Title

Respiratory effort during sleep and the rate of prevalent type 2 diabetes in obstructive sleep apnoea

Journal

Diabetes Obesity and Metabolism, 25(10)

ISSN

1462-8902

Authors

Martinot, Jean-Benoit

Le-Dong, Nhat-Nam

Borel, Anne-Laure

et al.

Publication Date

2023-10-01

DOI

10.1111/dom.15169

Peer reviewed

Published in final edited form as:

Diabetes Obes Metab. 2023 October ; 25(10): 2815–2823. doi:10.1111/dom.15169.

Respiratory effort during sleep and the rate of prevalent type 2 diabetes in obstructive sleep apnoea

Jean-Benoit Martinot, MD[1,2], **Nhat-Nam Le-Dong, MD**[3], **Anne-Laure Borel, MD**[4], **Renaud Tamisier, MD**[4], **Atul Malhotra, MD**[5], **Jean-Louis Pépin, MD**[4]

[1]Sleep Laboratory, CHU Université catholique de Louvain (UCL) Namur Site Sainte-Elisabeth, Namur, Belgium

[2]Institute of Experimental and Clinical Research, UCL Bruxelles Woluwe, Brussels, Belgium

[3]Sunrise, Namur, Belgium

[4]University of Grenoble Alpes, HP2 Laboratory, Inserm U1300, Grenoble, France

[5]University of California San Diego, La Jolla, California, USA

Abstract

Aim: To determine the association between total sleep time (TST) spent in increased respiratory effort (RE) and the prevalence of type 2 diabetes in a large cohort of individuals with suspected obstructive sleep apnoea (OSA) referred for in-laboratory polysomnography (PSG).

Materials and Methods: We conducted a retrospective cross-sectional study using the clinical data of 1128 patients. Non-invasive measurements of RE were derived from the sleep mandibular jaw movements (MJM) bio-signal. An explainable machine-learning model was built to predict

Correspondence Jean-Benoit Martinot, Centre du Sommeil et de la Vigilance, CHU Université catholique de Louvain (UCL) Namur Site Sainte-Elisabeth, 15 Place Louise Godin, 5000 Namur, Belgium. martinot.j@respisom.be.

AUTHOR CONTRIBUTIONS

Jean-Benoit Martinot, Nhat-Nam Le-Dong, Atul Mahotra and Jean-Louis Pépin designed the study. Jean-Benoit Martinot and Nhat-Nam Le-Dong conducted the data analysis. The first draft of the manuscript was prepared by Jean-Benoit Martinot, Jean-Louis Pépin and Nhat-Nam Le-Dong, who also had unrestricted access to the data. The manuscript was reviewed and edited by all the authors. Atul Mahotra, Anne-Laure Borel and Renaud Tamisier have personally reviewed the data, understands the statistical methods employed for all analyses, and confirms an understanding of these analyses, that the methods are clearly described and that they are a fair way to report the results. All authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses and for the fidelity of this report to the study protocol.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

CONFLICT OF INTEREST STATEMENT

Jean-Benoit Martinot reports being a scientific advisor to Sunrise and being an investigator in pharmacy trials for Jazz Pharmaceuticals, Theranexus and Desitin. Atul Mahotra is funded by the US National Institutes of Health. He reports income related to medical education from Jazz, Zoll, Eli Lilly, Sunrise and Livanova. ResMed provided a philanthropic donation to UCSD. Nhat-Nam Le-Dong is an employee of Sunrise. Renaud Tamisier reports receiving lecture fees from ResMed, Jazz pharmaceutical and Bioprojet and grant support through his institution from ResMed, Bioprojet, Agiradom and Philips, and travel grants form Agiradom. Jean-Louis Pépin reports being a scientific advisor to Sunrise; receiving grants and/or personal fees from ResMed, Philips, Fisher & Paykel, Sefam, AstraZeneca, AGIR à dom, Elevie, VitalAire, Boehringer Ingelheim, Jazz Pharmaceuticals, and Itamar Medical Ltd; and receiving research support for clinical studies from Mutualia and Air Liquide Foundation. Anne-Laure Borel declares no conflict of interest regarding this study.

prevalent type 2 diabetes from clinical data, standard PSG indices, and MJM-derived parameters (including the proportion of TST spent with increased respiratory effort [REMOV [%TST]).

Results: Original data were randomly assigned to training (n = 853) and validation (n = 275) subsets. The classification model based on 18 input features including REMOV showed good performance for predicting prevalent type 2 diabetes (sensitivity = 0.81, specificity = 0.89). Post hoc interpretation using the Shapley additive explanation method found that a high value of REMOV was the most important risk factor associated with type 2 diabetes after traditional clinical variables (age, sex, body mass index), and ahead of standard PSG metrics including the apnoea-hypopnea and oxygen desaturation indices.

Conclusions: These findings show for the first time that the proportion of sleep time spent in increased RE (assessed through MJM measurements) is an important predictor of the association with type 2 diabetes in individuals with OSA.

