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ORIGINAL ARTICLE

Adjustment of apnea-hypopnea index with severity of obstruction events enhances detection of sleep apnea patients with the highest risk of severe health consequences

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Abstract
Introduction Presently, the severity of obstructive sleep apnea (OSA) is estimated based on the apnea-hypopnea index (AHI). Unfortunately, AHI does not provide information on the severity of individual obstruction events. Previously, the severity of individual obstruction events has been suggested to be related to the outcome of the disease. In this study, we incorporate this information into AHI and test whether this novel approach would aid in discriminating patients with the highest risk. We hypothesize that the introduced adjusted AHI parameter provides a valuable supplement to AHI in the diagnosis of the severity of OSA.
Methods This hypothesis was tested by means of retrospective follow-up (mean ± sd follow-up time 198.2±24.7 months) of 1,068 men originally referred to night polygraphy due to suspected OSA. After exclusion of the 264 patients using CPAP, the remaining 804 patients were divided into normal (AHI<5) and OSA (AHI≥5) categories based on conventional AHI and adjusted AHI. For a more detailed analysis, the patients were divided into normal, mild, moderate, and severe OSA categories based on conventional AHI and adjusted AHI. Subsequently, the mortality and cardiovascular morbidity in these groups were determined.
Results Use of the severity of individual obstruction events for adjustment of AHI led to a significant rearrangement of patients between severity categories. Due to this rearrangement, the number of deceased patients diagnosed to have OSA was increased when adjusted AHI was used as the diagnostic index. Importantly, risk ratios of all-cause mortality and cardiovascular morbidity were higher in moderate and severe OSA groups formed based on the adjusted AHI parameter than in those formed based on conventional AHI.
Conclusions The adjusted AHI parameter was found to give valuable supplementary information to AHI and to potentially improve the recognition of OSA patients with the highest risk of mortality or cardiovascular morbidity.

Keywords Obstructive sleep apnea · AHI · ODI · Mortality · Adjusted AHI

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Introduction

Obstructive sleep apnea (OSA) is a common disorder recognized as an important public health issue [1]. This disorder is estimated to affect 9–24 % of the middle-aged populations [2]. OSA has been associated with increased morbidity, mortality, and diminished quality of life [3–7]. Obstructive apneas induce severe intermittent hypoxemia and CO_2 retention disrupting the normal autonomic and hemodynamic responses to sleep [8]. Apneas and desaturations are accompanied by chemoreflex-mediated increase in sympathetic activity of the peripheral blood vessels and resultant vasoconstriction [9]. Long-term consequences of OSA include various

disorders of the cardiovascular system [10]. OSA has also been suggested as an independent risk factor for essential hypertension [4].

OSA is defined by repeated episodes of total (apnea) or partial (hypopnea) cessation of airflow leading to arterial hypoxemia. Apnea-hypopnea index (AHI) (i.e., the number of apnea and hypopnea events per hour) is generally used in the diagnosis of OSA and its severity [11, 12]. Along the guidelines of American Academy of Sleep Medicine (AASM) 5≤AHI<15 indicates a mild disease, 15≤AHI<30 indicates a moderate disease, and AHI≥30 indicates a severe form of the disease.

However, AHI does not take into account the morphology of obstruction events, i.e., the duration and depth of obstruction and desaturation events. Recently, it has been suggested, especially in severe OSA, that AHI may not optimally reflect the true severity of the disease [13–16]. Obstruction severity parameter incorporating the severity of individual obstruction events and AHI has been shown to provide valuable diagnostic information over conventional AHI [13, 17]. Furthermore, Otero et al. 2012 reported that apnea-hypopnea-desaturation index, i.e., combined percentage of sleep time that the patient has been in apnea, hypopnea, or hypoxia, performs better in the diagnosis of OSA than conventional AHI [16].

