ORIGINAL ARTICLE

Pulse Wave Amplitude Drops Index: A Biomarker of Cardiovascular Risk in Obstructive Sleep Apnea

Geoffroy Solelhac[1]*, Manuel Sánchez-de-la-Torre[4,6,7]*, Margaux Blanchard[8,9]*, Mathieu Berger[1], Camila Hirotsu[1], Théo Imler[1], Alicia Sánchez-de-la-Torre[4,6,7], Jose Haba-Rubio[1], Nicola Andrea Marchi[1], Virginie Bayon[1], Sébastien Bailly[10], François Goupil[11], Adrien Waeber[1], Grégory Heiniger[1], Thierry Pigeanne[12], Esther Gracia-Lavedan[5], Andrea Zapater[4,6], Jorge Abad[13], Estrella Ordax[14], María José Masdeu[13], Valentin Cabriada-Nuño[16], Carlos Egea[7,17], Sandra Van Den Broecke[1,18], Peter Vollenweider[2], Pedro Marques-Vidal[2], Julien Vaucher[2], Giulio Bernardi[19], Monica Betta[19], Francesca Siclari[1,20,21], Ferran Barbé[7,5]‡, Frédéric Gagnadoux[22,23]‡, and Raphael Heinzer[1,3]‡

Abstract

Rationale: It is currently unclear which patients with obstructive sleep apnea (OSA) are at increased cardiovascular risk.

Objective: To investigate the value of pulse wave amplitude drops (PWADs), reflecting sympathetic activations and vasoreactivity, as a biomarker of cardiovascular risk in OSA.

Methods: PWADs were derived from pulse oximetry–based photoplethysmography signals in three prospective cohorts: HypnoLaus ($N = 1{,}941$), the Pays-de-la-Loire Sleep Cohort (PLSC; $N = 6{,}367$), and "Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome. Effect of intervention with CPAP" (ISAACC) ($N = 692$). The PWAD index was the number of PWADs (>30%) per hour during sleep. All participants were divided into subgroups according to the presence or absence of OSA (defined as ⩾15 or more events per hour or <15/h, respectively, on the apnea–hypopnea index) and the median PWAD index. Primary outcome was the incidence of composite cardiovascular events.

Measurements and Main Results: Using Cox models adjusted for cardiovascular risk factors (hazard ratio; HR [95% confidence interval]), patients with a low PWAD index and OSA had a higher incidence of cardiovascular events compared with the high-PWAD and OSA group and those without OSA in the HypnoLaus cohort (HR, 2.16 [1.07–4.34], $P = 0.031$; and 2.35 [1.12–4.93], $P = 0.024$) and in the PLSC (1.36 [1.13–1.63], $P = 0.001$; and 1.44 [1.06–1.94], $P = 0.019$), respectively. In the ISAACC cohort, the low-PWAD and OSA untreated group had a higher cardiovascular event recurrence rate than that of the no-OSA group (2.03 [1.08–3.81], $P = 0.028$). In the PLSC and HypnoLaus cohorts, every increase of 10 events per hour in the continuous PWAD index was negatively associated with incident cardiovascular events exclusively in patients with OSA (HR, 0.85 [0.73–0.99], $P = 0.031$; and HR, 0.91 [0.86–0.96], $P < 0.001$, respectively). This association was not significant in the no-OSA group and the ISAACC cohort.

Conclusions: In patients with OSA, a low PWAD index reflecting poor autonomic and vascular reactivity was independently associated with a higher cardiovascular risk.

Keywords: sleep apnea; cardiovascular risk; PWAD; pulse oximeter; pulse wave amplitude

(Received in original form June 28, 2022; accepted in final form April 4, 2023)

*Co–first authors.

‡Co–last authors.

The CoLaus study was supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of the University of Lausanne, and the Swiss National Science Foundation (grants 33CSCO-122661, 33CS30-139468, 33CS30-148401, and 32473B-182210). The HypnoLaus study received additional support from the "Ligue Pulmonaire Vaudoise," the Lancardis Foundation, and the Foundation Leenaards. The ISAACC study was funded by the Institut de Salud Carlos III (PI10/02763, PI10/02745, PI18/00449, and PI19/00907), cofunded by FEDER "Una manera de hacer Europa," SEPAR; the Catalonian Cardiology Society; ResMed, Ltd. (Australia); EsteveTeijin (Spain); Oxigen Salud (Spain); AllerGen; and CIBERES. M.S.-d.-l.-T. received financial support from a "Ramón y Cajal" grant (RYC2019-027831-I) from the "Ministerio de Ciencia e Innovación – Agencia Estatal de Investigación," cofunded by the European Social Fund/"Investing in your future." The Pays de la Loire Sleep Cohort is supported by research grants from the Pays de la Loire Respiratory Health Research Institute. F.S. is supported by the European Research Council Starting Grant 101039782 DREAMSCAPE.

Am J Respir Crit Care Med Vol 207, Iss 12, pp 1620–1632, Jun 15, 2023

Originally Published in Press as DOI: 10.1164/rccm.202206-1223OC on April 5, 2023
Internet address: www.atsjournals.org

[1]Center for Investigation and Research in Sleep, [2]Department of Medicine, Internal Medicine, and [3]Pulmonary Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [4]Precision Medicine in Chronic Diseases and [5]Translation Research in Respiratory Medicine, University hospital Arnau de Vilanova-Santa Maria, IRB Lleida, Lleida, Spain; [6]Department of Nursing and Physiotherapy, Faculty of Nursing and Physiotherapy, University of Lleida, Lleida, Spain; [7]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain; [8]Ecole Supérieur D'Electronique de l'Ouest, Angers, France; [9]Laboratoire d'Acoustique de l'Université du Mans, Le Mans, France; [10]Université Grenoble Alpes, INSERM, CHU Grenoble Alpes, HP2, Grenoble, France; [11]Department of Respiratory Diseases, Le Mans General Hospital, Le Mans, France; [12]Unité respiratoire, Pôle santé des Olonnes, Olonne sur Mer, France; [13]Respiratory Department, University hospital Germans Trias I Pujol, Barcelona, Spain; [14]Respiratory Department, Burgos University hospital, Burgos, Spain; [15]Respiratory and Sleep Department, University hospital Parc Taulí, Institut Investigació i Innovació Parc Taulí (I3PT), Universitat Autònoma de Barcelona, Sabadell, Spain; [16]Respiratory Department, Cruces University hospital, Bizkaia, Spain; [17]Servicio de Investigación OSI, Araba University hospital, IIS Bioaraba, Vitoria, Spain; [18]Service de Pneumologie et Centre du Sommeil, Hôpital Neuchâtelois, site de Pourtalès, Neuchâtel, Switzerland; [19]MoMiLab Research Unit, IMT School for Advanced Studies, Lucca, Italy; [20]The Netherlands Institute for Neuroscience, Amsterdam, The Netherlands; [21]The Sense Innovation and Research Center, Lausanne and Sion, Switzerland; [22]Department of Respiratory and Sleep Medicine, Angers University Hospital, Angers, France; and [23]INSERM, CNRS, MITOVASC, Equipe CarME, SFR ICAT, University of Angers, Angers, France

ORCID IDs: 0000-0002-7135-133X (G.S.); 0000-0002-5695-348X (M.S.-d.-l.-T.); 0000-0001-8382-4037 (M. Blanchard); 0000-0002-7809-4399 (N.A.M.); 0000-0002-2179-4650 (S.B.); 0000-0002-2340-8928 (F.B.); 0000-0002-4231-5102 (F. Gagnadoux); 0000-0002-3215-7788 (R.H.).

At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea (OSA) severity has traditionally been assessed using the apnea–hypopnea index. This index does not take into account the complexity of respiratory events and may not be sufficient to assess OSA-associated cardiovascular risk or to select patients likely to respond to continuous positive airway pressure treatment.

What This Study Adds to the Field: In patients with OSA, a low pulse wave amplitude drop index was associated with a higher cardiovascular risk.

Obstructive sleep apnea (OSA) severity has traditionally been assessed using the apnea–hypopnea index (AHI), but this index does not take into account the complexity of respiratory events and may not be sufficient to assess OSA-associated cardiovascular risk (1, 2) or to select patients likely to respond to continuous positive airway pressure (CPAP) treatment (3–5). Therefore, more specific biomarkers are needed to assess cardiovascular risk in OSA.

In contrast to the measurement of arm pulse analysis, which requires an arm cuff, finger pulse wave analysis can be easily assessed using photoplethysomography (PPG), a signal derived from a pulse oximeter. PPG is a simple, low-cost, and noninvasive technique that assesses oscillations in pulsatile finger blood volume on the basis of variations of blood red and infrared light absorption (6). Extremities such as the fingers play an important role in heat regulation by modulating their highly variable skin blood flow, which is predominantly regulated by sympathetic vasoconstrictor tone: Stimulation and blockade of vascular α receptors generate finger skin vasoconstriction and vasodilation, respectively (7–9). Grote and colleagues showed that pulse wave amplitude drops (PWADs; Figure 1) reflect transient vasoconstriction followed by a vasodilation that occurs in response to surges in sympathetic activity, which are then followed by a compensatory parasympathetic response (10). PWADs are typically observed concomitantly with cortical arousals that occur spontaneously or after nocturnal events such as sleep apneas/hypopneas and leg movements (11). The number of PWAD events per hour (PWAD index) has been shown to vary according to the sleep stage, with a lower frequency in deep sleep stage N3 compared with stage N2 sleep, and a higher frequency in stage N1 and REM sleep (11, 12), suggesting a strong association with autonomic nervous system reactivity. It is interesting that a low PWAD index was observed in conditions associated with increased cardiovascular risk, such as older age, diabetes, and hypertension, and in patients with an existing cardiovascular disease (12).

