Early View

Original article

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Evaluation of a multicomponent grading system (Baveno classification) for obstructive sleep apnoea

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Take home message:

The Baveno classification separates the OSA population in equivalent groups, which are clearly separated with respect to clinical symptoms and comorbidities. These groups are characterized by differences in hypoxic load and patient-related outcome parameters.

Abstract

New findings on pathophysiology, epidemiology, and outcome have raised concerns on the relevance of the apnoea-hypopnoea index (AHI) in the classification of obstructive sleep apnoea (OSA) severity. Recently, a multicomponent grading system, decision integrating symptomatology and comorbidities (Baveno classification), was proposed to characterize OSA and to guide therapeutic decisions. We evaluated if this system reflects the OSA population, if it translates into differences in outcomes, and if the addition of AHI improves the scheme. 14,499 OSA patients from the European Sleep Apnoea Database (ESADA) cohort were analysed. The groups were homogeneously distributed and were found to clearly stratify the population with respect to baseline parameters. Differences in sleepiness and blood pressure between the groups were analysed in a subgroup of patients after 24-36 months of treatment. Group A (minor symptoms and comorbidities) did not demonstrate any effect of treatment on outcome. However, groups B (severe symptoms, minor comorbidities), C (minor symptoms, severe comorbidities) and D (severe symptoms and comorbidities) were associated with improvement in either or both parameters with treatment. The AHI is an essential prerequisite of the diagnosis. However, adding the AHI did not improve the classification. Rather, it was inferior with respect to guiding the treatment decision. Thus, the Baveno classification allows a better stratification of the OSA population and may provide a better guidance for therapeutic decisions in OSA.

Introduction

The relevance of obstructive sleep apnoea (OSA) for the individual and the society is well recognised relating to its prevalence and impact on societal health-related costs and patient-related outcomes [1-4]. OSA affects 9–13% of the general population, substantially reduces quality of life and increases morbidity [5-7] and mortality at least in subgroups of affected patients [8-9]. This constellation encouraged clinicians, manufacturers and health care administrators to seek simple and easily accessible markers of the disease to screen risk groups, to predict outcome and to more precisely select optimal treatment. Breathing disturbances during sleep, often associated with snoring, are the most prominent quantifiable markers of OSA. Thus, the number of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index, AHI) became the most widely used metric to define the disease and to classify the severity in most national and international guidelines and health care standards including those related to reimbursement [10-13].

However, criticism and concern regarding the clinical and prognostic relevance of the AHI have recently been raised [13-14]. First, experimental data and clinical experiences have demonstrated that the pathophysiology of OSA is not reflected by upper airway obstruction alone. Second, several cluster analyses of large databases have consistently shown that the classical phenotype of obesity, male gender, older age and severe daytime sleepiness represents only one quarter of the OSA population [15-21]. Other phenotypes, such as breathing disturbances associated with movement phenomena or insomnia, young age with comorbidities, or female sex with less distinct or atypical symptoms, may also be identified [15-23]. Finally, the AHI is a poor predictor for endpoints like cardiovascular comorbidities or mortality. Other aspects, such as hypoxic burden or sleepiness seem to better predict outcome in OSA [15, 24-29].

Based on these considerations, an *ad hoc working group* of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society developed a new approach (beyond the AHI) to predict the disease, to integrate symptoms and cardiometabolic comorbidities. This workshop, which took place in Baveno, Italy [30] , resulted in a two-dimensional scheme divided into four groups, A to D, and with the level of symptoms on the X-axis and the presence and severity of comorbidities on the Y-axis (Figure 1).. It grades OSA in a

The classification may guide indication and optimisation of treatment independent of the AHI. Affiliation to group D will strongly suggest treatment, while affiliation to group A will hardly indicate any active treatment other than general lifestyle recommendations. Groups B and C may warrant treatment either due to reduced quality of life or presence of relevant comorbidities.

However, this innovative proposal requires further validation before reshaping OSA routine care. Therefore, we evaluated if the multicomponent grading system, namely the Baveno classification, which can be transferred to the real-life situation in OSA patients. A slightly modified version of the Baveno classification system was applied to the large clinical cohort of the European Sleep Apnoea Database (ESADA) in order to determine if:

1. the Baveno classification A-D sufficiently reflects the distribution of the patients in the ESADA cohort, and
2. the addition of the AHI to the classification system might improve the characterisation of sleep apnoea patients, and
3. the classification translates in clinically relevant outcome parameters.

Methods

The ESADA registry is a multi-centre, prospective patient cohort reflecting a network of 37 sleep centres in 20 countries in Europe and Israel [31-32]. The overall objective of the ESADA is to generate a clinically representative cohort of subjects recently evaluated for suspected sleep-disordered breathing. A central web-based platform is applied to record patient information from the participating sleep centres. In brief, unselected patients (age 18-80 years) with suspected OSA are eligible for inclusion in the registry. At the time of initial sleep laboratory diagnostic work-up, anthropometric characteristics, information on daytime symptoms and health-related lifestyle, such as smoking and alcohol consumption, blood tests, medical history, medications and sleep data are collected. Subjective daytime sleepiness is quantified by the Epworth Sleepiness Scale (ESS) score [33]. The severity of sleep-disordered breathing is assessed by polysomnography (PSG) or polygraphy (PG) according to the prevailing clinical routine at each participating sleep centre [34]. The scoring criteria defined by the AASM 2007 definition have been used in the ESADA study

protocol which allowed hypopnoea scoring with either the recommended or the alternative definition [35]. The ESADA has previously analysed the impact of centre-specific differences in hypopnea scoring and the difference between AHI values from polysomnography and polygraphy [34]. Office blood pressure is measured according to the current ESH/ESC guidelines [36]. Corresponding follow-up data is collected when patients return as part of the clinical routine. The research ethics committee at each participating centre approved the ESADA protocol, and informed consent is obtained from all included patients.

For this analysis, we considered all patients with an AHI ≥5/h and included all complete data sets for the parameters needed for allocation to the four Baveno groups. These parameters comprise symptoms and cardiometabolic comorbidities. Symptoms include daytime sleepiness, insomnia, and hypersomnia. Comorbidities include atrial fibrillation, (uncontrolled) arterial hypertension, heart failure, stroke, and diabetes mellitus (see online supplement for further details). For the baseline analysis, patients were classified as positive airway pressure (PAP) users based on the clinical decision to initiate any kind of PAP therapy, including continuous (CPAP), automatic (APAP) and bilevel PAP.

