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Early View

Heart Rate response and cardiovascular risk during OSA: an easy biomarker derived from pulse oximetry

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Heart Rate response and cardiovascular risk during OSA: an easy biomarker derived from pulse oximetry.

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All authors were substantially involved in data acquisition, data analysis, or interpretation of data.

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Take-Home Message

The magnitude of pulse rate response to oxygen desaturations automatically derived from pulse oximetry, could constitute a reliable and easy to measure biomarker of cardiovascular risk and posititive airway pressure therapy benefit the patients with OSA.

Abstract

Background: Sleep apnoea specific heart rate response (ΔHR) has been identified as a promising biomarker for stratifying cardiovascular (CV) risk, and predicting positive airway pressure (PAP) benefit in obstructive sleep apnoea (OSA). However, the need for prior manual scoring of respiratory events potentially limits the accessibility and reproducibility of ΔHR. We aimed to evaluate the association of pulse rate response to oxygen desaturations automatically derived from pulse oximetry (ΔHR_{oxi}) with CV risk in OSA.

Methods: ΔHR_{oxi} and ΔHR were measured in OSA patients from the *IRSR Pays de la Loire Sleep Cohort* (*PLSC;* n=5,002) and the *HypnoLaus* cohort (n=1,307). The primary outcome was major adverse CV events (MACEs), a composite of mortality, stroke, and cardiac diseases. Cox regressions analyses were conducted to evaluate the association of ΔHR_{oxi} and ΔHR categorized into low, midrange and high categories, with MACEs.

Results: MACEs occured in 768 patients from *PLSC* and 87 patients from *HypnoLaus* (median follow-up: 8.0 and 7.5 years respectively). Multivariable Cox models showed that subjects with high ΔHR_{oxi} (vs midrange) had higher risk of MACEs in *PLSC* (hazard ratio, HR: 1.42 [95% CI:1.18-1.71]) and *HypnoLaus* (HR: 1.72 [1.03-2.87]). Similar findings were observed for high ΔHR. Among 2,718 patients from *PLSC* treated with PAP, the association of PAP adherence (PAP use $\geq$ 4h/night, vs non adherence) with MACEs was modified by baseline ΔHR and ΔHR_{oxi} (p for interaction<0.05).

Conclusions: ΔHR_{oxi} could constitute a reliable and easy to measure biomarker for stratifying CV risk and predicting CV benefit of PAP in OSA.

Keywords: obstructive sleep apnoea, cardiovascular risk, positive airway pressure, heart rate response.

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Introduction

Obstructive sleep apnoea (OSA) is a prevalent disorder characterized by repetitive episodes of partial (hypopnea) or complete (apnoea) obstruction of the upper airways during sleep, resulting in intermittent hypoxia, increased intrathoracic pressure swings, and sleep fragmentation [1, 2]. Data from population-and clinic-based cohorts showed that OSA is associated with increased risks of incident hypertension, cardiovascular (CV) diseases and all-cause mortality [3–5]. There is also increasing evidence that the apnoea-hypopnea index (AHI) during sleep does not adequately capture the physiological consequences of OSA and the susceptibility to adverse CV outcomes[5, 6]. The failure to consider OSA heterogeneity might have contributed to the overall null findings of randomized controlled trials (RCTs) with CV endpoints in OSA [7–9].

Significant efforts have been made to better capture the heterogeneity of OSA by classifying it into homogeneous symptom subtypes, and developing biomarkers of CV vulnerability derived from sleep studies [6]. Among these novel biomarkers, the magnitude of post-event increase in heart rate (ΔHR) reflects the severity and duration of the preceding obstructive event, and is greater when the event is also terminated by an electroencephalogram arousal [10]. Individuals with OSA who demonstrated an elevated ΔHR were at increased risk of CV morbidity and mortality in the population-based cohort *Sleep Heart Health Study (SHHS)* [11]. Furthermore, in a *post hoc* analysis of the *RICCADSA (Randomized Intervention with CPAP in CAD and Sleep Apnoea)* trial that included non-sleepy patients with OSA and coronary heart disease, those with higher ΔHR obtained greater CV benefit from PAP therapy [12]. In its initial description, the ΔHR was dependent on prior manual scoring of respiratory events [11, 12]. Automatic calculation of ΔHR from a simple nocturnal oximetry would offer many advantages including its ease of access, its repeatability [13] and the ability to overcome interobserver variability in the manual scoring of respiratory events, particularly hypopneas [14].

The objectives of this study were to evaluate the predictive value of ΔHR with respect to CV risk in patients with OSA from two distinct European cohorts, the multicenter clinic-based *IRSR Pays de la Loire Sleep Cohort (PLSC)* and the population-based H*ypnoLaus* cohort, and to develop a new version

(ΔHR_{oxi}) derived from single-channel pulse oximetry without reliance on manual scoring. The ability of ΔHR and ΔHR_{oxi} to predict the CV benefit of adherent PAP use was also evaluated in the *PLSC*.

Methods

Study Design and Participants

PLSC

The study relied on data collected by the multicenter *PLSC*, further linked with data from the French administrative health care database (SNDS, see Online Supplementary Material and references [15–19] for details). All CV disease-free patients diagnosed with OSA (AHI ≥5 events/h of sleep [or recording]) by in-lab polysomnography (PSG, CID102L8DTM, CIDELEC, France) or home sleep apnoea testing (HSAT, CID102LTM, CIDELEC, France), between 15 May 2007 and 31 December 2018 were eligible for the study. Patients with AHI ≥15 events/h who had started PAP therapy were included in the analysis of CV outcomes according to PAP adherence, baseline ΔHR and ΔHR_{oxi}. Approval was obtained from the University of Angers Ethics Committee and the 'Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé' (CCTIRS; 07.207bis). All patients had given their written informed consent.

HypnoLaus cohort

The *HypnoLaus* sleep cohort study was designed to assess the prevalence and correlates of OSA in a general unselected middle-to-older-age population of Lausanne, Switzerland [1]. Briefly, 2,162 participants underwent a complete clinical assessment and overnight unattended PSG (Titanium, Embla Flaga, Reykjavik, Iceland) between 2009 and 2013, followed by clinical follow-up. The ethics committee of the University of Lausanne approved the HypnoLaus Sleep Cohort study. Written informed consent was obtained from all participants.

Cardiovascular endpoint

In *PLSC* the primary composite outcome, major adverse CV events (MACEs), was defined using the first occurrence in the SNDS database of hospitalization for coronary arterial diseases (CAD: myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery), stroke,

exacerbation of congestive heart failure (HF), or all-cause death [17–19]. In the *HypnoLaus* cohort, the composite incident CV endpoint included fatal CV events (death from myocardial infarction or stroke) and nonfatal CV events (myocardial infarction, stroke, transient ischemic attack, and coronary heart disease) that were adjudicated by a local expert committee according to international recommendations [19].

ΔHR assessment

The original ΔHR was defined as the difference between a maximum pulse rate during a subject-specific search window and an event-related minimum pulse. The individual-level ΔHR was defined as the mean of all event-specific responses [11, 12]. The original ΔHR calculation method was then modified to calculate the ΔHR_{oxi}. Pulse rate segments centered (100 seconds before and 100 seconds after) around the minimum oxygen saturation of automatically identified 3% oxygen desaturations, were synchronized and ensemble averaged to obtain the subject-specific search window [20]. The ΔHR_{oxi} was defined as the difference between a maximum and a previous minimum pulse rate during the subject-specific search window. The individual-level ΔHR_{oxi} was defined as the mean of all pulse rate responses over the total recording time (HSAT) or the sleep periods (PSG). Additional analyses were conducted using 2% and 4% oxygen desaturation threshold. Algorithms were developed using MATLAB (MathWorks, Natick MA) software (see Figure 1, Figure S1 and Online Supplementary Material for details).

Statistical Analysis

The primary outcome was MACEs. The primary independent variables were ΔHR_{oxi} and ΔHR. Spearman's rank correlation and Bland-Altman plots were used to assess the association and agreement between ΔHR_{oxi} and ΔHR. Additional correlation analyses were conducted to investigate how these metrics compare to indices of OSA severity including the sleep apnoea specific hypoxic burden (SASHB) [18], heart rate variability (HRV) [16, 21, 22] and the pulse wave amplitude drops (PWAD) index [19]. To assess the association of ΔHR and ΔHR_{oxi} with incident MACEs risk, we evaluated three Cox proportional hazards models: one with ΔHR and ΔHR_{oxi} as continuous linear variables, one

using restricted cubic splines, and one with ΔHR and ΔHR_{oxi} as categorical variables with three modalities (lower quartile, two middle quartiles as reference, and upper quartile). This last model reported the best Akaike Information Criterion (AIC) and was considered for the final analysis, as in a prior study [11] (Figure S2). The following clinically relevant covariates with regard to CV risk in OSA were included in the model (see direct acyclic graph [DAG], Figure S3): age (years), gender, body mass index (BMI, Kg/m^2), smoking status (current vs former or never smoker), medical history of diabetes (yes/no), hypertension (yes/no), dyslipidaemia (yes/no), use of beta blockers (yes/no) and calcium channel blockers (yes/no), event-related minimum pulse rate (beats per minute) and sleep apnoea-specific hypoxic burden (%.min/h) in *PLSC* and *HypnoLaus*, and for chronic obstructive pulmonary disease (yes/no), positive airway pressure (PAP) status (non-treated, PAP adherent or PAP non-adherent), study site (A, B, C), and type of sleep study (PSG/HSAT) in PLSC. Exploratory analyses were conducted in order to evaluate the association of ΔHR_{oxi} and ΔHR with distinct outcomes using a Fine and Gray model to consider death as a competing event for non-fatal CV events. Subgroup analyses were performed to evaluate the association of ΔHR_{oxi} and ΔHR with MACEs according to anthropomorphic data and indices of OSA severity. In patients from *PLSC* with moderate-to-severe OSA who started PAP, a secondary analysis was conducted to determine whether the association of MACEs incidence with PAP adherence differed according to baseline ΔHR_{oxi} and ΔHR. Patients who had not discontinued PAP and used it on average 4h or more per night during the entire follow-up period were assigned to the PAP adherent group. Patients who stopped the use of PAP, or those who used the device on average less than 4h per night constituted the non-adherent group. Based on previous reports [12], we hypothesize only high ΔHR group would benefit from PAP and therefore did this analysis in two groups, assuming that low ΔHR group would not benefit from PAP. All statistical analyses were performed with R statistical package (R Foundation for Statistical Computing; http://www.r-project.org). Results were expressed as hazard ratios (HR) with 95% confidence interval [95% CI] values. P values <0.05 were considered statistically significant (see Online Supplementary Material for details).

Results

Study populations

A flow diagram of study populations is presented in Figure 2. Of 7,307 patients from *PLSC* investigated for suspected OSA with available SNDS dataset, 1,190 had received a diagnosis of MACEs prior to the diagnostic sleep study, 1,049 had an AHI <5 events/h and 66 had total sleep (or recording) time <240 minutes. The final *PLSC* study sample size comprised 5,002 typical OSA patients predominantly male (64.3%), obese or overweight, with frequent CV and metabolic comorbidities (Table 1). Of 2,162 patients from *HypnoLaus* 261 had prior diagnosis of MACEs, 565 had an AHI <5 events/h and 29 had total sleep time <240 minutes. The final *HypnoLaus* study sample size comprised 1,307 OSA patients (45.2% of women) with less severe OSA, lower ΔHR and ΔHR_{oxi} values than in *PLSC*. Participants characteristics according to ΔHR_{oxi} and ΔHR categories are presented in Table 1 and in the Online Supplementary Material (Table S1 and S2) respectively. Patients belonging to the low ΔHR_{oxi} group were older, with more frequent comorbidities and less severe OSA than those from the midrange and high ΔHR_{oxi} groups, both in *PLSC* and *HypnoLaus*.

