

## Decreased Perception of High Frequency Sound in Severe Obstructive Sleep Apnea

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Short title:

Decreased Sound Perception in Severe OSA

## Summary

**Introduction:** Obstructive sleep apnea (OSA) is characterized by recurrent episodes of upper airway obstruction during sleep, which is manifested by apnea or hypopnea. Decreased blood oxygen saturation, changes in heart rate, fluctuations in brain perfusion, changes in intracranial pressure, snoring and vibration are factors that may potentially affect hearing in patients with OSA. The aim of the present study was to test the hypothesis that hearing is affected in OSA.

**Methods:** 43 males aged 34-74 years (mean 48.2) with suspected sleep-disordered breathing without other comorbidity or medication that may affect sleep or hearing were included.

Nocturnal polysomnography, pure tone audiometry (PTA), transient evoked otoacoustic emissions (TEOAE) and brainstem auditory evoked potentials (BAEP) were evaluated. The severity of OSA was indicated by the number of apneas and hypopneas per hour of sleep (apnoe/hypopnoe index - AHI).

**Results:** OSA ( $AHI \geq 5$ ) was detected in 28 patients by polysomnography. Mild OSA ( $AHI 5-15$ ) was confirmed in 11 patients, severe OSA ( $AHI \geq 30$ ) in 17 patients. Simple snoring ( $AHI < 5$ ) was diagnosed in 15 males. In patients suffering from severe OSA, tone audiometry demonstrated higher auditory threshold at frequencies of 4000 and 8000 Hz than in patients with  $AHI < 15$  ( $p < 0,005$ ). Auditory threshold values correlated with age in all groups. At a frequency of 8000 Hz, auditory threshold additionally correlated with BMI, AHI, oxygen desaturation index and decreased oxygen saturation. No differences were detected in TEOAE and BAEP between subjects with OSA and snoring. PTA and TEOAE decreased with increasing age.

**Conclusion:** The present results show decreased perception of high frequency sound in severe OSA.

**Key words:** obstructive sleep apnea, pure tone audiometry, transient evoked otoacoustic emissions, organ of Corti, brainstem auditory evoked potential

## **Introduction**

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of complete or partial upper airway obstruction during sleep (ICSD -2 2005). Excessive fluctuations in intrathoracic pressure, decreased blood oxygen saturation, tissue hypercapnia, changes in heart rate and changes in intracranial pressure result from apnea or hypopnea. OSA is considered a risk factor for cardiovascular disease (Marin et al 2005; Gilat et al. 2014; Gami et al. 2013), and its influence on the development of arterial pulmonary hypertension, cardiac arrhythmias, atherosclerosis and type 2 diabetes has been demonstrated (Drager et al. 2010; Namtvedt et al. 2013; Manin et al. 2015; Kendzerska et al. 2014; Dumitrascu et al. 2013). Cognitive dysfunction dependent on the severity of OSA has been documented, as well as structural brain changes in OSA compared to control subjects (Canessa et al. 2011; Torelli et al. 2011).

It may be hypothesized that hearing is negatively affected in OSA, as the peripheral auditory perceptual organ (inner ear), vestibulocochlear nerve and central nuclei and pathways are intimately connected with or are a part of the brain, and share a common blood supply. The aim of the present study was to investigate potential auditory dysfunction in OSA at the level of the organ of Corti, the auditory pathway and the brainstem auditory areas. To fulfill this objective, the following three tests were employed.

1. Pure tone audiometry (PTA) determines the auditory threshold after standard frequency stimuli.
2. Transient evoked otoacoustic emissions (TEOAE) are sounds given off by the inner ear when the cochlea is stimulated by a sound (click). TEOAE evaluates preneuronal auditory transmission and does not reflect the ability to transmit sound from the hair cells centrally (Kemp 2010; Reichenbach et al. 2012).

3. Brainstem auditory evoked potentials (BAEP) measure the function of the auditory nerve and auditory pathways in the brainstem (Evans 2012).

