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Impact of three hypopnea-scoring criteria on OSA prevalence and associated comorbidities in the general population

--Manuscript Draft--

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Abstract:	Study Objectives: Apnea-hypopnea index (AHI) is the main polysomnographic measure to diagnose obstructive sleep apnea (OSA). We aimed to evaluate the impact of three standard hypopnea definitions on the prevalence of OSA and its association with cardiometabolic outcomes in the general population. Methods: We analyzed data from the Hypnolaus study (Lausanne, Switzerland), in which 2,162 participants (51% women, 57±19 years) underwent in-home full polysomnography. AHI was calculated using three hypopnea definitions: AASM1999 (≥50% decrease in airflow or lower airflow reduction associated with oxygen desaturation ≥3% or an arousal), AASM2007 (>30% airflow reduction associated with >4% oxygen desaturation), and AASM2012 (>30% airflow reduction associated with >3% oxygen desaturation or an arousal). Participants underwent clinical assessment for hypertension, diabetes and metabolic syndrome. Results: Median AHI of AASM1999, AASM2007 and AASM2012 criteria were 10.9/h, 4.4/h, and 10.1/h, respectively. OSA prevalence defined as AHI ≥5/h, ≥15/h and ≥30/h was 74.5%, 39.3%, and 16.3% using AASM1999; 46.9%, 18.8%, and 6.8% using AASM2007; and 72.2%, 36.6%, and 14.9% using AASM2012. Different AHI thresholds derived from AASM1999, AASM2007 and AASM2012 criteria, respectively, were associated with hypertension (11.5/h, 4.8/h, 10.7/h), diabetes (15.7/h, 7.1/h, 14.4/h) and metabolic syndrome (12.8/h, 5.5/h, 11.8/h). Conclusions: Hypopnea definition has a major impact on AHI and on OSA prevalence in the general population and, hence, important implications for public health policies. There is a two-fold difference in the threshold above which an association with diabetes, hypertension and metabolic syndrome is observed using AASM2007 instead compared to AASM1999 or AASM2012 criteria.
Suggested Reviewers:	Erna Sif Arnardóttir Landspitali University Hospital ernasif@landspitali.is

	Expertise in the area
	Warreb Ruehland Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia Warren.Ruehland@austin.org.au Expertise in the area
Opposed Reviewers:	
Response to Reviewers:	Reviewer #1: This was an interesting study designed to assess the impact of different scoring criteria on OSA prevalence from a community based standpoint. Overall, I thought the paper was well written and I have few comments. The authors used the Hypnolaus cohort and used 3 different hyponea definitions. Not surprisingly, AHI varied substantially depending on the definition. I had the following comments/questions: We are very grateful for these positive comments. 1.It might be interesting to determine which indices predict ESS. Arousal associated measures may have more impact on these than the CV measures. We found no significant correlation between AHI and ESS, independently of the hypopnea criteria used. These results were included as supplemental material as they would not enrich the study. We believe that an objective measure of sleepiness would better answer this relevant question since ESS does not seem to be a reliable measure of sleepiness in our cohort. 2.Can you report the r values between the different definitions to determine the degree of collinearity? The “r” values are very high as expected. R=0.996 for correlation between AASM1999 and AASM2012-derived AHI; R=0.959 for correlation between AASM2007 and AASM2012-derived AHI; and R=0.951 for correlation between AASM2007 and AASM1999-derived AHI. This information has been included in the revised version of the manuscript on page 12. Reviewer #2: This a clearly written manuscript documenting the impact of different PSG scoring rules (AASM1999, 2007-recommended, and 2012) on AHI and thereby the reported prevalence and severity of OSA as defined by AHI thresholds of 5,15 and 30. The authors have used a population sample which is major strength. These thresholds were not redefined in 2007 when the first substantive changes were made to hypopnea definitions - which surprised a lot of people, this reviewer included. Furthermore, the authors show not only how these changes impact on AHI thresholds for OSA diagnosis and severity ratings, but then show, using their own data, how this affects the reported associations between AHI and hypertension, diabetes and metabolic syndrome. The study is one of several to point out the challenge that these scoring rule changes have created for clinicians and epidemiologists alike. We are very grateful for these positive comments. The results largely mirror previous findings with respect to AHI thresholds and in this sense the report is not particularly original. What would be of greater help to researchers, and add more value to this field of research would be if the authors could, as part their report, review (in table form) the major cohort studies performed over the last two decades with respect to scoring methods and show how the rule changes might have affected the ORs reported for "mild" "moderate" and "severe" OSA on cardio-metabolic risk. We understand the Reviewer’s point of view, however, this is the first study performed in a general population sample using standard and up to date techniques, which evaluated not only the correspondence between AHI thresholds, but also the association with cardiometabolic outcomes. As suggested, we have provided 3 new tables with the main cohort studies performed in the last 2 decades describing its scoring method, cardiometabolic outcomes (diabetes, hypertension and metabolic syndrome) and AHI thresholds associated with each outcome. However, as none of them provided their findings using different scoring criteria in the same work, it is not possible to infer about the differences in OR by comparing only their scoring methods since several methodological differences including sample size, outcome definition,

gender, and adjusted covariates exist and may play a role in the OR differences among studies. Moreover, none of them used the AASM 2012 criteria for hypopneas and some used no-AASM scoring criteria. We inserted the following paragraph in the discussion section:
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Thank you for the suggestion. We have added this issue in the Discussion (page 14).

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Additional Information:	
Question	**Response**
Can you confirm that the manuscript has been submitted solely to this journal and is not published, in press, or submitted elsewhere?	Yes
Can you confirm that all the research meets the ethical guidelines, including adherence to the legal requirements of the study country?	Yes
Is the corresponding author a member of the AASM?	No
If the corresponding author is a member of the AASM, please provide your membership number (if known).	
Has this manuscript been previously submitted to JCSM?	No
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Dear Dr. Collop,

We thank the Journal and Reviewers for their comments, which were very useful to guide our revisions. All suggested modifications were incorporated into our manuscript, and we hope that we have adequately addressed the Reviewers' concerns. Please find below a point-by-point response to all of the Reviewers' comments and a list of the changes made to the manuscript.

Yours sincerely,

C. Hirotsu for the coauthors

Reviewer #1: This was an interesting study designed to assess the impact of different scoring criteria on OSA prevalence from a community based standpoint. Overall, I thought the paper was well written and I have few comments. The authors used the Hypnolaus cohort and used 3 different hyponea definitions. Not surprisingly, AHI varied substantially depending on the definition. I had the following comments/questions:

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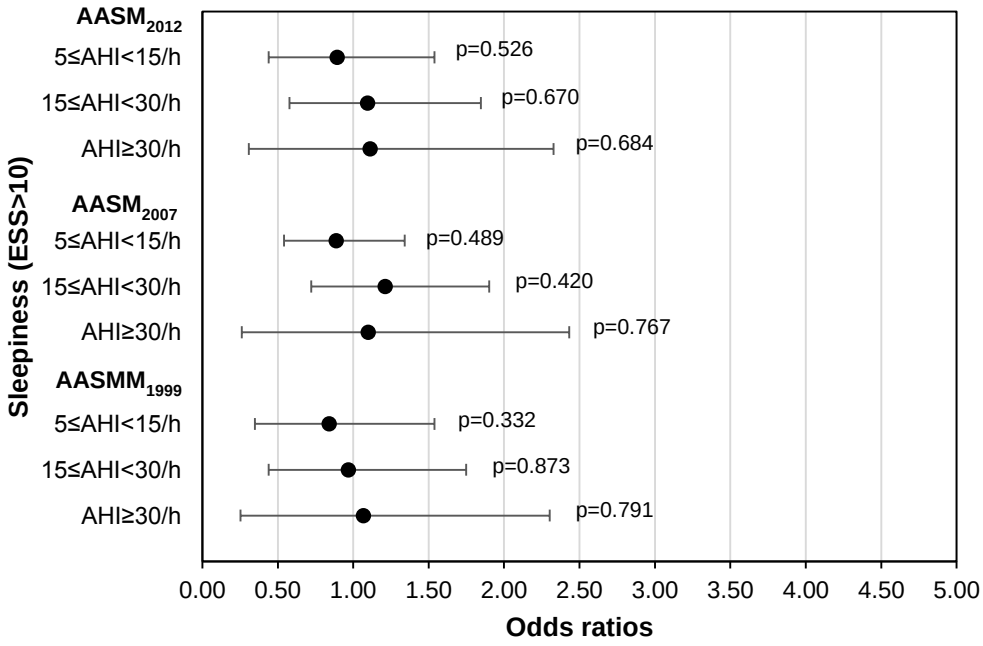
We found no significant correlation between AHI and ESS, independently of the hypopnea criteria used. These results were included as supplemental material as they would not enrich the study. We believe that an objective measure of sleepiness would better answer this relevant question since ESS does not seem to be a reliable measure of sleepiness in our cohort.

Lack of association between AHIs and subjective sleepiness.



Odds ratio and 95% confidence intervals of the association between apnea-hypopnea index (AHI) categories (15<AHI≤5/h, 30<AHI≤15/h and AHI≥30/h compared to AHI<5/h) derived from three different recommended AASM criteria (1999, 2007 and 2012) and the presence of sleepiness assessed by Epworth Sleepiness Score (ESS) (n=1,982) in the HypnoLaus cohort. Data analyzed with multivariable logistic regression adjusted for age, body mass index and sex.

Lack of association between subjective sleepiness (ESS>10) and different polysomnographic parameters in the HypnoLaus cohort.

Variable	p-value	AUC	95% CI	
			Lower	Upper
AHI				
$AASM_{2012}$	0.433	0.485	0.447	0.523
$AASM_{2007}$	0.262	0.478	0.440	0.517
$AASM_{1999}$	0.412	0.484	0.446	0.522
3% ODI	0.412	0.484	0.446	0.523
4% ODI	0.372	0.483	0.444	0.521
Arousal index	0.826	0.496	0.458	0.534

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: "Chicago criteria" hypopnea definition, $AASM_{2007}$: 2007 AASM recommended hypopnea definitions, $AASM_{2012}$: 2012 AASM recommended hypopnea definitions, AHI: apnea-hypopnea index, AUC: area under the curve, CI: confidence interval, ODI: oxygen desaturation index. Data expressed as AUC, 95% CI, and analyzed using receiver operating characteristic (ROC) operating curve.

2. Can you report the r values between the different definitions to determine the degree of collinearity?

The "r" values are very high as expected. R=0.996 for correlation between $AASM_{1999}$ and $AASM_{2012}$-derived AHI; R=0.959 for correlation between $AASM_{2007}$ and $AASM_{2012}$-derived AHI; and R=0.951 for correlation between $AASM_{2007}$ and $AASM_{1999}$-derived AHI. This information has been included in the revised version of the manuscript on page 12.

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Impact of three hypopnea-scoring criteria on OSA prevalence and associated comorbidities in the general population

Camila Hirotsu PhD,[1,2] Jose Haba-Rubio MD,[1,2] Daniela Andries,[1] Nadia Tobback,[1] Pedro Marques-Vidal MD, PhD,[3] Peter Vollenweider MD,[3] Gérard Waeber MD,[3] Raphael Heinzer MD, MPH[1,4]

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[2]C. Hirotsu and J. Haba-Rubio contributed equally to this study as co-first authors

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[4]Pulmonary Department, University Hospital of Lausanne (CHUV), Lausanne, Switzerland

Subtitle: Hypopnea scoring criteria and OSA

[1]Institution where the work was performed

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Brief summary

Current knowledge/Study rationale

The American Academy of Sleep Medicine's rules for scoring hypopneas have changed thrice over the last 20 years, but their clinical impact on the prevalence of obstructive sleep apnea and their association with hypertension, diabetes and metabolic syndrome in the general population are unknown.

Study Impact

Our findings indicate that the method used for scoring hypopneas significantly influences the prevalence of obstructive sleep apnea and its association with cardiometabolic outcomes. We could provide predictive equations to translate the differences in apnea-hypopnea indexes within three recommended criteria of the American Academy of Sleep Medicine in a general population-based sample. Further, this study highlights the need for standardization of the scoring method to allow compatibility among epidemiological studies.

ABSTRACT

Study Objectives: Apnea-hypopnea index (AHI) is the main polysomnographic measure to diagnose obstructive sleep apnea (OSA). We aimed to evaluate the impact of three standard hypopnea definitions on the prevalence of OSA and its association with cardiometabolic outcomes in the general population.

Methods: We analyzed data from the Hypnolaus study (Lausanne, Switzerland), in which 2,162 participants (51% women, 57±19 years) underwent in-home full polysomnography. AHI was calculated using three hypopnea definitions: $AASM_{1999}$ (≥50% decrease in airflow or lower airflow reduction associated with oxygen desaturation ≥3% or an arousal), $AASM_{2007}$ (≥30% airflow reduction associated with ≥4% oxygen desaturation), and $AASM_{2012}$ (≥30% airflow reduction associated with ≥3% oxygen desaturation or an arousal). Participants underwent clinical assessment for hypertension, diabetes and metabolic syndrome.

Results: Median AHI of $AASM_{1999}$, $AASM_{2007}$ and $AASM_{2012}$ criteria were 10.9/h, 4.4/h, and 10.1/h, respectively. OSA prevalence defined as AHI ≥5/h, ≥15/h and ≥30/h was 74.5%, 39.3%, and 16.3% using $AASM_{1999}$; 46.9%, 18.8%, and 6.8% using $AASM_{2007}$; and 72.2%, 36.6%, and 14.9% using $AASM_{2012}$. Different AHI thresholds derived from $AASM_{1999}$, $AASM_{2007}$ and $AASM_{2012}$ criteria, respectively, were associated with hypertension (11.5/h, 4.8/h, 10.7/h), diabetes (15.7/h, 7.1/h, 14.4/h) and metabolic syndrome (12.8/h, 5.5/h, 11.8/h).

Conclusions: Hypopnea definition has a major impact on AHI and on OSA prevalence in the general population and, hence, important implications for public health policies. There is a two-fold difference in the threshold above which an association with diabetes, hypertension and metabolic syndrome is observed using $AASM_{2007}$ instead compared to $AASM_{1999}$ or $AASM_{2012}$ criteria.

Keywords: obstructive sleep apnea; hypopnea; methodology; polysomnography; general population.

