ERJ Express. Published on October 4, 2018 as doi: 10.1183/13993003.01150-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original Article

Obstructive sleep apnoea as a risk factor for incident metabolic syndrome: a joined Episono and Hypnolaus prospective cohorts study

Camila Hirotsu, Jose Haba-Rubio, Sonia M. Togeiro, Pedro Marques-Vidal, Luciano F. Drager, Peter Vollenweider, Gérard Waeber, Lia Bittencourt, Sergio Tufik, Raphael Heinzer

Please cite this article as: Hirotsu C, Haba-Rubio J, Togeiro SM, *et al*. Obstructive sleep apnoea as a risk factor for incident metabolic syndrome: a joined Episono and Hypnolaus prospective cohorts study. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01150-2018).

Obstructive sleep apnoea as a risk factor for incident metabolic syndrome: a joined Episono and Hypnolaus prospective cohorts study

*Camila Hirotsu PhD,[1,2] *Jose Haba-Rubio MD,[2] Sonia M Togeiro PhD,[1] Pedro Marques-Vidal PhD[3], Luciano F Drager MD,[4] Peter Vollenweider MD,[3] Gérard Waeber MD,[3] Lia Bittencourt PhD,[1] **Sergio Tufik PhD,[1] **Raphael Heinzer MD[2,5]

[1]Department of Psychobiology, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil; [2]Center for Investigation and Research in Sleep (CIRS), University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [3]Department of Internal Medicine, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [4]Hypertension Unit, Heart Institute (InCor) and Renal Division, University of São Paulo Medical School, São Paulo, Brazil; [5]Pulmonary Department, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [*]Co-first authors/[**]Co-last authors

Corresponding authors:

Raphael Heinzer

Center for Investigation and Research in Sleep

University Hospital of Lausanne (CHUV), Lausanne University, Switzerland

1011 Lausanne, Switzerland

Tel: +41 21 314 67 54 Fax: +41 21 314 67 52

Email: raphael.heinzer@chuv.ch

Sergio Tufik

Department of Psychobiology

Universidade Federal de São Paulo (UNIFESP), Brazil

04024002 Sao Paulo, Brazil

Tel: +55 11 2149 01 55 Fax: +55 11 5572 50 92

Email: sergio.tufik@unifesp.br

"Take home" message: Obstructive sleep apnea (OSA) is an independent risk factor for incident metabolic syndrome (MetS) through mediation of nocturnal hypoxaemia in the general population. Conversely, MetS does not appear to be independently associated with incident OSA.

Abstract

Cross-sectional studies have demonstrated that obstructive sleep apnoea (OSA) and metabolic syndrome (MetS) are often associated, but whether a temporal relationship exists is unknown. We aimed to investigate the effect of OSA on the risk of developing MetS in the general population. A prospective study was conducted combining two population-based samples: Episono (Brazil) and HypnoLaus (Switzerland). MetS was assessed according to the Joint Interim Statement. Polysomnography (PSG) was performed at baseline and follow-up in Episono, and at baseline in HypnoLaus. OSA was defined according to apnoea-hypopnoea index as mild (5.0-14.9/h) and moderate-to-severe (≥15.0/h). We included 1853 participants (52±13 years, 56% female) without MetS at baseline. After 6±1 years, 318 (17.2%) developed MetS. Moderate-to-severe OSA was independently associated with incident MetS (OR=2.58 [1.61-4.11]) and increased the number of MetS components from baseline to follow-up through mediation of %time spent with oxygen saturation <90%. Subset analysis in Episono confirmed that the increase in this parameter between baseline and follow-up PSGs represented a risk factor for incident MetS (OR=1.42 [1.04-1.95] for each 10% increase). In conclusion, OSA is independently associated with an increased risk of developing MetS through mediation of nocturnal hypoxaemia in the general population.

Introduction

Metabolic syndrome (MetS) is a worldwide major public health concern [1]. It is characterized by a cluster of interrelated cardiometabolic risk factors, such as abdominal obesity, atherogenic dyslipidaemia, high blood pressure and hyperglycaemia [2].

Previous investigations have demonstrated that obstructive sleep apnoea (OSA) and MetS tend to cluster in clinical populations [3, 4]. Considering that OSA independently predicts weight gain,[5] it has been postulated that obesity could be the main mediator of the association between OSA and MetS [6, 7]. However, a meta-analysis of 10 cross-sectional studies revealed that OSA was significantly associated with MetS independently of body mass index (BMI) [8]. Intermittent hypoxaemia and sleep fragmentation due to multiple arousals are among the most plausible pathophysiological hypothesis linking OSA to MetS, as they could mediate oxidative stress, impair glucose and lipid metabolism and contribute to a pro-inflammatory state [9].

The relationship between OSA and MetS could be bidirectional with OSA increasing the risk of developing MetS or the opposite. It is thus important to determine the temporal relationship between these two conditions.

Thus, the primary aim of the current study was to evaluate the impact of OSA on the incidence of MetS in a multiethnic sample combining two population-based samples (Episono in Brazil and HypnoLaus in Switzerland). Secondary aims included the analysis of the MetS components affected by OSA and the mediators of this association, as well as the possible bidirectional relationship between MetS and OSA (in Episono cohort).

Material and methods

Study design and population

The sample was derived from two prospective population-based studies: Episono [10] and HypnoLaus [11] (a nested-study of CoLaus/PsyCoLaus) [12]. Episono and HypnoLaus sleep cohorts were designed to assess the prevalence and determinants of OSA in a general population from the cities of São Paulo, Brazil (August 2007 to January 2008) and Lausanne, Switzerland (September 2009 to June 2013), respectively. The design, sampling and procedures of both cohorts were described elsewhere [10, 11]. Briefly, 1074 individuals from Episono and 2162 from HypnoLaus had a baseline examination including demographic, medical history, anthropometric and blood pressure measurements, blood sample collection for biological assays, subjective sleep assessment, and underwent an overnight full polysomnography (PSG).

After a mean follow-up of 7.9 years (Episono) and 5.2 years (HypnoLaus), participants underwent a second examination (July 2015 to April 2016 for Episono, n=712; May 2014 to May 2017 for HypnoLaus, n=1990), in which demographic, clinical and biochemical parameters were reassessed.

Ethics

Episono was approved by the Ethics Committee of Universidade Federal de São Paulo (593/06 and 610514/14) and HypnoLaus by the Ethics Committee of the University of Lausanne (16/03 and 33/09). Written informed consent forms were completed and signed by all participants.

Questionnaires

Information about demographic data, socioeconomic and marital status, self-reported ethnicity, menopausal status, frequency of smoking and alcohol consumption, physical activity, current medications and subjective aspects of sleep was collected using questionnaires in both cohorts. Self-reported sleep duration was obtained from the fourth question of the Pittsburgh Sleep Quality Index, while subjective sleepiness was assessed through the Epworth Sleepiness Scale (ESS) [13].

Clinical data

All measurements were made by trained observers with standard techniques. Body weight was measured in kilograms (kg) using a calibrated scale to within 0·1 kg (Seca®, Hamburg, Germany, HypnoLaus/CoLaus; InBody 720 Biospace, Cerritos, USA, Episono). Height was measured using a vertical stadiometer (Seca®, Hamburg, Germany, HypnoLaus; Professional Stadiometer Sanny, São Paulo, Brazil, Episono) to within 0·5 cm. Waist (at the level of the umbilicus) circumference was measured to within 1 mm with plastic tape.

Systolic (SBP) and diastolic (DBP) blood pressure were assessed in triplicate on the left arm at 5-min intervals with the participant seated and resting for at least 10 min using calibrated automated oscillometric sphygmomanometers (Omron® HEM-907, Matsusaka, Japan for HypnoLaus and Geratherm Desktop 995, Geratherm, Germany, for Episono). The mean of the second and third measurements was used for analysis. Exceptionally in Episono, only one measurement of blood pressure was performed at baseline.

Blood assays

Overnight fasting blood samples were taken from the antecubital vein of each participants in the morning attendance to the outpatient clinic (HypnoLaus) or after PSG (Episono). Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were quantified by colorimetric assays as previously described [10, 12]. C-reactive protein was measured by immunoassay in both cohorts. The assays were performed on fresh blood samples by the CHUV Clinical Laboratory (Lausanne, Switzerland) and the Associação Fundo de Incentivo à Pesquisa (AFIP) Medicina Diagnóstica (São Paulo, Brazil).

