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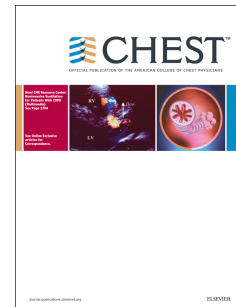
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Sleep Apnea and Hypertension: Are there gender differences?

The Vitoria Sleep Cohort.

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ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring

BMI = body mass index

CT90 = cumulative time percentage of saturation <90%

DBP = diastolic blood pressure

EDS = excessive daytime sleepiness

ODI = oxygen desaturation index

OSA= obstructive sleep apnea

RDI = respiratory disturbance index

SBP = systolic blood pressure

ABSTRACT

Background: Evidence from longitudinal studies has reported contradictory results regarding the association between obstructive sleep apnea (OSA) and hypertension. In a previous analysis of the Vitoria Sleep Cohort, we evaluated the relationship between OSA and the risk of developing hypertension and we did not find an independent association after adjustment for confounding factors. In the present study, we perform a *post hoc* analysis to assess the association between OSA and incident stage 2 hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg) based on gender differences.

Methods: A prospective study was performed over 7.5 ± 0.8 years on a middle-aged general population, which included 1,155 normotensive subjects (43.7% men) who completed the follow-up. Blood pressure measurements (at baseline and follow up) and polygraphy at baseline were performed. Logistic regression models were used to determine the association between the respiratory disturbance index (RDI) and stage 2 hypertension and a recursive partitioning method was used to determine the variables related to the incidence of stage 2 hypertension. The RDI was divided into subgroups (0-2.9, 3-6.9, 7-13.9 and ≥ 14), using the first subgroup as reference.

Results: For men, an RDI ≥ 14 was associated with a significantly increased odds ratio (OR) for stage 2 hypertension [OR = 2.54 (95% CI 1.09-5.95), $p = 0.032$]. This association was not statistically significant among women ($p = 0.371$).

Conclusions: Our results suggest an association between moderate to severe OSA and the incidence of more severe forms of hypertension in men but not in women. However, as this is a community-based study, our women's population characteristics may differ from women usually seen in sleep-disorders clinics.

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INTRODUCTION

Evidence from several cross-sectional studies¹⁻³ suggests an association between obstructive sleep apnea (OSA) and hypertension. However, conflicting results have emerged from prospective studies⁴⁻⁷ and currently, the pathophysiological interactions between OSA and hypertension are not completely understood. Evidence of an association between OSA and hypertension is also indicated by several intervention trials, in which CPAP was shown to reduce blood pressure⁸⁻¹⁰ or in which CPAP withdrawal resulted in a clinically relevant increase in blood pressure.¹¹ However, this improvement in blood pressure control is not equally observed in all OSA patients on CPAP treatment, suggesting the occurrence of different OSA subgroups. Studies performed on subjects without daytime sleepiness have failed to show a significant effect of CPAP on blood pressure,^{12, 13} other studies reported only a minor blood pressure reduction in normotensive subjects,^{14, 15} a modest reduction in hypertensive patients,¹⁶ or no significant effect in resistant hypertension,¹⁷ whereas others have shown a significant blood pressure reduction in patients with severe or refractory hypertension.^{18, 19}

We evaluated in a previous analysis of the Vitoria Sleep Cohort the relationship between OSA and the risk of developing hypertension and our findings did not suggest an independent association between OSA and the incidence of hypertension, and revealed no sex differences.⁶ In the present study we performed a *post hoc* analysis to assess the relationship between OSA and the risk of developing moderate to severe hypertension, which corresponds to grade 2 and 3 in the European Task Force for the management of arterial hypertension²⁰ and to stage 2 in the American guidelines.²¹ This

stage has at least a moderate 10-year risk of cardiovascular mortality and, for this reason, current guidelines recommend treating these patients with antihypertensive treatment regardless of the presence of other cardiovascular risk factors.²⁰ Recent guidelines have also underlined the paucity of data for treating grade 1 hypertension,²² recommending treatment only after confirming hypertension by ABPM and restricting treatment to grade 1 hypertensive patients with signs of organ damage or at high total cardiovascular risk.

