# Physical activity as a moderator for obstructive sleep apnoea and cardiometabolic risk in the EPISONO study

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ABSTRACT Obstructive sleep apnoea (OSA) is positively associated with cardiometabolic diseases; however, high levels of physical activity could decrease the incidence of OSA and associated comorbidities.

In this study we aimed to examine the incidence of OSA in relation to physical activity, and its role as a protective factor in individuals with OSA on the incidence of cardiometabolic diseases, in an 8–9-year follow-up study. We analysed data of 658 volunteers from the São Paulo Epidemiologic Sleep Study (EPISONO), a cohort study of individuals aged 20–80 years, collected through polysomnography, the International Physical Activity Questionnaire and an assessment of cardiometabolic profile.

Active subjects had a lower risk of developing OSA compared with nonactive subjects (relative risk 0.877, 95% CI 0.296–0.855) and there was a reduced risk of developing type 2 diabetes mellitus in active/apnoeic subjects (relative risk 0.493, 95% CI 0.252–0.961) compared with nonactive subjects. Metabolic equivalent was negatively associated to cardiometabolic markers, such as C-reactive protein (exp($B$)=0.720; p=0.001), interleukin-6 (exp($B$)=0.991; p=0.03), insulin (exp($B$)=0.982; p=0.03), triglycerides (exp($B$)=0.997; p<0.001), homeostasis model assessment for insulin resistance (exp($B$)⩽0.946; p<0.024), quantitative insulin sensitivity check index (exp($B$)=992.4; p<0.001) and mean arterial pressure (exp($B$)=0.987; p=0.001).

Physical activity was a protective factor against type 2 diabetes mellitus in apnoeic individuals; moreover, being active reduced the risk of developing OSA and was associated with a better cardiometabolic profile.

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## Introduction

The intermittent hypoxaemia and sleep fragmentation experienced by obstructive sleep apnoea (OSA) patients is associated with several metabolic and inflammatory changes that contribute to the pathophysiology of cardiometabolic diseases, including type 2 diabetes mellitus (T2DM), hypertension, myocardial infarction and metabolic syndrome [1]. Increases in pro-inflammatory factors, such as C-reactive protein (CRP) and interleukin (IL)-6, and impairment of glucose metabolism have been described as being responsible for these associations [2].

Over the last few decades, the literature has extensively described the protective capacity of physical activity on cardiometabolic disease development. Increased physical activity is associated with better glucose metabolism, body composition, blood pressure, inflammatory profile and increased life expectancy [3]. Given the unfavourable cardiometabolic profile found in OSA patients, increased physical activity could be an adjunctive tool in the treatment of OSA [4]. Some cross-sectional studies and clinical trials have suggested that physical activity has a beneficial effect on OSA, including reducing CRP, apnoea–hypopnoea index (AHI) and excessive daytime sleepiness, and improving sleep quality and quality of life [5–8]. However, there is no evidence showing that a high physical activity level is associated with a better inflammatory profile and lower incidence of cardiometabolic disease in OSA patients [4].

In OSA patients, increased physical activity could improve body composition and inflammatory profile [9, 10], reduce fat accumulation in the cervical region [7, 11], improve the sensitivity of chemoreceptors [12], improve the strength of respiratory muscles [11] and decrease overnight fluid shift from the legs to the pharynx wall [13]. Thus, we hypothesised that the better metabolic profile of active individuals plays a protective role against OSA and reduces the relative risk of cardiometabolic diseases. In this study, we aimed to examine the effect of physical activity as a moderator of the association between cardiometabolic diseases and OSA. Physical activity was identified as a protective factor that reduced OSA severity, and the incidence of T2DM, hypertension, myocardial infarction and metabolic syndrome, in an 8–9-year follow-up study.

## Methods

A sample of 658 volunteers of both sexes from the São Paulo Epidemiologic Sleep Study (EPISONO) aged 20–80 years was evaluated. The selection process and study methods have been described previously [14]. Baseline data were collected between July and December 2007; follow-up data were collected from January 2015 to December 2016. The study was approved by the Ethics Committee for Research of the Universidade Federal de São Paulo/Hospital, São Paulo, Brazil (CEP 0593/06), registered with ClinicalTrials.gov (NCT00596713) and informed consent was obtained.

### *Data collection*

The volunteer arrived at the sleep laboratory 2 h before their habitual bedtime and had a light meal before data collection (questionnaires and polysomnography (PSG)). The habitual bedtime was observed and blood samples for biochemical assays were collected on the following morning.

### *Anthropometric measures and questionnaires*

Body mass index (BMI), blood pressure and waist circumference were evaluated before the light meal. The International Physical Activity Questionnaire (IPAQ) version 6 was employed to assess physical activity level. IPAQ classifies individual physical activity levels as low, moderate and high, and is able to estimate the metabolic equivalent (MET) based on the reported time spent on slow, moderate and vigorous activities over 1 week [15]. A quality control group for the IPAQ was formed by three researchers to exclude questionnaires with inconsistent information, *e.g.* >7 days of activity during the week or too many minutes of activity (7000–10 000 min per week). Participants were also asked to complete a sleep diary, and in cases where the activity time reported in the IPAQ was very long and would leave only a short period for sleep, it was consulted to verify the responses. Detailed information on the classification of volunteers by IPAQ is given in supplementary tables S2 and S3.