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent partial (hypopneas) or total (apneas) episodes of upper airway obstruction during sleep,[1] and has been widely recognized as an important and treatable risk factor for cardiovascular and metabolic conditions.[2, 3] Polysomnography (PSG) is considered the gold standard for identifying individuals with OSA. Among the several parameters measured by PSG, the apnea-hypopnea index (AHI), which comprises the average number of apneas and hypopneas per hour of sleep, is the main metric for diagnosing OSA, as well as for assessing the disease severity and responsiveness to the treatment. A recent systematic review showed that, in general populations, OSA prevalence as AHI ≥5 events/h varies considerably among studies (9% to 38%).[4] Higher estimates were also observed over time in the most recent epidemiological studies.[5] Among the possible explanations for these findings, ethnical composition, equipment-related issues and changes in respiratory events definition might have an important role.

Indeed, several definitions of hypopnea have been used in research and the clinical setting, leading to large inter-laboratory variations in AHI depending on the definition used.[6-10] These differences relate to the degree of airflow reduction, the amplitude of oxygen desaturation and the association with electroencephalographic arousal required to define a hypopnea. Since OSA diagnosis and treatment decision are largely based on AHI, the definition of hypopnea may have a direct impact on OSA prevalence estimates and the patients' management. Thus, the aim of our study was to evaluate the impact of three hypopnea definitions on the prevalence and severity of OSA in a middle-aged general population sample. We compared three standard definitions for identifying hypopneas: the 1999 American Academy of Sleep Medicine (AASM) criteria (also known as Chicago criteria)[11], the recommended 2007 AASM[12]

and 2012 AASM[13] definitions. Secondarily, we sought to establish the AHI thresholds that could predict the presence of hypertension, diabetes and metabolic syndrome as well as to compare the association between OSA severity and these cardiometabolic outcomes using each hypopnea definition.

METHODS

Population sample

This is a cross-sectional study that analyzed data from HypnoLaus, a population-based sleep cohort study (Lausanne, Switzerland) performed between September 1, 2009 and June 30, 2013. HypnoLaus participants were recruited among subjects form the CoLaus/PsyCoLaus cohort.[14] CoLaus/PsyCoLaus is a population-based cohort of 6,734 participants (52.5% women) aged 35-75 years, identified from a random sample of all age-eligible adults living in the city of Lausanne, Switzerland (117,161 habitants). The CoLaus/PsyCoLaus study was conducted to assess the prevalence of cardiovascular risk factors and to identify new determinants of these risk factors and their association with mental disorders.[15] For the HypnoLaus nested study, participants of the CoLaus/PsyCoLaus study were invited to answer sleep questionnaires regarding their sleep habits and potential sleep disorders, and the first consecutive 3,043 were contacted to have a full sleep study at home. Of these, 71% (n=2,168) accepted the invitation and underwent PSG, among which 3% (n=60) had technical problems. Of these, six participants declined to undergo a second PSG, and 54 participants agreed.[16] Therefore, 2,162 PSG recordings comprised the HypnoLaus cohort and were included in this study. The Institutional Review Board in Lausanne approved the study, and all participants gave their written informed consent.

Clinical data collection

Participants from HypnoLaus study were invited to attend the outpatient clinic at the University Hospital of Lausanne (CHUV, Lausanne, Switzerland). After an overnight fasting they were also invited for questionnaires completion, clinical assessment and blood samples collection. Body weight and height were measured using a calibrated scale and a vertical stadiometer, respectively (Seca®, Hamburg, Germany). Body mass index (BMI) was calculated as body mass in kg divided by the square of the participant's height in meters. Waist circumference (at the level of the umbilicus) was measured to within 0.5 cm with plastic tape. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were evaluated in triplicate on the left arm at 5-min intervals with the participant seated and resting for at least 10 min using a calibrated automated oscillometric sphygmomanometer (Omron® HEM-907, Matsusaka, Japan).[17] Overnight fasting blood samples were taken of each participant. Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were quantified by colorimetric assays as previously described.[18] These assays were performed on fresh blood samples by the CHUV Clinical Laboratory (Lausanne, Switzerland).

Polysomnography

An in-home overnight full PSG was performed, using a digital portable sleep-wake recording system (EMBLA Titanium®, Embla systems, Inc, Broomfield, USA). A trained technician hooked-up the subject in the CIRS facility (Center for Investigation and Research in Sleep, CHUV, Lausanne, Switzerland). The electrodes and recorder were installed at the laboratory and recordings were done in the normal home environment. PSG measurements included: electroencephalograms (EEG) from

frontal, central and occipital areas (F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1) according to the international 10/20 electrode configuration system, right and left electrooculograms (EOG), mental-submental electromyogram (EMG), right and left leg EMG, thoracic and abdominal breathing movements by respiratory inductance plethysmography, respiratory airflow by a nasal-cannula connected to a pressure transducer, oxygen saturation (SpO_2) by pulse oxymetry, heart rate by electrocardiogram (ECG), and body position.

Scoring of polysomnography

PSGs were scored using Somnologica software (Embla systems, Inc, Broomfield, USA) by two experienced scorers (DA, NT), with an inter-agreement concordance greater than 90%. Sleep, arousal and movements during sleep were scored based on the 2007 AASM manual for the scoring of sleep and associated events.[19] Concerning respiratory events, an apnea was defined by a complete or almost complete (>90%) cessation of airflow (measured by nasal pressure) lasting 10 seconds or longer. Hypopneas were initially scored based on the Chicago criteria ($AASM_{1999}$), being defined by criterion 1 or 2, plus criterion 3:

1. A clear decrease (>50%) of airflow amplitude from the baseline. Baseline was defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).
2. A clear reduction of airflow amplitude, not reaching the above criterion but associated with either an oxygen desaturation of ≥3% or an arousal. From an

operational standpoint, a discernible reduction in airflow was considered a >30% reduction in the airflow signal.

3. The event lasts 10 seconds or longer.

An AHI for each individual was calculated, consisting of the number of apneas and hypopneas per hour of sleep. Each recording was reviewed for validation of the respiratory scoring by a single investigator (JHR).

Since both recommended 2007 and 2012 AASM criteria represent a subset of Chicago criteria's events, we derived the other two AHI definitions from the first scoring. For the recommended 2007 AASM criteria ($AASM_{2007}$), we removed hypopneas that did not fulfill the stricter AASM hypopnea definition, i.e., hypopneas that were not associated with ≥4% oxygen desaturation. For the recommended 2012 AASM criteria ($AASM_{2012}$), we removed hypopneas that were not associated with either an arousal or a ≥3% oxygen desaturation (Table S1).

OSA severity was classified according to standard criteria as mild (5≤AHI<15 events per hour of sleep), moderate (15≤AHI<30 events per hour of sleep), and severe (AHI≥30 events per hour of sleep). AHI<5/h was defined as no-OSA.

Outcomes

Hypertension was defined as a SBP≥140 mmHg and/or DBP≥90 mmHg, and/or use of anti-hypertensive medication. Diabetes was considered positive when fasting plasma glucose levels were ≥7.0 mmol/L or there was use of antidiabetic medication.[20] Metabolic syndrome was defined according to the Joint Interim Statement (JIS),[21] as the presence of at least three risk factors among: high blood pressure (SBP≥130 mm Hg or DBP≥85 mm Hg or use of antihypertensive medication); visceral obesity (waist circumference ≥88 cm in women or ≥102 cm in men); high triglycerides (≥1.7 mmol/L,

or use of fibrates or nicotinic acid); low HDL levels (<1.30 mmol/L in women or <1.03 mmol/L in men, or use of fibrates or nicotinic acid); and high fasting plasma glucose (≥5.6 mmol/L or use of antidiabetic medication).

Statistical analysis

We used AHI as the primary variable in this study for analysis of the differences between hypopnea scoring criteria. AHI is displayed according to the median and interquartile range (IQR) values. The differences between the three different AHIs obtained through $AASM_{1999}$, $AASM_{2007}$, and $AASM_{2012}$ criteria were assessed using the Friedman test, with pairwise comparisons performed by Wilcoxon signed-rank test. Bar graphs were constructed to represent the prevalence of OSA using each AASM criteria at AHI thresholds of ≥5/h, ≥15/h and ≥30/h. Equivalent thresholds for the three AHIs were estimated using the receiver operator curves (ROC) with each AHI as the gold standard, giving equal weight to maximize both sensitivity and specificity. Bland-Altman plots representing the mean difference between each pair of AHI according to each scoring criteria was built to illustrate the agreement between AHIs. Conversion equations between each pair of AHI were established with linear or quadratic regressions, with the latter being employed when appropriate. AHI thresholds significantly associated with the presence of hypertension, diabetes and metabolic syndrome were estimated by ROC analysis using each hypopnea criteria. Multivariable logistic regression was used for testing the association between OSA severity (mild, moderate or severe OSA *vs* no-OSA) and the presence of hypertension, diabetes and metabolic syndrome using each scoring criteria.

RESULTS

Population sample and OSA prevalence

The patient characteristics and PSG results are shown in Table 1. Participants were 57.2 ± 19.2 (median ± IQR) years of age with a BMI of 25.7 ± 5.4 kg/m^2. The sample included 51% of women. The average total sleep time was 404.0 ± 89.0 min and the sleep efficiency 87.6 ± 13 %.

The prevalence of OSA in the HypnoLaus cohort based on different AASM scoring criteria is presented in Figure 1. When using AHI thresholds of ≥5/h, ≥15/h and ≥30/h, respectively, $AASM_{2007}$ would provide 34.9%, 48.6% and 54.2% lower OSA diagnosis rate compared to $AASM_{2012}$ as well as 37.0%, 52.1% and 58.1% lower OSA diagnosis rate compared to $AASM_{1999}$ criteria. Compared to $AASM_{1999}$ criteria, $AASM_{2012}$ would provide 3.2%, 6.8% and 8.5% lower OSA diagnosis rate when using the same AHI thresholds.

AHI agreement

Table 2 shows median ± IQR of AHI in the HypnoLaus population according to the three scoring criteria. All AHIs were significantly different from each other ($p<0.001$) by Friedman test and post-hoc comparisons. The median AHI of $AASM_{2007}$ and $AASM_{2012}$ criteria were approximately 40% and 93% of the median AHI of $AASM_{1999}$. In turn, the median AHI of $AASM_{2007}$ was approximately 44% of the median AHI of $AASM_{2012}$. Bland-Altman plots (Figure 2) show the agreement between each pair of AHI according to the different scoring criteria. The variation in the mean AHI difference between each pair of scoring criteria was greater according to the AHI magnitude, except for the comparison between $AASM_{1999}$ and $AASM_{2012}$ criteria, which was more stable. The Bland Altman plots demonstrate a mean increase of 6.4 events/h when

comparing AHI definitions between $AASM_{2007}$ and $AASM_{2012}$; a mean reduction of 0.9/h when comparing $AASM_{2012}$ and $AASM_{1999}$; and a mean reduction of 7.3/h when comparing $AASM_{2007}$ and $AASM_{1999}$ criteria.

Equivalent AHIs and prediction equations

Table 3 shows the equivalence between the scoring criteria for each AHI threshold. For instance, when using $AASM_{2012}$ according to AHI thresholds of ≥5/h, ≥15/h and ≥30/h, to achieve a similar OSA prevalence $AASM_{2007}$ would have to shift its thresholds down to about 2.0/h, 6.6/h and 14.9/h, respectively. In male and female subsamples, the equivalent AHI threshold conversion factors were similar to those of the whole sample.

Prediction equations to determine the relationship between each pair of AHI are represented in Figure 3. All equations showed a R^2 ≥0.90 as high collinearity was present between criteria (R=0.996 for correlation between $AASM_{1999}$ and $AASM_{2012}$-derived AHI; R=0.959 for correlation between $AASM_{2007}$ and $AASM_{2012}$-derived AHI; and R=0.951 for correlation between $AASM_{2007}$ and $AASM_{1999}$-derived AHI). In the prediction equations between $AASM_{2007}$ and $AASM_{2012}$ as well as $AASM_{2007}$ and $AASM_{1999}$, a quadratic regression better fitted the relationship, but with a small increase in R^2 of 0.02 compared to the linear regression.

Impact of scoring criteria on the association between OSA and outcomes

The AHI thresholds significantly associated with hypertension, diabetes and metabolic syndrome according to the three scoring criteria are represented in Table 4. For all outcomes assessed, the area under the curves (AUCs) as well as the sensitivity and specificity were similar among the three scoring criteria. Overall, higher AHI

thresholds emerged from $AASM_{1999}$, followed by $AASM_{2012}$. AHI thresholds derived from $AASM_{2007}$ criteria were approximately half of the respective AHI thresholds derived from both $AASM_{1999}$ and $AASM_{2012}$.

The association between OSA severity and the presence of cardiometabolic outcomes adjusted for age, sex and BMI is represented in Figure 4. For hypertension, we observed an independent association with severe OSA *vs* no-OSA using both $AASM_{2012}$ (OR=1.46, 1.01-2.10) and $AASM_{1999}$ (OR=1.55, 1.08-2.22), but not $AASM_{2007}$ (OR=1.30, 0.83-2.05). For diabetes, there was significant associations with all OSA groups *vs* no-OSA in both $AASM_{2012}$ (mild OSA: OR=2.13, 1.16-3.91; moderate OSA: OR=2.31, 1.23-4.32; severe OSA: OR=2.44, 1.28-4.68) and $AASM_{1999}$ (mild OSA: OR=1.92, 1.02-3.62; moderate OSA: OR=2.34, 1.23-4.43; severe OSA: OR=2.35, 1.21-4.55). Regarding $AASM_{2007}$, diabetes was significantly associated with moderate (OR=1.61, 1.02-2.56) and severe OSA (OR=1.81, 1.07-3.05), but not with mild OSA (OR=1.46, 0.99-2.17) when compared to no-OSA.

For metabolic syndrome, we found significant associations with all OSA groups *vs* no-OSA using the three scoring criteria as follows: $AASM_{2012}$ (mild OSA: OR=1.58, 1.12-2.22; moderate OSA: OR=1.68, 1.16-2.43; severe OSA: OR=2.38, 1.58-3.60); $AASM_{2007}$ (mild OSA: OR=1.48, 1.13-1.93; moderate OSA: OR=1.66, 1.17-2.35; severe OSA: OR=2.26, 1.42-3.59); $AASM_{1999}$ (mild OSA: OR=1.63, 1.14-2.33; moderate OSA: OR=1.68, 1.15-2.46; severe OSA: OR=2.41, 1.59-3.64).

There was no associations between the different AHI thresholds and subjective sleepiness (Epworth score) regardless the hypopnea scoring criteria used (Figure S1 and supplementary Table S2).

