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### ► To cite this version:

Vanessa Bironneau, Renaud Tamisier, Wojciech Trzepizur, Ramaroson Andriantsitohaina, Mathieu Berger, et al.. Sleep apnoea and endothelial dysfunction: An individual patient data meta-analysis. *Sleep Medicine Reviews*, 2020, 52, pp.101309. 10.1016/j.smr.2020.101309 . hal-03048015

**HAL Id: hal-03048015**

**<https://hal.science/hal-03048015v1>**

Submitted on 17 Dec 2020

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**Sleep apnoea and endothelial dysfunction: an individual patient data meta-analysis.**

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### **Conflict of interest**

FGag reports personal fees from AIR LIQUIDE SANTE, CIDELEC, RESMED, SEFAM, outside the submitted work; non-financial support from AIR LIQUIDE SANTE, ASTEN SANTE, SEFAM, outside the submitted work.

JLP reports grants from AGIRADOM, AIR LIQUIDE FOUNDATION, PHILIPS RESPIRONICS, RESMED, SEFAM, VITALAIR, outside the submitted work; personal fees from AGIRADOM, ITAMAR, JAZZ PHARMACEUTICALS, PHILIPS RESPIRONICS, RESMED, SEFAM, outside the submitted.

VB, RT, WT, RA, Mathieu Berger, FGou, MJF, IJD, SL, MLV, MCM, and FR report no conflict of interest.

### **Funding**

JLP, IJD, MJF and RT are supported by a research grant from the French National Research Agency (ANR-12-TECS-0010), in the framework of the “Investissements d’avenir” program (ANR-15-IDEX-02) and the “e-health and integrated care” Chair of excellence from the Grenoble Alpes University Foundation.

### **Acknowledgements**

We are grateful to the co-authors who made this meta-analysis possible by accepting to share their individual patient data.

## Summary

We performed an individual patient data meta-analysis to investigate the association between obstructive sleep apnoea (OSA) severity and the reactive hyperaemia index (RHI) measured by peripheral arterial tonometry (PAT), a validated measurement of endothelial function, and a strong predictor of late cardiovascular (CV) events. Patients from 12 studies underwent PAT and overnight polysomnography or respiratory polygraphy for suspected OSA. Endothelial dysfunction was defined by a log-transformed  $RHI < 0.51$ . Subgroup analyses were performed to investigate this relationship in specific populations. Among 730 patients without overt CV disease, 387 (53.0%) had severe OSA (apnoea-hypopnea index  $\geq 30$ ) and 164 (22.5%) exhibited endothelial dysfunction. After adjustment for age, gender, diastolic blood pressure, obesity, diabetes and **chronic obstructive pulmonary disease**, endothelial dysfunction was associated with severe OSA (odds ratio, OR [95% confidence interval]: **2.27 [1.12-4.60];  $p=0.02$** ), and nocturnal hypoxemia defined by  $>20$  minutes with oxygen saturation  $<90\%$  (**OR: 1.83 [1.22-2.92];  $p=0.004$** ) or mean oxygen saturation  $<92\%$  (**OR: 1.52 [1.17-1.96];  $p=0.002$** ). On subgroup analyses, the association between severe OSA and endothelial dysfunction was not significant in patients with hypertension, obesity and/or diabetes. Among adults without overt CV disease, severe OSA is independently associated with an increased risk of endothelial dysfunction that may predispose to late CV events.

**Key words:** obstructive sleep apnoea, endothelial function, reactive hyperaemia index

## **Abbreviations**

AHI: apnoea-hypopnoea index

BMI: body mass index

CV: cardiovascular

**COPD: chronic obstructive pulmonary disease**

FMD: Flow-mediated dilatation

IPDMA: individual patient data meta-analysis

OSA: Obstructive sleep apnoea

PAT: Peripheral arterial tonometry

PSG: Polysomnography

PWV: Pulse-wave velocity

RHI: Reactive hyperaemia index

RP: respiratory polygraphy

T90: sleep time with SaO<sub>2</sub> <90%

SaO<sub>2</sub>: oxyhaemoglobin saturation SaO<sub>2</sub>

## **Introduction**

The endothelium plays important roles in modulating vascular tone by synthesizing and releasing endothelium-derived relaxing factors. Endothelial dysfunction caused by reduced production or action of endothelium-derived relaxing factors is considered to be an initial step toward cardiovascular (CV) disease in at-risk patients [1,2]. In the clinical setting, non-invasive evaluation of peripheral endothelial function constitutes an excellent surrogate marker for prediction of incident CV events [2]. Many studies have correlated endothelial dysfunction with CV risk in patients with risk factors such as systemic hypertension, diabetes mellitus, dyslipidaemia and obesity/insulin resistance [3]. A recent systematic review and meta-analysis showed that brachial artery flow-mediated dilation (FMD), and reactive hyperaemia index (RHI) determined by peripheral arterial tonometry (PAT) significantly predicted CV events, with similar reliability [4]. From a technical viewpoint, PAT offers the advantages of being completely non-invasive, easy to perform, and less prone to inter-observers variability and thus more reproducible than FMD [3,5].

Evidence from population- and clinic-based cohort studies supports a causal association between obstructive sleep apnoea (OSA) and the incidence of CV diseases, including hypertension, coronary heart disease, arrhythmia, heart failure, and stroke [6,7]. Endothelial dysfunction is considered to be a key trigger mechanism linking OSA and its hypoxia-related consequences with CV morbidity [8,9]. Given the marked heterogeneity of OSA in terms of clinical phenotypes [10,11], comorbidities and health outcomes [12], endothelial function could be used as a predictive tool to more accurately identify OSA patients with preclinical vascular disease at high risk of subsequent CV events. However, the evidence of the relationship between OSA and endothelial dysfunction needs to be strengthened, taking into account indices of sleep-disordered breathing severity and influencing covariates. Previous systematic reviews and meta-analyses in the field have included heterogeneous studies with a

limited description of comorbid conditions with a potential important contribution to OSA-associated CV risk, such as hypertension and metabolic disorders [9,13–15]. Furthermore, the majority of these studies were small single-centre studies evaluating endothelial function by FMD which is subject to intra- and inter-operator variability [3,5]. Approaches using individual patient data meta-analysis (IPDMA) do not aggregate summary data, but address study questions by including actual patient data from different data sources [16]. Using individual data of OSA indices of severity overcomes limitations related to the selective cut-offs used in previous publications and allows specific subgroup analyses. Individual patient data concerning confounders allow more reliable adjustment.

The aim of this IPDMA was to investigate with appropriate adjustment for confounders the relationship between OSA severity indices and RHI, a validated and reproducible measurement of endothelial function.

## **Methods**

We pooled individual data from patients with clinical suspicion of OSA and no overt CV disease involved in 12 separate studies (7 randomized controlled trials and 5 observational studies) initiated between 2007 and 2013 by the Departments of Respiratory and Sleep Medicine of Angers and Grenoble University Hospitals. Only data obtained at the baseline evaluation of interventional and observational studies were included in the present IPDMA. Patients with technical failure of PAT and/or history of CV disease, including coronary heart disease, heart failure, arrhythmias, and stroke, were excluded from the studies. All studies were approved by an independent Ethics Committee, and were conducted in accordance with applicable good clinical practice requirements in Europe, French law, ICH E6 guidelines and the ethical principles of the Helsinki Declaration (1996 and 2000). All randomized controlled trials were registered on the ClinicalTrials.gov site (online supplementary Table S1).

