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Contribution of obstructive sleep apnoea to arterial stiffness: a meta-analysis using individual patient data

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3 **Contribution of obstructive sleep apnoea to arterial stiffness:**
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5 **a meta-analysis using individual patient data**
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Abbreviations list

AHI	Apnoea-hypopnea index
BP	Blood pressure
BMI	Body mass index
CAVI	Cardio-ankle vascular index
CPAP	Continuous positive airway pressure
DBP	Diastolic blood pressure
ESS	Epworth sleepiness scale
IPD	Individual patient data
OSA	Obstructive sleep apnoea
PAD	Peripheral arterial disease
PSG	Polysomnography
PWV	Pulse wave velocity
SaO ₂	Oxygen saturation
SBP	Systolic blood pressure

ABSTRACT

Background. Arterial stiffness, measured by Pulse Wave Velocity (PWV), is a strong independent predictor of late cardiovascular events and mortality. It is recognized that obstructive sleep apnoea (OSA) is associated with cardiovascular co-morbidities and mortality. Although previous meta-analyses concluded that PWV is elevated in OSA, we feel that an individual patient data analysis from 9 relatively homogeneous studies could help answer: to what extent does OSA drive arterial stiffness?

Methods. Individual data from well-characterized patients referred for suspicion of OSA, included in 9 studies in which carotid-femoral PWV was measured using a Complior™ device, were merged for an individual patient data meta-analysis.

Results. 893 subjects were included (age: 56 ± 11 (mean \pm SD), 72% male, 84% with confirmed OSA). BMI varied from 15 to 81 kg/m^2 ($30 \pm 7 \text{ kg/m}^2$). PWV ranged from 5.3 to 20.5 m/s ($10.4 \pm 2.3 \text{ m/s}$). In univariate analysis, log(PWV) was strongly related to age, gender, systolic blood pressure, presence of type 2 diabetes (all $p < 0.01$) as well as to dyslipidaemia ($p = 0.03$) and an Epworth sleepiness score ≥ 9 ($p = 0.04$), whereas it was not related to obesity ($p = 0.54$), a severe apnoea-hypopnea index ($p = 0.14$), mean nocturnal saturation ($p = 0.33$), or sleep time with oxygen saturation below 90% ($p = 0.47$). In multivariable analysis, PWV was independently associated with age, SBP and diabetes (all $p < 0.01$) whereas severe OSA was not significantly associated with PWV.

Conclusion. Our individual patient meta-analysis showed that elevated arterial stiffness in OSA patients is driven by conventional cardiovascular risk factors rather than apnoea parameters.

SUMMARY 'BOX'

- **What is the key question?** What are the relative impacts of obstructive sleep apnoea severity and conventional risk factors on arterial stiffness?
- **What is the bottom line?** The elevation of arterial stiffness in obstructive sleep apnoea patients is driven more by the conventional cardiovascular risk factors (age, hypertension and the presence of diabetes) than by apnoea severity indices.
- **Why read on?** This meta-analysis used individual patient data from 9 studies performed by the same centre with 893 well characterized patients and pulse wave velocity measured using the same technique for all studies.

INTRODUCTION

Arteries not only carry oxygen and nutrients but also attenuate cardiac pulsatility due to their elastic properties. With aging and in the presence of cardio-vascular disease, large arteries, in particular the aorta, tend to stiffen.[1] In the European Hypertension and Cardiology Society guidelines elevated arterial stiffness is recognized as a strong predictor of end organ damage and cardiovascular mortality that is independent of other usual cardiovascular risk factors.[2-4] The international expert committee recommends carotid-femoral pulse wave velocity (PWV) as the “gold standard” for the assessment of aortic stiffness.[1] Patients with chronic diseases that have high cardiovascular risk such as hypertension or diabetes exhibit higher PWV.[5,6] However, contrary to what may be intuitively expected, in obese subjects conflicting results regarding arterial stiffness are reported.[7] This might be partly explained by heterogeneity of obesity patients including its association, or not, with obstructive sleep apnoea (OSA).

Obstructive sleep apnoea syndrome is strongly associated with cardiovascular morbidity and mortality.[8] Data summarized in a systematic review by Doonan *et al.*[9] and later in a critical review by Phillips *et al.*[10] reported that severe OSA patients have elevated PWV compared to healthy volunteers or control groups exhibiting no or mild OSA.[11–17] A relationship between PWV and OSA severity[11,18] was suggested but was not systematically confirmed.[14,19,20]

OSA syndrome is associated with several clusters of co-morbidities[21] such as hypertension,[22] obesity,[23,24] diabetes, coronary heart disease and cardiac failure. These co-existing chronic diseases also each strongly contribute towards elevated PWV.[5] The relationship between OSA severity and arterial stiffness assessed by PWV, needs clarifying particularly as previous meta-analyses and reviews in the field have included heterogeneous

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2
3 studies with relatively limited sample sizes and poorly described comorbidities.[10,25] To
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5 determine the relative impacts of OSA severity and conventional risk factors on arterial
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7 stiffness we conducted an individual patient data meta-analysis on data from a large group
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9 of nearly 900 patients with suspicion of OSA, explored in the same centre, for whom PWV
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11 and comorbidities were systematically and carefully assessed.
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16 **METHODS**