According to the heterogeneity of clinical practice and local health care regulations, follow-up data were available in a subgroup of the cohort. Follow-up data of 12-24 months were available for 1,724 patients, 24-36 months for 1,081, and >36 months for 953 patients. For the longitudinal analysis in this study, we used the data of those patients treated with continuous (CPAP, 474) or automatic positive airway pressure (APAP, 468) at the time of their follow-up visits which occurred within a time window of 24 to 36 months. These groups and time windows were selected to generate a substantial number of patients and a relevant time frame for evaluation of an objective cardiovascular outcome parameter. Patients treated with bilevel PAP (95), or non-PAP therapies (29) were excluded.

In some part of the analyses, the data was grouped according to the established severity levels of the baseline AHI (mild ≥5 to <15/h, moderate ≥15 to <30/h, severe ≥30/h).

Statistical analysis

Continuous variables are expressed as median and quartiles 1 and 3. Data distribution was tested using the Shapiro-Wilk test. Data across patient groups were tested for significant differences applying one-way ANOVA with Tukey post-hoc test for pairwise comparisons when normal distribution could be assumed. Otherwise, the Kruskal-Wallis test with Bonferroni post-hoc tests was used. For comparisons between two groups, the t-test or the Mann-Whitney U test were used as appropriate. Differences between baseline and follow-up within the same patients were tested with the One-Sample Wilcoxon Signed Rank Test. Differences in percentages (if >0%) between two groups were tested with the two-proportions z-test with Bonferroni adjustment. The level of significance for all statistical tests was set at alpha=0.001. All analyses were performed using IBM SPSS Statistics™ for Windows (version 26.0.; IBM Corp., Armonk, N.Y., USA).

Results

Baseline characteristics of the patients

The ESADA database currently includes 30,235 patients. After exclusion of files with missing data required for allocation to Baveno groups, 14,499 data sets were included for further evaluation, among which 943 were considered for follow-up analysis (Figure 2). Study characteristics were as follows: 28% female, median age 55 [46;63] years (median [quartile 1; quartile 3]) and body mass index (BMI) 31.6 [28.0;36.2] kg/m^2.

The median ESS score was 10 [6;13]; 47% of the patients had a score <11 and 53% had ≥11. The median AHI was 30.8 [16.3;52.9] /h and the oxygen desaturation index (ODI) was 27.0 [12.0;50.8] /h. The mean oxygen saturation (SpO$_2$) was 93 [91;95] (%), the minimum SpO$_2$ 81 [73;86] (%), and the cumulative sleep time with SpO$_2$ below 90% (T90) was 15 [2;65] (min).

Distribution according to the Baveno classification

The patient distribution of the total sample across Baveno groups A-D was: group A 3,447 (24%), group B 2,771 (19%), group C 4,482 (31%), and group D 3,799 (26%). There was a slight decrease of group A and increase of group D in patients with an AHI ≥30/h (Figure 3).

There were no substantial differences in the sex distribution in each group. BMI increased linearly but slightly from groups A to D. The median age was highest (57 [48;65]) in group C and lowest (52 [43;60]) in group B (Table 1).

AHI and ODI were higher in the groups with increased levels of clinical symptomatology (groups B and D). However, only group D showed relevantly lower median values of the mean and minimum SpO_2. Interestingly, there were substantial differences in the T90, which was substantially higher in groups B–D as compared to A. Groups B and C differed only mildly from each other, while the figure for group D was remarkably higher (Table 1).

Data on glycated haemoglobin (HbA_{1c}) were available in 6104 patients. It was slightly and significantly ($p<0.001$) elevated in groups C (5.7 [5.4;6.2]) and D (5.9 [5.5;6.5]) as compared to the groups A (5.6 [5.3;5.8]) and B (5.6 [5.4;5.9]) (%).

Clinical outcome according to the Baveno classification

The individual clinical decisions on therapy had obviously been made independent of the Baveno classification. Here we analysed how these decisions fit to the new system. At least 70% of the patients in every single Baveno group were prescribed PAP. However, therapy was more often considered for the symptomatic groups B and D (A: 71%, B: 80%, C: 70%, D: 82%). 943 patients on CPAP or APAP presented to follow-up visits between 24 and 36 months and all were considered for analysis. The median compliance was 6.0 [5.2;7.0] h/day and did not differ significantly according to Baveno groups, BMI quartiles, age or sex (see online supplement).

The median systolic and diastolic blood pressure improved significantly ($p<0.001$) and substantially by 5-10 mmHg compared to baseline in group C and group D, whereas there was no difference in group A and group B (Figure 5).

The ESS score improved in all groups; however, the greatest changes were noted in groups B and D (Figure 6).

Discussion

The aims of this study focussed on the translation of the Baveno classification system of OSA to the ESADA cohort, a large real-life database. First, the findings demonstrate that integration of clinical symptoms and comorbidities as proposed in the Baveno system [30, 37] stratifies the population, independent of the AHI without considerable over- or underrepresentation any of the groups. The groups with severe symptoms and less comorbidity (B) and less symptoms and severe comorbidity (C) were similar regarding to hypoxic burden while the most severe group in both parameters (D) clearly differed in most measurements of hypoxemia and treatment indication. Second, symptoms seemed to drive the indication to treat more strongly than did comorbidities as shown by the different proportions of treated and untreated patients. Importantly, there was a substantial reduction of blood pressure in the groups with high prevalence of comorbidity. The median reduction of systolic blood pressure was 8.5 and 10.0 mmHg in groups C and D, respectively, which even exceeded the effects of CPAP on resistant arterial hypertension previously reported [38-39]. Finally, the distribution of patients to the Baveno groups A-D did not differ substantially between AHI groups, except for a relatively higher value of group D in the AHI ≥30 group. This is in line with the results of recent studies emphasising the dominant relevance of other parameters than AHI to outcomes of OSA, such as symptoms, comorbidities, and hypoxic burden [13, 24-25]. While the AHI is essential for the diagnosis of OSA, the Baveno classification may guide physicians better in their treatment decision.

