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Early View

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Physical activity as a moderator for OSA and cardiometabolic risk in EPISONO study

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***Take Home*:**
Physical activity reduces OSA incidence and protects against cardiometabolic diseases.

Abstract

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

In this study we aimed to examine the incidence of OSA in relation to PA, 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 analyzed data of 658 volunteers from Sao Paulo Epidemiologic Sleep Study, a cohort study of individuals between 20-80 years of age, collected through polysomnography, the international physical activity questionnaire and an assessment of cardiometabolic profile.

Active subjects had a lower risk of developing OSA compared to non-active subjects (RR=0.877, 95%CI=0.296-0.855), and there was a reduced risk of developing type 2 diabetes mellitus (T2DM) in active/apneic subjects (RR=0.493, 95%CI=0.252-0.961), compared to non-active subjects. Metabolic equivalent was negatively associated to cardiometabolic markers, such as C-reactive protein (β=0.72, *P*=0.001), interleukin-6 (β=0.991, P=0.03), insulin (β=0.982, P=0.03), triglycerides (β=0.997, P<0.001), HOMA-IR (β=0.946, P<0.02), QUICKI (β=0.992, P<0.001) and mean arterial pressure (β=0.987, P=0.001).

PA was a protective factor against T2DM in apneic individuals, moreover, being active reduced the risk of developing OSA and was associated with a better cardiometabolic profile.

Introduction

The intermittent hypoxemia and sleep fragmentation experienced by obstructive sleep apnea (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 (MI) and metabolic syndrome (MS) [1]. Increases in pro-inflammatory factors such as C-reactive protein (CRP), interleukin-6 (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 (PA) on cardiometabolic disease development. Increased PA is associated with better glucose metabolism, body composition, blood pressure, inflammatory profile and increased life expectancy [3]. Given the unfavorable cardiometabolic profile found in OSA patients, increased PA could be an adjunctive tool in the treatment of OSA [4]. Some cross-sectional studies and clinical trials have suggested that PA has a beneficial effect on OSA, including reducing CRP, apnea/hypopnea index (AHI), excessive daytime sleepiness, and improving sleep quality and quality of life [5-8]. However, there is no evidences showing that a high PA level is associated with a better inflammatory profile and lower incidence of cardiometabolic disease in OSA patients [4].

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

Methods

A sample of 658 volunteers of both genders from the São Paulo Epidemiologic Sleep Study (EPISONO), aged between 20 and 80 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, Sao Paulo (CEP 0593/06), registered with ClinicalTrials.gov (NCT00596713) and informed consent was obtained.

Data collection

The volunteer arrived at the sleep lab 2 h before their habitual bedtime, and had a light dinner 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 PA level. IPAQ classifies individual PA 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 a week [15]. A quality control group for the IPAQ was formed by three researchers to exclude questionnaires with inconsistent information, i.e., more than 7 days of activity during the week, or too many minutes of activity (7,000 to 10,000 minutes/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 the supplementary data online (Tables S2 and S3).

A questionnaire about general health was applied to identify diagnosed diseases, such as MI, 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 MS according to the criteria of the International Diabetes Federation [16].

Polysomnography

A full-night PSG was scored according to standardized 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 (SL), REM sleep latency, sleep efficiency (SE [the ratio between total sleep time

and total recorded time multiplied by 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), mild OSA (AHI≥ 5 and < 15 events/h), moderate OSA (AHI≥ 15 and ≤ 30 events/h) and severe OSA (AHI> 30 events/h) [18].

Biochemical and hematological assays

Serum and plasma were obtained by venipuncture to analyze cardiometabolic markers, including CRP, IL-6, insulin, blood glucose, high density lipoprotein (HDL) and triglycerides (TG). 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 21.0 software (SPSS Inc., Chicago, Illinois, USA). A generalized linear model (GzLM) using gamma distribution determined by Akaike information criterion (AIC) was used to determine the differences between OSA groups and the association between variables.