In OSA, there is a nightly occurrence of hundreds of respiratory events, generating blood pressure peaks, sympathetic and parasympathetic activations that could blunt autonomic nervous system responsiveness, possibly through a "tolerance" of the baroreflex, as observed by Parati and colleagues (13). OSA has also been shown to be associated with reduced endothelial function (impaired flow-mediated vasodilation) (14). Considering that both a poorly responsive autonomic system and impaired endothelial function are associated with increased cardiovascular risk and that they also tend to decrease PWA variations, we hypothesized that patients with OSA who have a low PWAD index could be at higher risk of incident cardiovascular diseases.

Author Contributions: Drafting/revision of the manuscript for content, including medical writing for content: G.S., M.S.-d.-l.-T., M. Blanchard, M. Berger, C.H., T.I., A.S.-d.-l.-T., N.A.M., A.W., G.H., S.B., F. Goupil, T.P., E.G.-L., A.Z., J.A., E.O., M.J.M., V.C.-N., C.E., V.B., S.V.D.B., J.H.-R., P.V., P.M.-V., J.V., G.B., M. Betta, F.S., F.B., F. Gagnadoux, and R.H. Verification of the underlying data: G.S., M. Blanchard, M.S.-d.-l.-T., and R.H. Analysis or interpretation of data: G.S., M. Blanchard, M. Berger, C.H., T.I., F. Gagnadoux, and R.H. Study concept or design: M.S.-d.-l.-T., F.B., F. Gagnadoux, and R.H. Acquisition of funding resources: F.B. and R.H. M.S.-d.-l.-T., J.H.-R., P.V., P.M.-V., J.V., F.B., F. Gagnadoux, and R.H. All had a major role in the acquisition of data.

Correspondence and requests for reprints should be addressed to Raphael Heinzer, M.D., M.P.H., Center for Investigation and Research in Sleep, Lausanne University Hospital and University of Lausanne, Rue de Bugnon 46, 1011 Lausanne, Switzerland. E-mail: raphael.heinzer@chuv.ch.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

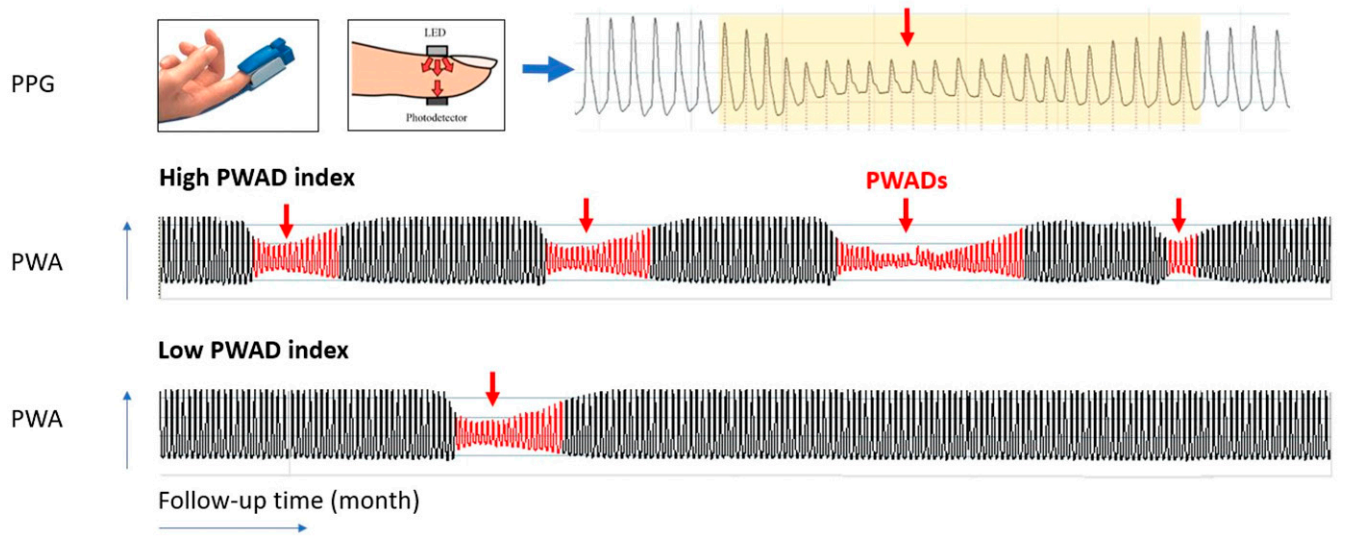

Figure 1. PPG and PWA assessment. PPG = photoplethysmography; PWA = pulse wave amplitude; PWAD = pulse wave amplitude drop.

Therefore, this study evaluated the association between PWAD index and incident or recurrent cardiovascular events in three prospective cohorts: HypnoLaus, ISAACC, and the Pays de la Loire Sleep Cohort [PLSC]). A secondary objective was to assess the response to CPAP according to the PWAD index. Some of these data have been previously reported in an abstract form (15, 16).

Methods

Data from three independent prospective cohorts were used: the HypnoLaus population-based cohort, the PLSC clinic-based cohort, and the ISAACC cardiovascular cohort. (For a detailed description of these cohorts, *see* the online supplement.)

HypnoLaus Cohort

The HypnoLaus sleep cohort study was designed to assess the prevalence and correlates of sleep-disordered breathing in a general unselected middle-to-older-age population of Lausanne, Switzerland (17). Briefly, 2,162 participants underwent a complete clinical assessment and overnight unattended full polysomnography (PSG) between 2009 and 2013, followed by clinical follow-up.

PLSC

This study used data collected by the French clinic-based multicenter longitudinal study, which was further linked with data from the French administrative healthcare database (SNDS) (18, 19). All overt cardiovascular disease–free patients investigated for OSA using in-lab PSG or type 3 polygraphy between May 15, 2007 and December 31, 2018, who had available SNDS data were included in the study ($N = 6,367$).

ISAACC Cohort

The ISAACC cohort study is a Spanish multicenter, prospective, randomized controlled trial (ClinicalTrials.gov identifier NCT01335087) including adults admitted for an acute coronary syndrome event who had an Epworth Sleepiness Scale score of 10 or less (20). Patients with OSA were randomly assigned (1:1) to CPAP treatment plus usual care (CPAP group) or usual care alone. A group of patients with acute coronary syndrome but without OSA was included as a reference group.

OSA

OSA was defined as an AHI of ⩾15 or more events per hour, as assessed by PSG using the 2012 and 2007 American Academy of Sleep Medicine (AASM) criteria (21) in the HypnoLaus study, by polygraphy using the 2007 AASM criteria (22) in the ISAACC study, and by polygraphy or PSG using the 2012 AASM criteria (21) in the PLSC study.

PWA Assessment

In all three cohorts, PWADs on the PPG signal of the pulse oximeter were identified using the same validated algorithm (23). PWADs with an amplitude >30% from baseline (*see* the online supplement) and a duration of more than four heartbeats were identified (Figure 1). The total number of PWADs during the whole night was averaged per hour of sleep as the PWAD index (number of >30% drops in PWA per hour).

Cardiovascular Endpoint

In the HypnoLaus cohort, the composite incident cardiovascular endpoint included fatal cardiovascular events (death from myocardial infarction or stroke) and nonfatal cardiovascular events (myocardial infarction, stroke, transient ischemic attack, and coronary heart disease) (24). In PSLC, a major adverse cardiovascular event (MACE), the primary composite outcome of the study, was defined using SNDS data as fatal events (all-cause death) and nonfatal cardiovascular events (myocardial infarction, stroke, transient ischemic attack, coronary heart disease, and hospitalization for heart failure). Participants were followed from their first diagnostic sleep study to the end of December 2019, or the occurrence of a primary outcome event, whichever occurred first (18).

In the ISAACC cohort, the composite cardiovascular endpoint included fatal cardiovascular events (death from myocardial infarction or stroke) or nonfatal cardiovascular events (myocardial infarction, stroke, transient ischemic attack,

hospitalization for heart failure, coronary heart disease, and atrial fibrillation).

Statistical Analysis

Baseline characteristics of participants with and without cardiovascular events and groups with (OSA+, AHI ⩾15/h) or without (OSA–, AHI <15/h) OSA were compared using Student's *t* test or chi-square test as appropriate.

Interaction between OSA and PWAD (high or low) was tested. Four groups were created in the HypnoLaus cohort and the PLSC on the basis of the presence or absence of OSA (OSA+ and OSA–, respectively) and the median PWAD index (high or low); that is, low PWAD and OSA+, high PWAD and OSA+, low PWAD and OSA–, and high PWAD and OSA–.

For the ISAACC cohort, five groups were defined to take into account the treatment intervention: OSA–; OSA+ (usual care) and low PWAD, OSA+ (usual care) and high PWAD, OSA+ (CPAP)/low PWAD, and OSA+ (CPAP)/high PWAD.

To determine the association between PWAD and the occurrence of a cardiovascular composite endpoint, multivariable-adjusted Cox regressions were performed in each cohort according to the different population subgroups defined earlier and according to PWAD quartiles. For each cohort, Cox models were adjusted for age, sex, body mass index, alcohol intake, smoking, diabetes, hypertension, lipid-lowering drugs, and vasodilators, plus CPAP usage (for PLSC only). Adjustment factors representing clinically recognized or historical cardiovascular risk factors were used. The directed acyclic graph describing the relationships between PWAD, risk of cardiovascular events, and adjustment factors is shown in the online supplement (*see* Figure E1 in the online supplement). Results are expressed as hazard ratios (HRs) with 95% confidence interval (95% CI) values. The association between PWAD index as a continuous variable with cardiovascular events was analyzed in Cox models adjusted for the same confounding factors among groups with an AHI ⩾15 and <15/h in the three cohorts. The model assumptions were investigated using a Schoenfeld's test.