Comparison between ΔHR, ΔHR_{oxi} and other metrics of OSA severity and autonomic response

There was a strong correlation between ΔHR and ΔHR_{oxi} both in *PLSC* and *HypnoLaus* with Spearman correlation coefficient of 0.89 ($p<0.001$) and 0.87 ($p<0.001$) respectively (Figure S4). The comparison between ΔHR and ΔHR_{oxi} using Bland Altman plots (Figure S5) showed a mean difference of 0.21 beat per minute (BPM) in *PLSC* and 0.68 BPM in *HypnoLaus*. As shown in Figure S6, both ΔHR and ΔHR_{oxi} were strongly correlated with indices of HRV but not with metrics of OSA severity, nor with the PWAD index.

Primary outcome analysis

During a median follow-up of 8.0 [5.8-10.7] years, MACEs occurred in 768 (15.3%) patients in *PLSC*. In *HypnoLaus*, 87 (6.6%) participants experienced MACEs during a median follow-up of 7.5 [6.3-8.6] years. Kaplan-Meier curves of the MACE-free survival according to ΔHR_{oxi} and ΔHR categories are presented in Figure S7. Considering midrange ΔHR_{oxi} as the reference group, multivariable adjusted Cox models

showed that subjects with high ΔHR_{oxi} were at increased risk of MACEs both in *PLSC* (HR: 1.42 [95% CI: 1.18-1.71], p<0.001) and *HypnoLaus* (HR: 1.72 [95% CI: 1.03-2.87], p=0.037). The same findings were observed for subjects with high ΔHR (HR: 1.21 [95% CI: 1.00-1.47], p=0.049 in *PLSC* and 1.68 [95% CI: 1.00-2.82], p=0.049 in *HypnoLaus*) (See Figure 3). Patients with low ΔHR_{oxi} were also at increased risk of MACEs in *PLSC* (HR: 1.24 [95% CI: 1.04-1.47], p=0.014). Adjusted Cox models assessing the association of ΔHR_{oxi} and with incident MACEs according to different oxygen desaturation thresholds are presented in Table S3. High ΔHR_{oxi} was associated with a higher risk of MACEs whatever the oxygen desaturation threshold used.

Exploratory analyses

As shown in Figure 4, high ΔHR_{oxi} was associated with higher incidences of all non-fatal CV events (n=442; subdistribution hazard ratio (sdHR): 1.34 [95%CI: 1.05-1.70], p=0.018), strokes (n=151; sdHR: 1.58 [95%CI: 1.02-2.43], p=0.039), heart failure (n=133; sdHR: 1.90 [95%CI: 1.24-2.90], p=0.003) and all-cause mortality (n=433; HR: 1.38 [95%CI: 1.07-1.78], p=0.014) in the *PLSC*. Among non-fatal CV events, high ΔHR was only associated with a increased risk of heart failure (n=133; sdHR: 1.63 [95%CI: 1.06-2.52], p=0.026) (Figure S8). All-cause mortality was also increased in patients with low ΔHR_{oxi} (HR: 1.34 [95%CI: 1.07-1.68], p=0.010) and low ΔHR (HR: 1.43 [95%CI: 1.15-1.79], p=0.002) compared with midrange values (Figure 4 and S8). In the *HypnoLaus* cohort, high ΔHR_{oxi} was associated with a higher incidence of strokes (n=20; sdHR: 2.60 [1.02-6.63], p=0.045) (Table S4).

On examining differences in the association of ΔHR_{oxi} and ΔHR with incident MACEs, formal tests for interaction showed no significant difference in the relationship by anthropomorphic data, indices of OSA severity (AHI, SASHB), Epworth sleepiness score (Table 2), and study type (PSG vs HSAT, Table S5).

Association of PAP adherence with MACEs according to baseline ΔHR_{oxi} and ΔHR in PLSC

Of 2,718 patients with moderate-to severe OSA who started PAP therapy, 1,678 patients were PAP adherent (median PAP use: 6.76 [5.70-7.56] hours/day). The non-adherent group included 203 patients using PAP less than 4 hours/day (median use: 1.65 [0.23-2.40] h/day) and 837 patients who had terminated PAP therapy during the follow-up. Using the median + 1/2 standard deviation as cut-off

values, patients who started PAP therapy were divided in two groups according to baseline ΔHR_{oxi} and ΔHR (high [≥15.6 BPM] vs low ΔHR_{oxi} and high [≥15.9 BPM] vs low ΔHR). As shown in Figure 5, PAP adherence vs non-adherence was associated with a lower risk of incident MACEs in patients with high ΔHR_{oxi} (HR: 0.70 [95%CI: 0.49–0.99]) but not in those with low ΔHR_{oxi} at diagnosis (p value for interaction= 0.039). Similar findings were observed for the association of PAP adherence with MACEs according to high vs low ΔHR at baseline (p value for interaction= 0.029).

Discussion

In this study, we demonstrated in two distinct cohorts that post-event increase in heart rate can be reliably estimated by pulse rate response to oxygen desaturations, automatically derived from pulse oximetry (ΔHR_{oxi}). In CV disease-free patients with OSA, we found that high ΔHR and ΔHR_{oxi} at diagnosis were both associated with an increased risk of MACEs, in clinical and population-based cohorts. Furthermore, the association of PAP adherence with the incidence of MACEs was modified by baseline ΔHR and ΔHR_{oxi}.

Among novel prognostic biomarkers that could potentially facilitate CV risk stratification in patients with OSA, a high ΔHR was recently found to be associated with increased risks of CV morbidity and mortality in the population-based *SHHS* [11]. Apart from differences in patient's characteristics, the lower median ΔHR values in previous reports (6.5 BPM) compared to those observed in the present study (12.7 BPM in *PLSC;* 10.9 BPM in *HypnoLaus*) suggest that the authors used smoothed photoplethysmography signal to estimate heart rate response, which may have blunted the peak values [11, 12]. Despite these differences in median values, our study confirms that individuals with OSA who demonstrate high ΔHR values at diagnosis are at higher risk of MACEs in the general population and in a sleep-clinic cohort. These results reinforce the potential value of ΔHR for CV risk stratification in clinical setting.

However, the need for prior manual scoring of respiratory events constitutes a potential limitation of the original version of ΔHR in terms of accessibility, but also reproducibility due to interscorer variability in manual scoring [14]. To overcome this limitations, we developed a simpler version of the

biomarker based on automatic estimation of heart rate response to oxygen desaturations from the oximetry signal alone. We found that ΔHR and ΔHR_{oxi} were strongly correlated with each other, and showed the same level of association with incident MACEs in the *HypnoLaus* Cohort. In *PLSC*, the magnitude of the association with MACEs appeared stronger for high ΔHR_{oxi} (HR: 1.42 [95% CI: 1.18-1.71]) than for high ΔHR (HR: 1.21 [95% CI: 1.00-1.47]). Stronger effect sizes were also observed for the incidence of all non fatal CV events and stroke, which were associated with high ΔHR_{oxi} but not with high ΔHR.

The strong association of ΔHR and ΔHR_{oxi} with incident HF in OSA patients free of overt CV disease is consistent with data from population-based cohort demonstrating the implication of autonomic nervous system dysfunction in the development of HF [23, 24]. As discussed previously [11], the magnitude of post-event increases in heart rate may reflect both the parasympathetic and sympathetic responses to the event. The strong association between higher values of ΔHR_{oxi} (but not ΔHR) and stroke incidence is also consistent with the literature on the adverse effects of OSA on vascular outcomes. The association between OSA and stroke appears to be stronger than that between OSA and CAD, potentially due to the chronic effects of hypertension on this vascular bed and to dysregulation of cerebral blood flow in response to recurrent gas exchange abnormalities [5]. We previously showed that among patients with OSA, those with low sympathetic/parasympathetic tone during sleep, were at increased risks of new onset atrial fibrillation and stroke [16, 21, 22].

Beyond the identification of patients at high CV risk, determining whether a prognostic biomarker can also predict treatment response is a critical issue. A *post hoc* analysis of the *RICCADSA* clinical trial demonstrated that the CV benefit from PAP therapy, in highly selected non-sleepy OSA patients with CAD, was higher in those with elevated ΔHR values at inclusion [12]. More recently, a *post hoc* analysis involving 168 participants from the *HeartBEAT* study (Heart Biomarker Evaluation in Apnoea Treatment), treated with PAP or nocturnal supplemental oxygen, showed that a high ΔHR predicted a more favorable blood pressure response to therapy [25]. Consistent with these previous findings, we found that adherence to PAP therapy was associated with a reduced risk of MACEs only in patients

with high values of ΔHR or ΔHR_{oxi}. Patients with low ΔHR_{oxi} were older with more frequent comorbidities but less severe OSA than those with high ΔHR_{oxi}, both in *PLSC* and *HypnoLaus*. One can hypothesize that low ΔHR_{oxi} values is found in individuals with advanced vascular dysfunction due to prolonged exposure to OSA and associated comorbidites, thus unlikely to improve with PAP therapy. Conversely, high values of ΔHR_{oxi} would preferentially identify individuals with preserved autonomic reactivity, and more likely to respond to adherent PAP therapy.

Our study suggests that ΔHR_{oxi} could constitute a simple and reliable tool for stratifying CV risk and predicting the CV benefit of PAP therapy. Oximetry is easy to use in the ambulatory setting and widely available regardless of the level of sleep recording. In our study ΔHR_{oxi} was associated with the risk of MACEs in patients diagnosed with OSA by PSG or HSAT. Conversely, ΔHR was associated with the risk of MACEs only in patients investigated by HSAT. Among novel methods that have been proposed to better quantify OSA-induced intermittent hypoxemia, SASHB has been shown to predict CV outcomes in population- and clinic-based cohorts [18, 26]. Esmaeili et al. have recently developed a simplified version of SASHB based on automatically identified desaturations (HB_{oxi}), which was highly correlated with SASHB based on manually scored respiratory events and associated with excessive daytime sleepiness, hypertension and CV mortality [20]. Furthermore, high HB_{oxi} levels were associated with a long-term protective effect of PAP on CV prognosis in a *post hoc* analysis of the *ISAACC* study (Impact of Sleep Apnoea syndrome in the evolution of Acute Coronary syndrome. Effect of intervention with CPAP) [27]. Altogether, our findings and those of previous reports [20, 27] suggest that pulse oximetry could make it possible to evaluate simultaneously two prognostic biomarkers of CV risk and PAP response, ΔHR_{oxi} and HB_{oxi}. Although formal test for interaction was not significant, the association of ΔHR or ΔHR_{oxi} with MACEs appeared stronger in patients with elevated SASHB in our study. This finding suggests a cumulative effect of OSA-induced hypoxia and autonomic dysfunction on CV risk.