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18 Individual data from participants involved in separate studies performed by our group
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20 between 2006 and 2015 were pooled. We excluded studies in which PWV was recorded for
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22 less than 80% of patients, or in which there was heterogeneity in the PWV or
23
24 polysomnography methods used. Only data from baseline measurements from observational
25
26 studies and randomized clinical trials were used in this individual data meta-analysis.
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30 All studies were conducted in accordance with applicable good clinical practice requirements
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32 in Europe, French law, ICH E6 recommendations, and the ethical principles of the Helsinki
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34 Declaration (1996 and 2000). They were approved by an independent Ethics Committee
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36 (Comité de Protection des Personnes, Sud Est V IRB0006705 France) and registered on the
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38 ClinicalTrials.gov site (Table S1 in the online supplementary file). All patients gave their
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40 written informed consent.
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46 **Clinical evaluation**

47
48 Hypertension was defined as systolic blood pressure (SBP) greater than 140 mmHg, diastolic
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50 blood pressure (DBP) greater than 90 mmHg or need for anti-hypertensive treatment.
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52 Clinical blood pressure (BP) was measured in triplicate using a mercury sphygmomanometer
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54 or with validated oscillometric devices. The average of 3 measurements was used. Diabetes
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3 was defined based on current use of antidiabetic medications and dyslipidaemia on current
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5 lipid-lowering medications. Body mass index (BMI) was determined and obesity classes were
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7 defined according to World Health Organization (WHO) definitions: normal: BMI < 25 kg/m²;
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9 overweight: 25 ≤ BMI < 30 kg/m²; obese: 30 ≤ BMI < 35 kg/m²; severely obese: 35 ≤ BMI < 40
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11 kg/m², and morbidly obese: ≥ 40 kg/m².
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14 15 16 **Sleep studies**

17
18 All patients were diagnosed with OSA using overnight respiratory polygraphy or
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20 polysomnography (PSG), performed with spontaneous breathing to characterize abnormal
21
22 respiratory events during sleep. Details the procedure as well as of the definitions of apnoea
23
24 and hypopnea can be found in the e-Appendix 1 of our previous publication.[26] The
25
26 apnoea-hypopnoea index (AHI) was calculated as the number of apnoea and hypopnoea
27
28 events per hour of sleep (full PSG). Patients also completed the Epworth sleepiness scale
29
30 (ESS). Subjects were classified as controls if AHI < 5 events/h, or suffering from mild (5 ≤ AHI
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32 < 15 events/h), moderate (15 ≤ AHI < 30 events/h) or severe OSA (AHI ≥ 30 events/h). Mean
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34 nocturnal oxygen saturation (SaO₂) and time spent under 90% of SaO₂ were also collected in
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36 order to characterize sleep apnoea severity. Overnight Sleep studies were scored according
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38 to international guidelines.[27]
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46 **Arterial stiffness assessed by pulse wave velocity**

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48 PWV was measured using the same technique for all studies: carotid and femoral waveforms
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50 were acquired with the Complior SP device (Alam Medical, France). The validation and
51
52 reproducibility of Complior measurements have been published elsewhere.[28,29] PWV is
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54 automatically calculated by the Complior from the transit time between simultaneous
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3 carotid and femoral tracings and the arterial distance between these two sites. At the time
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5 of the studies, the arterial distance pathway was estimated from surface measurements and
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7 later multiplied by 0.8 as advised by the latest expert consensus on PWV measurements.[30]
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9 At least two measurements of PWV were systematically performed. When the difference
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11 between measurements was less than 0.5 m/s, the mean value was keep. When the
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13 difference was above 0.5 m/s, a third measurement was done and the median value was
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15 taken into account. The same procedure and methodology was conducted across studies.
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21 **Statistical analysis**

22
23 Qualitative variables were described using numbers and proportion and quantitative
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25 variables are described using mean and standard deviation. Missing values were imputed
26
27 using a multiple imputation method when the proportion of missing values was < 20%. Five
28
29 datasets were generated using logistic regression for qualitative variables or linear
30
31 regression for quantitative variables, considering that missing values were random. More
32
33 information about data imputation methods are given in the online supplementary file
34
35 (Table S3). As PWV distribution was skewed, the analysis was first performed with log[PWV].
36
37 However, a sensitivity analysis using untransformed PWV showed that the results did not
38
39 differ from those using log[PWV]. Hence, we re-analysed and present results from non-log
40
41 transformed PWV for easier interpretation by clinicians and readers.
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46 A one-step IPD meta-analysis was performed to adjust on patient variables. A univariate
47
48 linear mixed model with a random effect by study was built to identify factors associated
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50 with PWV. Factors significantly associated with PWV and severe OSA (AHI \geq 30 events/h)
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52 were introduced in a multivariate linear mixed model to identify independent factors
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3 associated with PWV. A backward selection was performed to identify the final multivariable
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5 model.

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7 Comparisons of patients' characteristics according to the AHI were performed using a
8
9 univariate linear mixed model for quantitative values or logistic regression for qualitative
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11 ones.

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14 P-values < 0.05 were considered statistically significant. Data were analysed using SAS v9.4
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16 (SAS Institute Inc., Cary, NC, USA).