A questionnaire about general health was used to identify diagnosed diseases, such as myocardial infarction, hypertension and T2DM. The volunteers were asked if they had been diagnosed with any of these disorders by a physician (day/month/year of diagnosis), if they had done or did any medical monitoring and if they used any medication related to these diseases. Volunteers were classified in respect of metabolic syndrome according to the criteria of the International Diabetes Federation [16].

### *Polysomnography*

Full-night PSG was scored according to standardised criteria for investigating sleep [17]. The parameters of interest were stages N1, N2, N3 and rapid eye movement (REM) sleep, AHI, total sleep time (TST), sleep onset latency, REM sleep latency, sleep efficiency (TST/total recorded time×100), arousal index, and

wake after sleep onset (WASO). The volunteers were then classified according to their AHI as non-OSA (AHI <5 events·h$^{-1}$), mild OSA (AHI ⩾5– <15 events·h$^{-1}$), moderate OSA (AHI ⩾15– ⩽30 events·h$^{-1}$) and severe OSA (AHI >30 events·h$^{-1}$) [18].

### *Biochemical and haematological assays*

Serum and plasma were obtained by venipuncture to analyse cardiometabolic markers, including CRP, IL-6, insulin, blood glucose, high-density lipoprotein (HDL) and triglycerides. Insulin resistance was evaluated using the homeostasis model assessment for insulin resistance (HOMA-IR) [19] and insulin sensitivity by the quantitative insulin sensitivity check index (QUICKI) [20].

### *Statistical analysis*

Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). A generalised linear model (GzLM) using gamma distribution determined by Akaike information criterion was used to determine the differences between OSA groups and the association between variables.

The GzLM model of the association between variables (PSG and biochemical parameters as independent variables) used follow-up MET as a dependent variable and basal MET as covariates. This model assesses the differences in the follow-up values after accounting for basal values. In the GzLM approach, the focus is on whether one group has higher values after 8–9 years. The adjustment for the basal score in GzLM has two benefits: 1) to make sure that any follow-up differences truly result from the physical activity level and are not some leftover effect of (usually random) basal differences between the groups, and 2) to account for variation around the follow-up means that comes from the variation resulting from the patient's baseline level.

The GzLM used to compare groups was constructed from the dependent variables at follow-up (physical characteristics, PSG parameters and blood markers), covariating by their respective baseline values. The pairwise comparison was performed through a Bonferroni test.

Chi-squared tests were used to analyse the distribution of sex in the groups and the association between the categorical variables (physical activity level and OSA severity). The groups with OSA were stratified by IPAQ classification into low active and active (moderate active plus+high active (supplementary table S3)) to compute the relative risk of diseases through log-linear analysis. Statistical significance was considered when $p \leqslant 0.05$.

## Results

In total, 1042 volunteers were evaluated and 712 volunteers completed all steps, giving a dropout of 31.66%. After the IPAQ assessment, 658 volunteers were included, with 211 classified as non-OSA, 201 as mild OSA, 123 as moderate OSA and 123 as severe OSA. A participant flowchart and additional patient characteristics are presented in figure 1 and table 1.

The comparison of age between groups showed that the non-OSA group had lower values compared with the other groups ($p<0.001$), and that the mild OSA group had lower values than the moderate and severe OSA groups ($p=0.001$) (Wald=158.8, d.f.=3; $p<0.001$). The same was found in relation to waist circumference (Wald=35.621, d.f.=3; $p<0.001$). BMI was higher in the moderate and severe OSA groups compared with the non-OSA group ($p=0.04$); in addition, the severe OSA group showed increased values in relation to the mild OSA group ($p=0.05$) (Wald=12.972, d.f.=3; $p=0.005$). There was a higher frequency of females in all groups, except the mild OSA group (Pearson Chi-squared=35.203, d.f.=4; $p<0.001$). In the PSG parameters, statistical differences in WASO were observed, with higher values in the moderate ($p=0.019$) and severe OSA groups ($p<0.001$) compared with the non-OSA group, and in the severe OSA group compared with the mild OSA group ($p=0.002$) (Wald=22.893, d.f.=3; $p<0.001$); differences between AHI were observed among all groups (Wald=1514.961, d.f.=3; $p<0.001$). The severe OSA group showed higher stage N1 sleep than the other groups ($p<0.001$) and the moderate OSA group showed higher values than the non-OSA group ($p<0.001$) (Wald=59.679, d.f.=3; $p<0.001$). Stage N3 sleep was lower in the severe OSA group compared with all groups (Wald=22.609, d.f.=3; $p<0.001$). There were no differences between groups in TST, sleep onset latency, sleep efficiency, REM latency, stage N2 sleep and REM sleep (table 1).