### ***Clinical evaluation***

All clinical examinations and evaluations were conducted during the morning following sleep studies. Clinical evaluation included anthropometric data, smoking habits, medical history, medication use and questionnaires. Obesity was defined by a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>. Excessive daytime sleepiness was assessed by the Epworth sleepiness score [17]. Clinic blood pressure was measured using a periodically calibrated mercury sphygmomanometer and an appropriate cuff size. Recorded blood pressure was the average of 3 consecutive readings during a 5-min period following at least 5 min of rest in the sitting position. Only patients who were previously diagnosed as hypertensive and who were taking antihypertensive medication were considered to have hypertension. Diabetes was defined on the basis of current use of antidiabetic medications and dyslipidaemia was defined on the basis of current use of lipid-lowering medications. **Chronic obstructive pulmonary disease (COPD) was defined as a physician diagnosis combined with treatment with appropriate medication.**

### ***Sleep studies***

All patients were investigated for suspected OSA using overnight in-laboratory respiratory polygraphy (RP), or polysomnography (PSG) while breathing spontaneously to characterize abnormal respiratory events during sleep. Recorded data included nasal-oral airflow (thermistor and nasal pressure cannula), chest and abdominal wall motion (respiratory inductance plethysmograph belts), arterial oxygen saturation (finger oximetry), body position and electrophysiological signals for sleep evaluation (PSG). Respiratory events were scored manually using recommended criteria [18]. The apnoea–hypopnoea index (AHI) was calculated as the number of apnoea and hypopnoea events per hour of sleep (PSG) or recording (RP).



### ***Assessment of endothelial function***

As previously described [19], endothelial function was assessed in the morning following the sleep study by digital pulse amplitude, using PAT (EndoPAT<sup>®</sup>, Itamar Medical Ltd., Caesarea, Israel). All participating centres followed the same procedure. Patients laid down in a quiet room with probes mounted on both index fingers and a blood pressure cuff around the right arm above the elbow for the hyperaemia testing. The left finger was used as the control. Finger arterial pulse wave amplitude was recorded throughout the protocol which included 3 consecutive stages each of 5 min duration: 1-baseline recording; 2-occlusion of the brachial artery by inflating the blood pressure cuff to 50 mm Hg above the baseline systolic pressure and 3-post-occlusion recording after deflation of the cuff to measure of the generated reactive hyperaemia response. The RHI was calculated by a computer in an operator-independent manner, as the ratio of the average amplitude of the PAT signal post- to pre-occlusion of the tested arm, normalized to the concurrent signal from the contralateral finger. The log-transformed ratio, expressed as Ln-RHI, was calculated from the same ratio between the digital pulse volume during reactive hyperaemia and at baseline. Based on previous reports [20–22], a Ln-RHI cut-off value <0.51 was used to define the presence of significant endothelial dysfunction.

### ***Statistical analysis***

The IPDMA has been performed in accordance with the PRISMA-IPD Statement (see online Supplement for PRISMA-IPD checklist) and submitted for registration in PROSPERO. Results are expressed as percentages, mean (standard deviation, SD) and odds ratio (OR), 95% confidence interval (CI). Statistical comparisons were performed using the Chi<sup>2</sup> test for categorical variables and the unpaired t-test for continuous variables. The primary dependent variable of interest was the presence of endothelial dysfunction (Ln-RHI <0.51). Factors significantly associated with endothelial dysfunction were introduced in a multivariate logistic

mixed model with a random effect by study. The primary independent variables included the AHI and 2 different indices of nocturnal hypoxemia, mean oxyhemoglobin saturation (SaO<sub>2</sub>) during sleep and sleep time with SaO<sub>2</sub> <90% (T90). The following commonly used cut-offs for AHI were used to define categories of OSA severity: <5 (no OSA), 5 to <30 (mild-to-moderate OSA), ≥30 (severe OSA). The study sample was grouped into tertiles for the 2 nocturnal hypoxemia indices. To avoid potential bias when choosing an RHI cut-off value for endothelial dysfunction, multivariate linear mixed models with a random effect by study were performed to characterize the associations between Ln-RHI as a continuous variable and indices of OSA severity. In order to estimate the effect size of increasing OSA severity on endothelial function, adjusted means of Ln-RHI were calculated according to categories of OSA severity. Subgroup analyses were performed to determine whether there were any differences across categories of patients with OSA.

According to the DerSimonian and Laird method we use a two-level random logistic model to assess the heterogeneity between studies. The model provided an estimation of RHI variability between and within studies. The i<sup>2</sup> consistency index deducted from these estimations provided an estimation of the part of variation due to heterogeneity. An i<sup>2</sup> index greater than 60% reflects high heterogeneity. The result of the model estimation showed that the variation of RHI between studies is statistically significant (p=0.028) but the i<sup>2</sup> index was estimated at 12%, which means that only limited heterogeneity was observed across the 12 studies.

All statistical analyses were performed with SAS software (SAS/STAT Package 2002–2003; SAS Institute Inc., Cary, NC). A two-tailed p value < 0.05 was considered significant.

## Results

The details of the 12 studies included in the IPDMA are presented in the online supplement (Table S1). Seventy-two of the 802 eligible patients were excluded due to history of CV disease (n=42) or PAT technical failure (n=30). Our final sample size comprised 730 patients with clinical suspicion of OSA and no overt CV disease (Figure 1). Patient characteristics according to the original studies are presented in the online supplement (Table S2). As shown in Table 1, the prevalence of endothelial dysfunction increased from 14.9% in the no OSA group, to 26.9% in patients with severe OSA (p=0.0086). As expected, patients with severe OSA were older, with a marked male predominance, higher prevalence of obesity and hypertension. **There were also significant differences between OSA categories for COPD prevalence.** Patients with endothelial dysfunction were characterized by higher prevalence's of obesity, diabetes and severe OSA, and higher diastolic blood pressure compared to subjects with normal endothelial function (Table 2).

On multivariate analysis, severe OSA was significantly associated with an increased risk of endothelial dysfunction (**OR [95%CI], 2.27 [1.12-4.60]**) after adjustment for age, gender, diastolic blood pressure, obesity, diabetes and **COPD** (Figure 2). We further investigated the association between endothelial dysfunction and 2 indices of nocturnal hypoxemia. As shown in Table 3, increasing nocturnal hypoxemia, as assessed by mean SaO<sub>2</sub> and T90, was associated with a significant increase in the risk of endothelial dysfunction after adjustment for confounders.

Multivariate regression analyses were also performed to characterize the association between categories of OSA severity and Ln-RHI as a continuous variable. Figure 3 presents adjusted mean **[95%CI]** values of Ln-RHI according to tertiles of T90 and mean SaO<sub>2</sub>. The adjusted mean value of Ln-RHI decreased from **0.76 [0.71-0.80]** in the lowest tertile of T90 to **0.69**

[0.66-0.71] in the highest tertile ( $p=0.0004$ ), and from 0.75 [0.71-0.78] in highest tertile of mean SaO<sub>2</sub> to 0.68 [0.65-0.72] in the lowest tertile ( $p<0.0001$ ).