## **Methods**

### Study participants

The study was conducted from 2010-13 at a tertiary university hospital in patients referred for suspected sleep apnea. All patients had a history of snoring, were subjected to standard physical, neurological and ENT examinations, as well as nocturnal polysomnography and ultrasound examination of the carotid arteries. Additionally, the following inclusion criteria were imposed: a) male gender, b) 18 years of age and over, c) generally good health, d) absence of sleep disorders (restless legs syndrome, periodic limb movements in sleep, insomnia, narcolepsy, parasomnias, circadian rhythm disorder), e) absence psychiatric disorders (including anxiety disorders), f) no previous or concurrent use of medications that may affect hearing, sleep or breathing while asleep (e.g., statins, diuretics, chemotherapeutic agents, benzodiazepines), g) normal findings on physical, neurological and ENT examinations, including negative history for any serious internal diseases (e.g., disorders of extrapyramidal system and cerebellum, migraine, cluster headache, demyelinating disease, autoimmune disease, tumor or arteriovenous malformation, stroke, epilepsy, anemia, diabetes mellitus, decompensated hypertension, ischemic heart disease, head injury with loss of consciousness, labyrinth contusion, fracture of the pyramid, Meniere's disease, vestibular schwannoma or other intracranial tumors, peripheral vestibulopathy, vertigo, previously diagnosed deafness or hearing loss), h) the absence of atherosclerotic changes in the carotid artery and i) written informed consent to participate in the study. The study included 43 consecutively recruited males aged 34-74 years (mean  $48,2 \pm SD=8,9$ ).

## Examination

1. Polysomnography (PSG) was performed by means of a BrainLab 3.1 (Schwarzer, Germany). The PSG recording included four electroencephalographic leads (C3-A2, C4-A1, O1-A2, O2-A1), two electro-oculographic leads (E1-M2, E2-M2) and chin and bilateral anterior tibialis surface electromyograms, one electrocardiographic lead, respiratory sounds, nasal airflow (thermistors), thoracic and abdominal movements (piezoelectric belts), finger probe oximetry and body position record. Sleep was scored according to Rechtschaffen and Kales criteria (Rechtschaffen and Kales 1968). Apnea was defined as complete airflow cessation  $\geq 10$  seconds and hypopnea as 50% or greater reduction of air inflow leading to 3% or greater oxyhemoglobin desaturation of  $\geq 10$  seconds duration. Periodic limb movements (PLM) were defined according to WASM standards (Zucconi et al. 2006). A PLM index (number of PLM per hour of sleep) smaller than 10 was selected as an inclusion criterion. All patients were allowed to sleep from 22:00 to 6:00 (polysomnography duration, time in bed). For statistical purposes, the following parameters were processed: apnea/hypopnea index (AHI - number of apneas and hypopneas per hour of sleep), oxygen desaturation index (ODI; number of saturation drops by 3% and more per hour) and percent of time with oxygen saturation below 90% (T90).

2. Ultrasound examination of the carotid arteries was performed on a Toshiba 4D Aplio 300 device (Toshiba Medical Systems, Japan). Potential atherosclerotic changes in the carotid arteries were assessed by evaluating the intimal-medial thickness of the bilateral common carotid arteries. An intimal-medial thickness of less than 0.82 mm was imposed as an inclusion criterion, according to Czech neurosonological standard (Škoda et al. 2002).

3. PTA was examined by a two-channel audiometer Madsen Orbiter 922 (GN Otometrics, Taastrup, Denmark). Stimulus step was 5 dB. The auditory threshold was measured at frequencies of 125-8000 Hz, according to international standards. Frequencies of 1000, 2000,

4000 and 8000 Hz were statistically evaluated. According to the same standards, the normal auditory threshold is in the range of 0–25 dB (Mathers et al. 2000).