The GzLM model of the association between variables (polysomnography 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. The first is to make sure that any follow up differences truly result from the PA level, and are not some left-over effect of (usually random) basal differences between the groups. The second is 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) values, covariating by their respective baseline values. The pairwise comparison was performed through a Bonferroni test.

To analyze the distribution of sex in the groups and the association between the categorical variables (PA level and OSA severity) chi-square tests were used. The groups with OSA were stratified by IPAQ classification into low active and active (moderate active + high active [Table S3]) to compute the relative risk (RR) of diseases through log-linear analysis. Statistical significance was considered when $p \leq 0.05$.

Results

A total of 1042 volunteers were evaluated, and 715 volunteers completed all steps, a dropout of 34.7%. 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 to 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, df=3, P<0.001). The same was found in relation to waist circumference (Wald=35.621, df=3, P<0.001). BMI was higher in the moderate and severe OSA groups compared to 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, df=3, P=0.005). There was a higher frequency of women in all groups, except mild OSA (Pearson χ^2=35.203, df=4, P<0.001). In the polysomnographic parameters, statistical differences in WASO were observed, with higher values in the moderate (P=0.019) and severe OSA groups (P<0.001) compared to the non-OSA group, and in the severe OSA group compared to the mild OSA group (P=0.002) (Wald=22.893, df=3, P<0.001); differences between AHI were observed among all groups (Wald=1514.961, df=3, P<0.001). The severe OSA group showed higher N1 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, df=3, P<0.001). N3 stage was lower in the severe OSA group compared to all groups (Wald=22.609, df=3, P<0.001). There were no differences between groups in TST, SL, SE, REM latency, Stage N2 and REM sleep (**Table 1**).

The comparisons of blood markers showed high insulin values in all OSA groups compared to the non-OSA group (Wald=23.126, df=3, P<0.001). The moderate and severe OSA groups showed higher blood glucose values compared to the non-OSA (P=0.008) and mild OSA (P=0.01) groups (Wald=21.314, df=3, P<0.001). HOMA-IR was increased in all groups compared to the non-OSA group (Wald=28.742, df=3, P<0.001). The severe OSA group had higher values compared to the mild OSA group (P=0.036). QUICKI values were also higher in all apnea groups (Wald=36.574, df=3, P<0.001), moreover, the severe OSA group showed higher values compared to 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 to the non-OSA group (P=0.03), TG was higher in the mild and severe OSA groups compared to the non-OSA group (P<0.001). More information with means at baseline and follow up values can be seen in the supplemental data (Table S1).

The incidence of OSA was 52.9% and presents an association with low PA levels ($\chi^2(1)=5.291$, P=0.021). Participants with low PA levels had a 1.123-fold higher risk of developing OSA compared to active subjects. Considering OSA as a risk exposure, there was an interaction between OSA and MS ($\chi^2(1)=28.437$, P<0.001), with a 1.407- fold higher risk of apneic individuals developing MS. The same was found in relation to T2DM ($\chi^2(1)=32.334$, P<0.001; RR= 2.52-fold), MI ($\chi^2(1)=7.813$, P=0.005; RR= 4.374-fold) and hypertension ($\chi^2(1)=34.977$, P<0.001; RR= 2.016-fold) **(Table 2)**.

The apneic 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 ($\chi^2(1)=4.848$, P=0.028). The calculation of RR indicated that apneic individuals classified as active were protected against T2DM, with a RR of 0.493. There were no interactions between active OSA patients with hypertension ($\chi^2(1)=0.705$, P=0.4), MI ($\chi^2(1)=2.452$, P=0.117) and MS ($\chi^2(1)=0.005$, 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). SL, SE, TST and stages N1, N2 and N3 did not shown an association with MET's (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, df= 3, P<0.001). Compared to the non-OSA group, MET 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 to the severe OSA group (P=0.019). The MET/week in different groups is shown in supplemental data (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 PA in respect of the association between OSA and cardiometabolic markers. In this study, the RR to develop T2DM increased by 3.527-fold in subjects with OSA after 8-9 years of follow up, however this association was inverted in apneic individuals classified as physically active, with an RR of 0.493-fold. Apneic individuals also had increased RR to develop hypertension (2.016-fold), MI (4.374-fold) and MS (1.407-fold). Moreover, at follow up, the RR of developing OSA was reduced by 0.877-fold in active subjects, and we observed that increased MET is negatively associated with OSA severity, even when adjusted for BMI.