On subgroup analyses, the association between severe OSA and endothelial dysfunction was not significant in patients with hypertension, obesity and/or diabetes. (see figure S1 in the online supplement).

## **Discussion**

To the best of our knowledge, this is the first IPDMA evaluating the association between OSA severity and endothelial dysfunction with appropriate adjustment for confounding factors. Our study included a relatively large sample of typical OSA patients, predominantly male, without overt CV disease. All data were obtained using standard operating procedures and a validated measurement of endothelial function with low inter-observer variability. We found that both severe OSA and nocturnal hypoxemia were significantly associated with an increased risk of endothelial dysfunction after adjustment for age, gender, diastolic blood pressure, metabolic comorbidities and COPD.

Recent reviews and meta-analyses have concluded that moderate-to-severe OSA might impair endothelial function [9,13]. By pooling the summary data from 11 case-control studies including a total of 445 subjects, Wang et al. found that endothelial function assessed by FMD was lower in patients with OSA than in controls[13]. The authors performed meta-regression to examine the impact of potential confounders on OSA-related changes in FMD. In the whole OSA population, the association between OSA and FMD was significantly modified by BMI and serum triglycerides. Conversely, none of the confounders significantly modified the association in the subgroup of patients with moderate-to-severe OSA. However, this meta-analysis has potential limitations related the use of FMD that may be prone to intra- and inter-operator variability [3,5], heterogeneity of small single-centre studies, and the exclusion of patients with traditionally known CV risk factors, such as hypertension, diabetes,

dyslipidaemia. By pooling pulse-wave velocity (PWV) data from 5 case-control studies including 253 patients, Wang et al. also concluded that OSA increased arterial stiffness [13]. This finding was not confirmed by a recent IPDMA [15]. This meta-analysis used individual patient data from 9 studies performed by the same centre with 893 well-characterized patients and PWV measured using the same technique for all studies. The authors concluded that the elevation of arterial stiffness in patients with OSA was driven more by conventional CV risk factors (age, hypertension and the presence of diabetes) than by indices of sleep-disordered breathing severity [15]. The current IPDMA provides evidence to support an independent association between OSA severity and endothelial dysfunction after adjustment for traditional CV risk factors. Several factors may have contributed to this apparent discrepancy. Joyeux-Faure et al. included patients with a very high prevalence of hypertension (78%) and diabetes (45%) [15]. In line with previous reports from large clinic-based cohort studies [10,23], the prevalence of hypertension and diabetes was markedly lower in our IPDMA (39 and 15%, respectively). Another issue concerns a possible lack of correlation between endothelial function and arterial stiffness indices in patients with OSA. The major determinants of reflection wave magnitude are the vascular characteristics of the arterial branching regions and impedance mismatch between proximal and distal arteries, rather than the degree of peripheral vascular reactivity [24]. Recent studies have shown no correlation between endothelial function assessed by PAT and arterial stiffness measured by augmentation index and PWV in patients with hypertension or acute ischaemic stroke [24,25].

Several mechanisms might be involved in the pathophysiology of endothelial dysfunction in patients with OSA [26]. OSA is recognized as a condition that causes oxidative stress and systemic inflammation, resulting in a reduction in nitric oxide availability [27,28]. OSA is associated with increased levels of adhesion molecules (intracellular adhesion molecule-1 [ICAM-1], the vascular cell adhesion molecule-1 [VCAM- 1] and E-selectin), as well as

several disorders of coagulation and lipid metabolism [26]. Moreover, recent findings suggest that circulating micro particles might also contribute to the pathophysiology of OSA-associated vascular impairment by promoting endothelial dysfunction, inflammation and vascular hyper reactivity [29]. OSA, hypertension and diabetes are frequently associated and share several intermediate mechanisms that contribute to the development of endothelial dysfunction and CV diseases, including reduced plasma nitric oxide level, increased generation of reactive oxygen species, increased leukocyte adhesion to the vascular wall and consequent inflammatory load in the vasculature [30]. In our IPDMA, OSA severity and nocturnal hypoxemia were associated with endothelial dysfunction independent of major CV risk factors, but the subgroup analysis suggested that the association might be less significant in the presence of hypertension, obesity and diabetes. In line with a recent trial showing no impact of OSA therapy on endothelial function in patients with multiple CV risk factors [31], these findings suggest that hypertension and diabetes have major vascular adverse effects, and that endothelial dysfunction could not be made any worse by OSA. However, the result from our subgroup analysis need to be interpreted with caution due to unbalanced sample sizes. It might simply reflect a lack of statistical power as hypertension, obesity and diabetes accounted for only 38.6, 30.4 and 15.5% of the entire cohort respectively. A recent study found that moderate-to-severe OSA was associated with endothelial dysfunction assessed by FMD among subjects with metabolic syndrome but not among subjects with normal metabolic function [32]. However, this population-based study included less than 5% of severe OSA. Using laser speckle contrast imaging in patients with diabetes, Tahrani et al. found that OSA was not associated with endothelial-dependent micro-vascular reactivity after adjustment for confounders [33].

The main limitation of our IPDMA is the observational design of the eligible studies, which prevents the demonstration of any temporal or causal relationship between severe OSA and

endothelial dysfunction. Further studies are required to investigate whether PAT assessment of endothelial function predicts CV outcomes in patients with OSA. As up to 50% of OSA patients are minimally symptomatic [34], targeting CV outcomes has emerged as a therapeutic objective in patients with OSA. Endothelial function assessment also has a potential value in identifying responders and non-responders to therapy [3,35]. Previous randomized controlled trials found no impact of continuous positive airway pressure or mandibular advancement therapy of OSA on endothelial function assessed by PAT [19,31,36]. However, these studies had potential limitations including small sample size [36], the inclusion of patients with multiple CV risk factors [31] or baseline RHI values within the normal range [19]. Future interventional studies should evaluate whether improvement of endothelial function after OSA therapy predicts a better CV prognosis in patients who exhibit endothelial dysfunction at diagnosis.

In conclusion, among adults without overt CV disease, severe OSA is independently associated with an increased risk of endothelial dysfunction that may predispose to a higher risk of late CV events.

**Practices points**

1. Endothelial dysfunction is considered to be a key trigger mechanism linking OSA and its hypoxia-related consequences with CV morbidity
2. The RHI assessed by PAT is a validated measurement of endothelial function with low inter-observer variability and a strong predictor of late CV events in at-risk subjects
3. The present IPDMA demonstrates that among adults without overt CV disease, severe OSA and nocturnal hypoxemia are independently associated with an increased risk of endothelial dysfunction that may predispose to late CV events.

**Research agenda**

Future research should determine whether:

1. Endothelial dysfunction assessed by PAT predicts CV outcomes in patients with OSA
2. Improvement of endothelial function after OSA therapy predicts a better CV prognosis in patients who exhibit endothelial dysfunction at diagnosis.



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**Figure legends:**

**Figure 1:** Flow diagram of the subjects during the study.

Abbreviations: PAT, peripheral arterial tonometry; RP, respiratory polygraphy; PSG, polysomnography; OSA, obstructive sleep apnoea.

**Figure 2:** Adjusted odds ratio (OR) for endothelial function according to categories of obstructive sleep apnoea (OSA) severity.