Discussion

To the best of our knowledge, this is the first study that explored the extent to which different hypopnea definitions influence OSA recognition and its association with cardiometabolic outcomes in a general population sample. Using three standard hypopnea definitions with airflow assessed by nasal-cannula pressure transducer, we could provide conversion equations between AHIs and equivalent thresholds among the scoring criteria. Our results show up to two-fold difference in AHI level above which an association was found with cardiometabolic outcomes between $AASM_{2007}$ and $AASM_{1999}$/$AASM_{2012}$. Lastly, an independent association between severe OSA and hypertension was only found using $AASM_{1999}$ or $AASM_{2012}$ criteria after adjusting for confounders.

To date, all studies that aimed to evaluate the association between OSA and metabolic syndrome[22-26], diabetes[27-33] or hypertension[34-42] have used older AASM criteria ($AASM_{1999}$/$AASM_{2007}$) or non-AASM criteria for hypopnea scoring, hampering a reliable comparison among them. Besides the differences in scoring criteria, important heterogeneity in study design, sample size, outcome definition, and demographic factors may have played a role in the inconsistent results found, as shown in Tables 5 to 7.

Previous studies have examined the agreement between different approaches to determine AHI, showing significant differences in OSA frequency and mean AHI scores using different hypopnea scoring definitions.[43, 44] These studies were conducted in small clinical populations using a thermistor to assess airflow. It is also important to highlight, that these results may not be relevant any longer considering the technical differences with current clinical practice, as most sleep centers use the nasal-cannula pressure transducer to evaluate hypopneas.

As in our study, Ruehland *et al* compared AHIs derived from $AASM_{1999}$ criteria, $AASM_{2007}$ recommended criteria, and $AASM_{2007}$ alternative criteria (≥50% airflow reduction associated with 3% desaturation or an arousal).[10] They explored the impact of hypopnea definition on the prevalence of OSA in a clinical population using nasal pressure for airflow assessment, and demonstrated that using these standard hypopnea definitions leads to marked differences in AHI. For example, the median AHI obtained using the $AASM_{2007}$ recommended criteria for scoring hypopneas was approximately 30% of the median AHI obtained using the $AASM_{1999}$ criteria. In our study, this correspondence was a little higher, 40% of the $AASM_{1999}$ criteria and could be explained by the differences in the source of sample used (clinical *vs* general population), the sample size (328 *vs* 2,162) and the more liberal interpretation of "discernible" difference in flow used by the authors.[10]

Few studies have evaluated the impact of different hypopnea scoring criteria in population-based research samples. Redline *et al* analyzed data from the Sleep Heart Health Study.[45] They examined the effect of using 11 different criteria for scoring hypopneas on the prevalence of disease and found that the median values of respiratory disturbance index (RDI) varied by approximately 10-fold for definitions that used the most liberal criteria for event identification (using amplitude changes without any requirement for associated desaturation or arousal) to the most conservative definition (requiring an associated >5% desaturation with amplitude changes).

Our findings showing that the $AASM_{2012}$ recommended criteria results in higher AHI compared to the $AASM_{2007}$ recommended criteria and doubles approximately the number of patients diagnosed with OSA are in agreement with previous studies.[8, 9] BaHamman *et al*[9] showed that the AHI derived from $AASM_{2007}$ recommended was 62% lower than the $AASM_{2012}$ recommended criteria. Considering the AHI thresholds of

≥5/h, ≥15/h and ≥30/h, they found that the $AASM_{2007}$ recommended criteria underestimated by 45%, 52% and 32%, respectively, the OSA patients identified by the $AASM_{2012}$ recommended criteria. In our study, we found a lower underdiagnosis rate for mild (34.9%) and moderate OSA (48.6%), but higher for severe OSA (54.2%). This could be because they used a clinical sample suspected for OSA, in which the proportion of OSA severity was overestimated compared to a general population sample.

In a retrospective study performed in 112 consecutive patients of an Australian clinical sleep laboratory in a tertiary hospital, Duce *et al* [8] investigated the equivalent AHI thresholds regarding the $AASM_{1999}$, $AASM_{2012}$ recommended, and both the $AASM_{2007}$ recommended and alternative criteria. To achieve the same OSA prevalence as the $AASM_{2012}$ recommended criteria at AHI thresholds of ≥5/h, ≥15/h and ≥30/h, they showed that the $AASM_{2007}$ recommended criteria would have to change their thresholds to 2.6/h, 7.2/h and 14.1/h, respectively and the $AASM_{1999}$ criteria to 7.3/h, 17.4/h and 31.7/h, respectively. Overall, these findings are in agreement with our results from a general population sample. They also established equations to convert the different AHIs to one another, which were close to ours.

In terms of clinical relevance, our study additionally compared the association of OSA, based on different AHI thresholds, with the presence of cardiometabolic outcomes using the three scoring criteria. We observed more significant associations with hypertension and diabetes using the $AASM_{2012}$ and $AASM_{1999}$ criteria, both of which require a lower oxygen desaturation and consider arousal for defining a hypopnea when compared to the $AASM_{2007}$ recommended criteria. While there is apparently an equivalence in the 3% or 4% criterion of oxygen desaturation for hypopnea definition in terms of increased cardiovascular risk,[46, 47] a debate about the

clinical relevance of the arousal as part of the hypopnea definition exists. The inclusion of an arousal or the decrease in oxygen desaturation threshold (4% *vs* 3%) from the $AASM_{2007}$ to $AASM_{2012}$ recommended criteria seem to contribute almost equally to the resulting AHI increase.[8] When testing 3% oxygen desaturation index (ODI), 4% ODI and arousal index as predictors of hypertension, diabetes and metabolic syndrome in our sample (data not shown), we found independent associations of both 3% ODI and 4% ODI with diabetes and metabolic syndrome, but not with hypertension. No significant association was observed with arousal index alone. On the other hand, the treatment of sleep-disordered breathing associated with sleep fragmentation, but not with oxygen desaturation, has shown benefits on daytime sleepiness,[48, 49] suggesting that the inclusion of arousals may be clinically relevant. Through ROC analysis, we observed that the AHIs derived from the three scoring criteria were significantly and similarly associated with the presence of hypertension, diabetes and metabolic syndrome. However, the AHI thresholds (considering equal weight to sensitivity and specificity) that better predicted each of these outcomes using the $AASM_{2007}$ recommended criteria were approximately half of the AHI values established for both the $AASM_{2012}$ recommended and the $AASM_{1999}$ criteria. Thus, we believe that the most important is that AHI thresholds need to be adjusted when using stricter hypopnea criteria for a proper interpretation and decision to treat OSA. In our study, we could provide correction factors, reliably translating AHIs from $AASM_{1999}$, $AASM_{2007}$ and $AASM_{2012}$ criteria in a large middle-aged general population sample.

There are several limitations in our study. First, it could be argued that scoring respiratory effort related arousals (RERAs) would capture events scored with the $AASM_{1999}$ criteria that do not fulfill the hypopnea requirements of the $AASM_{2012}$ criteria, and the RDI would be similar using both scoring criteria. Although we did not look

specifically at this point, Ruehland *et al* have shown that the AHI differences between $AASM_{1999}$ and $AASM_{2012}$ were mostly due to events with ≥50% flow reduction, and not associated with significant desaturation or arousal, so these events could not be scored as RERAs (as they are not associated with arousal).[10] We do not believe that including RERAs in the analysis could explain the differences found since these events are rather rare in our population.[50] Second, in this study, OSA was estimated in the presence of respiratory events at different AHI thresholds, but we did not consider other elements as symptoms (sleepiness, fatigue, headache) or associated comorbidities as suggested by the International Classification of Sleep Disorders (ICSD-3).[1] Although we believe that symptoms such as sleepiness are important for clinical decision, the very inclusive ICSD-3 definition for OSA syndrome would have led to a much higher and unrealistic rate of OSA.[51] Third, due to the cross-sectional design of the study, we cannot infer causality regarding the associations between OSA severity derived from each scoring criteria and the cardiometabolic outcomes.

Lastly, this study focused on different AHI definitions but other biomarkers such as autonomic activation, inflammation, genetic and demographic-related factors may prove to be a better predictor or may be used in combination with AHI to stratify OSA-associated risks. Prospective studies are thus required to better understand the parameters that should be used to determine OSA associated risk.

In conclusion, our study demonstrates that using different standard hypopnea definitions leads to marked differences in AHI. The use of $AASM_{2007}$ hypopnea criteria leads to lower equivalent AHI cutoffs for the association with OSA related comorbidities compared to both $AASM_{1999}$ and $AASM_{2012}$ criteria. However, prospective studies are necessary to further evaluate the extent to which cardiovascular and other health

outcomes may be differentially predicted by different AHI definitions, and to identify other sleep-related metrics that may be even more efficient to do so.

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Figure titles and captions

Figure 1 – Prevalence of obstructive sleep apnea.

Prevalence of apnea hypopnea index (AHI) thresholds ≥5/h, ≥15/h and ≥30/h according to three different recommended American Academy of Sleep Medicine (AASM) criteria (1999, 2007 and 2012) in the whole (A), male (B) and female (C) sample of HypnoLaus cohort (n=2,162).

Figure 2 – AHI agreement among different hypopnea criteria.

Bland-Altman plots demonstrating the level of agreement for apnea-hypopnea index (AHI) between American Academy Sleep Medicine (AASM) criteria from 2012 vs 2007, 2012 vs 1999, and 2007 vs 1999, respectively in the HypnoLaus cohort (n=2,162). The dashed line represents the mean difference between the two measured AHIs and the dotted lines represent the mean difference ± 1.96 standard deviation (SD). The x-axis

presents the mean of the two AHIs and the y-axis presents the difference (Δ) between the two measurements.

Figure 3 – AHI equivalence equations among different hypopnea criteria.

Least squares regression showing the apnea-hypopnea indexes (AHIs) equations of equivalence according to the different recommended American Academy of Sleep Medicine (AASM) criteria in the HypnoLaus cohort (n=2,162).

Figure 4 – Association between AHIs and cardiometabolic outcomes.

Odds ratio and 95% confidence intervals of the association between apnea-hypopnea index (AHI) categories (15<AHI≤5/h, 30<AHI≤15/h and AHI≥30/h compared to AHI<5/h) derived from three different recommended AASM criteria (1999, 2007 and 2012) and the presence of hypertension (n=2,147), diabetes (n=2,147) and metabolic syndrome (n=2,149) in the HypnoLaus cohort. Data analyzed with multivariable logistic regression adjusted for age, body mass index and sex.

Abbreviations

AASM, American Academy of Sleep Medicine

$AASM_{1999}$, “Chicago criteria” hypopnea definitions

$AASM_{2007}$, 2007 AASM recommended hypopnea definitions

$AASM_{2012}$, 2012 AASM recommended hypopnea definitions

AHI, apnea-hypopnea index

AUC, area under the curve

BMI, body mass index

CHUV, Centre Hospitalier Universitaire Vaudois

DBP, diastolic blood pressure

ECG, electrocardiogram

EEG, electroencephalogram

EMG, electromyogram

EOG, electrooculogram

HDL, high-density lipoprotein

ICSD, International Classification of Sleep Disorders

IQR, interquartile range

JIS, Joint Interim Statement

No-OSA, without obstructive sleep apnea

OR, odds ratio

OSA, obstructive sleep apnea

PSG, polysomnography

RDI, respiratory disturbance index

RERA, respiratory effort related arousal

ROC, receiver operator curve

SBP, systolic blood pressure

SpO_2, oxygen saturation

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Table 1 - Sample's characteristics.

Parameter	
n	2,162
Age, years	57.2 ± 19.2
Sex, M/F	1,056/1,106
BMI, kg/m^2	25.7 ± 5.4
TST, min	404.0 ± 89.0
Sleep onset latency, min	10.9 ± 16.5
Sleep efficiency, %	87.6 ± 13.0
N1, %	10.2 ± 7.5
N2, %	45.6 ± 12.8
N3, %	19.3 ± 10.9
REM, %	22.3 ± 7.9
Arousal index	18.9 ± 12.4
3% ODI	10.0 ± 15.2
4% ODI	4.1 ± 9.1
Mean SpO_2, %	94.3 ± 2.2
TST with SpO_2<90%, %	0.2 ± 2.1

BMI: body mass index; M/F: male/female; n: sample size; N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3 or slow-wave sleep; ODI: oxygen desaturation index; REM: rapid eye movement; SpO_2: percutaneous oxygen saturation; TST: total sleep time.
Data expressed as median ± interquartile range or number of participants.

Table 2 - Apnea-hypopnea index changes according to hypopnea definitions in the HypnoLaus cohort.

	Apnea-hypopnea index			
	$AASM_{1999}$	**$AASM_{2007}$**	**$AASM_{2012}$**	**p-value**
Whole sample	10.9 ± 17.5	4.4 ± 10.1*	10.1 ± 16.9*#	<0.0001
Male sample	16.0 ± 20.9	6.8 ± 13.5*	15.1 ± 20.4*#	<0.0001
Female sample	7.6 ± 12.1	2.6 ± 6.2*	7.0 ± 11.4*#	<0.0001

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: "Chicago criteria" hypopnea definition; $AASM_{2007}$: 2007 AASM recommended hypopnea definitions; $AASM_{2012}$: 2012 AASM recommended hypopnea definitions; *p<0.0001 compared with AASM1999; #p<0.0001 compared with $AASM_{2007}$.
Data expressed as median ± interquartile range and analyzed using Friedman test with pairwise comparisons performed by Wilcoxon's test.

Table 3 - Equivalent apnea-hypopnea index thresholds for different hypopnea definitions in the HypnoLaus cohort.