The idea of advancing the classification of OSA based only on the AHI by a multi-component scheme based on symptoms and comorbidities arose from several recent cluster analyses. Keenan BT et al. [16] studied 972 patients with OSA (AHI ≥15/h) in the Sleep Apnea Global Interdisciplinary Consortium clustering the population based on 18 symptoms, cardiovascular and metabolic comorbidities. This study identified five groups as "disturbed sleep", "minimally symptomatic", "upper airway symptoms with sleepiness", "upper airway symptoms dominant", and "sleepiness dominant". Bailly et al. [18] performed a cluster analysis of 18,263 participants of the French Sleep Apnoea Registry based on symptoms, findings, risk factors, and comorbidities and identified six clusters with 10-23% of the populations ("young symptomatic", "old obese", "multi-disease old obese", "young snorer", "drowsy obese", "multi-disease obese symptomatic"). Zinchuk et al. [18] included polysomnographic parameters to their cross-sectional and longitudinal data analyses of 1,247 patients. In a Cox-

analysis, survival was significantly reduced in the clusters of "periodic limb movement syndrome", "hypopnoea and hypoxia", and "combined severe". Importantly, the risk did not increase with AHI. Ye et al. [20] analysed 822 patients with moderate-to-severe OSA from the Icelandic Sleep Apnea Cohort, and described three clusters ("insomnia", "minimally symptomatic", "excessive daytime sleepiness") each containing 25-43% of the population. The clusters did not differ regarding sex, BMI, or AHI. "Insomnia" and "minimally symptomatic" patients showed the highest prevalence of cardiovascular comorbidities. In addition, data from Arnardottir et al. [5, 15] and Heinzer et al. [5, 15], referring to the general population, showed no or limited association between the AHI and symptoms or comorbidities.

In our analysis, all classification groups contained substantial numbers of patients between one fifth and one third of the whole population. This suggests that the quartering of the OSAS entirety based on symptoms and comorbidities represents an epidemiologically reasonable and clinically practicable compromise, supported by the distribution of recent cluster analyses [16, 18-19].

The proportion of groups A-D did not differ substantially depending on the baseline AHI group. Therefore, the addition of the severity of breathing disturbances did not influence the relevance of symptoms and comorbidities to the classification of OSA in this population and underlines the previous findings from huge cluster analyses. There were almost no variations in patients with less comorbidities (A and B). Interestingly, there was a shift mainly from group A to D with increasing baseline AHI severity. These groups did not differ regarding comorbidities but symptoms so that a therapy decision solely based on the AHI seems to miss severely ill patients with mild symptoms.

The mild but linear increase of the mean BMI from groups A to D probably reflects the association of comorbidities with the risk factor of obesity. Although there is no linear increase in the retrospective data for age, it was nevertheless higher in groups C and D (higher comorbidities) as compared to groups A and B.

Parameters of breathing disturbances during sleep also increased with the Baveno groups. This is especially true comparing groups A, B and C versus D. However, differences between B and C are much less pronounced. Interestingly, group B (more symptoms, less comorbidities) showed higher AHI and ODI as compared to C (less

symptoms, more comorbidities), while the hypoxic burden, as reflected by the T90 [40-41], did not differ between groups B and C. This suggests that the relevance of the disease and the indication for treatment of this half of the population is similar in patients who are either symptomatic or suffer from cardiometabolic comorbidities. However, the co-existence of symptoms and comorbidities (group D) results in the highest burden of the disease compared to all other groups.

The baseline AHI seems to play the most important role in PAP prescription in real-life, irrespective of symptoms and comorbidities (Figure 4): In the subgroup with low AHI (<15/h) PAP was prescribed in less than 30% of patients, although more than 70% had severe symptoms and/or comorbidities. In contrast, almost all patients with AHI ≥30/h were prescribed PAP, although one fifth presented neither symptoms nor comorbidities. Despite these findings, clinicians seem to indicate treatment in real-life preferably based on symptoms rather than comorbidities as groups B and D show 10% higher prescription rates compared to C. As the recently published [42] MERGE trial has found, even in mild OSA, PAP treatment significantly improves quality of life.

The PAP compliance in the complete follow-up population was 6.0 h/d and did not differ when stratifying for the various comparisons of Baveno groups, sex, age and BMI. It is important to note that there were no relevant compliance differences between the Baveno groups A-D, which excludes an influence on the outcome parameters. The baseline data on hypoxic burden and the follow-up data on sleepiness and blood pressure confirmed the relevance of the classification system in several aspects: They proved the plausibility of the parameters included; they confirmed the separation of each of the four groups, and they confirmed the treatment indication based on the system. The median ESS score improved significantly in groups B and D by 9 points each, which is of high clinical relevance. This shows that the parameters clearly discriminated between symptomatic and asymptomatic patients and confirms that CPAP has a huge effect in symptomatic patients. In addition, both systolic and diastolic blood pressure improved significantly and relevantly in patients with high impact of comorbidities (groups C and D). These results support the idea of indicating treatment based on the groups: groups B, C, and D improved in symptoms, in blood pressure, or in both parameters. In contrast, group A differs in hypoxic burden, symptoms and comorbidities from all other groups and fails to show any benefit in the parameters investigated here despite similar

compliance and thus, PAP treatment for these patients seems not indicated. While the observed changes in blood pressure and ESS, especially in groups B and D, may in part be due to a regression to the mean, the (albeit lesser) improvement of ESS in groups A and C and the absence of an increase in median blood pressure in groups A and B strongly suggest that this is to a large extent an actual treatment effect. Our data reflect blood pressure recordings during clinical routine assessments with and without concomitant antihypertensive medication and thus, a large variability between blood pressure assessments in a proportion of patients could be expected. As each group comprises several thousand patients, a small group of patients with very large variability in blood pressure accounts for the occurrence of a certain proportion of elevated values on follow-up. Moreover, the proportion of hypertensive OSA patients was higher in groups C&D when compared to A&B (55 versus 30%). It is therefore expected that the blood pressure response to CPAP would be more pronounced in these groups.