OR were adjusted for age, gender, diastolic blood pressure, presence of obesity, diabetes and chronic obstructive pulmonary disease.

Abbreviations: CI, confidence interval.

**Figure 3:** Adjusted mean values of Ln-RHI according to indices of nocturnal hypoxemia.

Abbreviations: Ln-RHI, natural logarithmic transformation of the reactive hyperaemia index; T90, sleep time with oxygen saturation < 90%; SaO<sub>2</sub>, oxygen saturation; CI, confidence interval.

Mean values of Ln-RHI were adjusted for age, gender, diastolic blood pressure, presence of obesity, diabetes and chronic obstructive pulmonary disease.

**Table 1:** Characteristics of the study population according to categories of obstructive sleep apnoea severity

|                             | All          | No OSA       | Mild-to-moderate OSA | Severe OSA   | p value       |
|-----------------------------|--------------|--------------|----------------------|--------------|---------------|
| n                           | 730          | 67           | 276                  | 387          | -             |
| Age, years                  | 54.3 (11.6)  | 46.8 (12.3)  | 54.8 (11.8)          | 55.3 (11.0)  | <0.0001       |
| Females, %                  | 20.1         | 32.8         | 23.9                 | 15.3         | 0.0006        |
| BMI, kg/m <sup>2</sup>      | 28.7 (5.9)   | 26.9 (6.4)   | 27.9 (5.7)           | 29.6 (5.8)   | <0.0001       |
| Obesity, %                  | 30.4         | 25.4         | 21.7                 | 37.5         | <0.0001       |
| SBP, mmHg                   | 130.5 (16.0) | 124.7 (15.0) | 131.2 (15.4)         | 131.0 (16.4) | 0.0072        |
| DBP, mmHg                   | 78.1 (11.6)  | 73.4 (13.8)  | 77.2 (10.6)          | 79.5 (11.7)  | <0.0001       |
| Hypertension, %             | 38.6         | 25.4         | 32.6                 | 45.2         | 0.0003        |
| Diabetes, %                 | 15.5         | 18.2         | 17.5                 | 13.6         | 0.3243        |
| <b>COPD, %</b>              | <b>7.0</b>   | <b>6.0</b>   | <b>11.6</b>          | <b>3.9</b>   | <b>0.0006</b> |
| Dyslipidaemia               | 20.5         | 17.7         | 21.2                 | 20.4         | 0.8280        |
| Non-smokers, %              | 48.1         | 50.8         | 47.3                 | 48.2         | 0.8750        |
| Epworth score               | 9.3 (4.8)    | 8.2 (4.5)    | 9.0 (5.0)            | 9.8 (4.6)    | 0.0209        |
| EDS, %                      | 40.4         | 29.0         | 38.2                 | 44.3         | 0.0556        |
| T90, min                    | 32.9 (65.4)  | 14.3 (54.6)  | 22.5 (56.9)          | 45.1 (71.4)  | <0.0001       |
| Mean SaO <sub>2</sub> , %   | 92.8 (2.5)   | 94.1 (1.9)   | 93.1 (2.6)           | 92.4 (2.5)   | <0.0001       |
| Ln-RHI                      | 0.72 (0.27)  | 0.74 (0.25)  | 0.75 (0.27)          | 0.70 (0.27)  | 0.0490        |
| Endothelial dysfunction*, % | 22.5         | 14.9         | 18.1                 | 26.9         | 0.0086        |

Data are expressed as mean (standard deviation) or percentages.

Abbreviations: OSA, obstructive sleep apnoea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; **COPD, chronic obstructive pulmonary disease**; EDS, excessive daytime sleepiness (Epworth score > 10); T90, sleep time with oxygen saturation < 90%; SaO<sub>2</sub>, oxygen saturation; Ln-RHI, natural logarithmic transformation of the reactive hyperaemia index.

\* Endothelial dysfunction was defined by Ln-RHI<0.51

**Table 2:** Comparison of patients with and without endothelial dysfunction

|                           | No endothelial dysfunction<br>(Ln-RHI $\geq$ 0.51) | Endothelial dysfunction<br>(Ln-RHI $<$ 0.51) | p value       |
|---------------------------|--|--|---------------|
| n                         | 566  | 164  | -             |
| Age, years                | 54.1 (11.4)  | 55.2 (12.3)                                  | 0.2788        |
| Females, %                | 19.8   | 21.3   | 0.6639        |
| BMI, kg/m <sup>2</sup>    | 28.1 (5.8)   | 30.7 (6.0)                                   | <0.0001       |
| Obesity, %                | 26.1   | 45.1   | <0.0001       |
| SBP, mmHg                 | 130.4 (15.9)                                       | 130.6 (16.2)                                 | 0.9018        |
| DBP, mmHg                 | 77.6 (11.4)  | 79.7 (12.2)                                  | 0.0494        |
| Hypertension, %           | 37.8   | 41.5   | 0.3988        |
| Diabetes, %               | 11.3   | 29.9   | <0.0001       |
| Dyslipidaemia, %          | 20.6   | 20.1   | 0.9059        |
| <b>COPD, %</b>            | <b>8.0</b>   | <b>3.7</b>                                   | <b>0.0576</b> |
| Non-smokers, %            | 47.2   | 50.9   | 0.4074        |
| Epworth score             | 9.3 (4.8)  | 9.3 (4.8)                                    | 0.9805        |
| EDS, %                    | 40.6   | 39.9   | 0.8833        |
| No OSA, %                 | 10.1   | 6.1  | 0.0079        |
| Mild-to-moderate OSA, %   | 39.9   | 30.5   |               |
| Severe OSA                | 50.0   | 63.4   |               |
| AHI, n                    | 31.7 (23.2)  | 36.3 (23.5)                                  | 0.0264        |
| T90, min                  | 29.1 (58.8)  | 46.1 (83.2)                                  | 0.0218        |
| Mean SaO <sub>2</sub> , % | 93.1 (2.2)   | 92.0 (3.1)                                   | <0.0001       |

Data are expressed as mean (standard deviation) or percentages.