Polysomnography

Participants of the Episono cohort were subjected to a full-night PSG at both baseline and follow-up periods in the sleep laboratory (São Paulo, Brazil) using Embla N7000 recorders (Embla Systems Inc., Broomfield, USA). Participants of the HypnoLaus study were equipped with a Titanium PSG recorder (Embla Flaga, Reykjavik, Iceland) and underwent a full-night PSG at their home.

Both sleep cohort studies followed the 2007 American Academy Sleep Medicine (AASM) recommended setup specifications [14]. Physiological variables evaluated during PSG included: electroencephalogram, electrooculogram, surface electromyogram, electrocardiogram, airflow (thermistor and nasal cannula in Episono; nasal cannula in HypnoLaus), respiratory effort by inductance plethysmography belts, oxygen saturation (SpO_2) by pulse oximeter, snoring and body position.

Sleep stages and arousals scorings were performed according to the 2007 AASM manual in both sleep cohorts [14], with the exception of the baseline sleep staging

and arousals scoring from Episono that followed older manuals [15]. Respiratory events were rescored according to the recommended rules of the 2012 AASM manual. OSA severity was classified according to the apnoea-hypopnoea index (AHI) as mild (AHI ≥5 and <15 events/h) or moderate-to-severe (AHI ≥15 events/h). A further dichotomization of OSA as AHI ≥15 events/h vs. <15 events/h was performed based on the lack of substantial evidence about the cardiometabolic consequences of mild OSA [16].

Outcome

MetS was defined according to the Joint Interim Statement[2], i.e. by the presence of at least three risk factors: high blood pressure (SBP ≥130 mm Hg or DBP ≥85 mm Hg or antihypertensive medication); visceral obesity (waist circumference ≥88 cm in women and ≥102 cm in men); high triglycerides (≥1.7 mmol/L or fibrates or nicotinic acid medication); low HDL levels (<1.30 mmol/L in women and <1.03 mmol/L in men, or fibrates or nicotinic acid medication) and high fasting plasma glucose (≥5.6 mmol/L or antidiabetic medication). In the Episono cohort, due to the high ethnical miscegenation, we considered additional cutoffs for waist circumference in those who declared themselves as Asian: ≥80 cm in women or ≥90 cm in men, as recommended by World Health Organization (WHO) [17]. The difference between the number of MetS components between the follow-up and the baseline was denominated as changes in MetS components.

Comorbidities and insulin resistance

Hypertension was defined as a SBP ≥140 mmHg and/or DBP ≥90 mmHg, and/or use of antihypertensive medication. Diabetes was defined by fasting plasma glucose

levels ≥7.0 mmol/L and/or presence of antidiabetic medication [18]. Insulin resistance was evaluated using the homeostatic model assessment (HOMA-IR) defined as fasting serum insulin ($\mu U.ml^{-1}$) × fasting plasma glucose ($mmol.L^{-1}$)/22.5 [19].

Inclusion criteria

Inclusion criteria were: 1) absence of MetS at baseline; 2) complete clinical and biological data for MetS diagnosis at baseline and follow-up; 3) total sleep time (TST) >4 h (to avoid the risk of a misrepresentation of sleep pattern); and absence of central sleep apnoea (CSA), defined as an AHI ≥5 events/h and more than 50% of the events as central.

Statistical analysis

Descriptive data were presented as number of participants (% or 95% confidence interval, CI) for categorical variables or as mean ± standard deviation or median ± interquartile interval for continuous variables. Bivariate analyses were performed using Pearson's chi-square and Mann-Whitney tests. Each sleep-related variable was tested separately as risk factors of incident MetS through multivariable logistic regression adjusted for cohort, age, BMI, and number of MetS components at baseline (Model 1). Then, a fully adjusted model including age, BMI, sex with menopausal status, cohort, number of MetS components, education, physical activity, and marital status at baseline was performed (Model 2). Results from logistic regression were presented as odds ratio (OR) and 95% CI. Since OSA prevalence is different in males and females, a stratified analysis was performed. To understand the mechanisms underlying the effect of OSA on incident MetS, a multivariable-

adjusted logistic regression analyses were performed with the incidence of each MetS component as an independent outcome.

Mediation analysis adjusting for confounders was performed to calculate the direct and indirect effects of OSA on the changes of MetS's number of components by testing possible mediators based on their biological plausibility. The direct effect (c' pathway) indicates the effect of OSA on the changes of MetS's number of components taking into consideration the mediator in the model. Mediation effect was assessed by bootstrap with 1000 replications and Sobel test. Results are presented as effect coefficient (b) and standard error (SE).

From 1046 participants with OSA (AHI>5/h), only 4.2% (n=44) self-reported being on continuous positive airway pressure (CPAP) treatment. However, as sensitivity analysis did not show any impact on the results when including or excluding those subjects, we included all individuals in the results. All analyses were performed using the SPSS software version 21 (IBM, Chicago, USA) with a statistical significance set as two-sided test with $p<0.05$. For mediation analysis, we used the PROCESS procedure for SPSS, version 2.16.3 (model 4).

Results

Studied population

Of the initial 3236 participants of both cohorts, 534 (16.5%) dropped from the follow-up study due to death or consent withdrawal. There were no significant differences between included and excluded participants regarding BMI, MetS and sex

distribution. Conversely, excluded participants were younger, singles, with lower AHI and education, and coming mostly from Episono cohort (Supplementary Table 1).

A comparison of demographic characteristics showed some differences between the cohorts. HypnoLaus had a higher prevalence of MetS at the baseline evaluation compared to Episono (30.7% vs 25.6%). The mean age (54.3 ± 16.6 vs 39.5 ± 19.5 years) as well as the prevalence of AHI≥15/h (27.2% vs 13.2%) were higher in HypnoLaus. On the other hand, the incidence of MetS was greater in Episono (5.6% per year) compared to HypnoLaus (1.5% per year) and associated with older age. In addition, the incidence of MetS was associated with male sex and low education only in HypnoLaus (Supplementary Table 2).

After exclusion of participants with missing data (n=20), baseline MetS (n=768), CSA (n=4), and TST<4 h (n=57), 1853 participants were included in our study (Figure 1). The mean ± standard deviation of age and BMI in the merged sample were 51.9 ± 13.1 years and 24.9 ± 3.7 kg/m^2, respectively. Approximately 56% were female and 88% were white/Caucasian.

After a mean follow-up of 5.9 ± 1.3 years, the incidence of MetS was 17.2% (n=318). Participants who developed MetS were younger and presented higher BMI, lower frequency of postmenopausal women, white/Caucasian ethnicity and higher frequency of middle educational level, Asian, Mixed-race and Black ethnicities and married individuals compared to those who did not (Table 1).

At baseline, participants who developed MetS had a higher number of MetS components as well as higher proportions of diabetes, hypertension, dyslipidaemia, visceral obesity, antihypertensive and antidiabetic medication use, waist circumference, SBP, DBP, insulin, HOMA-IR and triglycerides levels, compared to those who did not (Table 1). Additionally, we observed a lower frequency of weekly

and daily alcohol consumption as well as lower levels of total, LDL, and HDL cholesterol in participants who developed MetS compared to those who did not. Table 2 shows the univariate analysis of the sleep parameters according to the incidence of MetS. At baseline, participants who developed MetS presented lower values of TST, sleep efficiency, REM sleep, arousal index; and higher values of time with SpO_2<90% and ESS score compared to those who did not. Participants who developed MetS also had higher proportion of moderate-to-severe OSA and lower of mild OSA compared to those who did not.

Sleep and incident MetS

Table 3 shows the effect of sleep parameters on incident MetS after adjustment for cohort, age, BMI and number of MetS components at baseline (Model 1). Participants with moderate-to-severe OSA had a 2-fold increased risk of developing MetS compared to no-OSA. After inclusion of age, BMI, sex with menopausal status, cohort, number of MetS components, education, marital status, physical activity, and ethnicity, the effect of moderate-to-severe OSA remained significant (Model 2). Similar findings were obtained when the analysis was split in male and female subsamples (Supplementary Table 3).

Components of MetS affected by OSA status

Among the five components of MetS (Figure 2), we found a significant effect of moderate-to-severe OSA only on the incidence of visceral obesity (OR=1·65, [95% CI: 1.13-3.25]) when compared to no-OSA.