Keywords

mandibular jaw movements; obstructive sleep apnoea; respiratory effort; type 2 diabetes

1 | INTRODUCTION

Obstructive sleep apnoea (OSA) is a common chronic condition. It has been estimated that nearly 1 billion adults aged 30 to 69 years have at least mild OSA, with more than half of the population affected in some countries.[1] Repetitive complete or partial collapse of the upper airway during sleep in individuals with OSA and the associated increased respiratory effort (RE) and arousals have a number of physiological consequences. These include intermittent hypoxia and marked changes in intrathoracic pressure,[2] which contribute to a variety of adverse clinical consequences, such as excessive daytime sleepiness,[3] cognitive dysfunction,[4] and cardiovascular disease.[5,6]

The presence of OSA has also consistently been shown to be independently associated with prevalent and incident type 2 diabetes mellitus.[7-13] In addition, untreated OSA is associated with poor glycaemic control in individuals with type 2 diabetes and increases the risk of microvascular and macrovascular complications.[13-16] Key intermediary mechanisms underlying the association between OSA, and type 2 diabetes include intermittent hypoxia (hypoxic burden) and sleep fragmentation leading to oxidative stress, low-grade inflammation and sympathetic overactivity.[11]

The severity of OSA has traditionally been defined using the apnoea-hypopnea index (AHI), which describes the number of respiratory events that occur per hour of sleep. However, this metric does not provide any information about the duration of obstructive events or the associated hypoxic burden, which have been shown to be associated with cardiometabolic outcomes and mortality in individuals with OSA.[17,18] Therefore, there is increasing recognition of the fact that more comprehensive and/or combined metrics are needed to improve prediction of cardiometabolic disease risk in individuals with OSA.[19,20]

One such measure is RE, which is consistently increased in response to episodes of asphyxia, named obstructive apnoeas and hypopnoeas. Physiological data show that

intrathoracic pressure swings during respiratory events generate sympathetic nervous system overactivity,[21-23] which may contribute to the development of insulin resistance and type 2 diabetes. However, the role that increased RE might play in the metabolic consequences of OSA has been poorly studied to date. This lack of data may be due, at least in part, to the challenge of assessing and measuring RE clinically.

Measurement of mandibular jaw movements (MJM) during sleep has been shown to provide powerful information about RE and the proportion of sleep time spent with high RE.[24] During normal sleep, the mandibular jaw only moves by a few tenths of a millimetre at the breathing frequency around a fixed position and the mouth is almost closed. Changes in MJM characteristics therefore reflect the level of respiratory drive and RE that occur due to the variations in upper airway resistance that typically occur during abnormal respiratory events.[24] Essentially, MJM yields information about respiratory drive initiated by the motor trigeminal nucleus which is transmitted to the mandibular jaw musculature a few tenths of a millisecond before diaphragmatic contraction. The technique leverages discrete movements which help stiffen the pharyngeal walls to maintain or restore local airway patency. This study evaluated the association between sleep time spent in increased RE derived from measurements of MJM (REMOV, % total sleep time [TST]) and the prevalence of type 2 diabetes mellitus in individuals referred for investigation of suspected OSA. It was hypothesized that increased MJM amplitudes during sleep (reflecting increased RE) would be independently associated with prevalent type 2 diabetes, over and above traditional measures of hypoxic load and sleep fragmentation.

2 | METHODS

2.1 | Study design and population

This cross-sectional study included subjects aged ≥18 years who were referred to a sleep laboratory for assessment of suspected OSA. The study protocol was approved by the *Comité d'Ethique Hospitalo-Facultaire-Universitaire de Liège* (IRB-00004890-NB707201523388) and written informed consent was obtained from all participants prior to their enrolment in the study.

2.2 | Polysomnographic data acquisition and scoring

In-laboratory polysomnography (PSG) recording was performed using standard equipment (Somnoscreen Plus; Somnomedics). The system collected the following data: electroencephalogram (EEG); right and left electro-oculogram (EOG); submental electromyogram (EMG); tibial EMG; motion of the chest and abdomen based on respiratory inductance plethysmography (RIP; SleepSense S.L.P. Inc.); oral and nasal airflow using a thermistor and pressure transducer, respectively; and oxygen saturation (SpO_2) based on data from a digital pulse oximeter (Nonin; Nonin Medical).

Manual scoring of PSG recordings was performed by two experienced investigators who were unaware of participant demographic details, MJM data and diabetes diagnosis. Sleep stages, EEG arousals and sleep-related respiratory events were visually scored according to the latest American Academy of Sleep Medicine criteria.[25] Interobserver agreement for PSG

scoring was evaluated by intra-class correlation coefficient using two-way random model for single measure (ICC 2.1) and was found to be 92.1% (95% confidence interval 0.891-0.942; $P < 0.001$).

Individuals with overlap syndrome (sleep apnoea and chronic obstructive pulmonary disease), obesity hypoventilation syndrome, or central apnoea syndrome, as defined in the International Classification of Sleep Disorders 3rd edition,[25] were excluded.

2.3 | Recording and analysis of MJM

MJM bio–signals were acquired using the Sunrise system. This system includes a coin-sized tri-axial sensor including a gyroscope and an accelerometer that is attached to the patient's chin and positioned between the inferior labial sulcus and the pogonion. MJM are recorded via an embedded inertial measurement unit that is controlled externally by a smartphone application. Mandibular displacement is calculated from the integration of the rotational speed measured by the gyroscope. The accelerometer is used to determine the position of the mandible resulting from elevation or depression.

At the end of the night, all data were automatically transferred to a cloud-based infrastructure and analysed using a dedicated machine-learning algorithm that has been previously validated in a large clinical dataset.[26] This algorithm is designed to automatically identify obstructive and mixed apnoea/hypopnoea events as well as RE-related arousals (RERAs) based on stereotypical MJM patterns. It is also able to identify specific MJM patterns to determine whether the subject is awake, asleep, or experiencing an arousal.