METHODS

Study design and patients

Details of the study design have been previously published.^{6, 23} Briefly, it is a prospective study performed over 7.5 ± 0.8 years on the middle-aged (30-70 years) general population of the Vitoria Sleep Cohort to assess the association between OSA and hypertension. This cohort enrolled a group of 1,521 subjects who met the inclusion criteria for the cross-sectional baseline study²³ and underwent a structured interview that included sleep questionnaires, a physical examination with anthropometric and blood pressure measurements and a nocturnal polygraphy. At the end of the monitoring period, blood pressure was measured again. The exclusion criteria for the present study included subjects treated with CPAP or uvulopalatopharyngoplasty and subjects who had hypertension at baseline. The main objective of the present study was to assess the association between OSA and the risk of developing more clinically significant hypertension (i.e. moderate to severe hypertension) and to evaluate sex differences.

The study was approved by the OSI Araba Hospital Ethics Committee (approval no. 2010-027) and written informed consent was obtained from all patients.

Study variables

An unattended at-home polygraphy (MESAM IV; Medizintechnik für Arzt und Patient, Munich, Germany) ²⁴ was performed for all participants to classify the population according to the respiratory disturbance index (RDI). In our analyses, the RDI was divided into subgroups (0-2.9, 3-6.9, 7-13.9 and $\geq 14/h$), using the first subgroup as reference.

Blood pressure was measured at the beginning and at the end of the study with a mercury sphygmomanometer following standard recommendations ²⁵. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or current treatment with antihypertensive medications and it was classified in three grades following standard guidelines: ²⁰ grade 1 included all subjects with SBP = 140-159 mmHg and/or DBP = 90-99 mmHg; grade 2 included subjects with SBP = 160-179 mmHg and/or DBP = 100-109 mmHg; and grade 3 included subjects with SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg. For our study, we classified our patients in two stages: stage 1 corresponded to mild hypertension and included all subjects with grade 1 hypertension and stage 2 corresponded to moderate-to-severe hypertension and included all subjects with grade 2 or 3 hypertension or those on current treatment with antihypertensive medications.

Excessive daytime sleepiness (EDS) was defined as sleepiness occurring at least 3 or more days a week during the past 3 months under one or more of the following conditions: after waking, during free time (leisure time), at work or driving, or during daytime in general according to the Basic Nordic Sleep Questionnaire.²⁶

Statistical analysis

Univariate associations with hypertension after follow up were assessed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Logistic regression models were used to determine the association between RDI and stage 2 hypertension incidence. Age, sex, body mass index (BMI) and neck circumference were included in the adjusted models because they were significantly associated based on the univariate analysis (e-Table 1). A recursive partitioning method (AnswerTree Software for SPSS Inc., Chicago, IL, USA) was used to determine the variables that were related to stage 2 hypertension incidence. The tree-building process involved the variables: age, sex, BMI, neck circumference and RDI. Recursive partitioning identified the threshold value for each variable that provided the best separation for identifying stage 2 hypertension with the highest purity, except for the BMI variable, which was previously categorized in two groups: BMI < 30 Kg/m² and BMI ≥ 30 Kg/m². The variable that achieved the most precise separation of patients with and without stage 2 hypertension was selected as the best predictor for the first branch of the tree. The recursive partitioning procedure was repeated for the two subgroups resulting from each split until reaching a subgroup that contained fewer than 25 patients or was more than three levels deep. Logistic regression analyses were used to estimate the odds ratios for

stage 2 hypertension within each subgroup defined according to the previous tree and in reference to the subgroup with the lowest prevalence of stage 2 hypertension. All statistical analyses were performed using IBM SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) or R,²⁷ with a significance level of 0.05.

RESULTS

The flow chart of the patients included in the study is depicted in Figure 1 and the main characteristics of the normotensive patients at baseline are presented in Table 1. These subjects were middle-aged and normoweight on average. Almost one-fifth of the population had excessive daytime sleepiness and a high percentage of participants reported smoking and alcohol consumption. Greater than two-thirds of the female participants were premenopausal according to their average age. The presence of moderate to severe sleep apnea was higher in men than in women and men showed a higher cumulative time percentage of SaO₂ <90% (CT90) than women. After 7.5 ± 0.8 years of follow up (Table 2), the incidence of hypertension in the general sample was 33%, and 90 (23%) of these patients developed stage 2 hypertension. In addition, a statistically significant difference in the stage 2 hypertension incidence was observed between men and women (13.7% and 3.2%, respectively ($p < 0.001$)). Almost three-quarters (72%) of the subjects who developed stage 2 hypertension were on antihypertensive medication, being this percentage higher in women than in men (86% vs. 68% respectively, $p < 0.001$).