Mediators between OSA and MetS

Mediation analyses using OSA as the independent variable and changes in MetS components as the outcome were performed adjusting for cohort, BMI, age, sex, and number of MetS components at baseline (Table 4). Among sleep parameters, mediation was significant only for time with SpO_2<90%. OSA was a significant predictor of time with SpO_2<90% (b=3.334, SE=0.489, p<0.0001), which in turn was a significant predictor of the changes in MetS components (b=0.005, SE=0.002, p=0.038), supporting the mediational hypothesis. OSA remained a significant predictor of the increase in the number of MetS components after controlling for time with SpO_2<90% (b=0.183, SE=0.046, p<0.0001), indicating partial mediation (Figure 3). Among cardiometabolic parameters, mediation was significant for the increase from baseline to follow-up of waist circumference, fasting glucose and insulin levels, and HOMA-IR. OSA was a significant predictor of increased waist circumference, fasting glucose, fasting insulin and HOMA-IR, which in turn were significant predictors of changes in MetS components. OSA did not remain a significant predictor of changes in MetS components after controlling for each of these mediators, indicating total mediation (Figure 3). In addition, we verified that OSA increased waist circumference and HOMA-IR (but not glucose levels) through partial mediation of time with SpO_2<90% (Figure 4).

Evolution of sleep parameters and MetS incidence

Considering that the Episono's participants also underwent a full PSG at follow-up, we sought to confirm our findings using the evolution of sleep parameters between baseline and follow-up as possible risk factors of MetS incidence (Supplementary Table 4). After adjustment for sex, age, baseline BMI, number of MetS components

and difference in BMI, we found significant effects of the difference in time with SpO_2<90% and in oxygen desaturation index (ODI) on the risk of developing MetS. Each 10% increase in time with SpO_2<90% and each 10 desaturations/h increase of ODI were associated with 36% and 22% higher risk of developing MetS, respectively.

Bidirectional relationship between OSA and MetS

To assess whether the relationship between OSA and MetS could be bidirectional, a subset analysis was performed in 547 participants free of OSA from the Episono cohort (Supplementary Table 5). After adjustment for sex, age and baseline AHI, the presence of baseline MetS was significantly associated with incident OSA (OR=1.92, [95% CI: 1.13-3.25]). Nevertheless, with additional adjustment for baseline BMI, MetS was no longer a significant predictor of incident OSA.

Discussion

To the best of our knowledge, this is the first prospective study to evaluate the impact of OSA and other objectively assessed sleep parameters on the incidence of MetS. Our results show a 6-year MetS incidence of 17.2% in this large multiethnic population-based sample. Moderate-to-severe OSA was independently associated with two-fold increased risk of developing MetS, mainly through an increase in waist circumference mediated by nocturnal hypoxaemia. On the opposite, baseline MetS was not an independent predictor of incident OSA since its effect was mainly attributable to baseline BMI.

Previous cross-sectional studies have demonstrated an independent association between OSA and MetS [8]. Dose-response relationship between OSA severity and some components of MetS have also been shown [11, 20].

In a prospective community-based study, only loud snoring among several subjective sleep symptoms was independently associated with increased risk of MetS [21]. In a subset of 290 participants of this study, AHI was measured using a portable monitor and showed a significant association with incident MetS after adjustment for baseline sociodemographic and lifestyle factors. These results are in line with ours although the authors did not adjust this analysis for the baseline number of MetS components.

Recently, a large prospective Korean population-based study assessed the combined effects of OSA (AHI>10) and inflammation (hs-CRP levels >75th percentile) on the risk of developing MetS [22]. They showed that the coexistence of both baseline OSA and high hs-CRP levels increased the risk of developing MetS over 6 years. Although the authors suggested a possible incremental effect of these factors, baseline OSA or high hs-CRP levels by themselves were also independently associated with a higher risk of MetS. In our results, although hs-CRP was not a significant mediator of the relationship between OSA and incident MetS (Table 4), we found that its increase from baseline to follow-up was greater in the OSA group that developed MetS compared to the others (data not shown).

Our data suggest that nocturnal hypoxaemia, but not sleep fragmentation, is the main mediator of the increased MetS risk induced by OSA. Higher percentage of time with SpO_2<90% at baseline partially mediated the effect of OSA on the increased number of MetS components as well as on the increase of waist circumference and insulin resistance. This was confirmed by a subanalysis of Episono cohort, in which the increase in both ODI and percentage of time with

SpO_2<90% from baseline to follow-up PSGs were the only parameters independently associated with MetS incidence, even after controlling for BMI difference. In a cross-sectional analysis of the Sleep Heart Health Study cohort, participants with respiratory disturbance index (RDI) >15/h showed higher HOMA-IR compared to those with RDI<5/h and 5≤RDI<15/h. Among the possible sleep-related contributors, the authors found independent associations with nocturnal hypoxaemia parameters (mean SpO_2 and time with SpO_2<90%), but not with arousal index [23].

In our study, OSA independently contributed to a higher MetS risk mainly through an increase in waist circumference, leading to higher risk of visceral obesity. Our findings are in agreement with a previous prospective study in which OSA was associated with 0.5 kg/m^2 increase in BMI over 5-year follow-up compared to no-OSA [5]. Additionally, men with ODI≥10/h submitted to a one-year physical exercise intervention program showed smaller reductions in BMI and waist circumference compared to those with ODI<10/h, despite the similar compliance to the program [24].

Besides visceral obesity, our study showed that OSA also increased the number of MetS components by disturbing glucose/insulin homeostasis. Several prospective cross-sectional studies have shown an independent association between OSA and insulin resistance in individuals without type 2 diabetes [25]. Moreover, a meta-analysis of six prospective cohort studies have demonstrated that OSA was independently associated with a greater risk of diabetes [26].

Although our study and others suggest a significant role of OSA in the risk of incident MetS, there is still no clear evidence supporting metabolic benefits of CPAP in OSA patients. Evidence showing modest effects of CPAP in reversing some of the MetS components [20] are somehow contradicted by a metanalysis of randomized

controlled trials (RCT), in which a modest increase in body weight and BMI was found after CPAP therapy [27]. Whether this inconsistency could be explained by a combination of lean mass gain and loss of visceral fat still needs to be determined. In patients with both MetS and OSA, one-year CPAP therapy decreased by 45% the prevalence of MetS due to significant differences in waist circumference and HDL cholesterol [28]. However, there are still inconsistent evidence [29], reinforcing the need of large RCTs to determine whether treatment of OSA may help preventing MetS. In our sample, the increased MetS risk induced by OSA does not seem to rely on blood pressure and lipid changes. Although several RCTs have demonstrated a small but significant reduction in blood pressure with CPAP therapy, it is still unclear whether it could reduce the incidence of hypertension due to a lack of studies and the presence of compliance bias [30]. The contribution of OSA to dyslipidaemia is also not well established. Meta-regressions failed to show reductions in triglycerides or increased levels of HDL cholesterol with CPAP therapy, despite decreased levels of total cholesterol having been demonstrated [31].

On the other hand, our results suggest that MetS by itself is not independently associated with an increased risk of developing OSA. The preponderant effect of BMI indicates a role for obesity on the development of OSA as expected, but it represents only one component of MetS [20]. Currently, no other prospective study evaluated this reverse relationship between OSA and MetS.

Although both Episono and HypnoLaus cohorts were derived from unselected general populations and applied similar standardized methodologies for both sleep and metabolic assessments, there are some limitations to be acknowledged. Episono's PSGs were conducted in the sleep laboratory while HypnoLaus's PSGs were performed at the participants'home. The lack of a night of adaptation in both

cohorts, but mainly in Episono could lead to changes in TST and thus affect AHI. However, in our study we elected to exclude those who had TST<4 h to reduce this bias. Additionally, in the baseline evaluation of Episono, blood pressure was assessed in a single measure, which could possibly lead to an increased number of "white coat" hypertension.

In conclusion, our study shows that, in a multiethnic sample of two population-based samples, moderate-to-severe OSA is an independent risk factor for incident MetS, mainly through the mediation of nocturnal hypoxaemia. Given the high prevalence of OSA and its association with high morbidity and mortality rates, our findings could have far-reaching implications for public health, but RCTs are needed to determine whether recognition and treatment of OSA may lead to a decrease in the incidence of MetS.