The comparison of blood markers showed high insulin values in all OSA groups compared with the non-OSA group (Wald=23.126, d.f.=3; $p<0.001$). The moderate and severe OSA groups showed higher blood glucose values compared with the non-OSA ($p=0.008$) and mild OSA ($p=0.01$) groups (Wald=21.314, d.f.=3; $p<0.001$). HOMA-IR was increased in all groups compared with the non-OSA group (Wald=28.742, d.f.=3; $p<0.001$). The severe OSA group had higher values compared with the mild OSA group ($p=0.036$). QUICKI values were also higher in all apnoea groups (Wald=36.574, d.f.=3;

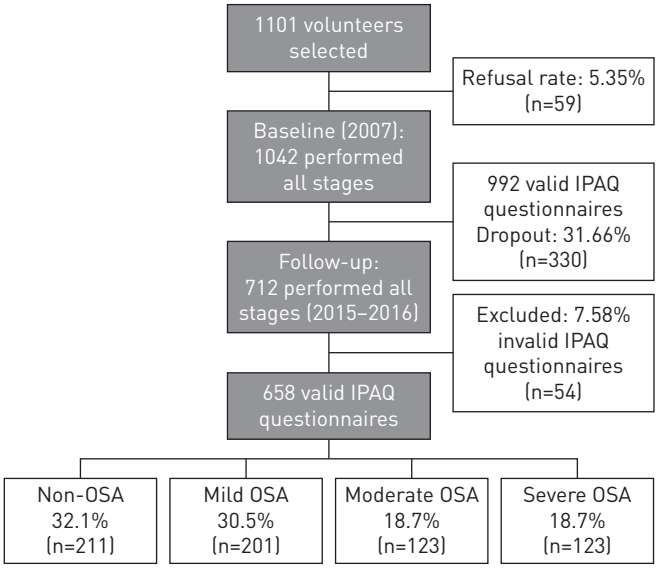


FIGURE 1 Participant flowchart. IPAQ: International Physical Activity Questionnaire; OSA: obstructive sleep apnoea.

p<0.001); moreover, the severe OSA group showed higher values compared with the mild OSA group (p=0.008). There were no differences between the OSA groups for CRP and IL-6 (p>0.05) (table 1). HDL was lower in the severe OSA group compared with the non-OSA group (p=0.03). Triglycerides were higher in the mild and severe OSA groups compared with the non-OSA group (p<0.001). More information with means at baseline and follow-up values is provided in supplementary table S1.

The incidence of OSA was 52.9% and presents an association with low physical activity levels (Chi-squared (1)=5.291; p=0.021). Participants with low physical activity levels had a 1.123-fold higher risk of developing OSA compared with active subjects. Considering OSA as a risk exposure, there was an interaction between OSA and metabolic syndrome (Chi-squared(1)=28.437; p<0.001), with a 1.407-fold higher risk of apnoeic individuals developing metabolic syndrome. The same was found in relation to T2DM (Chi-squared (1)=32.334; p<0.001; relative risk 3.527), myocardial infarction (Chi-squared(1)=7.813; p=0.005; relative risk 4.374) and hypertension (Chi-squared(1)=34.977; p<0.001; relative risk 2.016) (table 2).

The apnoeic individuals were stratified into "active OSA" and "low active OSA", with the log-linear analysis indicating that the highest-order interaction (active OSA patients×cardiometabolic outcomes) was significant for T2DM (Chi-squared(1)=4.848; p=0.028). The calculation of relative risk indicated that apnoeic individuals classified as active were protected against T2DM, with a relative risk of 0.493. There were no interactions between active OSA patients with hypertension (Chi-squared(1)=0.705; p=0.4), myocardial infarction (Chi-squared(1)=2.452; p=0.117) and metabolic syndrome (Chi-squared(1)=0.005; p=0.9) in the population studied (table 2).

Higher MET values were negatively correlated with AHI (p<0.001), arousals (p=0.01) and WASO (p<0.001). The association between AHI and MET was maintained even when adjusted for BMI (p=0.003). A positive association was found between MET and REM sleep (p=0.02). Sleep onset latency, sleep efficiency, TST, and N1, N2 and N3 sleep did not show an association with METs (p>0.05). Negative associations were found between MET and CRP (p=0.001), IL-6 (p=0.03), insulin (p=0.03) and HOMA-IR (p=0.024). QUICKI was positively associated to MET (p<0.001), but blood glucose did not show an association with MET (p>0.05). Regression data can be seen in table 3.

The analyses showed a statistical difference for MET among groups (Wald=26.146, d.f.=3; p<0.001). Compared with the non-OSA group, MET values were on average 47.4% lower in the mild OSA group (p<0.001), 57.8% lower in the moderate group (p<0.001) and 69.7% lower in the severe OSA group (p<0.001). Moreover, the mild OSA group showed higher MET values compared with the severe OSA group (p=0.019). The MET per week in different groups is shown in supplementary figure S1.