Others authors reported the increased incidences of T2DM in apneic individuals. The Wisconsin Sleep Study (2005) showed an odds ratio (OR) of 2.30 for individuals with an AHI≥15, and the value increased to 3.48 in individuals with an AHI>30 compared to individuals with AHI<5 [21]. Botros and colleagues observed a hazard ratio of 1.43, with RR being reduced in individuals submitted to treatment [22]. Knowing that OSA and T2DM have many common risk factors, PA could act on these factors and reduce the incidence of both diseases, but so far, no study has reported the protective effect of PA on T2DM development in OSA patients [4].

The possible mechanism by which PA 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 sensibility [23]. PA can also affect body mass, reducing the percent of fat and TG accumulation, which is directly associated to obesity-related insulin resistance [24]. Measurements of insulin resistance and sensitivity in apneic subjects suggest they have impaired glucose metabolism, which provides further evidence of the association between OSA and T2DM. The negative association between MET with insulin, HOMA-IR and QUICKI, also reinforces the protective effect of PA against T2DM in active/apneic subjects. Previous studies have shown an association between T2DM and PA level [25, 26], however, the present study demonstrates for the first time the protective effect of PA on the incidence of T2DM in apneic subjects. The findings highlight the importance of encouraging apneic 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 PA 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 programs support this hypothesis, showing that after an intervention, apneic subjects have reduced AHI and OSA [5-7, 9]. Although there has been extensive research into the association between OSA and PA, our study is the first to address etiological 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 TG. 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 reduce as MET increases, suggesting a protective effect of PA [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 PA 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 to 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 RR for the comorbidities, such as dyslipidemia (HDL and TG), 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 PA on PSG parameters in apneic individuals, and the physiological significance of these changes are not well understood [6, 13]. We believe that the more superficial sleep found in apneic 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 the PA. Although the IPAQ has been validated for the Brazilian population, it is possible that individuals overestimate or underestimate the intensity of activities. To minimize 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 4.7% of the questionnaires at baseline and 7.9% at follow-up, making the results more reliable. A limitation of our study is the fact that the presence of cardiometabolic diseases are 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, 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, Sao Paulo has a great amount of population movement, which made contacting the volunteers difficult, reducing the population representativeness of the sample.