In clinical practice, patients must be classified as having no, mild, moderate, or severe disease. However, there are no published guidelines on how this could be done based on the obstruction severity parameter. In this study, we propose a method of converting obstruction severity parameter values to values of parameter called adjusted AHI. This would allow the use of the AASM guidelines (i.e., AHI limits) for the diagnosis of the severity of the disease. We hypothesize that the adjusted AHI parameter provides valuable supplement to conventional AHI in the diagnosis and assessment of the severity of OSA. Presently, this hypothesis is evaluated in a long-term (mean±sd follow-up time 198.2±24.7 months) retrospective follow-up of 1,068 men originally referred to night polygraphy based on suspected OSA.

Patients and methods

The database used in this study consists of retrospective follow-up (mean ± sd, median, and interquartile range of follow-up time 198.2±24.7, 195.8, and 180.5–224.1 months, respectively) of 1,068 men referred to night polygraphy due to initial clinical suspicion of OSA in the Department of Clinical Neurophysiology at Kuopio University Hospital. The polygraphic recording was conducted at baseline. During the follow-up period, 187 men died. The primary and secondary causes of death were obtained from the Statistics Finland (Helsinki, Finland) in October 2012. Two hundred sixty-four patients having had continuous positive airway pressure (CPAP) treatment were omitted from further analysis. The remaining patients (804 men) were included in this study. Out of these, 127 patients died during the follow-up period. The study protocol is summarized in Fig. 1. The Research Ethics Committee of Hospital District of Northern Savo, Kuopio, Finland had a favorable opinion on conducting this study (decision numbers 127/2004 and 24/2013).

In the present study, a state-of-the-art (in years 1993–2001) four-channel ambulatory polygraphic device was used; for details, see [14, 18]. The recordings were analyzed based on the standard AASM respiratory rules [12]. An apnea event was detected when thermistor signal amplitude fell below 20 % of the reference level for at least 10 s. Rule 4A was used for scoring the hypopnea events [12]. To score hypopnea, the thermistor signal had to drop below 70 % of the reference level and a desaturation event (≥4 %) had to occur within 20 s after the start of the hypopnea. In addition to conventional AHI, an obstruction severity parameter was determined; for details, see [13, 17, 18]. The obstruction severity parameter incorporates durations of individual apnea and hypopnea events and areas of related desaturation events and is normalized with the total analyzed time (Eq. 1). Thus, this parameter provides information on the duration and morphology of apnea, hypopnea, and desaturation events.

$$\text{Obstruction severity} = \frac{\sum_{n=1}^{L} n(\text{HypDur}_n \times \text{DesArea}_n) + \sum_{n=1}^{L} n(\text{ApDur}_n \times \text{DesArea}_n)}{\text{Index time}}, \quad (1)$$

where single apnea event duration is denoted as ApDur (s), single hypopnea event duration as HypDur (s), and total analyzed time as Index time (s). DesArea (s%) is the area of a single desaturation event. L is the number of analyzed events in the recording.

Subsequently, the values of obstruction severity were converted to values of adjusted AHI through linear fit between the square root of obstruction severity parameter and AHI in the population of all 1,068 patients (Fig. 2, Eq. 2). We used linear fit instead of quadratic or polynomial fit as it was found in the preliminary test as the most capable of discerning patients with the highest risk. The square root of obstruction severity was selected for fitting as obstruction severity parameter is defined as a product of obstruction

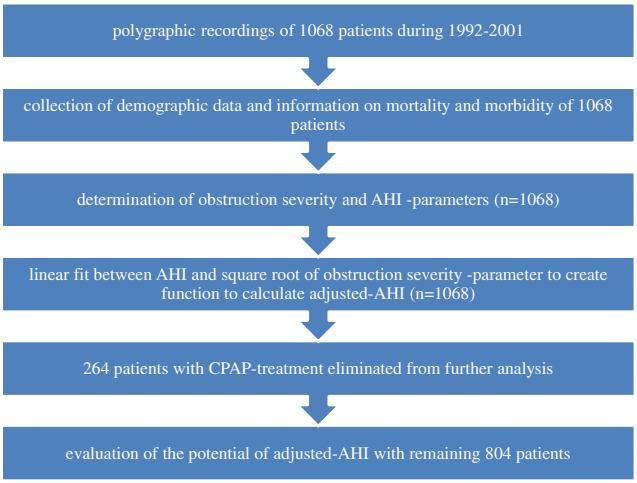

Fig. 1 A flowchart describing the study protocol

duration and area of desaturation. The potential of adjusted AHI was tested in a subpopulation of 804 patients (CPAP-treated patients were excluded). Since the mortality and morbidity data were not used in the creation of adjusted AHI, patient pools applied in the creation and testing of the method are in this respect independent.