## Discussion

To the best of our knowledge, this is the first prospective study based on data from a probabilistic sample (EPISONO study) that assesses the impact of physical activity in respect of the association between OSA and cardiometabolic markers. In this study, the relative risk of developing T2DM increased to 3.527 in subjects with OSA after 8–9 years of follow-up; however, this association was inverted in apnoeic individuals classified as physically active, with a relative risk of 0.493. Apnoeic individuals also had

TABLE 1 Sample description

| | Total sample | Groups | | | | p-value |
|---|---|---|---|---|---|---|
| | | Non-OSA | Mild OSA | Moderate OSA | Severe OSA | |
| **Subjects** | 658 | 211 | 201 | 123 | 123 | |
| **Age years** | 50±13.01 (49.05–51.08) | 42±10.4 | 49±12.3$^{\#}$ | 55±12.4$^{\#,\P}$ | 58±13.4$^{\#,\P}$ | <0.001 |
| **BMI kg·m$^{-2}$** | 28±5.43 (27.82–28.65) | 26±0.2 | 27±0.2 | 22±0.2$^{\#}$ | 28±0.2$^{\#,\P}$ | 0.005 |
| **Waist circumference cm** | 97±13 (96.05–98.16) | 93±0.9 | 96±0.9$^{\#}$ | 99±1$^{\#,\P}$ | 101±0.9$^{\#,\P}$ | <0.001 |
| **SBP mmHg** | 136.7±18.3 (135.1–138) | 130±1.1 | 136±1.2$^{\#}$ | 140±1.6$^{\#}$ | 143±1.6$^{\#,\P}$ | <0.001 |
| **DBP mmHg** | 86.4±12.3 (85.56–87.46) | 84.1±0.8 | 85.9±0.8 | 88.4±1.1$^{\#}$ | 89.2±1.1$^{\#}$ | 0.001 |
| **MAP mmHg** | 103.2±13.5 (102.1–104.1) | 98.7±1.2 | 101.7±1.2 | 105.2±1.2$^{\#}$ | 107.3±1.2$^{\#,\P}$ | <0.001 |
| **Sex** | | | | | | |
| Male | 291 (44) | 61 | 91 | 69 | 70 | <0.001 |
| Female | 367 (56)$^{\S}$ | 150$^{\S}$ | 110 | 54$^{\S}$ | 53$^{\S}$ | |
| **PSG parameters** | | | | | | |
| TST min | 356±80 (350.5–362.7) | 348±7.9 | 356±7.6 | 340±7.1 | 336±6.8 | >0.05 |
| Sleep latency min | 15±11 (13.77–16.99) | 17±1.6 | 14±1.3 | 14±1.3 | 15±1.3 | >0.05 |
| Sleep efficiency % | 80±11 (79.87–81.7) | 79±1.1 | 81±1.1 | 78±1 | 77±1 | >0.05 |
| REM latency min | 97.8±57 (93.41–102.2) | 93±4.8 | 95±4.7 | 99±4.9 | 111±5.2 | >0.05 |
| Arousals events·night$^{-1}$ | 81±59 (77.3–84.7) | 93.6±36 | 112.4±46$^{\#}$ | 133.7±51$^{\#}$ | 198.9±80$^{\#,\P,+}$ | <0.001 |
| WASO min | 84.5±53.8 (80.4–88.6) | 75.5±3 | 78.6±3.2 | 92.8±4.9$^{\#}$ | 101.4±5.4$^{\#,\P}$ | <0.001 |
| AHI events·h$^{-1}$ | 16.5±18 (15.18–17.94) | 3±0.3 | 10±0.4$^{\#}$ | 21±0.7$^{\#,\P}$ | 45±1.3$^{\#,\P,+}$ | <0.001 |
| Stage N1 sleep % | 13.8±9.9 (13.1–14.6) | 12.3±0.6 | 13.2±0.6 | 15±0.7$^{\#}$ | 21.3±0.9$^{\#,\P,+}$ | <0.001 |
| Stage N2 sleep % | 40±8 (39.85–41.17) | 40.2±0.8 | 38.8±0.8 | 38.8±0.8 | 38.4±0.7 | >0.05 |
| Stage N3 sleep % | 25±8.9 (24.23–25.63) | 26±0.9 | 27±0.9 | 25±0.8 | 21±0.7$^{\#,\P,+}$ | <0.001 |
| REM sleep % | 20.8±6.9 (20.13–21.23) | 20.4±0.7 | 20.2±0.7 | 19.6±0.7 | 18.2±0.6 | >0.05 |
| **Blood markers** | | | | | | |
| CRP mg·dL$^{-1}$ | 0.35±0.59 (0.304–0.395) | 0.29±0.05 | 0.32±0.04 | 0.34±0.04 | 0.34±0.04 | >0.05 |
| IL-6 pg·mL$^{-1}$ | 10±13.8 (8.98–11.08) | 9.1±0.9 | 10.5±0.9 | 11±0.9 | 10.1±0.8 | >0.05 |
| Insulin mmol·L$^{-1}$ | 10.1±6.6 (9.58–10.60) | 8.2±0.4 | 9.5±0.4$^{\#}$ | 10.2±0.4$^{\#}$ | 11.1±0.5$^{\#}$ | <0.001 |
| Blood glucose mg·dL$^{-1}$ | 107.8±31.9 (105.3–110.2) | 111.7±1.7 | 113.7±1.6 | 120.8±1.7$^{\#,\P}$ | 120.9±1.6$^{\#,\P}$ | <0.001 |
| HOMA-IR | 2.79±2.38 (2.59–2.95) | 2.16±0.12 | 2.55±0.13$^{\#}$ | 2.87±0.15$^{\#}$ | 3.13±0.16$^{\#,\P}$ | <0.001 |
| QUICKI | 0.343±.035 (0.340–0.345) | 0.355±0.002 | 0.344±0.002$^{\#}$ | 0.337±0.002$^{\#}$ | 0.332±0.002$^{\#,\P}$ | <0.001 |
| HDL mg·dL$^{-1}$ | 48.6±12.7 (45–51.8) | 50±0.9 | 49.4±0.8 | 48.3±0.8 | 46.4±0.7$^{\#}$ | 0.03 |
| Triglycerides mg·dL$^{-1}$ | 146.9±95 (140.2–154.5) | 121.9±4.9 | 137±5.1$^{\#}$ | 137.4±5.2 | 153.1±5.5$^{\#}$ | <0.001 |