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

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Table 1. Sample description

Dependent variables	Total Sample (n=658)		Groups				
			Non-OSA (n=211)	Mild OSA (n=201)	Moderate OSA (n=123)	Severe OSA (n=123)	
	Mean±SD	95% CI	mean±SD	mean±SD	mean±SD	mean±SD	*P*
Age (years)	50±13.01	49.05 – 51.08	42±10.4	49±12.3 [a]	55±12.4 [a,b]	58±13.4 [a,b]	**<0.001**
BMI (kg/m^2)	28±5.43	27.82 – 28.65	26±0.2	27±0.2	22±0.2 [a]	28±0.2 [a,b]	**0.005**
Waist circumference (cm)	97±13	96.05 – 98.16	93±0.9	96±0.9 [a]	99±1 [a,b]	101±0.9 [a,b]	**<0.001**
SBP (mmHg)	136.7±18.3	135.1 - 138	130±1.1	136±1.2 [a]	140±1.6 [a]	143±1.6 [a,b]	**<0.001**
DBP (mmHg)	86.4±12.3	85.56 – 87.46	84.1±0.8	85.9±0.8	88.4±1.1 [a]	89.2±1.1 [a]	**0.001**
MAP (mmHg)	103.2±13.5	105.1 – 109.5	98.7±1.2	101.7±1.2	105.2±1.2 [a]	107.3±1.2 [a,b]	**<0.001**
Sex							
Men (nº/%)	291/44%	-	61	91	69	70	**<0.001**
Women (nº/%)	367/55%[†]	-	150[†]	110	54[†]	53[†]	
Polysomnography parameters							
Total sleep time (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.)	108±56	93.41 – 102.2	93±4.8	95±4.7	99±4.9	111±5.2	>0.05
Arousals (nº/night)	81±59	77.3 – 84.7	93.6±36	112.4±46 [a]	133.7±51 [a]	198.9±80 [a,b,c]	**<0.001**
WASO (min.)	84.5±53.8	80.4 – 88.6	75.5±3	78.6±3.2	92.8±4.9 [a]	101.4±5.4 [a,b]	**<0.001**
AHI (events/h)	16.5±18	15.18 – 17.94	3±0.3	10± 0.4 [a]	21± 0.7 [a,b]	45±1.3 [a,b,c]	**<0.001**
Stage N1 of Sleep (%)	13.8±9.9	13.1 – 14.6	12.3±0.6	13.2±0.6	15±0.7 [a]	21.3±0.9 [a,b,c]	**<0.001**
Stage N2 of 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 (%)	25±8.9	24.23 – 25.63	26±0.9	27±0.9	25±0.8	21±0.7 [a,b,c]	**<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)	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)	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)	10.1±6.6	9.20 – 9.81	8.2±0.4	9.5±0.4 [a]	10.2±0.4 [a]	11.1±0.5 [a]	**<0.001**
Blood glucose (mg/dL)	107.8±31.9	105.3 – 110.2	111.7±1.7	113.7±1.6	120.8±1.7 [a,b]	120.9±1.6 [a,b]	**<0.001**
HOMA-IR	2.79±2.38	2.59 – 2.95	2.16±0.12	2.55±0.13 [a]	2.87±0.15 [a]	3.13±0.16 [a,b]	**<0.001**
QUICKI	0.343±.035	0.340 – .345	0.355±.002	0.344±.002 [a]	0.337±.002 [a]	0.332±.002 [a,b]	**<0.001**
HDL (mg/dL)	48.6±12.7	45 – 51.8	50±0.9	49.4±0.8	48.3±0.8	46.4±0.7 [a]	**0.03**
TG (mg/dL)	146.9±95	140.2 – 154.5	121.9±4.9	137±5.1 [a]	137.4±5.2	153.1±5.5 [a]	**<0.001**

Comparisons of data using GzLM test with pairwise comparison of Bonferroni test. The dependent variables were covariates by basal moment and group. Comparisons between sex were made using Chi-square. ([a]) Different from non-OSA; ([b]) different from mild OSA, ([c]) different from moderate OSA, (†) difference between sex. AHI- apnea ans hypopnea index, WASO- wake after sleep onset, BMI- body mass index, REM- rapid eyes movement, CRP- C-reactive protein, IL-6- interleukin-6, HOMA-IR- homeostasis model assessment, QUICKI- quantitative insulin sensivity check index, HDL- high density lipoprotein, TG- triglyceride, SBP- systolic blood pressure, DBP- diastolic blood pressure, MAP- mean arterial pressure, SD- standard deviation, 95% CI- confidence interval of 95%. Statistical significance when $P \leq 0.05$.

Table 2. Interaction between OSA, physical activity level and risk to develop cardiometabolic disease.

	OSA		**Diabetes mellitus**		**Hypertension**		**Myocardial infarction**		**Metabolic syndrome**	
	RR	95%CI	RR	(95%CI)	RR	(95%CI)	RR	(95%CI)	RR	(95%CI)
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)

Relative ratio (RR), obstructive sleep apnea (OSA). * $P \leq 0.05$.

