Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study

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ABSTRACT Systemic hypertension is associated with obstructive sleep apnoea syndrome (OSAS) but the pathophysiological mechanisms are incompletely understood. A collaborative European network of 24 sleep centres established a European Sleep Apnoea Database to evaluate cardiovascular morbidity associated with OSAS.

11 911 adults referred with suspected OSAS between March 2007 and September 2013 underwent overnight sleep studies, either cardiorespiratory polygraphy or polysomnography. We compared the predictive value of the apnoea–hypopnoea index (AHI) and 4% oxygen desaturation index (ODI) for prevalent hypertension, adjusting for relevant covariates including age, smoking, obesity, dyslipidaemia and diabetes.

Among patients (70% male, mean $\pm$ SD age 52 $\pm$ 12 years), 78% had AHI >5 events·h^{-1} and 41% systemic hypertension. Both AHI and ODI independently related to prevalent hypertension after adjustment for relevant covariates ($p<0.0001$ for linear trend across quartiles (Q) of severity for both variables). However, in multiple regression analysis with both ODI and AHI in the model, ODI was, whereas AHI was not, independently associated with prevalent hypertension: odds ratios (95% CI) for Q4 *versus* Q1 regarding ODI were 2.01 (1.61–2.51) and regarding AHI were 0.92 (0.74–1.15) ($p<0.0001$ and $p=0.3054$, respectively).

This cross sectional study suggests that chronic intermittent hypoxia plays an important role in OSAS-related hypertension.

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These findings indicate that ODI is superior to AHI in the prediction of hypertension in patients with OSAS http://ow.ly/xFn6R

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Introduction

Obstructive sleep apnoea syndrome (OSAS) affects at least 4% of adult males and 2% of adult females in the developed world [1]. OSAS is characterised by repetitive upper airway obstruction during sleep with consequent arterial oxygen desaturation, and apnoeas/hypopnoeas are frequently terminated by microarousals [2]. Cardiovascular diseases represent an important comorbidity and there is evidence that OSAS independently relates to prevalent and incident systemic hypertension in many [3, 4], but not all [5, 6] population-based studies. There is also evidence supporting an independent association with ischaemic heart disease, stroke, heart failure, atrial fibrillation and cardiac sudden death [7]. Effective treatment for OSAS with continuous positive airway pressure (CPAP) is associated with considerable benefits in cardiovascular comorbidity, particularly hypertension, both in short-term randomised controlled studies and in long-term observational studies [8–12].

Potential mechanisms of hypertension in OSAS include intermittent hypoxia [13, 14], which stimulates systemic inflammation [15], oxidative stress [16] and endothelial dysfunction [17, 18], as well as recurring arousals, which contribute to sympathetic activation [19]. However, the respective contribution of these mechanisms to established hypertension is unclear, and previous population studies of the association of hypertension and OSAS have not addressed this question in detail [4, 20].

A collaborative European network of sleep centres was established in 2005, enabled by the European Union Cooperation in Science and Technology Action B26 programme. Within the framework of B26 activities, the European Sleep Apnoea Database (ESADA) project was initiated with the objective to recruit a large prospective international cohort of patients with suspected OSAS. It was argued that a large volume of data collected from a multicentric sleep laboratory population would generate information adding to that obtained in population based cohorts in North America, such as the Wisconsin Sleep Cohort [3] and the Sleep Heart Health Study [4]. In particular, comorbidity and pathophysiological associations may be addressed. Additionally, the cohort also reflects topics such as quality of care, regional differences and influence of local technical routines in patients representing a wide range of European countries.

The present report describes the relationship of OSAS with systemic hypertension in the ESADA cohort and examines the role of various consequences of OSAS in this relationship. The principal objective was to compare measures of recurring intermittent hypoxaemia to measures of sleep disordered breathing and arousal from sleep in the prediction of hypertension.

Methods

ESADA employs a specifically designed, web-based data collection format constructed for transfer of data from individual centres to the central database at the University of Gothenburg, Sweden. The details of ESADA are described in a separate report, which provides extensive details regarding the study population and the investigative techniques employed [21].

Subjects

Between March 2007 and September 2013, a cohort of 11 911 subjects suspected of having OSAS (8293 males and 3618 females; age 18–80 years, mean$\pm$SD 52$\pm$12 years; 78% with an apnoea–hypopnoea index (AHI) >5 events·h^{-1}) was assembled in 24 centres across 15 European countries and Israel (20 centres were University-affiliated sleep clinics). Three principal exclusion criteria were specified: treatment of OSAS with CPAP or an oral device, severe comorbidity unrelated to OSAS with limited life expectancy, and alcohol or drug abuse within 1 year of inclusion. The appropriate local ethics committee approved the agreed basic protocol.