4. TEOAE were measured by an ILO 88 instrument (Otodynamics Ltd., Hatfield, UK) placed in the external auditory canal. The probe emits a wide frequency spectrum stimulus and detects a response from the organ of Corti. A range of signals emitted by the external hair cells of the organ of Corti were registered, up to frequencies of 6000 Hz and frequencies of 1000, 2000, 4000, and 6000 Hz were used in statistical analyses. The duration of the electric pulse applied to the transducer was 80  $\mu$ s using a nonlinear stimulus mode. The number of stimuli employed in the default condition was 260 transients for each ear. Clicks elicit broad-spectrum responses that are most robust in the mid-frequency region, likely reflecting the fact that middle ear transfer is most sensitive in the range of 1000–3000 Hz. TEOAE were evaluated with respect to reproducibility (in %) and amplitude of the signal to noise ratio (S/N). S/N is defined as the ratio of signal power to the noise power, expressed in decibels. A ratio higher than 1:1 (greater than 0 dB) indicates more signal than noise, reproducible response is evident at a S/N of 3 dB or more. The result is expressed as the proportion of clicks causing otoacoustic emissions. Normally TEOAE have a value in the range of 75–100%, using an objective criterion based on an entire reproducibility score greater than 70 % (Robinette et al. 2002).

5. BAEP was examined with a Dantec Keypoint device (Natus Medical Inc., Pleasanton, CA). The time window was 10 s, the stimulus was an acoustic click created by a pulse of 0.1 ms, and the stimulus was presented 2,000 times for each recording trial. BAEPs were examined using a monaural rarefaction click stimulation of 69 dB sensation level intensity and 10 Hz frequency. We evaluated wave peak latency I (normal <2.05 ms), III (normal <4.06 ms), V (normal <6.21 ms) and interpeak latencies I-III (normal <2.52 ms), III-V (normal <2.36 ms) and I-V (normal <4.61ms). Normal values were determined from the examinations performed at our institution in healthy volunteer subjects (30 males, 30 females) (Jech and Růžička 1996).

PTA, TEOAE and BAEP were examined in the afternoon.

## Statistical analyses

We compared the results of tone audiometry, TEOAE and BAEP between groups with varying severity of OSA expressed by AHI, including adjustment for body mass index (BMI), which was conducted using ANCOVA. We conducted the following comparisons: a)  $AHI \geq 30$  vs.  $AHI < 5$ , b)  $AHI 5-15$  vs.  $AHI < 5$ , c)  $AHI \geq 30$  vs.  $AHI 5-15$ , and d)  $AHI \geq 30$  vs.  $AHI < 15$ . None of the parameters were normally distributed. For comparisons between two groups the Mann-Whitney-U test was used, for comparison between 3 groups the Kruskal-Wallis test. When performing ANCOVA the residuals were found to be normally distributed, thus despite the abnormal distribution of raw data, these results are interpretable. All tests were performed using the STATISTICA 12 software package (StatSoft, Inc., Tulsa, OK).

The study was approved by Ethical committee of the General University Hospital in Prague.

## Results

OSA ( $AHI \geq 5$ ) was detected by polysomnography in 28 patients, of which 11 patients were diagnosed with mild OSA ( $AHI 5-15$ ) and 17 patients with severe OSA ( $AHI \geq 30$ ). None of the patients were diagnosed with moderate OSA ( $AHI 15-30$ ). Sleep-disordered breathing was not detected in 15 patients, who were diagnosed with the simple snoring ( $AHI < 5$ ). Table 1 shows study participants grouped according to severity of OSA, expressed by AHI. ODI statistically differed between groups. No difference in age was detected between OSA positive patients and those in whom OSA was not observed. Patients diagnosed with severe OSA demonstrated higher average BMI than patients with mild OSA and controls.

PTA demonstrated significantly higher auditory thresholds in patients with severe OSA than all the other subjects examined at the frequencies of 4000 and 8000 Hz (Table 2), and the



difference remained significant when correcting for BMI using ANCOVA at the frequency of 8000 Hz. No difference was detected between groups with mild OSA and simple snoring. PTA values correlated with age, and at a frequency of 8000 Hz, with all examined parameters (i.e., age, BMI, AHI, ODI and T90; Table 3). Correlation between AHI and PTA at 4000 and 8000 Hz is illustrated in Fig. 1 and 2.

