Long-term incident severe outcomes in a prospective cohort of non-obese obstructive sleep apnoea patients free of comorbidities at inclusion

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To the Editor:

Obstructive sleep apnoea (OSA) is one of the most frequent chronic diseases affecting up to nearly 1 billion individuals worldwide [1], and is characterised by the repetitive occurrence of apnoeas and hypopneas during sleep. OSA is associated with elevated cardiovascular and metabolic morbidity and mortality [2–5]. Mortality in OSA patients is mainly driven by comorbidities [6], and interpretation of observational studies addressing the impact of OSA on long-term cardiovascular outcomes and mortality are often flawed by associated obesity and comorbidities [7, 8]. Data regarding long-term outcomes in lean OSA patients free of comorbidities at diagnosis are scarce.

This observational study addressed long-term severe cardiovascular outcomes (cardiovascular and metabolic diseases, cancer, and all-cause mortality) in a well-defined prospective cohort of OSA patients free of any comorbidity at inclusion and non-OSA controls.

This cohort included 114 people referred to the Grenoble University Hospital sleep laboratory for suspicion of OSA. This study was approved by the French Ethics Committee (Comité de Protection des Personnes Sud-Est III and V, France; number 07-CHUG-8), per the Declaration of Helsinki, and all subjects gave written informed consent.

All subjects underwent a full polysomnography and extensive cardiovascular phenotyping at baseline, including office blood pressure measurement, 24-h ambulatory blood pressure monitoring, arterial stiffness and peripheral arterial tone (baseline evaluations 2007–2012). The exclusion criteria were obesity, smoking, any known or treated cardiovascular disease, diabetes, COPD, and ongoing disease or medications that may have an impact on blood pressure regulation.

All the subjects were contacted by telephone calls up to 11 years after inclusion. A survey was used to document any incident health events, including cardiovascular disease, metabolic diseases, cancer or death. Data on OSA treatment, continuous positive airway pressure (CPAP) adherence and current medications were also collected. Any participant not answering after five call attempts was automatically excluded from the study.

Comparison between OSA and non-OSA patients and between patients with and without health events was performed through the Chi-squared test for qualitative variables and nonparametric Wilcoxon test for quantitative variables. Long-term outcomes were analysed using univariate and multivariate Cox models.

From the 114 included subjects with polysomnography data, 76 patients had data available on long-term follow-up. Among them, 52 (68.42%) were identified as OSA patients and 24 (31.58%) as non-OSA controls.

23 (30%) out of the 76 subjects presented at least one significant incident severe outcome over 11 years of follow-up. They were distributed as follows: three had type 2 diabetes (all in OSA group), eight cancers

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(all in OSA group), 17 cardiovascular events (four in non-OSA and 13 in OSA groups) including three coronary heart events (in OSA group), three arrhythmias (in OSA group), one had heart valve disease (in OSA group), one had vascular diseases (in OSA group), one had incident hypertension (four in non-OSA and seven in OSA groups) and one stroke (in OSA group). No dyslipidaemia, hepatic diseases, heart failure, heart infarction or death were recorded.

The incidence of events over 11 years was 36.5% in OSA patients *versus* 16.7% in controls (p=0.08, Chi-squared test).

When comparing subjects with and without events, subjects with events were older (median (interquartile range) 60 (52–66) *versus* 53 (47–61) years old, p=0.02) but had similar body mass index (BMI) (25.5 (23.4–28.1) *versus* 25.6 (23.7–27.5) $kg \cdot m^{-2}$, p=0.83), anthropometric measurements, smoking status and alcohol consumption. Patients presenting events had higher 24-h mean blood pressure (MBP) at inclusion (99 (95–101) *versus* 92 (87–96) mmHg, p<0.01) and a higher 24-h heart rate (74 (68–79) *versus* 68 (63–76) beats per min, p=0.03). They had lower minimum arterial oxygen saturation (S_{aO_2}) (80% (78–83%) *versus* 88% (84–91%), p<0.01) but similar mean S_{aO_2} (94% (93–96%) *versus* 95% (93–95%), p=0.33) and apnoea–hypopnoea index (AHI) (23.4 (17.7–34.9) *versus* 21.0 (5.7–32.3) events per h, p=0.11). Finally, they had elevated levels of blood soluble vascular endothelial (VE)-cadherin (1.0 (0.8–1.2) *versus* 0.6 (0.5–1.9) AU, p<0.01), a marker of endothelial dysfunction upregulated in OSA patients [9].