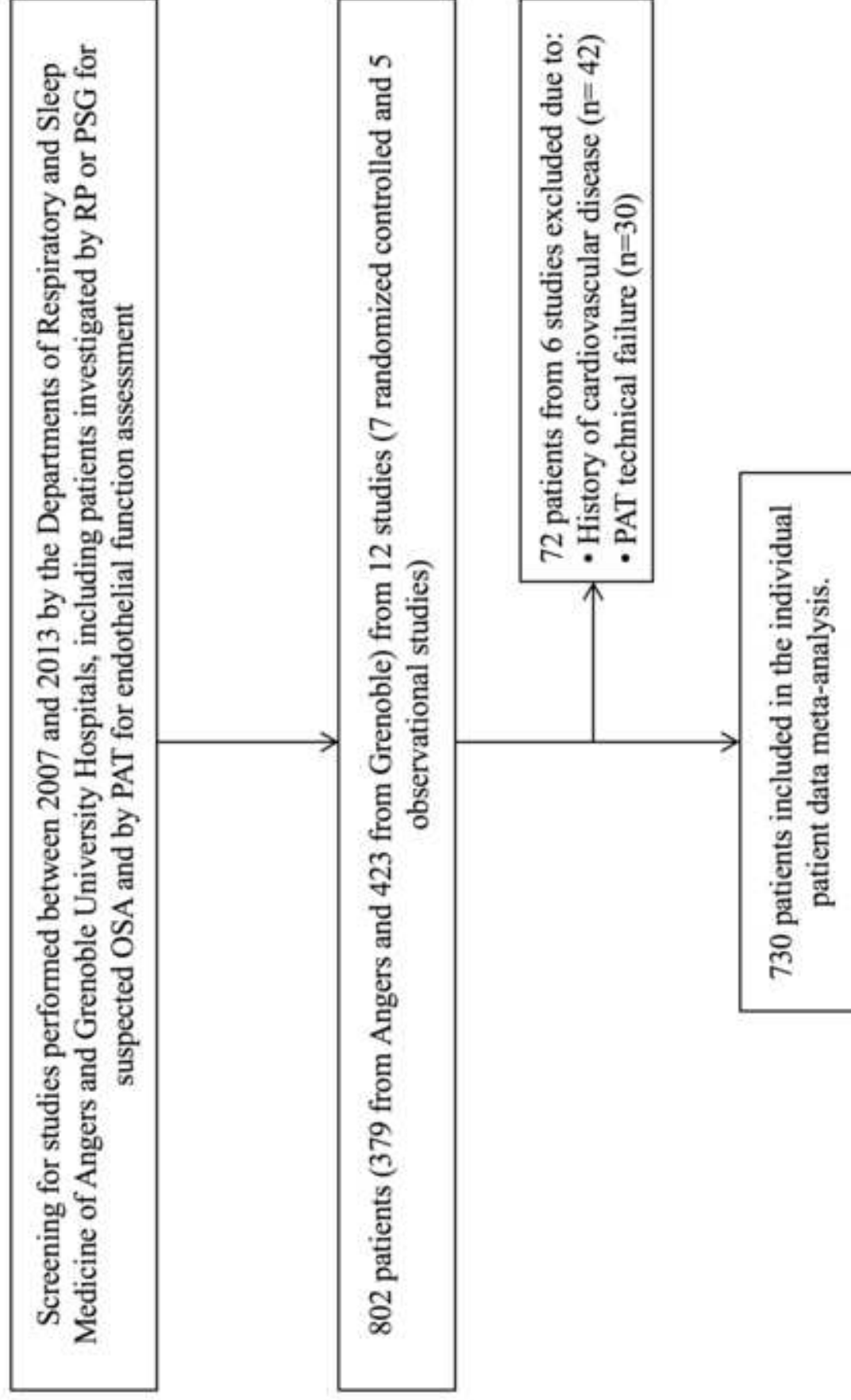
Abbreviations: OSA, obstructive sleep apnoea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; **COPD, chronic obstructive pulmonary disease**; EDS, excessive daytime sleepiness (Epworth score > 10); AHI, apnoea-hypopnoea index; T90, sleep time with oxygen saturation < 90%; SaO<sub>2</sub>, oxygen saturation; Ln-RHI, natural logarithmic transformation of the reactive hyperaemia index.

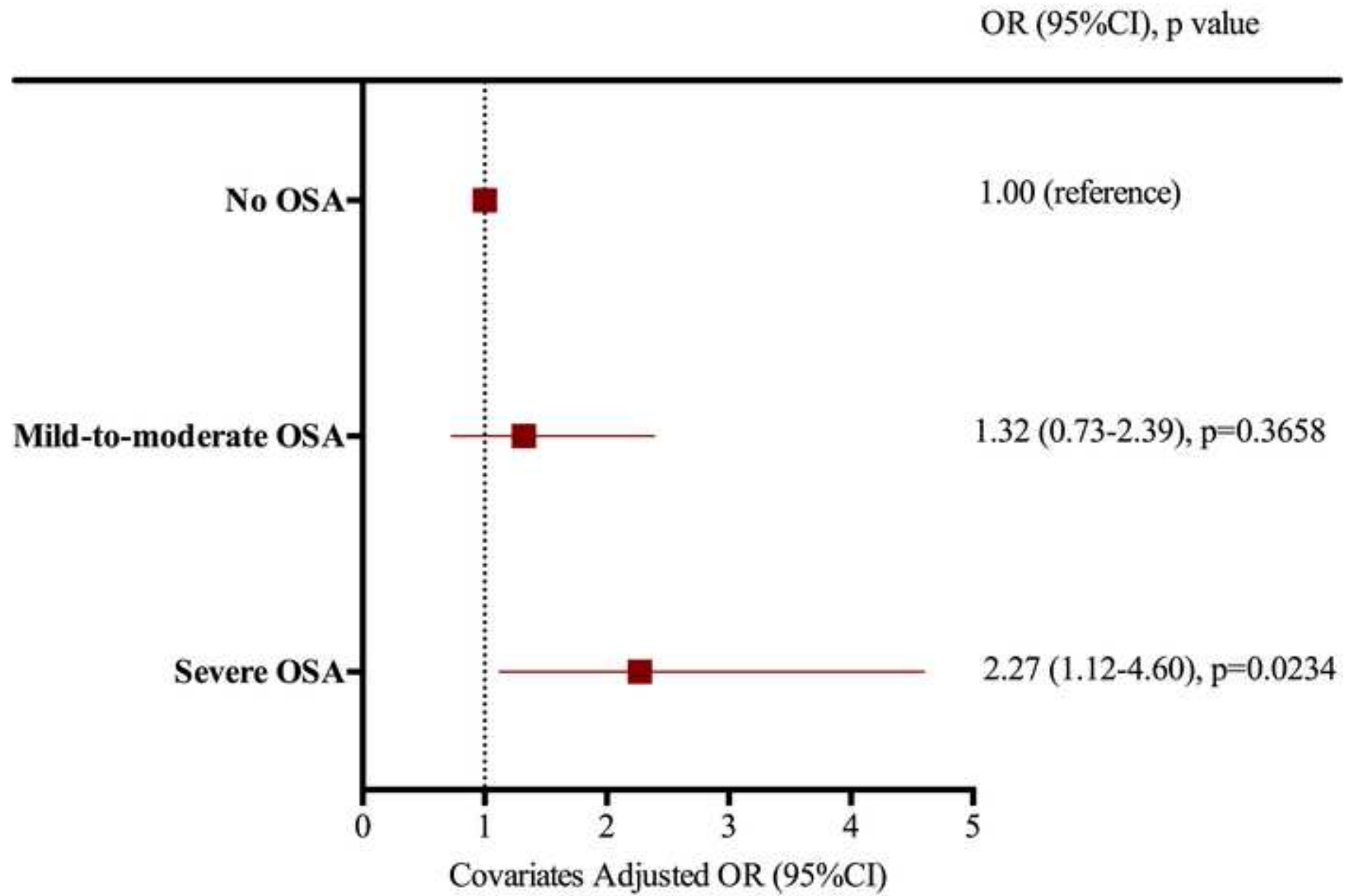


**Table 3:** Adjusted odds ratios for endothelial dysfunction according to variables of nocturnal hypoxemia.

| Predictor  | Adjusted odds ratio | 95% confidence interval | p value |
|--|---------------------|-------------------------|---------|
| Sleep time with oxygen saturation below 90%, min |                     |                         |         |
| <1.7 min (ref)                                   | 1                   | -                       | -       |
| 1.7-20 min                                       | 1.52                | 1.21-1.92               | 0.0003  |
| >20 min  | 1.83                | 1.22- 2.92              | 0.0041  |
| Mean oxygen saturation during sleep, %           |                     |                         |         |
| >94.0% (ref)                                     | 1                   | -                       | -       |
| 92-94.0%   | 1.32                | 1.04-1.69               | 0.0291  |
| <92%   | 1.52                | 1.17-1.96               | 0.0016  |

Odds ratios were adjusted for age, gender, diastolic blood pressure, presence of obesity, diabetes and chronic obstructive pulmonary disease.