A secondary analysis was conducted to evaluate CPAP response according to the PWAD index by including patients with OSA from PLSC who had started CPAP treatment at home between May 15, 2007, and December 31, 2018. As described previously, patients using CPAP at least 4 hours per night during the entire follow-up period were assigned to the CPAP-adherent group (25). Those who stopped the use of CPAP or used the device for less than 4 hours per night constituted the nonadherent group. Subgroups were defined according to CPAP usage (adherent vs. nonadherent) and PWAD (high vs low) index. The same analysis was performed in the ISAACC cohort, with subgroups defined according to CPAP usage (CPAP treatment vs. usual care) and PWAD (high vs low) index.

Sensitivity analyses were conducted using the 2007 AASM criteria (22) for AHI in the HypnoLaus cohort and different AHI cutoffs (10/h, 20/h, and 30/h) for the HypnoLaus cohort and PLSC. Additional sensitivity analyses were performed to better harmonize the MACE outcome by removing heart failure hospitalizations in PLSC and atrial fibrillation and heart failure hospitalizations in the ISAACC cohort. (For additional methodological details, *see* the online supplement.)

Results

HypnoLaus Cohort

Of the 2,162 participants initially included in the HypnoLaus cohort, 1,941 with complete PSG and PWAD analysis who had no cardiovascular events at baseline, were included in this study (Table 1; *see* Figure E2). In this study, 3.9% of participants experienced a cardiovascular event over a (mean ± SD) follow-up period of 49.2 ± 12.1 months. The median (interquartile range [IQR]) PWAD index was 51.8 (37.7–65.5) per hour (Figure 2).

There was no difference in the incidence of cardiovascular events between patients with and without OSA (AHI ⩾15/h vs. <15/h) in an adjusted Cox model. Results were similar when other AHI cutoff values, continuous AHI, or AASM 2007 AHI criteria (22) were used instead of the AASM 2012 definition of AHI (21) (*see* Table E1).

The risk of incident cardiovascular events was significantly higher in the low-PWAD and OSA+ group compared with the high-PWAD and OSA+ group (HR, 2.16 [95% CI, 1.07–4.34]), the high-PWAD and OSA– group (HR, 2.35 [95% CI, 1.12–4.93]), and the low-PWAD and OSA– group (HR, 1.90 [95% CI, 1.02–3.54]). In OSA– participants, no significant difference in cardiovascular event rate was found between the low-PWAD and high-PWAD groups ($P = 0.575$) (Figure 3; Table E1). OSA+ participants in PWAD index quartiles 1 and 2 (Q1 and Q2) had a significantly higher risk of incident cardiovascular events compared with those from quartile 4 (Q4) (Q4 vs. Q1: adjusted HR, 3.09 [95% CI, 1.00–9.55], $P = 0.049$; Q4 vs. Q2: HR, 3.43 [95% CI, 1.05–11.1], $P = 0.041$). There was no significant difference between quartiles in OSA− participants (Figure 4). When used as a continuous variable, PWAD index (+10 events/h) was significantly associated with lower risk of incident cardiovascular events in participants with an AHI ⩾15/h but not in those with an AHI <15/h (HR, 0.85 [95% CI, 0.73–0.99], $P = 0.031$; and HR, 0.94 [95% CI, 0.78–1.13], $P = 0.495$, respectively). Adjusted Cox models showed a significant interaction between PWAD and AHI as continuous variables ($P = 0.016$) but not when AHI was dichotomized (⩾15/h and <15/h, respectively, $P = 0.190$).

A sensitivity analysis showed the same differences between the low-PWAD and OSA+ and high-PWAD and OSA+ groups for other AHI cutoff values (*see* Table E2). A significant interaction between a continuous AHI defined using the 2007 AASM criteria and a continuous PWAD index was also found ($P = 0.007$). Slight variations in associations were seen at different AHI cutoff values when 2007 AASM criteria were used (Table E2).

PLSC

Among 9,790 patients from the PLSC, 1,995 had no available SNDS data, 1,428 were excluded because of prior cardiovascular disease and 6,367 were included in the present study (Table 1; *see* Figure E3). In the PLSC, 10.5% experienced a MACE over (mean ± SD) follow-up period of 72.2 ± 35.4 months, including 256 all-cause deaths and 413 nonfatal cardiovascular events. The median (IQR) PWAD index was 46.9 (33.6–60.3) per hour (Figure 2).

The highest MACE risk was seen in the OSA+/low-PWAD group (adjusted HR, 1.36 [95% CI, 1.13–1.63], when compared with the OSA+/high-PWAD group; HR, 1.44 [95% CI, 1.06–1.94], when compared with the OSA–/high-PWAD group; and HR, 1.10 [95% CI, 0.88–1.38], when compared with the OSA–/low-PWAD group) (Figure 5; *see* Table E3). Similar findings were observed for other AHI threshold values (Table E3). In the OSA+ group, patients in the lowest PWAD index quartile (Q1) had a

Table 1. Baseline Demographic Characteristics of the HypnoLaus Cohort, Pays de la Loire Sleep Cohort, and ISAACC Cohort in Patient Subgroups that Are Based on the Presence or Absence of Recurrent Cardiovascular Events

	HypnoLaus			ISAACC			PLSC		
Variable	**No incident CVEs (*n* = 1,866)**	**Incident CVEs (*n* = 75)**	***P* Value**	**No recurrent CVEs (*n* = 575)**	**Recurrent CVEs (*n* = 117)**	***P* Value**	**No incident MACEs (*n* = 5,698)**	**Incident MACEs (*n* = 669)**	***P* Value**
Age, yr	57 [49–68]	68 [55–74]	<0.001	59.0 ± 10.1	61.2 ± 10.5	0.040	58 [48–68]	70 [61–78]	<0.001
Female, *n* (%)	1,000 (53.6)	28 (37.3)	0.006	93 (16.2)	21 (17.9)	0.637	2,301 (40.4)	181 (27.1)	<0.001
BMI, kg/m^2	25.5 [23.0–28.4]	27.2 [24.3–29.9]	0.002	28.4 [25.9–31.2]	28.7 [26.0–32.0]	0.328	29.0 [25.3–34.0]	30.3 [26.9–34.5]	<0.001
SBP, mm Hg	125 ± 17	134 ± 21	<0.001	120 [111–132]	122 [110–131]	0.873	128 [120–135]	130 [125–140]	<0.001
DBP, mm Hg	78 ± 10	78 ± 13	0.559	72 [65–80]	71.0 [55–79]	0.524	77 [73–81]	77 [72–83]	0.111
Education, yr	13 [12–16]	12 [11–14]	0.028	—	—	—	—	—	—
Medication use, *n* (%)									
Vasodilators*	406 (21.8)	36 (48.0)	<0.001	240 (41.7)	69 (59.0)	<0.001	510 (9.0)	155 (23.2)	<0.001
Antidiabetics	81 (4.3)	8 (10.7)	0.010	106 (18.4)	40 (34.2)	<0.001	544 (9.5)	149 (22.3)	<0.001
Lipid-lowering agents	341 (18.3)	25 (33.3)	0.001	196 (34.1)	62 (53.0)	<0.001	968 (17.0)	269 (40.2)	0.007
Comorbidities, *n* (%)									
Hypertension	706 (37.9)	53 (70.7)	<0.001	291 (50.6)	75 (64.1)	0.008	1,297 (22.8)	290 (43.3)	<0.001
Diabetes	159 (8.5)	14 (18.7)	0.003	126 (21.9)	46 (39.3)	<0.001	544 (9.5)	149 (22.3)	<0.001
Dyslipidemia	480 (25.8)	29 (38.7)	0.013	325 (56.5)	76 (65.0)	0.092	968 (17.0)	269 (40.2)	0.007
Smoking, *n* (%)	—	—	0.001	—	—	0.816	—	—	<0.001
Current smoker	325 (17.6)	24 (32.4)	—	294 (51.1)	59 (50.4)	—	1,365 (24.0)	144 (21.5)	—
Ex-smoker	731 (39.6)	32 (43.2)	—	153 (26.6)	29 (24.8)	—	1,829 (32.0)	269 (40.2)	—
Alcohol consumption	—	—	0.718	—	—	0.146	—	—	<0.001
Alcohol units, standard drinks,† wk	4 [1–9]	4 [0–11]	—	—	—	—	0 [0–7]	7 [0–14]	—
Cessation, *n* (%)	—	—	—	4 (0.7)	3 (2.6)	—	—	—	—
Current consumption, *n* (%)	—	—	—	126 (21.9)	22 (18.8)	—	—	—	—
Sleep parameters									
ESS score	6 [3–9]	5 [2–8]	0.095	4.0 [3.0–6.0]	5.0 [43.0–7.0]	0.660	10 [6–14]	9 [6–13]	<0.001
TST, min	402 ± 72	395 ± 90	0.356	—	—	—	421 [372–463]‡	390 [348–447]‡	0.193
Sleep efficiency, %	88.2 [80.3–92.8]	83.4 [75.2–90.4]	0.002	—	—	—	87 [79–92]‡	81 [73–89]‡	0.051
N1 sleep, %	10.1 [7.2–14.4]	11.3 [7.2–16.7]	0.086	—	—	—	6.3 [3.4–10.3]‡	7.9 [4.0–13.5]‡	<0.001
N2 sleep, %	46.4 ± 10.3	50.0 ± 11.6	0.003	—	—	—	50.5 [43.2–57.7]‡	50.0 [42.0–58.3]‡	0.032
N3 sleep, %	19.9 ± 8.4	16.3 ± 8.6	<0.001	—	—	—	21.8 [16.5–28.2]‡	21.1 [15.0–27.8]‡	0.054
REM sleep, %	21.9 ± 6.1	19.6 ± 7.1	0.002	—	—	—	19.3 [14.3–23.5]‡	17.9 [12.0–22.9]‡	0.125