Strenghts and Limitations

Our study has several strengths including the consistency of association of ΔHR and ΔHR_{oxi} with the risk of MACEs across two distinct clinic- and population-based cohorts with multiple adjustement for

relevant covariates with regard to CV risk in OSA. The association of PAP adherence with MACEs according to ΔHR and ΔHR_{oxi} was evaluated in a large sample of unselected patients, suggesting that our findings are generalizable to most OSA patients. Some limitation should also be considered when interpreting the findings of our study. The main limitation of the present study is its observational design, which does not allow us to draw a formal conclusion as to the causal link between PAP adherence and MACEs. Concern for residual confounding remains including the healthy adherer effect [28]. We also acknowledge that we did not have precise data on the specific causes of death in the *PLSC*. Cancer and CV diseases are the 2 leading causes of death in patients with OSA [29–31]. An association of PAP adherence with cancer mortality seems very unlikely given the lack of relationship between PAP use and cancer risk in the *PLSC* [32]. Furthermore, ΔHR_{oxi} was associated with the incidence of non-fatal CV events.

Conclusion

In patients with OSA, high values of ΔHR_{oxi} were associated with an increased CV risk and predicted a CV benefit of PAP adherence. ΔHR_{oxi} could constitute a reliable and an easy to measure biomarker for stratifying CV risk and predicting CV benefit of adherent PAP therapy.

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Figure legends

Figure 1: Illustration of post-event increases in heart rate (ΔHR) derived from manually scored sleep recording (panel A) and heart rate response to oxygen desaturations (ΔHR_{oxi}) automatically derived from single-channel pulse oximetry (panel B).

Figure 2: Flow diagram of the study populations.

Abbreviations: *PLSC, Pays de la Loire Sleep Cohort*; PSG, polysomnography; HSAT, home sleep apnoea testing; OSA, obstructive sleep apnoea; SNDS, French administrative health care database; MACEs, major adverse cardiovascular events; AHI, apnoea-hypopnea index; TST, total sleep time; TRT, total recording time; PAP, positive airway pressure.

Figure 3: Adjusted cumulative incidence curves showing the incidence of MACEs according to ΔHR_{oxi} categories in *PLSC* (panel A) and *HypnoLaus* (panel B), and according to ΔHR categories in *PLSC* (panel C) and *HypnoLaus* (panel D).

Data were adjusted for age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, use of beta blockers and calcium channel blockers, event-related minimum pulse rate and sleep apnoea-specific hypoxic burden in *PLSC* and *HypnoLaus*, and for chronic obstructive pulmonary disease, positive airway pressure (PAP) status (non treated, PAP adherent or PAP non-adherent), study site, and type of sleep study in *PLSC*.

Abbreviations: *PLSC, Pays de la Loire Sleep Cohort*; HR, hazard ratio; CI, confidence interval; MACEs, major adverse cardiovascular events; ΔHR, delta heart rate; ΔHR_{oxi}, oximetry-derived delta heart rate.

Figure 4: Multivariable Cox regression analyses assessing the association of ΔHR_{oxi} with distinct incident non-fatal cardiovascular outcomes and all-cause mortality in the *Pays de la Loire Sleep Cohort*. Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, use of beta blockers and calcium channel blockers, study site, type of sleep study, event-related minimum pulse rate, positive airway pressure (PAP) status (non-treated, PAP adherent or PAP non-adherent), sleep apnoea-specific

hypoxic burden, and the competing risk of death for non-fatal cardiovascular events. We used a Fine and Gray model to consider death as a competing event for non-fatal CV events.

Abbreviations: ΔHR_{oxi}, oximetry-derived delta heart rate; CI, confidence interval; CV, cardiovascular; CAD, coronary artery diseases.

Figure 5: Adjusted cumulative incidence curves showing the incidence of MACEs according to PAP adherence in patients with low (panel A) or high (panel B) ΔHR_{oxi} and those with low (panel C) or high (panel D) ΔHR in *PLSC*.

Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, use of beta blockers and calcium channel blockers, study site, type of sleep study and event-related minimum pulse rate and sleep apnoea-specific hypoxic burden.

Abbreviations: PAP, positive airway pressure; *PLSC, Pays de la Loire Sleep Cohort*; HR, hazard ratio; CI, confidence interval; MACEs, major adverse cardiovascular events; ΔHR, delta heart rate; ΔHR_{oxi}, oximetry-derived delta heart rate.

Table 1: Baseline characteristics of the study populations.

	PLSC				*HypnoLaus*			
	Total	**Low ΔHR_{oxi}**	**Midrange ΔHR_{oxi}**	**High ΔHR_{oxi}**	**Total**	**Low ΔHR_{oxi}**	**Midrange ΔHR_{oxi}**	**High ΔHR_{oxi}**
N	5002	1251 (25.0)	2500 (50.0)	1251 (25.0)	1307	327	654	326
Age, years	53.0 [44.0-62.0]	**59.0 [51.0-66.0]**	**52.0 [44.0-61.0]**	**47.0 [37.0-57.0]**	59.1 [51.0-69.0]	**66.9 [56.8-71.7]**	**57.7 [51.0-67.5]**	**54.2 [47.8-67.0]**
Female gender	1786 (35.7)	**485 (38.8)**	**927 (37.1)**	**374 (29.9)**	591 (45.2)	**187 (57.2)**	**295 (45.1)**	**108 (33.1)**
Body mass index, kg/m²	29.4 [26.0-34.5]	**29.0 [26.0-33.0]**	**29.4 [26.1-34.4]**	**30.1 [25.9-36.1]**	26.4 [24.1-29.2]	26.7 [24.5-29.8]	26.2 [24.0-28.8]	26.6 [23.7-29.6]
Current smokers	2822 (57.0)	**652 (52.1)**	**1406 (56.2)**	**790 (63.1)**	229 (17.5)	48 (14.7)	125 (19.1)	56 (17.2)
Comorbidities								
Diabetes	679 (13.7)	**209 (16.7)**	**306 (12.2)**	**172 (13.7)**	152 (11.6)	**50 (15.3)**	**64 (9.8)**	**37 (11.3)**
Hypertension	1635 (32.8)	**517 (41.3)**	**779 (31.2)**	**344 (27.5)**	588 (45.0)	**186 (56.9)**	**277 (42.4)**	**125 (38.3)**
Dyslipidaemia	971 (19.7)	**302 (24.1)**	**470 (18.8)**	**218 (17.4)**	389 (29.7)	109 (33.3)	184 (28.1)	95 (29.1)
COPD	527 (10.5)	149 (11.9)	252 (10.1)	126 (10.1)	-	-	-	-
CV active drugs								
Beta blockers	508 (10.2)	**206 (16.5)**	**219 (8.8)**	**83 (6.6)**	93 (7.11)	**41 (12.5)**	**33 (5.1)**	**19 (5.8)**
Calcium channel blockers	369 (7.4)	**123 (9.8)**	**164 (6.6)**	**82 (6.6)**	80 (6.12)	**32 (9.8)**	**34 (5.2)**	**14 (4.3)**
Sleep study type, PSG	2555 (51.1)	655 (52.4)	1279 (51.2)	621 (49.6)	1307 (100)	-	-	-
Epworth sleepiness scale	10.0 [6.0-14.0]	**9.0 [6.0-13.0]**	**10.0 [6.0-14.0]**	**11.0 [7.0-15.0]**	6.0 [3.0-8.0]	5.0 [3.0-8.0]	6.0 [3.0-8.0]	6.0 [4.0-9.0]
AHI, events/h	25.1 [13.2-39.7]	**21.4 [12.2-34.4]**	**24.8 [13.5-38.7]**	**30.1 [14.8-52.6]**	14.4 [9.0-24.7]	**12.1 [8.0-21.1]**	**14.3 [9.3-24.9]**	**17.5 [9.2-28.4]**
ΔHR, BPM	12.7 [10.1-16.3]	**8.6 [7.4-9.8]**	**12.7 [11.2-14.6]**	**19.7 [16.9-23.0]**	10.9 [8.6-13.8]	**7.4 [6.4-8.8]**	**10.9 [9.33-12.5]**	**16.4 [14.2-20.0]**
ΔHR_{oxi}, BPM	12.4 [9.6-16.3]	**7.9 [6.8-8.8]**	**12.4 [11.0-14.1]**	**19.9 [17.9-23.8]**	10.2 [7.71-13.4]	**6.3 [5.5-7.0]**	**10.2 [9.0-11.5]**	**16.2 [14.7-19.5]**
Pulse rate baseline, BPM	58.0 [52.2-63.8]	58.0 [52.1-63.8]	58.1 [52.3-63.9]	57.7 [52.0-63.4]	57.8 [52.2-62.7]	**58.2 [52.4-64.3]**	**58.4 [53.2-63.0]**	**55.6 [50.2-60.5]**
Pulse $rate_{oxi}$ baseline, BPM	59.1 [53.6-65.1]	**58.5 [53.0-64.8]**	**59.8 [54.2-65.6]**	**58.2 [52.9-64.2]**	59.1 [53.7-64.1]	**59.3 [53.6-65.0]**	**60.1 [54.6-64.4]**	**57.2 [52.0-62.5]**
SASHB, %.min/h	35.6 [15.3-78.8]	**29.2 [14.3-62.3]**	**35.7 [15.2-75.3]**	**45.7 [16.5-126.4]**	17.5 [8.91-32.9]	**14.2 [8.3-29.9]**	**17.7 [9.0-32.8]**	**19.8 [9.7-35.6]**
HB_{oxi}, %.min/h	49.4 [24.5-97.6]	**42.8 [23.7-80.0]**	**47.9 [24.4-95.0]**	**60.9 [26.5-145.8]**	38.8 [25.3-59.5]	**35.4 [24.1-54.7]**	**39.0 [25.4-61.0]**	**42.2 [28.0-64.2]**
PAP treatment status								
No PAP therapy	2284 (45.7)	**221 (17.7)**	**547 (21.9)**	**272 (21.7)**	-	-	-	-
PAP non-adherent	1040 (20.8)	**639 (51.1)**	**1133 (45.3)**	**512 (40.9)**	-	-	-	-
PAP adherent*	1678 (33.5)	**391 (31.3)**	**820 (32.8)**	**467 (37.3)**	-	-	-	-
Incident MACEs	768 (15.4)	**255 (20.4)**	**319 (12.8)**	**194 (15.5)**	87 (6.7)	25 (7.7)	35 (5.4)	27 (8.3)

Data are presented as number of patients (%), median [25th–75th percentile].

Abbreviations: *PLSC, Pays de la Loire Sleep Cohort*; COPD, chronic obstructive pulmonary disease; PSG, polysomnography; AHI, apnoea-hypopnea index; ΔHR, delta heart rate; ΔHR_{oxi}, oximetry-derived delta heart rate; BPM, beats per minute; SASHB, sleep apnoea-specific hypoxic burden; HB_{oxi}, oximetry-derived hypoxic burden calculated as previously described [20]; PAP, positive airway pressure; MACEs, major adverse cardiovascular events. *PAP adherent: patients who had not discontinued PAP and used it on average 4h or more per night.

Data were analyzed using Pearson's chi-square test, or Mann-Whitney pairwise comparisons, as appropriate. Bold denotes significant ($p<0.05$).

Table 2: Adjusted Cox models assessing the association of ΔHR_{oxi} and ΔHR with incident MACEs according to anthropomorphic data and indices of OSA severity in the *Pays de la Loire Sleep Cohort*.

