# Physical activity: the key to cardiometabolic risk reduction in obstructive sleep apnoea

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**Physical activity is a pivotal variable for cardiometabolic risk reduction in obstructive sleep apnoea**
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Obstructive sleep apnoea (OSA) is a prevalent sleep disorder, with recent estimates reporting prevalence ranging between 3% and 17% for moderate-severe OSA depending on age and sex [1].

Sleep fragmentation and chronic intermittent hypoxia, which characterise OSA, induce intermediate mechanisms such as activation of the sympathetic nervous system [2], oxidative stress and systemic inflammation, all of which contribute to cardiometabolic morbidity [3]. OSA has been associated with a number of cardiometabolic diseases, including hypertension, type 2 diabetes and myocardial infarction [4].

Regular physical activity is considered a cornerstone in the prevention and management of hypertension and cardiovascular disease [5]. An abundance of data demonstrates a reduced risk of both cardiovascular morbidity and mortality with increasing levels of physical activity [6]. Physical activity has also been shown to improve glycaemic control [7] and insulin sensitivity [8] in patients with type 2 diabetes. This is important because it has been shown that OSA is associated with insulin resistance, glucose intolerance and type 2 diabetes, independent of obesity [9].

Regular physical activity reduces the severity of OSA by ∼28% [10]. The precise mechanisms underlying the improvement in apnoea–hypopnoea index following exercise training have not been entirely elucidated. One possibility is that regular physical activity decreases the overnight fluid shift from the legs to the upper airway [11]. Another possibility is that body composition modification and, in particular, changes in fat mass distribution with exercise training may also contribute to alleviation of OSA [12].

Physical activity levels can also influence maximal exercise capacity (*i.e.* peak oxygen consumption ($V'O_2$peak)) [13]. A recent meta-analysis published in the *European Respiratory Journal* reported significantly lower mean $V'O_2$peak (expressed in $mL \cdot kg^{-1} \cdot min^{-1}$) in patients with OSA when compared with controls [14]. This result is noteworthy because reduced maximal exercise capacity has been associated with an increased risk of cardiovascular disease and all-cause mortality in a variety of patient populations [13, 15–17].

In a number of observational studies, physical activity levels in patients with OSA, measured both objectively and subjectively, have been shown to be low. The mean number of measured steps per day in

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eight studies using objective physical activity monitoring was 5388, which was by far lower than the recommended threshold of 10 000 steps per day [10].

In patients with OSA, increasing physical activity levels could contribute to reducing cardiometabolic risk. To date, no prospective study has assessed the association between physical activity and polysomnographic and biochemical variables. In the current issue of the *European Respiratory Journal*, Mônico-Neto *et al.* [18] hypothesised that the healthier metabolic profile of active individuals would play a protective role against OSA and reduce the relative risk of cardiometabolic diseases. To test this hypothesis, the authors analysed a sample of 658 volunteers aged 20–80 years from the São Paulo Epidemiologic Sleep Study (EPISONO) during an 8–9-year follow-up period. All participants underwent polysomnography and a number of biochemical markers were measured (C-reactive protein (CRP), interleukin-6, insulin, blood glucose, high-density lipoprotein 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]. Participants were administered the International Physical Activity Questionnaire (IPAQ) to assess physical activity levels. The 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 [21]. The authors then used a generalised linear model using gamma distribution to determine the differences between OSA groups and the association between variables. The authors found in an 8–9-year follow-up that the risk ratio to develop type 2 diabetes was increased by 3.527-fold in OSA patients; however, OSA patients who were active had a reduced risk of developing type 2 diabetes (risk ratio of 0.493-fold). Furthermore, the risk ratio of developing OSA was reduced by 0.877-fold in active participants and increased MET was negatively associated with OSA severity, even when adjusted for body mass index (BMI). MET was also negatively associated with a number of cardiometabolic markers, including CRP, HOMA-IR, QUICKI and mean arterial blood pressure. The findings of this study imply that physical activity is a protective factor against type 2 diabetes in patients with OSA and that being active reduces the risk of developing OSA and is associated with a better cardiometabolic profile. This noteworthy result confirms the preventive effects of exercise training that our team observed in mice on insulin resistance induced by chronic intermittent hypoxia exposure [22].