(*Continued*)

Table 1. (*Continued*)

Variable	HypnoLaus			ISAACC			PLSC		
	No incident CVEs (n = 1,866)	Incident CVEs (n = 75)	*P* Value	No recurrent CVEs (n = 575)	Recurrent CVEs (n = 117)	*P* Value	No incident MACEs (n = 5,698)	Incident MACEs (n = 669)	*P* Value
Arousal index, events/h	18.9 [13.9–26.0]	20.5 [15.9–30.3]	0.026	—	—	—	24 [15–34]‡	29 [17–40]‡	0.146
AHI, events/h	9.6 [4.0–19.9]	17.5 [6.9–31.6]	<0.001	22.6 [14.0–40.8]	28.4 [19.1–44.5]	0.005	17.6 [7.5–32.5]	27.5 [13.0–43.0]	<0.001
T90, %	0.1 [0–1.7]	1.1 [0–8.6]	<0.001	7.0 [0.7–35.9]	11.2 [2.0–82.5]	0.024	0.8 [0.1–5.2]	3.4 [0.5–13.8]	<0.001
OSA, *n* (%)	647 (34.7)	43 (57.3)	<0.001	427 (74.3)	101 (86.3)	0.007	3,190 (56.0)	474 (70.9)	<0.001
Mean Sp_{O_2}, %	94.3 [93.2–95.4]	93.5 [92.0–94.4]	<0.001	93.1 [92.0–94.2]	93.0 [91.4–94.2]	0.091	94.1 [92.8–95.3]	93.3 [92.1–94.6]	<0.001
PWAD index, events/h	52.2 [38.2–65.7]	44.9 [26.4–58.9]	<0.001	39.8 [25.5–54.2]	34.5 [22.1–51.6]	0.115	47.4 [34.2–60.7]	41.9 [29.6–56.5]	<0.001

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CVEs = cardiovascular events; DBP = diastolic blood pressure; ESS = Epworth Sleepiness Scale; MACEs = major adverse cardiovascular events; N1 = sleep stage 1; N2 = sleep stage 2; N3 = sleep stage 3; PLSC = Pays de la Loire Sleep Cohort; OSA = obstructive sleep apnea (defined as AHI ⩾15 events/h); PWAD = pulse wave amplitude drop; SBP = systolic blood pressure; Sp_{O_2} = oxygen saturation as measured by pulse oximetry; TST = total sleep time; T90 = percentage of total sleep time with oxygen saturation below 90%.

Data are presented as number of patients (%), median [25th–75th percentile], or mean ± SD. Data were analyzed using Pearson's chi-square test, independent *t* test, or Mann-Whitney pairwise comparisons, as appropriate.

*Vasodilators: α-adrenoreceptor antagonists, antiadrenergic agents, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and β-blockers for the HypnoLaus study; angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and β-blockers for the ISAACC study; and β blockers or calcium channel blockers for the PLSC study.

†A standard drink contains 10 g of alcohol.

‡Data were available for 3,374 patients who were investigated by polysomnography.

significantly higher incidence of MACEs compared with those in the highest quartile (Q4): For Q4 vs. Q1, HR, 1.55 (95% CI, 1.18–2.04), $P = 0.002$. There was no significant difference between quartiles in the OSA− group (Figure 4).

Similar to the HypnoLaus findings, the continuous PWAD index (+10 events/h) was significantly associated with a lower risk of incident cardiovascular events in participants with an AHI ⩾15/h but not in those with an AHI <15/h (HR, 0.91 [95% CI, 0.86–0.96], $P < 0.001$; and HR, 0.97 [95% CI, 0.89–1.05], $P = 0.460$, respectively). The interaction between continuous PWAD index and continuous or dichotomized AHI (⩾15/h and <15/h) in the adjusted Cox model did not reach statistical significance (*P*s = 0.068 and 0.706, respectively).

Similar findings were also observed when the analysis was restricted to nonfatal cardiovascular events alone and when excluding heart failure hospitalizations (*see* Figures E4 and E5).

Patients with OSA who had started CPAP between May 15, 2007, and December 31, 2018, (n = 3,669) were divided into four groups according to treatment adherence (⩾4 h per night and <4 h or treatment stop) and high versus low PWAD index values (*see* Table E4). As shown in Figure 6, CPAP adherence versus nonadherence was associated with a significant reduction in incident MACEs in the high-PWAD group (HR, 0.74 [0.55–0.98], $P = 0.036$) but not in the low-PWAD group (HR, 0.91 [0.72–1.15], $P = 0.431$), even though the interaction between PWAD index and CPAP adherence was not significant ($P = 0.229$).

ISAACC

Of the 1,773 ISAACC participants, a subset of 692 studied in the last 5 years of the study and for whom PPG signal data were available was included in the present analysis (Table 1; *see* Figure E6). (For characteristics of included and excluded ISAACC participants, *see* Table E5). Overall, 16.9% of the ISAACC cohort experienced a cardiovascular event over a mean follow-up period of 24.3 ± 15.8 months. The median (IQR) PWAD index was 39.2 (25.0–53.5) per hour (Figure 2).

Patients in the low-PWAD and OSA+/usual care group had a higher risk of recurrent cardiovascular events compared with the OSA− group (HR, 2.03 [95% CI, 1.08–3.81]); this difference was not found in other OSA groups (treated patients with

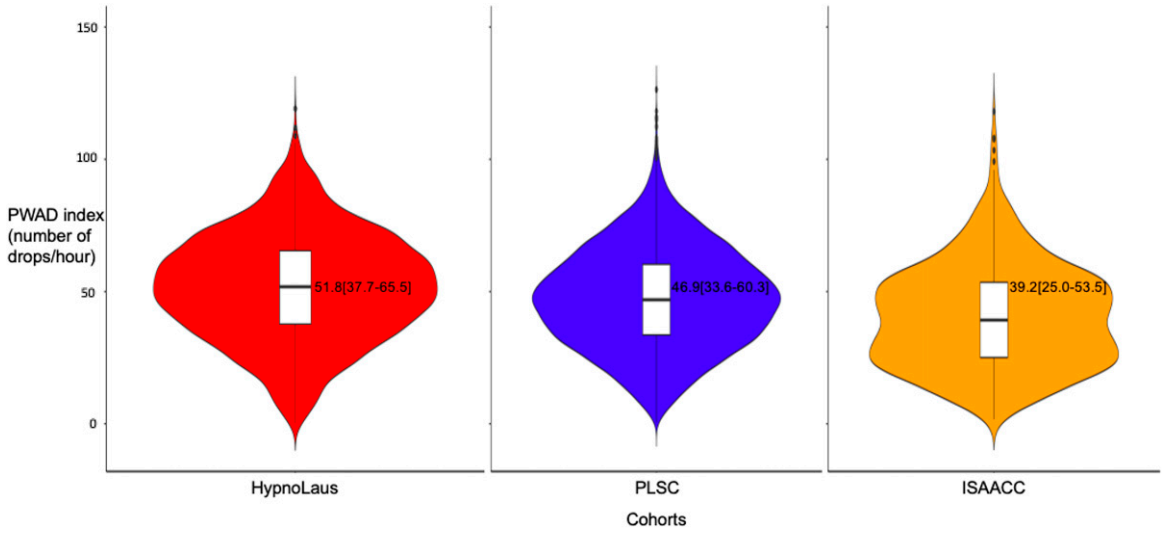

Figure 2. PWAD index distributions in the three different cohorts. Values are presented as hazard ratios and 95% confidence intervals. PLSC = Pays de la Loire Sleep Cohort; PWAD = pulse wave amplitude drop.

OSA who had a low PWAD index: HR, 1.73 [95% CI, 0.90–3.36] compared with OSA–; and high-PWAD and OSA+/usual care: HR, 1.56 [95% CI, 0.78–3.10] compared with OSA–) or when atrial fibrillation or heart failure hospitalizations were removed from the cardiovascular composite endpoint (Figure 7; *see* Figures E7 and E8). There was also no significant difference between PWAD index quartiles in OSA+ and OSA− groups (Figure 4).