Gold standard AHI	**Whole sample** Equivalent AHI thresholds		**Male sample** Equivalent AHI thresholds		**Female sample** Equivalent AHI thresholds	
$AASM_{2012}$	**$AASM_{1999}$**	**$AASM_{2007}$**	**$AASM_{1999}$**	**$AASM_{2007}$**	**$AASM_{1999}$**	**$AASM_{2007}$**
5.0/h	5.7 (99.8, 98.0, 97.5)	2.0 (97.6, 90.9, 91.2)	5.9 (99.8, 98.0, 98.2)	2.1 (97.9, 92.0, 92.3)	5.7 (99.8, 97.3, 97.7)	1.9 (97.1, 90.2, 90.8)
15.0/h	15.6 (99.7, 98.6, 97.5)	6.6 (98.3, 93.0, 92.9)	15.8 (99.8, 98.7, 97.1)	6.7 (97.9, 92.5, 92.4)	15.2 (99.6, 98.8, 97.6)	6.5 (98.5, 93.8, 93.1)
30.0/h	30.4 (99.9, 100.0, 98.6)	14.9 (99.1, 94.7, 94.3)	30.2 (99.9, 100.0, 98.7)	15.0 (98.6, 92.9, 92.7)	30.5 (99.9, 100.0, 98.6)	16.0 (99.5, 98.8, 97.2)
$AASM_{2007}$	**$AASM_{1999}$**	**$AASM_{2012}$**	**$AASM_{1999}$**	**$AASM_{2012}$**	**$AASM_{1999}$**	**$AASM_{2012}$**
5.0/h	11.8 (97.3, 90.0, 90.5)	10.9 (97.7, 91.0, 91.3)	13.0 (96.8, 90.2, 88.9)	12.4 (97.4, 90.2, 91.9)	10.7 (97.4, 91.0, 91.3)	9.4 (97.8, 93.3, 90.8)
15.0/h	23.9 (98.7, 94.3, 94.2)	22.4 (99, 95.1, 94.1)	25.5 (98.2, 93.3, 93.3)	24.0 (98.6, 95.0, 93.9)	21.0 (99.1, 99.2, 94.6)	20.2 (99.3, 99.2, 95.2)
30.0/h	38.2 (99.3, 97.3, 96.1)	37.0 (99.5, 99.3, 96.4)	40.9 (99.0, 97.4, 95.5)	39.8 (99.2, 97.4, 96.1)	35.9 (99.5, 100.0, 96.8)	35.9 (99.6, 100.0, 98.1)
$AASM_{1999}$	**$AASM_{2007}$**	**$AASM_{2012}$**	**$AASM_{2007}$**	**$AASM_{2012}$**	**$AASM_{2007}$**	**$AASM_{2012}$**
5.0/h	1.7 (97.0, 90.7, 91.5)	4.9 (99.8, 97.3, 99.6)	1.7 (93.7, 93.6, 90.3)	4.9 (99.7, 98.6, 99.4)	1.6 (96.4, 90.7, 89.2)	4.6 (99.8, 97.2, 98.5)
15.0/h	6.4 (97.7, 90.2, 93.6)	13.9 (99.8, 97.4, 98.5)	6.4 (97.3, 90.1, 92.9)	13.9 (99.8, 97.7, 98.6)	5.9 (97.9, 93.3, 91.8)	13.9 (99.7, 96.8, 98.4)
30.0/h	13.0 (98.7, 96.3, 92.2)	26.5 (99.9, 98.6, 97.9)	14.4 (98.3, 92.5, 92.9)	28.2 (99.9, 98.8, 99.0)	11.4 (99.1, 100.0, 93.3)	25.9 (99.9, 99.0, 98.8)

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: “Chicago criteria” hypopnea definition; $AASM_{2007}$: 2007 AASM recommended hypopnea definitions; $AASM_{2012}$: 2012 AASM recommended hypopnea definitions; AHI: apnea-hypopnea index.
Data expressed as threshold (area under the curve, sensitivity, specificity) and analyzed using receiver operating characteristic curve.

Table 4 - Equivalent apnea-hypopnea index thresholds associated with cardiometabolic outcomes according to different hypopnea criteria in the HypnoLaus cohort.

AHI	AUC	95% CI	p-value	Threshold	Sensitivity	Specificity
Hypertension						
$AASM_{2012}$	0.67	0.65 - 0.69	<0.0001	10.7	0.62	0.62
$AASM_{2007}$	0.68	0.65 - 0.70	<0.0001	4.8	0.63	0.63
$AASM_{1999}$	0.67	0.65 - 0.69	<0.0001	11.5	0.62	0.61
Diabetes						
$AASM_{2012}$	0.71	0.68 - 0.75	<0.0001	14.4	0.64	0.65
$AASM_{2007}$	0.72	0.68 - 0.75	<0.0001	7.1	0.66	0.67
$AASM_{1999}$	0.71	0.67 - 0.74	<0.0001	15.7	0.65	0.66
Metabolic syndrome						
$AASM_{2012}$	0.71	0.69 - 0.74	<0.0001	11.8	0.65	0.65
$AASM_{2007}$	0.73	0.70 - 0.75	<0.0001	5.5	0.66	0.66
$AASM_{1999}$	0.71	0.68 - 0.73	<0.0001	12.8	0.65	0.64

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: "Chicago criteria" hypopnea definition; $AASM_{2007}$: 2007 AASM recommended hypopnea definitions; $AASM_{2012}$: 2012 AASM recommended hypopnea definitions; AHI: apnea-hypopnea index; AUC: area under the curve; CI: confidence interval.
Data expressed as AUC, 95% CI, AHI threshold, sensitivity and specificity, and analyzed using receiver operating characteristic (ROC) operating curve.
Number of participants with missing data: hypertension (2), diabetes (2).

Table 5 - Population-based studies about the association between obstructive sleep apnea and metabolic syndrome.

Study/Year	Country	Sample size	Gender (male, %)	Age, mean (years)	BMI, mean (kg/m^2)	Outcome definition	Study design	Diagnostic method	Hypopnea criteria	OSA category (AHI)	Results	Association
Nieto et al/2009[1]	USA	546	56.0	59.9	31.1	NCEP ATPIII	Cross-sectional	Standard PSG	Discernible decrease in airflow with at least a 4% desaturation	AHI≥15/h	OR=2.20 [1.20 - 3.90]	Yes
										5≥AHI<15/h	OR=2.5 [1.50 - 4.20]	Yes
										AHI<5		
Chin et al/2010[2]	Japan	275	100	44.0	23.9	NCEP ATPIII	Cross-sectional	Portable PSG	>50% decrease in airflow with at least a 3% desaturation	AHI≥30/h	OR=2.57 [0.68 - 9.69]	No
										15≥AHI<30/h	OR=0.77 [0.30 - 1.99]	No
										5≥AHI<15/h	OR=1.00 [0.47 - 2.13]	No
										AHI<5/h		
Troxel et al/2010[3]	USA	290	N/A	N/A	N/A	NCEP ATPIII	Case-control	PG	≥30% but < 80% decrease in airflow	AHI as continuous variable	OR=1.23 [1.02 - 1.47] per 5 units	Yes
Theorell et al/2011[4]	Sweden	400	0	50.1	26.7	NCEP ATPIII	Cross-sectional	Standard PSG	>50% decrease in airflow with at least a 3% desaturation or an arousal	AHI as continuous variable	OR=1.04 [1.01 - 1.07] per 1 unit	Yes
Hall et al/2012[5]	USA	340	0	51.2	29.8	NCEP ATPIII	Case-control	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	AHI as continuous variable	OR=1.36 [0.97 - 1.92] per 1 unit	No

AHI: apnea-hypopnea index; BMI: body mass index; N/A: not available; NCEP ATPIII: National Cholesterol Education Program Adult Treatment panel III; OR: odds ratio; OSA: obstructive sleep apnea; PG: polygraphy; PSG: polysomnography.

Table 6 - Population-based studies about the association between obstructive sleep apnea and diabetes.

Study/Year	Country	Sample size	Gender (male, %)	Age, mean (years)	BMI, mean (kg/m^2)	Outcome definition	Study design	Diagnostic method	Hypopnea criteria	OSA category (AHI)	Results	Association
Resnick et al/2003[6]	USA	4872	44.5	62.3	28.4	Self-reported diabetes and use of antidiabetic medications	Cross-sectional	Standard PSG	70% decrease in airflow	AHI≥15/h AHI<5/h	OR=1.02 [0.82 - 1.26]	No
Reichmuth et al/2005[7]	USA	1387	56.4	49.0	28.9	Self-report of physician-diagnosed diabetes	Cross-sectional	Standard PSG	Discernible reduction in airflow with at least a 4% desaturation	AHI≥15/h 5≥AHI<15/h AHI<5/h	OR=2.30 [1.28 - 4.11] OR= 1.25 [0.75 - 2.07]	Yes
Ronksley et al/2009[8]	Canada	2149	62.6	50.1	31.3	Self-reported diabetes and use of antidiabetic medications	Cross-sectional	Portable PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=2.18 [1.22 - 3.89] OR=1.02 [0.54 - 1.93] OR= 0.95 [0.53 - 1.71]	Yes No
Reichmuth et al/2005[7]	USA	978	N/A	N/A	N/A	Fasting glucose ≥126 mg/dL or self-report of physician-diagnosed diabetes	Prospective	Standard PSG	Discernible reduction in airflow with at least a 4% desaturation	AHI≥15/h 5≥AHI<15/h AHI<5/h	OR=0.91 [0.36 - 2.33] OR=1.00 [0.49 - 2.02]	No
Botros et al/2009[9]	USA	544	93.4	61.5	33.2	Fasting glucose ≥126 mg/dL and self-report of physician-diagnosed diabetes	Prospective	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	Quartiles of AHI	HR=1.43 [1.10 - 1.86] per quartile	Yes
Kendzerska et al/2014[10]	Canada	8678	62	48	28.4	Validated algorithm that identifies people with diabetes as those having at least 1 hospitalization record or at least 2 physician services claims bearing a diagnosis of diabetes within 2-years	Prospective	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=1.31 [1.07 - 1.61] OR= 1.23 [1.00 - 1.51] OR=1.23 [1.00 - 1.50]	Yes No No
Appleton et al/2015[11]	Australia	736	100	59.7	28.4	Fasting glucose ≥126 mg/dL or HbA1c ≥ 6.5% or self-report of physician-diagnosed diabetes or use of antidiabetic medication	Prospective	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	AHI≥30/h 20≥AHI<30/h 10≥AHI<20/h AHI<10/h	OR=2.6 [1.1 - 6.1] OR=1.1 [0.4 - 3.0] OR=1.5 [0.7 - 3.4]	Yes No No
Nagayoshi et al/2016[12]	USA	1453	46.3	62.5	28.3	Self-report of physician-diagnosed diabetes or use of antidiabetic medication	Prospective	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=2.03 [1.20 - 3.44] OR=1.18 [0.72 - 1.95] OR=0.59 [0.36 - 0.96]	Yes No No

AHI: apnea-hypopnea index; BMI: body mass index; N/A: not available; HbA1c: glycated hemoglobin; HR: hazard ratio; OR: odds ratio; OSA: obstructive sleep apnea; PSG: polysomnography.

Table 7 - Population-based studies about the association between obstructive sleep apnea and hypertension.

Study/Year	Country	Sample size	Gender (male, %)	Age, mean (years)	BMI, mean (kg/m^2)	Outcome definition	Study design	Diagnostic method	Hypopnea criteria	OSA category (AHI)	Results	Association
Young et al/1997[13]	USA	1069	57.7	45.3	29.4	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=3.07 [1.65 - 1.74]	Yes
										15≥AHI<30/h	OR=1.75 [1.28 - 2.40]	Yes
										5≥AHI<15/h	OR=1.21 [1.09 - 1.34]	Yes
										AHI=0/h		
Nieto et al/2000[14]	USA	6132	47.2	N/A	28.5	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=1.37 [1.03 - 1.83]	Yes
										15≥AHI<30/h	OR=1.25 [1.00 - 1.56]	No
										5≥AHI<15/h	OR=1.20 [1.01 - 1.42]	Yes
										1.5≥AHI<5/h	OR=1.07 [0.91 - 1.26]	No
										AHI<1.5/h		
Durán et al/2001[15]	Spain	555	58.4	N/A	N/A	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Portable PSG	Discernible 50% reduction in airflow with at least a 4% desaturation or an arousal	AHI≥15/h	OR=2.28 [0.92 - 5.66]	No
										5≥AHI<15/h	OR=1.30 [0.54 - 4.14]	No
										0>AHI<5/h	OR=2.47 [1.06 - 5.76]	Yes
										AHI=0/h		
Haas et al/2005[16]	USA	2477	45.7	40-59	28.9	SBP≥140 mmHg and DBP≥90 mmHg or SBP<140 mmHg and DBP≥90 mmHg	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=2.27 [1.13 - 4.56]	Yes
										15≥AHI<30/h	OR=2.32 [1.27 - 4.24]	Yes
										5≥AHI<15/h	OR=1.78 [1.09 - 2.92]	Yes
										1.5≥AHI<5/h	OR=1.30 [0.80 - 2.12]	No
										AHI<1.5/h		
Haas et al/2005[16]	USA	3643	48.1	≥60	28.2	SBP≥140 mmHg and DBP≥90 mmHg or SBP<140 mmHg and DBP≥90 mmHg	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=1.30 [0.63 - 2.71]	No
										15≥AHI<30/h	OR=1.04 [0.56 - 1.94]	No
										5≥AHI<15/h	OR=0.93 [0.55 - 1.55]	No
										1.5≥AHI<5/h	OR=1.14 [0.69 - 1.91]	No
										AHI<1.5/h		

Kapur et al/2008[17] (sleepy)	USA	787	44.9	61.8	29.3	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h 1.5≥AHI<5/h AHI<1.5/h	OR=2.83 [1.33 - 6.04] OR=1.94 [0.97 - 3.89] OR=1.26 [0.77 - 2.07] OR=1.04 [0.63 - 1.70]	Yes No No No
Kapur et al/2008[17] (not sleepy)	USA	5259	47.6	63.2	28.4	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h 1.5≥AHI<5/h AHI<1.5/h	OR=1.22 [0.89 - 1.68] OR=1.07 [0.84 - 1.36] OR=1.16 [0.97 - 1.40] OR=1.05 [0.88 - 1.25]	No No No No
Redline et al/2014[18]	USA	14440	39.8	41.2	29.4	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	PG	30% decrease in airflow with at least a 3% desaturation	AHI≥15/h AHI<15/h	OR=1.4 [1.2 - 1.7]	Yes
Peppard et al/2000[19]	USA	893	56	47	29	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Prospective	Standard PSG	Discernible reduction in airflow with at least a 4% desaturation	AHI≥15/h 5≥AHI<15/h 0>AHI<5/h AHI=0/h	OR=2.89 [1.46 - 5.64] OR=2.03 [1.13 - 1.78] OR=1.42 [1.13 - 1.78]	Yes Yes Yes
O'Connor et al/2009[20]	USA	2470	44.7	59.6	27.9	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Prospective	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=1.50 [0.91 - 2.46] OR=1.09 [0.77 - 1.54] OR=0.94 [0.73 - 1.22]	No No No
Guillot et al/2013[21]	France	372	34.7	68.1	24.4	Mean 24-hour SBP>140 mmHg and DBP>85 mmHg or the use of antihypertensive medication	Prospective	PG	Discernible 50% reduction in airflow with at least a 3% desaturation	AHI≥30/h 15≥AHI<30/h AHI<15/h	OR=1.77 [1.11 - 2.80] OR=1.31 [0.86 - 1.99]	Yes No

AHI: apnea-hypopnea index; BMI: body mass index; DBP: diastolic blood pressure; N/A: not available; HR: hazard ratio; OR: odds ratio; OSA: obstructive sleep apnea; PG: polygraphy; PSG: polysomnography; SBP: systolic blood pressure.