Data are presented as n, mean±SD (95% CI), mean±SD or n (%), unless otherwise stated. OSA: obstructive sleep apnoea; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PSG: polysomnography; TST: total sleep time; REM: rapid eye movement; WASO: wake after sleep onset; AHI: apnoea–hypopnoea index; CRP: C-reactive protein; IL: interleukin; HOMA-IR: homeostasis model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check index; HDL: high-density lipoprotein. Comparisons of data using the generalised linear model with pairwise comparison through a Bonferroni test. The dependent variables were covariates by basal moment and group. Comparisons between sex were made using the Chi-squared test. $^{\#}$: different from non-OSA; $^{\P}$: different from mild OSA; $^{+}$: different from moderate OSA; $^{\S}$: different between sex. Statistical significance when $p \leqslant 0.05$.

increased relative risk of developing hypertension (2.016), myocardial infarction (4.374) and metabolic syndrome (1.407). Moreover, at follow-up, the relative risk of developing OSA was reduced to 0.877 in active subjects and we observed that increased MET was negatively associated with OSA severity, even when adjusted for BMI.

Others authors reported the increased incidence of T2DM in apnoeic individuals. The Wisconsin Sleep Study showed an OR of 2.30 for individuals with AHI $\geqslant$15 events·h$^{-1}$ and the value increased to 3.48 in individuals with AHI >30 events·h$^{-1}$ compared with individuals with AHI <5 events·h$^{-1}$ [21]. Botros *et al.* [22] observed a hazard ratio of 1.43, with relative risk being reduced in individuals submitted to treatment. Knowing that OSA and T2DM have many common risk factors, physical activity could act on these factors and reduce the incidence of both diseases, but so far no study has reported the protective effect of physical activity on T2DM development in OSA patients [4].

The possible mechanism by which physical activity treats/prevents T2DM is probably through increased amounts of glucose transporter type 4 in skeletal muscle and activating its translocation to the cell membrane, thereby improving insulin sensitivity [23]. Physical activity can also affect body mass, reducing the percentage of fat and triglyceride accumulation, which is directly associated to obesity-related insulin resistance [24]. Measurements of insulin resistance and sensitivity in apnoeic subjects suggest they have impaired glucose metabolism, which provides further evidence of the association between OSA and

TABLE 2 Interaction between obstructive sleep apnoea (OSA), physical activity level and risk of developing cardiometabolic disease

| | OSA | Diabetes mellitus | Hypertension | Myocardial infarction | Metabolic syndrome |
|---|---|---|---|---|---|
| **OSA** | | 3.527# (2.212–5.624) | 2.016# (1.594–2.555) | 4.374# (1.408–13.589) | 1.407# (1.246–1.588) |
| **Active/OSA** | | 0.493# (0.252–0.961) | 0.873 (0.631–1.207) | 0.230 (0.030–1.785) | 1.006 (0.853–1.185) |
| **Active subjects** | 0.877# (0.780–0.986) | 0.503# (0.296–0.855) | 0.830 (0.642–1.074) | 0.456 (0.130–1.600) | 0.969 (0.848–1.107) |

Data are presented as relative risk (95% CI). #: $p \leqslant 0.05$.