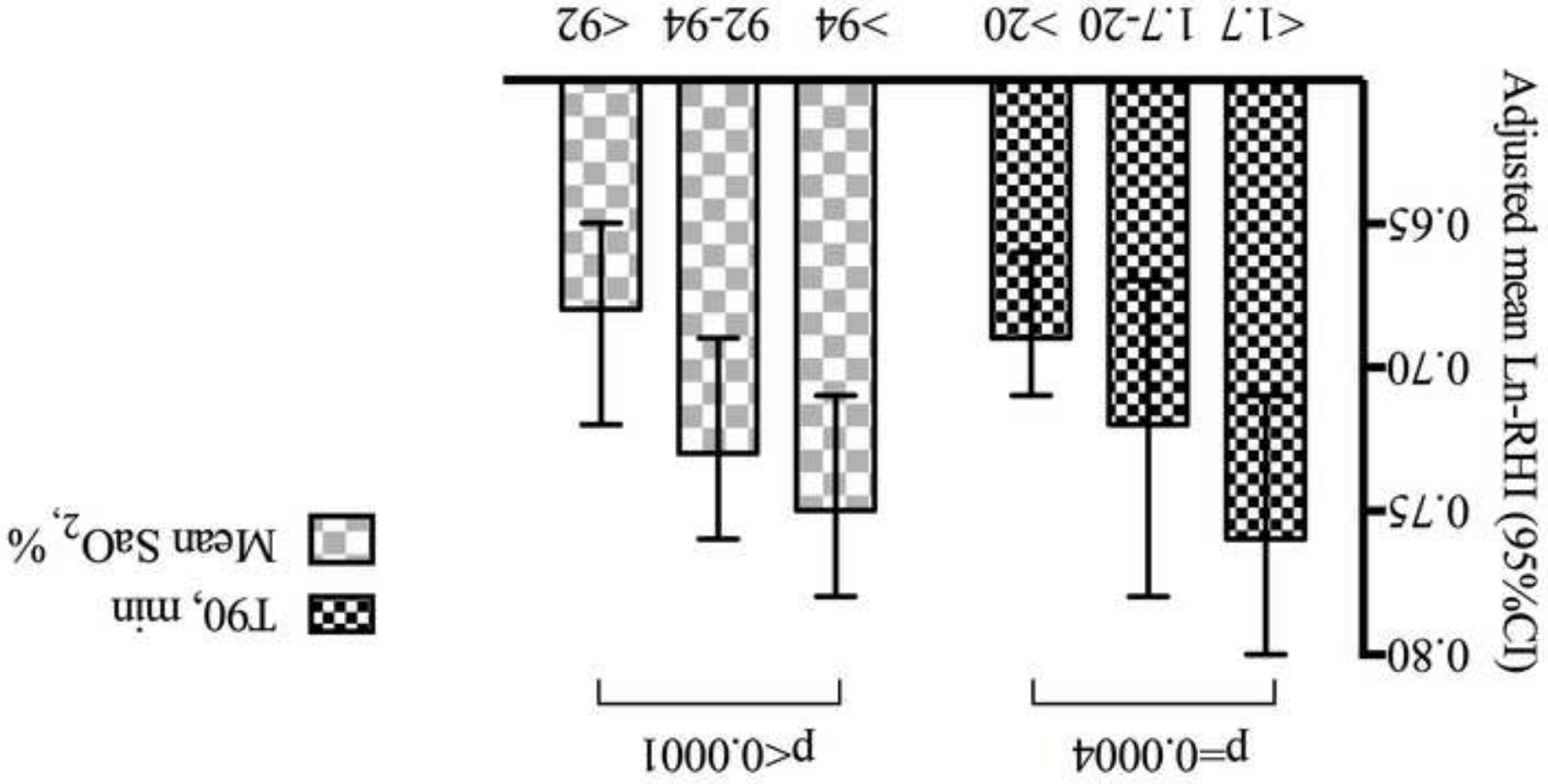


Figure 3

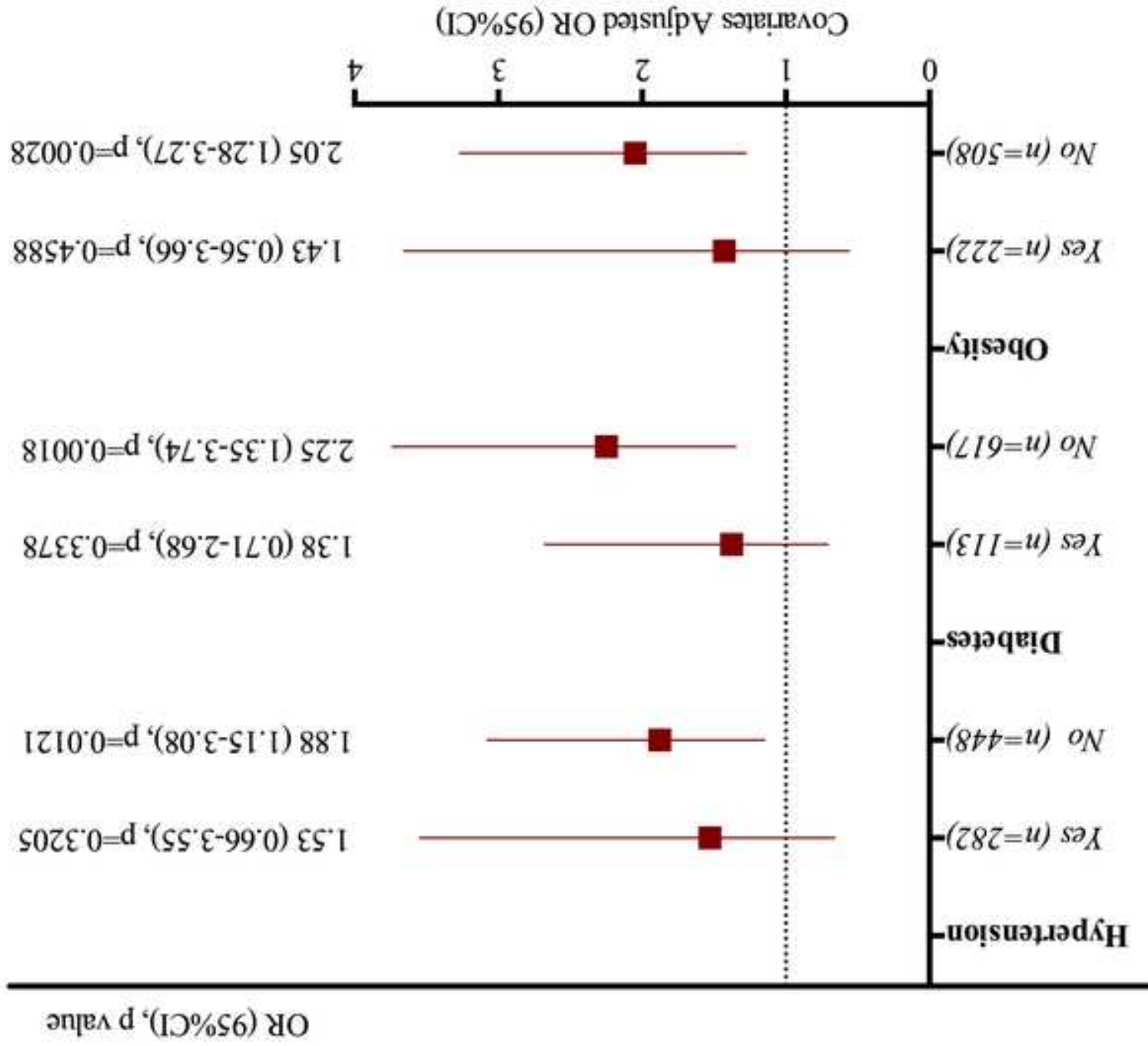


Figure S1

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### AUTHOR(S) NAMES

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## Supplementary material

### **Sleep apnoea and endothelial dysfunction: an individual patient data meta-analysis.**

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## Methods

### PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

| Section/Topic             | Item # | Checklist Item  | Reported on Page #       |
|---------------------------|--------|---|--------------------------|
| <b>TITLE</b>              |        |   |                          |
| Title                     | 1      | Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .  | <b>1</b>                 |
| <b>ABSTRACT</b>           |        |   |                          |
| Structured summary        | 2      | Provide a structured summary including, as applicable:<br><b>Background:</b> main objectives<br><b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> .<br><b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i><br><b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings.<br><b>Other:</b> primary source of funding; systematic review registration number with registry name. | 4                        |
| <b>INTRODUCTION</b>       |        |   |                          |
| Rationale                 | 3      | Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .   | <b>5-6</b>               |
| Objectives                | 4      | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).   | 6                        |
| <b>METHODS</b>            |        |   |                          |
| Protocol and registration | 5      | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.  | No                       |
| Eligibility criteria      | 6      | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .  | 7-8                      |
| Information sources       | 7      | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Tables S1 and S2 (Online |

|  |           |   |                       |
|--|-----------|---|-----------------------|
|  |           |   | supplement)           |
| Search                                 | 8         | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | NA                    |
| Study selection                        | 9         | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | 6                     |
| Data collection process                | 10        | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | NA                    |
| Data items                             | 11        | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | 8                     |
| <b>Geometry of the network</b>         | <b>S1</b> | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.  | NA                    |
| Risk of bias within individual studies | 12        | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 4 (Online supplement) |
| Summary measures                       | 13        | State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>   | 8                     |
| Planned methods of analysis            | 14        | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>  | 8                     |
| <b>Assessment of Inconsistency</b>     | <b>S2</b> | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.   | NA                    |
| Risk of bias across studies            | 15        | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 4 (Online supplement) |
| Additional analyses                    | 16        | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian</i></li> </ul> | NA                    |

analyses (if applicable).

## RESULTS†

|  |           |  |                                     |
|--|-----------|--|-------------------------------------|
| Study selection                          | 17        | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 9                                   |
| <b>Presentation of network structure</b> | <b>S3</b> | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.  | NA                                  |
| <b>Summary of network geometry</b>       | <b>S4</b> | Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.  | NA                                  |
| Study characteristics                    | 18        | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | Table S1 and S2 (Online supplement) |
| Risk of bias within studies              | 19        | Present data on risk of bias of each study and, if available, any outcome level assessment.  | NA                                  |