Sensitivity analyses showed that a continuous PWAD index (+10 events/h) was not significantly associated with lower risk of recurrent cardiovascular events in patients with an AHI ⩾15/h (without CPAP treatment) and in those with AHI <15/h (HR, 0.94 [95% CI, 0.81–1.10], $P = 0.438$; and HR, 1.14 [95% CI, 0.80–1.63], $P = 0.458$, respectively). Adjusted Cox models showed a significant interaction between continuous AHI and continuous PWAD index ($P = 0.018$) but not when AHI was dichotomized in ⩾15/h and <15/h ($P = 0.713$). CPAP

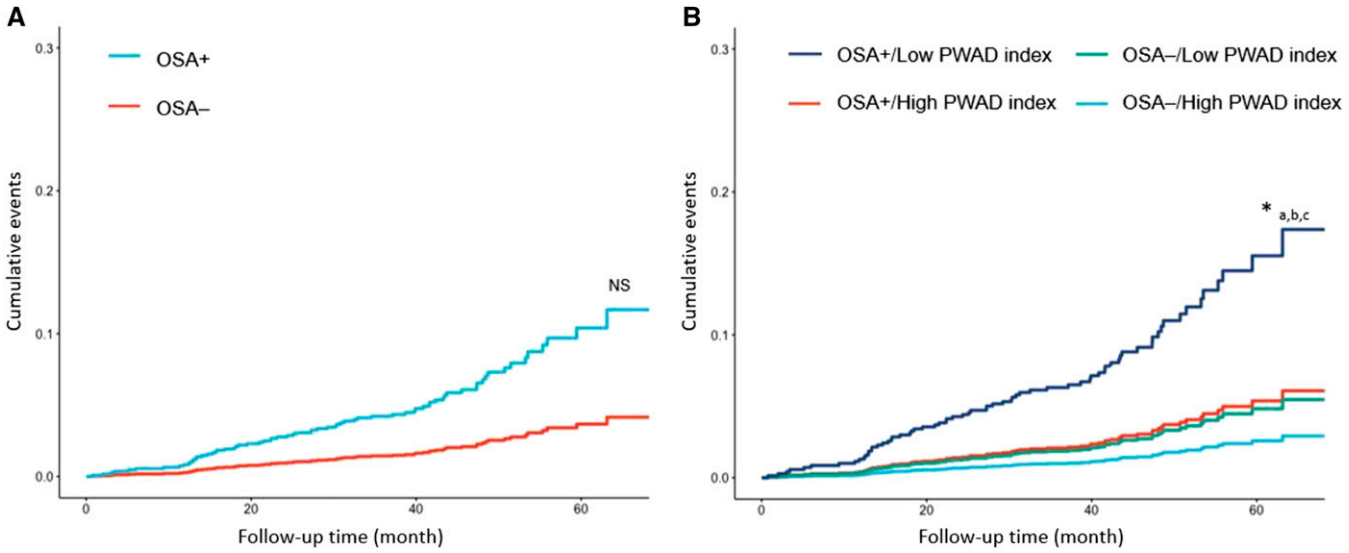

Figure 3. HypnoLaus study: adjusted Cox regression curves showing the incidence of composite cardiovascular events on the basis of (*A*) the presence or absence of obstructive sleep apnea (OSA+ and OSA– , respectively) and (*B*) OSA+ or OSA– and high or low pulse wave amplitude drop (PWAD) index. Models were adjusted for age (continuous), sex (categorical), body mass index (continuous), weekly alcohol consumption (continuous), smoking (continuous), diabetes (categorical), hypertension (categorical), lipid-lowering drugs (categorical), and vasodilators (categorical). Group description (*n*, median PWAD index value as *n*/h [95% confidence interval]): OSA– (1,251, 51.4 [37.2–64.5]), OSA+ (690, 52.4 [38.9–67.6]), OSA–/high PWAD index (629, 64.3 [57.9–73.1]), OSA–/low PWAD index (618, 37.1 [26.9–44.5]), OSA+/high PWAD index (359, 66.3 [58.4–75.2]), and OSA+/low PWAD index (323, 38.4 [28.4–44.9]). [a]$P = 0.031$ for OSA+/low PWAD index versus OSA+/high PWAD index. [b]$P = 0.045$ for OSA+/low PWAD index versus OSA–/low PWAD index. [c]$P = 0.024$ for OSA+/low PWAD index versus OSA–/high PWAD index. *$P < 0.05$, statistically significant. NS = not statistically significant.

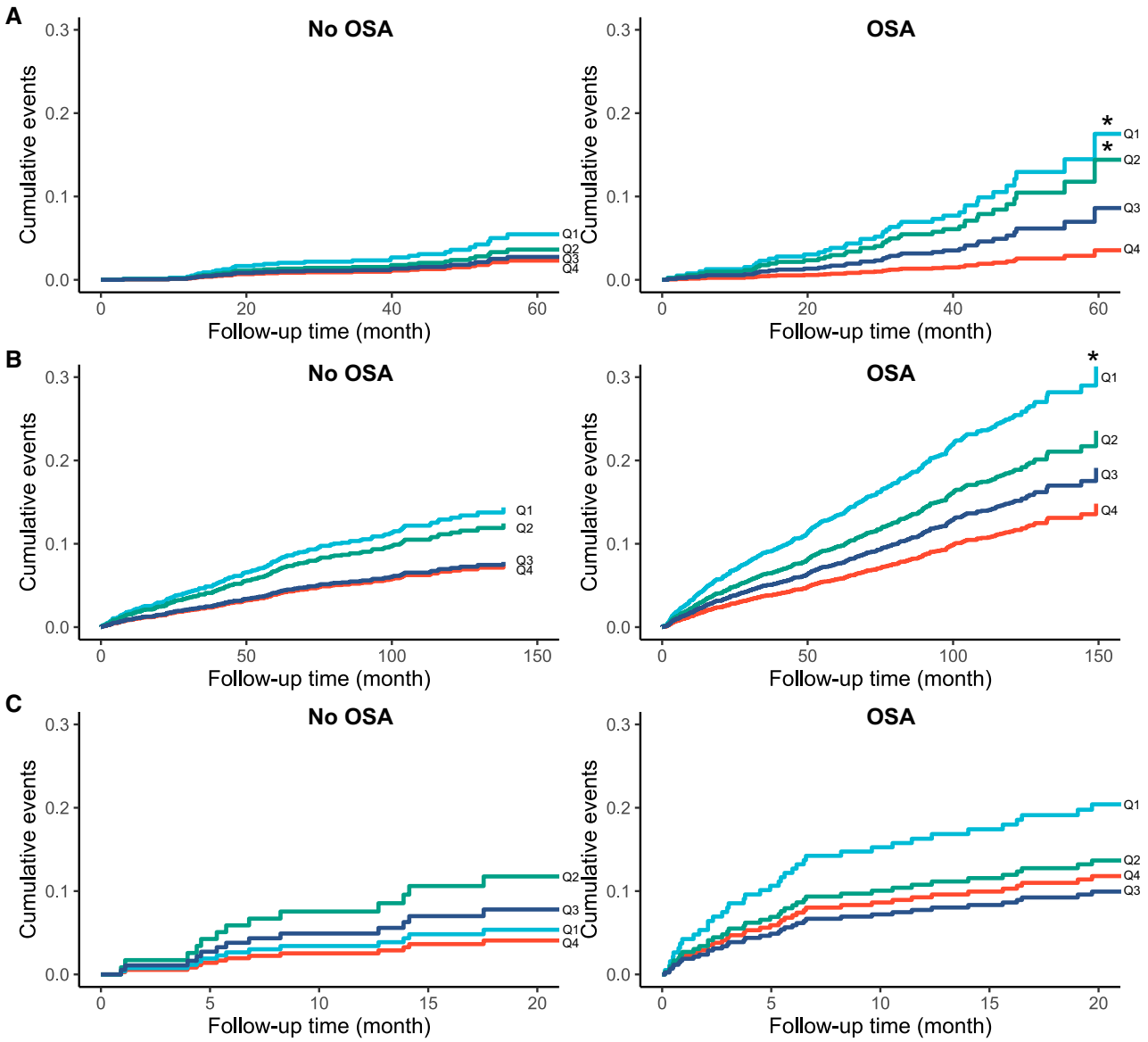

Figure 4. Adjusted Cox regression curves showing the incidence or recurrence of cardiovascular events on the basis of pulse wave amplitude drop index quartiles (Qs) in the presence (right) or absence (left) of obstructive sleep apnea (OSA) in the three cohorts: *$P < 0.05$ and **$P < 0.01$, statistically significant. Models were adjusted according to the same variables as described in Figure 3 for HypnoLaus, Figure 5 for Pays de la Loire Sleep Cohort (PLSC), and Figure 7 for ISAACC. Values for each cohort are hazard ratios and 95% confidence intervals (HRs [95% CIs]). (*A*) HRs [95% CIs] for the HypnLaus cohort. No OSA: Q4 versus Q1, 1.27 [0.41–3.88], $P = 0.677$; Q4 versus Q2, 1.32 [0.43–4.07], $P = 0.629$; Q4 versus Q3, 1.004 [0.30–3.55], $P = 0.994$. OSA: Q4 versus Q1, 3.09 [1.00–9.55], $P = 0.049$; Q4 versus Q2, 3.43 [1.05–11.1], $P = 0.041$; and Q4 versus Q3, 2.50 [0.69–9.12], $P = 0.165$. No OSA quartiles (events/h): Q1, 0.23–37.11; Q2: 37.11–51.29; Q3: 51.29–64.52; and Q4: 64.52–119.14. OSA quartiles (events/h): Q1: 0.14–38.80; Q2: 38.80–52.36; Q3: 52.36–67.26; and Q4: 67.26–111.76. (*B*) HRs [95% CIs] for the PLSC. No OSA: Q4 versus Q1, 1.00 [0.65–1.53], $P = 0.984$; Q4 versus Q2, 1.10 [0.72–1.69], $P = 0.652$; and Q4 versus Q3, 0.80 [0.50–1.28], $P = 0.356$. OSA: Q4 versus Q1, 1.55 [1.18–2.04], $P = 0.002$; Q4 versus Q2, 1.30 [0.98–1.72], $P = 0.069$; and Q4 versus Q3, 1.11 [0.83, 1.49], $P = 0.467$. No OSA quartiles (event/h): Q1, 0.50–31.60; Q2, 31.60–44.08; Q3, 44.08–56.44; and Q4, 56.44–118.18. OSA quartiles (event/h): Q1, 2.20–35.39; Q2, 35.39–49.34; Q3, 49.34–62.78; and Q4, 62.78–126.36. (*C*) HRs [95% CIs] for the ISAACC cohort. No OSA: Q4 versus Q1, 0.50 [0.06–4.02], $P = 0.512$; Q4 versus Q2, 1.34 [0.24–7.25], $P = 0.736$; and Q4 versus Q3, 1.29 [0.21–7.72], $P = 0.780$. OSA: Q4 versus Q1, 1.26 [0.58–2.97], $P = 0.520$; Q4 versus Q2, 1.00 [0.41–2.44], $P = 0.992$; Q4 versus Q3, 0.79 [0.32–1.98], $P = 0.628$. No OSA quartiles (event/h): Q1, 4.44–23.19; Q2, 23.19–35.79; Q3, 35.79–47.90; and Q4, 47.90–92.81. OSA quartiles (events/h): Q1, 1.70–24.76; Q2, 24.76–40.30; Q3, 40.30–53.08; and Q4, 53.08–118.10.