Limitations

The retrospective design generally limits the conclusions of any study, mainly to incomplete or insufficient data. However, a strict exclusion process allowed for analysing only patient files with all relevant data required for the Baveno classification.

The classification of patients based on dichotomisation of continuous biological parameters might be seen as an oversimplification. However, the cut-off values for the ESS score and blood pressure we used are well established and substantiated in that they relate to outcome. Dichotomous cut-offs were deliberately chosen to make the Baveno system intuitive and accessible in the clinical routine. It may also be extended at a later stage by the introduction of parameters such as hypoxic load and/or therapeutic recommendations.

The ESADA database has its greatest strength in the baseline data while follow-up data are available only for a subgroup of patients. The validation of the Baveno classification on long-term outcome has to remain limited. Therefore, the system will require prospective evaluation of a large unselected population based on both patient-related outcome parameters, morbidity and mortality. Nevertheless, the ESS, the hypoxic burden, the blood pressure, and the treatment compliance between 24-

36 months in a subgroup of this study may be considered as a surrogate of the outcome.

We are aware that the interpretation of the compliance may underlie a selection bias due to loss of non-compliant patients. Nevertheless, the data demonstrate that sufficient compliance is associated with cardiovascular improvement in those with severe comorbidities and a substantial improvement of severe symptoms.

Conclusions

The Baveno classification system is likely superior than the traditional OSA classification based on AHI as it combines patient-related parameters of symptomatology on one hand and prognostic parameters on the other. It integrates findings of several recent cluster analyses. Furthermore, the scheme is easily applicable in clinical practice as it uses simply available, but reliable data. Using the system for therapeutic decisions, it may avoid unnecessary treatments in patients with moderate-to-severe OSA, but without symptoms or comorbidities, and missing treatments in symptomatic or comorbid OSA patients with low AHI. However, these findings require further investigation in prospective studies.

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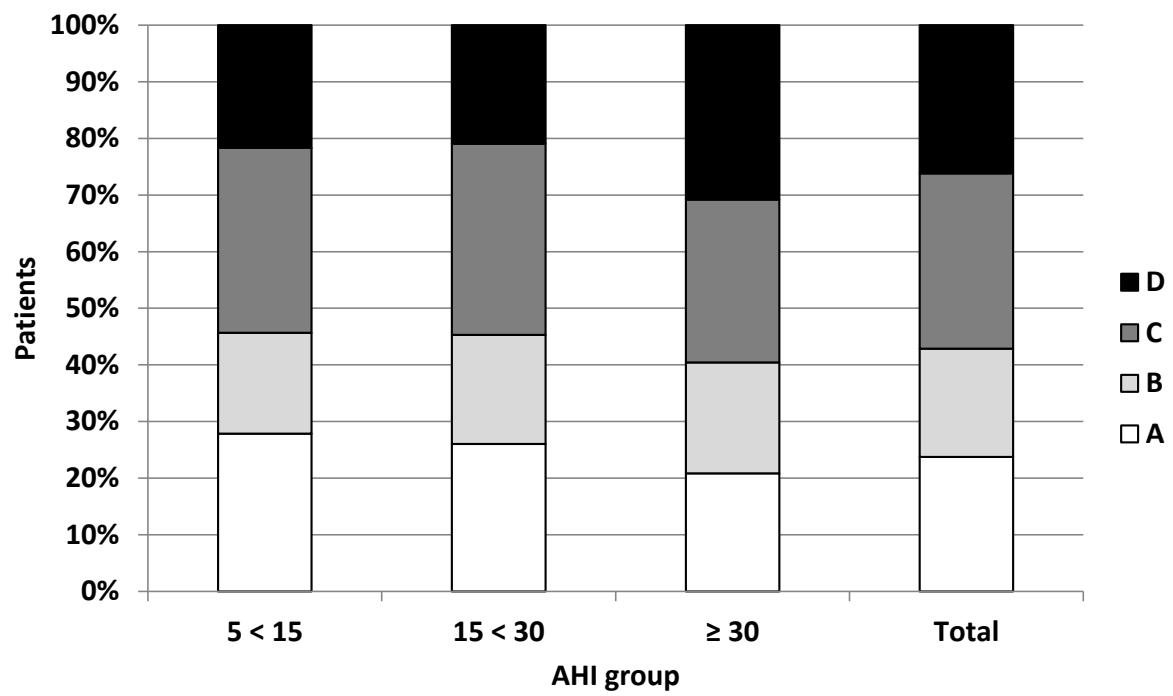
Figures

|		
C Mild symptoms Major end-organ Impact	**D** Severe symptoms Major end-organ Impact	Recurrent/ poorly controlled
A Mild symptoms Minor end-organ Impact	**B** Severe symptoms Minor end-organ impact	Not detectable/ well controlled
ESS<11 No hypersomnia Insomnia−	ESS≥11 Hypersomnia Insomnia+	End-organ impact/ comorbidities