| Results of individual studies            | 20        | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>  | Table S2 (Online supplement)        |
| Synthesis of results                     | 21        | Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented. | <b>9-10 and Figures</b>             |
| <b>Exploration for inconsistency</b>     | <b>S5</b> | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.  | NA                                  |
| Risk of bias across studies              | 22        | Present results of any assessment of risk of bias across studies for the evidence base being studied.  |                                     |
| Results of additional analyses           | 23        | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses</i> , and so forth).  | NA                                  |

## DISCUSSION

|                     |    |  |    |
|---------------------|----|--|----|
| Summary of evidence | 24 | Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).  | 10 |
| Limitations         | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>  | 12 |
| Conclusions         | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 13 |
| <b>FUNDING</b>      |    |  |    |
| Funding             | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. | 2  |

PICOS = population, intervention, comparators, outcomes, study design.

\* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

## Results

**Table S1.** Details for the 12 clinical studies included

| Short name (publication references) | Clinical trial number | Ethics committee approval | Design              | Primary outcome                        | Key eligibility criteria  | Referral base |
|-------------------------------------|-----------------------|---------------------------|---------------------|--|---|---------------|
| BOSAS                               | NCT00777985           | 07/11/2007**              | RCT                 | Ambulatory blood pressure monitoring   | Patients with OSA and hypertension  | 14            |
| BPCO                                | NCT00404430           | 10/01/2007**              | Observational study | Endothelial function                   | Patients with exacerbated COPD  | 40            |
| BPCO-SAS                            | NCT01195064           | 16/10/2009**              | Observational study | Peripheral arterial tone               | Patient suspected for OSA or COPD with planned coronary artery bypass graft surgery or vascular surgery | 91            |
| DIAMETASAS                          | NA                    | 02/08/2006**              | RCT                 | Flow-deviated vasodilatation           | Patients with metabolic syndrome  | 25            |
| DIVAS                               | NA                    | 17/05/2011*               | Observational study | Peripheral arterial tone               | Patients with type 2 diabetes and suspected OSA   | 62            |
| INFRASAS                            | NCT01089257           | 04/07/2007**              | Observational study | Anatomic and functional vascular study | Patients with suspected OSA   | 108           |
| MIRSAS                              | NA                    | 20/11/2012*               | Observational study | Circulating micro particles            | Patients with suspected OSA   | 127           |
| NIV-OHS                             | NCT00603096           | 10/05/2006**              | RCT                 | Diurnal PaCO <sub>2</sub>              | Patients with OHS   | 71            |
| POLYSAS                             | NCT01977924           | 16/06/2013*               | RCT                 | Peripheral arterial tone               | Patients with severe OSA  | 40            |
| STATINFASAS                         | NCT00669695           | 07/11/2007**              | RCT                 | Peripheral arterial tone               | Patients with OSA and hypertension  | 52            |
| VALSAS                              | NCT00409487           | 07/06/2006**              | RCT                 | Ambulatory blood pressure monitoring   | Patients with OSA and hypertension  | 22            |
| VASOAM                              | NCT01426607           | 20/07/2010*               | RCT                 | Peripheral arterial tone               | Patients with severe OSA intolerant to CPAP   | 150           |

\* Comité de Protection des Personnes-OUEST II

\*\* Comité de Protection des Personnes-SUD EST V IRB0006705

Abbreviations: NA, not applicable since confidential trial; OSA, obstructive sleep apnoea; RCT, randomized controlled trial; CPAP, continuous positive airway pressure; OHS, obesity hypoventilation syndrome; COPD, chronic obstructive pulmonary disease.