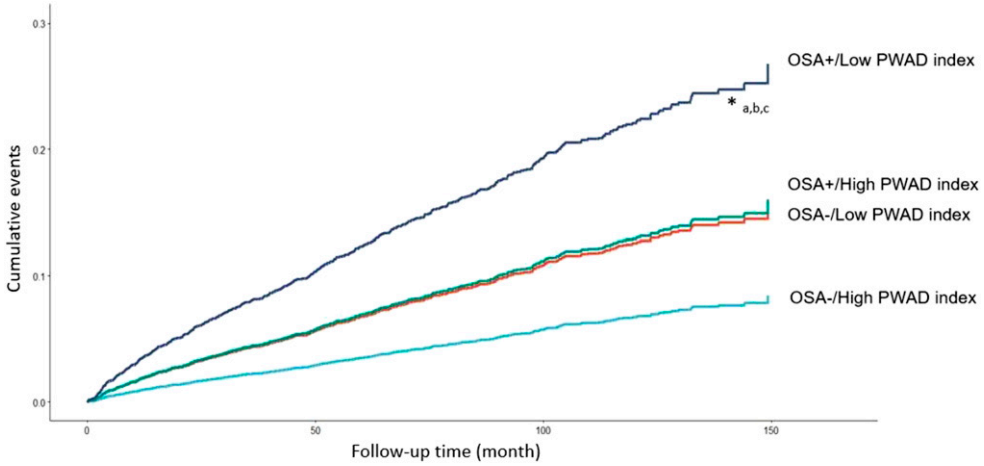

Figure 5. Pays de la Loire Sleep Cohort: adjusted Cox regression curves showing the incidence of major adverse cardiovascular events on the basis of the presence or absence of obstructive sleep apnea (OSA+ and OSA–, respectively) and high or low pulse wave amplitude drop (PWAD) index. Models were adjusted for age (continuous), sex (categorical), body mass index (continuous), diabetes (categorical), hypertension (categorical), smoking status (categorical), type of sleep study (categorical), study site (categorical), β blocker/calcium channel blocker medications (categorical), and treatment status (categorical). Group description (*n*, median PWAD index value as *n*/h [95% confidence interval]): OSA–/high PWAD index (1,182, 58.5 [52.2–67.2]), OSA–/low PWAD index (1,522, 33.3 [24.2–40.0]), OSA+/high PWAD index (2,001, 61.1 [53.8–70.7]), and OSA+/low PWAD index (1,662, 33.9 [25.7–40.7]). [a]$P = 0.001$ for OSA+/low PWAD index versus OSA+/high PWAD index. [b]$P = 0.410$ for OSA+/low PWAD index versus OSA–/low PWAD index. [c]$P = 0.019$ for OSA+/low PWAD index versus OSA–/high PWAD index. *$P < 0.05$, statistically significant.

treatment group (vs. usual care group) was not associated with a reduction in incident cardiovascular events in the high-PWAD group (HR, 1.16 [95% CI, 0.60–2.26], $P = 0.662$) or in the low-PWAD group (HR, 0.76 [95% CI, 0.41–1.39], $P = 0.370$). The interaction between PWAD index and CPAP usage was not significant ($P = 0.347$).

Differences between OSA+ and OSA– participants from all three cohorts are summarized (*see* Table E6). Differences between participant characteristics of the four groups in the HypnoLaus cohort and PLSC (*see* Table E7) and the five groups in ISAACC (*see* Table E8) are also provided.

Discussion

In this analysis of data from three prospective cohorts, a low PWAD index in patients with OSA was independently associated with a higher risk of incident cardiovascular events compared with participants who had OSA and a high PWAD index or those without OSA. The fact that similar findings were obtained in different populations (general, clinical, and cardiovascular) and that studies that utilized slightly different cardiovascular endpoint outcome definitions suggest a good reproducibility and generalizability of these results. In addition, a subanalysis of PLSC showed that a good adherence to CPAP in patients with OSA with a high PWAD index (i.e., without major alterations of autonomic or vascular function) was associated with a reduction in incident cardiovascular events.

Benefits of Adding PWAD Index to the AHI

In our analysis, the AHI alone at different thresholds was not a reliable predictor of incident or recurrent cardiovascular events in any of the three cohorts analyzed. Several prospective studies that selected participants on the basis of the AHI have failed to demonstrate a preventive effect of CPAP on recurrent cardiovascular events in patients with OSA (3–5), probably because the AHI alone may not be sufficient to select patients who are likely to benefit from a reduction in cardiovascular risk during CPAP therapy. Our results suggest that adding the PWAD index to the AHI significantly improves the prediction of cardiovascular risk in patients with OSA and possibly allows the selection of patients likely to benefit from treatment with CPAP.

The statistical interaction found between OSA and PWAD, as well as the presence of significant difference in cardiovascular risk between high and low PWAD and between PWAD index quartiles exclusively in participants with OSA, suggests that the PWAD index is influenced by OSA and could represent a specific marker of cardiovascular alterations caused by OSA. We can further hypothesize that this marker could reflect the duration of exposure to OSA, with a progressive blunting of autonomic nervous system and vascular reactivity over time. This could explain why only patients with OSA who have high PWAD (i.e., those with preserved endothelial and autonomic nervous system reactivity) obtained some cardiovascular protection from CPAP treatment in PLSC, whereas those with low PWAD (i.e., with greater and maybe irreversible impact of OSA on cardiovascular system) and patients from ISAACC who had established cardiovascular disease did not. This hypothesis requires confirmation in other prospective cohorts.

Impact of OSA on PWAD: Physiological Hypothesis

There are several potential explanations for the observed association between low

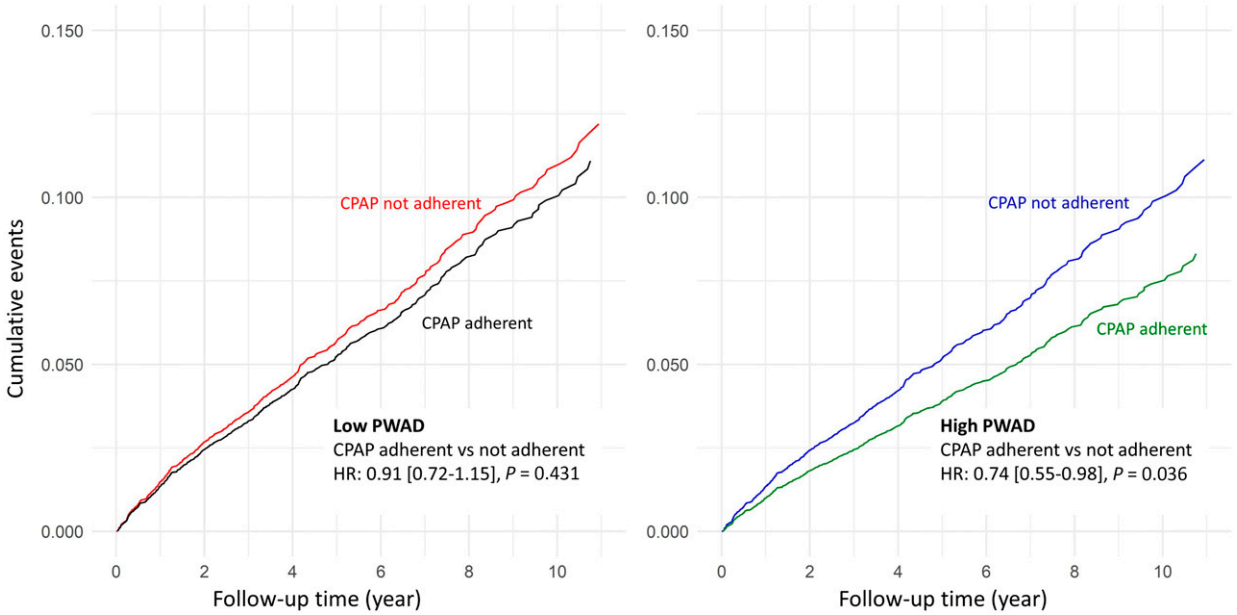

Figure 6. Pays de la Loire Sleep Cohort: adjusted Cox regression curves showing the incidence of major adverse cardiovascular events on the basis of the use of (or not using) continuous positive airway pressure (CPAP) in high (left) or low (right) pulse wave amplitude drop (PWAD) index. Models were adjusted for age (continuous), sex (categorical), body mass index (continuous), diabetes (categorical), hypertension (categorical), smoking status (categorical), type of sleep study (categorical), study site (categorical), β blocker/calcium channel blocker medications (categorical), and treatment status (categorical). Group description (*n*, median PWAD index value as *n*/h [95% confidence interval]): high PWAD index-CPAP adherent (1,382, 60.7 [53.7–70.3]), high PWAD index-no CPAP adherent (454, 61.3 [52.9–69.6]), low PWAD index-CPAP adherent (1,308, 33.2 [24.1–40.8]), and low PWAD index-no CPAP adherent (525, 33.3 [25.8–39.9]). HR = hazard ratio.