Symptoms

Figure 1: The revised version of the Baveno classification, adapted from Randerath et al. [30] (used with permission from ERJ). Details about symptom and comorbidity criteria are provided in the online supplement.
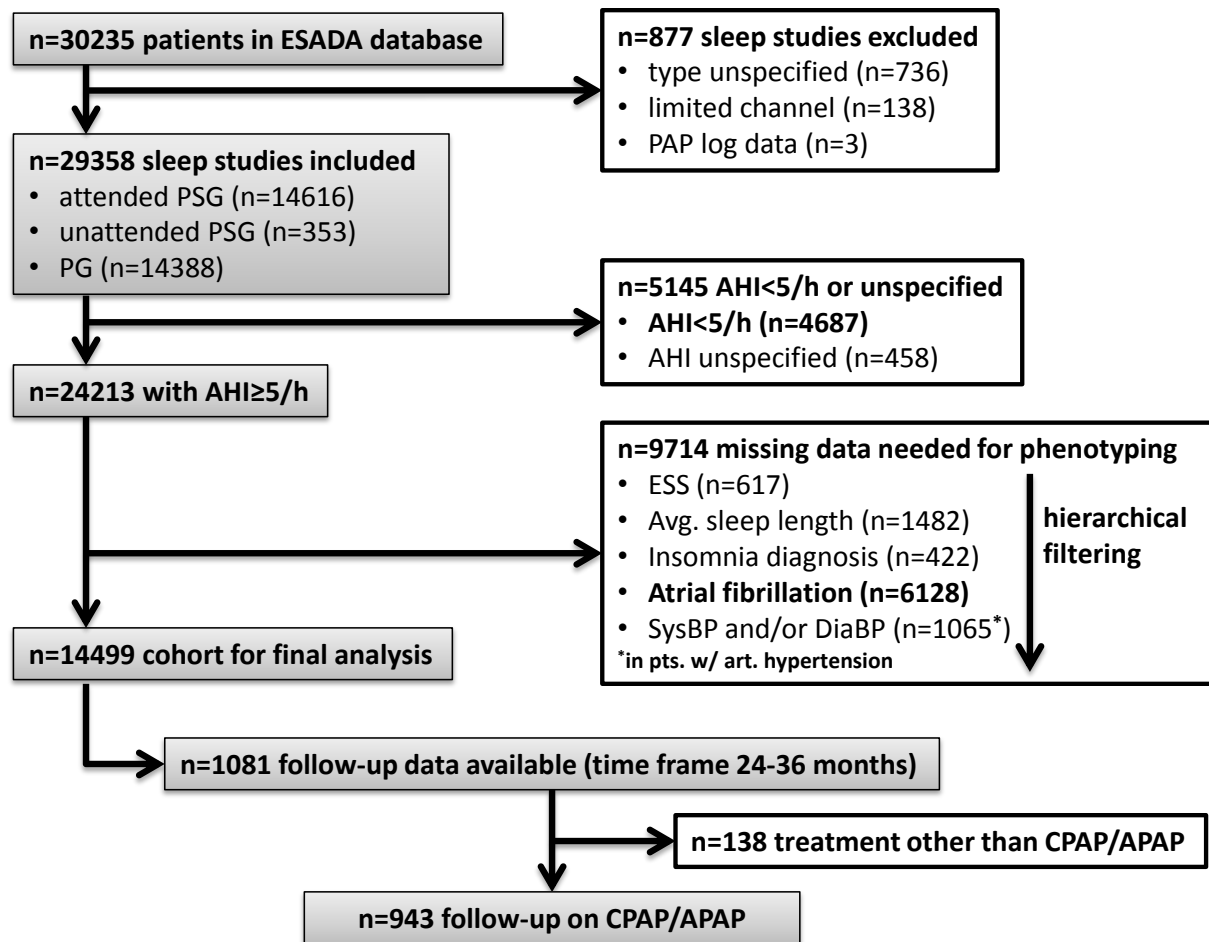
Figure 2: Flow-chart of the inclusion process.

Figure 3: Distribution of the Baveno groups A-D in different AHI groups and in the overall patients
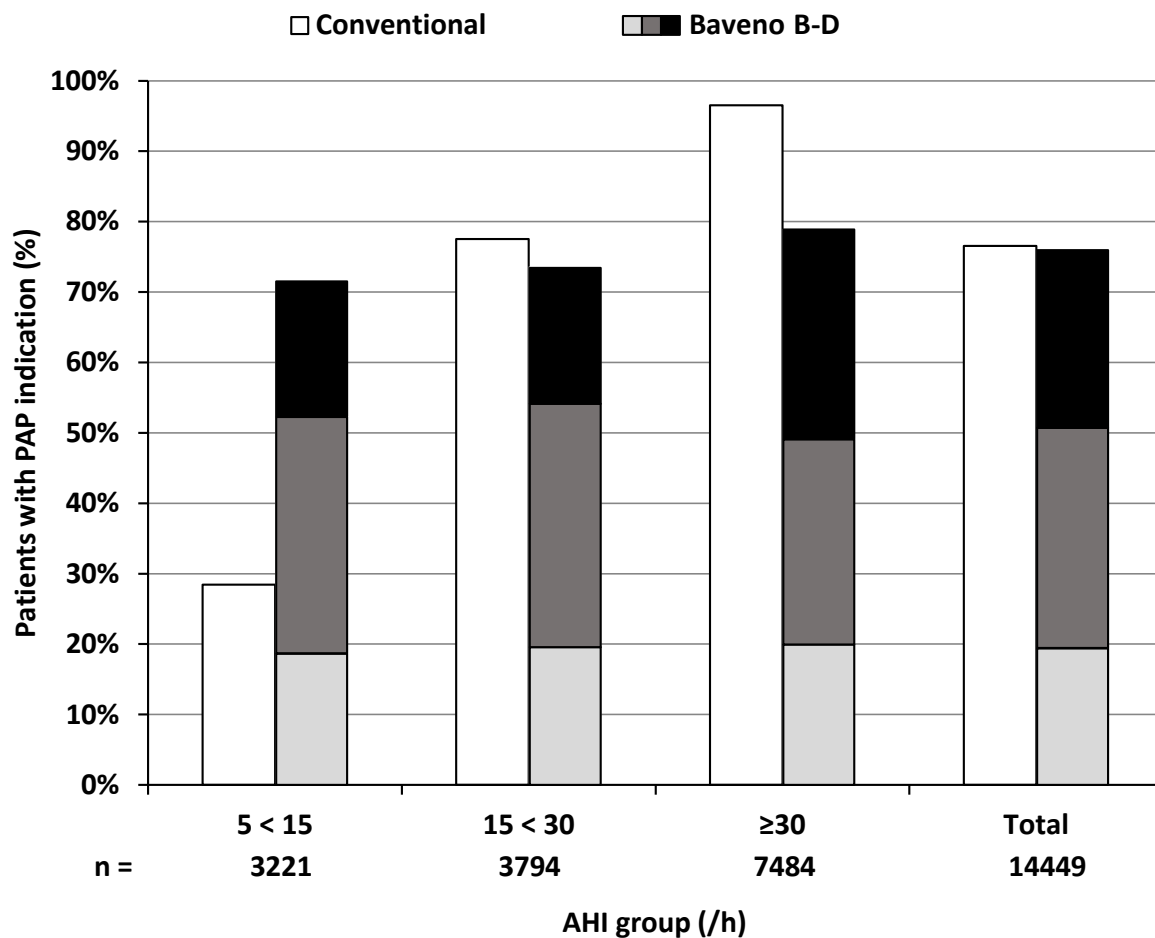
Figure 4: Percent of patients with PAP prescription at baseline in the different AHI groups and in the whole study population. White columns represent actual PAP prescription as per conventional clinical routine decision; shaded columns represent PAP prescription as indicated by Baveno classification (i.e. Baveno groups B-D).
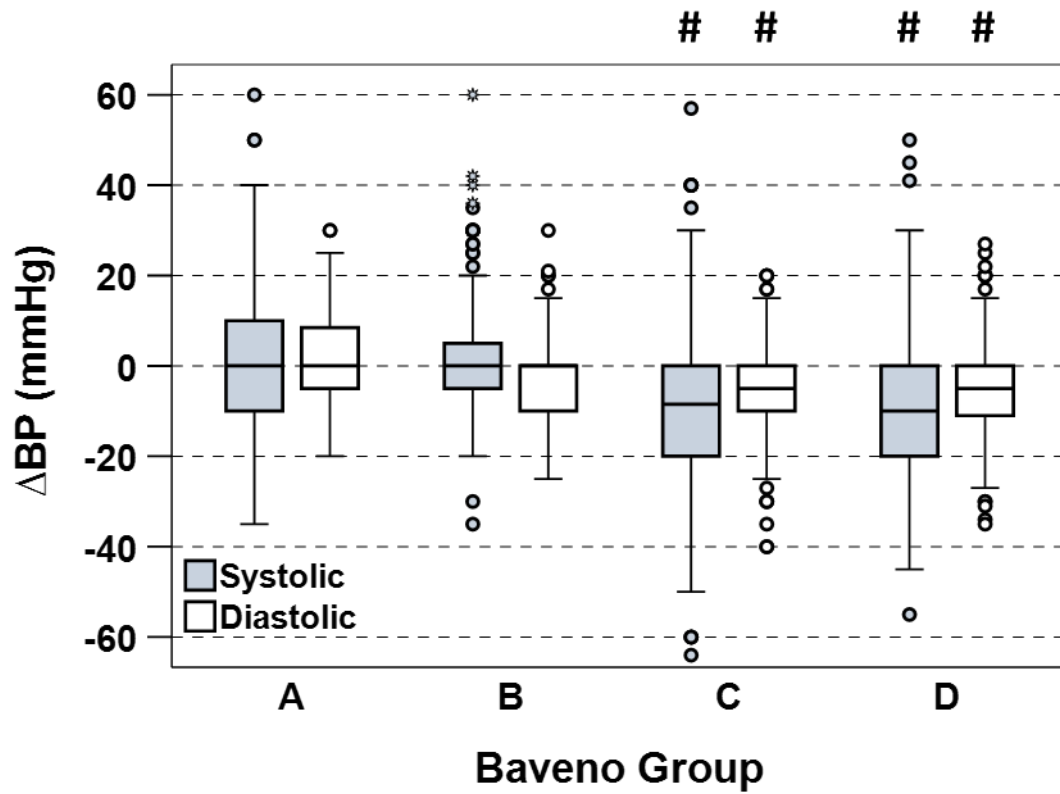
Figure 5: Changes in systolic and diastolic blood pressure between baseline and follow-up in the different Baveno groups A-D

