Mean apnoea duration s                       | −0.14     | −0.35² |

MVPA-2010: time spent undertaking moderate to vigorous physical activity (MVPA) during 2010 collection; MVPA-Δ: change in time spent undertaking MVPA from baseline (2002–2006) to 2010; AHI: apnoea/hypopnoea index; REM: rapid eye movement; T90%: amount of sleep with oxygen saturation <90%. #: significant association.

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Anatomically, MVPA reduces the fat mass around the upper airway and in the tongue, which has been shown to improve symptoms of OSA [29, 30]. In addition, increased MVPA may target non-anatomical contributors of OSA. For example, the upper airway muscles of patients with OSA fatigue easily, meaning people with OSA are predisposed to experiencing narrowing and collapsing of the upper airway during sleep [31]. In adults without OSA, MVPA results in upper airway muscles that are less susceptible to fatigue [32, 33]. Another non-anatomical contributor is unstable respiratory control, where a person experiences cycles of hyperventilation and hypoventilation due to small changes in blood gasses. Adults who regularly undertake MVPA show more stable respiratory control [34]. Importantly, similar results have been shown in adults with congestive heart failure, a condition increases a person’s susceptibility to unstable respiratory control [35]. As these potential mechanisms have not been examined, however, it remains uncertain why undertaking MVPA is associated with reduced odds of severe OSA and less severe nocturnal hypoxaemia indices, and therefore should be the focus of future research.

Although the changes in hypoxaemia indices per hour of MPVA in this study were not large, epidemiological studies examining other heath conditions have shown small improvements convey large protective benefits at a population level. For example, a 2-mmHg reduction in systolic blood pressure reduced the risk of death due to ischaemic heart disease and stroke by 7% and 10% respectively [36]. Similarly, in the UK, a 1% improvement in HbA1c resulted in approximately GBP 2.5bn reduction over 25 years in healthcare costs due to complications from diabetes [37].

The strength of this study lies in the clinical polysomnography collected in a large cohort of participants representative of the urban dwelling population. A further strength of this study is longitudinal nature of the MVPA data, with the Active Australia questionnaires already used extensively in other epidemiological studies [38, 39].

Only examining the male population can be considered a limitation of this study, as the findings cannot be applied to women. A further limitation is the lack of objectively measured MVPA data; however, as large scale actigraphy measurement was unfeasible until the mid-2010s, this was unavoidable.

As there has only been small, short-duration studies examining the effect of MVPA interventions on OSA, future large randomised, controlled trials are needed to determine the effect of undertaking MVPA without CPAP, and the combination of both MVPA and CPAP, has on OSA severity indices. Additionally, future studies should examine potential mechanisms by which MVPA improves hypoxaemia indices. To do this, longitudinal changes in OSA metrics, as well as studies that can directly measure the anatomical and non-anatomical contributors to OSA, are needed. Importantly, all future studies should objectively measure MVPA by actigraphy, as well as examine all genders.

Our study provides evidence more time spent undertaking MVPA was associated with lower odds of severe OSA, and less severe hypoxaemia. Importantly, whilst CPAP is effective at eliminating hypoxaemia [40], cardiovascular and metabolic health problems still remain in patients with OSA [9, 10]. Therefore, the results of this study, when coupled with the well-established benefits of MVPA on other health conditions [11–13], suggest that MVPA should be prescribed for all patients with OSA.

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Data sharing: De-identified participant data used in this analysis can be shared upon reasonable request. Please contact the corresponding author.

Author contributions: D. Stevens conceived the overall analysis. D. Stevens and Y. Melaku planned the analysis, whilst D. Stevens carried out the analysis. S. Appleton, S. Martin, R. Adams and G. Wittert are key investigators on the MAILES study. All authors contributed to the interpretation and analysis, as well as the final manuscript. D. Stevens takes full responsibility for the integrity of the data and accuracy of the analysis results.

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