Impact of three hypopnea-scoring criteria on OSA prevalence and associated comorbidities in the general population

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Brief summary

Current knowledge/Study rationale

The American Academy of Sleep Medicine's rules for scoring hypopneas have changed thrice over the last 20 years, but their clinical impact on the prevalence of obstructive sleep apnea and their association with hypertension, diabetes and metabolic syndrome in the general population are unknown.

Study Impact

Our findings indicate that the method used for scoring hypopneas significantly influences the prevalence of obstructive sleep apnea and its association with cardiometabolic outcomes. We could provide predictive equations to translate the differences in apnea-hypopnea indexes within three recommended criteria of the American Academy of Sleep Medicine in a general population-based sample. Further, this study highlights the need for standardization of the scoring method to allow compatibility among epidemiological studies.

ABSTRACT

Study Objectives: Apnea-hypopnea index (AHI) is the main polysomnographic measure to diagnose obstructive sleep apnea (OSA). We aimed to evaluate the impact of three standard hypopnea definitions on the prevalence of OSA and its association with cardiometabolic outcomes in the general population.

Methods: We analyzed data from the Hypnolaus study (Lausanne, Switzerland), in which 2,162 participants (51% women, 57±19 years) underwent in-home full polysomnography. AHI was calculated using three hypopnea definitions: $AASM_{1999}$ (≥50% decrease in airflow or lower airflow reduction associated with oxygen desaturation ≥3% or an arousal), $AASM_{2007}$ (≥30% airflow reduction associated with ≥4% oxygen desaturation), and $AASM_{2012}$ (≥30% airflow reduction associated with ≥3% oxygen desaturation or an arousal). Participants underwent clinical assessment for hypertension, diabetes and metabolic syndrome.

Results: Median AHI of $AASM_{1999}$, $AASM_{2007}$ and $AASM_{2012}$ criteria were 10.9/h, 4.4/h, and 10.1/h, respectively. OSA prevalence defined as AHI ≥5/h, ≥15/h and ≥30/h was 74.5%, 39.3%, and 16.3% using $AASM_{1999}$; 46.9%, 18.8%, and 6.8% using $AASM_{2007}$; and 72.2%, 36.6%, and 14.9% using $AASM_{2012}$. Different AHI thresholds derived from $AASM_{1999}$, $AASM_{2007}$ and $AASM_{2012}$ criteria, respectively, were associated with hypertension (11.5/h, 4.8/h, 10.7/h), diabetes (15.7/h, 7.1/h, 14.4/h) and metabolic syndrome (12.8/h, 5.5/h, 11.8/h).

Conclusions: Hypopnea definition has a major impact on AHI and on OSA prevalence in the general population and, hence, important implications for public health policies. There is a two-fold difference in the threshold above which an association with diabetes, hypertension and metabolic syndrome is observed using $AASM_{2007}$ instead compared to $AASM_{1999}$ or $AASM_{2012}$ criteria.

Keywords: obstructive sleep apnea; hypopnea; methodology; polysomnography; general population.

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent partial (hypopneas) or total (apneas) episodes of upper airway obstruction during sleep,[1] and has been widely recognized as an important and treatable risk factor for cardiovascular and metabolic conditions.[2, 3] Polysomnography (PSG) is considered the gold standard for identifying individuals with OSA. Among the several parameters measured by PSG, the apnea-hypopnea index (AHI), which comprises the average number of apneas and hypopneas per hour of sleep, is the main metric for diagnosing OSA, as well as for assessing the disease severity and responsiveness to the treatment. A recent systematic review showed that, in general populations, OSA prevalence as AHI ≥5 events/h varies considerably among studies (9% to 38%).[4] Higher estimates were also observed over time in the most recent epidemiological studies.[5] Among the possible explanations for these findings, ethnical composition, equipment-related issues and changes in respiratory events definition might have an important role.

Indeed, several definitions of hypopnea have been used in research and the clinical setting, leading to large inter-laboratory variations in AHI depending on the definition used.[6-10] These differences relate to the degree of airflow reduction, the amplitude of oxygen desaturation and the association with electroencephalographic arousal required to define a hypopnea. Since OSA diagnosis and treatment decision are largely based on AHI, the definition of hypopnea may have a direct impact on OSA prevalence estimates and the patients' management. Thus, the aim of our study was to evaluate the impact of three hypopnea definitions on the prevalence and severity of OSA in a middle-aged general population sample. We compared three standard definitions for identifying hypopneas: the 1999 American Academy of Sleep Medicine (AASM) criteria (also known as Chicago criteria)[11], the recommended 2007 AASM[12]

and 2012 AASM[13] definitions. Secondarily, we sought to establish the AHI thresholds that could predict the presence of hypertension, diabetes and metabolic syndrome as well as to compare the association between OSA severity and these cardiometabolic outcomes using each hypopnea definition.

METHODS

Population sample

This is a cross-sectional study that analyzed data from HypnoLaus, a population-based sleep cohort study (Lausanne, Switzerland) performed between September 1, 2009 and June 30, 2013. HypnoLaus participants were recruited among subjects form the CoLaus/PsyCoLaus cohort.[14] CoLaus/PsyCoLaus is a population-based cohort of 6,734 participants (52.5% women) aged 35-75 years, identified from a random sample of all age-eligible adults living in the city of Lausanne, Switzerland (117,161 habitants). The CoLaus/PsyCoLaus study was conducted to assess the prevalence of cardiovascular risk factors and to identify new determinants of these risk factors and their association with mental disorders.[15] For the HypnoLaus nested study, participants of the CoLaus/PsyCoLaus study were invited to answer sleep questionnaires regarding their sleep habits and potential sleep disorders, and the first consecutive 3,043 were contacted to have a full sleep study at home. Of these, 71% (n=2,168) accepted the invitation and underwent PSG, among which 3% (n=60) had technical problems. Of these, six participants declined to undergo a second PSG, and 54 participants agreed.[16] Therefore, 2,162 PSG recordings comprised the HypnoLaus cohort and were included in this study. The Institutional Review Board in Lausanne approved the study, and all participants gave their written informed consent.

Clinical data collection

Participants from HypnoLaus study were invited to attend the outpatient clinic at the University Hospital of Lausanne (CHUV, Lausanne, Switzerland). After an overnight fasting they were also invited for questionnaires completion, clinical assessment and blood samples collection. Body weight and height were measured using a calibrated scale and a vertical stadiometer, respectively (Seca®, Hamburg, Germany). Body mass index (BMI) was calculated as body mass in kg divided by the square of the participant's height in meters. Waist circumference (at the level of the umbilicus) was measured to within 0.5 cm with plastic tape. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were evaluated in triplicate on the left arm at 5-min intervals with the participant seated and resting for at least 10 min using a calibrated automated oscillometric sphygmomanometer (Omron® HEM-907, Matsusaka, Japan).[17] Overnight fasting blood samples were taken of each participant. Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were quantified by colorimetric assays as previously described.[18] These assays were performed on fresh blood samples by the CHUV Clinical Laboratory (Lausanne, Switzerland).

Polysomnography

An in-home overnight full PSG was performed, using a digital portable sleep-wake recording system (EMBLA Titanium®, Embla systems, Inc, Broomfield, USA). A trained technician hooked-up the subject in the CIRS facility (Center for Investigation and Research in Sleep, CHUV, Lausanne, Switzerland). The electrodes and recorder were installed at the laboratory and recordings were done in the normal home environment. PSG measurements included: electroencephalograms (EEG) from

frontal, central and occipital areas (F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1) according to the international 10/20 electrode configuration system, right and left electrooculograms (EOG), mental-submental electromyogram (EMG), right and left leg EMG, thoracic and abdominal breathing movements by respiratory inductance plethysmography, respiratory airflow by a nasal-cannula connected to a pressure transducer, oxygen saturation (SpO_2) by pulse oxymetry, heart rate by electrocardiogram (ECG), and body position.

Scoring of polysomnography

PSGs were scored using Somnologica software (Embla systems, Inc, Broomfield, USA) by two experienced scorers (DA, NT), with an inter-agreement concordance greater than 90%. Sleep, arousal and movements during sleep were scored based on the 2007 AASM manual for the scoring of sleep and associated events.[19] Concerning respiratory events, an apnea was defined by a complete or almost complete (>90%) cessation of airflow (measured by nasal pressure) lasting 10 seconds or longer. Hypopneas were initially scored based on the Chicago criteria ($AASM_{1999}$), being defined by criterion 1 or 2, plus criterion 3:

1. A clear decrease (>50%) of airflow amplitude from the baseline. Baseline was defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).
2. A clear reduction of airflow amplitude, not reaching the above criterion but associated with either an oxygen desaturation of ≥3% or an arousal. From an

operational standpoint, a discernible reduction in airflow was considered a >30% reduction in the airflow signal.

3. The event lasts 10 seconds or longer.

An AHI for each individual was calculated, consisting of the number of apneas and hypopneas per hour of sleep. Each recording was reviewed for validation of the respiratory scoring by a single investigator (JHR).

Since both recommended 2007 and 2012 AASM criteria represent a subset of Chicago criteria's events, we derived the other two AHI definitions from the first scoring. For the recommended 2007 AASM criteria ($AASM_{2007}$), we removed hypopneas that did not fulfill the stricter AASM hypopnea definition, i.e., hypopneas that were not associated with ≥4% oxygen desaturation. For the recommended 2012 AASM criteria ($AASM_{2012}$), we removed hypopneas that were not associated with either an arousal or a ≥3% oxygen desaturation (Table S1).

OSA severity was classified according to standard criteria as mild (5≤AHI<15 events per hour of sleep), moderate (15≤AHI<30 events per hour of sleep), and severe (AHI≥30 events per hour of sleep). AHI<5/h was defined as no-OSA.

Outcomes

Hypertension was defined as a SBP≥140 mmHg and/or DBP≥90 mmHg, and/or use of anti-hypertensive medication. Diabetes was considered positive when fasting plasma glucose levels were ≥7.0 mmol/L or there was use of antidiabetic medication.[20] Metabolic syndrome was defined according to the Joint Interim Statement (JIS),[21] as the presence of at least three risk factors among: high blood pressure (SBP≥130 mm Hg or DBP≥85 mm Hg or use of antihypertensive medication); visceral obesity (waist circumference ≥88 cm in women or ≥102 cm in men); high triglycerides (≥1.7 mmol/L,

or use of fibrates or nicotinic acid); low HDL levels (<1.30 mmol/L in women or <1.03 mmol/L in men, or use of fibrates or nicotinic acid); and high fasting plasma glucose (≥5.6 mmol/L or use of antidiabetic medication).

Statistical analysis

We used AHI as the primary variable in this study for analysis of the differences between hypopnea scoring criteria. AHI is displayed according to the median and interquartile range (IQR) values. The differences between the three different AHIs obtained through $AASM_{1999}$, $AASM_{2007}$, and $AASM_{2012}$ criteria were assessed using the Friedman test, with pairwise comparisons performed by Wilcoxon signed-rank test. Bar graphs were constructed to represent the prevalence of OSA using each AASM criteria at AHI thresholds of ≥5/h, ≥15/h and ≥30/h. Equivalent thresholds for the three AHIs were estimated using the receiver operator curves (ROC) with each AHI as the gold standard, giving equal weight to maximize both sensitivity and specificity. Bland-Altman plots representing the mean difference between each pair of AHI according to each scoring criteria was built to illustrate the agreement between AHIs. Conversion equations between each pair of AHI were established with linear or quadratic regressions, with the latter being employed when appropriate. AHI thresholds significantly associated with the presence of hypertension, diabetes and metabolic syndrome were estimated by ROC analysis using each hypopnea criteria. Multivariable logistic regression was used for testing the association between OSA severity (mild, moderate or severe OSA *vs* no-OSA) and the presence of hypertension, diabetes and metabolic syndrome using each scoring criteria.

RESULTS

Population sample and OSA prevalence

The patient characteristics and PSG results are shown in Table 1. Participants were 57.2 ± 19.2 (median ± IQR) years of age with a BMI of 25.7 ± 5.4 kg/m^2. The sample included 51% of women. The average total sleep time was 404.0 ± 89.0 min and the sleep efficiency 87.6 ± 13 %.

The prevalence of OSA in the HypnoLaus cohort based on different AASM scoring criteria is presented in Figure 1. When using AHI thresholds of ≥5/h, ≥15/h and ≥30/h, respectively, $AASM_{2007}$ would provide 34.9%, 48.6% and 54.2% lower OSA diagnosis rate compared to $AASM_{2012}$ as well as 37.0%, 52.1% and 58.1% lower OSA diagnosis rate compared to $AASM_{1999}$ criteria. Compared to $AASM_{1999}$ criteria, $AASM_{2012}$ would provide 3.2%, 6.8% and 8.5% lower OSA diagnosis rate when using the same AHI thresholds.

AHI agreement

Table 2 shows median ± IQR of AHI in the HypnoLaus population according to the three scoring criteria. All AHIs were significantly different from each other ($p<0.001$) by Friedman test and post-hoc comparisons. The median AHI of $AASM_{2007}$ and $AASM_{2012}$ criteria were approximately 40% and 93% of the median AHI of $AASM_{1999}$. In turn, the median AHI of $AASM_{2007}$ was approximately 44% of the median AHI of $AASM_{2012}$. Bland-Altman plots (Figure 2) show the agreement between each pair of AHI according to the different scoring criteria. The variation in the mean AHI difference between each pair of scoring criteria was greater according to the AHI magnitude, except for the comparison between $AASM_{1999}$ and $AASM_{2012}$ criteria, which was more stable. The Bland Altman plots demonstrate a mean increase of 6.4 events/h when

comparing AHI definitions between $AASM_{2007}$ and $AASM_{2012}$; a mean reduction of 0.9/h when comparing $AASM_{2012}$ and $AASM_{1999}$; and a mean reduction of 7.3/h when comparing $AASM_{2007}$ and $AASM_{1999}$ criteria.

Equivalent AHIs and prediction equations

Table 3 shows the equivalence between the scoring criteria for each AHI threshold. For instance, when using $AASM_{2012}$ according to AHI thresholds of $\geq$5/h, $\geq$15/h and $\geq$30/h, to achieve a similar OSA prevalence $AASM_{2007}$ would have to shift its thresholds down to about 2.0/h, 6.6/h and 14.9/h, respectively. In male and female subsamples, the equivalent AHI threshold conversion factors were similar to those of the whole sample.