21 **RESULTS**

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23 The 9 studies included in the meta-analysis are detailed in the online supplement in terms of
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25 regulatory approval, design and publications (Figure 1 and Table S1 in the online
26
27 supplementary file). All these studies concerned patients with OSA or suspected of OSA.
28
29 There were 6 randomized and 3 observational studies.

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31
32 The characteristics of the whole group of 893 patients are shown in Table 1 and patients'
33
34 characteristics per study are shown in Table S2 of the online supplementary file. Most
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36 subjects were male (72%) and 84% had confirmed OSA syndrome. We had a large range of
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38 PWV: from 5.3 to 20.5 m/s with a mean value of 10.4 ± 2.3 m/s and also a large range of
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40 BMI: from 15 to 81 kg/m² (mean value: 30 ± 7 kg/m²) with 22% normal, 39% overweight,
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42 18% obese, 12% severely obese and 9% morbidly obese patients.
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Table 1. Patients' characteristics for the whole population

	N = 893
Male (n (%))	644 (72)
Age (yrs)	56 ± 11
BMI (kg/m ²)	29.9 ± 6.9
Normal (n (%))	199 (22)
Overweight (n (%))	345 (39)
Obese (n (%))	163 (18)
Severely obese (n (%))	106 (12)
Morbidly obese (n (%))	80 (9)
Hypertension (n (%))	694 (78)
Type 2 diabetes (n (%))	401 (45)
Dyslipidaemia (n (%))	551 (62)
OSA (n (%))	683 (84)
SBP (mmHg)	133 ± 17
DBP (mmHg)	81 ± 12
HR (bpm)	69 ± 12
PWV (m/s)	10.4 ± 2.3
AHI (events/h)	36.8 ± 24.1
Mean nocturnal SaO ₂ (%)	92.9 ± 2.7
SaO ₂ < 90% (% of recording time)	10.8 ± 18.3
ESS score	9.5 ± 5.2

Results are observed data. They are expressed as mean ± SD or n (%). These percentages are before imputation of missing data. The imputation of missing data is shown in table S3 in the online supplement file. AHI, apnoea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; DBP, diastolic blood pressure; HR, heart rate; PWV, Pulse wave velocity; SaO₂ < 90%, percentage of recording time spent at a SaO₂ < 90%; SBP, systolic blood pressure.

Patients with confirmed OSA were older and had higher BP (Table 2).

Table 2. Patients' characteristics according to OSA severity

	Controls AHI < 5	Mild 5 ≤ AHI < 15	Moderate 15 ≤ AHI < 30	Severe AHI ≥ 30
N	58	97	237	501
Male n (%)	30 (52)	55 (57)	168 (71)	392 (78)*
Age (yrs)	52.0 ± 13.1	56.4 ± 13.6*	57 ± 11.3*	56.0 ± 11.5*
BMI (kg/m ²)	29.3 ± 7.9	29 ± 7.5	28.7 ± 6.8	30.7 ± 6.9
Hypertension (n (%))	33 (56)	65 (67)	185 (78)	413 (82)*
Type 2 diabetes (n (%))	19 (33)	48 (50)	106 (45)	227 (45%)
Dyslipidaemia (n (%))	34 (59)	56 (58)	138 (58)	323 (64)
SBP (mmHg)	126 ± 18	131 ± 18	134 ± 19*	134 ± 17*
DBP (mmHg)	74 ± 15	74 ± 12	81 ± 13*	82 ± 12*
HR (bpm)	68 ± 15	67 ± 14	69 ± 13	71 ± 15
PWV (m/s)	10.1 ± 2.6	10.7 ± 3	10.3 ± 2.4	10.4 ± 2.3
Mean nocturnal SaO ₂ (%)	93.6 ± 2.3	93.2 ± 2.5	93.1 ± 3.1	92.6 ± 2.9*
SaO ₂ < 90% (%)	6.1 ± 16.6	6.8 ± 14.3	6.4 ± 14.1	14.0 ± 20.9*
ESS score	7.9 ± 5.7	8.5 ± 8.4	9.2 ± 6.5	10 ± 5.3*

Results are observed data. They are expressed as mean ± SD or n (%). These percentages are before imputation of missing data.

AHI, apnoea-hypopnea index (events/h); BMI, body mass index; ESS, Epworth Sleepiness Scale; DBP, diastolic blood pressure; SaO₂, oxygen saturation; HR, heart rate; PWV, Pulse wave velocity; SaO₂ < 90%, percentage of recording time spent at a SaO₂ < 90%; SBP, systolic blood pressure.