Circles denote outlier values (>1.5 interquartile ranges outside the box), asterisks denote extreme values (>3 interquartile ranges outside the box).

#: p<0.001 baseline vs. follow-up.
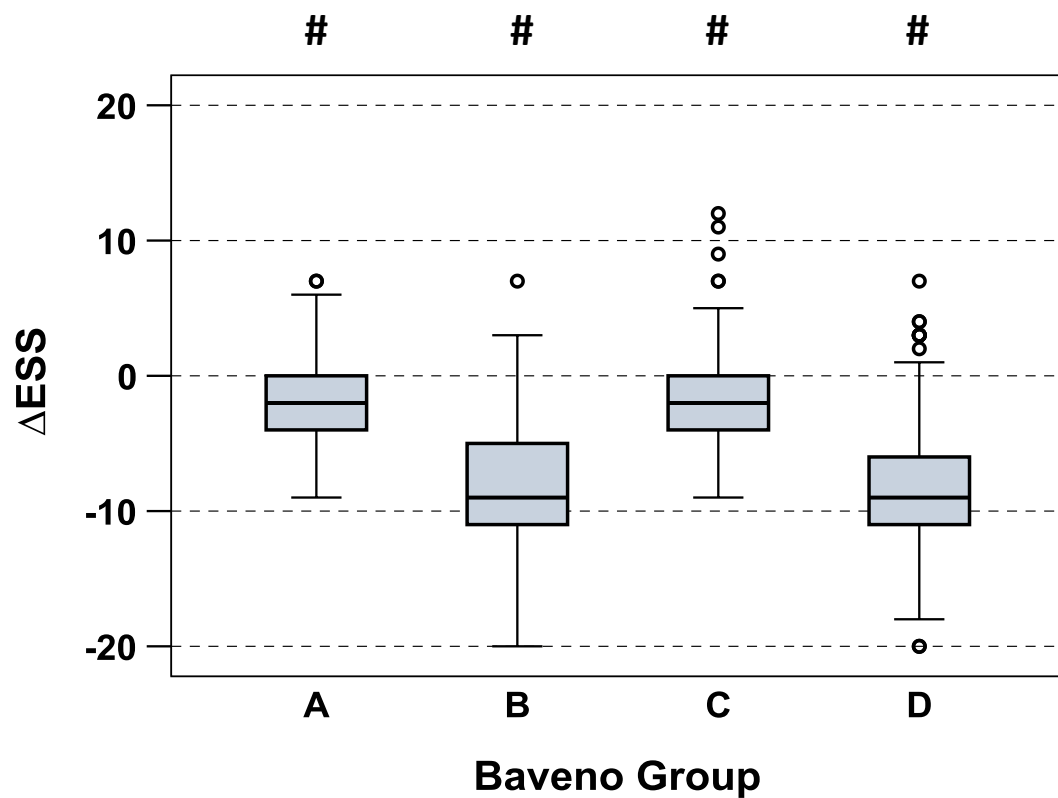
Figure 6: Change of the Epworth Sleepiness Scale (ESS) score between baseline and follow-up in the different Baveno groups A-D

Circles denote outlier values (>1.5 interquartile ranges outside the box).