No significant differences were detected in TEOAE (including S/N, Supplementary Table 4) and BAEP between patients with severe OSA and patients with AHI < 15.

PTA and TEOAE decreased with increasing age: PTA left – correlation  $r = -0.4996$ ,  $p = 0.001$ ; PTA right – correlation  $r = -0.4862$ ,  $p = 0.002$ ; TEOAE left - correlation  $r = -0.3389$ ,  $p = 0.026$ ; TEOAE right – correlation  $r = -0.3409$ ,  $p = 0.025$  (correlations of age with each TEOAE frequencies 1000, 2000, 4000 and 6000 Hz are displayed in Supplementary Table 5). PTA (frequencies 1000 – 4000 Hz) and TEOAE correlate in whole patients group (not in OSA severity subgroups). BAEP showed no age-related changes.

## **Discussion**

In the present study, we show that the auditory threshold is increased while listening to sounds of higher frequency in patients with severe OSA, and that this increase correlates with the severity of OSA. We did not observe any change in TEOAE and BAEP due to OSA. A few studies have examined the influence of OSA on hearing, however their results are not conclusive (Hwang et al. 2011; Casale et al.2012; Kotterba and Rasche 1996; Cimino et al. 1995; Schlegel and Urban 1999; Paquereau et al. 1994; Urban et al. 1996, Mosko et al. 1981) perhaps due to differing patient characteristics.

PTA in severe OSA was measured by Casale et al. While they reported that patients with severe OSA had a higher auditory threshold when averaging stimulation results from 5 tones between 250–4000 Hz, in examining individual frequencies, the auditory threshold was higher in only their highest frequency (Casale et al. 2012). Thus, our results are in agreement with this study. PTA results in mild and moderate OSA were normal as in our study, as well as in a study by Hwang et al., which included 34 subjects (Hwang et al. 2011).

TEOAE in OSA has only been assessed by Casale et al. (Casale et al.2012). In contrast to the present study, they reported less reproducibility in patients with severe OSA. TEOAE methodology and patient selection were virtually the same as in the present work. The differing results may be explained by differences in patient age, and more importantly, by the stringent selection criteria of patients in our study. In this respect, exclusion of atherosclerotic disease by ultrasound in the present study was particularly important. Additionally, in contrast to other studies, we included only male subjects. But the effect of gender on TEOAE results remains the subject of debate (McFadden 1993).

BAEP in OSA has been evaluated in several studies. In contrast to our results, Casale et al. reported prolonged mean latencies of waves I, III and V in a group of OSA patients in comparison to healthy volunteers (Casale et al. 2012). Kotterba et al. evaluated BAEP in 20 OSA patients (17 men, 3 women; mean age 54 years) and reported prolonged latency in wave I and intervals I-V in comparison to controls (Kotterba and Rasche 1996). The BAEP results reported by Kotterba et al. and Casale et al. are unique, as in addition to the present study, normal BAEP in OSA has been reported by Cimino et al. (Cimino et al. 1995), Schlegel et al. (Schlegel and Urban 1999), Paquereau et al. (Paquereau et al. 1994), Urban et al. (Urban et al. 1996) and Mosko et al. (Mosko et al. 1981). Differences in BAEP results between the current study and those by Kotterba et al. and Casale et al. may also be explained by our rigorous inclusion criteria, which excluded patients with hearing impairment of other etiology.

Increased auditory threshold at higher frequencies as determined by PTA and the absence of abnormalities on TEOAE and BAEP examinations in patients with severe OSA can have several interpretations. PTA reflects the function of the inner ear, specifically the hair cells. The outer hair cells function in amplifying the signal, while the inner hair cells function as a receptor. Hair cells of the organ of Corti react to sound frequencies according to their tonotopic arrangement; high frequency sounds are registered peripherally, specifically, at the base of the organ of Corti (Kinely and Zwolan 2010). This periphery is supplied by end arterioles without anastomoses, and thus may be more sensitive to fluctuations in oxygen than areas of the retina remote from the fovea centralis (Ficker et al. 1997; Nomura 1977).