* *p*-value versus controls < 0.01

A two-step meta-analysis was also performed. Results are provided in the online supplement. A limited heterogeneity was observed across the 9 studies (Figure S1)

The univariate analysis for the one-step IPD meta-analysis (Figure 2) showed that PWV was strongly related to age (*p*<0.01), male gender (*p*<0.01), SBP (*p*<0.01), presence of diabetes

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2
3 (p<0.01), presence of dyslipidaemia (p=0.03) and ESS score ≥ 9 (p=0.04), and was not related
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5 to severe OSA defined by AHI ≥ 30 events/h (p=0.14).
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7 In multivariable analysis, PWV was independently associated with age, SBP and diabetes (all
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9 p<0.01) whereas severe OSA was not significantly associated with PWV (Figure 3).
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12 13 14 **DISCUSSION**

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16 To our knowledge, this is the first meta-analysis using individual patient data aiming to
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18 disentangle the respective influences of OSA and comorbidities on arterial stiffness. Most
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20 reviews and previous meta-analyses used data from different groups with several different
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22 methods of arterial stiffness assessment.[9,10] A strength of our meta-analysis using
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24 individual patient data was that all data came from a single centre with standard operating
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26 procedures and long expertise in performing PWV and sleep studies. The use of complete
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28 individual data sets allowed subgroup analyses to be made, to adjust for co-variables and
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30 hence increase power, as recommended by Bratton *et al.*[31]
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35 The systematic review of Doonan *et al.*,[9] published in 2011, found 24 studies investigating
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37 the effect of OSA on arterial stiffness, while that of Phillips *et al.*[10] published 2 years later
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39 included 28 studies. A broad variety of techniques had been used to assess arterial stiffness,
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41 some studies used carotid-femoral PWV, other studies used brachial-ankle PWV and some
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43 authors only estimated arterial stiffness indirectly by derivatives such as the augmentation
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45 index. Although most studies found a significant difference in arterial stiffness between
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47 controls and OSA patients, almost a third did not find a difference.[14,19] Recently, Kim *et*
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49 *al.* reported no association between OSA severity and arterial stiffness assessed by brachial-
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51 ankle PWV in a population of patients over 60 years of age.[20] Ankle-brachial PWV, as
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53 opposed to carotid-femoral PWV used in our meta-analysis, is not the internationally
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3 recognized standard method of measuring arterial stiffness. Indeed ankle-brachial PWV
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5 assesses arterial stiffness not only over the aortic segment but also in the lower limbs. The
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7 brachial-ankle PWV or the cardio-ankle vascular index (CAVI), another non-standard
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9 measure of arterial stiffness, should not be used in patients with peripheral arterial disease
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11 (PAD), a very highly prevalent condition in OSA patients.[32] Alberto *et al.* carefully excluded
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13 PAD patients in their study and only observed a non-significant trend between CAVI and
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15 nocturnal intermittent hypoxia.[33]
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19 In the present study, we systematically used the gold standard carotid-femoral PWV
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21 methodology to assess arterial stiffness. In univariate analysis, ESS ≥ 9 was the only OSA
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23 parameter statistically associated with PWV. When studying non-selected OSA groups
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25 reflecting the diverse populations referred to a sleep clinic, the relationship between OSA
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27 and arterial stiffness is modest and only identifiable in univariate analysis in the most severe
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29 OSA patients, who also have the highest prevalence of comorbidities.
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33 As confirmed by our data, PWV and OSA syndrome share confounders. Besides age, BP is the
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35 strongest confounding factor of PWV.[5] The prevalence of hypertension among OSA
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37 patients is particularly high[22] and OSA and hypertension are also linked in a dose-response
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39 fashion.[34,35].
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43 The association between age SBP and PWV is complex, as shown by AlGhatrif *et al.*[36]. In
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45 our study, the interaction between age and SBP was tested in the model and was found to
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47 be not significant ($p=0.06$) showing that the impact of OSA on PWV remained unchanged.
48
49 Obesity is very often associated with OSA syndrome.[24] Seetho *et al.* observed that
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51 normotensive obese subjects with OSA had a higher augmentation index than normotensive
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53 obese subjects without OSA.[23] The augmentation index is sometimes used as a surrogate
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55 measure of arterial stiffness however it is highly dependent on vascular tone and cardiac
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3 characteristics.[37] In obesity and metabolic syndrome vascular tone is modified. In our
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5 analysis, confirming previous results in non-OSA patients,[7] obesity did not play a significant
6
7 role in the increased arterial stiffness. As stated by Drager *et al*, while OSA is one of the
8
9 consequence of obesity, it might not have a large additional influence on cardiovascular
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11 risk.[38] Chirinos *et al* showed that continuous positive airway pressure (CPAP) treatment
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13 has an incremental effect over weight loss alone in reducing blood pressure but the impact
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15 of combined therapy on arterial stiffness was not evaluated.[24]
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21 Despite the use of brachial-ankle PWV, it is interesting to note that Kim *et al* observed a
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23 relationship between arterial stiffness and OSA severity in a sub-group of patients over the
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25 age of 60 with no other comorbidity or medical treatment.[20] They hypothesized that
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27 chronic diseases (hypertension, diabetes and dyslipidaemia) increased arterial stiffness while
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29 the use of anti-hypertensive, anti-diabetic or lipid lowering drugs, might have a positive
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31 impact on PWV, blunting the association between arterial stiffness and OSA severity.[20] In a
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33 meta-analysis Wang *et al* looked at studies only comparing controls to OSA patients free of
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35 other cardiovascular risk factors and also concluded that carotid-femoral PWV is elevated by
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37 OSA per se.[17] Our meta-analysis showed that arterial stiffness measured by PWV was
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39 marginally influenced by OSA in the presence of co-morbidities. As stronger association
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41 might be found in the conduit arteries in of younger OSA patients, which are more sensitive
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43 to sympathetic activation compared to the aorta. This requires further studies. The impact of
44
45 OSA syndrome per se on the arteries seems negligible compared to the impact of
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47 hypertension, diabetes and dyslipidaemia. This might explain why CPAP treatment has
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49 relatively modest impact on BP or PWV.[25,35,39] Only the most severe OSA patients with
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51 higher baseline values significantly benefit from CPAP in terms of BP reduction.[40,41]
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Careful management of OSA associated comorbidities in combination with CPAP is more likely to have a greater impact on the occurrence of late cardiovascular events and survival.