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

Independent variables	Mean±SD	Wald	Exp(B)	95% CI to Exp(B)	*P*
Polysomnography parameters					
AHI (n/h)	16.5±18.04	53.06	.976	.970 – .983	**<0.001***
AHI adjusted to BMI (n/h)	16.5±18.04	47.721	.971	.953 – .990	**0.003***
Sleep latency (min)	25.4±21.08	0.882	1.003	.997 – 1.008	0.3
Arousals (events/h)	22.3±12	6.251	0.988	.979 – .997	**0.01***
WASO (min)	126.6±64	13.429	0.997	.995 – .998	**<0.001***
Sleep eficiency (%)	80.7±11.9	0.256	0.998	.989 – 1.007	0.6
Total sleep time (min)	356.5±80	0.997	1.001	.999 – 1.002	0.3
Stage N1 of sleep %	23.8±9.9	1.918	0.993	.983 – 1.003	0.1
Stage N2 of sleep %	40.5±8.6	0.016	1.001	.989 – 1.013	0.8
Stage N3 of sleep %	24.9±9.1	0.156	0.998	.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)	0.35±0.59	11.770	0.720	.597 – .869	**0.001***
IL-6 (pg/mL)	10.09±13.8	4.538	0.991	.982 – .999	**0.03***
Insulin (mmol/L)	10.12±6.6	4.719	0.982	.966 – .998	**0.03***
Blood glucose (mg/dL)	107.8±32	0.317	0.999	.994 – 1.003	0.5
HDL (mg/dL)	48.6±12.7	5.777	1.014	1.003 – 1.025	**0.016***
Triglycerides (mg/dL)	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	.902 – .993	**0.024***
QUICKI	0.342±0.03	16.592	992.4	35.8 – 27456.4	**<0.001***
SBP (mmHg)	136.7±18.4	11.091	0.991	.985 – .996	**0.001***
DBP (mmHg)	86.4±12.4	9.767	0.987	.980 – .995	**0.002***
MAP (mmHg)	103.2±13.5	11.783	0.987	.980 – .994	**0.001***

Generalized linear model (GzLM) using gamma distribution and pairwise comparison of Bonferroni test. MET (metabolic equivalent) was used as dependent variable. (*) statistical significant value. AHI (apnea-hypopnea index), WASO (wake after sleep onset), CRP (C-reactive protein), IL-6 (interleukin-6), HDL (high density lipoprotein), HOMA (homeostasis model assessment insulin resistance), QUICKI (quantitative insulin sensitivity check index), SBP (systolic blood pressure), DBP (diastolic blood pressure), MAP (mean arterial pressure).