The relationship between the baseline RDI and final hypertension stage for normotensive patients at baseline is presented in Figure 2. Differences were

not observed in the baseline RDI between the subjects who developed stage 1 hypertension and the subjects who remained normotensive (median RDI of 4/h). However, a significant difference was observed in the baseline RDI between both groups and the group that developed stage 2 hypertension (median RDI of 8/h and Bonferroni adjusted p-value < 0.0001 for both comparisons).

The association between the baseline RDI and the incidence of stage 2 hypertension is presented in Table 3. The OR significantly increased with higher RDI categories and after controlling for age, sex, BMI and neck circumference [at RDI ≥ 14 , OR = 2.51 (95% CI 1.18-5.33), overall $p_{\text{trend}} = 0.017$].

We also examined the association between the baseline RDI and the risk of developing stage 2 hypertension stratified by sex (Table 4) because of the significant interactions of sex with neck circumference ($p = 0.047$) and age ($p = 0.028$), and we controlled for the same variables except for sex. In the case of men, a baseline RDI ≥ 14 was associated with a significantly increased OR for the development of stage 2 hypertension [OR = 2.54 (95% CI 1.09-5.95), overall $p_{\text{trend}} = 0.032$]. This association was not statistically significant among women (overall $p_{\text{trend}} = 0.371$), although the OR for women increased with higher RDI categories.

The relationship between the RDI categories and the incidence of hypertension was also evaluated considering the presence or absence of EDS. The OR did not significantly increase with higher RDI categories in subjects with EDS (crude OR, $p = 0.228$) or in subjects without EDS (crude OR, $p = 0.102$). These results were also confirmed by the absence of statistical significance in the interaction between the RDI and sleepiness (p value for interaction = 0.653).

A decision tree of risk factors for incident stage 2 hypertension was constructed according to the recursive partitioning method and is presented in Figure 3, and the probability of developing stage 2 hypertension in each subgroup is shown in Table 5. Seven risk subgroups were noted based on the following risk variables (which had their own threshold values): age, sex, BMI, neck circumference and RDI. We estimated the odds ratios of presenting stage 2 hypertension using the subgroup with the lowest Stage 2 hypertension incidence (non-obese and ≤ 56 years women) as reference. An RDI $\geq 14/h$ was the main risk factor for hypertension incidence in men but not in women [OR in men = 25.33 (95% CI 9.76-65.73) $p < 0.001$, with an incidence of 22.6% of Stage 2 hypertension]. In the case of women, OSA presence was not a significant risk factor for stage 2 hypertension development. The majority of women in our sample (81%) belonged to the lowest risk subgroup for stage 2 hypertension incidence (young and non-obese women), although there was a subgroup of women (3.8%) (older than 56 years with a neck circumference diameter > 35.3 cm) who had the highest Stage 2 hypertension incidence of our sample (28.0%) [OR = 33.70 (95% CI 10.28-110.50), $p < 0.001$], regardless of their RDI.

DISCUSSION

Our *post hoc* analysis suggest an association between moderate to severe OSA and the risk of developing more severe forms of hypertension in middle-aged men of the general population after 7.5 years of follow up. Men with a RDI $\geq 14/h$ exhibited a 2.5-fold increased risk of developing stage 2

hypertension compared with those without OSA. In women, this relationship was not statistically significant. An analysis of the risk subgroups for stage 2 hypertension incidence confirmed this gender difference and showed that moderate to severe OSA was the main risk factor for hypertension development in men. EDS did not appear to modify this relationship.

As our previous findings did not support a causal relationship between OSA and hypertension in the middle-aged general population, we performed this *post hoc* analysis to evaluate the association between OSA and the risk of developing more clinically significant hypertension (i.e. stage 2 hypertension), due to the cardiovascular consequences of this stage of hypertension and the potential benefit of treating OSA patients to prevent them. Among the three prospective studies that have assessed the association between OSA and hypertension ^{4,5,7}, two of them ^{5,7} did not analyze the different stages of hypertension, while the Wisconsin Sleep Cohort Study ⁴ evaluated the prevalence of stage 1 and 2 of hypertension but did not determinate the incidence of both stages of hypertension because they could not precisely identify the participants normotensive at baseline.