Limitations

Data were merged from observational and interventional clinical trials. Therefore the population might not be completely homogenous depending on the specific inclusion and exclusion criteria of each trial. Moreover, while polygraphy was used in some studies, polysomnography was used in others, which might also have introduced some heterogeneity. Nevertheless, compared to other meta-analyses that included data from different centres with different techniques for PWV measurements, the impact was certainly small. Moreover, significant hypoxia was present in the control non-OSA group and was explained by documented COPD or morbid obesity and smoking were not included in the analysis. We cannot exclude a bias in patient recruitment and our results might not be generalizable to the general OSA population. However our population exhibited multiple comorbidities, which is clinically relevant. We observed a tendency to higher PWV in OSA patients than in controls, which was not significant after adjustment in multivariable analysis, potentially owing the small size of the control group. Finally, the cross-sectional nature of our meta-analysis does not allow us to explain any causality other than associations between the observed parameters.

Conclusion

Our individual patient meta-analysis showed that elevated arterial stiffness in OSA patients is mainly driven by the conventional cardiovascular risk factors; age, BP and the presence of diabetes and apnoea severity indices had limited influence.

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Author contributions

MJF, SB, RT, JCB, SM and JLP: Researched data, contributed to discussion, wrote the manuscript, reviewed/edited the manuscript.

LMG and MD: Researched data, contributed to discussion, reviewed/edited the manuscript.

Jean-Louis Pépin takes responsibility for the integrity of the work as a whole, including the data and analysis, from inception to revised article.

Summary of Competing Interest Statements:

None of the authors has a competing interest with respect to this study except Sandrine Millasseau. Sandrine Millasseau works as a freelance specialist on pulse wave analysis and receives revenues from several medical device companies including Alam Medical whose device was used in this study.

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Figure Legends

Figure 1. Flowchart of selected studies and patients.

Figure 2. Forest plot of the factors associated with PWV (univariate analysis).

Figure 3. Forest plot of the independent factors associated with PWV (multivariate analysis).

Online supplement

Table S1. Details of the 9 clinical studies included

Table S2. Patients' characteristics for the 9 clinical studies included

Table S3. Patients' characteristics for the whole population

Table S4. Result of the leave-one-out analysis

Figure S1. Forest plot of the influence of the OSA severity on PWV

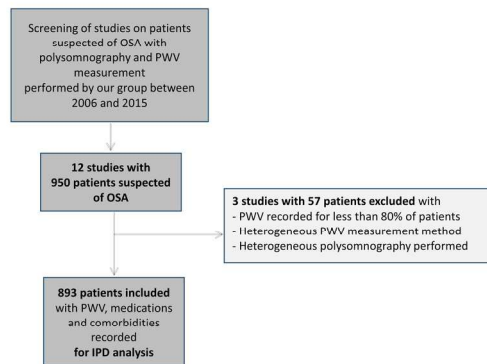


Figure 1

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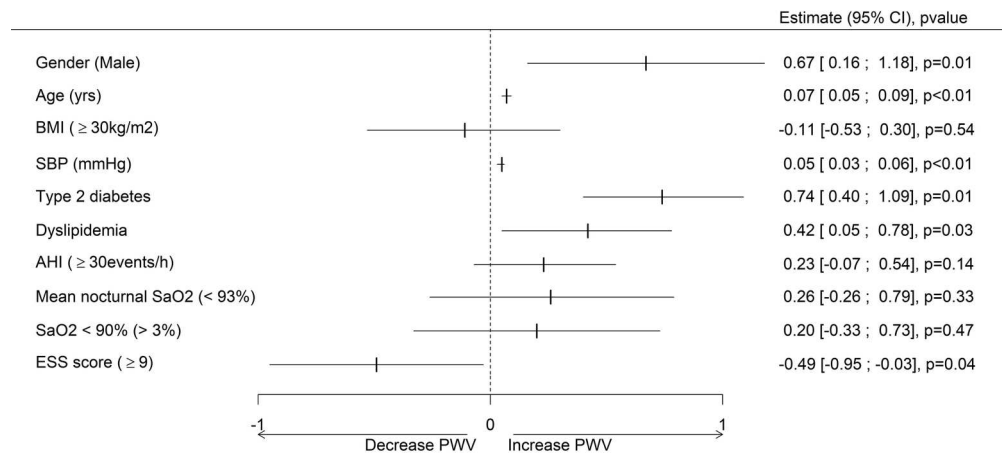