Demographic characteristics and prevalent hypertension

Mandatory variables for each subject are reported elsewhere [21]. Current analyses include age, sex, height, weight, neck circumference, waist/hip ratio, smoking history, alcohol intake, details of comorbidities (based on established diagnosis) and antihypertensive medication use. Overweight and obese categories were defined according to WHO classification based on various body mass index (BMI) cut-offs (table 1). Medication use was determined according to the Anatomical Therapeutic Chemical classification system [22]. The method of data collection permitted two levels of confidence in the diagnosis of hypertension, one based on the diagnosis provided by the referring physician without reference to therapy (broad definition) and a second, stricter definition based on those patients diagnosed as hypertensive who were also taking antihypertensive medication (strict definition). Blood pressure measurements taken in the sleep clinic were not used to diagnose hypertension, as these were single readings obtained in the sitting position, which cannot be used as a reliable indicator for a hypertension definition [23].

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TABLE 1 Distribution of selected characteristics of the European Sleep Apnoea Database study population across apnoea–hypopnoea index (AHI) quartiles (Q)

	Total	AHI quartile				p-value
		Q1	Q2	Q3	Q4	
Subjects n	11 911	2977	2965	2972	2997	
Males	8293 (69.6)	1658 (55.7)	1957 (66.0)	2250 (75.7)	2428 (81.0)	<0.0001
Age years mean±SD	52±12	47±13	52±12	54±12	53±12	<0.0001
Age ⩾60 years	3367 (28.3)	532 (17.9)	853 (28.8)	1041 (35.0)	941 (31.4)	<0.0001
Smoking						
Never	8944 (75.6)	2198 (74.1)	2274 (77.2)	2276 (77.0)	2196 (74.0)	
Former/current	2888 (24.4)	768 (25.9)	671 (22.8)	679 (23.0)	770 (26.0)	0.0019
Body weight						
Normal	1698 (14.3)	770 (25.9)	473 (16.0)	321 (10.8)	134 (4.5)	
Overweight	4058 (34.2)	1174 (39.5)	1161 (39.3)	1076 (36.3)	647 (21.7)	
Obese	6119 (51.5)	1026 (34.5)	1321 (44.7)	1566 (52.9)	2206 (73.9)	<0.0001
BMI kg·m^{-2}	31.3±6.7	28.8±5.8	30.2±6.0	31.3±6.1	34.9±7.3	<0.0001
Neck circumference cm	41.1±4.7	38.7±4.4	40.3±4.2	41.5±4.1	43.7±4.5	<0.0001
Waist/hip ratio	0.97±0.09	0.93±0.09	0.96±0.08	0.98±0.08	1.00±0.08	<0.0001
ESS score	9.7±5.3	9.0±5.2	9.3±5.0	9.7±5.0	11.0±5.5	<0.0001
Systemic hypertension	4930 (41.4)	714 (24.0)	1154 (38.9)	1398 (47.0)	1664 (55.6)	<0.0001
Type 2 diabetes	1154 (9.7)	144 (4.8)	239 (8.1)	325 (10.9)	446 (14.9)	<0.0001
Dyslipidaemia	2481 (20.8)	398 (13.4)	581 (19.6)	720 (24.2)	782 (26.1)	<0.0001
COPD	590 (5.0)	137 (4.6)	134 (4.5)	138 (4.6)	181 (6.0)	0.0181
Mean S_{pO_2} %	93.4±3.2	94.8±1.9	94.1±2.4	93.5±2.3	91.0±4.4	<0.0001
Lowest S_{pO_2} %	80.7±10.9	87.7±5.8	83.8±7.5	80.6±8.0	71.1±12.9	<0.0001
Systolic blood pressure mmHg	134±18	130±18	133±18	134±18	137±18	<0.0001
Diastolic blood pressure mmHg	82±12	81±11	82±11	83±12	84±12	<0.0001

Data are presented as n (%) unless otherwise stated. Normal weight defined as having a body mass index (BMI) between 18 and 24.9 kg·m^{-2}; overweight, between 25 and 29.9 kg·m^{-2}; and obese, more than 30 kg·m^{-2}. p-values are for overall F-test or χ^2-test. ESS: Epworth Sleepiness Scale; COPD: chronic obstructive pulmonary disease; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