To the best of our knowledge, this is the first attempt to explore different clinical OSA subgroups related to hypertension incidence using the recursive partitioning method. Our objective was to explore all risk factors for developing stage 2 hypertension to identify clinical subgroups and provide insights into the association between OSA and hypertension. In addition to the RDI, we found that age was a clinically and statistically significant risk factor for both genders (although the cut-off point was different), and neck circumference and BMI were

clinical variables that identified different risk subgroups only in women. In recent years, several studies have attempted to identify different OSA subgroups using a different statistical approach: the cluster analysis. Ye and co-workers²⁸ identified three distinct clusters and demonstrated an increased probability of hypertension in minimally symptomatic patients compared with those with EDS. In a recent paper, Lacedonia et al.²⁹ also identified three different subgroups of OSA patients, being those who belonged to the cluster with higher apnea-hypopnea index and higher nocturnal hypoxemia, who presented the highest prevalence of hypertension. In our study, neither symptoms (EDS) nor nocturnal hypoxia, which were assessed by CT90 and the oxygen desaturation index (ODI), were independently associated with incident hypertension.

The slight association between OSA and stage 2 hypertension observed in women in our study could be related to several factors: mainly, the small number of women with an RDI $\geq 14/h$ and with stage 2 hypertension in our sample; the high proportion of premenopausal (67.4%) and consequently young women (44.4 ± 9.6 years), a status with lower prevalence of OSA and hypertension;³⁰ the lower BMI for women compared with men (24.1 ± 3.7 Kg/m² vs. 26.0 ± 3.0 Kg/m² respectively, $p < 0.001$); and, finally, the lower prevalence of OSA and hypertension in women than in men.^{31,32} All these factors could suggest a possible increased level of cardiovascular protection and/or a longer required exposure time for the expression of hypertension in women than in men. Our data are consistent with a case-controlled study performed by Hedner et al.,³³ who found an independent association between OSA and hypertension with a dose-response effect in men but not in women and with the results from the cross-sectional study of the Yale Sleep Cohort

Study,³⁴ although gender differences were observed only in the highest BMI quartile. Our results differ from a recent large database study³⁵ and the SHHS results,⁵ which suggested that OSA might predict future hypertension among women but not men. Other population-based studies have not revealed an association with gender.^{1, 4, 36}

Regarding to daytime sleepiness, conflicting results have emerged.^{28, 37} In our study, EDS did not appear to modify this relationship. Consistent with our results, Marin and co-workers⁷ did not find an association between the Epworth Sleepiness Scale score and the incidence of hypertension in OSA patients who were not treated with CPAP. The discrepancies observed between our study and other studies could be related to the sample population (general population vs. sleep-disorder clinics) or the different methods used to assess sleepiness (we used the Basic Nordic Sleep Questionnaire, which is a questionnaire that has been widely used and shown to be a valid tool for epidemiological and genetic research for OSA).³⁸

Our study presented a number of potential limitations. We used office blood pressure measurements instead of 24-hour ABPM. However, the use of office blood pressure measurements has been validated in several studies and is recommended as the screening method for hypertension assessments,²¹ whereas ABPM is costly and time consuming when performed on a large population. Another potential limitation is that polysomnography was not performed on all subjects. However, the data obtained for participants who underwent both polygraphy and polysomnography did not show any significant differences in the association between OSA and hypertension.²³ Finally, the majority of our general population had mild to moderate sleep apnea; therefore,

patients with severe OSA were not well represented. This is especially relevant in the case of women, where the small number of women with a RDI $\geq 14/h$ and with stage 2 hypertension incidence, may reflect low study power rather than a lack of statistical significance for the association between OSA and stage 2 hypertension. Balancing these limitations, this study has several strengths that lend confidence to our findings: it was a prospective study, which lends support to the evidence of a causal role of OSA in hypertension development; our subjects were from the general population, thus minimizing selection bias; the sample size was large and included a similar proportion of men and women and the follow-up period was prolonged (7.5 ± 0.8 years).