Prediction equations to determine the relationship between each pair of AHI are represented in Figure 3. All equations showed a $R^2 \geq 0.90$ as high collinearity was present between criteria (R=0.996 for correlation between $AASM_{1999}$ and $AASM_{2012}$-derived AHI; R=0.959 for correlation between $AASM_{2007}$ and $AASM_{2012}$-derived AHI; and R=0.951 for correlation between $AASM_{2007}$ and $AASM_{1999}$-derived AHI). In the prediction equations between $AASM_{2007}$ and $AASM_{2012}$ as well as $AASM_{2007}$ and $AASM_{1999}$, a quadratic regression better fitted the relationship, but with a small increase in R^2 of 0.02 compared to the linear regression.

Impact of scoring criteria on the association between OSA and outcomes

The AHI thresholds significantly associated with hypertension, diabetes and metabolic syndrome according to the three scoring criteria are represented in Table 4. For all outcomes assessed, the area under the curves (AUCs) as well as the sensitivity and specificity were similar among the three scoring criteria. Overall, higher AHI

thresholds emerged from $AASM_{1999}$, followed by $AASM_{2012}$. AHI thresholds derived from $AASM_{2007}$ criteria were approximately half of the respective AHI thresholds derived from both $AASM_{1999}$ and $AASM_{2012}$.

The association between OSA severity and the presence of cardiometabolic outcomes adjusted for age, sex and BMI is represented in Figure 4. For hypertension, we observed an independent association with severe OSA *vs* no-OSA using both $AASM_{2012}$ (OR=1.46, 1.01-2.10) and $AASM_{1999}$ (OR=1.55, 1.08-2.22), but not $AASM_{2007}$ (OR=1.30, 0.83-2.05). For diabetes, there was significant associations with all OSA groups *vs* no-OSA in both $AASM_{2012}$ (mild OSA: OR=2.13, 1.16-3.91; moderate OSA: OR=2.31, 1.23-4.32; severe OSA: OR=2.44, 1.28-4.68) and $AASM_{1999}$ (mild OSA: OR=1.92, 1.02-3.62; moderate OSA: OR=2.34, 1.23-4.43; severe OSA: OR=2.35, 1.21-4.55). Regarding $AASM_{2007}$, diabetes was significantly associated with moderate (OR=1.61, 1.02-2.56) and severe OSA (OR=1.81, 1.07-3.05), but not with mild OSA (OR=1.46, 0.99-2.17) when compared to no-OSA.

For metabolic syndrome, we found significant associations with all OSA groups *vs* no-OSA using the three scoring criteria as follows: $AASM_{2012}$ (mild OSA: OR=1.58, 1.12-2.22; moderate OSA: OR=1.68, 1.16-2.43; severe OSA: OR=2.38, 1.58-3.60); $AASM_{2007}$ (mild OSA: OR=1.48, 1.13-1.93; moderate OSA: OR=1.66, 1.17-2.35; severe OSA: OR=2.26, 1.42-3.59); $AASM_{1999}$ (mild OSA: OR=1.63, 1.14-2.33; moderate OSA: OR=1.68, 1.15-2.46; severe OSA: OR=2.41, 1.59-3.64).

There was no associations between the different AHI thresholds and subjective sleepiness (Epworth score) regardless the hypopnea scoring criteria used (Figure S1 and supplementary Table S2).

Discussion

To the best of our knowledge, this is the first study that explored the extent to which different hypopnea definitions influence OSA recognition and its association with cardiometabolic outcomes in a general population sample. Using three standard hypopnea definitions with airflow assessed by nasal-cannula pressure transducer, we could provide conversion equations between AHIs and equivalent thresholds among the scoring criteria. Our results show up to two-fold difference in AHI level above which an association was found with cardiometabolic outcomes between $AASM_{2007}$ and $AASM_{1999}$/$AASM_{2012}$. Lastly, an independent association between severe OSA and hypertension was only found using $AASM_{1999}$ or $AASM_{2012}$ criteria after adjusting for confounders.

To date, all studies that aimed to evaluate the association between OSA and metabolic syndrome[22-26], diabetes[27-33] or hypertension[34-42] have used older AASM criteria ($AASM_{1999}$/$AASM_{2007}$) or non-AASM criteria for hypopnea scoring, hampering a reliable comparison among them. Besides the differences in scoring criteria, important heterogeneity in study design, sample size, outcome definition, and demographic factors may have played a role in the inconsistent results found, as shown in Tables 5 to 7.

Previous studies have examined the agreement between different approaches to determine AHI, showing significant differences in OSA frequency and mean AHI scores using different hypopnea scoring definitions.[43, 44] These studies were conducted in small clinical populations using a thermistor to assess airflow. It is also important to highlight, that these results may not be relevant any longer considering the technical differences with current clinical practice, as most sleep centers use the nasal-cannula pressure transducer to evaluate hypopneas.

As in our study, Ruehland *et al* compared AHIs derived from $AASM_{1999}$ criteria, $AASM_{2007}$ recommended criteria, and $AASM_{2007}$ alternative criteria (≥50% airflow reduction associated with 3% desaturation or an arousal).[10] They explored the impact of hypopnea definition on the prevalence of OSA in a clinical population using nasal pressure for airflow assessment, and demonstrated that using these standard hypopnea definitions leads to marked differences in AHI. For example, the median AHI obtained using the $AASM_{2007}$ recommended criteria for scoring hypopneas was approximately 30% of the median AHI obtained using the $AASM_{1999}$ criteria. In our study, this correspondence was a little higher, 40% of the $AASM_{1999}$ criteria and could be explained by the differences in the source of sample used (clinical *vs* general population), the sample size (328 *vs* 2,162) and the more liberal interpretation of "discernible" difference in flow used by the authors.[10]

Few studies have evaluated the impact of different hypopnea scoring criteria in population-based research samples. Redline *et al* analyzed data from the Sleep Heart Health Study.[45] They examined the effect of using 11 different criteria for scoring hypopneas on the prevalence of disease and found that the median values of respiratory disturbance index (RDI) varied by approximately 10-fold for definitions that used the most liberal criteria for event identification (using amplitude changes without any requirement for associated desaturation or arousal) to the most conservative definition (requiring an associated >5% desaturation with amplitude changes).

Our findings showing that the $AASM_{2012}$ recommended criteria results in higher AHI compared to the $AASM_{2007}$ recommended criteria and doubles approximately the number of patients diagnosed with OSA are in agreement with previous studies.[8, 9] BaHamman *et al*[9] showed that the AHI derived from $AASM_{2007}$ recommended was 62% lower than the $AASM_{2012}$ recommended criteria. Considering the AHI thresholds of

≥5/h, ≥15/h and ≥30/h, they found that the $AASM_{2007}$ recommended criteria underestimated by 45%, 52% and 32%, respectively, the OSA patients identified by the $AASM_{2012}$ recommended criteria. In our study, we found a lower underdiagnosis rate for mild (34.9%) and moderate OSA (48.6%), but higher for severe OSA (54.2%). This could be because they used a clinical sample suspected for OSA, in which the proportion of OSA severity was overestimated compared to a general population sample.

In a retrospective study performed in 112 consecutive patients of an Australian clinical sleep laboratory in a tertiary hospital, Duce *et al* [8] investigated the equivalent AHI thresholds regarding the $AASM_{1999}$, $AASM_{2012}$ recommended, and both the $AASM_{2007}$ recommended and alternative criteria. To achieve the same OSA prevalence as the $AASM_{2012}$ recommended criteria at AHI thresholds of ≥5/h, ≥15/h and ≥30/h, they showed that the $AASM_{2007}$ recommended criteria would have to change their thresholds to 2.6/h, 7.2/h and 14.1/h, respectively and the $AASM_{1999}$ criteria to 7.3/h, 17.4/h and 31.7/h, respectively. Overall, these findings are in agreement with our results from a general population sample. They also established equations to convert the different AHIs to one another, which were close to ours.

In terms of clinical relevance, our study additionally compared the association of OSA, based on different AHI thresholds, with the presence of cardiometabolic outcomes using the three scoring criteria. We observed more significant associations with hypertension and diabetes using the $AASM_{2012}$ and $AASM_{1999}$ criteria, both of which require a lower oxygen desaturation and consider arousal for defining a hypopnea when compared to the $AASM_{2007}$ recommended criteria. While there is apparently an equivalence in the 3% or 4% criterion of oxygen desaturation for hypopnea definition in terms of increased cardiovascular risk,[46, 47] a debate about the

clinical relevance of the arousal as part of the hypopnea definition exists. The inclusion of an arousal or the decrease in oxygen desaturation threshold (4% *vs* 3%) from the $AASM_{2007}$ to $AASM_{2012}$ recommended criteria seem to contribute almost equally to the resulting AHI increase.[8] When testing 3% oxygen desaturation index (ODI), 4% ODI and arousal index as predictors of hypertension, diabetes and metabolic syndrome in our sample (data not shown), we found independent associations of both 3% ODI and 4% ODI with diabetes and metabolic syndrome, but not with hypertension. No significant association was observed with arousal index alone. On the other hand, the treatment of sleep-disordered breathing associated with sleep fragmentation, but not with oxygen desaturation, has shown benefits on daytime sleepiness,[48, 49] suggesting that the inclusion of arousals may be clinically relevant. Through ROC analysis, we observed that the AHIs derived from the three scoring criteria were significantly and similarly associated with the presence of hypertension, diabetes and metabolic syndrome. However, the AHI thresholds (considering equal weight to sensitivity and specificity) that better predicted each of these outcomes using the $AASM_{2007}$ recommended criteria were approximately half of the AHI values established for both the $AASM_{2012}$ recommended and the $AASM_{1999}$ criteria. Thus, we believe that the most important is that AHI thresholds need to be adjusted when using stricter hypopnea criteria for a proper interpretation and decision to treat OSA. In our study, we could provide correction factors, reliably translating AHIs from $AASM_{1999}$, $AASM_{2007}$ and $AASM_{2012}$ criteria in a large middle-aged general population sample.

There are several limitations in our study. First, it could be argued that scoring respiratory effort related arousals (RERAs) would capture events scored with the $AASM_{1999}$ criteria that do not fulfill the hypopnea requirements of the $AASM_{2012}$ criteria, and the RDI would be similar using both scoring criteria. Although we did not look

specifically at this point, Ruehland *et al* have shown that the AHI differences between $AASM_{1999}$ and $AASM_{2012}$ were mostly due to events with $\geq$50% flow reduction, and not associated with significant desaturation or arousal, so these events could not be scored as RERAs (as they are not associated with arousal).[10] We do not believe that including RERAs in the analysis could explain the differences found since these events are rather rare in our population.[50] Second, in this study, OSA was estimated in the presence of respiratory events at different AHI thresholds, but we did not consider other elements as symptoms (sleepiness, fatigue, headache) or associated comorbidities as suggested by the International Classification of Sleep Disorders (ICSD-3).[1] Although we believe that symptoms such as sleepiness are important for clinical decision, the very inclusive ICSD-3 definition for OSA syndrome would have led to a much higher and unrealistic rate of OSA.[51] Third, due to the cross-sectional design of the study, we cannot infer causality regarding the associations between OSA severity derived from each scoring criteria and the cardiometabolic outcomes.

Lastly, this study focused on different AHI definitions but other biomarkers such as autonomic activation, inflammation, genetic and demographic-related factors may prove to be a better predictor or may be used in combination with AHI to stratify OSA-associated risks. Prospective studies are thus required to better understand the parameters that should be used to determine OSA associated risk.

In conclusion, our study demonstrates that using different standard hypopnea definitions leads to marked differences in AHI. The use of $AASM_{2007}$ hypopnea criteria leads to lower equivalent AHI cutoffs for the association with OSA related comorbidities compared to both $AASM_{1999}$ and $AASM_{2012}$ criteria. However, prospective studies are necessary to further evaluate the extent to which cardiovascular and other health

outcomes may be differentially predicted by different AHI definitions, and to identify other sleep-related metrics that may be even more efficient to do so.

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Figure titles and captions

Figure 1 – Prevalence of obstructive sleep apnea.

Prevalence of apnea hypopnea index (AHI) thresholds ≥5/h, ≥15/h and ≥30/h according to three different recommended American Academy of Sleep Medicine (AASM) criteria (1999, 2007 and 2012) in the whole (A), male (B) and female (C) sample of HypnoLaus cohort (n=2,162).

Figure 2 – AHI agreement among different hypopnea criteria.

Bland-Altman plots demonstrating the level of agreement for apnea-hypopnea index (AHI) between American Academy Sleep Medicine (AASM) criteria from 2012 vs 2007, 2012 vs 1999, and 2007 vs 1999, respectively in the HypnoLaus cohort (n=2,162). The dashed line represents the mean difference between the two measured AHIs and the dotted lines represent the mean difference ± 1.96 standard deviation (SD). The x-axis

presents the mean of the two AHIs and the y-axis presents the difference (Δ) between the two measurements.

Figure 3 – AHI equivalence equations among different hypopnea criteria.

Least squares regression showing the apnea-hypopnea indexes (AHIs) equations of equivalence according to the different recommended American Academy of Sleep Medicine (AASM) criteria in the HypnoLaus cohort (n=2,162).

Figure 4 – Association between AHIs and cardiometabolic outcomes.

Odds ratio and 95% confidence intervals of the association between apnea-hypopnea index (AHI) categories (15<AHI≤5/h, 30<AHI≤15/h and AHI≥30/h compared to AHI<5/h) derived from three different recommended AASM criteria (1999, 2007 and 2012) and the presence of hypertension (n=2,147), diabetes (n=2,147) and metabolic syndrome (n=2,149) in the HypnoLaus cohort. Data analyzed with multivariable logistic regression adjusted for age, body mass index and sex.

Abbreviations

AASM, American Academy of Sleep Medicine

$AASM_{1999}$, “Chicago criteria” hypopnea definitions

$AASM_{2007}$, 2007 AASM recommended hypopnea definitions

$AASM_{2012}$, 2012 AASM recommended hypopnea definitions

AHI, apnea-hypopnea index

AUC, area under the curve

BMI, body mass index

CHUV, Centre Hospitalier Universitaire Vaudois

DBP, diastolic blood pressure

ECG, electrocardiogram

EEG, electroencephalogram

EMG, electromyogram

EOG, electrooculogram

HDL, high-density lipoprotein

ICSD, International Classification of Sleep Disorders

IQR, interquartile range

JIS, Joint Interim Statement

No-OSA, without obstructive sleep apnea

OR, odds ratio

OSA, obstructive sleep apnea

PSG, polysomnography

RDI, respiratory disturbance index

RERA, respiratory effort related arousal

ROC, receiver operator curve

SBP, systolic blood pressure

SpO_2, oxygen saturation

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Table 1 - Sample's characteristics.