PWAD index and cardiovascular events in patients with OSA. First, because drops in PWA occur concomitantly with EEG activations (11) associated with sudden increases in heart rate and that they can be reproduced by the infusion of norepinephrine (10), we believe that PWADs reflect sudden activations of the sympathetic nervous system followed by a compensatory parasympathetic response. A low rate of PWAD in OSA may, therefore, reflect a poorly reactive autonomic nervous system. An association between OSA and impaired autonomous nervous system activity has been previously described and could be mediated through a decrease in baroreceptor sensitivity: untreated OSA with nightly occurrence of hundreds of respiratory events generating blood pressure peaks, sympathetic and parasympathetic activations could induce a "tolerance" of the baroreflex (13). This tolerance effect could then decrease the amplitude and the frequency of PWAD because of blunted response of the autonomic system. The fact that a lower PWAD index is associated with older age and with higher blood pressure also supports this hypothesis (12). Because adequate autonomous nervous system reactivity is needed for the cardiovascular system to adapt to environmental events and stress, an impaired response could potentially increase cardiovascular risk. Lombardi and colleagues, who extensively studied autonomic nervous system alterations in OSA, even proposed that reduced baroreflex sensitivity could be a feature of OSA before the onset of cardiovascular complications and that the chronic hypertensive state associated with OSA might be viewed as the result of autonomic nervous system maladaptation (26). Furthermore, in the Multicentre Obstructive Sleep Apnea Interventional Cardiovascular study, patients treated with therapeutic levels of CPAP showed a significant increase in baroreflex sensitivity compared with patients randomized to subtherapeutic CPAP, suggesting that OSA does impact baroreflex sensitivity (27, 28).

The second hypothesis is that a low PWAD index may reflect impaired endothelial function or arterial stiffness. Because PWAD episodes are characterized by vasoconstriction (drop in PPG signal) followed by vasodilation when the PWA signal returns to normal values, a low PWAD index could suggest that finger arteries and capillaries have an impaired ability to rapidly redilate after vasoconstriction. Impaired endothelial function (based on flow-mediated vasodilation) has previously been described in patients with OSA (14). Given that impaired vascular (endothelial) function has been associated with elevated cardiovascular risk, it is likely that lower PWAD index would be associated with a higher incidence of cardiovascular events (29).

Finally, patients with OSA have been shown to have increased sympathetic activity on the basis of microneurography, heart rate variability, and catecholamine levels (30–35). It could thus be hypothesized that patients with OSA who have a low PWAD index have a constantly increased sympathetic tone with consistent vasoconstriction. This vasoconstriction could generate a ceiling effect, making further variations in finger blood flow less likely. Constant sympathetic activation could then have deleterious effects on the cardiovascular system. These three hypotheses are not mutually exclusive, but further physiological studies are needed to determine the specific mechanisms linking low PWAD to OSA, increased

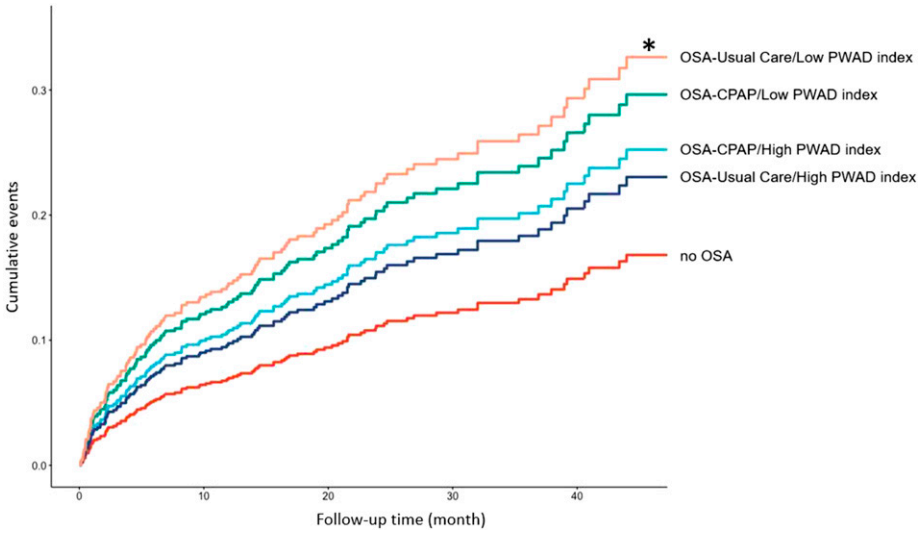

Figure 7. ISAACC study: adjusted Cox regression curves showing incident or recurrent cardiovascular events based on low or high pulse wave amplitude drop (PWAD) index and treatment with continuous positive airway pressure (CPAP) or usual care for participants with obstructive sleep apnea (OSA) compared with the control group without OSA. Models were adjusted for age (continuous), sex (categorical), body mass index (continuous), alcohol (categorical), smoking (categorical), diabetes (categorical), hypertension (categorical), lipid-lowering drugs (categorical), and vasodilators (categorical). Group description (*n*, median PWAD index value as *n*/h [95% confidence interval]): no OSA (164, 34.0 [22.7–46.7]); OSA-CPAP/high PWAD index (151, 54.6 [47.3–63.0]); OSA-CPAP/low PWAD index (112, 25.5 [19.7–32.0]); OSA-usual care and high PWAD index (129, 53.1 [46.7–62.8]); and OSA-usual care and low PWAD index (135, 24.4 [18.5–31.0]). **P* = 0.028 for OSA-usual care and low PWAD index versus no OSA; *P* = 0.110 for OSA-CPAP/high PWAD index versus no OSA; *P* = 0.102 for OSA-CPAP/low PWAD index group versus no OSA; *P* = 0.208 for OSA-usual care and high PWAD index group versus no OSA.

cardiovascular risk, and the direction of these associations.

PWAD and Response to CPAP Treatment

Although patients with OSA who had low PWAD appeared to be at higher risk for cardiovascular events, a subanalysis of PLSC showed that good adherence to CPAP was associated with a decrease in incident cardiovascular events only in patients with OSA who had a high PWAD index. Although the interaction between PWAD and CPAP was not statistically significant, this may suggest that CPAP could prevent incident cardiovascular disease in OSA only in the presence of preserved autonomic nervous system and/or vascular reactivity. In contrast, patients with OSA who have a low PWAD index might have more advanced cardiovascular disease that may not be reversible with CPAP. The absence of a significant impact of CPAP on recurrent cardiovascular events in ISAACC may be due to the type of patients included in this study with established cardiovascular disease (secondary prevention), the exclusion of sleepy patients, and the low use of CPAP (<3 h/night).

Azarbarzin and colleagues recently showed that the sleep apnea–specific pulse-rate response predicted cardiovascular morbidity and mortality in patients with OSA, with a U-shaped relationship where both high and low pulse rate responses to respiratory events were associated with increased cardiovascular risk in the Sleep Heart Heath study (36). In the cardiovascular cohort RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in coronary artery disease [CAD] and OSAtrial cohort), the same group found that CPAP only reduced the risk of recurrent cardiovascular events in OSA patients with OSA who had a higher pulse rate response (37).

PWAD and pulse rate response differ in several aspects: First, PWAD events likely reflect both autonomic nervous system reactivity and vascular endothelial responsiveness, whereas the pulse rate response reflects mainly autonomic nervous system reactivity. Second, the PWAD index takes into account all variations of the PPG signal (vasoconstrictions occurring spontaneously or after respiratory events), whereas the pulse rate response was analyzed exclusively in association with respiratory events. Despite these differences, we suggest that patients with OSA who have a low PWAD index could correspond to the left part of the "U" shaped curve, with a blunted autonomic response (low pulse rate response) contributing to increased cardiovascular risk. We could also hypothesize that, similar to patients with a high heart rate response, patients with OSA who have a high PWAD index can respond to CPAP treatment in terms of cardiovascular risk reduction, because they do not have irreversible alteration of endothelial function and the autonomic nervous system. However, further prospective analysis of combinations of different cardiovascular risk markers such as hypoxic burden, time spent with an oxygen saturation below 90%, respiratory event durations, and OSA-associated symptoms are needed before any clinical recommendations can be proposed (18, 38, 39).

Strengths and Limitations

The prospective design of the three cohorts, the adjudication of incident cardiovascular events by a panel of experts (in HypnoLaus and ISAACC), and the replication of the results despite differences in the types of populations and outcome definitions are the

main strengths of this analysis. There are, however, limitations that need to be acknowledged. First, the underlying mechanisms of the association between the PWAD index and cardiovascular risk are still unknown, and physiological studies in patients with OSA who have a high or low PWAD index are needed to address this question. Second, it is not yet clear whether the PWAD index can be used in patients with preexisting cardiovascular disorders, such as atrial fibrillation, because these conditions may affect PWAD analysis. Third, although the PWAD index seems to contribute to cardiovascular risk prediction in association with AHI and, possibly, relate to the response to CPAP, this study focused on the PWAD index (events per hour), with an arbitrary threshold of 30% drop. However, other PPG signal–derived parameters such as the duration or magnitude (area under the curve) of PWAD will need to be investigated further and may potentially improve the performance of this signal as a predictor of cardiovascular risk in OSA. A recent study showed that the "pulse wave attenuation index" was negatively correlated with estimated cardiovascular risk on the European Society of Cardiology and European Society of Hypertension matrix (40), which seems to corroborate the results presented here.