Conclusions

In summary, our results suggest an association between OSA patients and the risk of developing stage 2 hypertension in men. Increasing age was a significant factor explaining the presence of hypertension in men and women. Neither symptoms (EDS) nor nocturnal hypoxia were independently associated with the incidence of hypertension.

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ACCEPTED MANUSCRIPT

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TABLES

Table 1. Baseline characteristics of normotensive patients at baseline included in the hypertension incidence analysis.

Characteristics	All (n = 1155)	Men (M) (n = 505)	Women (W) (n = 650)	M/W p
Age (years)	44.0 [37.0-52.0]	46.0 [39.0-54.0]	43.0 [37.0-50.3]	< 0.001
BMI (Kg/m ²)	24.7 [22.6-27.0]	25.8 [23.9-27.7]	23.7 [21.5-26.0]	< 0.001
Neck circumference (cm)	36.0 [33.0-39.5]	40.0 [38.0-42.0]	33.0 [32.0-35.0]	< 0.001
DM	56 (4.9)	25 (5.2)	31 (4.8)	0.749
EDS ^a	209 (18.1)	105 (20.8)	104 (16.0)	0.036
Habitual Snoring ^b	281 (26.8)	149 (35.6)	132 (21.0)	< 0.001
Smoking ^c	690 (59.7)	361 (71.5)	329 (50.6)	< 0.001
Alcohol use	503 (44.4)	321 (66.6)	182 (28.0)	< 0.001
Fitness level	561 (49.6)	263 (54.6)	298 (45.8)	0.004
Hormonal status				
Premenopausal	436 (67.4)		436 (67.4)	
Perimenopausal	26 (4.0)	-	26 (4.0)	-
Postmenopausal	185 (28.6)		185 (28.6)	
RDI (events/h)	4.0 [2.0-8.0]	5.0 [2.0-11.0]	3.0 [2.0-6.3]	< 0.001
RDI 0-2.9	366 (31.7)	130 (25.7)	236 (36.3)	< 0.001
RDI 3-6.9	417 (36.1)	165 (32.7)	252 (38.8)	0.032
RDI 7-13.9	240 (20.8)	126 (25.0)	114 (17.5)	0.002
RDI ≥ 14	132 (11.4)	84 (16.6)	48 (7.4)	< 0.001
RDI ≥ 30	18 (1.6)	10 (2.0)	8 (1.2)	0.308
CT90	0.0 [0.0-2.0] 5.7 ± 17.7 ^d	1.0 [0.0-5.0] 10.5 ± 24.5 ^d	0.0 [0.0-1.0] 1.8 ± 7.0 ^d	< 0.001
ODI	4.0 [2.0-9.0]	5.0 [2.0-10.0]	4.0 [2.0-8.0]	< 0.001
SBP (mm Hg)	119.0 [110.0-126.0]	122.0 [116.0-130.0]	114.0 [107.0-124.0]	< 0.001
DBP (mm Hg)	76.0 [70.0-80.0]	79.0 [73.0-80.5]	73.0 [68.0-80.0]	< 0.001

Data are presented as median [25th-75th percentiles] or number of patients (%) unless otherwise stated.

^a EDS was defined as sleepiness for at least 3 or more days a week during the past 3 months in one or more of the following: after waking, during free time (leisure time), at work or driving, or during daytime in general according to the Basic Nordic Sleep Questionnaire.²⁶

^b habitual snoring was defined as snoring more than five days per week.

^c current and former included.

^d mean \pm standard deviation.

Abbreviations: BMI: body-mass index; DM: diabetes mellitus; EDS: excessive daytime sleepiness; RDI: respiratory disturbance index; CT90: cumulative time percentage with SaO₂ <90%; ODI: oxygen desaturation index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Follow-up characteristics of normotensive patients at baseline.