Subgroups	ΔHR_{oxi} Hazard Ratio [95% CI]	ΔHR Hazard Ratio [95% CI]
Men (n=3,216)		
Low vs midrange values	1.11 [0.91-1.35]	1.07 [0.87-1.30]
High vs midrange values	**1.35 [1.09-1.68]** ‡	**1.30 [1.05-1.62]** *
Women (n=1,786)		
Low vs midrange values	**1.56 [1.11-2.18]** ‡	1.16 [0.84-1.61]
High vs midrange values	**1.70 [1.15-2.51]** ‡	1.01 [0.67-1.52]
Age ≥ 53 (n=2,558)		
Low vs midrange values	1.10 [0.90-1.35]	1.11 [0.91-1.36]
High vs midrange values	**1.26 [1.03-1.54]** *	1.18 [0.97-1.45]
Age < 53 (n=2,444)		
Low vs midrange values	**1.44 [1.01-2.05]** *	**1.41 [1.01-1.96]** *
High vs midrange values	**1.67 [1.14-2.46]** ‡	0.91 [0.60-1.39]
BMI ≥ 30 kg/m² (n=2,373)		
Low vs midrange values	1.20 [0.94-1.52]	1.13 [0.89-1.44]
High vs midrange values	**1.56 [1.21-2.01]** †	**1.44 [1.12-1.86]** *
BMI < 30 kg/m² (n=2,629)		
Low vs midrange values	1.17 [0.92-1.50]	1.17 [0.92-1.50]
High vs midrange values	1.19 [0.90-1.58]	1.12 [0.84-1.49]
AHI ≥15 events/h (n=3,538)		
Low vs midrange values	1.12 [0.92-1.36]	1.07 [0.88-1.30]
High vs midrange values	**1.43 [1.16-1.76]** †	**1.26 [1.02-1.56]** *
AHI <15 events/h (n=1,464)		
Low vs midrange values	**1.46 [1.02-2.08]** *	1.39 [0.98-1.97]
High vs midrange values	1.43 [0.92-2.22]	1.39 [0.89-2.19]
AHI ≥30 events/h (n=2,077)		
Low vs midrange values	1.21 [0.95-1.53]	1.12 [0.89-1.42]
High vs midrange values	**1.61 [1.25-2.07]** †	**1.34 [1.04-1.72]** *
AHI <30 events/h (n=2,925)		
Low vs midrange values	**1.40 [1.10-1.79]** ‡	1.15 [0.90-1.47]
High vs midrange values	**1.50 [1.12-1.99]** ‡	1.16 [0.86-1.56]
SASHB ≥35.6 %min/h (n=2,501)		
Low vs midrange values	1.23 [0.99-1.53]	1.19 [0.96-1.49]
High vs midrange values	**1.56 [1.23-1.97]** †	**1.43 [1.13-1.80]** ‡
SASHB <35.6 %min/h (n=2,501)		
Low vs midrange values	1.18 [0.90-1.54]	1.10 [0.84-1.44]

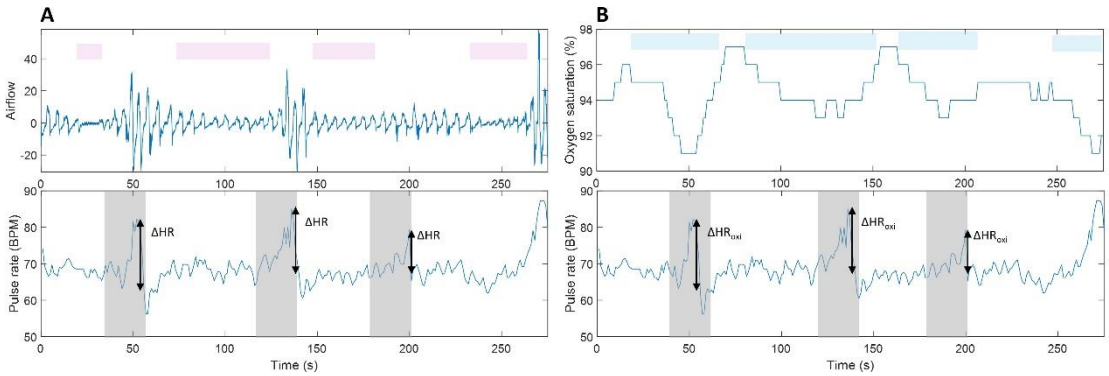
High vs midrange values	1.32 [0.96-1.82]	1.04 [0.74-1.47]
HB_{oxi} ≥49.4 %min/h (n=2,501)		
Low vs midrange values	1.18 [0.95-1.46]	1.08 [0.87-1.34]
High vs midrange values	**1.57 [1.25-1.97]** †	**1.36 [1.08-1.71]** ‡
HB_{oxi}<49.4 %min/h (n=2,501)		
Low vs midrange values	**1.36 [1.03-1.79]** *	1.27 [0.97-1.67]
High vs midrange values	1.35 [0.97-1.89]	0.96 [0.67-1.38]
ESS ≥11 (n=2,263)		
Low vs midrange values	1.28 [0.97-1.68]	1.15 [0.88-1.51]
High vs midrange values	**1.38 [1.01-1.88]** *	1.22 [0.89-1.67]
ESS <11 (n=2,625)		
Low vs midrange values	**1.26 [1.01-1.58]** *	1.20 [0.96-1.49]
High vs midrange values	**1.40 [1.09-1.78]** ‡	**1.30 [1.02-1.66]** *

Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, use of beta blockers and calcium channel blockers, study site, type of sleep study, event-related minimum pulse rate, positive airway pressure (PAP) status (non treated, PAP adherent or PAP non-adherent) and sleep apnoea-specific hypoxic burden (SASHB) or oximetry-derived hypoxic burden (HB_{oxi}) for the corresponding variable.

Abbreviations: ΔHR_{oxi}, oximetry-derived delta heart rate; ΔHR, delta heart rate; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnoea; HR, hazard ratio; CI, confidence interval; AHI, apnoea-hypopnea index; HB_{oxi} was calculated as previously described [20]; ESS, Epworth sleepiness score.

*$p<0.05$. ‡$p<0.01$. †$p<0.001$

Formal tests for interaction were not significant.



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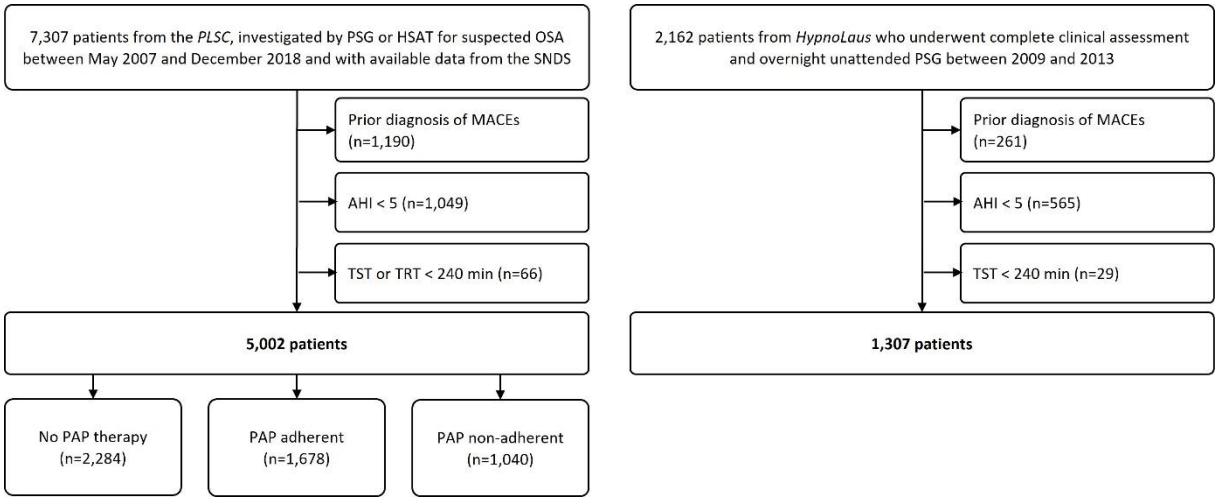

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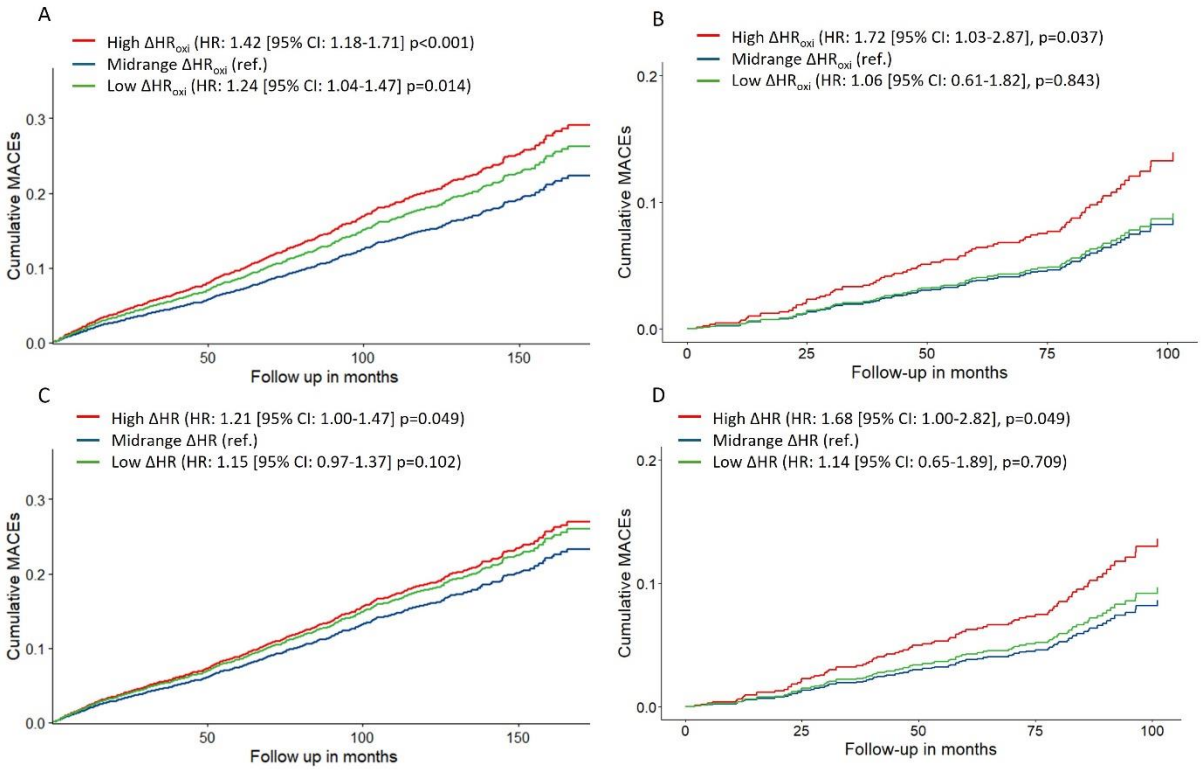