2.4 | Assessment of RE by the Sunrise system

Accurate detection of RE during sleep is critical for correct classification of sleep breathing disturbances and to inform appropriate therapeutic decisions. Oesophageal manometry is the “gold standard” for measuring RE but is invasive, causes sleep disturbance, and is rarely used in routine daily practice. The most widely used signals, such as RIP abdominal and thoracic belts and nasal pressure, provide important information but have limitations in some clinical scenarios (eg, obesity or mouth breathing). This issue can lead to misclassification of a significant percentage of respiratory events, particularly hypopnoeas. MJM have been shown to correlate strongly with oesophageal pressure, providing an efficient and reliable way to differentiate between central and obstructive events, and identify mixed episodes.[24,28]

Periods of increased RE were identified based on the presence of MJM of increased and variable amplitudes oscillating at the breathing frequency compared to normal breathing[24] (Figure S1). The intensity of RE during sleep captured on MJM bisignals can be quantitatively assessed via two metrics:

i. *Sr_ORDI*: the Sunrise obstructive respiratory disturbance index (Sr_ORDI) measures the hourly frequency of respiratory disturbance accompanied by RE events (including obstructive and mixed apnoeas/hypopnoeas or RERAs); the magnitude of the Sr_ORDI has the same physiological meaning as the obstructive respiratory disturbance index (ORDI) derived from PSG.[26]

ii. *RE burden* (REMOV, %TST): this metric provides an indication of the proportion of sleep time spent in increased RE assessed through MJM; it is determined based on the cumulative duration of periods with increased RE divided by TST.

2.5 | Prevalent type 2 diabetes

The presence of type 2 diabetes was determined by a sleep specialist based on values for fasting blood glucose and glycated haemoglobin (HbA1c) in the electronic medical history report (according to the criteria established by the American Diabetes Association[27]), and documented treatment including at least one antidiabetic drug.

2.6 | Data analysis

Data analysis included inputs for 19 demographic and physiological metrics that can be categorized into five distinct groups:

i. *PSG indices*: measures of sleep-related breathing events per hour, including AHI, obstructive apnea-hypopnea index (OAHI), respiratory disturbance index (RDI), ORDI and arousal index (ArI). These indices were closely correlated with each other and characterized by a positively skewed distribution, with a clear difference between patients with and without type 2 diabetes (those with type 2 diabetes had a significantly higher AHI, ORDI, ArI versus those without type 2 diabetes).

ii. *Metrics related to TST*: values for TST were consistent between PSG- and MJM-based methods. TST and the Epworth Sleepiness Scale (ESS) showed a random distribution and did not differ significantly between individuals with or without type 2 diabetes.

iii. *Demographic and anthropometric measurements*: including age, body mass index (BMI) and neck circumference. These metrics were characterized by a normal distribution and were slightly (but statistically significantly) higher in individuals with versus without type 2 diabetes.

iv. *Measures related ito oxygen saturation*: including minimum and average SpO_2 values. These metrics were characterized by a negatively skewed distribution and a clear difference between the subgroups with or without type 2 diabetes (being significantly lower in those who had type 2 diabetes).

v. *Oxygen desaturation metrics*: related to both the hourly rate and cumulative duration of oxygen desaturation (Desat_dt <90%, Desat_dt <95% and ODI); these metrics were correlated with each other and showed clear differences between individuals with and without type 2 diabetes.

Data analysis was carried out using Python programming language. Overall, key components of the data analysis procedure (Figure S2) were as follows:

i. *Exploratory data analysis*: Descriptive statistics and principal component analysis (PCA) were performed to compare the distribution characteristics of clinical features between patients with and without type 2 diabetes.

ii. *Data preparation for machine-learning experiment*: the original dataset was randomly divided into two subsets; a training subset (76%) was used to benchmark the performance of machine-learning models using a 10-fold cross-validation procedure, and for optimizing the model configuration. A smaller test subset (24%) was used for independent validation. The size of the training sample was estimated to satisfy two criteria: to achieve a proportion of at least 10% of positive label (having type 2 diabetes) and to optimize the performance of a binary classifier using the XGBoost algorithm and chosen input features. The input data represent a multidimensional structure of co-expression and interactions between metrics of physical body status, sleep quality, and magnitude of RE and oxygen desaturation. This complex interaction is compatible with the operating mechanism of tree-based ensemble machine-learning algorithms such as Random Forest (RF) and eXtremeGradientBoosting (XGB).

iii. and v. *Optimization and selection of the machine-learning model*: RF and XGB algorithms were evaluated as potential solutions for the binary classification task of type 2 diabetes prediction. RF uses bootstrap-aggregating techniques and XGB uses gradient-boosting techniques to improve model performance by assembling the prediction of multiple tree-based classification rules. Performances were compared between the two models using a 10-fold cross-validation procedure, which utilized multiple data splitting and random resampling, thus allowing unbiased evaluation of model performance on 10% of unseen data. Final models were then trained on the whole training set using the optimized parameter values and validated on unseen data in the testing subset. The following evaluations were conducted for both repeated *k*-folds cross-validation and independent validation: normalized confusion matrix (to evaluate model accuracy [rows represent the true observation, columns indicate the classification by model]); and conventional metrics for evaluating the accuracy of binary classification and the efficiency of diagnosis (sensitivity, specificity, balanced accuracy [BAC], positive/negative likelihood ratios [LR+, LR−], positive predictive value [PPV], negative predictive value [NPV] and area under the receiver-operating characteristic curve [ROC-AUC]). A sensitivity analysis was performed that created specific models for respiratory events occurring specifically in non-rapid eye movement (REM) and REM sleep.

v. *Post hoc model interpretation*: the Lundberg's Shapley additive explanation (SHAP) method[28] was applied to the best-performing model to identify the most important risk factors from the original set of features.

3 | RESULTS

3.1 | Study population

The study included 1128 subjects who were randomly allocated to the training subset (n = 853, 75.6%) or the test subset (n = 275, 24.4%; Table 1). The prevalence of type 2 diabetes was 10.3%. At baseline, mean ± standard deviation fasting blood glucose was 126.8 ± 49.7 mg/dL and HbA1c was 48.9 ± 13.1 mmol/mol (7.9 ± 9.7%) in patients with a confirmed

diagnosis of type 2 diabetes (n = 116). Antidiabetic medications in individuals with type 2 diabetes included oral biguanides in 77.6%, insulin-related therapy in 20.7%, and other anti-diabetics in 24.1% of patients.