Characteristics	All (n = 1155)	Men (M) (n = 505)	Women (W) (n = 650)	M/W p
Time of follow up (years)	7.4 [6.9-8.0]	8.2 [7.6-8.7]	7.1 [6.8-7.4]	< 0.001
Age (years)	51.9 [45.0-59.7]	54.0 [47.0-62.0]	50.0 [43.7-57.7]	< 0.001
BMI (kg/m ²)	25.7 [23.4-28.2]	27.1 [25.1-29.2]	24.3 [22.3-26.8]	< 0.001
Change in weight (kg)	2.0 [1.0-3.0] 2.1 ± 4.0 ^a	2.0 [0.0-5.0] 2.6 ± 5.0 ^a	2.0 [1.0-3.0] 1.7 ± 2.9 ^a	< 0.001
SBP (mm Hg)	126.7 [120.0-138.3]	130.0 [120.0-140.0]	123.3 [116.7-133.3]	< 0.001
DBP (mm Hg)	80.0 [73.3-86.7]	80.0 [76.7-90.0]	80.0 [70.0-83.3]	< 0.001
Hypertension follow-up				
No hypertension	770 (66.7)	289 (57.2)	481 (74.0)	< 0.001
Stage 1 hypertension	295 (25.5)	147 (29.1)	148 (22.8)	0.014
Stage 2 hypertension	90 (7.8)	69 (13.7)	21 (3.2)	< 0.001

Data are presented as median [25th-75th percentiles] or number of patients (%) unless otherwise stated.

^a mean ± standard deviation.

Abbreviations: BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Change in weight was defined as the difference between follow-up and baseline weight.

Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or current treatment with antihypertensive medication.

Stage 1 hypertension included all subjects with SBP 140-159 mmHg and/or DBP 90-99 mmHg.

Stage 2 hypertension included subjects with SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg or those currently treated with antihypertensive medication.

Table 3. Odds ratios (OR) of the incidence of stage 2 hypertension according to the RDI.

RDI by subgroups	Hypertension frequency n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
0-2.9 (n = 366)	14 (3.8)	1	1
3-6.9 (n = 417)	25 (6.0)	1.60 (0.82-3.13)	1.22 (0.61-2.44)
7-13.9 (n = 240)	26 (10.8)	3.06 (1.56-5.98)	1.69 (0.83-3.45)
≥ 14 (n = 132)	25 (18.9)	5.87 (2.95-11.70)	2.51 (1.18-5.33)
n = 1155	n = 90		
	P trend	< 0.001	0.017

^a adjusted for sex, age, BMI and neck circumference

Abbreviations: RDI: respiratory disturbance index.

Table 4. Adjusted odds ratios (OR) for the incidence of stage 2 hypertension according to the RDI and stratified by sex.

Men			Women		
RDI by subgroups	Hypertension frequency n (%)	Adjusted OR ^a (95% CI)	RDI by subgroups	Hypertension frequency n (%)	Adjusted OR ^a (95% CI)
0-2.9 (n = 130)	11 (8.5)	1	0-2.9 (n = 236)	3 (1.3)	1
3-6.9 (n = 165)	21 (12.7)	1.42 (0.65-3.10)	3-6.9 (n = 252)	4 (1.6)	0.73 (0.15-3.47)
7-13.9 (n = 126)	18 (14.3)	1.53 (0.67-3.47)	7-13.9 (n = 114)	8 (7.0)	1.99 (0.46-8.61)
≥ 14 (n = 84)	19 (22.6)	2.54 (1.09-5.95)	≥ 14 (n = 48)	6 (12.5)	2.14 (0.40-11.36)
n = 505	n = 69		n = 650	n = 21	
	P trend	0.032		P trend	0.371

^a adjusted for age, BMI and neck circumference.

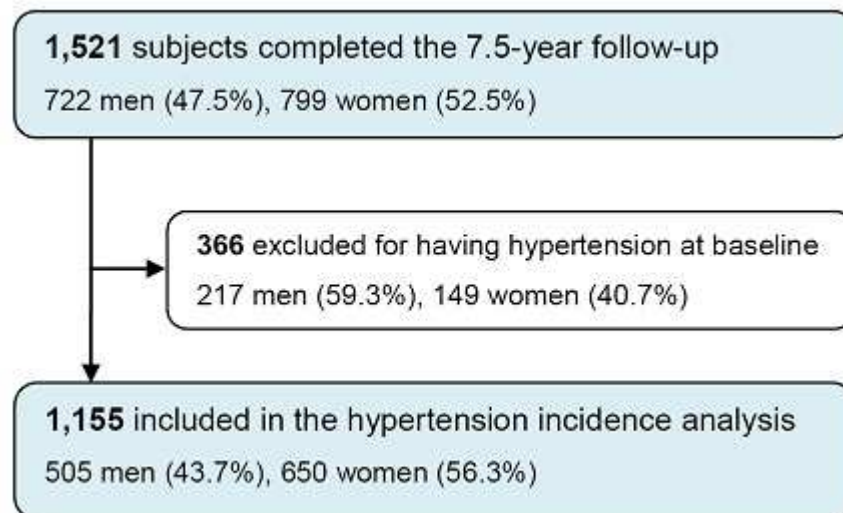
Abbreviations: RDI: respiratory disturbance index.