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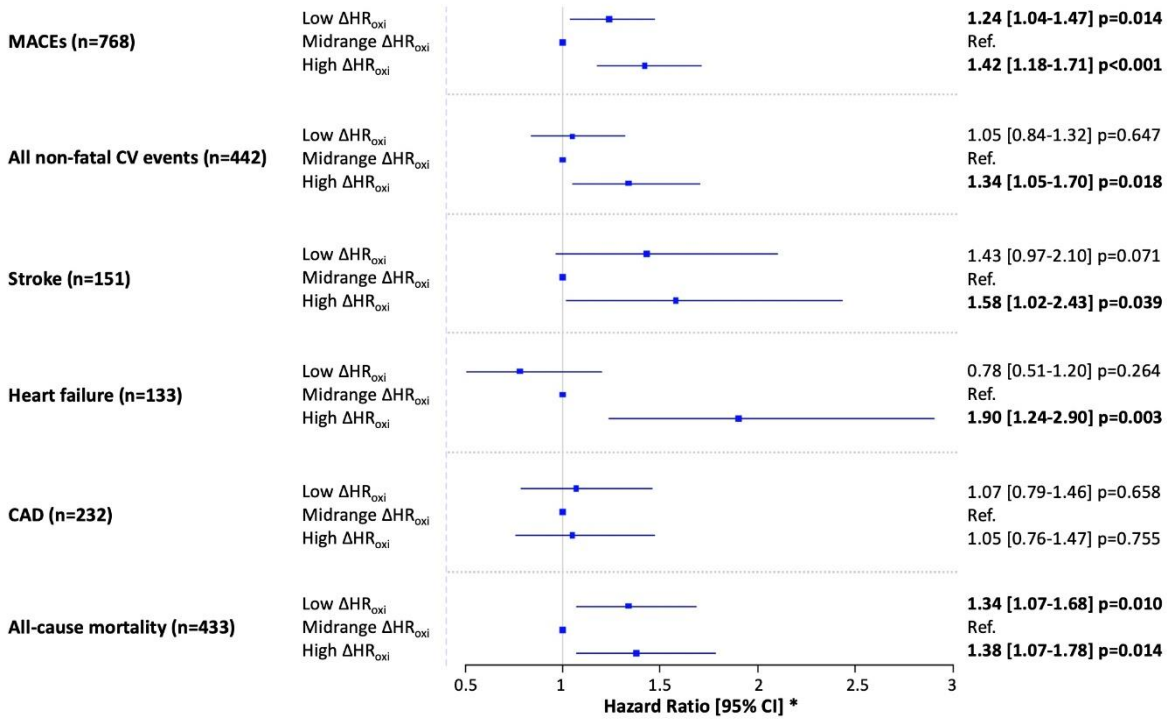

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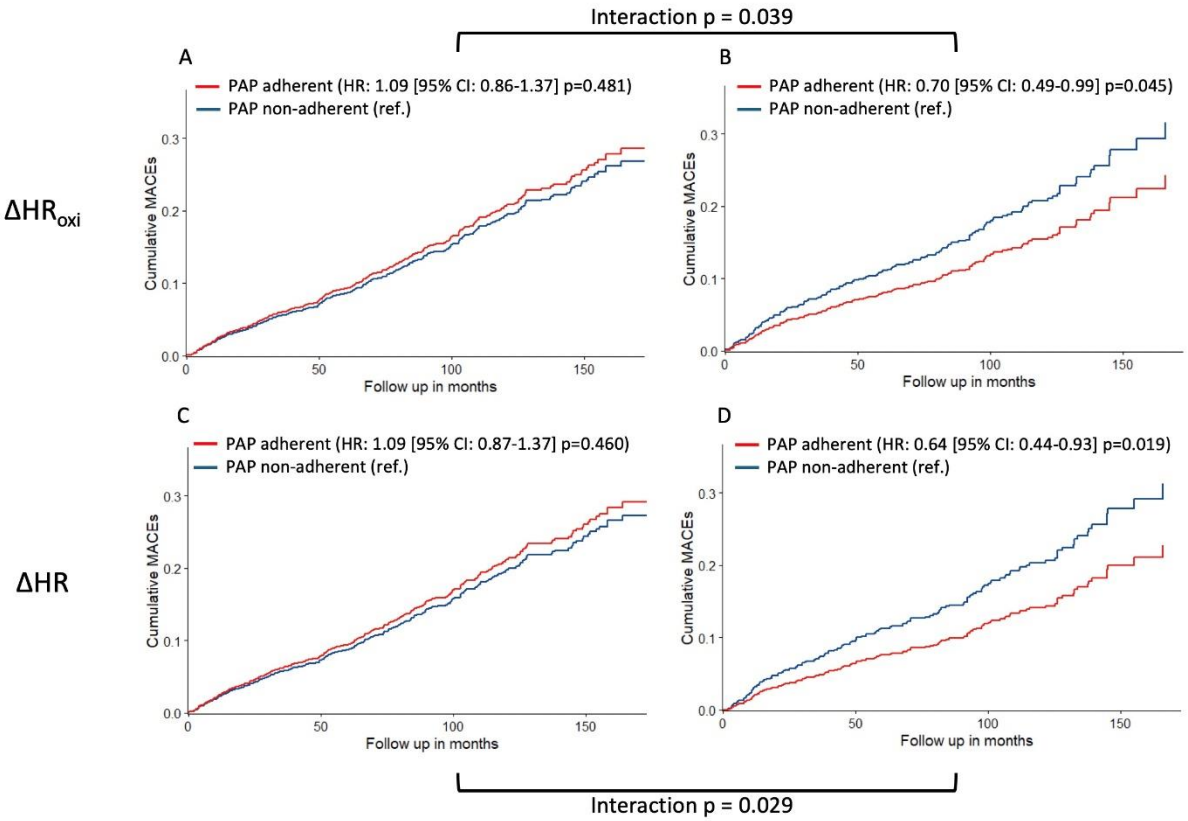

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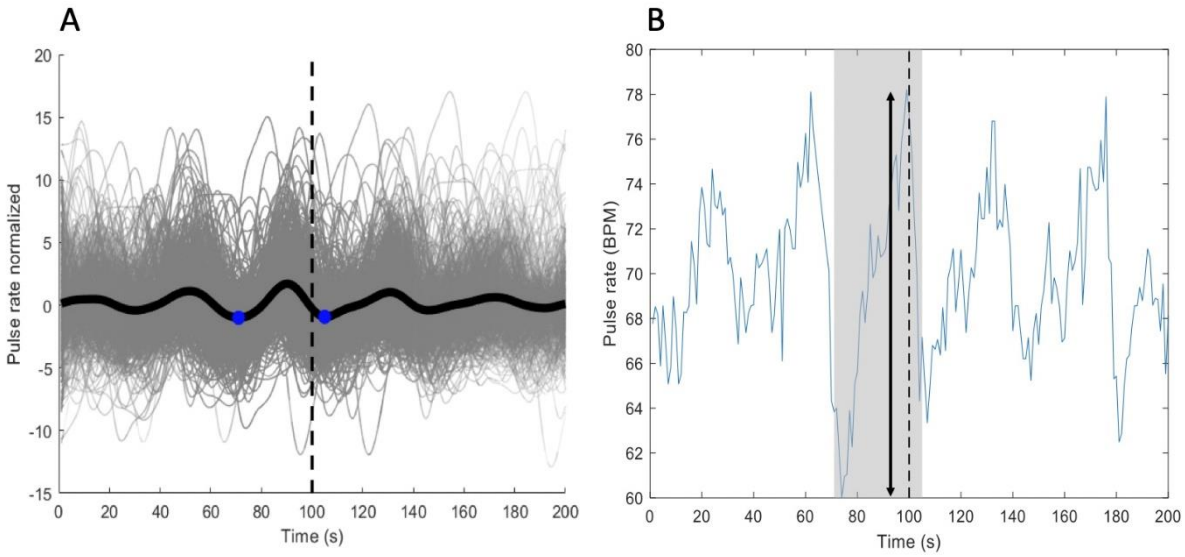

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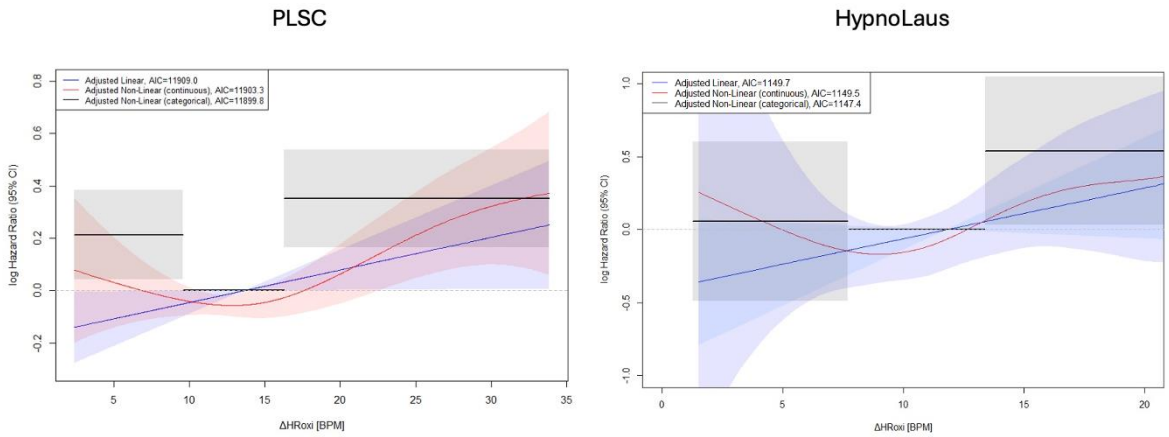

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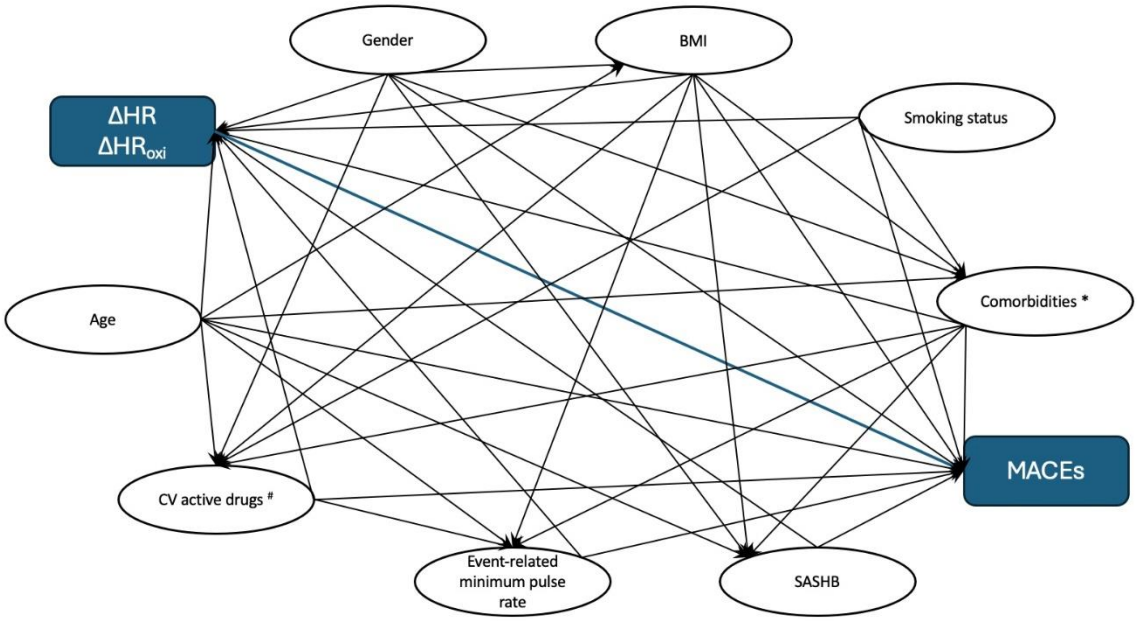