3.2 | Clinical characteristics and RE burden

There were clear differences in the distribution of a variety of demographic and anthropometric characteristics and some sleep-related breathing features based on the presence or absence of type 2 diabetes (Table 1 and Figure S3). The distribution of PSG-derived ORDI and ArI and the corresponding Sunrise system (MJM)-derived indices were similarly distributed between the groups with and without type 2 diabetes. RE burden (REMOV, %TST) was higher in patients with versus without type 2 diabetes. On PCA, TST and ESS score did not contribute to the risk of prevalent type 2 diabetes, whereas other respiratory measures and demographic/clinical features were associated with the presence of type 2 diabetes (Figure 1).

3.3 | Machine-learning model for predicting prevalent type 2 diabetes

The results of both cross-validation and independent validation indicated that the XGB classifier outperformed the RF model for predicting the presence of type 2 diabetes (Table 2, Figure S4). In cross-validation, the average accuracy of the XGB and RF models was 85% and 80%, respectively. The XGB model also performed better than the RF model in terms of sensitivity (0.81 vs. 0.80), specificity (0.89 vs. 0.80) and ROC-AUC (0.93 vs. 0.88).

When validated on unseen data, the XGB classification rule allowed the detection of individuals with type 2 diabetes with a sensitivity of 77%, specificity of 85% and a BAC of 81%. The XGB model also showed a better ROC AUC of 0.92 (vs. 0.88 for the RF model; $P < 0.001$).

The results of the sensitivity analysis were consistent with the main analysis, whereby the relationship between RE and prevalent type 2 diabetes was preserved, with slight and nonsignificant improvements in model performance (Table S1).

3.4 | Model explanation by the SHAP method

Adding SHAP to the XGB model that included all clinical features allowed to determine the independent effect of each feature value to predict the risk of having type 2 diabetes. As summarized in Figure 2 and Figure S5, this analysis revealed the 10 most important factors that contribute significantly to the risk of prevalent type 2 diabetes in patients referred to the sleep laboratory for OSA suspicion (in order of importance): low average nocturnal SpO_2, being female, high BMI (≥30 kg/m^2), long periods under RE (≥60% of TST), long duration of O_2 desaturation at thresholds of 95% or 90% (≥10% and 5% of TST, respectively), age greater than 45 years, high ODI score (≥15 events/h), high neck circumference (≥ 40 cm) and high ORDI score (≥20 events/h) determined by MJM analysis (Sr_ORDI). In a subgroup analysis of patients without significant oxygen desaturation (ODI <5 events/h) and limited sleep fragmentation, the presence of RE for >60% of the night remained a significant independent predictor of prevalent type 2 diabetes (Figure S6).

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate the association between sleep time spent with increased RE and the prevalence of type 2 diabetes in individuals with OSA. These findings show that RE detected by MJM analysis is strongly and independently associated with type 2 diabetes in this large clinical cohort. In addition, RE burden is a stronger predictor of type 2 diabetes than common PSG-derived metrics such as the AHI.

The AHI is the conventional metric that has traditionally been used to diagnose and classify OSA despite an increasing recognition that this index may not fully capture the pathophysiology and impact of OSA.[29] Nevertheless, most previous studies investigating the contribution of OSA to the development or presence of type 2 diabetes used the AHI to assess OSA severity.[7,9,13] Relatively few studies have evaluated the relevance of other metrics, such as the proportion of sleep time spent with an oxygen saturation below 90%.[8,13] Increased RE in individuals with OSA has recently been associated with an increased prevalence of hypertension[30] but has otherwise been poorly studied and is probably underestimated as a risk factor for the cardiovascular and metabolic consequences of OSA.

The current findings showed that RE burden was an independent predictor of type 2 diabetes in OSA, over and above the risk associated with intermittent hypoxia. This is a new finding because previous epidemiological studies in general populations[10,31] and clinical cohorts[32] have only reported a direct linear relationship between hypoxic load and prevalent or incident diabetes (as reviewed by Kent et al. 2015[14]). However, an association with type 2 diabetes has been found even for mild OSA with limited oxygen desaturation.[10] The findings of the current study suggest that RE could be the missing information to help explain this relationship. Specifically, our subgroup analysis (Figure S6) identified a significant association between OSA and prevalent type 2 diabetes when RE burden was >60% of TST even in individuals with a low hypoxic load (ODI <5 events/h).

Studies show that there is a specific link between sleep-related breathing events occurring during REM sleep and the presence of diabetes.[35,36] The results of our sensitivity analysis showed that RE is a determinant of the relationship between prevalent type 2 diabetes for respiratory events occurring in both non-REM and REM sleep.

There is a sound pathophysiological rationale for the observed association between greater proportions of time spent in increased RE during sleep and prevalent type 2 diabetes. Alterations in upper airway patency during obstructive respiratory events result in repetitive attempts to force inspiration against the obstructed upper airway, which causes substantial negative changes in intrathoracic pressures.[33] These large intrathoracic pressure swings activate the sympathetic nervous system and, in turn, there is compelling mechanistic evidence that sympathetic activation negatively affects insulin secretion and sensitivity.[34,35]

Overall, there appears to be a role for a tool that can objectively measure sleep time spent in increased RE, as measured in the current study. Other options have important limitations, given that RE is not well documented by respiratory bands, and the number of central events is overestimated.[36,37] In addition, while the presence of snoring indicates upper airway

resistance, and provides indirect and qualitative information about RE, the relationship between increasing RE and the flattening of the inspiratory curve is not linear.[37]

The benefits of early diagnosis and treatment of sleep apnoea in individuals with diabetes mellitus are increasingly being recognized,[38] as of course are the benefits of treating diabetes. Furthermore, adherence to positive airway pressure therapy for the treatment of OSA has recently been shown to improve control of type 2 diabetes and to decrease health-related costs.[39] The current challenge in this large, minimally symptomatic population is to improve access to OSA diagnosis. The MJM diagnosis solution utilized in the current study has been validated against in-laboratory PSG and for use in the home as an ambulatory diagnostic tool over multiple nights of assessment.[26] It could therefore be used to expand screening and diagnosis programmes, and to provide objective data on RE burden, a parameter that is increasingly being recognized as an important prognostic factor in OSA.