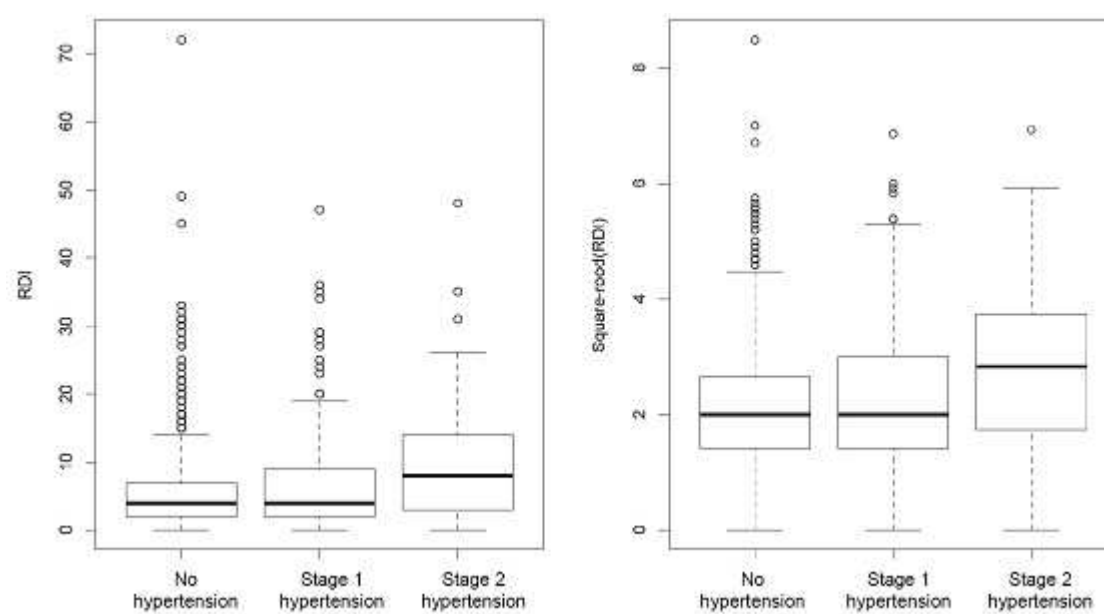
Table 5. Risk subgroups for Stage 2 hypertension incidence obtained by the recursive partitioning method.

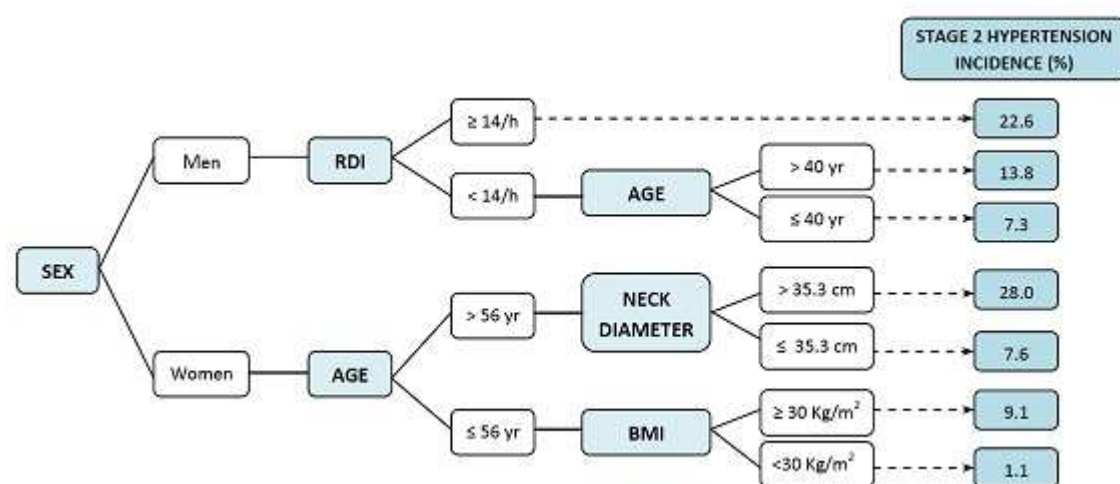
Node	Risk subgroup	Stage 2 hypertension incidence		OR (95% CI)	p
		N	%		
1	Women > 56 years and neck diameter > 35.3 cm	7/25	28.0%	33.70 (10.28-110.50)	< 0.001
2	Men and RDI \geq 14/h	19/84	22.6%	25.33 (9.76-65.73)	< 0.001
3	Men and RDI < 14/h and > 40 years	41/297	13.8%	13.88 (5.82-33.12)	< 0.001
4	Women \leq 56 years and obese ^a	3/33	9.1%	8.67 (2.07-36.36)	0.003
5	Women > 56 years and neck diameter < 35.3 cm	5/66	7.6%	7.10 (2.11-23.97)	0.002
6	Men and RDI < 14 and \leq 40 years	9/124	7.3%	6.78 (2.37-19.43)	< 0.001
7	Women \leq 56 years and non-obese ^a	6/526	1.1%	1	