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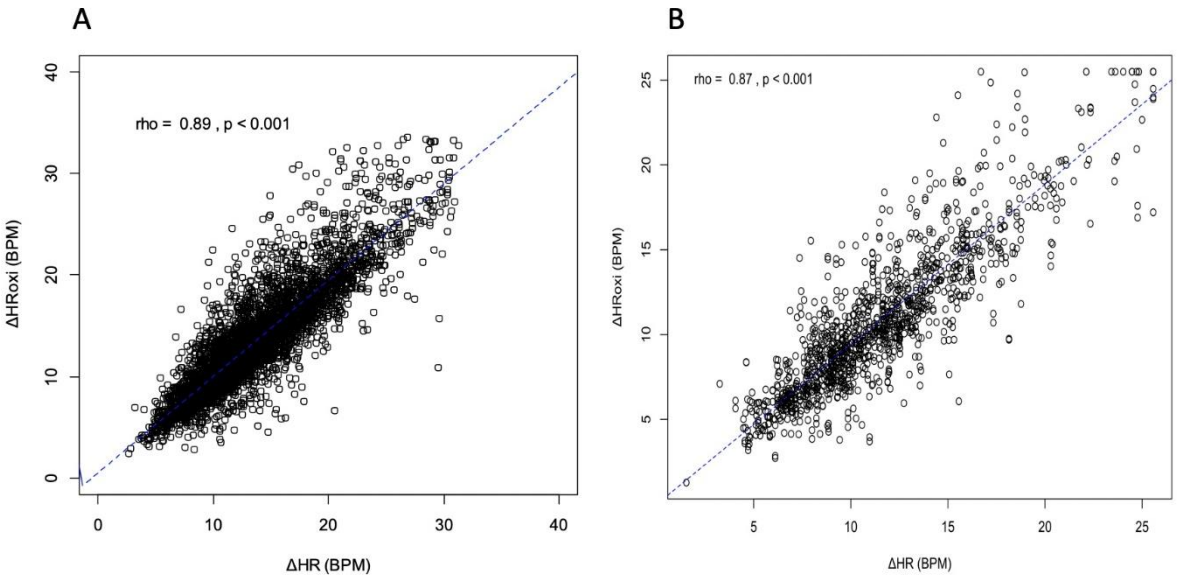

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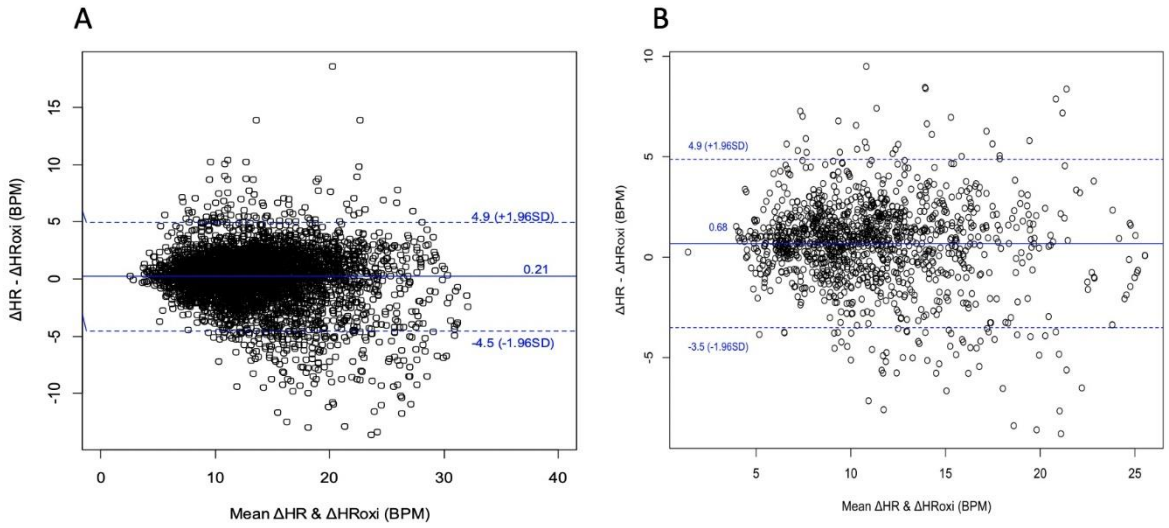

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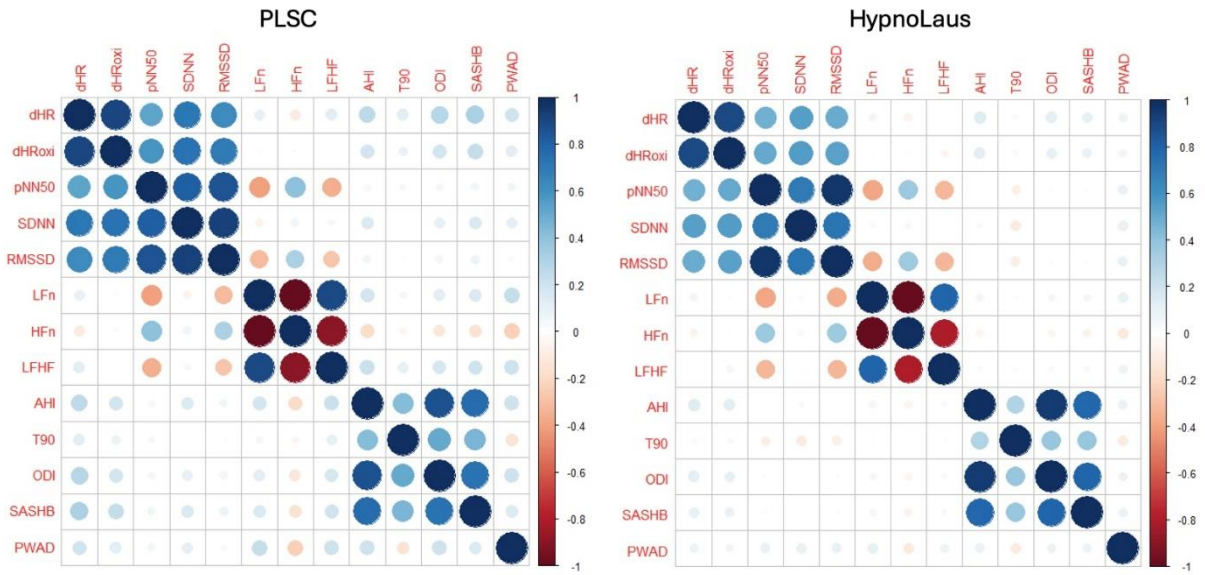

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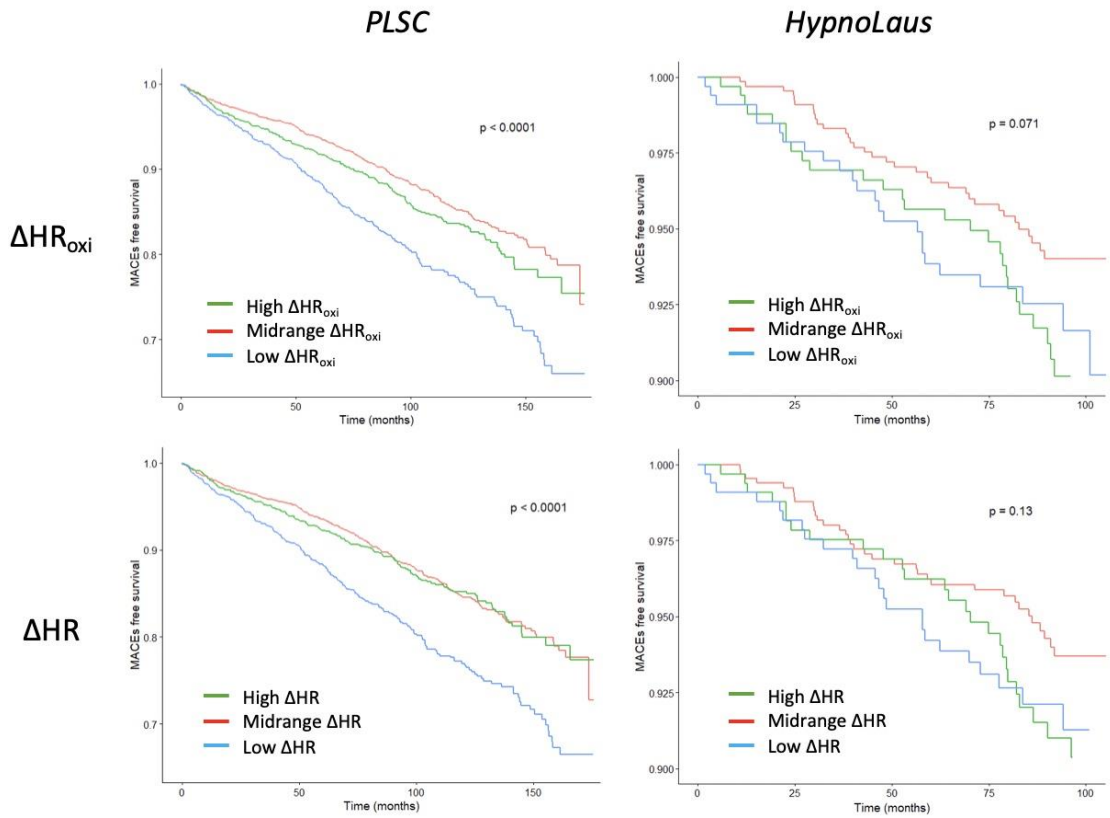

Figure S7

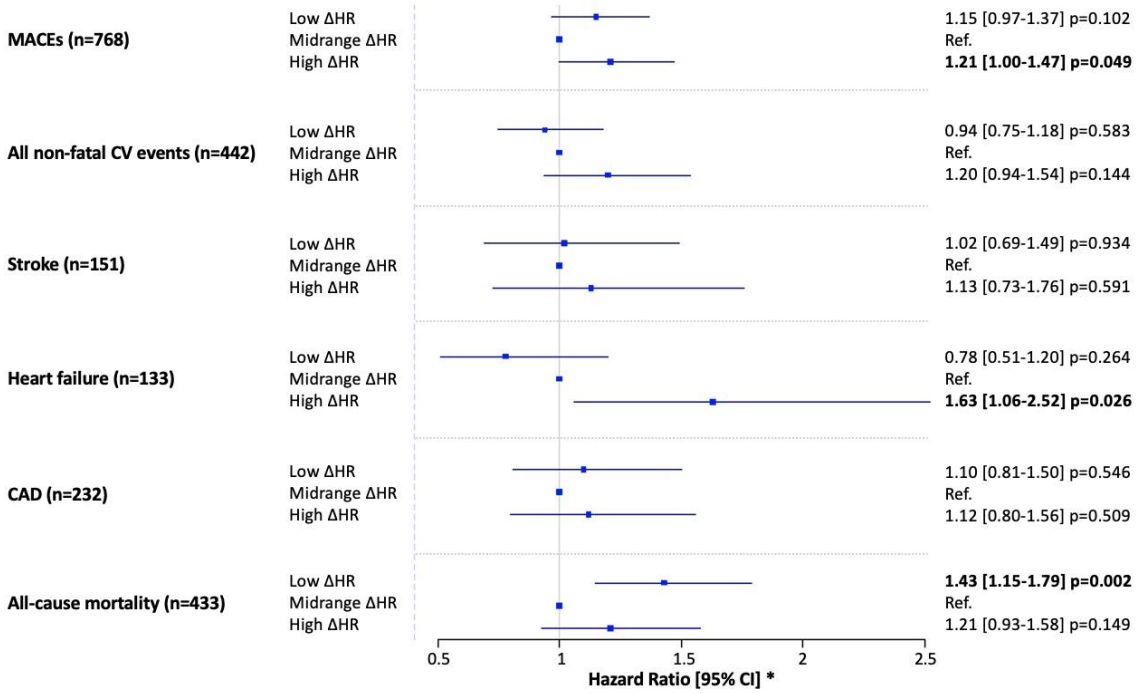

Figure S8

Online Supplementary Material

Heart Rate response and cardiovascular risk during OSA: an easy biomarker derived from pulse oximetry.