There is a growing agreement in the field that the AHI does not provide a good indication of several dimensions of sleep apnoea syndrome.[20] The new concept is to complement the AHI with new metrics including hypoxic burden, acute cardiovascular responses to arousals and now, better characterization of RE. Our paper is clinically relevant because it demonstrates an independent association between burden of RE and prevalent diabetes beyond, and independently of, the classical AHI metric. We have previously reported that RE is also independently associated with prevalent hypertension even in individuals without significant hypoxic burden.[30,40] Our data have clinical significance because some future therapeutic decisions for Continuous Positive Airway Press CPAP or alternative primary treatment for OSA will be based on high levels of RE during sleep and not only AHI, especially in individuals with hypertension and/or type 2 diabetes.

A key strength of this study is the large, prospective clinical dataset, which means that the study findings can be reliably generalized to other similar populations. However, additional validation of the data in other clinical cohorts would be appropriate. Another strength is the use of a validated tool for the direct measurement of RE during sleep. This measure was incorporated into two different models to determine the best approach to predict prevalent type 2 diabetes in individuals with OSA. One potential limitation of this analysis is that the presence of type 2 diabetes was determined only from patient's medical records without any indication of disease severity or control status. Therefore, the potential influence of these factors on RE metrics and whether measures of RE are affected by variables such as glucose levels, glucose level variability and duration of diabetes could not be determined in the current analysis. Additional studies are needed to determine these important relationships, facilitating evidence-based application of RE assessment in individuals with diabetes mellitus.

Another important point to note is that MJM data in the current study were validated against a single night of PSG only. There is increasing interest in the use of multiple night assessments of sleep apnoea to reduce misclassification that may occur with a single night of in–laboratory PSG.[41] Therefore, using multiple night assessment would be appropriate in future studies to help determine whether night-to-night variability in sleep test results has any influence on the relationship between RE and prevalent diabetes.

In conclusion, this study identified a significant association between RE burden during sleep measured from MJM analysis and prevalence of type 2 diabetes in individuals with OSA. This finding suggests that RE burden should be recognized as one of the intermediary mechanisms and factors contributing to the association between OSA and type 2 diabetes. It also highlights the importance of documenting the RE burden in individuals with type 2 diabetes, especially in those with mild to moderate OSA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors wish to thank Mrs Ravzat Ashurlaeva and Ms Bao Truc Nguyen Ham for their secretarial assistance. English language editing and formatting assistance was provided by Nicola Ryan (New Zealand), independent medical writer. The authors are also grateful to Michael Polkey for his constructive review of the manuscript.

FUNDING INFORMATION

Jean-Louis Pépin is supported by the French National Research Agency in the framework of the “Investissements d'avenir” program (ANR-15-IDEX-02) and the “e-health and integrated care and trajectories medicine and MIAI artificial intelligence” chairs of excellence from the Grenoble Alpes University Foundation. This work has been partially supported by MIAI @ Grenoble Alpes (ANR-19-P3IA-0003).

DATA AVAILABILITY STATEMENT

Data could be provided upon reasonable request.

REFERENCES

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019;7(8):687–698. [PubMed: 31300334]
2. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol. 2010;7(12):677–685. [PubMed: 21079639]
3. Jennum P, Coaquira Castro J, Mettam S, Kharkevitch T, Cambron-Mellott MJ. Socioeconomic and humanistic burden of illness of excessive daytime sleepiness severity associated with obstructive sleep apnoea in the European Union 5. Sleep Med. 2021;84:46–55. [PubMed: 34102429]
4. Alomri RM, Kennedy GA, Wali SO, Alhejaili F, Robinson SR. Association between nocturnal activity of the sympathetic nervous system and cognitive dysfunction in obstructive sleep apnoea. Sci Rep. 2021;11(1):11990. [PubMed: 34099794]
5. Ryan S, Cummins EP, Farre R, et al. Understanding the pathophysiological mechanisms of cardiometabolic complications in obstructive sleep apnoea: towards personalised treatment approaches. Eur Respir J. 2020;56(2):1902295. [PubMed: 32265303]
6. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2021;144(3):e56–e67. [PubMed: 34148375]
7. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. Am J Med. 2009;122(12):1122–1127. [PubMed: 19958890]
8. Kendzerska T, Gershon AS, Hawker G, Tomlinson G, Leung RS. Obstructive sleep apnea and incident diabetes. A historical cohort study. Am J Respir Crit Care Med. 2014;190(2):218–225. [PubMed: 24897551]