Finally, we recognize that the three cohorts included in this analysis differ substantially not only in terms of population type but also in participant characteristics and recording methods (brands of recorders and pulse oximeters) used. The three cohorts also used slightly different definitions for their composite cardiovascular endpoint: Hospitalization for heart failure was not available in the HypnoLaus cohort. The ISAACC cardiovascular endpoint included atrial fibrillation, whereas the other cohorts did not (results were nonsignificant without atrial fibrillation in ISAACC), and there was no adjudication of the primary outcome in PLSC. However, sensitivity analysis of ISAACC and PLSC with and without hospitalizations for heart failure showed consistent results. Moreover, the fact that a low PWAD index was associated with increased cardiovascular risk using polygraphy or PSG, in younger and older subjects, with shorter or longer follow-up, and in the general, clinical, and cardiovascular samples is reassuring and confirms the strength and generalizability of this marker.

In conclusion, these results suggest that adding the PWAD index to AHI provides a better indication of increased cardiovascular risk and may reflect the specific impact of OSA on autonomic and/or vascular reactivity. In patients with OSA who have a higher PWAD index and who may have a lower impact of OSA on their cardiovascular system, good adherence to CPAP treatment appears to have the potential to prevent incident cardiovascular events. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Prof. Gérard Waeber, Prof. Vincent Mooser, Prof. Mehdi Tafti, Daniela Andries, and Nadia Tobback for their important contribution to the HypnoLaus and CoLaus Cohorts; the Lausanne population who volunteered to participate in the CoLaus and HypnoLaus studies; and the whole team of CoLaus|PsyCoLaus. The authors also thank the sleep technicians Gianpaolo Lecciso, David Albir-Haba, and Brian Bradley for their important help with photoplethysmography analysis. English-language editing assistance was provided by Nicola Ryan, independent medical writer, funded by Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. The Pays de la Loire Sleep Cohort (PLSC) investigators thank the French National Health Insurance for giving access to the French administrative healthcare database; the Pays de la Loire Respiratory Health Research Institute; promoter of the PLSC from which the data used for this study were obtained; Sandrine Kerbrat and Emmanuel Oger, EA 7449 [Pharmacoepidemiology and Health Services Research]; and Julien Godey, Laetitia Moreno and Marion Vincent, sleep technicians in the Department of Respiratory and Sleep Medicine of Angers University Hospital.

References

1. Pevernagie DA, Gnidovec-Strazisar B, Grote L, Heinzer R, McNicholas WT, Penzel T, *et al.* On the rise and fall of the apnea-hypopnea index: a historical review and critical appraisal. *J Sleep Res* 2020;29:e13066.
2. Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, McArdle N, *et al.* Metrics of sleep apnea severity: beyond the apnea-hypopnea index. *Sleep* 2021;44:zsab030.
3. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, *et al.*; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375: 919–931.
4. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.
5. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, *et al.* Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2019; 8:359–367.
6. Hertzman AB. The blood supply of various skin areas as estimated by the photoelectric plethysmograph. *Am J Physiol* 1938;124:328–340.
7. Babchenko A, Davidson E, Ginosar Y, Kurz V, Faib I, Adler D, *et al.* Photoplethysmographic measurement of changes in total and pulsatile tissue blood volume, following sympathetic blockade. *Physiol Meas* 2001;22:389–396.
8. Alian AA, Shelley KH. Photoplethysmography. *Best Pract Res Clin Anaesthesiol* 2014;28:395–406.
9. Colombo R, Marchi A, Borghi B, Fossali T, Rech R, Castelli A, *et al.* Pulse photoplethysmographic analysis estimates the sympathetic activity directed to heart and vessels. *Anesthesiology* 2015;123: 336–345.
10. Grote L, Zou D, Kraiczi H, Hedner J. Finger plethysmography – a method for monitoring finger blood flow during sleep disordered breathing. *Respir Physiol Neurobiol* 2003;136:141–152.
11. Delessert A, Espa F, Rossetti A, Lavigne G, Tafti M, Heinzer R. Pulse wave amplitude drops during sleep are reliable surrogate markers of changes in cortical activity. *Sleep* 2010;33:1687–1692.
12. Hirotsu C, Betta M, Bernardi G, Marques-Vidal P, Vollenweider P, Waeber G, *et al.* Pulse wave amplitude drops during sleep: clinical significance and characteristics in a general population sample. *Sleep (Basel)* 2020;43:zsz322.
13. Parati G, Di Rienzo M, Bonsignore MR, Insalaco G, Marrone O, Castiglioni P, *et al.* Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. *J Hypertens* 1997;15:1621–1626.
14. Kohler M, Craig S, Nicoll D, Leeson P, Davies RJ, Stradling JR. Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea. *Am J Respir Crit Care Med* 2008;178: 984–988.
15. Heinzer R, Sánchez-De-La-Torre M, Solelhac G, Berger M, Hirotsu C, Haba-Rubio J, *et al.* Pulse wave amplitude variations: a new biomarker

of cardiovascular risk in patients with obstructive sleep apnea in HypnoLaus and ISAACC cohorts. *Eur Respir J* 2021;58:OA3011.
16. Solelhac G, Sanchez-de-la-Torre M, Berger M, Hirotsu C, Marchi N, Haba-Rubio J, *et al.* Le PWAD (pulse wave amplitude drops), un nouveau biomarqueur du risque cardiovasculaire lié au SAOS dans les cohortes prospectives HypnoLaus + ISAACC. *Med du Sommeil* 2022; 19:52–53.
17. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, *et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310–318.
18. Trzepizur W, Blanchard M, Ganem T, Balusson F, Feuilloy M, Girault JM, *et al.* Sleep apnea–specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *Am J Respir Crit Care Med* 2022;205:108–117.
19. Blanchard M, Gervès-Pinquié C, Feuilloy M, Le Vaillant M, Trzepizur W, Meslier N, *et al.* Association of nocturnal hypoxemia and pulse rate variability with incident atrial fibrillation in patients investigated for obstructive sleep apnea. *Ann Am Thorac Soc* 2021;18:1043–1051.
20. Esquinas C, Sánchez-de-la Torre M, Aldomá A, Florés M, Martínez M, Barceló A, *et al.*; Spanish Sleep Network. Rationale and methodology of the impact of continuous positive airway pressure on patients with ACS and nonsleepy OSA: the ISAACC Trial. *Clin Cardiol* 2013;36: 495–501.
21. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, *et al.*; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8:597–619.
22. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
23. Betta M, Handjaras G, Ricciardi E, Pietrini P, Haba-Rubio J, Siclari F, *et al.* Quantifying peripheral sympathetic activations during sleep by means of an automatic method for pulse wave amplitude drop detection. *Sleep Med* 2020;69:220–232.
24. Beuret H, Hausler N, Nanchen D, Méan M, Marques-Vidal P, Vaucher J. Comparison of Swiss and European risk algorithms for cardiovascular prevention in Switzerland. *Eur J Prev Cardiol* 2021;28: 204–210.
25. Justeau G, Bailly S, Gervès-Pinquié C, Trzepizur W, Meslier N, Goupil F, *et al.*; ERMES Study Group. Cancer risk in patients with sleep apnoea following adherent 5-year CPAP therapy. *Eur Respir J* 2022;59: 2101935.
26. Lombardi C, Pengo MF, Parati G. Obstructive sleep apnea syndrome and autonomic dysfunction. *Auton Neurosci* 2019;221:102563.
27. Kohler M, Pepperell JC, Casadei B, Craig S, Crosthwaite N, Stradling JR, *et al.* CPAP and measures of cardiovascular risk in males with OSAS. *Eur Respir J* 2008;32:1488–1496.
28. Bonsignore MR, Parati G, Insalaco G, Marrone O, Castiglioni P, Romano S, *et al.* Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002; 166:279–286.
29. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, *et al.* Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010;31:1142–1148.
30. Dissanayake HU, Bin YS, Ucak S, de Chazal P, Sutherland K, Cistulli PA. Association between autonomic function and obstructive sleep apnea: a systematic review. *Sleep Med Rev* 2021;57:101470.
31. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96: 1897–1904.
32. Tamisier R, Tan CO, Pepin JL, Levy P, Taylor JA. Blood pressure increases in OSA due to maintained neurovascular sympathetic transduction: impact of CPAP. *Sleep (Basel)* 2015;38: 1973–1980.
33. Solin P, Kaye DM, Little PJ, Bergin P, Richardson M, Naughton MT. Impact of sleep apnea on sympathetic nervous system activity in heart failure. *Chest* 2003;123:1119–1126.
34. Hilton MF, Chappell MJ, Bartlett WA, Malhotra A, Beattie JM, Cayton RM. The sleep apnoea/hypopnoea syndrome depresses waking vagal tone independent of sympathetic activation. *Eur Respir J* 2001;17: 1258–1266.
35. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998;98:1071–1077.
36. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, *et al.* The sleep apnea-specific pulse-rate response predicts cardiovascular morbidity and mortality. *Am J Respir Crit Care Med* 2021;203:1546–1555.
37. Azarbarzin A, Zinchuk A, Wellman A, Labarca G, Vena D, Gell L, *et al.* Cardiovascular benefit of CPAP in adults with coronary artery disease and OSA without excessive sleepiness. *Am J Respir Crit Care Med* 2022;206:767–774.
38. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, *et al.* The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40: 1149–1157.
39. Blanchard M, Gervès-Pinquié C, Feuilloy M, Le Vaillant M, Trzepizur W, Meslier N, *et al.*; ERMES Study Group. Hypoxic burden and heart rate variability predict stroke incidence in sleep apnoea. *Eur Respir J* 2021; 57:2004022.
40. Strassberger C, Zou D, Penzel T, Fietze I, Hedner J, Ficker JH, *et al.* Beyond the AHI-pulse wave analysis during sleep for recognition of cardiovascular risk in sleep apnea patients. *J Sleep Res* 2021;30: e13364.