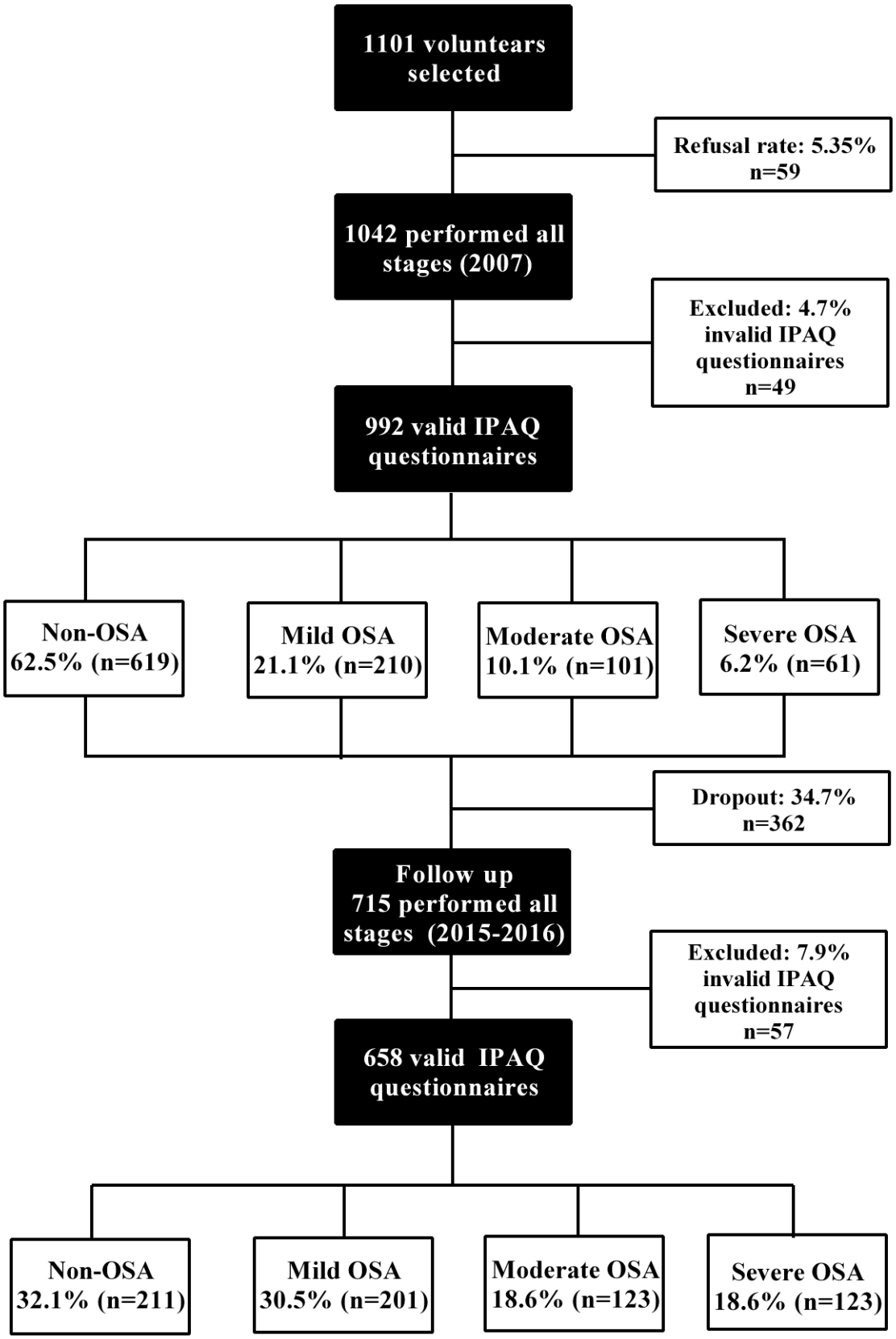
1101 voluntears selected
Refusal rate: 5.35% n=59
1042 performed all stages (2007)
Excluded: 4.7% invalid IPAQ questionnaires n=49
992 valid IPAQ questionnaires
Non-OSA 62.5% (n=619)
Mild OSA 21.1% (n=210)
Moderate OSA 10.1% (n=101)
Severe OSA 6.2% (n=61)
Dropout: 34.7% n=362
Follow up 715 performed all stages (2015-2016)
Excluded: 7.9% invalid IPAQ questionnaires n=57
658 valid IPAQ questionnaires
Non-OSA 32.1% (n=211)
Mild OSA 30.5% (n=201)
Moderate OSA 18.6% (n=123)
Severe OSA 18.6% (n=123)

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Table S1. Sample description at baseline and follow up.