9. Marshall NS, Wong KK, Phillips CL, Liu PY, Knuiman MW, Grunstein RR. Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med. 2009;5(1):15–20. [PubMed: 19317376]
10. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol. 2004;160(6):521–530. [PubMed: 15353412]
11. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. Chest. 2017;152(5):1070–1086. [PubMed: 28527878]
12. Subramanian A, Adderley NJ, Tracy A, et al. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. Diabetes Care. 2019;42(5):954–963. [PubMed: 30862657]
13. Xu PH, Hui CKM, Lui MMS, Lam DCL, Fong DYT, Ip MSM. Incident type 2 diabetes in OSA and effect of CPAP treatment: a retrospective clinic cohort study. Chest. 2019;156(4):743–753. [PubMed: 31128116]
14. Kent BD, McNicholas WT, Ryan S. Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea. J Thorac Dis. 2015;7(8):1343–1357. [PubMed: 26380761]
15. Leong WB, Jadhakhan F, Taheri S, Thomas GN, Adab P. The association between obstructive sleep apnea on diabetic kidney disease: a systematic review and meta-analysis. Sleep. 2016;39(2):301–308. [PubMed: 26414891]
16. Zhu Z, Zhang F, Liu Y, et al. Relationship of obstructive sleep apnoea with diabetic retinopathy: a meta-analysis. Biomed Res Int. 2017;2017:4737064. [PubMed: 29230409]
17. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. Eur Heart J. 2019;40(14):1149–1157. [PubMed: 30376054]
18. Butler MP, Emch JT, Rueschman M, et al. Apnea-hypopnea event duration predicts mortality in men and women in the Sleep Heart Health Study. Am J Respir Crit Care Med. 2019;199(7):903–912. [PubMed: 30336691]
19. Lévy P, Tamisier R, Pépin JL. Assessment of sleep-disordered-breathing: quest for a metric or search for meaning? J Sleep Res. 2020;29(4):e13143. [PubMed: 33189087]
20. Malhotra A, Ayappa I, Ayas N, et al. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. Sleep. 2021;44(7):zsab030. [PubMed: 33693939]
21. Dempsey JA, Sheel AW, St Croix CM, Morgan BJ. Respiratory influences on sympathetic vasomotor outflow in humans. Respir Physiol Neurobiol. 2002;130(1):3–20. [PubMed: 12380012]
22. Ryan S. Mechanisms of cardiovascular disease in obstructive sleep apnoea. J Thorac Dis. 2018;10(Suppl 34):S4201–S4211. [PubMed: 30687536]
23. Weiss JW, Remsburg S, Garpestad E, Ringler J, Sparrow D, Parker JA. Hemodynamic consequences of obstructive sleep apnea. Sleep. 1996;19(5):388–397. [PubMed: 8843530]
24. Pepin JL, Le-Dong NN, Cuthbert V, et al. Mandibular movements are a reliable noninvasive alternative to esophageal pressure for measuring respiratory effort in patients with sleep apnea syndrome. Nat Sci Sleep. 2022;14:635–644. [PubMed: 35444480]
25. Berry RB, Brooks R, Gamaldo C, et al. AASM scoring manual updates for 2017 (version 2.4). J Clin Sleep Med. 2017;13(5):665–666. [PubMed: 28416048]
26. Pépin JL, Letesson C, Le-Dong NN, et al. Assessment of mandibular movement monitoring with machine learning analysis for the diagnosis of obstructive sleep apnea. JAMA Netw Open. 2020;3(1):e1919657. [PubMed: 31968116]
27. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15–S33. [PubMed: 33298413]
28. Lundberg SM, Erion G, Chen H, et al. From local explanations to global understanding with explainable AI for trees. Nat Mach Intell. 2020;2(1):56–67. [PubMed: 32607472]
29. Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. Am J Respir Crit Care Med. 2019;200(6):691–703. [PubMed: 31022356]
30. Martinot JB, Le-Dong NN, Malhotra A, Pépin JL. Respiratory effort during sleep and prevalent hypertension in obstructive sleep apnoea. Eur Respir J. 2023;61(3):2201486. [PubMed: 36455958]

31. Nagayoshi M, Punjabi NM, Selvin E, et al. Obstructive sleep apnea and incident type 2 diabetes. Sleep Med. 2016;25:156–161. [PubMed: 27810258]
32. Kent BD, Grote L, Ryan S, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. Chest. 2014;146(4):982–990. [PubMed: 24831859]
33. Magder SA, Lichtenstein S, Adelman AG. Effect of negative pleural pressure on left ventricular hemodynamics. Am J Cardiol. 1983;52(5):588–593. [PubMed: 6613883]
34. Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Invest. 1980;65(3):717–721. [PubMed: 6243677]
35. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–1807. [PubMed: 19465235]
36. Luo YM, Tang J, Jolley C, et al. Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. Chest. 2009;135(5):1133–1141. [PubMed: 19118271]
37. Pamidi S, Redline S, Rapoport D, et al. An Official American Thoracic Society workshop report: noninvasive identification of inspiratory flow limitation in sleep studies. Ann Am Thorac Soc. 2017;14(7):1076–1085. [PubMed: 28665698]
38. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan – 2022 update. Endocr Pract. 2022;28(10):923–1049. [PubMed: 35963508]
39. Sterling KL, Cistulli PA, Linde-Zwirble W, et al. Association between positive airway pressure therapy adherence and health care resource utilization in patients with obstructive sleep apnea and type 2 diabetes in the United States. J Clin Sleep Med. 2022;19(3):563–571.
40. Mateika JH. Respiratory effort and hypertension in obstructive sleep apnoea. Eur Respir J. 2023;61(3):2202421. [PubMed: 36863731]
41. Punjabi NM, Patil S, Crainiceanu C, Aurora RN. Variability and misclassification of sleep apnea severity based on multi–night testing. Chest. 2020;158(1):365–373. [PubMed: 32081650]

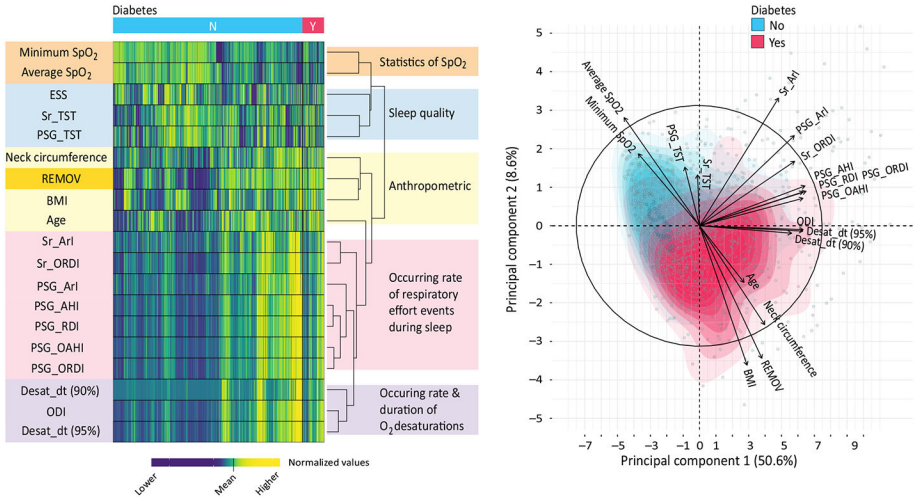

FIGURE 1.