Figure 2

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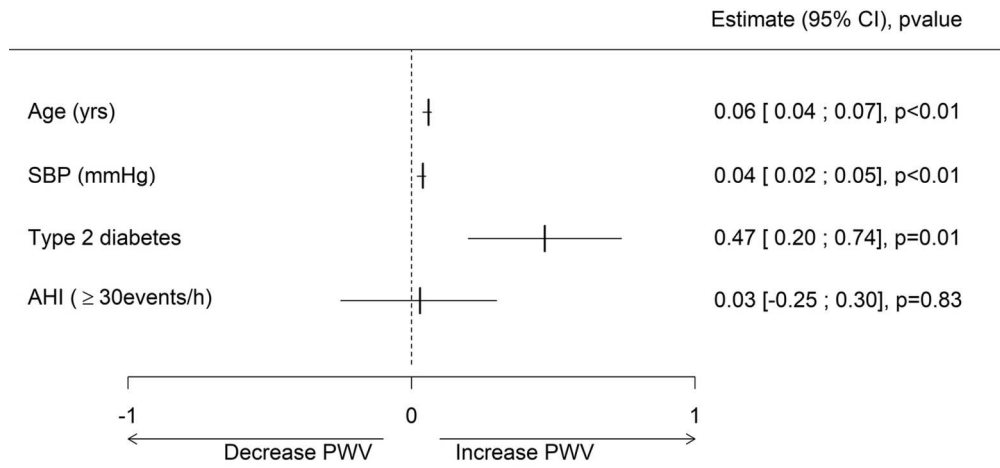


Figure 3

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Online supplement

Table S1. Details for the 9 clinical studies included

Short name	ADISAS	AGIRSAS ADOM	BPCO	BPCO-SAS	DIAMETASAS	Aortic Dissection	INFRASAS	VALSAS	NIV-OHS
Clinical trial number	NCT01196845	NCT01090297	NCT00404430	NCT01195064	NA	NCT01068691	NCT01089257	NCT00409487	NCT00603096
Ethics committee* approval date	07/10/2009	29/07/2009	10/01/2007	16/10/2009	02/08/2006	06/02/2008	04/07/2007	07/06/2006	10/05/2006
Design	RCT	RCT	Observational study	Observational study	RCT	RCT	Observational study	RCT	RCT
Primary outcome	Inflammation in adipose tissue	Clinical blood pressure	Peripheral arterial tone	Peripheral arterial tone	Flow-deviated vasodilatation	Ambulatory blood pressure monitoring	Anatomic and functional vascular study	Ambulatory blood pressure monitoring	Diurnal PaCO ₂
Key eligibility criteria	OSA patients obese or not who need CPAP treatment	OSA patients who need CPAP treatment	Patients with exacerbated COPD	Patient suspected for OSA or BPCO with planned coronary artery bypass graft surgery or vascular surgery	Patients with metabolic syndrome	Patients suspected for OSA or BPCO and surgically treated for type A acute aortic syndrome	Patients suspected for OSA	OSA patients with hypertension	Patients with obesity-hypoventilation syndrome
Referral base	24	322	102	58	37	156	95	28	160
Publications (reference)		1	2 to 5	5		6	7	8	9,10

* Ethics committee: Comité de Protection des Personnes- Sud Est V IRB0006705
NA, not applicable since confidential trial; RCT, randomized controlled trial