$$\text{Adjusted AHI} = 5.328 \times \sqrt{\text{ObsSev}} \quad (2)$$

First, patients (without CPAP treatment) were divided into normal (AHI<5) and OSA (AHI≥5) groups. For further analyses, the patients in the OSA group were divided into mild (5≤AHI<15), moderate (15≤AHI<30), and severe OSA (AHI≥30) categories based on conventional AHI and also based on the novel adjusted AHI parameter. Subsequently, total mortality, cardiovascular mortality, and cardiovascular morbidity (i.e., nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass surgery, and percutaneous coronary intervention) were compared between the severity categories. Information on cardiovascular morbidity was obtained from the patient's medical records collected in Kuopio University Hospital.

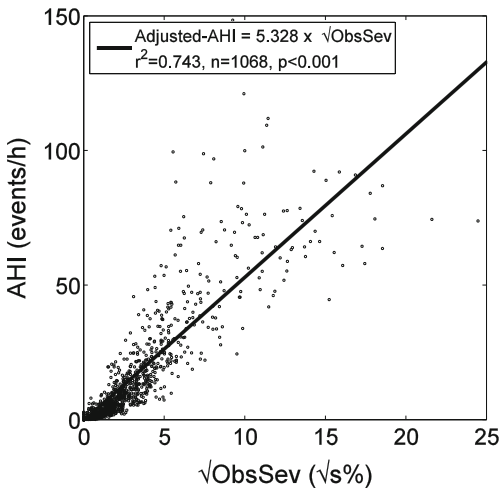

Fig. 2 Obstruction severity parameter values were converted to values of adjusted AHI using linear regression ($\sqrt{\text{ObsSev}}$ vs. AHI) in data consisting of all 1,068 patients

The demographic characteristics of the different OSA groups are presented in Table 1. Subgroups of 400 and 226 patients extracted from the pool of patients investigated in this study have been analyzed in our previous studies [14, 17].

Statistical analysis

Normal, mild, moderate, and severe groups were formed based on conventional AHI and adjusted AHI. Significance of differences between these groups was investigated using the Mann-Whitney U test. The relationship between square root of obstruction severity parameter and AHI was evaluated using linear regression analysis. The statistical significance of differences in morbidity and mortality between patients with and without OSA was evaluated by determining the risk ratios normalized with follow-up time using the *t* test. Statistical analyses were performed with SPSS (version 20.0, SPSS Inc, Chicago, IL, USA) and R (version 2.15.2, www.r-project.org).

Results

A significant rearrangement of patients between diagnostic categories took place when using the adjusted AHI instead of conventional AHI (Table 1, Fig. 3). Due to this rearrangement, the number of deceased patients (all-cause and cardiovascular mortalities) diagnosed to have OSA was increased when adjusted AHI was used as the diagnostic index (Fig. 4). Furthermore, the same trend was seen with patients suffering from cardiovascular morbidity (Fig. 4).

Arranging the patients to normal, mild, moderate, and severe OSA groups based on conventional and adjusted AHI was found to affect the risk ratios of all-cause and cardiovascular mortalities (Fig. 5). Importantly, the risk ratios for all-cause mortality were notably elevated (3.08 vs. 2.14) in severe disease when the diagnosis was based on the adjusted AHI instead of conventional AHI (Fig. 5a). Interestingly, the risk ratio of cardiovascular mortality in patients suffering from severe OSA

Table 1 Demographic data of 804 patients (median, range)