Contributors

CH, JHR, SMT, LFD, LB, RH and ST designed the study. CH, JHR, LB, RH and ST were the study investigators, enrolled patients, and collected the study data. All authors contributed equally to interpretation of the data, participated in the critical review and revision of the manuscript, and granted final approval for submission.

Declaration of interests

We declare no competing interests.

Acknowledgements

We thank Prof. Mehdi Tafti and Roberta Siuffi for their important contributions to the HypnoLaus and Episono studies, respectively. The CoLaus study was and is

supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne (FBM), and the Swiss National Science Foundation (SNF, grants 33CSCO-122661, 33CS30-139468 and 33CS30-148401). The Episono study was supported by research grants from AFIP and São Paulo Research Foundation (FAPESP, grant 2014/15259-2).

References

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005: 365(9468): 1415-1428.
2. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr., International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S, International Association for the Study of O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009: 120(16): 1640-1645.
3. Vgontzas AN, Bixler EO, Chrousos GP. Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Med Rev* 2005: 9(3): 211-224.
4. Drager LF, Lopes HF, Maki-Nunes C, Trombetta IC, Toschi-Dias E, Alves MJ, Fraga RF, Jun JC, Negrao CE, Krieger EM, Polotsky VY, Lorenzi-Filho G. The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. *PLoS One* 2010: 5(8): e12065.
5. Brown MA, Goodwin JL, Silva GE, Behari A, Newman AB, Punjabi NM, Resnick HE, Robbins JA, Quan SF. The Impact of Sleep-Disordered Breathing on Body Mass Index (BMI): The Sleep Heart Health Study (SHHS). *Southwest journal of pulmonary & critical care* 2011: 3: 159-168.
6. Sharma SK, Kumpawat S, Goel A, Banga A, Ramakrishnan L, Chaturvedi P. Obesity, and not obstructive sleep apnea, is responsible for metabolic abnormalities in a cohort with sleep-disordered breathing. *Sleep Med* 2007: 8(1): 12-17.
7. Vgontzas AN, Gaines J, Ryan S, McNicholas WT. CrossTalk proposal: Metabolic syndrome causes sleep apnoea. *J Physiol* 2016: 594(17): 4687-4690.
8. Qian Y, Xu H, Wang Y, Yi H, Guan J, Yin S. Obstructive sleep apnea predicts risk of metabolic syndrome independently of obesity: a meta-analysis. *Arch Med Sci* 2016: 12(5): 1077-1087.
9. Drager LF, Polotsky VY, O'Donnell CP, Cravo SL, Lorenzi-Filho G, Machado BH. Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2015: 309(7): H1101-1111.
10. Santos-Silva R, Tufik S, Conway SG, Taddei JA, Bittencourt LR. Sao Paulo Epidemiologic Sleep Study: rationale, design, sampling, and procedures. *Sleep Med* 2009: 10(6): 679-685.
11. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015: 3(4): 310-318.
12. Firmann M, Mayor V, Vidal PM, Bochud M, Pecoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008: 8: 6.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991: 14(6): 540-545.
14. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules terminology and technical specifications. 1st ed. American Academy of Sleep Medicine, Westchester, IL, 2007.
15. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992: 15(2): 173-184.

16. Chowdhuri S, Quan SF, Almeida F, Ayappa I, Batool-Anwar S, Budhiraja R, Cruse PE, Drager LF, Griss B, Marshall N, Patel SR, Patil S, Knight SL, Rowley JA, Slyman A, Apnea ATSAHCoMOS. An Official American Thoracic Society Research Statement: Impact of Mild Obstructive Sleep Apnea in Adults. *Am J Respir Crit Care Med* 2016: 193(9): e37-54.
17. Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H, Kadowaki T. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006: 29(5): 1123-1124.
18. American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010: 33 Suppl 1: S62-69.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985: 28(7): 412-419.
20. Phillips CL, Hoyos CM, Yee BJ, Grunstein RR. CrossTalk opposing view: Sleep apnoea causes metabolic syndrome. *J Physiol* 2016: 594(17): 4691-4694.
21. Troxel WM, Buysse DJ, Matthews KA, Kip KE, Strollo PJ, Hall M, Drumheller O, Reis SE. Sleep symptoms predict the development of the metabolic syndrome. *Sleep* 2010: 33(12): 1633-1640.
22. Kim J, Yoon DW, Lee SK, Lee S, Choi KM, Robert TJ, Shin C. Concurrent presence of inflammation and obstructive sleep apnea exacerbates the risk of metabolic syndrome: A KoGES 6-year follow-up study. *Medicine (Baltimore)* 2017: 96(7): e4488.
23. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, Sleep Heart Health Study I. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 2004: 160(6): 521-530.
24. Borel AL, Leblanc X, Almeras N, Tremblay A, Bergeron J, Poirier P, Despres JP, Series F. Sleep apnoea attenuates the effects of a lifestyle intervention programme in men with visceral obesity. *Thorax* 2012: 67(8): 735-741.
25. Reutrakul S, Mokhlesi B. Obstructive Sleep Apnea and Diabetes: A State of the Art Review. *Chest* 2017: 152(5): 1070-1086.
26. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology* 2013: 18(1): 140-146.
27. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Bensenor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015: 70(3): 258-264.
28. Oktay B, Akbal E, Firat H, Ardic S, Kizilgun M. CPAP treatment in the coexistence of obstructive sleep apnea syndrome and metabolic syndrome, results of one year follow up. *Acta Clin Belg* 2009: 64(4): 329-334.
29. Hoyos CM, Sullivan DR, Liu PY. Effect of CPAP on the metabolic syndrome: a randomised sham-controlled study. *Thorax* 2013: 68(6): 588-589.
30. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, Initiative I. Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation* 2017: 136(19): 1840-1850.
31. Xu H, Yi H, Guan J, Yin S. Effect of continuous positive airway pressure on lipid profile in patients with obstructive sleep apnea syndrome: a meta-analysis of randomized controlled trials. *Atherosclerosis* 2014: 234(2): 446-453.

Table 1. Baseline sample's characteristics according to the incidence of metabolic syndrome.

	Incident metabolic syndrome		N	p-value
	No (n=1535)	Yes (n=318)		
Age (years)	52.2 ± 17.6	46.9 ± 17.7*	1853	**<0.0001**
BMI (kg/m^2)	24.2 ± 4.4	27.0 ± 4.7*	1843	**<0.0001**
Normal (BMI<25)	60.4% (921)	25.1% (80)		**<0.0001**
Overweight (BMI 25-29)	34.4% (524)	55.7% (177)*		
Obesity (BMI≥30)	5.2% (80)	19.2% (61)*		
Sex			1853	0.127
Men	43.1% (662)	47.8% (152)		
Women	56.9% (873)	52.2% (166)		
Ethnicity			1853	**<0.0001**
White/Caucasian	91.9% (1412)	69.5% (221)*		
Mixed-race	3.5% (53)	17.6% (56)*		
Black	2.8% (43)	9.4% (30)*		
Indian	0.4% (6)	0.6% (2)		
Asian	0.7% (11)	2.2% (7)*		
Others	0.7% (10)	0.6% (2)		
Menopausal status			1010	**<0.0001**
Premenopausal	22.3% (337)	29.9% (94)		
Postmenopausal	33.8% (511)	21.7% (68)		
Education			1848	**0.006**
Low	43.2% (661)	44.2% (140)		
Middle	31.7% (486)	38.5% (122)*		
High	25.1% (384)	17.3% (55)*		
Marital status			1842	**0.009**
Single	21.3% (325)	22.4% (70)		
Married	59.0% (902)	65.8 (206)*		
Divorced/Separated	16.4% (252)	10.5% (33)*		
Widowed	3.3% (50)	1.3% (4)		
Number of MetS components	1.0 ± 2.0	2.0 ± 1.0	1838	**<0.0001**
Comorbidities				
Diabetes	2.5% (39)	7.6% (24)	1851	**<0.0001**
Hypertension	25.3% (386)	38.4% (121)	1843	**<0.0001**
Medications				
Antihypertensive	12.7% (195)	20.1% (64)	1853	**0.001**
Hypoglycemic	1.0% (16)	3.5% (11)	1853	**0.001**
Hypolipidemic	11.7% (180)	11.0% (35)	1853	0.715
Smoking			1798	0.346
No	81.1% (1214)	78.8% (238)		
Yes	18.9% (282)	21.2% (64)		
Alcohol consumption			1560	**<0.0001**
Never or rarely	28.1% (359)	52.6% (149)*		
Weekly	51.1% (653)	36.4% (103)*		
Daily	20.8% (265)	11.0% (31)*		
Physical activity			1839	**<0.0001**
No	74.5% (488)	87.3% (1034)		
Yes	25.5% (167)	12.7% (150)		
Waist circumference (cm)	85.1 ± 14.9	90.3 ± 15.8	1851	**<0.0001**
SBP (mmHg)	119.5 ± 20.0	120.0 ± 20.3	1851	**<0.0001**
DBP (mmHg)	75.5 ± 12.5	80.0 ± 12.8	1851	**<0.0001**
Fasting glucose (mmol/L)	5.4 ± 0.6	5.4 ± 0.7	1851	0.577
Fasting insulin (pmol/L)	38.9. ± 27.8	60.1 ± 47.2	1838	**<0.0001**
HOMA-IR	1.3 ± 1.0	2.1 ± 1.8	1838	**<0.0001**
Total cholesterol (mmol/L)	5.5 ± 1.4	5.1 ± 1.5	1851	**<0.0001**
HDL cholesterol (mmol/L)	1.7 ± 0.6	1.4 ± 0.4	1851	**<0.0001**
LDL cholesterol (mmol/L)	3.3 ± 1.2	3.1 ± 1.3	1849	**0.008**
Triglycerides (mmol/L)	1.0 ± 0.6	1.2 ± 0.6	1851	**<0.0001**
hs-CRP (nmol/L)	76.2 ± 128.6	29.5 ± 88.6	1809	**<0.0001**

BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; MetS: metabolic syndrome; SBP: systolic blood pressure; * adjusted residual $>|2|$.
Results expressed as frequency in percentage (n) within each group or median ± interquartile interval and analyzed with bivariate tests (Pearson's chi-square or Mann-Whitney test).

Table 2. Baseline sleep parameters according to incidence of metabolic syndrome.

	Incident metabolic syndrome		N	p-value
	No (n=1535)	Yes (n=318)		
TST (min)	402.0 ± 87.5	366.5 ± 91.9	1853	**<0.0001**
Sleep efficiency (%)	88.7 ± 11.4	86.9 ± 12.1	1853	**0.002**
N3 (%)	20.3 ± 10.4	20.5 ± 9.5	1853	0.469
REM sleep (%)	22.3 ± 7.3	20.3 ± 8.2	1853	**<0.0001**
Arousal index	16.5 ± 11.1	14.6 ± 13.9	1853	**<0.0001**
AHI	6.1 ± 11.2	6.6 ± 14.0	1853	0.065
<5 events/h	43.5% (668)	43.7% (139)		**0.004**
≥5 and <15 events/h	34.2% (525)	26.4% (84)*		
≥15 events/h	22.3% (342)	29.9% (95)*		
Mean SpO_2 (%)	94.9 ± 2.1	94.9 ± 2.4	1853	0.893
Lowest SpO_2 (%)	89.0 ± 7.0	88.0 ± 7.0	1853	0.811
3% ODI	5.5 ± 10.8	4.9 ± 12.9	1850	0.142
Time with SpO_2<90% (%)	0.0 ± 0.4	0.0 ± 0.8	1832	**0.007**
Self-reported sleep duration (h)	7.0 ± 2.0	7.0 ± 2.0	1793	0.115
ESS score	6.0 ± 5.0	8.0 ± 7.0	1755	**<0.0001**

AHI: apnoea-hypopnoea index; ESS: Epworth sleepiness scale; ODI: oxygen desaturation index; N3: slow-wave sleep; REM: rapid eyes movement; SpO_2: oxygen saturation; TST: total sleep time; * adjusted residual $>|2|$.
Results expressed as frequency in percentage (n) within each group or median ± interquartile interval and analyzed with bivariate tests (Pearson's chi-square or Mann-Whitney test).

Table 3. Sleep predictors of incident metabolic syndrome.

	Model 1				Model 2			
	OR	**95% CI**	**N**	**p-value**	**OR**	**95% CI**	**N**	**p-value**
TST (min)	0.998	0.996 - 1.000	1830	0.090	0.998	0.996 - 1.001	1777	0.177
Sleep efficiency (%)	0.990	0.974 - 1.007	1830	0.250	0.994	0.977 - 1.011	1777	0.512
N3 (%)	0.999	0.980 - 1.019	1830	0.960	1.002	0.982 - 1.022	1777	0.852
REM sleep (%)	0.987	0.963 - 1.012	1830	0.303	0.991	0.966 - 1.016	1777	0.467
Arousal index	1.006	0.991 - 1.021	1830	0.424	1.007	0.991 - 1.023	1777	0.395
AHI categories			1830				1777	
<5 events/h		Reference				Reference		
≥5 and <15 events/h	1.19	0.808 - 1.752		0.379	1.443	0.952 - 2.188		0.084
≥15 events/h	2.171	1.413 - 3.336		**<0.0001**	2.576	1.614 - 4.112		**<0.0001**
Mean SpO_2 (%)	0.979	0.940 - 1.020	1830	0.310	0.978	0.938 - 1.019	1777	0.287
Lowest SpO_2 (%)	0.991	0.964 - 1.018	1830	0.509	0.986	0.959 - 1.014	1777	0.328
3% ODI	1.012	0.999 - 1.026	1827	0.074	1.013	0.999 - 1.027	1774	0.077
Time with SpO_2<90% (%)	1.007	0.993 - 1.021	1809	0.320	1.007	0.993 - 1.021	1757	0.330
Self-reported sleep duration (h)	1.008	0.894 - 1.117	1770	0.994	0.996	0.889 - 1.115	1723	0.941
ESS score	1.009	0.976 - 1.045	1732	0.570	1.015	0.980 - 1.051	1683	0.399

AHI: apnoea-hypopnoea index; ESS: Epworth sleepiness scale; N3: slow-wave sleep; ODI: oxygen desaturation index; REM: rapid eyes movement; SpO_2: oxygen saturation; TST: total sleep time.
Results expressed as odds ratio and 95% confidence interval and analyzed using multivariable logistic regression. Adjustment for cohort, age, body mass index and number of metabolic syndrome components at baseline (Model 1); age, sex with menopausal status, body mass index, cohort, ethnicity, education, marital status, physical activity, number of metabolic syndrome components (Model 2).

Table 4. Mediators of the effect of obstructive sleep apnoea on the changes of metabolic syndrome's components.

	Indirect effect of OSA through mediation of:			N	p-value
	b	SE	95% CI		
Baseline sleep parameters					
Total sleep time (min)	0	0.002	-0.005 - 0.005	1805	0.971
Sleep efficiency (%)	0.002	0.003	-0.003 - 0.01	1805	0.543
N3 (%)	-0.005	0.006	-0.018 - 0.007	1805	0.454
REM sleep (%)	0.001	0.04	-0.007 - 0.007	1805	0.879
Arousal index	0.001	0.018	-0.034 - 0.037	1805	0.938
Mean SpO_2 (%)	0.004	0.012	-0.002 - 0.034	1805	0.304
Lowest SpO_2 (%)	0.004	0.015	-0.027 - 0.033	1805	0.762
3% ODI	0.005	0.039	-0.067 - 0.089	1802	0.887
Time with SpO_2<90% (%)	0.018	0.006	0.008 - 0.033	1784	**0.008**
Follow-up cardiometabolic parameters					
Waist circumference (cm)	0.072	0.022	0.029 - 0.118	1805	**0.002**
SBP (mm Hg)	0.021	0.016	-0.014 - 0.053	1802	0.207
DBP (mm Hg)	0.006	0.016	-0.028 - 0.037	1805	0.748
Total cholesterol (mmol/L)	-0.006	0.006	-0.019 - 0.004	1805	0.31
HDL cholesterol (mmol/L)	0.009	0.013	-0.016 - 0.034	1805	0.45
LDL cholesterol (mmol/L)	-0.006	0.005	-0.018 - 0.002	1798	0.243
Triglycerides (mmol/L)	0.013	0.022	-0.023 - 0.066	1805	0.447
Fasting glucose (mmol/L)	0.037	0.02	0 - 0.076	1804	**0.033**
Fasting insulin (pmol/L)	0.05	0.016	0.020 - 0.081	1783	**0.002**
HOMA-IR	0.053	0.016	0.022 - 0.083	1781	**0.001**
hs-CRP (nmol/L)	0.006	0.005	-0.001 - 0.022	1669	0.187

N3: slow-wave sleep; OSA: obstructive sleep apnoea; REM: rapid eyes movement; SpO_2: oxygen saturation; SBP: systolic blood pressure; TST: total sleep time.