Table S2. Patients' characteristics for the 9 clinical studies included

Short name	ADISAS	AGIRSAS ADOM	BPCO	BPCO-SAS	DIAMETASAS	Aortic dissection	INFRASAS	VALSAS	NIV-OHS
Number of patients*	22	313	99	53	34	131	90	28	123
Male (n (%))	22 (100)	221 (70.6)	81 (81.8)	43 (86)	18 (52.9)	113 (86.3)	74 (82.2)	22 (78.6)	50 (40.7)
Age (yrs)	54.4 (8.1)	57.4 (11.1)	63.7 (8.5)	62.7 (9.1)	59.4 (6.9)	49.1 (10.3)	52 (10.7)	56.4 (8.5)	53.2 (12.7)
BMI (kg/m ²)	31.2 (8.2)	31 (6.6)	25.4 (4.7)	26.3 (4)	29.5 (3.4)	26.6 (3.3)	25.2 (2.8)	28.9 (4.9)	39.3 (5.5)
Normal (n (%))	5 (22.7)	41 (13.1)	60 (60.6)	23 (43.4)	1 (2.9)	40 (30.5)	40 (44.4)	5 (17.9)	-
Overweight (n (%))	6 (27.3)	117 (37.4)	44 (44.4)	22 (41.5)	18 (52.9)	77 (58.8)	49 (54.4)	14 (50)	2 (1.6)
Obese (n (%))	5 (22.7)	86 (27.5)	40 (40.4)	6 (11.3)	12 (35.3)	12 (9.2)	1 (1.1)	5 (17.9)	24 (19.5)
Severely obese (n (%))	4 (18.2)	44 (14.1)	12 (12.1)	2 (3.8)	3 (8.8)	1 (0.8)	-	4 (14.3)	45 (36.6)
Morbidly obese (n (%))	2 (9.1)	25 (8)	3 (3)	-	-	1 (0.8)	-	-	52 (42.3)
Hypertension (n (%))	12 (54.5)	268 (85.6)	45 (45.5)	45 (84.9)	32 (94.1)	111 (84.7)	62 (68.9)	28 (100)	76 (61.8)
Diabetes (n (%))	6 (27.3)	175 (55.9)	37 (37.4)	29 (54.7)	24 (70.6)	24 (18.3)	15 (16.7)	12 (42.9)	71 (57.7)
Dyslipidemia (n (%))	18 (81.8)	207 (66.1)	56 (.)	48 (90.6)	29 (85.3)	81 (61.8)	42 (46.7)	15 (53.6)	74 (60.2)
OSA (n (%))	17 (100)	304 (97.1)	28 (65.1)	27 (56.3)	20 (58.8)	131 (100)	56 (62.2)	23 (82.1)	77 (68.8)
SBP (mmHg)	130.1 ± 11.3	134 ± 14.1	136.8 ± 16.8	132.9 ± 16.2	147 ± 17.3	131.6 ± 16.5	121.1 ± 13.8	153.2 ± 14.8	130.3 ± 16.9
DBP (mmHg)	79.7 ± 9.4	82.5 ± 9	77 ± 9.8	71.7 ± 11.6	89.6 ± 14	86.2 ± 10.1	74.7 ± 11.3	100.2 ± 11.4	73.8 ± 12.1
HR (bpm)	64.8 ± 13	75.5 ± 10.7	68.8 ± 13.2	65.7 ± 11.2	66.9 ± 12.2	64.4 ± 9.8	58.2 ± 8.3	68.9 ± 12.6	-
PWV (m/s)	10.2 ± 1.6	10.7 ± 2.2	12 ± 2.4	11.6 ± 2.7	10.4 ± 1.4	9.1 ± 1.5	9.6 ± 1.6	10.5 ± 2.3	9.7 ± 2.4
AHI (events/h)	44.9 ± 21.2	42.8 ± 21	30.1 ± 30.4	24.7 ± 23.6	22.2 ± 22.3	40.6 ± 16	23.8 ± 19.6	30.9 ± 17.8	38.3 ± 33.4
Mean nocturnal SaO ₂ (%)	92.7 ± 2.4	92.9 ± 2.9	91.7 ± 2.1	93.1 ± 2	92.9 ± 1.8	93.4 ± 2	94.1 ± 1.9	93.3 ± 2.3	92 ± 3.6
SaO ₂ < 90% (%)	7 ± 13.7	13.2 ± 19.5	14.8 ± 21.7	7.2 ± 14.4	4.3 ± 5.4	6.2 ± 12.8	4.2 ± 10.3	11 ± 22.4	16.8 ± 23.3
ESS score	10.3 ± 5.3	10 ± 5.3	-	5.6 ± 3.7	7.7 ± 5.2	10 ± 5.3	8.9 ± 5.1	9.9 ± 4	10.1 ± 4.8

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5 Results are expressed as mean \pm SD or n (%). The percentages correspond to patients with missing data before imputation. *Number of
6 patients from the referral base (Table S1) after exclusion of patients without PWV data.

7 AHI, apnea-hypopnea index; BMI, body mass index; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; SaO₂, oxygen saturation; HR,
8 heart rate; PWV, Pulse wave velocity; SaO₂ < 90%, percentage of recording time spent at a SaO₂ < 90%; SBP, systolic blood pressure.
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10 11 12 13 **Statistical complement about the data imputation method used**

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16 Missing values were imputed using a multiple imputation method when the proportion of missing values was < 20%. Five datasets were
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18 generated using logistic regression for qualitative variables or linear regression for quantitative variables, considering that missing values were
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20 random. Two regression models were used to impute missing data: a logistic regression model for qualitative (binary) variables and a linear
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22 regression method for quantitative variables. To confirm the imputation strategy, a sensitivity analysis was performed by comparing the results
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24 based on complete cases and multiple imputation. This comparison showed no difference. Categorical variables were first imputed using a
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26 continuous model and then the imputed values were categorized using the same threshold in each dataset. The initial study was introduced as
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28 a fixed effect in all regressions models. After imputation, the results of the five dataset were combined using the MI ANALYZE procedure from
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30 SAS, which corresponded to the Rubin's rules.
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Table S3. Patients' characteristics for the whole population

	Initial dataset N = 893	Missing N (%)	Imputed dataset N = 4465
Male (n (%))	644 (72)	3 (0.3)	3232 (72)
Age (yrs)	56 ± 11	1 (0.1)	56 ± 11
BMI (kg/m ²)	29.9 ± 6.9	0 (0)	29.9 ± 6.9
Normal (n (%))	199 (22)		995 (22)
Overweight (n (%))	345 (39)		1725 (39)
Obese (n (%))	163 (18)		815 (18)
Severely obese (n (%))	106 (12)		530 (12)
Morbidly obese (n (%))	80 (9)		400 (9)
Hypertension (n (%))	694 (78)	48 (5.4)	3470 (78)
Type 2 diabetes (n (%))	401 (45)	0	2005 (45)
Dyslipidaemia (n (%))	551 (62)	109 (12.2)	2755 (62)
OSA (n (%))	683 (84)	77 (8.6)	3691 (83)
SBP (mmHg)	133 ± 17	47 (5.3)	133 ± 17
DBP (mmHg)	81 ± 12	46 (5.2)	81 ± 12
HR (bpm)	69 ± 12	167 (18.7)	70 ± 13
PWV (m/s)	10.4 ± 2.3	0 (0)	10.4 ± 2.3
AHI (events/h)	36.8 ± 24.1	77 (8.6)	36.1 ± 23.9
Mean nocturnal SaO ₂ (%)	92.9 ± 2.7	86 (9.6)	92.8 ± 2.7
SaO ₂ < 90% (% of recording time)	10.8 ± 18.3	94 (10.5)	10.7 ± 18.0
ESS score	9.5 ± 5.2	162 (18.1)	9.4 ± 5.1

Results are expressed as mean ± SD or n (%). Percentages of initial data set correspond to patients with missing data before imputation.