	Normal			Mild			Moderate			Severe		
	AHI	Adjusted AHI	*p* value	AHI	Adjusted AHI	*p* value	AHI	Adjusted AHI	*p* value	AHI	Adjusted AHI	*p* value
Patients (*n*)	419	223		232	376		91	152		62	53	
Age (years)	46 (20–70)	45 (20–70)	0.073	50 (26–80)	47 (21–80)	0.060	50 (29–80)	51 (29–76)	0.310	51 (29–81)	51 (31–81)	0.922
BMI (kg/m^2)	26.5 (17.8–47.8)	26.0 (17.8–39.3)	0.150	28.4 (19.9–60.6)	27.8 (18.5–47.8)	*0.016*	30.6 (23.1–46.7)	29.6 (21.9–74.0)	0.590	32.0 (23.1–74.0)	32.3 (23.1–58.5)	0.893
Follow-up time (months)	193 (11–253)	191 (63–253)	0.962	198 (29–252)	194 (11–252)	0.435	195 (87–250)	195 (84–252)	0.824	192 (145–248)	200 (145–250)	0.180
AHI (events/h)	1.8 (0.0–4.9)	0.8 (0.0–8.0)	*<0.001*	8.3 (5.0–14.9)	4.7 (0.4–29.5)	*<0.001*	20.6 (15.1–29.7)	16.5 (5.4–99.5)	*<0.001*	47.3 (30.0–130.5)	45.5 (21.3–130.5)	0.387
Adjusted AHI (events/h)	4.8 (0.0–14.3)	2.5 (0.0–4.96)	*<0.001*	12.7 (1.8–29.0)	8.9 (5.0–14.9)	*<0.001*	20.0 (8.0–50.7)	20.0 (15.0–29.9)	0.830	37.5 (16.5–89.9)	43.6 (30.1–89.9)	0.061
ObsSev (s%)	0.8 (0.0–7.2)	0.2 (0.0–0.9)	*<0.001*	5.6 (0.1–29.5)	2.8 (0.9–7.8)	*<0.001*	14.1 (2.3–90.4)	14.2 (8.0–31.6)	0.831	49.6 (9.6–284.4)	67.0 (31.9–284.4)	0.061
Deaths (*n*)	50	21		36	55		25	35		16	16	
CV deaths (*n*)	24	10		20	27		14	21		7	7	
Nonlethal CV event (*n*)	44	17		32	47		20	34		10	8	

Normal, mild, moderate, and severe groups were formed based on conventional AHI and adjusted AHI. A significant rearrangement of patients between the groups takes place when using the adjusted AHI instead of conventional AHI. The significance of differences between the groups was evaluated using the Mann-Whitney U test. The limit for statistical significance was set to $p<0.05$. The statistically significant differences are indicated with italic typeface

