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

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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 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

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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 air-flow using a thermistor and pressure transducer, respectively; and oxygen saturation (SpO₂) 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 Inter-observer 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 breathing²⁴ (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 Association²⁷), 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 (OAH), 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 to oxygen saturation:* including minimum and average SpO₂ 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

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.

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 SpO₂, being female, high BMI (≥ 30 kg/m²), long periods under RE ($\geq 60\%$ of TST), long duration of

O₂ desaturation at thresholds of 95% or 90% ($\geq 10\%$ 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 hypertension³⁰ 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

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.

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.

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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 from 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, VitaAire, 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.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15169>.

DATA AVAILABILITY STATEMENT

Data could be provided upon reasonable request.

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SUPPORTING INFORMATION

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

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