Sleep data

Either polygraphic or polysomnographic (PSG) data were entered in the database, depending on local practice in each sleep centre. All sleep data were manually edited according to protocol definitions before entry. Polygraphic recordings (n=5910) included a minimum of four recording channels (level 3 devices according to the American Academy of Sleep Medicine (AASM)) and, at a minimum, the following variables were recorded: analysed time, subjective sleep time, AHI and oxygen desaturation index (ODI), and mean arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) and the lowest S_{pO_2} [24]. PSG studies (n=6001) were performed and analysed according to AASM criteria [25] and analysis comprised the following variables in addition to those indicated for polygraphic recordings: total sleep time; sleep efficiency; percentage of sleep stage 1, 2, 3 and rapid eye movement (REM) sleep; periodic limb movement (PLM) index; PLM arousal index; respiratory arousal index; spontaneous arousal index; and respiratory disturbance index. Following the 2007 AASM rules, in a polygraphic recording, an apnoea/hypopnoea event was scored if there was a decrease (⩾50%) in the amplitude of a valid measure of airflow (either by thermistor or nasal cannula pressure transducer) during sleep (for a hypopnoea, a ⩾3% oxygen desaturation is required) or the combination of a ⩾30% reduction in airflow (compared to pre-event baseline) with a ⩾4% reduction of oxygen saturation. A minimum event duration of 10 s was required. In a PSG study, in addition to the criteria above, an event (with ⩾50% flow reduction) associated with arousal was also classified as a hypopnoea. Sleep disordered breathing was assessed with AHI defined as the average number of apnoeas plus hypopnoeas per hour of sleep, and with ODI defined as the number of transient desaturations (⩾4%) per hour of sleep for PSG and per hour of analysed time (from lights off to lights on) for polygraphic recordings. The Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness [26]. Study centres were instructed to state the quality of each polygraphic and PSG recording as "excellent" (83.8% and 78.0%, respectively), "one or two channels missing" (9.4% and 7.8%, respectively), "three or four channels missing" (0.5% and 0.1%, respectively), "poor" (0.4% and 0.9%, respectively) and "no information" (5.9% and 13.2%, respectively).

Statistical analyses

The primary sample consisted of 11 911 participants; missing data for some covariates reduced the sample size for multivariable models to a minimum of 10 949 observations. Using the strict definition of hypertension further reduced the sample size to a minimum of 8533 observations. We examined the association of prevalent hypertension with the two sleep disordered breathing variables of interest, AHI and ODI. We created four equal size groups (quartiles) for AHI and ODI using their percentile distribution in the sample. The lowest quartile (<25th percentile) of the index distribution served as a reference category for the computation of the effect size and associations were quantified by computing relative prevalence odds. All models were adjusted for age, sex, BMI, waist/hip ratio, neck circumference, smoking status, type 2 diabetes, dyslipidaemia, sleep study type, ESS and chronic obstructive pulmonary disease. We refer to these models as "full models". Next, to test the robustness of covariate selection, we used forward stepwise selection procedures to identify parsimonious models of the covariates.

The relative predictive value of AHI *versus* ODI for prevalent hypertension was evaluated using four approaches. First, we examined individual logistic regression models, where AHI or ODI were entered separately as independent variables. Second, we entered both AHI and ODI simultaneously in logistic regression models, along with the respective covariates. Third, AHI and ODI were introduced into multiple forward stepwise logistic regression analysis together with covariates. Fourth, we examined the additional predictive value of ODI within the groups below and above the median AHI. In testing for the linear trend across the AHI or ODI quartiles in logistic regression models, we entered a single four-level ordinal variable that took the natural logarithm value of the within quartile median. Model fit was tested by Hosmer–Lemeshow goodness of fit test [27]. Age was considered continuously and categorically, as age groups of 18–59 and $\geqslant$60 years. The choice of 60 years was arbitrary to assess the role of these factors in an older population sufficiently large for statistical testing. Statistical analyses were conducted with SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

AHI range in the four quartiles was <6.0, 6.0–17.39, 17.4–38.9 and $\geqslant$39.0 events·h^{-1}. For ODI, the quartile ranges were <3.6, 3.6–11.9, 12.0–31.69 and $\geqslant$31.7 desaturations·h^{-1}. For mean S_{pO_2}, the quartile ranges were <92.2%, 92.2–93.9%, 94.0–94.9% and $\geqslant$95.0%. Descriptive characteristics of the study population and the distribution of covariates are presented in table 1. The study population was strongly dominated by Caucasian ethnicity (93.6%). Increasing AHI was associated with male sex, higher age, higher obesity indices, and higher prevalence of systemic hypertension, type 2 diabetes and dyslipidaemia.