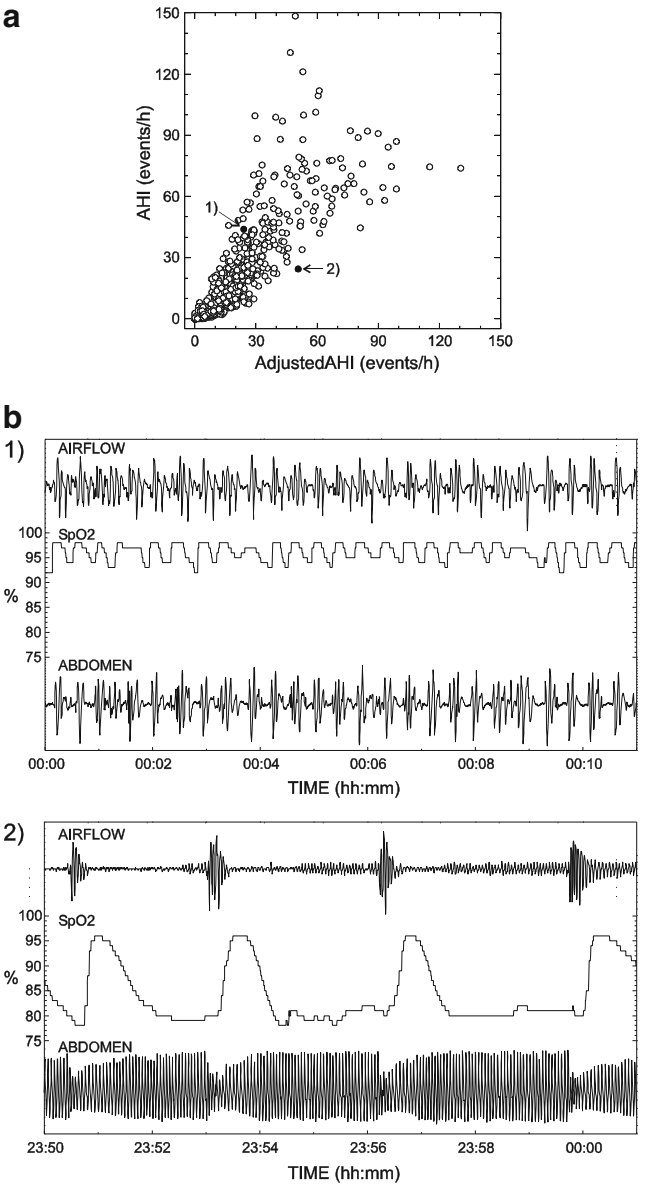

Fig. 3 **a** AHI as function of adjusted-AHI. Patients 1 (AHI=43.9, adjusted AHI=23.9) and 2 (AHI=24.4, adjusted AHI=50.6) represent typical cases receiving different OSA classification depending on the applied diagnostic parameter. **b** Polygraphic recordings of the patients *1* and *2*. Patient 1 has shorter obstruction event and less severe desaturation drops than patient 2. Due to high frequency of the events, patient 1 has higher AHI than patient 2. However, due to higher severity of individual events, patient 2 receives higher value of adjusted AHI

was significantly ($p<0.05$) elevated (3.29 vs. 2.18) only when the arrangement was done based on the adjusted AHI (Fig. 5b).

Discussion

In this study, we hypothesized that the adjusted AHI parameter gives supplementary information over