#: p<0.001 baseline vs. follow-up

Tables

Table 1. Patient characteristics within the four Baveno groups A-D

	Group A (n=3,447)	Group B (n=2,771)	Group C (n=4,482)	Group D (n=3,799)
Females (%)	28.1	28.1	27.8	27.8
Age (years)	54 [44;62]$^{*,\S,\&}$	52 [43;60]*,§	57 [48;65]*	56 [47;63]
BMI (kg/m²)	30.0 [26.9;33.8]$^{*,\S,\&}$	31.0 [27.4;35.3]*,§	31.7 [28.1;36.3]*	33.6 [29.8;38.3]
BP systolic (mmHg)	125 [120;130] *,§	125 [120;130] *,§	140 [130;150]	140 [130;150]
BP diastolic (mmHg)	77 [70;80] *,§	77 [70;80] *,§	85 [78;91]	85 [79;91]
ESS (0-24)	6 [4;8]$^{*,\&}$	14 [12;16]§	6 [4;8]*	14 [12;17]
AHI (/h)	27.0 [14.3;44.3]$^{*,\S,\&}$	31.5 [17.4;53.5]*,§	28.2 [15.6;49.8]*	37.7 [19.5;63.3]
ODI (/h)	22.8 [10.4;42.0]$^{*,\S,\&}$	27.4 [11.8;51.5]*	24.9 [11.9;47.0]*	35.0 [15.2;61.9]
Mean SpO$_2$ (%)	93.4 [92.0;95.0]$^{*,\S,\&}$	93.0 [91.0;95.0]*	93.0 [91.0;94.8]*	92.1 [90.0;94.0]
Minimum SpO$_2$ (%)	82 [77;87]$^{*,\S,\&}$	81 [74;86]*	81 [74;86]*	78 [70;84]
T90 (min)	8.7 [1.0;38.5]$^{*,\S,\&}$	15.0 [1.9;62.8]*	13.0 [2.0;59.0]*	31.0 [4.9;102.0]

BMI: body mass index, BP: blood pressure, ESS: Epworth Sleepiness Scale, AHI: apnoea-hypopnoea index, ODI: oxygen desaturation index, SpO$_2$: oxygen saturation as measured by pulse oximetry, T90: percentage of sleep time with a SpO$_2$ below 90%

Values are given as median and quartile 1 and 3 or within group percentage unless otherwise stated.

*p<0.001 vs. D

§p<0.001 vs. C

$^{\&}$p<0.001 vs. B

Online supplement

Evaluation of a multicomponent grading system (Baveno classification) for obstructive sleep apnoea

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Criteria for the Baveno classification

An *ad hoc working group* of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society developed this new approach to OSA beyond the AHI integrating symptoms and cardiometabolic comorbidities [1]. It grades OSA in a two-dimensional scheme into four groups on based the level of symptoms and the presence and severity of comorbidities. For the current analysis, we adapted the originally proposed classification criteria, partly owing to the limited availability of certain parameters in the data base. Symptoms include daytime sleepiness, insomnia, and hypersomnia. Comorbidities associated with OSA which were taken in account are atrial fibrillation, (uncontrolled) arterial hypertension, heart failure, stroke, and diabetes mellitus. Symptoms were classified according to their absence or presence and comprised the following: daytime sleepiness as defined by an ESS score ≥11, hypersomnia defined by subjective sleep length ≥11 hours, and diagnosis of insomnia. If at least one of these conditions was met, the patient was classified as having severe symptoms and thus allocated to the Baveno group B or D.

As distinguished from the Baveno paper we choose an ESS threshold of ≥11 according the general practice [1-2].

End-organ impact was classified considering the absence or presence of uncontrolled arterial hypertension, atrial fibrillation, heart failure, diabetes mellitus, and history of stroke. If at least one of these comorbidities was present, end-organ impact was deemed major calling for an allocation to Baveno group C or D. Uncontrolled hypertension was defined as a diagnosis of arterial hypertension accompanied by a systolic office blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg.

Selection

For this analysis we included all complete data sets for the following parameters: AHI≥5/h according to PSG or PG and baseline data needed for the allocation to the four Baveno groups including data on symptoms related to sleep-disordered breathing (ESS score, subjective sleep length, diagnosis of insomnia) and major end-organ impact (uncontrolled arterial hypertension, atrial fibrillation, heart failure, diabetes mellitus, and history of stroke).

8862 (61%) patients underwent full attended polysomnography, 128 (1%) unattended polysomnography, and 5509 (38%) cardiorespiratory polygraphy.

We decided for a strict inclusion management selecting only patients with complete data required for classification according to the Baveno system in order to minimize the limitations of a retrospective study. Daytime sleepiness as measured by ESS score and the diagnosis of insomnia were generally available symptoms.

The physician examined the health documents of each patient, including drug treatment. Data on arterial hypertension, atrial fibrillation, heart failure, diabetes and stroke, were also available in all included data sets and allowed for the description of comorbidities. Blood pressure ≥140/90 mmHg was used as a surrogate of uncontrolled hypertension.

The follow-up visits of the patients within a time window of 24 to 36 months after baseline were considered for the longitudinal analysis. Considering all participating clinical sites, the percentage of patients with follow-up varied between 0% and 50%. During follow-up, 1,042 patients were on positive airway pressure (PAP) therapy (474 APAP, 468 CPAP, 95 BPAP, 5 unspecified), 29 were treated with non-PAP therapies (10 mandibular advancement device, 1 surgery, 1 medical therapy, 27 unspecified).

Prevalence of comorbidities within Baveno groups

The Baveno classification differentiates the groups according to subjective symptoms and comorbidities. Regarding comorbidities, Groups C and D are characterized by severe (uncontrolled (e.g. hypertension) or recurrent (e.g. atrial fibrillation)) comorbidities. Minor (stable conditions and well-controlled) comorbidities are accepted for Groups A and B. Although hypertension is frequent in OSA, there are still substantial differences between the groups (Table e1).