The effects of AHI and ODI on prevalent hypertension in the entire cohort

Data were analysed for both broad and strict definitions of hypertension. First, we examined individual models (crude or adjusted) where AHI or ODI were entered separately as independent variables. Both AHI and ODI predicted prevalent hypertension for both broad and strict definitions ($p<0.0001$ for linear trend across ODI and AHI quartiles) (table 2 and online supplementary table 1a). In contrast, in the adjusted (both full and parsimonious) logistic regression models with both AHI and ODI entered simultaneously, only ODI remained a significant predictor of prevalent hypertension using both broad and strict definitions (table 2 and online supplementary table 1b). In the final model of multiple logistic regression analysis, ODI was, while AHI was not, retained as an independent predictor of prevalent hypertension using both definitions (table 3).

Analysis of the predictive value of ODI within the groups categorised by AHI (above and below the median AHI of 17.4 events·h^{-1}) revealed that prevalent hypertension increased across increasing quartiles of ODI using both broad and strict definitions ($p<0.0001$ for both comparisons) (fig. 1 and online supplementary fig. 1). The type of sleep study (PSG or polygraphy) did not affect the predictive value of AHI or ODI on prevalent hypertension (p-value for both interaction terms between the type of sleep study and AHI or ODI was >0.05) (broad definition: fig. 2; strict definition: online supplementary table 2).

To increase data robustness, we performed additional analyses on the predictive value of AHI *versus* mean S_{pO_2} on prevalent hypertension. Similarly to AHI and ODI, mean S_{pO_2} predicted prevalent hypertension for both broad and strict definitions ($p<0.0001$ for linear trend across mean S_{pO_2} quartiles). In the adjusted (both full and parsimonious) logistic regression models with AHI and mean S_{pO_2} entered simultaneously, AHI and mean S_{pO_2} remained significant predictors of prevalent hypertension (online supplementary table 3b).

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TABLE 2 Crude and adjusted odds ratios for prevalent systemic hypertension (broad definition) across quartiles (Q) of sleep disordered breathing variables in models containing either apnoea–hypopnoea index (AHI) or oxygen desaturation index (ODI) entered separately or simultaneously as categorical variables

Model	Subjects n	Q1 OR	Q2	Q3	Q4	p-value
AHI or ODI entered separately	10 494					
AHI						
Model 0	11 911	1.00	2.02 (1.81–2.26)	2.82 (2.52–3.14)	3.96 (3.54–4.42)	<0.0001
Model 1	10 949	1.00	1.29 (1.13–1.48)	1.40 (1.22–1.60)	1.52 (1.31–1.76)	<0.0001
Model 2	11 487	1.00	1.31 (1.15–1.49)	1.41 (1.23–1.60)	1.51 (1.31–1.73)	<0.0001
ODI						
Model 0	11 911	1.00	2.30 (2.05–2.58)	3.48 (3.11–3.90)	4.86 (4.34–5.45)	<0.0001
Model 1	10 949	1.00	1.49 (1.30–1.70)	1.73 (1.51–1.98)	1.87 (1.62–2.17)	<0.0001
Model 2	11 487	1.00	1.48 (1.30–1.69)	1.73 (1.52–1.98)	1.86 (1.62–2.14)	<0.0001
Both AHI and ODI entered simultaneously	8925					
AHI						
Model 0	11 911	1.00	1.27 (1.11–1.45)	1.38 (1.19–1.60)	1.50 (1.25–1.80)	<0.0001
Model 1	10 949	1.00	1.01 (0.87–1.17)	0.95 (0.79–1.13)	0.92 (0.74–1.15)	0.3054
Model 2	11 487	1.00	1.02 (0.88–1.18)	0.95 (0.80–1.13)	0.90 (0.73–1.12)	0.2363
ODI						
Model 0	11 911	1.00	2.03 (1.79–2.31)	2.77 (2.38–3.22)	3.56 (2.96–4.28)	<0.0001
Model 1	10 949	1.00	1.49 (1.28–1.73)	1.79 (1.49–2.13)	2.01 (1.61–2.51)	<0.0001
Model 2	11 487	1.00	1.48 (1.28–1.71)	1.79 (1.51–2.13)	2.03 (1.64–2.52)	<0.0001