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Details on *the IRSR Pays de la Loire Sleep Cohort (PLSC)* and the linkage process with the French administrative health care database

Since May 15, 2007, consecutive patients ≥ 18 years investigated for suspected obstructive sleep apnoea (OSA) in 7 centers from the Pays de la Loire were eligible for inclusion in the *PLSC*. Patients with a high clinical probability of OSA were investigated by home sleep apnoea testing (HSAT), those with a low likelihood of OSA and/or coexisting sleep disorders were diagnosed with in-lab polysomnography (PSG) (CID102LTM and CID102L8DTM respectively; CIDELEC, France), using recommended scoring rules [1]. Each patient enrolled in the *PLSC* completed questionnaires and surveys including anthropometric data, smoking habits, alcohol consumption, medical history, and medication use. Patients with learning difficulties, who were unable to fill in the questionnaires, or read and/or speak French, and patients with neuromuscular diseases or chronic respiratory failure were not included in *PLSC*. Patients were excluded from the present study if they had received a diagnosis of myocardial infarction, stroke, exacerbation of congestive heart failure, or a revascularization procedure (percutaneous coronary intervention, coronary artery bypass graft surgery) at any time before the sleep study. Approval was obtained from the University of Angers Ethics Committee and the 'Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé' (CCTIRS; 07.207bis). The database is anonymous and its linkage with the French administrative health care database (SNDS) database complied with the restrictive requirements of the 'Commission Nationale Informatique et Liberté' (CNIL), the French information technology, and personal data protection authority. Specific approval was obtained from the CNIL to perform this study. The *PLSC* data manager submitted personal identifiers (gender, date of birth [month/year], date and location where overnight PSG or HSAT was performed, and residency postcode) to the National Health Insurance Fund (CNAM), alongside a pseudo-anonymized patient record identifier (link ID) for all patients in their dataset. Pseudo-anonymized identifiers (NUM_ENQ) in the SNDS file were matched with pseudo-anonymized (link ID) identifiers from the *PLSC*, through an iterative deterministic method comprising a series of progressively less restrictive steps, generated

from combinations of gender, date of birth (year and month), date (+/- 3 days) and location (hospital identification) where overnight PSG or HSAT was performed, and residency postcode. Overnight PSG or HSAT were identified in the 'Programme de Médicalisation des Systèmes d'Information' (PMSI) database through six codes for medical acts (AMQP010-015). Records matched at a given step were not available for matching in subsequent steps. Steps included relaxation on codes for sleep recordings, which were no longer, required. The CNAM generated a linker file. The linker file contains a pair of pseudo-anonymized identifiers (NUM_ENQ, link ID) for each linked patient that was used to merge the *PLSC* dataset with the dataset extracted from SNDS.

Details on positive airway pressure (PAP) therapy initiation and follow-up in *PLSC*

According to the reimbursement criteria defined by the French national health insurance, PAP therapy was prescribed in patients reporting at least three OSA symptoms (including snoring, choking or gasping during sleep, unrefreshing sleep, daytime sleepiness, impaired concentration, and/or nocturia) with an apnoea-hypopnea index (AHI) ≥30 events/h on PSG or HSAT, or between 15 to <30 events/h in patients with cardiovascular comorbidities or severe daytime sleepiness. Based on the digital downloads from PAP devices, objective daily PAP use (average number of daily hours of PAP use since the last visit) was collected at each follow-up visit (3 months, 6 months and at least annually) by the home care provider (ASTEN SANTE, Beaucouzé, France) and documented in the database.

Details on ΔHR assessment

Pulse rate was obtained from the oximeter photoplethysmography signal derived from diagnostic sleep studies (Nonin Medical B.V. Netherlands, for both *PLSC* and *HypnoLaus*). The beat-to-beat difference was extracted, and ectopic beat or artefact (pulse rate < 30 or > 180 beats per minute [BPM], pulse rate change between two consecutive intervals > 80 BPM) were removed. As described previously [2, 3], the original sleep apnoea–specific pulse-rate response (ΔHR) was defined as the difference between a maximum pulse rate during a subject-specific search window (a search window extended from the pre-event minimum to the post-event minimum of the event-related, ensemble-averaged pulse rate) and an event-related minimum pulse rate (the minimum pulse rate during

apnoeas and hypopneas). Finally, individual-level ΔHR was defined as the mean of all event-specific responses.

The original ΔHR calculation method was modified to calculate the heart rate response to oxygen desaturations derived from single-channel pulse oximetry (ΔHR_{oxi}) using desaturations detected automatically from pulse oximetry. All oxygen desaturations exceeding a 3% drop were automatically identified from the SpO_2 signal. Pulse rate segments centred (100 seconds before and 100 seconds after) around the minimum oxygen saturation of automatically identified 3% oxygen desaturations, were synchronized and ensemble averaged to obtain the subject-specific search window (defined between the two lowest points around the minimum average oxygen desaturation) [4]. The ΔHR_{oxi} was defined as the difference between a maximum and a previous minimum pulse rate during the subject-specific search window. Finally, the individual-level ΔHR_{oxi} was defined as the mean of all pulse rate responses over the total recording time (HSAT) or the sleep periods (PSG). Algorithms were developed using MATLAB (MathWorks) software.

Details on statistical analyses

Variables were described using median and interquartile range [IQR] for continuous variables, and number and percentage for qualitative variables. Comparison between groups were performed using Chi-squared test for qualitative variables and Mann-Whitney test for quantitative variables. Multiple imputation method (MICE procedure from R software) was used for missing data [5]. The primary dependent variable of interest was the incidence of MACEs. The primary independent variables were ΔHR_{oxi} and ΔHR. Spearman's rank correlation and Bland-Altman plots were used to assess the association and agreement between ΔHR_{oxi} and ΔHR. To assess the association of ΔHR and ΔHR_{oxi} with incident MACEs risk, we evaluated three Cox proportional hazards models: one with ΔHR and ΔHR_{oxi} as continuous linear variables, one using restricted cubic splines, and one with ΔHR and ΔHR_{oxi} as categorical variables with three modalities (lower quartile, two middle quartiles as reference, and upper quartile). This last model reported the best Akaike Information Criterion (AIC) and was considered for the final analysis, as a prior study [11]. The following clinically relevant covariates with

regard to CV risk in OSA were included in the model (see direct acyclic graph [DAG], Figure S3): age (years), gender, body mass index (BMI, Kg/m^2), smoking status (current vs former or never smoker), medical history of diabetes (yes/no), hypertension (yes/no), dyslipidaemia (yes/no), use of beta blockers (yes/no) and calcium channel blockers (yes/no), event-related minimum pulse rate (beats per minute) and sleep apnoea-specific hypoxic burden (%.min/h) in *PLSC* and *HypnoLaus*, and for chronic obstructive pulmonary disease (yes/no), positive airway pressure (PAP) status (non-treated, PAP adherent or PAP non-adherent), study site (A, B, C), and type of sleep study (PSG/HSAT) in PLSC. Exploratory analyses were conducted in order to evaluate the association of ΔHR_{oxi} and ΔHR with distinct outcomes using a Fine and Gray model to consider death as a competing event for non-fatal CV events. Subgroup analyses were performed to evaluate the association of ΔHR_{oxi} and ΔHR with MACEs according to anthropomorphic data and indices of OSA severity. In patients from *PLSC* with moderate-to-severe OSA who started PAP, a secondary analysis was conducted to determine whether the association of MACEs incidence with PAP adherence differed according to baseline ΔHR_{oxi} and ΔHR. Patients who had not discontinued PAP and used it on average 4h or more per night during the entire follow-up period were assigned to the PAP adherent group. Patients who stopped the use of PAP, or those who used the device on average less than 4h per night constituted the non-adherent group. Based on previous reports [12], we hypothesize only high ΔHR group would benefit from PAP and therefore did this analysis in two groups, assuming that low ΔHR group would not benefit from PAP. All statistical analyses were performed with R statistical package (R Foundation for Statistical Computing; http://www.r-project.org). Results were expressed as hazard ratios (HR) with 95% confidence interval [95% CI] values. P values <0.05 were considered statistically significant.

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Figure legends

Figure S1: Illustration of ΔHR_{oxi} calculation. All automatically scored desaturations were synchronized at their minimum saturation level and ensemble averaged to obtain the search window which was defined between the two minimum values around the minimum average saturation level (panel A). ΔHR_{oxi} was defined as the mean of the difference between a maximum and a previous minimum pulse rate during the subject-specific search window around all desaturations (panel B).

Figure S2: Visualisation of the ΔHR_{oxi} U-shaped curve in *Pays de la Loire Sleep Cohort* (panel A) and the *HypnoLaus* cohort (panel B). To assess the functional form of the relationship between ΔHR_{oxi} and MACEs, we applied three Cox proportional hazards models, each incorporating ΔHR_{oxi} differently: as a continuous linear variable, using restricted cubic splines, and as a categorical variable. The spline model revealed a U-shaped relationship between ΔHR_{oxi} and CV risk. The model that considered ΔHR_{oxi} as a categorical variable had the best Akaike Information Criterion (AIC) values and was selected as the best model.

Figure S3: Direct acyclic graph (DAG) common for both cohorts for the minimal sufficient adjustment sets for estimating the total effect of ΔHR_{oxi} or ΔHR on MACEs (direct effect: blue arrow). *Comorbidities included diabetes, hypertension, dyslipidaemia.

#CV active drugs included use of beta blockers and calcium channel blockers.

Figure S4: Correlation between ΔHR and ΔHR_{oxi} in the *Pays de la Loire Sleep Cohort* (panel A) and the *HypnoLaus* cohort (panel B).

Figure S5: Comparison between ΔHR and ΔHR_{oxi} using Bland Altman plots in the *Pays de la Loire Sleep Cohort* (panel A) and the *HypnoLaus* cohort (panel B). The solid horizontal blue line shows the mean of

the differences (=bias) between ΔHR and ΔHR_{oxi}, and the doted blue horizontal lines show the upper and lower 95% limits of agreement (= bias ± 1.96 × SD).

Figure S6: Pairwise correlations between ΔHR (BPM), ΔHR_{oxi} (BPM), indices of OSA severity and cardiovascular autonomic response in the *Pays de la Loire Sleep Cohort* (PLSC) and the *HypnoLaus* cohort.