	Groups									
	Total sample		**Non-OSA**		**Mild OSA**		**Moderate OSA**		**Severe OSA**	
	Baseline (n=993)	**Follow-up** (n=658)	**Baseline** (n=619)	**Follow-up** (n=211)	**Baseline** (n=211)	**Follow-up** (n=201)	**Baseline** (n=101)	**Follow-up** (n=123)	**Baseline** (n=61)	**Follow-up** (n=123)
Age (years)	42±13	50±13	34±0.6	42±0.7	41±0.8	49±0.8	47±1.2	55±1.1	50±1.3	58±1.2
BMI (kg/m^2)	28.1±0.28	29.3±0.29	24.6±0.3	26.2±0.3*	28.8±0.9	28.5±0.8	30.6±0.7	30.6±0.8	32±1.3	33.6±1.1
Sex (men/women)[#]	441/552†	292/371†	230/389†	61/150†	108/103	91/110	65/36†	69/54	37/24	70/53†
Waist circumference (cm)	91.5±08	100.9±0.9*	78.3±0.7	90.3±0.8*	91.2±2.3	99.2±2*	98.5±1.8	103.7±1.6	96.3±4.2	108.6±2.5
Sleep parameters										
Total sleep time (min.)	334±8	336±5	363±5	371±5	349±11	368±15	360±16	337±14	336±10	318±13
Sleep latency (min.)	17±1.1	15.9±1.3	13.4±1.1	16.1±1.7	17±2.9	11.8±2.2	19.4±5.4	32±5.4	23±1.7	27.3±3.6
Sleep efficiency (%)	79.9±1.2	77.6±0.8*	85.8±0.8	83.5±0.7	81.4±1.8	80.9±1.9	81.9±2.6	77.4±3.1	79.2±1.8	73.2±2.7
REM sleep latency (min.)	109.4±3.9	103.2±4.4	92.1±2.8	88.8±3.1	103.7±9.5	114.3±11.6	116.6±17.7	98.4±17	112.9±11.6	123±12.3
Apnea/hypopnea index (n/h)	14.5±0.4	17.2±0.7*	1.8±0.07	2.3±0.09*	8.1±0.3 [a]	9.7± 0.4	19±0.6	22.1± 0.9	47.9±2.3	53.4±3.1
Stage N1 of Sleep (%)	5.01±0.2	16.2±0.9*	4.1±0.2	9.9±0.4*	4.3±0.4	12.8±1.3*	4.3±0.5	13.2±1.2*	6.5±0.7	27.4±2.5*
Stage N2 of Sleep (%)	55.7±0.6	39.2±0.8*	53.9±0.5	42±0.5*	54.8±1	41.8±1.4*	55.7±2.5	39±2.3*	60.3±2.2	36.3±1.8*
Stage N3 (%)	20.8±0.4	24±1*	22.5±0.5	25.8±0.5*	21.2±1.1	26±1.8	19.8±1.7	26.9±2	16.5±1.4	20.7±1.4
REM Sleep (%)	18.8±0.3	19.2±0.5	19.4±0.4	22.4±0.4*	20±0.9	19.2±1.2	19.7±1.7	20.8±1.5	17.1±1	16.5±1.4
Blood Markers										
Homocysteine (µmol/L)	10.1±0.1	9.7±0.2	8.9±0.1	8.5±0.2	10.4±0.6	10.5±1	10.1±0.7	9.7±0.7	11.9±0.9	12.6±1.3
CRP (mg/dL)	0.37±0.02	0.4±0.03	0.26±0.02	0.30±0.04	0.31±0.04	0.24±0.04	0.35±0.06	0.32±0.06	0.48±0.15	0.33±0.06
IL-6 (pg/mL)	3.7±0.3	10.7±0.6*	3±0.2	8.3±0.8*	3.1±0.15	9.8±0.7	3.2±0.3	9.7±1.5*	3.1±0.3	10.6±3.3
Insulin (mmol/L)	11.8±0.3	11.4±0.7	9.8±0.4	8.5±0.3	10.5±0.4	10±0.3	13.3±1.6	11.9±1.4	13.9±2.2	12.5±1.4
Blood glucose (mg/dL)	104.4±2.2	115.8±2.3*	91.4±0.6	98.6±1.4*	99.3±3.3	105.1±3.8	110.7±7.2	115±3.9	112.7±3.3	109±3.6
IPAQ Classification[##]										
High activity (n / %)	41 / 4.12	32 / 4.86	30 / 4.84	18 / 8.53	7 / 3.31	10 / 4.97	2 / 1.98	3 / 2.43	2 / 3.22	1 / 0.81
Moderate activity (n / %)	304 / 30.61	237 / 36.01	206 / 33.27	85 / 40.28	63 / 29.85	75 / 37.31	25 / 24.75	42 / 34.14	10 / 16.12	35 / 28.45
Low activity (n / %)	647 / 65.15	388 / 58.96	383 / 61.87	108 / 51.18	141 / 66.82	115 / 57.21	74 / 73.26	78 / 63.41	50 / 80.64	87 / 70.73

Comparisons between baseline and follow up made through generalized estimating equation (GEE) test, whit gamma distribution and Bonferroni post hoc test. Data presented as mean±standard deviation, except # (data presented as absolute number) and ## (data presented as absolute number/percentage). * indicate difference between baseline and follow up in the same group. Differences between groups are shown in table 1.