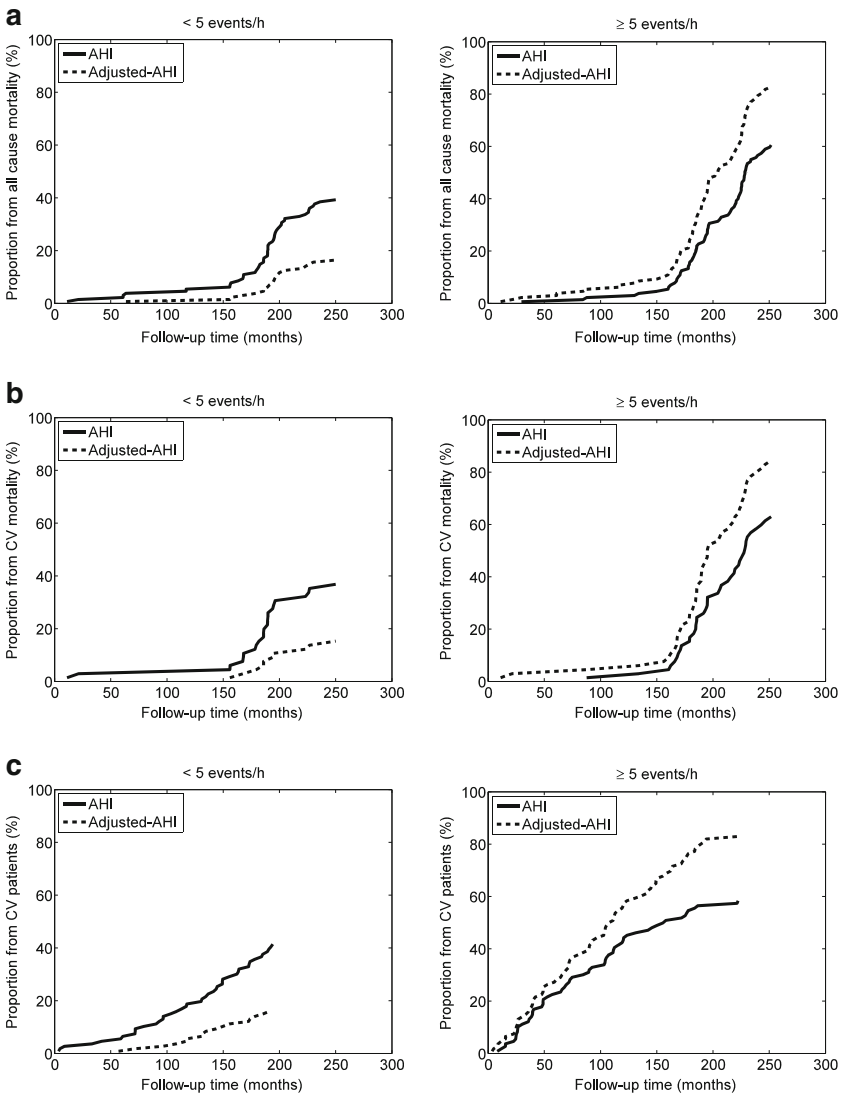

Fig. 4 **a** Proportion of deceased (all-cause mortality) patients diagnosed not to have OSA (AHI <5) or to have OSA (AHI≥5). **b** Proportion of deceased (cardiovascular mortality) patients diagnosed not to have OSA (AHI <5) or to have OSA (AHI≥5). **c** Proportion of patients (with nonfatal cardiovascular events) diagnosed not to have OSA (AHI <5) or to have OSA (AHI≥5). When the diagnosis was based on the adjusted AHI parameter, a higher number of deceased patients or patients with nonfatal cardiovascular event was found in the OSA groups (AHI≥5)

conventional AHI on the severity of OSA. This hypothesis was tested by means of retrospective follow-up (mean±sd follow-up time 198.2±24.7 months) of mortality and cardiovascular morbidity in 804 men having had no CPAP treatment.

When the patients were classified to OSA severity categories based on the adjusted AHI parameter, notable rearrangement was seen. Furthermore, the correlation between AHI and adjusted AHI was $R^2=0.758$ ($p<0.05$), suggesting that patients with similar AHI can have different values of adjusted AHI. This supports the idea that adjusted AHI provides supplementary information over conventional AHI. Due to the rearrangement, a higher number of deceased patients was found in the OSA group (AHI≥5). This is in line with a recent study reporting that conventional AHI underestimates the severity of the disorder [19]. Also Kulkas et al. reported that parameters incorporating the severity of individual obstruction events show a significant variation between patients having similar values of AHI [18]. This is important as longer obstruction and deeper desaturation events cause greater physiological stress, e.g., in the form of increased sympathetic activity and oxidative stress [9].

Importantly, we found that risk ratios of all-cause and cardiovascular mortalities were higher in the moderate and severe OSA groups formed based on the adjusted AHI parameter than in those formed based on conventional AHI. Based on the present findings, the adjusted AHI parameter provides valuable supplementary information for the evaluation of the severity of OSA. Potentially, the adjusted AHI could improve the recognition of those OSA patients with presumably the highest risks of severe health consequences. The