Abbreviations: N: number of patients; RDI: respiratory disturbance index.

^a Obesity was defined as BMI \geq 30 Kg/m².









e-Table 1. Predictive factors for the incidence of stage 2 hypertension, according to univariate and multivariate analyses.

Variables n=1155	Univariate analysis				Multivariate analysis			
	B	Standard error	OR (95% CI)	p	B	Standard error	OR (95% CI)	p
Sex (men)	1.556	0.257	4.74 (2.87-7.84)	<0.001	1.618	0.413	5.04 (2.25-11.33)	<0.001
Age (years)	0.054	0.011	1.06 (1.03-1.08)	<0.001	0.034	0.012	1.03 (1.01-1.06)	0.005
BMI (kg/m²)	0.181	0.030	1.20 (1.13-1.27)	<0.001	0.148	0.040	1.16 (1.07-1.25)	<0.001
Weight change^a (kg)	0.018	0.027	1.02 (0.97-1.07)	0.507				
Neck circumference (cm)	0.167	0.027	1.18 (1.12-1.25)	<0.001	-0.051	0.050	0.95 (0.86-1.05)	0.311
DM	0.388	0.447	1.47 (0.61-3.54)	0.386				
EDS^b	0.849	0.240	2.34 (1.46-3.74)	<0.001				
Smoking^c	-0.088	0.222	0.92 (0.59-1.42)	0.693				
Alcohol	0.518	0.225	1.68 (1.08-2.61)	0.021				
Fitness activity (no)	-0.044	0.223	0.96 (0.62-1.48)	0.844				
Postmenopause	2.029	0.524	7.61 (2.72-21.25)	<0.001				
RDI 0-2.9			<0.001					0.064
RDI 3-6.9	0.472	0.342	1.60 (0.82-3.13)	0.167	0.197	0.354	1.22 (0.61-2.44)	0.578
RDI 7-13.9	1.117	0.343	3.06 (1.56-5.98)	0.001	0.527	0.363	1.69 (0.83-3.45)	0.147
RDI ≥ 14	1.771	0.352	5.87 (2.95-11.70)	<0.001	0.920	0.384	2.51 (1.18-5.33)	0.017
CT90	0.013	0.004	1.01 (1.00-1.02)	0.005				
ODI	0.040	0.010	1.04 (1.02-1.06)	<0.001				

^a Change in weight was defined as the difference between follow-up and baseline weight.

^b EDS was defined as sleepiness for at least 3 or more days a week during the past 3 months in one or more of the following: after waking, during free time (leisure time), at work or driving, or during daytime in general according to the Basic Nordic Sleep Questionnaire.²⁶

^c current and former included.

Abbreviations: BMI: body-mass index; DM: diabetes mellitus; EDS: excessive daytime sleepiness; RDI: respiratory disturbance index; CT90: cumulative time percentage with SaO₂ <90%; ODI: oxygen desaturation index; OR: odds ratio.