Results expressed as effect coefficient (b) and standard error (SE) and analyzed with mediation regressions using PROCESS procedure for SPSS version 2.16.3 with adjustment for sex, age, cohort, body mass index, and number of metabolic syndrome's components at baseline. Additional covariates for SBP and DBP (use of antihypertensive medication at baseline and follow-up); total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (use of hypolipidemic medication at baseline and follow-up); fasting glucose, fasting insulin and HOMA-IR (use of hypoglycemic medication at baseline and follow-up). For cardiometabolic parameters, each follow-up measure was additionally adjusted by its respective baseline measure.

hs-CRP: high-sensitivity C-reactive protein; DBP: diastolic blood pressure; HOMA-IR: homeostatic model assessment of insulin resistance; ODI: oxygen desaturation index;

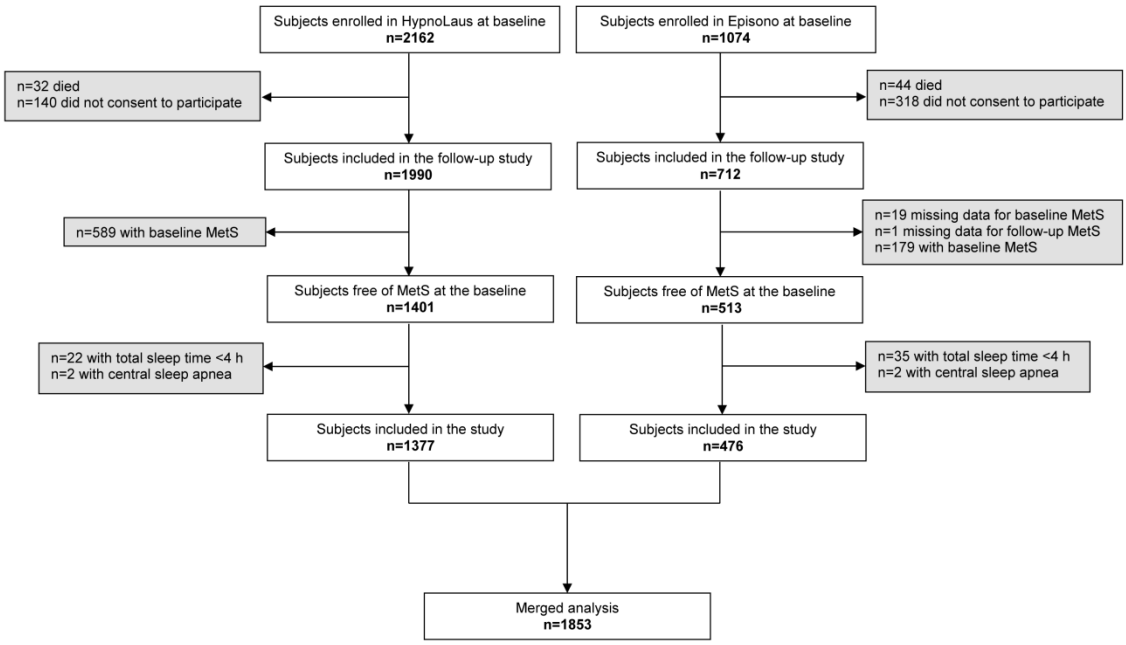
Figure captions

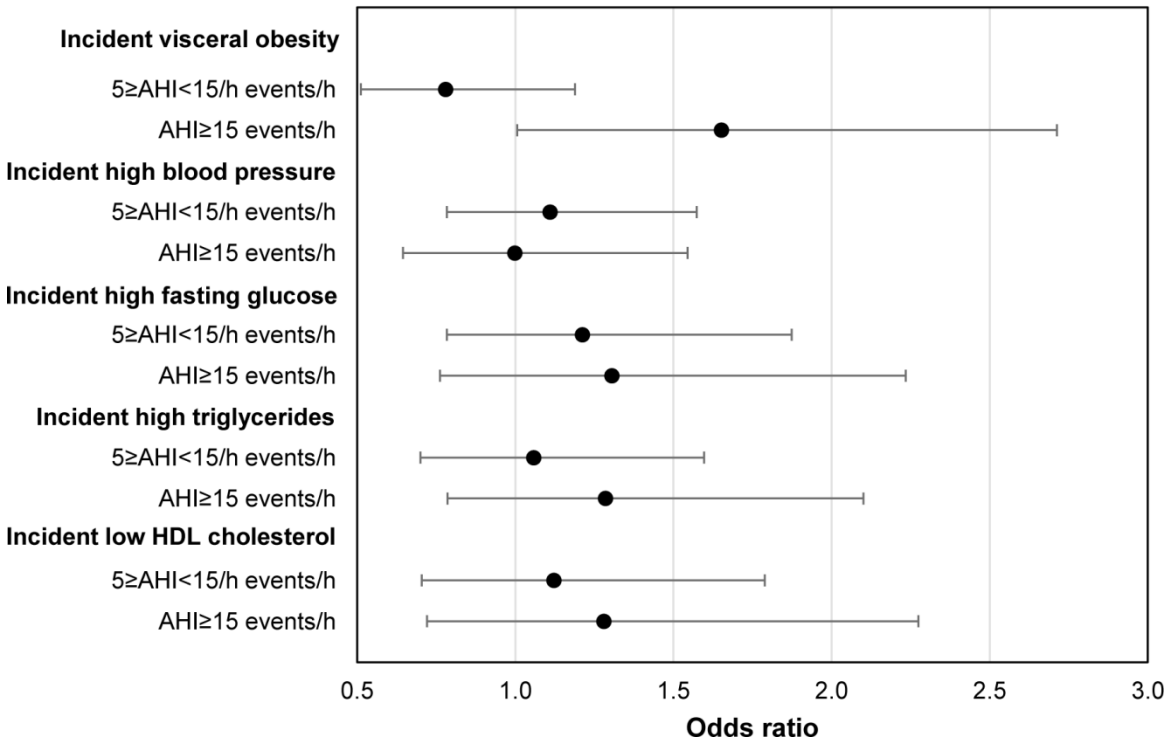
Figure 1. Study design.
PSG: polysomnography; MetS: metabolic syndrome.
Flowchart of the study showing the selection process from initial participant enrollment to final analysis subset.

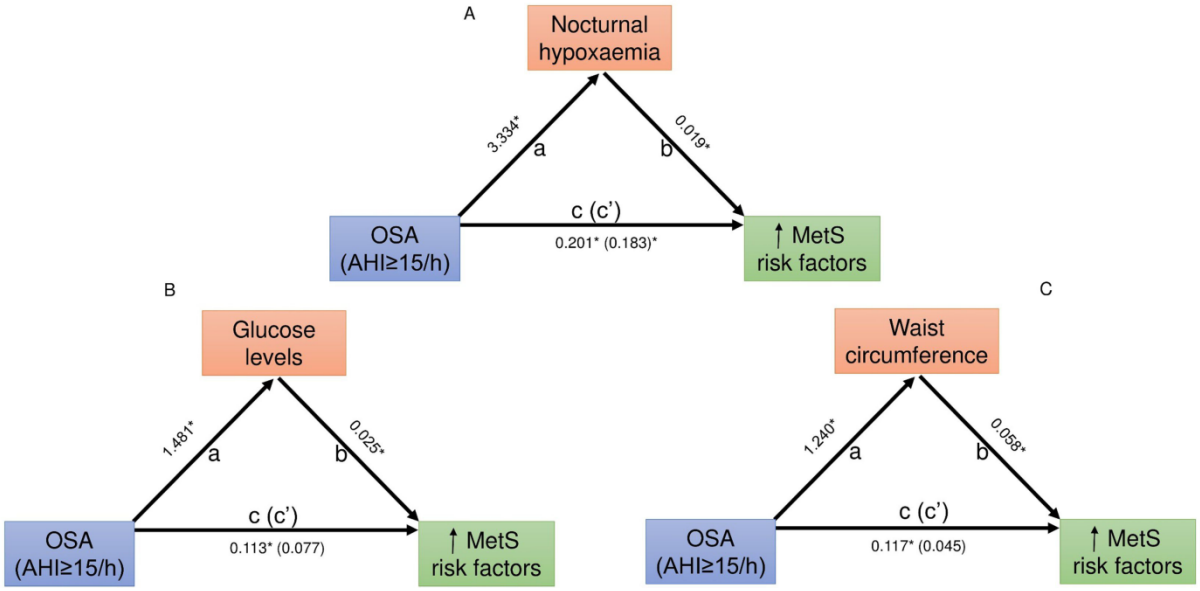
Figure 2. The effect of obstructive sleep apnoea severity by apnoea-hypopnoea index categories on the risk of developing components of metabolic syndrome.
AHI: apnoea-hypopnoea index; HDL: high-density lipoprotein.
Results expressed as odds ratio and 95% confidence interval and analyzed using multivariable logistic regression with adjustment for age, sex, body mass index, cohort, and number of metabolic syndrome components. For each metabolic syndrome component, analyses are restricted to participants devoid of the condition at baseline. Number of participants included: incident visceral obesity (1485), incident high blood pressure (1175), incident high fasting plasma glucose levels (1173), incident high triglycerides (1625), and incident low HDL cholesterol (1698).