T2DM. The negative association between MET with insulin, HOMA-IR and QUICKI also reinforces the protective effect of physical activity against T2DM in active/apnoeic subjects. Previous studies have shown an association between T2DM and physical activity level [25, 26]; however, the present study demonstrates for the first time the protective effect of physical activity on the incidence of T2DM in apnoeic subjects. The findings highlight the importance of encouraging apnoeic individuals to have more active lifestyles as an adjuvant for the prevention/treatment of T2DM.

Another important finding of our study is the negative association between physical activity level and OSA severity, even when adjusted for BMI. Previous epidemiological studies suggested this association; however, it was not possible to establish a causal relationship because they were cross-sectional [27–30]. A case–control study showed an OR for moderate–severe OSA of 0.6 (95% CI 0.5–0.8), 1.6 (95% CI 1.2–2.0) and 2.7 (95% CI 1.9–3.7) in high, low and nil exercise groups, respectively [8]. Studies based on physical training programmes support this hypothesis, showing that after an intervention, apnoeic subjects have

TABLE 3 Association between metabolic equivalent (MET), sleep, blood parameters and physiological indices

| | Mean±SD | Wald | Exp(*B*) (95% CI) | p-value |
|---|---|---|---|---|
| **PSG parameters** | | | | |
| AHI events·h$^{-1}$ | 16.5±18.04 | 53.06 | 0.976 (0.970–0.983) | <0.001 |
| AHI adjusted to BMI events·h$^{-1}$ | 16.5±18.04 | 47.721 | 0.971 (0.953–0.990) | 0.003 |
| Sleep latency min | 25.4±21.08 | 0.882 | 1.003 (0.997–1.008) | 0.3 |
| Arousals events·h$^{-1}$ | 22.3±12 | 6.251 | 0.988 (0.979–0.997) | 0.01 |
| WASO min | 126.6±64 | 13.429 | 0.997 (0.995–0.998) | <0.001 |
| Sleep efficiency % | 80.7±11.9 | 0.256 | 0.998 (0.989–1.007) | 0.6 |
| TST min | 356.5±80 | 0.997 | 1.001 (0.999–1.002) | 0.3 |
| Stage N1 sleep % | 23.8±9.9 | 1.918 | 0.993 (0.983–1.003) | 0.1 |
| Stage N2 sleep % | 40.5±8.6 | 0.016 | 1.001 (0.989–1.013) | 0.8 |
| Stage N3 sleep % | 24.9±9.1 | 0.156 | 0.998 (0.986–1.010) | 0.6 |
| REM sleep % | 20.6±7.1 | 5.437 | 1.018 (1.003–1.034) | 0.02 |
| **Blood parameters** | | | | |
| CRP mg·dL$^{-1}$ | 0.35±0.59 | 11.770 | 0.720 (0.597–0.869) | 0.001 |
| IL-6 pg·mL$^{-1}$ | 10.09±13.8 | 4.538 | 0.991 (0.982–0.999) | 0.03 |
| Insulin mmol·L$^{-1}$ | 10.12±6.6 | 4.719 | 0.982 (0.966–0.998) | 0.03 |
| Blood glucose mg·dL$^{-1}$ | 107.8±32 | 0.317 | 0.999 (0.994–1.003) | 0.5 |
| HDL mg·dL$^{-1}$ | 48.6±12.7 | 5.777 | 1.014 (1.003–1.025) | 0.016 |
| Triglycerides mg·dL$^{-1}$ | 145.2±85 | 14.336 | 0.997 (0.996–0.999) | <0.001 |
| **Physiological indices** | | | | |
| HOMA-IR | 2.78±2.38 | 5.078 | 0.946 (0.902–0.993) | 0.024 |
| QUICKI | 0.342±0.03 | 16.592 | 992.4 (35.8–27 456.4) | <0.001 |
| SBP mmHg | 136.7±18.4 | 11.091 | 0.991 (0.985–0.996) | 0.001 |
| DBP mmHg | 86.4±12.4 | 9.767 | 0.987 (0.980–0.995) | 0.002 |
| MAP mmHg | 103.2±13.5 | 11.783 | 0.987 (0.980–0.994) | 0.001 |

PSG: polysomnography; AHI: apnoea–hypopnoea index; BMI: body mass index; WASO: wake after sleep onset; TST: total sleep time; REM: rapid eye movement; CRP: C-reactive protein; IL: interleukin; HDL: high-density lipoprotein; HOMA: homeostasis model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure. Generalised linear model using gamma distribution and pairwise comparison through a Bonferroni test. MET was used as dependent variable. Statistical significance when $p \leqslant 0.05$.

reduced AHI and OSA [5–7, 9]. Although there has been extensive research into the association between OSA and physical activity, our study is the first to address aetiological hypotheses and produce incidence estimates.