Data are presented as OR (95% CI) unless otherwise stated. p-values are for linear trend across quartiles. Model 0: unadjusted; model 1: full model included the covariates age, sex, body mass index, waist/hip ratio, neck circumference, type 2 diabetes, dyslipidaemia, chronic obstructive pulmonary disease, smoking status, Epworth Sleepiness Scale (ESS) score, type of sleep study and sleep disordered breathing variables (*i.e.* quartiles of AHI or quartiles of ODI) entered separately or simultaneously into model; model 2: parsimonious model excluded from the full model the covariates waist/hip ratio, ESS score, chronic obstructive pulmonary disease and current smoking status.

Subgroup analysis

Further analysis in subgroups stratified by age or sex demonstrated similar findings as in the entire cohort; both AHI and ODI predicted prevalent hypertension for both broad and strict definitions but only ODI remained a significant predictor of the outcome variable in both age category groups when AHI and ODI were included together in the statistical analysis. In multiple logistic regression analyses within the respective age categories, ODI was, while AHI was not, retained as an independent predictor of prevalent hypertension (broad definition: online supplementary table 4; strict definition: online supplementary table 5). Analysis of the predictive value of ODI within the groups categorised by AHI (below and above AHI median) in patients <60 years revealed similar effect of ODI compared to that seen in the entire cohort: prevalent hypertension increased across increasing quartiles of ODI (p-value for linear trend across ODI quartiles below and above the median AHI: $p=0.0004$ and $p<0.0001$, respectively). A similar analysis in patients $\geqslant$60 years indicated increases of prevalent hypertension across increasing quartiles of ODI in the subgroup of patients with AHI below but not in the subgroup with AHI above the median AHI value ($p<0.0001$ and $p=0.1161$, respectively).

Stratification by sex revealed similar effects of AHI and ODI on prevalent hypertension to those observed in the entire cohort; and in logistic regression analysis stratified by sex, ODI was, while AHI was not, retained as an independent predictor of prevalent hypertension (broad definition: online supplementary table 6; strict definition: online supplementary table 7).

Further, we analysed additional potential confounding factors including study centre for both the broad and strict definitions of hypertension (online supplementary table 8a) and the method for hypopnoea scoring (recommended or alternative criteria according to AASM 2007) for the broad (online supplementary table 8b) and strict (online supplementary table 8c) definition of hypertension. ODI remained the stronger and independent predictor of arterial hypertension in all models.

Discussion

The present findings confirm previous population-based hallmark studies showing that OSAS is independently associated with prevalent systemic hypertension. While both AHI and ODI were independent predictors of hypertension, ODI was superior to AHI in this prediction. ODI provides a solid reflection of

TABLE 3 Multiple stepwise logistic regression analysis of the relationship between systemic hypertension and various independent variables