The univariate Cox analysis to identify factors influencing the occurrence of health events showed that age (hazard ratio (HR) 1.07, 95% CI 1.02–1.13), mean S_{aO_2} (HR 0.96, 95% CI 0.94–0.99), minimum S_{aO_2} (HR 0.94, 95% CI 0.91–0.98) and 24-h MBP (HR 1.09, 95% CI 1.04–1.14) were associated with occurrence of events (p<0.01 for all), while presence of OSA (HR 2.72, 95% CI 0.92–8.06; p=0.07) and peripheral arterial tone (HR 1.9, 95% CI 0.91–3.99; p=0.09), a clinical parameter assessing endothelial dysfunction with prognostic value [10, 11], tended to be associated with events.

Two multivariate Cox analyses were performed with mean S_{aO_2} and minimum S_{aO_2}, which were correlated parameters. These analyses confirmed that age, mean S_{aO_2} (figure 1a), minimum S_{aO_2} (figure 1b) and 24-h MBP were independently associated with the occurrence of events (p<0.01 for all). Indeed, the higher the age and 24-h MBP, and the lower the mean and minimum S_{aO_2}, the more events occurred.

Among OSA patients, the incidence of events was 22% in patients not treated with CPAP (five events in 22 patients including seven untreated patients and 15 patients with mandibular advancement devices) and was 47% in patients treated with CPAP (14 events in 30 patients) (p=0.08).

Among patients treated with CPAP, the incidence of events was not different between non-adherent and adherent patients (33% *versus* 55%, p=0.23). CPAP adherence was not significantly associated with events occurrence in univariate Cox analysis (p=0.20). In this subpopulation, again, baseline mean S_{aO_2} (p=0.03), minimum S_{aO_2} (p<0.01) and 24-h MBP (p=0.03) were associated with the occurrence of events in univariate Cox analysis. Indeed, the higher the 24-h MBP, and the lower the mean and minimum S_{aO_2}, the more events occurred.

Our study reports that age and 24-h blood pressure measurements had a major impact on the occurrence of health events in a cohort of comorbidity-free OSA patients and non-OSA controls. We also found that

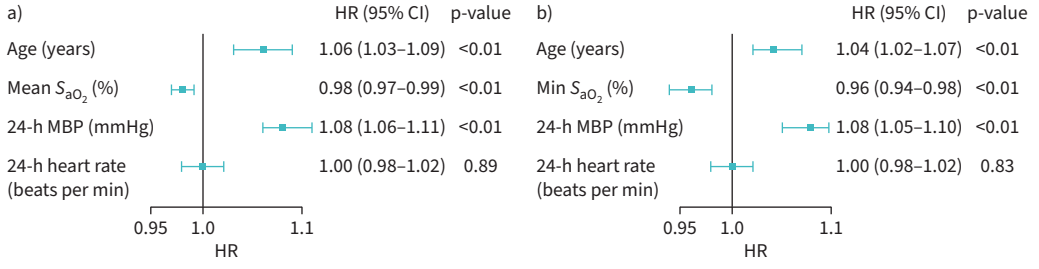

FIGURE 1 Multivariate Cox analyses on imputed data to identifying factors influencing the occurrence of health events, with a) mean arterial oxygen saturation (S_{aO_2}) and b) minimum (min) S_{aO_2}, two correlated parameters. Whiskers represent 95% confidence intervals. HR: hazard ratio; MBP: mean blood pressure.

soluble levels of VE-cadherin, a marker of endothelial dysfunction recently described as elevated in OSA patients [9], was associated with events in the univariate Cox analysis. This supports the hypothesis of a link between early endothelial dysfunction and further cardiovascular events in OSA patients.

Moreover, we show that mean S_{aO_2} and minimum S_{aO_2} were associated with events, while AHI was not. These findings highlight the importance of the severity of intermittent hypoxia in the physiopathological consequences of OSA and are in line with recent data suggesting that hypoxic burden, rather than classical polysomnographic parameters such as AHI, could be the main predictor of cardiovascular risk in various OSA patient cohorts [7, 8, 12]. However, the uniqueness of our study was to include comorbidity-free OSA patients and to confirm the importance of these factors even in lean individuals.

Our study has limitations. Due to the loss to follow-up, only 76 patients could be analysed (out of the initial 114) and collection of events by telephone calls may have led to missing some events. Among the 76 patients, only 23 (30%) presented any health event over the 11-year follow-up. This low number of events can be explained by the relatively healthy state of the subjects at inclusion. Indeed, they were quite young (54 years), non-obese (mean BMI 25.6 $kg \cdot m^{-2}$) and free of any history of cardiovascular disease, so not surprisingly at low risk of cardiometabolic events or death. The design of this cohort, although limiting the inclusion of patients, represents a unique opportunity to investigate the impact of OSA syndrome on OSA trajectories independently of previous comorbidities. Future studies with larger cohorts and longer follow-up will be mandatory to confirm the impact of hypoxic burden on the occurrence of health events in young and non-obese OSA patients.

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