It is to be expected that a lower risk for the development of OSA and T2DM would be reflected in better metabolic profiles [31]. To support the incidence estimates, we measured biomarkers such as CRP, IL-6, insulin, blood glucose, HDL and triglycerides. Investigations have associated CRP and IL-6 with increased cardiovascular risk [32], but in our study neither were increased in OSA groups. Previous research has not found an association between increases in these biomarkers and OSA, suggesting that others risk factors may be responsible for increased IL-6 and CRP, such as obesity [33, 34]. It has been shown that IL-6 and CRP levels decrease as MET increases, suggesting a protective effect of physical activity [35] independent of OSA. IL-6 is produced in a variety of cells, including adipocyte cells, which stimulates the synthesis of CRP in the liver. A large amount of adipose tissue is, therefore, associated with increased IL-6 and CRP levels [36]. Increased physical activity reduces CRP and IL-6 levels, but this response is strongly linked to a reduction in BMI and body fat [37]. In our study, although the BMI of subjects with moderate–severe OSA was higher than in non-OSA subjects, there was an increase in BMI at follow-up compared with baseline in the non-OSA group, with no changes in the OSA groups. This may be the reason we observed no differences in IL-6 and CRP between groups.

The differences in cardiovascular markers observed in the OSA groups reflect the increased relative risk for the comorbidities, such as dyslipidaemia (HDL and triglycerides), insulin resistance, reduced insulin sensitivity, higher BMI values, waist circumference and blood pressure [1, 2]. The negative association between MET and cardiometabolic markers could explain this, since MET was negatively associated with all of these markers and with AHI. These findings corroborate previous studies that show a better metabolic profile and reduced cardiovascular risk in active individuals [3, 35, 38].

Finally, we highlight the differences in sleep patterns between groups, finding poorer sleep quality in OSA groups, with increased arousals, WASO and N1 sleep, and reduced N3 sleep. Few studies have examined the influence of physical activity on PSG parameters in apnoeic individuals and the physiological significance of these changes is not well understood [6, 13]. We believe that the more superficial sleep found in apnoeic subjects is exclusively due to the higher AHI, which would be reflected in greater excessive daytime sleepiness (not reported here). Moreover, we highlight the fact that increased MET is related to lower AHI, arousals, WASO and REM sleep, which reflects the lower incidence of OSA in active individuals.

This study benefits from a high-quality evaluation of sleep, since PSG is the gold standard for the diagnosis of OSA. However, some limitations should be considered, such as the lack of objective measurement of physical activity. Although the IPAQ has been validated for the Brazilian population, it is possible that individuals overestimate or underestimate the intensity of activities. To minimise these weaknesses, we applied the short self-administered version of the questionnaire, which is more suitable for use in low- and middle-income countries [39]. The group set up specifically to assess the validity of the IPAQ responses excluded 4.79% of the questionnaires at baseline and 7.58% at follow-up, making the results more reliable. A limitation of our study is the fact that the presence of cardiometabolic diseases is based on the participants responses to the questionnaires. Although a diagnosis made by a physician was reported, as well as any treatment or monitoring of the diseases, we did not have access to the medical reports of each volunteer and thus the criteria used for each disease may have variations. Finally, there was a high dropout of volunteers who did not return for the follow-up evaluation. In addition, São Paulo has a large amount of population movement, which made contacting the volunteers difficult, reducing the population representativeness of the sample. Finally, it is important to mention that the number of myocardial infarction events is low (n=15), with only five new events occurring between baseline and follow-up. Although this data suggests an increased risk of myocardial infarction in apnoeic individuals, the estimate of relative risk may be different in other studies.

In conclusion, the present study indicates physical activity has a protective effect on the incidence of T2DM in apnoeic subjects. In addition, a lower incidence of OSA was observed in active subjects and a potential protective effect of increased MET on cardiometabolic markers.

Conflict of interest: M. Mônico-Neto has nothing to disclose. H.K. Moreira Antunes has nothing to disclose. R.V.T. dos Santos has nothing to disclose. V. D'Almeida has nothing to disclose. A. Alves Lino de Souza has nothing to disclose. L.R. Azeredo Bittencourt has nothing to disclose. S. Tufik has nothing to disclose.