Variable	Broad definition of hypertension					Strict definition of hypertension				
	β	SE	p-value	OR (95%CI)	Final model	β	SE	p-value	OR (95%CI)	Final model
ODI										
Q2 *versus* Q1	0.40	0.08	<0.0001	1.49 (1.28–1.73)	Yes	0.43	0.09	<0.0001	1.54 (1.29–1.83)	Yes
Q3 *versus* Q1	0.58	0.09	<0.0001	1.79 (1.49–2.13)	Yes	0.54	0.11	<0.0001	1.71 (1.39–2.11)	Yes
Q4 *versus* Q1	0.70	0.11	<0.0001	2.01 (1.61–2.51)	Yes	0.81	0.13	<0.0001	2.24 (1.73–2.90)	Yes
Age	0.07	0.00	<0.0001	1.07 (1.06–1.07)	Yes	0.08	0.00	<0.0001	1.08 (1.08–1.09)	Yes
Body mass index	0.06	0.00	<0.0001	1.06 (1.05–1.07)	Yes	0.05	0.01	<0.0001	1.05 (1.04–1.07)	Yes
Neck circumference	0.04	0.01	<0.0001	1.04 (1.03–1.06)	Yes	0.06	0.01	<0.0001	1.07 (1.05–1.09)	Yes
Type 2 diabetes	0.78	0.08	<0.0001	2.18 (1.86–2.55)	Yes	0.95	0.10	<0.0001	2.59 (2.15–3.12)	Yes
Dyslipidaemia	0.66	0.05	<0.0001	1.93 (1.73–2.14)	Yes	0.77	0.06	<0.0001	2.16 (1.91–2.44)	Yes
ESS score	-0.01	0.00	0.0202	0.99 (0.98–1.00)	Yes	-0.01	0.01	0.0038	0.99 (0.98–1.00)	Yes
COPD	-0.02	0.10	0.8681	0.98 (0.81–1.20)	No	0.07	0.12	0.5496	1.07 (0.85–1.35)	No
AHI										
Q2 *versus* Q1	0.01	0.08	0.9168	1.01 (0.87–1.17)	No	0.05	0.09	0.6068	1.05 (0.88–1.25)	No
Q3 *versus* Q1	-0.05	0.09	0.5527	0.95 (0.79–1.13)	No	-0.02	0.11	0.8857	0.98 (0.80–1.22)	No
Q4 *versus* Q1	-0.08	0.11	0.4594	0.92 (0.74–1.15)	No	-0.17	0.13	0.2110	0.85 (0.65–1.10)	No
Female *versus* male	0.15	0.07	0.0266	1.17 (1.02–1.34)	Yes	0.32	0.08	<0.0001	1.38 (1.17–1.62)	Yes
Smoking	-0.20	0.05	0.0003	0.82 (0.74–0.91)	Yes	-0.20	0.06	0.0020	0.82 (0.73–0.93)	Yes
Waist/hip ratio	0.87	0.34	0.0112	2.39 (1.22–4.70)	Yes	1.74	0.41	<0.0001	5.69 (2.54–12.70)	Yes

Quartile (Q)1 is the lowest quartile and reference category. β: parameter estimate (regression coefficient); ODI: oxygen desaturation index; ESS: Epworth Sleepiness Scale; AHI: apnoea–hypopnoea index.

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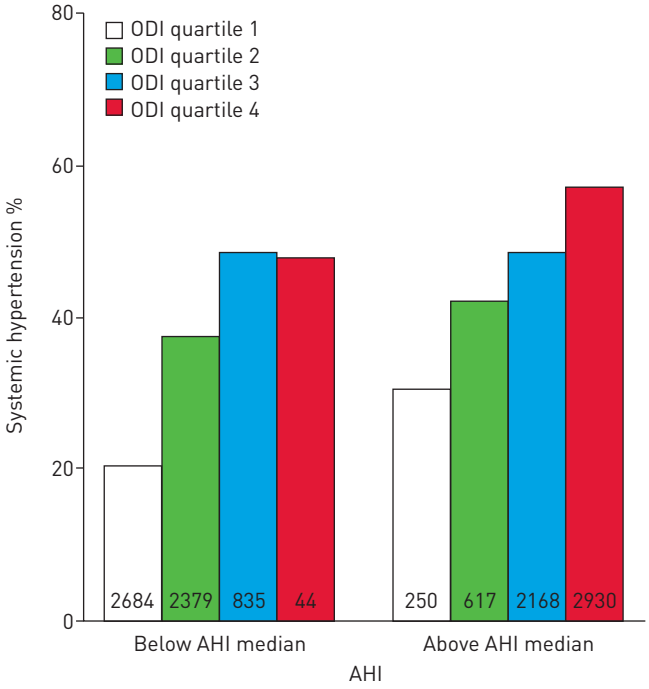

FIGURE 1 Prevalence of systemic hypertension (broad definition) across quartiles of oxygen desaturation index (ODI) within the groups categorised by apnoea–hypopnoea index (AHI) (above and below the median AHI value). Number of subjects per subgroup is shown within bars. $p<0.0001$ for linear trend across quartiles of ODI for both groups, *i.e.* below and above the median AHI value.

the degree of intermittent hypoxaemia during sleep. AHI is a more complex measure also reflecting respiratory effort and arousal from sleep, and therefore susceptible to variability in the clinical setting. Our data suggest not only that measures of intermittent hypoxaemia better predict OSA related hypertension but also that intermittent hypoxia is an important mechanism in the pathogenesis of hypertension in OSAS.