The increased incidence of type 2 diabetes in OSA patients has been previously reported [23]. However, this study by Mônico-Neto *et al.* [18] is the first to document a protective effect of physical activity on the development of type 2 diabetes in OSA patients. These authors also observed a negative association of physical activity with insulin, HOMA-IR and QUICKI in the active OSA patient group. The potential mechanism of this protective effect of physical activity is likely to be through an improvement in insulin sensibility, which is caused by increased amounts of glucose transporter type 4 in skeletal muscle [24]. Furthermore, the effect of physical activity on body composition can also improve obesity-related insulin resistance [25]. In addition, it has been shown in mice that an increase in AKT Thr308 phosphorylation in liver as a consequence of exercise training is a potential factor contributing to improvement in insulin resistance induced by chronic intermittent hypoxia [22].

Another important result is the negative association between physical activity and OSA severity, even when adjusted for BMI. The relationship between physical activity and OSA severity has been explored extensively. Previous epidemiological [26] and interventional [11] studies have supported this association; however, Mônico-Neto *et al.* [18] provide the first prospective data with incidence estimates.

The negative association between MET and cardiometabolic markers is another noteworthy finding of this study [18]. Continuous positive airway pressure (CPAP), the first-line therapy for OSA, has a limited effect on cardiometabolic risk factors [27]. Conversely, physical activity has a strong potential to improve metabolic profile and reduce cardiovascular risk. However, it seems surprising that Mônico-Neto *et al.* [18] did not observe a significantly reduced risk of developing hypertension in active patients. In a previous study, we observed an inverse association between objectively measured physical activity and evening blood pressure in severe OSA patients [28]. Lack of statistical power or insufficient follow-up time might have explained the results of Mônico-Neto *et al.* [18].

Interestingly, the group of non-obese moderate OSA patients presents some cardiometabolic alterations, such as insulin resistance and increased HOMA-IR [18]. Therefore, strategies to prevent the progression of cardiometabolic disease in these patients are needed. Taken together, the results of Mônico-Neto *et al.* [18] serve as robust arguments to develop combined treatment strategies that encourage increased physical activity in order to improve prognosis in OSA patients with or without concomitant cardiometabolic diseases. This point is important, since a number of observational studies have shown that OSA patients treated with CPAP do not increase their spontaneous physical activity levels [10, 29]. Furthermore, structured and targeted exercise training programmes aimed at improving maximal exercise capacity

(*i.e.* $V'O_2peak$) may be necessary in order to ensure reduction in cardiovascular risk. In studies that have explored the relationship between improved maximal exercise capacity and survival benefit, it has been shown that each 1-MET higher maximal exercise capacity is associated with considerable (10–25%) improvement in survival [30].

An important limitation in the study of Mônico-Neto *et al.* [18] is the use of subjective physical activity data. It is well known that questionnaires are subject to widely varying bias [31]. More specifically, the short-form IPAQ, which was administered in the present study, has been shown to overestimate physical activity compared to an objective device [32]. The use of objective physical activity monitoring can allow self-reporting bias to be overcome and also captures the participant's sedentary time. This can provide noteworthy information because time spent in sedentary behaviours is known to be a unique and independent risk factor for cardiovascular disease [33].

In conclusion, Mônico-Neto *et al.* [18] provide interesting large-scale data on the relationship between physical activity and type 2 diabetes in patients with OSA. Further research is required to explore the relationship between objectively measured physical activity levels and cardiometabolic risk in patients with and without OSA. Their results also support the need for combined treatment strategies including physical activity in OSA patients with or without concomitant cardiometabolic disease.

Conflict of interest: None declared.

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