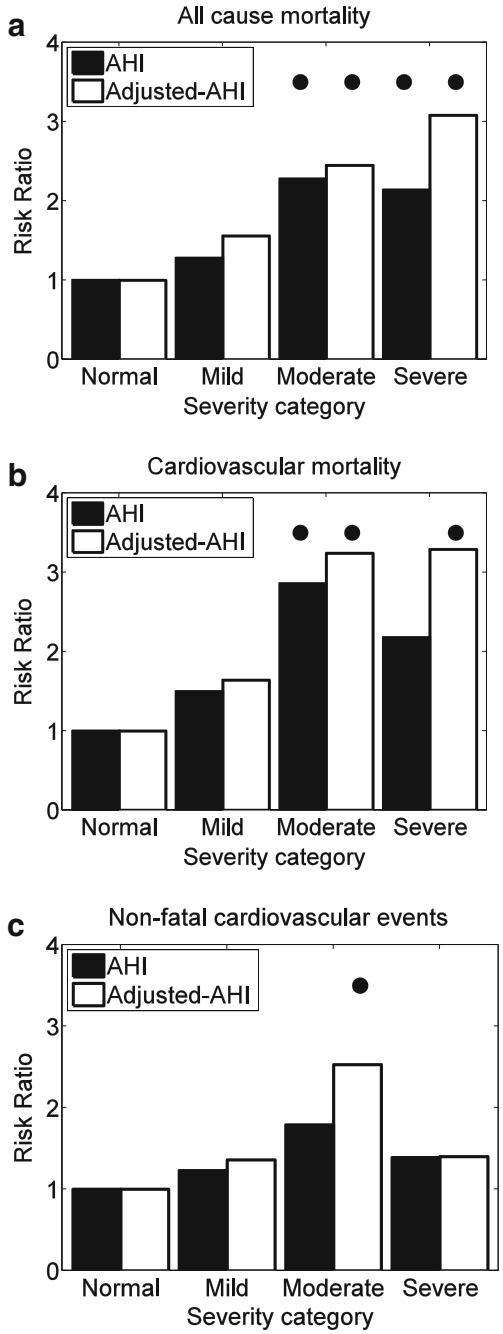

Fig. 5 Follow-up time adjusted risk ratio of all cause of mortality (**a**), cardiovascular mortality (**b**), nonfatal cardiovascular events (**c**) in severity categories formed based on AHI or adjusted AHI. Importantly, the risk ratio was elevated in moderate and severe diseases when the diagnosis was based on the adjusted AHI. The *black dot* indicates a statistically significantly ($p<0.05$, *t* test) elevated risk ratio

present findings are in agreement with a recent study reporting that the combined percentage of apnea, hypopnea, and desaturation duration from total sleep time enables the differentiation of OSA patients with increased precision compared to conventional AHI [16]. Furthermore, Punjabi et al. reported that the degree of nocturnal hypoxemia is an independent predictor of mortality [20]. It has been also reported that patients who suffer from excessive daytime sleepiness have longer mean durations of apnea events and lower minimum and mean nocturnal peripheral oxygenation compared to patients with equivalent AHI but have less severe daytime sleepiness [21]. It has been demonstrated that OSA is associated with stroke and all-cause mortalities and that the risk increases along the severity of OSA [22]. Based on a 10-year follow-up study of patients with coronary artery disease, there is a dose-response effect between severity of OSA and health consequences [23]. In that study, patients with mild and moderate/severe OSA were 2.4 and 3.6 times more likely to get stroke, respectively, than patients diagnosed having no OSA [23]. This is supported by Redline, in 2010, reporting that the risk of stroke increases as a function of AHI in men [24]. Furthermore, it has been reported that the percentage of total sleep time with oxygen saturation below 90 % is independently associated with mortality [20] and risk of coronary artery disease [25].

Along the guidelines of the AASM, hypopnea may be detected using rules 4A or 4B [12]. The selection of the rule affects the values of conventional and adjusted AHI. In the present study, a four-channel (thermistor, pulse oximeter, breathing movement, and body position) ambulatory polygraphy device, typical to early the 1990s, was used. As EEG was not recorded, thereby, e.g., arousals could not be detected. Rule 4A was chosen based on the clinical practice of Kuopio University Hospital and recommendation of AASM. Furthermore, missing the EEG affects the accuracy of the determination of the total sleep time. In the present study, the total sleep time was estimated by inspecting the raw signals. Also, at that time, nasal cannulas with sensitive pressure transducers were not widely clinically available for the recording of airflow. The use of the thermistor can have some effect on the duration of the hypopnea and may lead to underestimation of the number of hypopnea events.

In conclusion, the results of this study suggest that risk ratios of all-cause mortality and cardiovascular mortality may be higher in moderate and severe OSA groups formed based on the adjusted AHI parameter than in those formed based on conventional AHI. To confirm the statistical significance of this finding, a study with a considerably higher number of patients is warranted. However, based on the present results, we believe that the adjusted AHI parameter gives valuable supplementary information to AHI and improves the recognition of OSA patients with the highest risk of mortality or cardiovascular morbidity.

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