Evidence regarding association of hypertension and OSAS

The relationship of hypertension and OSAS is complicated by important confounding variables, particularly obesity. Nonetheless, there is convincing evidence from large population studies that OSAS represents an independent risk factor for systemic hypertension, both in the general population [3, 4, 20] and in carefully defined cohort studies of sleep clinic patients [28–30]. The Wisconsin Sleep Cohort Study indicated a dose-dependent relationship between AHI at baseline and the incidence of hypertension 4 years later, independent of confounding factors [3]. OSAS is also highly prevalent in patients with systemic hypertension, particularly those with drug-resistant hypertension [31], and the condition is listed as an identifiable cause of hypertension in major hypertension guideline documents [32]. A loss of the normal nocturnal dipping pattern of blood pressure is particularly common in OSAS and may be an early marker of systemic hypertension [33]. Furthermore, prospective randomised trials have shown that effective OSAS treatment decreases blood pressure [8], especially in hypertensive subjects [9].

The present findings provide further evidence supporting an association between OSAS and systemic hypertension, independent of confounding variables such as age, sex, BMI, and relevant comorbidities such as diabetes and dyslipidaemia. They also indicate that the frequency of intermittent hypoxaemia is particularly important in this relationship. Previous reports linking OSAS with hypertension have used AHI as the marker of disease severity and few reports have addressed the contribution of hypoxaemia [4, 34]. In the report from the Sleep Heart Health Study [4] involving over 6000 subjects, both high AHI or sleep time below 90% oxygen saturation were associated with greater odds of hypertension in a dose-response fashion. However, AHI and ODI were not directly compared in this association. Thus, the present report is the first to detect a specific contribution of intermittent hypoxaemia to prevalent hypertension in a large clinic population.

Mechanisms of hypertension in OSAS

Obstructive apnoeas/hypopnoeas are typically characterised by systemic hypoxaemia, increased respiratory effort with associated changes in intrathoracic pressure and ultimately microarousal from sleep [35]. These

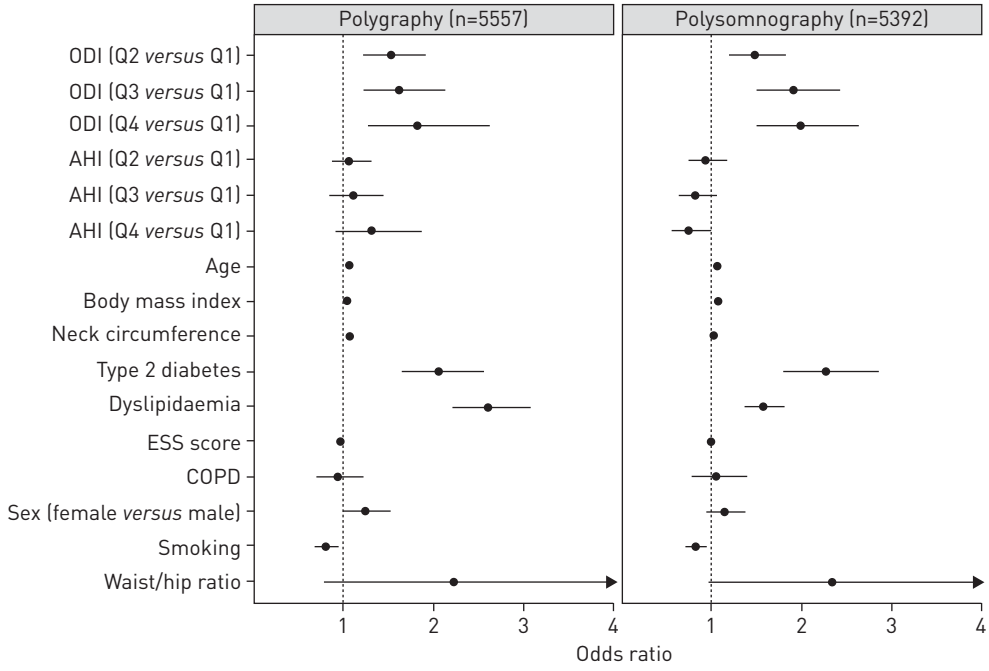

FIGURE 2 Multiple logistic regression analysis of the relationship between systemic hypertension (broad definition) and various independent variables according to type of study (polygraphy or polysomnography). Error bars indicate 95% confidence intervals. Quartile (Q)1 is the lowest quartile and the reference category. ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index; ESS: Epworth Sleepiness Scale; COPD: chronic obstructive pulmonary disease.

episodes are accompanied by surges in sympathetic nerve activity, with associated increased blood pressure and heart rate. In chronic OSAS, sympathetic drive is persistently elevated, even during wakefulness [36], and muscle sympathetic nerve activity is attenuated during apnoea under hyperoxic conditions [37], supporting a direct link with hypoxaemia. Furthermore, baroreflex sensitivity is diminished in OSAS [35], an effect most closely linked to intermittent hypoxaemia [38]. This derangement of autonomic activity and baroreflex function was attenuated following CPAP treatment [39].