Table e1: Prevalence of comorbidities according to the Baveno groups

	Group A	Group B	Group C	Group D
Systemic hypertension	33.5[*],[§]	31.1[*],[§]	55.2	56.6
Ischaemic heart disease	6.2[*],[§]	6.1[*],[§]	10.2	12.7
Left ventricular hypertrophy	0.9	0.8	1.8	1.9
Valvular heart disease	0.9[*]	0.9[*]	2.1	1.2
History of TIA or stroke	0.0	0.0	4.3	4.0
Atrial fibrillation	0.0	0.0	15.1[§]	10.1
Pulmonary hypertension	0.2[*],[§]	0.4	1.0	0.9
History of myocardial infarction	1.1[*]	0.9[*]	2.3	1.8
Cardiac failure	0.0	0.0	5.9	7.4
Hyperlipidaemia	24.8[*],[§]	21.8[*],[§]	29.8	32.0
Diabetes mellitus	0.0	0.0	27.8[§]	32.5
Hyperuricaemia	2.9[*],[§]	2.0[*],[§]	4.6	4.7
Restrictive pulmonary disease	0.4	0.4	0.8	0.7
Respiratory failure	0.3[§]	0.4[§]	0.8	1.6
COPD	5.3[§]	6.6[§]	6.6[§]	10.4
Bronchial Asthma	4.4[§]	5.9	6.2	6.8
Neurological Disease	5.2	3.7	4.8	4.5

Psychiatric disease	8.1	10.3*	7.7	9.9
Inflammatory Disease	1.8	1.6	1.8	1.9
Gastrointestinal disease	7.7	9.3	8.2	9.7
Malignant disease	1.7	1.0	2.2	1.8

Data are given as within-group percentage.

TIA: transitory ischaemic attack, COPD: chronic obstructive pulmonary disease

* = $p<0.001$ vs. C, § = $p<0.001$ vs. D

Blood serum parameters

For subsets of patients results from clinical routine blood serum analysis regarding total cholesterol (n=9356), triglycerides (n=9248) and C-reactive protein (n=8220) were available at baseline (Table e2).

Table e2: Baseline parameters of lipid and inflammatory parameters according to the Baveno groups

	Group A	Group B	Group C	Group D	p
Total cholesterol (mg/dL)	199 [172;226]	200 [175;226]§	195 [167;224]	197 [168;226]	<0.001
Triglycerides (mg/dL)	136 [98;185]*	137 [99;195]*	145 [104;200]*	151 [110;206]	<0.001
CRP (mg/dL)	0.29 [0.12;0.50]*	0.29 [0.13;0.52]*	0.30 [0.14;0.57]*	0.33 [0.17;0.65]	<0.001

CRP: C-reactive protein

Values are given as median and quartile 1 and 3.

*$p<0.001$ vs. D

§$p<0.001$ vs. C

Comparison of patients with and without follow-up

To evaluate the representativeness of the subgroup of patients considered for follow-up analysis (n=943) they were compared to all other patients with prescription of CPAP or APAP at baseline, who did not return for a follow-up visit within the specified time window of 24 to 36 months (n=9926) (Table e3).

Table e3: Comparison of PAP-treated patients with vs. without follow-up

	CPAP/APAP patients without follow-up (n=9926)	CPAP/APAP patients with follow-up (n=943)	p
Age (years)	55 [47;64]	56 [48;64]	0.043
BMI (kg/m²)	32.6 [29.0;37.1]	31.2 [28.2;35.1]	<0.001
ESS	10 [6;14]	11[7;14]	0.002
AHI (/h)	38.0 [24.2;59.8]	38.0 [24.7;58.0]	0.588
ODI (/h)	35.0 [20.7;58.6]	27.6 [13.0;50.0]	<0.001
Mean SpO_2 (%)	93 [90;94]	93 [91;94]	<0.001
Minimum SpO_2 (%)	79 [71;83]	80 [76;84]	<0.001
T90 (min)	26.1 [4.9;83.0]	29.0 [5.1;82.0]	0.635
Total cholesterol (mg/dL)	196 [167;225]	199 [171;224]	0.127
Triglycerides (mg/dL)	142 [104;196]	153 [106;212]	0.002
HbA_{1c} (%)	5.7 [5.4;6.2]	5.7 [5.4;6.1]	0.086
CRP (mg/dL)	0.30 [0.15;0.60]	0.29 [0.20;0.50]	0.694
Systolic BP (mmHg)	130 [123;141]	130 [120;140]	0.235

Diastolic BP (mmHg)	80 [73;90]	80 [76;90]	0.087
Females (%)	26.5	23.3	0.033
Group A	23	19	0.003
Group B	20	25	<0.001
Group C	29	28	0.348
Group D	28	29	0.551

BMI: body mass index, ESS: Epworth Sleepiness Scale, AHI: apnoea-hypopnoea index, ODI: oxygen desaturation index, SpO_2: oxygen saturation as measured by pulse oximetry, T90: percentage of sleep time with a SpO_2 below 90%, HbA_{1c}: glycated haemoglobin, CRP: C-reactive protein, BP: blood pressure

Values are given as median and quartile 1 and 3 or percentage.

Treatment compliance

The median compliance was 6.0 [5.2;7.0] h/day and did not differ significantly according to Baveno groups, BMI quartiles, age or sex (Table e4).

Table e4: Comparison of treatment compliance between Baveno groups, BMI and age quartiles as well as between sexes

Baveno group	A	B	C	D	p
	6.0 [5.4;7.0]	6.0 [6.0;7.0]	6.0 [5.0;7.0]	6.0 [5.5;7.0]	0.416
BMI (kg/m²) quartiles	<28.0	28.0-31.6	31.7-36.2	>36.2	-
	6.0 [5.0;7.0]	6.0 [5.3;7.0]	6.0 [5.4;7.0]	6.0 [5.3;7.0]	0.825
Age (years) quartiles	<46	46-55	56-63	>63	-
	6.0 [5.0;7.0]	6.0 [5.0;7.0]	6.0 [6.0;7.0]	6.0 [6.0;7.0]	0.063
Sex	female		male		-
	6.0 [5.5;7.0]		6.0 [5.2;7.0]		0.081

BMI: body mass index

Values are given as median and quartile 1 and 3

References

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