Results of principal component analysis (PCA) and features clustering analysis. The left panel shows a heatmap that visualizes the distribution of normalized scores for 19 features in the study population (n = 1128). Each row represents a feature; features are arranged based on a hierarchical clustering analysis. Columns indicate patient ID (observation units), stratified by the presence or absence of type 2 diabetes. A dendrogram groups the 19 features into five clusters, based on measurement of similarity in distribution and of normalized score, and the inter-correlation between those features. The image in the right panel summarizes the PCA results. The graph consists of a bi-dimensional density layer, representing the joint distribution of two principal components, and coordinates of the 19 original variables as vectors, including age, body mass index (BMI), neck circumference, Epworth Sleepiness Scale (ESS), four mandibular jaw movement–derived indices estimated by the Sunrise system (Sr_TST, Sr_ArI, Sr_ORDI, sleep time spent with increased respiratory effort [REMOV]), six polysomnography (PSG)-derived indices (total sleep time [TST], respiratory disturbance index [RDI], obstructive respiratory disturbance index [ORDI], apnoea-hypopnoea index [AHI], obstructive apnoea-hypopnoea index [OAHI] and arousal index [ArI]) and five metrics of oxygen desaturation (oxygen desaturation index [ODI], average oxygen saturation [SpO_2], minSpO_2, and time with oxygen desaturation [Desat_dt] 90% and 95%). Each vector represents a variable; its orientation with respect to a principal component axis and length indicates how much the variable contributes to that principal component. The angles between the vectors and direction allow evaluation of their correlation: small angles indicate strong positive correlation; opposite angles represent a negative correlation. REMOV is based on mandibular jaw movement measurement; “Sr” indicates variable derived from automatic analysis of mandibular jaw movements by the Sunrise system

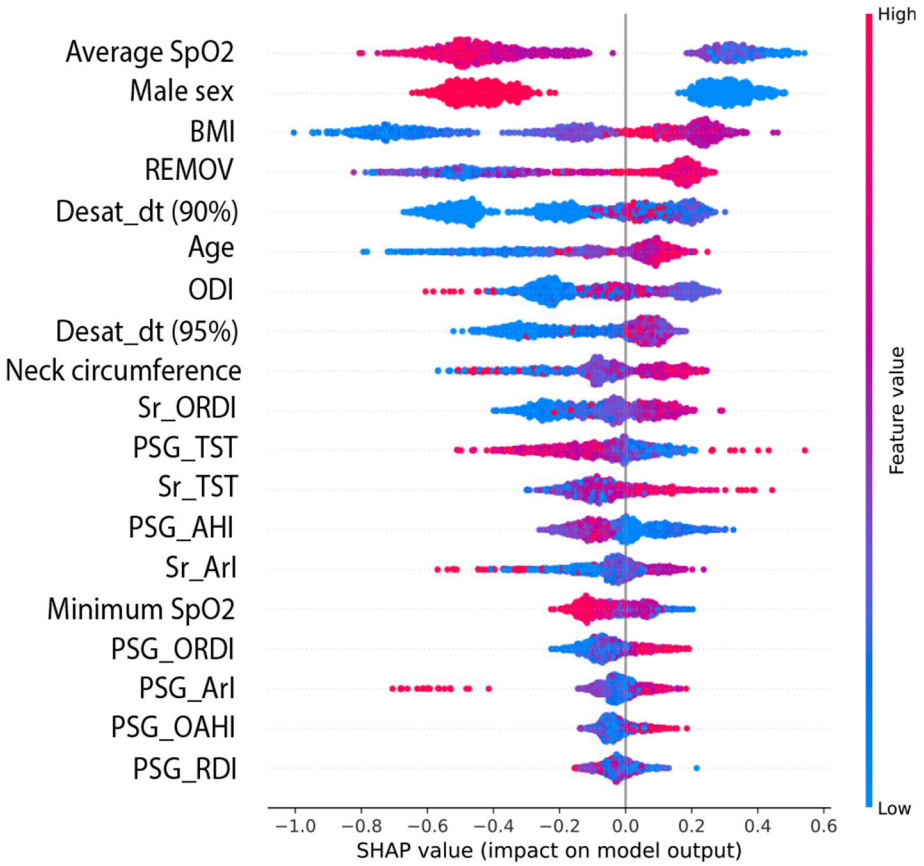

FIGURE 2.