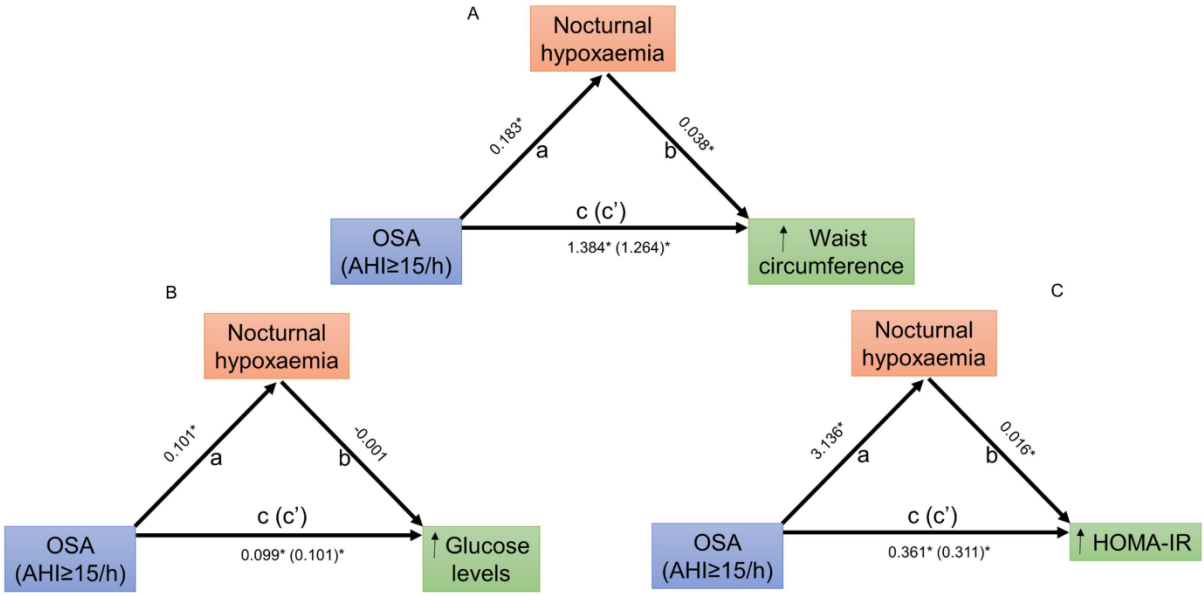
Figure 3. The effect of obstructive sleep apnoea on metabolic syndrome and its mediators.
a: indirect effect; b: indirect effect; c': direct effect; c: total effect; AHI: apnea-hypopnea index; OSA: obstructive sleep apnoea; MetS: metabolic syndrome; *p<0.05.
Standardized regression coefficients for the relationship between OSA and MetS as partially mediated by nocturnal hypoxaemia (A) and totally mediated by waist circumference (B) and glucose levels (C). Results adjusted for sex, age, body mass index, cohort, and number of MetS'components at baseline as well as for the use of antidiabetic medication at both baseline and follow-up when the mediator was the glucose levels change from baseline to follow-up.

Figure 4. The effect of obstructive sleep apnoea on glucose and waist circumference.
a: indirect effect; b: indirect effect; c': direct effect; c: total effect; AHI: apnea-hypopnea index; HOMA-IR: homeostatic model assessment of insulin resistance; OSA: obstructive sleep apnea; *p<0.05.
Standardized regression coefficients for the relationship between OSA and insulin resistance (A) as well as OSA and visceral obesity (B) through mediation of nocturnal hypoxaemia. OSA increased waist circumference and HOMA-IR mediated by nocturnal hypoxaemia independently from age, sex, body mass index, and cohort. Nocturnal hypoxaemia did not mediate the effect of OSA on fasting glucose levels.


Subjects enrolled in HypnoLaus at baseline
n=2162
Subjects enrolled in Episono at baseline
n=1074
n=32 died
n=140 did not consent to participate
n=44 died
n=318 did not consent to participate
Subjects included in the follow-up study
n=1990
Subjects included in the follow-up study
n=712
n=589 with baseline MetS
n=19 missing data for baseline MetS
n=1 missing data for follow-up MetS
n=179 with baseline MetS
Subjects free of MetS at the baseline
n=1401
Subjects free of MetS at the baseline
n=513
n=22 with total sleep time <4 h
n=2 with central sleep apnea
n=35 with total sleep time <4 h
n=2 with central sleep apnea
Subjects included in the study
n=1377
Subjects included in the study
n=476
Merged analysis
n=1853


Incident visceral obesity
5≥AHI<15/h events/h
AHI≥15 events/h
Incident high blood pressure
5≥AHI<15/h events/h
AHI≥15 events/h
Incident high fasting glucose
5≥AHI<15/h events/h
AHI≥15 events/h
Incident high triglycerides
5≥AHI<15/h events/h
AHI≥15 events/h
Incident low HDL cholesterol
5≥AHI<15/h events/h
AHI≥15 events/h
0.5
1.0
1.5
2.0
2.5
3.0
Odds ratio


A
Nocturnal hypoxaemia
3.334*
a
b
0.019*
OSA (AHI≥15/h)
c (c')
0.201* (0.183)*
↑ MetS risk factors
B
Glucose levels
1.481*
a
b
0.025*
OSA (AHI≥15/h)
c (c')
0.113* (0.077)
↑ MetS risk factors
C
Waist circumference
1.240*
a
b
0.058*
OSA (AHI≥15/h)
c (c')
0.117* (0.045)
↑ MetS risk factors


A
Nocturnal hypoxaemia
0.183*
a
b
0.038*
c (c')
OSA (AHI≥15/h)
1.384* (1.264)*
↑ Waist circumference
B
Nocturnal hypoxaemia
0.101*
a
b
-0.001
c (c')
OSA (AHI≥15/h)
0.099* (0.101)*
↑ Glucose levels
C
Nocturnal hypoxaemia
3.136*
a
b
0.016*
c (c')
OSA (AHI≥15/h)
0.361* (0.311)*
↑ HOMA-IR

Supplementary Table 1. Baseline characteristics of the merged sample according to included and excluded participants.

		Included sample (n=2702)	Excluded sample (n=534)	N	p-value
Age (years)		53.5 ± 19.1	47.7 ± 25.0	3236	**<0.0001**
BMI (kg/m2)		25.8 ± 5.8	26.2 ± 5.5	3223	0.573
AHI		8.3. ± 15.1	5.7 ± 13.1	3236	**<0.0001**
Sex				3236	0.074
	Men	53.1% (1,435)	48.9% (261)		
	Women	46.9% (1,267)	51.1% (273)		
Cohort				3236	**<0.0001**
	Episono	26.4% (712)	67.8% (362)		
	HypnoLaus	73.6% (1990)	32.2% (172)		
MetS				3185	0.401
	Yes	28.6% (768)	30.5% (153)		
	No	71.4% (1,915)	69.5% (349)		
Education				3224	**0.028**
	Low	47.1% (1,269)	51.8% (274)*		
	Middle	30.5% (823)	30.8% (163)		
	High	22.4% (603)	17.4% (92)*		
Marital status				3191	**0.001**
	Single	19.5% (522)	26.1% (133)*		
	Married	61.6% (1651)	59.8% (305)		
	Divorced/Separated	15.3% (409)	10.4% (53)*		
	Widowed	3.7% (99)	3.7% (19)		

AHI: apnoea-hypopnoea index, BMI: body mass index, MetS: metabolic syndrome.
Results are expressed as percentage (number of participants) or as median ± interquartile interval. Between-group comparisons performed using Pearson's chi-square for categorical variables and Mann-Whitney test for continuous variables.