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## References


1 Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. *Am J Respir Crit Care Med* 2008; 177: 369–375.
2 Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003; 290: 1906–1914.
3 Myers J, McAuley P, Lavie CJ, *et al.* Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis* 2015; 57: 306–314.
4 Dobrosielski DA, Papandreou C, Patil SP, *et al.* Diet and exercise in the management of obstructive sleep apnoea and cardiovascular disease risk. *Eur Respir Rev* 2017; 26: 160110.
5 Aiello KD, Caughey WG, Nelluri B, *et al.* Effect of exercise training on sleep apnea: a systematic review and meta-analysis. *Respir Med* 2016; 116: 85–92.
6 Sengul YS, Ozalevli S, Oztura I, *et al.* The effect of exercise on obstructive sleep apnea: a randomized and controlled trial. *Sleep Breath* 2011; 15: 49–56.
7 Norman JF, Von Essen SG, Fuchs RH, *et al.* Exercise training effect on obstructive sleep apnea syndrome. *Sleep Res Online* 2000; 3: 121–129.
8 Simpson L, McArdle N, Eastwood PR, *et al.* Physical inactivity is associated with moderate-severe obstructive sleep apnea. *J Clin Sleep Med* 2015; 11: 1091–1099.
9 Kline CE, Crowley EP, Ewing GB, *et al.* The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial. *Sleep* 2011; 34: 1631–1640.
10 Santos RV, Tufik S, De Mello MT. Exercise, sleep and cytokines: is there a relation? *Sleep Med Rev* 2007; 11: 231–239.
11 Schwartz AR, Gold AR, Schubert N, *et al.* Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991; 144: 3, 494–498.
12 Netzer N, Lormes W, Giebelhaus V, *et al.* Korperliches Training bei Patienten mit Schlafapnoe. [Physical training of patients with sleep apnea.] *Pneumologie* 1997; 51: Suppl. 3, 779–782.
13 Redolfi S, Bettinzoli M, Venturoli N, *et al.* Attenuation of obstructive sleep apnea and overnight rostral fluid shift by physical activity. *Am J Respir Crit Care Med* 2015; 191: 856–858.
14 Santos-Silva R, Tufik S, Conway SG, *et al.* Sao Paulo Epidemiologic Sleep Study: rationale, design, sampling, and procedures. *Sleep Med* 2009; 10: 679–685.
15 Craig CL, Marshall AL, Sjostrom M, *et al.* International Physical Activity Questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35: 1381–1395.
16 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469–480.
17 Iber C,Ancoli-Israel S, Chesson A Jr, *et al*. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, American Academy of Sleep Medicine, 2007.
18 Epstein LJ, Kristo D, Strollo PJ Jr, *et al.* Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009; 5: 263–276.
19 Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
20 Katz A, Nambi SS, Mather K, *et al.* Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000; 85: 2402–2410.
21 Reichmuth KJ, Austin D, Skatrud JB, *et al.* Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005; 172: 1590–1595.
22 Botros N, Concato J, Mohsenin V, *et al.* Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 2009; 122: 1122–1127.
23 Rose AJ, Richter EA. Skeletal muscle glucose uptake during exercise: how is it regulated? *Physiology* 2005; 20: 260–270.
24 Kelley DE, Goodpaster B, Wing RR, *et al.* Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. *Am J Physiol* 1999; 277: E1130–E1141.
25 Hjerkind KV, Stenehjem JS, Nilsen TI. Adiposity, physical activity and risk of diabetes mellitus: prospective data from the population-based HUNT study, Norway. *BMJ Open* 2017; 7: e013142.
26 Helmrich SP, Ragland DR, Leung RW, *et al.* Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 1991; 325: 147–152.
27 Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. *Sleep* 2004; 27: 480–484.
28 Quan SF, O'Connor GT, Quan JS, *et al.* Association of physical activity with sleep-disordered breathing. *Sleep Breath* 2007; 11: 149–157.
29 Sunwoo JS, Hwangbo Y, Kim WJ, *et al.* Prevalence, sleep characteristics, and comorbidities in a population at high risk for obstructive sleep apnea: a nationwide questionnaire study in South Korea. *PLoS One* 2018; 13: e0193549.
30 Murillo R, Reid KJ, Arredondo EM, *et al.* Association of self-reported physical activity with obstructive sleep apnea: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prev Med* 2016; 93: 183–188.
31 Kim J, Yoon DW, Lee SK, *et al.* Concurrent presence of inflammation and obstructive sleep apnea exacerbates the risk of metabolic syndrome: a KoGES 6-year follow-up study. *Medicine* 2017; 96: e4488.
32 Danesh J, Kaptoge S, Mann AG, *et al.* Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med* 2008; 5: e78.
33 Taheri S, Austin D, Lin L, *et al.* Correlates of serum C-reactive protein (CRP) – no association with sleep duration or sleep disordered breathing. *Sleep* 2007; 30: 991–996.
34 Sharma SK, Mishra HK, Sharma H, *et al.* Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi. *Sleep Med* 2008; 9: 149–156.
35 Howard B, Winkler EA, Sethi P, *et al.* Associations of low- and high-intensity light activity with cardiometabolic biomarkers. *Med Sci Sports Exerc* 2015; 47: 2093–2101.
36 Bastard JP, Maachi M, Lagathu C, *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006; 17: 4–12.

37 Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med* 2017; 51: 670–676.
38 Harber MP, Kaminsky LA, Arena R, *et al.* Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. *Prog Cardiovasc Dis* 2017; 60: 11–20.
39 Matsudo S AT, Matsudo V, Andrade D, *et al.* International physical activity questionnaire (IPAQ): study of validity and reliability in Brazil. *Braz J Phys Act Health* 2001; 6: 5–18.