Contribution of the input features to the classification output, evaluated by the Shapley additive explanation (SHAP) method. This graph summarizes the result of post hoc interpretation using the SHAP method for the extreme gradient boost (XGB) model. The *x*-axis represents the SHAP value scale, which measures the effect of individual feature values on the predicted probability of having diabetes. The features on *y*-axis are arranged by descending order of importance, determined based on the average of absolute SHAP values for each feature. Each dot indicates the feature attribution value to the XGB model final output for a respective patient. The dots are coloured according to the relative value of a specific feature, in which blue (cooler) or red (warmer) dots represent lower or higher feature values, respectively. AHI, apnoea-hypopnoea index; ArI, arousal index; BMI, body mass index; Desat_dt <90 or <95, time with oxygen desaturation <90% or <95%; ESS, Epworth Sleepiness Scale; OAHI, obstructive apnoea-hypopnoea index; ODI, oxygen desaturation index; ORDI, obstructive respiratory disturbance index; PSG, derived from polysomnography; RDI, respiratory disturbance index; REMOV, proportion of total sleep time with increased respiratory effort (based on mandibular jaw movement measurement); Sr, derived from automatic analysis of mandibular jaw movements by the Sunrise system; TST, total sleep time

TABLE 1

Characteristics of the study population

	Training subset (n = 853; 76%)		Test subset (n = 275; 24%)	
Parameters	**With diabetes (n = 86; 10%)**	**Without diabetes (n = 767; 90%)**	**With diabetes (n = 30; 11%)**	**Without diabetes (n = 245; 89%)**
Male sex, n (%)	37 (44.0%)	423 (55.1%) *	23 (76.7%)	135 (55.1%) *
Age, years	55.0 (15.0)	47.5 (19.8)	51.3 (20.4)	46.6 (18.5)
Neck circumference, cm	41.5 (5.0)	39.0 (4.0)	41.5 (5.8)	40.0 (5.0)
Body mass index, kg/m^2	34.6 (7.0)	29.7 (10.5)	35.0 (9.9)	28.8 (10.8)
ESS score	11.0 (7.8) **	11.0 (7.0)	11.0 (5.8) **	10.0 (7.0)
PSG indices				
TST, min	424.5 (102.1) **	430.5 (97.8)	395.3 (104.5)	441.0 (97.0)
ArI, n/h	29.1 (21.9)	24.2 (19.6)	30.8 (22.3)	23.0 (16.9)
AHI, n/h	23.9 (29.3)	16.9 (26.0)	27.5 (29.9)	17.1 (23.0)
OAHI, n/h	20.0 (22.2)	11.2 (21.1)	24.9 (29.5)	11.5 (20.4)
RDI, n/h	36.2 (28.9)	23.7 (27.7)	36.7 (25.8)	22.9 (22.4)
ORDI, n/h	28.8 (24.2)	18.0 (22.4)	35.0 (28.6)	18.00 (21.2)
Desaturation				
ODI, n/h	27.3 (27.2)	12.3 (27.5)	18.6 (16.1)	10.6 (16.8)
Minimum SpO_2, %	82.5 (10.5)	86.0 (9.0)	83.0 (10.5)	86.0 (10.0)
Average SpO_2, %	93.0 (2.0)	95.0 (3.0)	93.0 (1.8)	95.0 (3.0)
Time with SpO_2 <90%, % TST	5.0 (12.1)	0.6 (4.6)	6.4 (11.7)	0.7 (4.7)
Time with SpO_2 <95%, % TST	20.8 (20.9)	9.3 (18.7)	18.6 (16.1)	10.6 (16.8)
Sunrise indices				
TST, min	443.3 (75.8) **	437.0 (76.01)	457.0 (100.9) **	448.0 (69.0)
ORDI, n/h	19.9 (15.8)	15.0 (15.41)	23.5 (13.2)	15.5 (14.0)
ArI, n/h	19.9 (17.1)	18.9 (14.60)	22.8 (17.2)	18.8 (12.7)
REMOV, % TST	81.1 (20.9)	59.9 (43.30)	79.1 (21.9)	64.4 (42.0)

Note: Values are median (interquartile range) for numeric data or number of patients (%) for categorical data.

Abbreviations: AHI, apnoea-hypopnoea index; ArI, arousal index; ESS, Epworth Sleepiness Scale; OAHI, obstructive apnoea-hypopnoea index; ODI, oxygen desaturation index; ORDI, obstructive respiratory disturbance index; PSG, polysomnography; RDI, respiratory disturbance index; REMOV, sleep time spent with increased respiratory effort (based on mandibular movement measurement); SpO_2, oxygen saturation; TST, total sleep time.

*Significant association between male sex and presence of diabetes was determined using Pearson's χ^2 test ($P < 0.001$).

**All metrics, except for TST (PSG or Sunrise) and ESS score showed a statistically significant difference in distribution between the two outcome subgroups, based on a Mann-Whitney test at significance threshold of 0.05.

TABLE 2

Performance of two classification rules

	Random Forest classifier		XGboost classifier	
Metrics	**10 × 10 CV on training set**	**Validation on test set**	**10 × 10 CV on training set**	**Validation on test set**
Balanced accuracy	0.80 ± 0.08	0.73 ± 0.04	0.85 ± 0.07	0.81 ± 0.04
Sensitivity	0.80 ± 0.14	0.67 ± 0.09	0.81 ± 0.14	0.77 ± 0.08
Specificity	0.80 ± 0.04	0.79 ± 0.03	0.89 ± 0.03	0.85 ± 0.02
False-positive rate	0.20 ± 0.04	0.21 ± 0.03	0.11 ± 0.03	0.15 ± 0.02
False-negative rate	0.20 ± 0.14	0.33 ± 0.09	0.19 ± 0.14	0.23 ± 0.08
LR+	4.26 ± 1.33	3.25 ± 0.60	7.88 ± 3.33	5.21 ± 1.01
LR−	0.25 ± 0.18	0.42 ± 0.11	0.21 ± 0.16	0.27 ± 0.09
PPV	0.31 ± 0.09	0.28 ± 0.05	0.44 ± 0.12	0.38 ± 0.06
NPV	0.97 ± 0.02	0.95 ± 0.01	0.98 ± 0.02	0.97 ± 0.01
ROC-AUC	0.88 ± 0.05	0.87 ± 0.02	0.93 ± 0.04	0.92 ± 0.01

Abbreviations: CV, cross-validation; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; ROC-AUC, area under the receiver-operator characteristic curve.