Parameter	
n	2,162
Age, years	57.2 ± 19.2
Sex, M/F	1,056/1,106
BMI, kg/m^2	25.7 ± 5.4
TST, min	404.0 ± 89.0
Sleep onset latency, min	10.9 ± 16.5
Sleep efficiency, %	87.6 ± 13.0
N1, %	10.2 ± 7.5
N2, %	45.6 ± 12.8
N3, %	19.3 ± 10.9
REM, %	22.3 ± 7.9
Arousal index	18.9 ± 12.4
3% ODI	10.0 ± 15.2
4% ODI	4.1 ± 9.1
Mean SpO_2, %	94.3 ± 2.2
TST with SpO_2<90%, %	0.2 ± 2.1

BMI: body mass index; M/F: male/female; n: sample size; N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3 or slow-wave sleep; ODI: oxygen desaturation index; REM: rapid eye movement; SpO_2: percutaneous oxygen saturation; TST: total sleep time.
Data expressed as median ± interquartile range or number of participants.

Table 2 - Apnea-hypopnea index changes according to hypopnea definitions in the HypnoLaus cohort.

	Apnea-hypopnea index			
	$AASM_{1999}$	**$AASM_{2007}$**	**$AASM_{2012}$**	**p-value**
Whole sample	10.9 ± 17.5	4.4 ± 10.1*	10.1 ± 16.9*#	<0.0001
Male sample	16.0 ± 20.9	6.8 ± 13.5*	15.1 ± 20.4*#	<0.0001
Female sample	7.6 ± 12.1	2.6 ± 6.2*	7.0 ± 11.4*#	<0.0001

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: "Chicago criteria" hypopnea definition; $AASM_{2007}$: 2007 AASM recommended hypopnea definitions; $AASM_{2012}$: 2012 AASM recommended hypopnea definitions; *p<0.0001 compared with AASM1999; #p<0.0001 compared with $AASM_{2007}$.
Data expressed as median ± interquartile range and analyzed using Friedman test with pairwise comparisons performed by Wilcoxon's test.

Table 3 - Equivalent apnea-hypopnea index thresholds for different hypopnea definitions in the HypnoLaus cohort.

Gold standard AHI	**Whole sample** Equivalent AHI thresholds		**Male sample** Equivalent AHI thresholds		**Female sample** Equivalent AHI thresholds	
$AASM_{2012}$	**$AASM_{1999}$**	**$AASM_{2007}$**	**$AASM_{1999}$**	**$AASM_{2007}$**	**$AASM_{1999}$**	**$AASM_{2007}$**
5.0/h	5.7 (99.8, 98.0, 97.5)	2.0 (97.6, 90.9, 91.2)	5.9 (99.8, 98.0, 98.2)	2.1 (97.9, 92.0, 92.3)	5.7 (99.8, 97.3, 97.7)	1.9 (97.1, 90.2, 90.8)
15.0/h	15.6 (99.7, 98.6, 97.5)	6.6 (98.3, 93.0, 92.9)	15.8 (99.8, 98.7, 97.1)	6.7 (97.9, 92.5, 92.4)	15.2 (99.6, 98.8, 97.6)	6.5 (98.5, 93.8, 93.1)
30.0/h	30.4 (99.9, 100.0, 98.6)	14.9 (99.1, 94.7, 94.3)	30.2 (99.9, 100.0, 98.7)	15.0 (98.6, 92.9, 92.7)	30.5 (99.9, 100.0, 98.6)	16.0 (99.5, 98.8, 97.2)
$AASM_{2007}$	**$AASM_{1999}$**	**$AASM_{2012}$**	**$AASM_{1999}$**	**$AASM_{2012}$**	**$AASM_{1999}$**	**$AASM_{2012}$**
5.0/h	11.8 (97.3, 90.0, 90.5)	10.9 (97.7, 91.0, 91.3)	13.0 (96.8, 90.2, 88.9)	12.4 (97.4, 90.2, 91.9)	10.7 (97.4, 91.0, 91.3)	9.4 (97.8, 93.3, 90.8)
15.0/h	23.9 (98.7, 94.3, 94.2)	22.4 (99, 95.1, 94.1)	25.5 (98.2, 93.3, 93.3)	24.0 (98.6, 95.0, 93.9)	21.0 (99.1, 99.2, 94.6)	20.2 (99.3, 99.2, 95.2)
30.0/h	38.2 (99.3, 97.3, 96.1)	37.0 (99.5, 99.3, 96.4)	40.9 (99.0, 97.4, 95.5)	39.8 (99.2, 97.4, 96.1)	35.9 (99.5, 100.0, 96.8)	35.9 (99.6, 100.0, 98.1)
$AASM_{1999}$	**$AASM_{2007}$**	**$AASM_{2012}$**	**$AASM_{2007}$**	**$AASM_{2012}$**	**$AASM_{2007}$**	**$AASM_{2012}$**
5.0/h	1.7 (97.0, 90.7, 91.5)	4.9 (99.8, 97.3, 99.6)	1.7 (93.7, 93.6, 90.3)	4.9 (99.7, 98.6, 99.4)	1.6 (96.4, 90.7, 89.2)	4.6 (99.8, 97.2, 98.5)
15.0/h	6.4 (97.7, 90.2, 93.6)	13.9 (99.8, 97.4, 98.5)	6.4 (97.3, 90.1, 92.9)	13.9 (99.8, 97.7, 98.6)	5.9 (97.9, 93.3, 91.8)	13.9 (99.7, 96.8, 98.4)
30.0/h	13.0 (98.7, 96.3, 92.2)	26.5 (99.9, 98.6, 97.9)	14.4 (98.3, 92.5, 92.9)	28.2 (99.9, 98.8, 99.0)	11.4 (99.1, 100.0, 93.3)	25.9 (99.9, 99.0, 98.8)

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: “Chicago criteria” hypopnea definition; $AASM_{2007}$: 2007 AASM recommended hypopnea definitions; $AASM_{2012}$: 2012 AASM recommended hypopnea definitions; AHI: apnea-hypopnea index.
Data expressed as threshold (area under the curve, sensitivity, specificity) and analyzed using receiver operating characteristic curve.

Table 4 - Equivalent apnea-hypopnea index thresholds associated with cardiometabolic outcomes according to different hypopnea criteria in the HypnoLaus cohort.

AHI	AUC	95% CI	p-value	Threshold	Sensitivity	Specificity
Hypertension						
$AASM_{2012}$	0.67	0.65 - 0.69	<0.0001	10.7	0.62	0.62
$AASM_{2007}$	0.68	0.65 - 0.70	<0.0001	4.8	0.63	0.63
$AASM_{1999}$	0.67	0.65 - 0.69	<0.0001	11.5	0.62	0.61
Diabetes						
$AASM_{2012}$	0.71	0.68 - 0.75	<0.0001	14.4	0.64	0.65
$AASM_{2007}$	0.72	0.68 - 0.75	<0.0001	7.1	0.66	0.67
$AASM_{1999}$	0.71	0.67 - 0.74	<0.0001	15.7	0.65	0.66
Metabolic syndrome						
$AASM_{2012}$	0.71	0.69 - 0.74	<0.0001	11.8	0.65	0.65
$AASM_{2007}$	0.73	0.70 - 0.75	<0.0001	5.5	0.66	0.66
$AASM_{1999}$	0.71	0.68 - 0.73	<0.0001	12.8	0.65	0.64

AASM: American Academy of Sleep Medicine; $AASM_{1999}$: "Chicago criteria" hypopnea definition; $AASM_{2007}$: 2007 AASM recommended hypopnea definitions; $AASM_{2012}$: 2012 AASM recommended hypopnea definitions; AHI: apnea-hypopnea index; AUC: area under the curve; CI: confidence interval.
Data expressed as AUC, 95% CI, AHI threshold, sensitivity and specificity, and analyzed using receiver operating characteristic (ROC) operating curve.
Number of participants with missing data: hypertension (2), diabetes (2).

Table 5 - Population-based studies about the association between obstructive sleep apnea and metabolic syndrome.

Study/Year	Country	Sample size	Gender (male, %)	Age, mean (years)	BMI, mean (kg/m^2)	Outcome definition	Study design	Diagnostic method	Hypopnea criteria	OSA category (AHI)	Results	Association
Nieto et al/2009[1]	USA	546	56.0	59.9	31.1	NCEP ATPIII	Cross-sectional	Standard PSG	Discernible decrease in airflow with at least a 4% desaturation	AHI≥15/h	OR=2.20 [1.20 - 3.90]	Yes
										5≥AHI<15/h	OR=2.5 [1.50 - 4.20]	Yes
										AHI<5		
Chin et al/2010[2]	Japan	275	100	44.0	23.9	NCEP ATPIII	Cross-sectional	Portable PSG	>50% decrease in airflow with at least a 3% desaturation	AHI≥30/h	OR=2.57 [0.68 - 9.69]	No
										15≥AHI<30/h	OR=0.77 [0.30 - 1.99]	No
										5≥AHI<15/h	OR=1.00 [0.47 - 2.13]	No
										AHI<5/h		
Troxel et al/2010[3]	USA	290	N/A	N/A	N/A	NCEP ATPIII	Case-control	PG	≥30% but < 80% decrease in airflow	AHI as continuous variable	OR=1.23 [1.02 - 1.47] per 5 units	Yes
Theorell et al/2011[4]	Sweden	400	0	50.1	26.7	NCEP ATPIII	Cross-sectional	Standard PSG	>50% decrease in airflow with at least a 3% desaturation or an arousal	AHI as continuous variable	OR=1.04 [1.01 - 1.07] per 1 unit	Yes
Hall et al/2012[5]	USA	340	0	51.2	29.8	NCEP ATPIII	Case-control	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	AHI as continuous variable	OR=1.36 [0.97 - 1.92] per 1 unit	No

AHI: apnea-hypopnea index; BMI: body mass index; N/A: not available; NCEP ATPIII: National Cholesterol Education Program Adult Treatment panel III; OR: odds ratio; OSA: obstructive sleep apnea; PG: polygraphy; PSG: polysomnography.

Table 6 - Population-based studies about the association between obstructive sleep apnea and diabetes.

Study/Year	Country	Sample size	Gender (male, %)	Age, mean (years)	BMI, mean (kg/m^2)	Outcome definition	Study design	Diagnostic method	Hypopnea criteria	OSA category (AHI)	Results	Association
Resnick et al/2003[6]	USA	4872	44.5	62.3	28.4	Self-reported diabetes and use of antidiabetic medications	Cross-sectional	Standard PSG	70% decrease in airflow	AHI≥15/h AHI<5/h	OR=1.02 [0.82 - 1.26]	No
Reichmuth et al/2005[7]	USA	1387	56.4	49.0	28.9	Self-report of physician-diagnosed diabetes	Cross-sectional	Standard PSG	Discernible reduction in airflow with at least a 4% desaturation	AHI≥15/h 5≥AHI<15/h AHI<5/h	OR=2.30 [1.28 - 4.11] OR= 1.25 [0.75 - 2.07]	Yes
Ronksley et al/2009[8]	Canada	2149	62.6	50.1	31.3	Self-reported diabetes and use of antidiabetic medications	Cross-sectional	Portable PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=2.18 [1.22 - 3.89] OR=1.02 [0.54 - 1.93] OR= 0.95 [0.53 - 1.71]	Yes No
Reichmuth et al/2005[7]	USA	978	N/A	N/A	N/A	Fasting glucose ≥126 mg/dL or self-report of physician-diagnosed diabetes	Prospective	Standard PSG	Discernible reduction in airflow with at least a 4% desaturation	AHI≥15/h 5≥AHI<15/h AHI<5/h	OR=0.91 [0.36 - 2.33] OR=1.00 [0.49 - 2.02]	No
Botros et al/2009[9]	USA	544	93.4	61.5	33.2	Fasting glucose ≥126 mg/dL and self-report of physician-diagnosed diabetes	Prospective	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	Quartiles of AHI	HR=1.43 [1.10 - 1.86] per quartile	Yes
Kendzerska et al/2014[10]	Canada	8678	62	48	28.4	Validated algorithm that identifies people with diabetes as those having at least 1 hospitalization record or at least 2 physician services claims bearing a diagnosis of diabetes within 2-years	Prospective	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=1.31 [1.07 - 1.61] OR= 1.23 [1.00 - 1.51] OR=1.23 [1.00 - 1.50]	Yes No No
Appleton et al/2015[11]	Australia	736	100	59.7	28.4	Fasting glucose ≥126 mg/dL or HbA1c ≥ 6.5% or self-report of physician-diagnosed diabetes or use of antidiabetic medication	Prospective	Standard PSG	Discernible reduction in airflow or a <50% decrease in airflow with at least 3% desaturation or an arousal	AHI≥30/h 20≥AHI<30/h 10≥AHI<20/h AHI<10/h	OR=2.6 [1.1 - 6.1] OR=1.1 [0.4 - 3.0] OR=1.5 [0.7 - 3.4]	Yes No No
Nagayoshi et al/2016[12]	USA	1453	46.3	62.5	28.3	Self-report of physician-diagnosed diabetes or use of antidiabetic medication	Prospective	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=2.03 [1.20 - 3.44] OR=1.18 [0.72 - 1.95] OR=0.59 [0.36 - 0.96]	Yes No No