Table S2. Duration of activity at different intensities during the week.

	Non-OSA		Mild OSA		Moderate OSA		Severe OSA		
	Mean±SD	(95%CI)	Mean±SD	(95%CI)	Mean±SD	(95%CI)	Mean±SD	(95%CI)	*P*
Low activity (min/week)	260±17	(228 – 297)	305±34	(244 – 380)	258±42	(187 – 356)	226±43	(155 – 327)	>0.05
Moderate activity (min/week)	307±24	(263 – 359)	183±25 [a]	(139 – 241)	180±36 [a]	(121 – 266)	118±28 [a]	(73 – 187)	**<0.001**
Vigorous activity (min/week)	34±2	(29 – 39)	40±5.2	(31 – 52)	14±3.7 [a,b]	(8 – 23)	9±3.4 [a,b]	(4 – 17)	**<0.001**

Applied GzLM from gamma distribution to compare groups, using Bonferroni post hoc test. The mean values were obtained from the number of times that each activity was performed during the week multiplied by the time (min) of each activity. (a) Different from Non-OSA and (b) different from Mild OSA.

Table S3. IPAQ classification criteria

Categorical Score	Criteria
Category 1. Low active	No activity is reported OR a. Some activity is reported but not enough to meet Categories 2 or 3.
Category 2. Moderate active	Either of the following 3 criteria: **a.** 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR **b.** 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day OR **c.** 5 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum of at least 600 MET-min/week.
Category 3. High active	Any one of the following 2 criteria: • Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week OR • 7 or more days of any combination of walking, moderate- or vigorous- intensity activities accumulating at least 3000 MET-minutes/week

Validation based on Craig et al. (2003), Brazilian validation based on Matsudo et al. (2001). Criteria taken from https://sites.google.com/site/theipaq/scoring-protocol. MET (metabolic equivalent).

Figure S1.

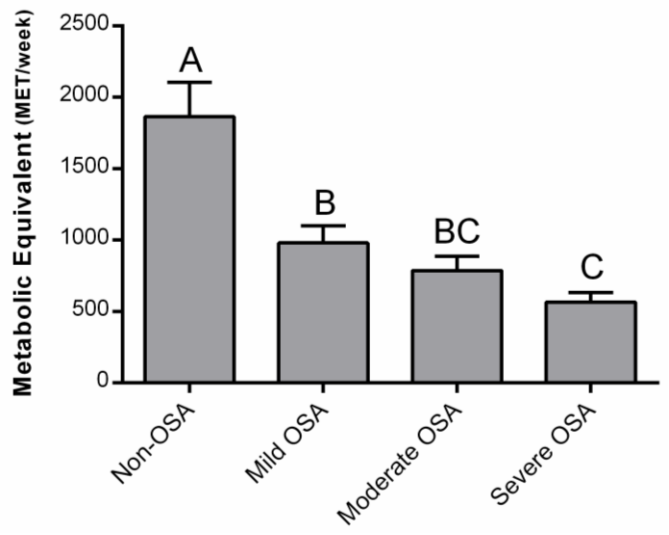

Figure S1. Metabolic equivalent (MET) for week in different groups, adjusted by body mass index. GzLM was applied from gamma distribution and MET at follow up was used as dependent variable, covariate by basal MET. Data shown as mean±standard deviation. OSA (obstructive sleep apnea). Bars with different letters are significantly different ($P \leq 0.05$).

MET calculation:

Walking MET-minutes/week = 3.3 * walking minutes * walking days

Moderate MET-minutes/week = 4.0 * moderate-intensity activity minutes * moderate days

Vigorous MET-minutes/week = 8.0 * vigorous-intensity activity minutes * vigorous-intensity days

Total physical activity MET (minutes/week) = sum of Walking + Moderate + Vigorous MET (minutes/week scores).