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5 AHI, apnoea-hypopnea index; BMI, body mass index; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; SaO₂, oxygen saturation; HR,
6 heart rate; PWV, Pulse wave velocity; SaO₂ < 90%, percentage of recording time spent at a SaO₂ < 90%; SBP, systolic blood pressure.
7 All comparisons between initial and imputed datasets were not significant.
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11 **Statistical complement about the two-step meta-analysis performed**

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14 A two-step individual patient data (IPD) meta-analysis was first performed to assess the heterogeneity between studies. The first step consisted
15 of aggregating the individual data and the second step used a DerSimonian and Laird random effects meta-analysis model. The heterogeneity
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17 between studies was measured using the I² inconsistency index, which provides an estimation of the variability due to the heterogeneity rather
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19 than chance. An I² index greater than 60% reflects high heterogeneity. Finally, the robustness of the results was assessed using sensitivity
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21 analysis by leaving out one study.
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27 The two-step IPD meta-analysis showed that the test for heterogeneity was not significant (I²=44.7%, p=0.09), which means that only limited
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29 heterogeneity was observed across the 9 studies.
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32 Finally, the result of the two-step meta-analysis showed a slight association between severe OSA and PWV (Figure S1). However, this result
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34 should be interpreted carefully because there was no adjustment on the different confounders. Moreover, the leave-one-out study we
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36 performed showed that the main heterogeneity was mainly due to one study (ADISAS) (Table S4) and by excluding this study the result was not
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38 significant. The observed trend was not significant after adjustment in the one-step meta-analysis.
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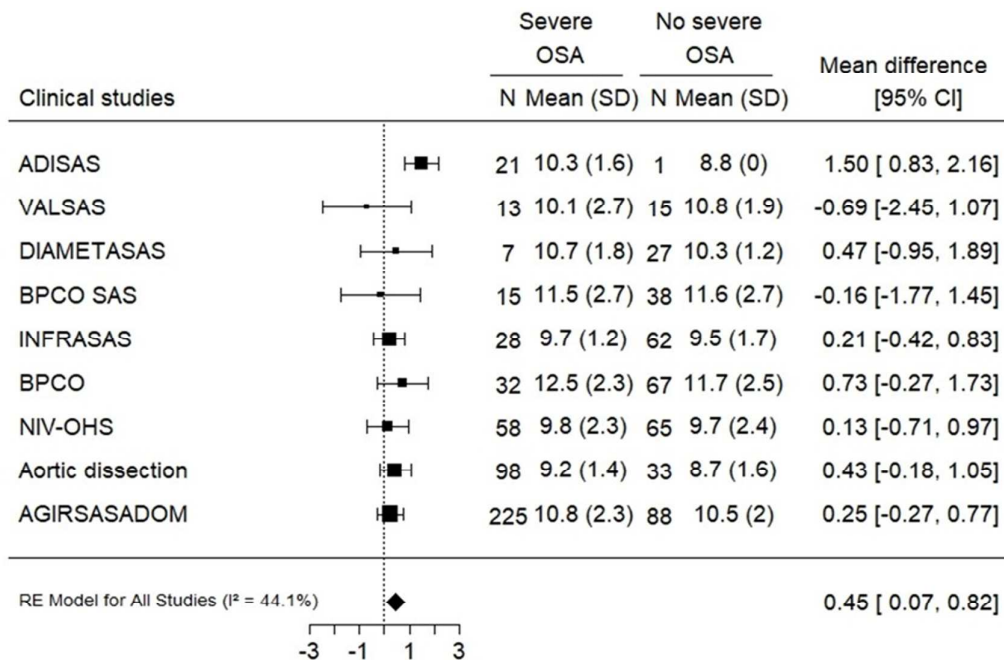
Table S4. Result of the leave-one-out analysis

Study	Estimate (SE)	P value	I ²
ADISAS	0.2761 (0.1443)	0.0557	0
AGIRSASADOM	0.4794 (0.2266)	0.0344	46.4611
BPCO	0.4097 (0.2130)	0.0544	50.0736
BPCO SAS	0.4739 (0.1993)	0.0174	47.689
DIAMETASAS	0.4405 (0.2053)	0.0319	49.7725
Aortic dissection	0.4380 (0.2285)	0.0553	50.0152
INFRASAS	0.4827 (0.2213)	0.0292	47.2912
VALSAS	0.4923 (0.1939)	0.0111	45.4131
NIV-OHS	0.4838 (0.2129)	0.023	47.9618

The leave-one-out verifies the robustness of the results by leaving out one study at a time.

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Figure S1. Forest plot of the influence of the OSA severity on PWV



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