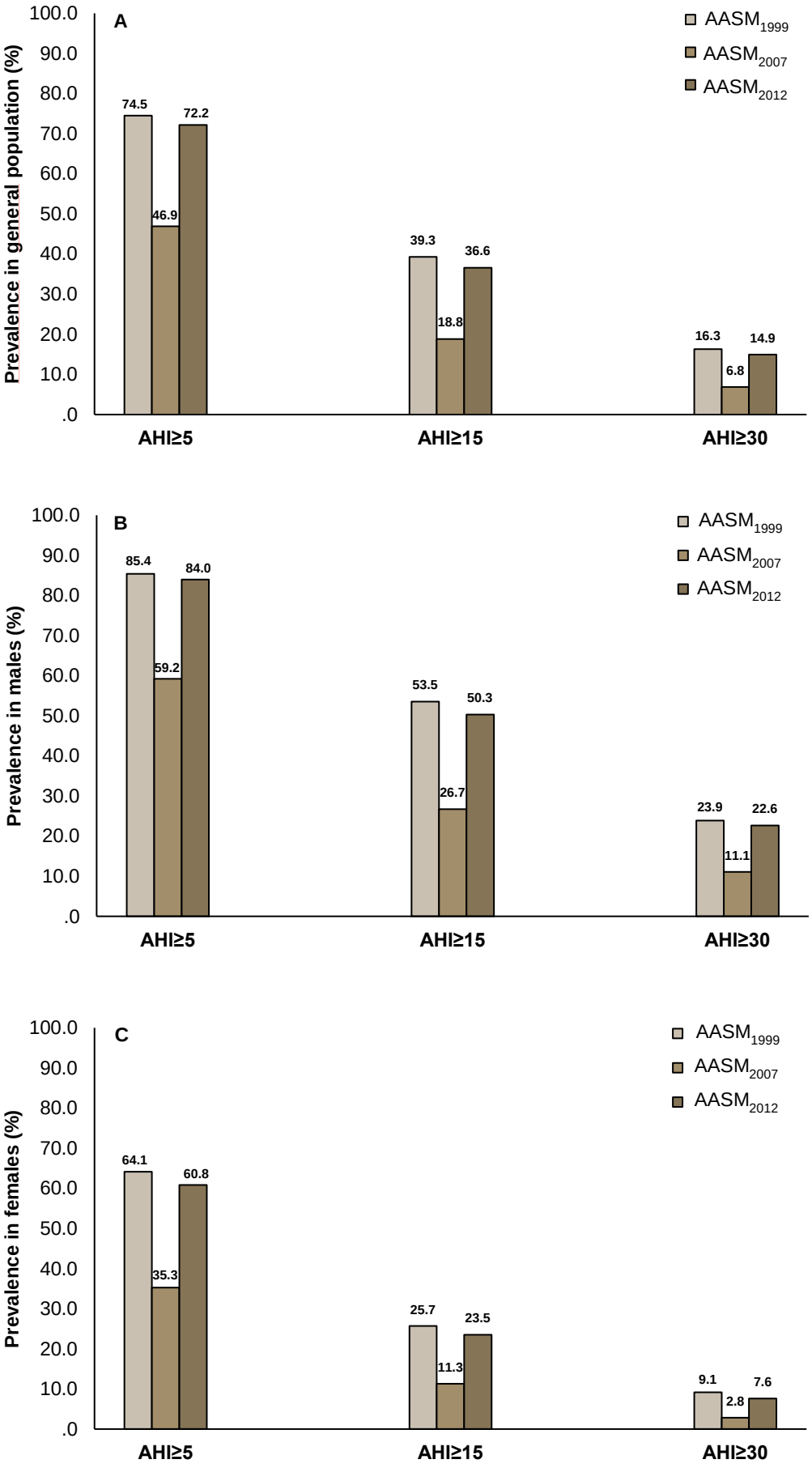
AHI: apnea-hypopnea index; BMI: body mass index; N/A: not available; HbA1c: glycated hemoglobin; HR: hazard ratio; OR: odds ratio; OSA: obstructive sleep apnea; PSG: polysomnography.

Table 7 - Population-based studies about the association between obstructive sleep apnea and hypertension.

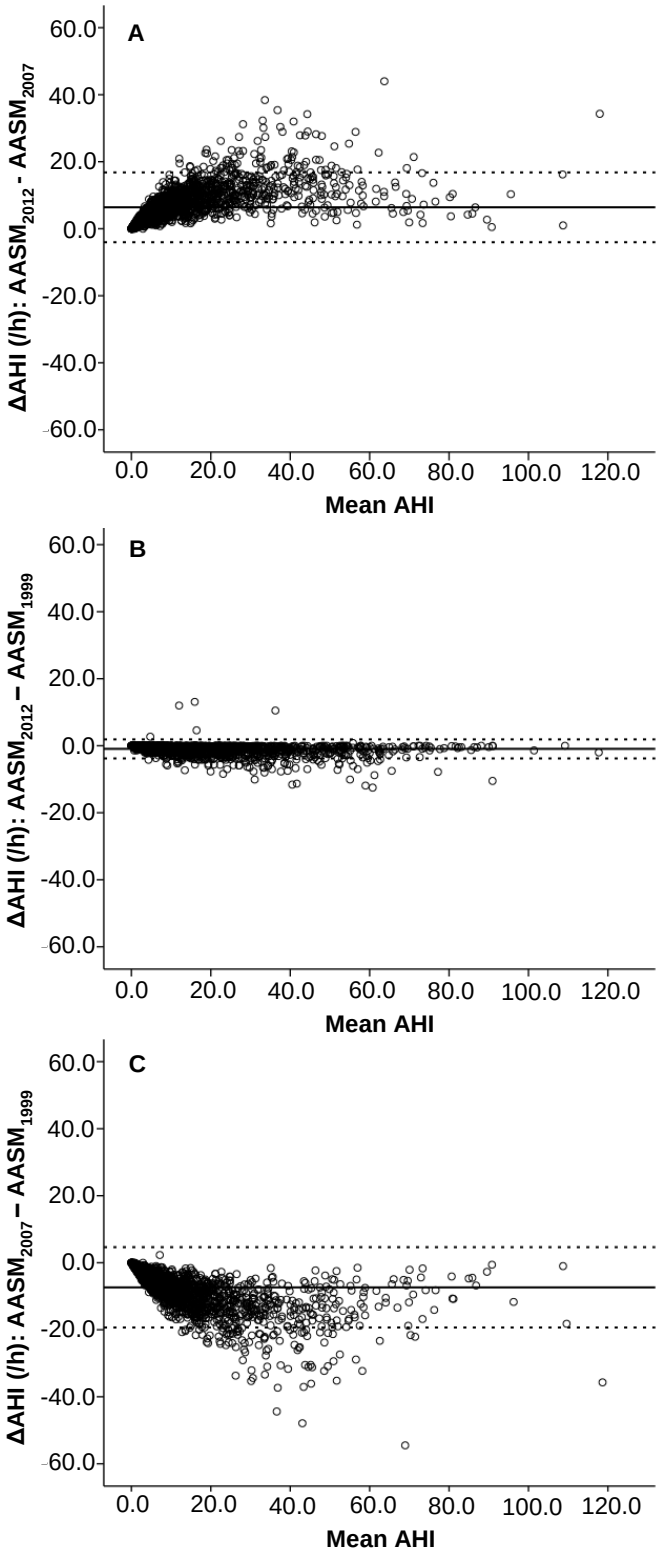
Study/Year	Country	Sample size	Gender (male, %)	Age, mean (years)	BMI, mean (kg/m^2)	Outcome definition	Study design	Diagnostic method	Hypopnea criteria	OSA category (AHI)	Results	Association
Young et al/1997[13]	USA	1069	57.7	45.3	29.4	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=3.07 [1.65 - 1.74]	Yes
										15≥AHI<30/h	OR=1.75 [1.28 - 2.40]	Yes
										5≥AHI<15/h	OR=1.21 [1.09 - 1.34]	Yes
										AHI=0/h		
Nieto et al/2000[14]	USA	6132	47.2	N/A	28.5	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=1.37 [1.03 - 1.83]	Yes
										15≥AHI<30/h	OR=1.25 [1.00 - 1.56]	No
										5≥AHI<15/h	OR=1.20 [1.01 - 1.42]	Yes
										1.5≥AHI<5/h	OR=1.07 [0.91 - 1.26]	No
										AHI<1.5/h		
Durán et al/2001[15]	Spain	555	58.4	N/A	N/A	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Portable PSG	Discernible 50% reduction in airflow with at least a 4% desaturation or an arousal	AHI≥15/h	OR=2.28 [0.92 - 5.66]	No
										5≥AHI<15/h	OR=1.30 [0.54 - 4.14]	No
										0>AHI<5/h	OR=2.47 [1.06 - 5.76]	Yes
										AHI=0/h		
Haas et al/2005[16]	USA	2477	45.7	40-59	28.9	SBP≥140 mmHg and DBP≥90 mmHg or SBP<140 mmHg and DBP≥90 mmHg	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=2.27 [1.13 - 4.56]	Yes
										15≥AHI<30/h	OR=2.32 [1.27 - 4.24]	Yes
										5≥AHI<15/h	OR=1.78 [1.09 - 2.92]	Yes
										1.5≥AHI<5/h	OR=1.30 [0.80 - 2.12]	No
										AHI<1.5/h		
Haas et al/2005[16]	USA	3643	48.1	≥60	28.2	SBP≥140 mmHg and DBP≥90 mmHg or SBP<140 mmHg and DBP≥90 mmHg	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h	OR=1.30 [0.63 - 2.71]	No
										15≥AHI<30/h	OR=1.04 [0.56 - 1.94]	No
										5≥AHI<15/h	OR=0.93 [0.55 - 1.55]	No
										1.5≥AHI<5/h	OR=1.14 [0.69 - 1.91]	No
										AHI<1.5/h		

Kapur et al/2008[17] (sleepy)	USA	787	44.9	61.8	29.3	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h 1.5≥AHI<5/h AHI<1.5/h	OR=2.83 [1.33 - 6.04] OR=1.94 [0.97 - 3.89] OR=1.26 [0.77 - 2.07] OR=1.04 [0.63 - 1.70]	Yes No No No
Kapur et al/2008[17] (not sleepy)	USA	5259	47.6	63.2	28.4	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h 1.5≥AHI<5/h AHI<1.5/h	OR=1.22 [0.89 - 1.68] OR=1.07 [0.84 - 1.36] OR=1.16 [0.97 - 1.40] OR=1.05 [0.88 - 1.25]	No No No No
Redline et al/2014[18]	USA	14440	39.8	41.2	29.4	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Cross-sectional	PG	30% decrease in airflow with at least a 3% desaturation	AHI≥15/h AHI<15/h	OR=1.4 [1.2 - 1.7]	Yes
Peppard et al/2000[19]	USA	893	56	47	29	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Prospective	Standard PSG	Discernible reduction in airflow with at least a 4% desaturation	AHI≥15/h 5≥AHI<15/h 0>AHI<5/h AHI=0/h	OR=2.89 [1.46 - 5.64] OR=2.03 [1.13 - 1.78] OR=1.42 [1.13 - 1.78]	Yes Yes Yes
O'Connor et al/2009[20]	USA	2470	44.7	59.6	27.9	SBP≥140 mmHg or DBP≥90 mmHg or use of antihypertensive medication	Prospective	Standard PSG	30% decrease in airflow with at least a 4% desaturation	AHI≥30/h 15≥AHI<30/h 5≥AHI<15/h AHI<5/h	OR=1.50 [0.91 - 2.46] OR=1.09 [0.77 - 1.54] OR=0.94 [0.73 - 1.22]	No No No
Guillot et al/2013[21]	France	372	34.7	68.1	24.4	Mean 24-hour SBP>140 mmHg and DBP>85 mmHg or the use of antihypertensive medication	Prospective	PG	Discernible 50% reduction in airflow with at least a 3% desaturation	AHI≥30/h 15≥AHI<30/h AHI<15/h	OR=1.77 [1.11 - 2.80] OR=1.31 [0.86 - 1.99]	Yes No

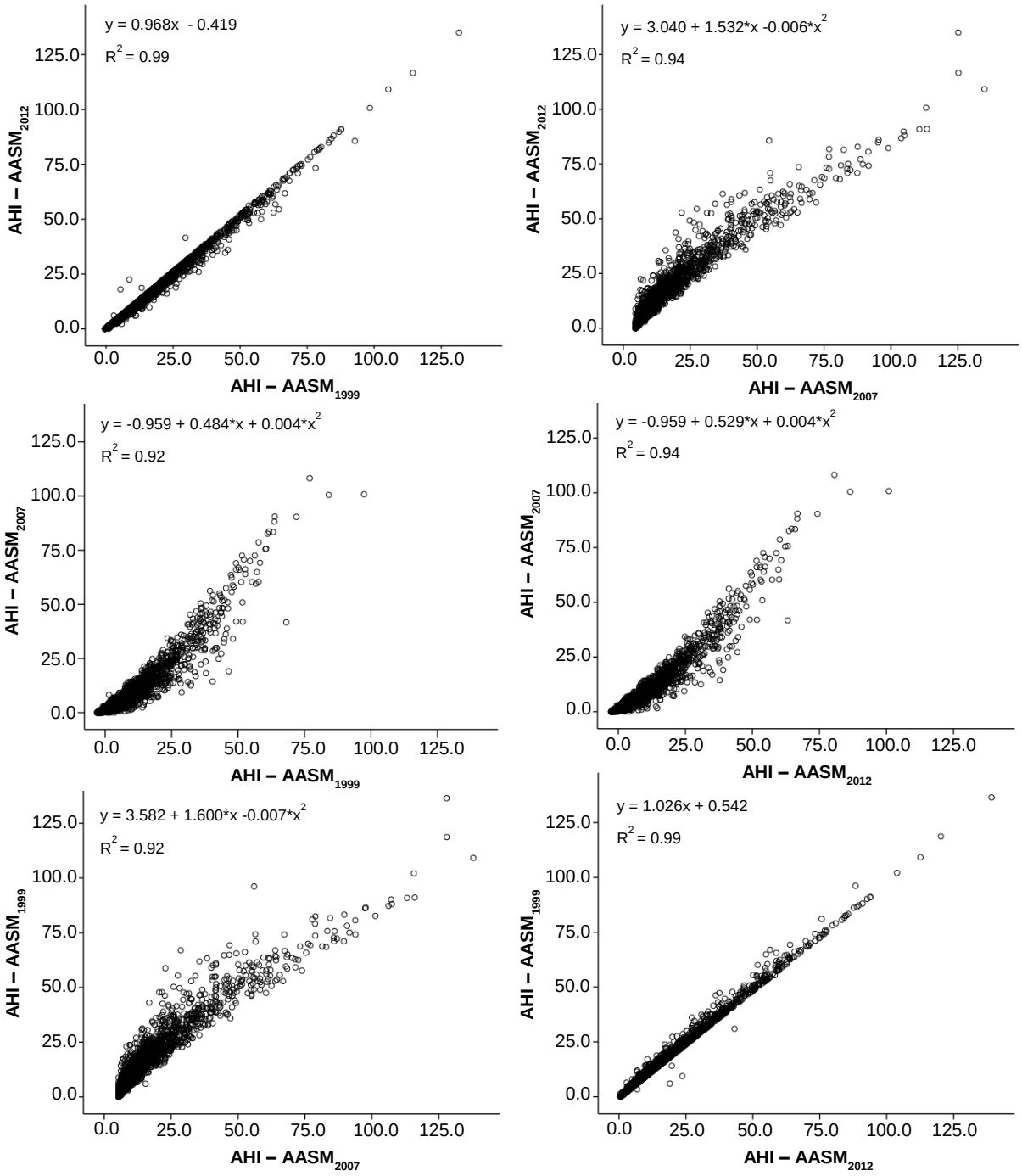
AHI: apnea-hypopnea index; BMI: body mass index; DBP: diastolic blood pressure; N/A: not available; HR: hazard ratio; OR: odds ratio; OSA: obstructive sleep apnea; PG: polygraphy; PSG: polysomnography; SBP: systolic blood pressure.



Figure



Figure



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