The repetitive hypoxia–reoxygenation associated with obstructive breathing has been suggested to generate systemic inflammation and oxidative stress, which contribute to endothelial dysfunction, vessel wall inflammation and atherosclerosis [16], although this association is still under debate [40]. Thus, by its effects on vascular endothelium, chronic intermittent hypoxaemia may further contribute to impaired blood pressure control both night and day. A causal relationship between intermittent hypoxaemia during sleep and systemic hypertension has been demonstrated in a rat model [41]. Acute intermittent hypoxaemia induces a pressor response in man [13], which is inhibited by angiotensin II receptor blockade [42]. Other proposed mechanisms for hypoxia-induced blood pressure elevation include activation of hypoxia-inducible factors [43]. One could also speculate that our data, which demonstrate that ODI may be superior to AHI in the prediction of prevalent hypertension, adds further support to a role for intermittent hypoxaemia in hypertension pathophysiology. Moreover, there may be several pathophysiological explanations including a direct damaging effect on the vascular endothelium as well as arousal-induced induction of increased sympathetic activity. The observational nature of our study does not enable us to determine either the cause or the nature of the better prediction provided by ODI. Finally, ODI may be superior to AHI for methodological reasons, as ODI as a metric has less variance than the more complex and derived AHI.

Study strengths and limitations

The present data are derived from a large, well-characterised, prospective cohort of patients with clinical features of OSAS [21]. Participating centres were formally evaluated, and agreed to ensure consistent standards of patient recruitment and data acquisition. Study initiation visits were performed at participating sites and a study monitor regularly reviews data quality in the central electronic database. The ESADA study constitutes a relevant clinical setting, recruiting patients from 24 sleep laboratories in 16 countries. Thus, the design mirrors differences in referral pattern and healthcare systems, thereby increasing the generalisability of the present findings. Furthermore, ESADA represents the largest multinational clinical

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cohort study to date exploring associations between OSAS and cardiovascular outcomes, and data derived from a clinic population may provide information with higher clinical validity compared to defined population studies.

The present report has a number of potential limitations. First, the cross-sectional design of this study does not permit us to draw conclusions on a causal relationship between intermittent hypoxaemia and arterial hypertension. Second, data obtained from a sleep clinic population may not be representative of the general population; however, this should not be a significant limitation since the principal objective was to examine relationships between OSAS and hypertension. Third, many patients had limited cardiorespiratory polygraphic sleep studies as opposed to full PSG, which introduces an additional variable in the calculation of AHI and ODI. OSAS severity in sleep studies is traditionally expressed by the AHI, which is the number of apnoeas and hypopnoeas per hour of sleep [44]. However, oxygen desaturation is not a prerequisite for the presence of apnoea or hypopnoea [25], and thus AHI and ODI will probably be different, particularly in PSG studies where arousal forms part of the definition of apnoea and hypopnoea. Therefore, we performed separate analyses for both sleep study types and found comparative results independent of the method used. Fourth, patients were classified as hypertensive based on referring physician diagnosis. Potential diagnostic inaccuracies were limited by performing additional analysis in those hypertensive patients taking antihypertensive medications. This approach was justified because single clinic blood pressure readings were affected by ongoing medication, may be considered to have limited reproducibility and were transiently elevated in some subjects because of a ''white coat'' effect [45]. Moreover, data in the ESADA reflect the clinical use of different recording systems and scoring routines at various sites across Europe over an extended time period. This practice is likely to introduce increased variability in the assessment of sleep apnoea severity indices. Nevertheless, the robustness of our findings is supported further by extensive confounder analyses addressing type of sleep test, scoring rules applied and recording site. These additional analyses suggest that between-site differences did not systematically influence the association between OSA and hypertension.

Clinical implications

The present findings confirm the high prevalence of systemic hypertension in OSAS, independent of relevant confounding variables. The finding that the ODI is superior to AHI in the prediction of hypertension is also clinically important, as oxygen saturation is easily measured with high reproducibility in the clinical setting. This may facilitate clinical screening of patients for further differential diagnosis, especially in a cardiology patient population [46].

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