**Table S2:** Patient's characteristics according to their original study

|                            |             |              |              |              |              |              |              |              |              |                    |              |                |
|----------------------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------------|--------------|----------------|
|                            | BOSAS       | BPCO[1-4]    | BPCO-SAS[3]  | DIAMET A-SAS | DIVAS[5]     | INFRA-SAS[6] | MIRSAS       | NIV-OHS[7,8] | POLYSAS [9]  | STATIN-FLASAS [10] | VAL-SAS[11]  | VASOAM [12,13] |
| n                          | 14          | 39           | 57           | 23           | 62           | 108          | 127          | 67           | 37           | 52                 | 22           | 122            |
| Age, years                 | 54.8 (6.6)  | 64.4 (6.4)   | 62.0 (10.0)  | 60.9 (3.9)   | 59.6 (9.2)   | 53.8 (10.6)  | 43.3 (11.4)  | 54.5 (9.3)   | 58.4 (9.4)   | 54.5 (11.5)        | 57.6 (8.1)   | 53.4 (10.5)    |
| Females, %                 | 21.4        | 23.8         | 17.5         | 43.5         | 37.1         | 19.4         | 0.0          | 44.8         | 27.0         | 21.2               | 18.2         | 13.1           |
| BMI, kg/m <sup>2</sup>     | 29.9 (4.3)  | 25.6 (4.9)   | 26.3 (4.0)   | 29.2 (3.1)   | 33.6 (5.2)   | 25.3 (2.8)   | 26.3 (3.5)   | 40.1 (5.9)   | 31.6 (4.3)   | 28.3 (4.5)         | 28.6 (4.7)   | 26.7 (3.2)     |
| Obesity, %                 | 35.7        | 12.8         | 17.5         | 34.8         | 75.8         | 0.9          | 11.8         | 100.0        | 59.5         | 32.7               | 27.3         | 15.6           |
| SBP, mmHg                  | 146.7 (5.5) | 138.2 (16.8) | 132.1 (19.4) | 148.8 (17.2) | 131.1 (14.7) | 123.7 (13.2) | 127.9 (10.6) | 133.4 (16.5) | 129.4 (16.2) | 127.3 (14.2)       | 154.5 (14.9) | 126.3 (14.2)   |
| DBP, mmHg                  | 85.3 (10.5) | 75.3 (11.7)  | 73.7 (11.1)  | 89.2 (11.2)  | 77.0 (8.8)   | 74.1 (10.7)  | 78.6 (9.1)   | 76.3 (13.8)  | 79.7 (10.4)  | 77.5 (11.4)        | 100.5 (12.0) | 78.4 (9.5)     |
| Hypertension, %            | 100.0       | 46.2         | 47.4         | 87.0         | 50.0         | 13.9         | 0.0          | 56.7         | 48.7         | 100.0              | 100.0        | 22.1           |
| Diabetes, %                | 7.1         | 7.7          | 14.3         | 30.4         | 100.0        | 0.0          | 0.0          | 26.9         | 24.3         | 0.0                | 0.0          | 4.1            |
| Dyslipidemia               | 35.7        | 35.9         | 47.9         | 4.4          | 40.3         | 15.7         | 0.0          | 100.0        | 29.7         | 8.2                | 27.3         | 10.7           |
| <b>COPD, %</b>             | <b>0.0</b>  | <b>94.9</b>  | <b>24.6</b>  | <b>0.0</b>   | <b>0.0</b>   | <b>0.0</b>   | <b>0.0</b>   | <b>0.0</b>   | <b>0.0</b>   | <b>0.0</b>         | <b>0.0</b>   | <b>0.0</b>     |
| Non-smokers, %             | 21.4        | 0.0          | 22.2         | 39.1         | 85.5         | 44.4         | 58.3         | 40.6         | 86.5         | 46.2               | 27.3         | 50.0           |
| Epworth score              | 9.6 (5.2)   | 7.7          | 5.6 (4.0)    | 8.6 (5.8)    | 7.9 (4.5)    | 9.2 (5.0)    | 9.9 (4.3)    | 12.0 (4.9)   | 11.1 (3.1)   | 0.0                | 9.8 (4.3)    | 9.4 (4.4)      |
| No OSA, %                  | 0.0         | 7.7          | 12.3         | 17.4         | 16.1         | 14.8         | 29.9         | 7.5          | 0.0          | 0.0                | 9.1          | 0.0            |
| Mild-to-moderate OSA, %    | 35.7        | 69.2         | 56.1         | 52.2         | 50.0         | 55.6         | 57.5         | 29.9         | 2.7          | 7.7                | 40.9         | 1.6            |
| Severe OSA, %              | 64.3        | 23.1         | 31.6         | 30.4         | 33.9         | 29.6         | 26.8         | 62.7         | 97.3         | 92.3               | 50.0         | 98.4           |
| AHI, n                     | 41.1 (21.2) | 25.7 (25.2)  | 25.7 (18.3)  | 24.0 (23.5)  | 26.3 (26.1)  | 24.7 (20.1)  | 20.6 (18.0)  | 46.0 (33.7)  | 46.4 (16.1)  | 44.6 (17.4)        | 33.0 (18.8)  | 45.2 (13.9)    |
| T90, min                   | -           | 61.9 (86.6)  | 35.0 (69.4)  | 13.7 (19.7)  | 47.5 (75.0)  | 15.6 (41.3)  | 3.6 (10.5)   | 96.8 (116.5) | 58.0 (74.9)  | -                  | 24.8 (37.1)  | 24.5 (33.5)    |
| Mean SaO <sub>2</sub> , %  |             | 91.6 (2.1)   | 92.9 (2.0)   | 92.5 (1.2)   | 91.8 (2.1)   | 94.1 (1.8)   | 93.7 (2.0)   | 90.6 (4.6)   | 92.0 (1.9)   | 92.4 (2.0)         | 93.4 (2.2)   | 92.3 (1.6)     |
| Ln-RHI                     | 0.71 (0.17) | 0.78 (0.24)  | 0.80 (0.22)  | 0.61 (0.24)  | 0.49 (0.29)  | 0.82 (0.22)  | 0.73 (0.26)  | 0.73 (0.27)  | 0.71 (0.25)  | 0.71 (0.26)        | 0.67 (0.25)  | 0.73 (0.29)    |
| Endothelial dysfunction, % | 14.3        | 15.4         | 12.3         | 34.8         | 58.1         | 6.5          | 21.3         | 23.9         | 21.6         | 21.2               | 22.7         | 25.4           |

Abbreviations: OSA, obstructive sleep apnoea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; **COPD**, chronic obstructive pulmonary disease; AHI, apnoea-hypopnoea index; T90, sleep time with oxygen saturation < 90%; SaO<sub>2</sub>, oxygen saturation; Ln-RHI, natural logarithmic transformation of the reactive hyperaemia index.

\* Endothelial dysfunction was defined by a Ln-RHI < 0.51

**Figure S1:** Subgroup analysis of the association between severe OSA (versus no OSA) and endothelial function.

Abbreviations: OSA, obstructive sleep apnoea

Covariates included age, gender, diastolic blood pressure, presence of obesity, diabetes and chronic obstructive pulmonary disease. For each subgroup, the corresponding covariate was excluded from the model.

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