Supplementary Table 2. Demographic characteristics of HypnoLaus and Episono cohorts by incidence of metabolic syndrome.

	HypnoLaus				Episono			
	No-incident MetS (n=1292)	**Incident MetS (n=109)**	**N**	**p-value**	**No-incident MetS (n=284)**	**Incident MetS (n=225)**	**N**	**p-value**
Age (years)	54.2 ± 17.0	55.6 ± 15.0	1401	0.246	36.6 ± 20.2	41.0 ± 18.2	509	**0.014**
Follow-up time (years)	5.2 ± 0.3	5.1 ± 0.2	1401	0.46	8.0 ± 0.4	8.0 ± 0.3	509	0.497
Sex			1401	**0.001**			509	0.115
Men	42.3% (547)	58.7% (64)*			47.9% (136)	40.9% (92)		
Women	57.7% (745)	41.3% (45)			52.1% (148)	59.1% (133)		
BMI (kg/m^2)			1391	**<0.0001**			509	**<0.0001**
≤24.9)	60.2% (772)	18.3% (20)			62.5% (177)	31.1% (70)		
BMI 25-29.9	35.0% (449)	64.2% (70)*			29.6% (84)	49.8% (112)*		
BMI>29.9	4.8% (61)	17.4% (19)*			8.1% (23)	19.1% (43)*		
Education			1400	**0.009**			505	0.069
Low	46.2% (597)	59.6% (65)*			30.6% (86)	37.1% (83)		
Middle	29.7% (383)	27.5% (30)			41.3% (116)	43.3% (97)		
High	24.1% (311)	12.8% (14)			28.1% (79)	19.6% (44)		
Marital status			1390	0.621			496	0.055
Single	16.0% (205)	13.0% (14)			38.8% (107)	27.7% (61)		
Married	58.2% (746)	60.2% (65)			54.3% (150)	66.4% (146)		
Divorced/Separated	21.2% (272)	24.1% (26)			4.0% (11)	3.6% (8)		
Widowed	4.6% (59)	2.8% (3)			2.9% (8)	2.3% (5)		

BMI: body mass index.
Results expressed as frequency in percentage (n) within each group or median ± interquartile interval and analyzed with bivariate tests (Pearson's chi-square or Mann-Whitney test).

Supplementary Table 3. Sleep predictors of metabolic syndrome according to sex in the merged sample.

	OR	95% CI	N	p-value
Men				
TST (min)	0.998	0.995 - 1.001	802	0.244
Sleep efficiency (%)	0.997	0.974 - 1.021	802	0.791
N3 (%)	1.014	0.986 - 1.043	802	0.318
REM sleep (%)	0.975	0.942 - 1.010	802	0.165
Arousal index	1.000	0.995 - 1.005	802	0.984
AHI	1.011	0.996 - 1.026	802	0.161
<5 events/h		Reference		
≥5 and <15 events/h	1.165	0.664 - 2.043		0.595
≥15 events/h	2.245	1.214 - 4.149		**0.010**
Mean SpO_2 (%)	0.993	0.935 - 1.054	802	0.811
Lowest SpO_2 (%)	0.971	0.941 - 1.002	802	0.068
3% ODI	1.011	0.994 - 1.027	800	0.212
Time with SpO_2<90% (%)	0.995	0.975 - 1.016	797	0.658
Self-reported sleep duration (h)	0.945	0.803 - 1.112	775	0.495
ESS score	1.045	0.993 - 1.099	755	0.090
Women				
TST (min)	0.999	0.995 - 1.002	1028	0.427
Sleep efficiency (%)	0.988	0.965 - 1.012	1028	0.327
N3 (%)	0.994	0.966 - 1.022	1028	0.652
REM sleep (%)	1.001	0.967 - 1.036	1028	0.963
Arousal index	1.003	0.997 - 1.008	1028	0.322
AHI	1.003	0.980 - 1.026	1028	0.825
<5 events/h		Reference		
≥5 and <15 events/h	1.618	0.888 - 2.947		0.116
≥15 events/h	2.197	1.091 - 4.426		**0.028**
Mean SpO_2 (%)	0.838	0.719 - 0.977	1028	**0.024**
Lowest SpO_2 (%)	1.023	0.975 - 1.074	1028	0.348
3% ODI	1.006	0.981 - 1.032	1027	0.629
Time with SpO_2<90% (%)	1.019	0.998 - 1.041	1012	0.070
Self-reported sleep duration (h)	1.047	0.895 - 1.224	995	0.567
ESS score	0.966	0.921 - 1.013	975	0.159

AHI: apnoea-hypopnoea index, ESS: Epworth sleepiness scale, ODI: oxygen desaturation index, N3: slow-wave sleep, REM: rapid eyes movement, SpO_2: oxygen saturation, TST: total sleep time.
Data analyzed using multivariable logistic regression with adjustment for cohort, age, body mass index and number of metabolic syndrome components at baseline.

Supplementary Table 4. Changes in sleep parameters from baseline to follow-up as predictors of metabolic syndrome in the Episono cohort.

	OR	95% CI	N	p-value
TST (10-min increment)	0.990	0.970 - 1.020	464	0.683
Sleep efficiency (10% incremet)	1.062	0.886 - 1.268	464	0.512
N3 (10% increment)	0.842	0.672 - 1.051	464	0.133
REM sleep (10% increment)	1.000	0.753 - 1.318	464	0.986
Arousal index (10 events/h increment)	1.149	0.932 - 1.411	464	0.184
AHI (10 events/h increment)	1.172	0.990 - 1.397	464	0.072
Mean SpO_2 (1% increment)	0.882	0.762 - 1.038	464	0.093
Lowest SpO_2 (1% increment)	0.960	0.916 - 1.037	464	0.084
3% ODI (10 events/h increment)	1.243	1.041 - 2.004	461	**0.018**
Time with SpO_2<90% (10% increment)	1.424	1.041 -1.949	459	**0.028**
Self-reported sleep duration (1h increment)	0.919	0.810 - 1.056	462	0.19
ESS score (1-unit increment)	1.016	0.971 - 1.027	463	0.494

Changes were computed as follow-up - baseline
AHI: apnoea-hypopnoea index, ESS: Epworth sleepiness scale, ODI: oxygen desaturation index, N3: slow-wave sleep, REM: rapid eyes movement, SpO_2: oxygen saturation, TST: total sleep time.
Data analyzed using multivariable logistic regression with adjustment for age, sex, body mass index, difference in body mass index from baseline to follow-up and number of metabolic syndrome components at baseline.

Supplementary Table 5. Metabolic syndrome as a risk factor for incident obstructive sleep apnoea in the Episono cohort.

	OR	95% CI	p-value
Model 1			
Constant	0.018	-	**<0.0001**
Age (years)	1.028	1.009 - 1.048	**0.004**
Sex (men)	2.166	1.345 - 3.486	**0.001**
Apnoea-hypopnoea index	1.300	1.210 - 1.395	**<0.0001**
Metabolic syndrome	1.915	1.130 - 3.245	**0.016**
Model 2			
Constant	0.005	-	**<0.0001**
Age (years)	1.030	1.010 - 1.050	**0.003**
Sex (men)	0.379	0.230 - 0.625	**<0.0001**
BMI (kg/m^2)	1.091	1.037 - 1.149	**0.001**
Apnoea-hypopnoea index	1.272	1.183 - 1.367	**<0.0001**
Metabolic syndrome	1.276	0.714 - 2.279	0.411

Data analyzed using multivariable logistic regression (N=476).
Adjustment for sex, age and baseline AHI (Model 1); + baseline BMI (Model 2).