Abbreviations: pNN50, percentage of consecutive normal to normal intervals differing by more than 50 ms (%); SDNN, standard deviation of all normal to normal intervals (ms); RMSSD, root mean square of successive differences in normal to normal intervals (ms); LFn, low-frequency normalized power (%); HFn, high-frequency normalized power (%); LFHF, ratio of low-frequency to high-frequency power; AHI, apnoea hypopnea index (events/h); T90, time below 90% of oxygen saturation (%); ODI, 3% oxygen desaturation index (events/h); SASHB, sleep apnoea specific hypoxic burden (%.min/h); PWAD, pulse wave amplitude drops (events/h).

Figure S7: Kaplan-Meier curves of the MACE-free survival according to ΔHR_{oxi} and ΔHR categories.

Figure S8: Multivariable Cox regression analyses assessing the association of ΔHR with distinct incident non-fatal cardiovascular outcomes and all-cause mortality in the *Pays de la Loire Sleep Cohort*. Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, use of beta blockers and calcium channel blockers, study site, type of sleep study, event-related minimum pulse rate, positive airway pressure (PAP) status (non-treated, PAP adherent or PAP non-adherent), sleep apnoea-specific hypoxic burden, and the competing risk of death for non-fatal cardiovascular events. We used a Fine and Gray model to consider death as a competing event for non-fatal CV events.

Abbreviations: CI, confidence interval; CV, cardiovascular; CAD, coronary artery diseases.

Table S1: Baseline characteristics of the population by ΔHR categories in *PLSC*.

	Low ΔHR	Midrange ΔHR	High ΔHR	P value**
n	1251 (25.0)	2500 (50.0)	1251 (25.0)	
Age, years	60.0 [52.0 - 66.0]	52.0 [44.0 - 61.0]	46.0 [36.0 - 56.0]	<0.001
Female gender	476 (38.8)	901 (36.7)	369 (30.0)	<0.001
Body mass index, kg/m²	29.1 [25.9 - 33.0]	29.4 [26.0 - 34.3]	30.8 [26.6 - 36.7]	<0.001
Current smokers	627 (51.6)	1391 (57.1)	753 (62.4)	<0.001
Comorbidities				
Diabetes	195 (16.1)	304 (12.5)	176 (14.4)	0.011
Hypertension	531 (43.4)	757 (31.0)	330 (26.9)	<0.001
Dyslipidaemia	306 (25.3)	457 (18.9)	194 (16.0)	<0.001
COPD	153 (12.5)	227 (9.2)	138 (11.2)	0.007
CV active drugs				
Beta blockers	209 (17.0)	213 (8.7)	79 (6.4)	<0.001
CCB	128 (10.4)	152 (6.2)	88 (7.2)	0.001
Epworth sleepiness scale	9.0 [6.0 - 13.0]	10.0 [6.0 - 14.0]	11.0 [7.0 - 14.0]	<0.001
AHI, events/h	21.7 [12.2 - 34.9]	24.8 [13.9 - 38.0]	31.4 [16.3 - 54.9]	<0.001
ΔHR, BPM	8.4 [7.4 - 9.3]	12.7 [11.3 - 14.3]	19.9 [17.9 - 23.2]	<0.001
Pulse rate baseline, BPM	58.0 [52.1 - 63.7]	58.3 [52.4 - 64.2]	57.3 [52.2 - 63.0]	0.092
SASHB, %.min/h	29.7 [13.5 - 63.3]	35.0 [16.4 - 73.0]	51.0 [18.8 - 140.4]	<0.001
PAP treatment status				<0.001
No PAP therapy	625 (50.9)	1109 (45.2)	468 (38.1)	
PAP non-adherent	212 (17.3)	558 (22.7)	270 (22.0)	
PAP adherent*	391 (31.8)	789 (32.1)	491 (40.0)	
Incident MACEs	255 (20.8)	330 (13.4)	174 (14.2)	<0.001

Data are presented as number of patients (%), median [25th–75th percentile].

Abbreviations: ΔHR, delta heart rate; *PLSC, Pays de la Loire Sleep Cohort*; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CCB, calcium channel blockers; AHI, apnoea hypopnea index; SASHB, sleep apnoea-specific hypoxic burden; PAP, positive airway pressure; MACEs, major adverse cardiovascular events.

*PAP adherent: patients who had not discontinued PAP and used it on average 4h or more per night.

**Data were analysed using Pearson's chi-square test, or Mann-Whitney pairwise comparisons, as appropriate.

Table S2: Baseline characteristics of the population by ΔHR categories in *HypnoLaus*.

	Low ΔHR	Midrange ΔHR	High ΔHR	P value**
n	327	654	326	
Age, years	67.5 [57.2-72.1]	57.9 [50.6-67.2]	54.3 [47.9-66.3]	<0.001
Female gender	193 (59.0)	290 (44.3)	107 (32.8)	<0.001
Body mass index, kg/m²	26.3 [24.0-29.4]	26.2 [24.1-28.8]	26.8 [24.0-29.7]	0.383
Current smokers	50 (15.3)	117 (17.9)	62 (19.0)	0.429
Comorbidities				
Diabetes	54 (16.5)	59 (9.02)	39 (12.0)	0.003
Hypertension	175 (53.5)	280 (42.8)	134 (41.1)	0.002
Dyslipidaemia	98 (30.0)	185 (28.3)	106 (32.5)	0.393
COPD	-	-	-	-
CV active drugs				
Beta blockers	41 (12.5)	32 (4.89)	20 (6.13)	<0.001
CCB	32 (9.79)	28 (4.28)	20 (6.13)	0.003
Epworth sleepiness scale	5.00 [3.00-8.00]	6.00 [3.00-9.00]	6.00 [4.00-9.00]	0.021
AHI, events/h	12.8 [8.15-21.1]	14.1 [8.83-24.6]	16.9 [9.75-30.2]	<0.001
ΔHR, BPM	7.13 [6.25-7.99]	10.9 [9.61-12.3]	16.7 [15.3-20.0]	<0.001
Pulse rate baseline, BPM	58.2 [52.2-63.8]	58.1 [53.1-62.9]	56.1 [50.6-61.3]	<0.001
SASHB, %.min/h	15.5 [8.49-32.6]	17.4 [8.86-32.1]	18.8 [9.04-36.1]	0.252
Incident MACEs	24 (7.34)	34 (5.20)	29 (8.90)	0.078

Data are presented as number of patients (%), median [25th–75th percentile].

Abbreviations: ΔHR, delta heart rate; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CCB, calcium channel blockers; AHI, apnoea hypopnea index; SASHB, sleep apnoea-specific hypoxic burden; MACEs, major adverse cardiovascular events.

**Data were analysed using Pearson's chi-square test, or Mann-Whitney pairwise comparisons, as appropriate.

Table S3: Adjusted Cox models assessing the association of ΔHR_{oxi} with incident MACEs according to different oxygen desaturation thresholds.

	Hazard Ratio [95% CI] for incident MACEs	
	PLSC	***HypnoLaus***
ΔHR_{oxi} 2%		
Midrange values	1.00	1.00
Low values	**1.20 [1.01-1.42] ***	**1.11 [0.65-1.90]**
High values	**1.31 [1.09-1.59]** ‡	**1.71 [1.02-2.87] ***
ΔHR_{oxi} 3%		
Midrange values	1.00	1.00
Low values	**1.24 [1.04-1.47] ***	**1.06 [0.61-1.82]**
High values	**1.42 [1.18-1.71]** †	**1.72 [1.03-2.87] ***
ΔHR_{oxi} 4%		
Midrange values	**1.00**	1.00
Low values	1.15 [0.97-1.36]	**1.06 [0.62-1.83]**
High values	**1.40 [1.16-1.69]** †	**1.75 [1.05-2.91] ***

Abbreviations: *PLSC*, Pays de la Loire Sleep Cohort; ΔHR_{oxi}, oximetry-derived delta heart rate; MACEs, major adverse cardiovascular events; CI, confidence interval; HSAT, home sleep apnoea testing; PSG, polysomnography.

*p<0.05. ‡p<0.01. †p<0.001.

Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, use of beta blockers and calcium channel blockers, event-related minimum pulse rate and sleep apnoea-specific hypoxic burden in *PLSC* and *HypnoLaus*, and for chronic obstructive pulmonary disease, positive airway pressure (PAP) status (non-treated, PAP adherent or PAP non-adherent), study site, and type of sleep study in *PLSC*.

Table S4: Multivariable Cox regression analyses assessing the association of ΔHR_{oxi} and ΔHR with distinct incident non-fatal cardiovascular outcomes in the *HypnoLaus* cohort.

	ΔHR_{oxi} HR [95%CI]	**ΔHR HR [95%CI]**
MACEs (n=87)		
Midrange	1.00	1.00
Low	1.06 [0.61-1.82], p=0.843	1.68 [1.01-2.81], p=0.709
High	1.72 [1.03-2.87], p=0.037	1.68 [1.00-2.82], p=0.049
Stroke (n=20)		
Midrange	1.00	1.00
Low	0.51 [0.13-2.02], p=0.339	0.76 [0.22-2.63], p=0.687
High	2.60 [1.02-6.63], p=0.045	2.45 [0.94-6.40], p=0.066
CAD (n=58)		
Midrange	1.00	1.00
Low	1.10 [0.58-2.10], p=0.773	1.09 [0.57-2.05], p=0.800
High	1.22 [0.64-2.32], p=0.544	1.25 [0.65-2.40], p=0.499

Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, use of beta blockers and calcium channel blockers, event-related minimum pulse rate, sleep apnoea-specific hypoxic burden, and the competing risk of death for non-fatal cardiovascular events. We used a Fine and Gray model to consider death as a competing event for non-fatal CV events.

Abbreviations: ΔHR_{oxi}, oximetry-derived delta heart rate; ΔHR, delta heart rate; CI, confidence interval; CV, cardiovascular; CAD, coronary artery diseases (including non-fatal myocardial infarctions).

Table S5: Adjusted Cox models assessing the association of ΔHR_{oxi} and ΔHR with incident MACEs according to type of sleep recording in the *Pays de la Loire Sleep Cohort*.

Subgroups	**ΔHR_{oxi} Hazard Ratio [95% CI]**	**ΔHR Hazard Ratio [95% CI]**
HSAT (n=2,447)		
Midrange values	1.00	1.00
Low values	1.15 [0.92-1.43]	1.07 [0.86-1.33]
High values	**1.50 [1.18-1.91]** †	**1.29 [1.01-1.65]** *
PSG (n=2,555)		
Midrange values	1.00	1.00
Low values	**1.45 [1.10-1.90]** ‡	1.30 [0.99-1.70]
High values	**1.37 [1.00-1.88]** *	1.17 [0.85-1.61]

Abbreviations: ΔHR_{oxi}, oximetry-derived delta heart rate; ΔHR, delta heart rate; MACEs, major adverse cardiovascular events; CI, confidence interval; HSAT, home sleep apnoea test; PSG, polysomnography. *p<0.05. ‡p<0.01. †p<0.001.

Data were adjusted for: age, gender, body mass index, smoking status, medical history of diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, use of beta blockers and calcium channel blockers, study site, event-related minimum pulse rate, positive airway pressure (PAP) status (non-treated, PAP adherent or PAP non-adherent), and sleep apnoea-specific hypoxic burden.

Formal tests for interaction were not significant.