In contrast to PTA, TEOAE was not able to localize which part of the organ of Corti may be dysfunctional, nor did it detect hearing impairment at the highest frequencies, as the acoustic click is uniform and contains a wide range of frequencies of up to 6000 Hz (Kemp 2002). Deterioration of hearing is dependent on age, is commonly known and is due to changes in the organ of Corti (Pearson et al. 1995; Popelar et al. 2006). This also corresponds with the results of the present study, where an association was shown between increased auditory threshold and decreased reproducibility of TEOAE with age. The absence of BAEP abnormalities in OSA indicates that the retrocochlear auditory pathway is not damaged. This result was expected given the richer blood supply, making the retrocochlear auditory pathway more resistant to inadequate blood supply or oxygen reduction than the organ of Corti (Bamiou 2015).

Assuming dysfunctional vascular supply (oxygen delivery), the lower part of the organ of Corti is implicated in the decreased perception of higher frequency sounds. Snoring has also been cited as a potential risk factor for hearing disorders as it represents noise load and

vibrations (Pevernagie et al. 2010). However, we do not expect any impact in the present study as all patients had a history of snoring.

The limitations of the present study include the number patients examined and the absence of snoring intensity and frequency measurements, however this parameter has little value when it is measured only once. More extensive studies are needed to further elucidate the etiology of hearing impairment in OSA.

## **Conclusion**

In the present study, we observed increased auditory threshold by PTA following auditory stimuli at frequencies of 4000 and 8000 Hz in males with severe OSA. This decreased auditory perception correlated with the severity of sleep apnea. TEOAE and BAEP results were not affected by OSA. Our results suggest a selective hearing pathway impairment at the base of the organ of Corti in severe OSA.

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**Table 1.** Patient demographic information by AHI classification

	Normal breathing during sleep (AHI < 5) Average (SD)	OSA (AHI ≥ 5) Average (SD)		P-value AHI < 15 vs. AHI ≥ 30 (ANCOVA)
		AHI 5 - 15	AHI ≥ 30	
Number	15	11	17	
Age (years)	47.3 (8.0)	46.4 (9.2)	50.8 (10.2)	NS
BMI (kg/m <sup>2</sup> )	26.8 (1.9)	28.3 (3.1)	<b>33.4 (5.6)</b>	< 0.001
AHI	1.9 (1.5)	8.4 (3.0)	<b>60.5 (31.9)</b>	< 0.001
ODI	2.9 (2.8)	9.5 (3.6)	<b>60.3 (29.7)</b>	< 0.001
T90	0.1 (0.5)	0 (0.1)	<b>0.4 (0.4)</b>	< 0.001

OSA, obstructive sleep apnea; SD, standard deviation; BMI, body mass index; AHI, apnea-hypopnea-index; ODI, oxygen desaturation index; T90, proportion of time peripheral blood oxygen saturation below 90% relative to time in bed; NS, not significant. Significantly different means are highlighted.

**Table 2.** Tone audiometry in groups by AHI classification

Tone audiometry	Normal breathing during sleep (AHI < 5) Average (SD)	OSA (AHI ≥ 5) Average (SD)		P-value AHI < 15 vs. AHI ≥ 30 (ANOVA)
		AHI 5 - 15	AHI ≥ 30	
1000 Hz	11.33 (5.74)	10.55 (1.04)	11.47 (4.24)	NS
2000 Hz	10.77 (3.65)	10.73 (1.67)	15.59 (9.66)	NS
4000 Hz	12.73 (6.55)	14.55 (9.34)	<b>29.71 (19.72)</b>	< 0.005
8000 Hz	11.33 (4.43)	11.82 (4.01)	<b>33.24 (20.99)</b>	< 0.005

SD, standard deviation; AHI, apnea-hypopnea-index; Hz, Hertz; NS, not significant.

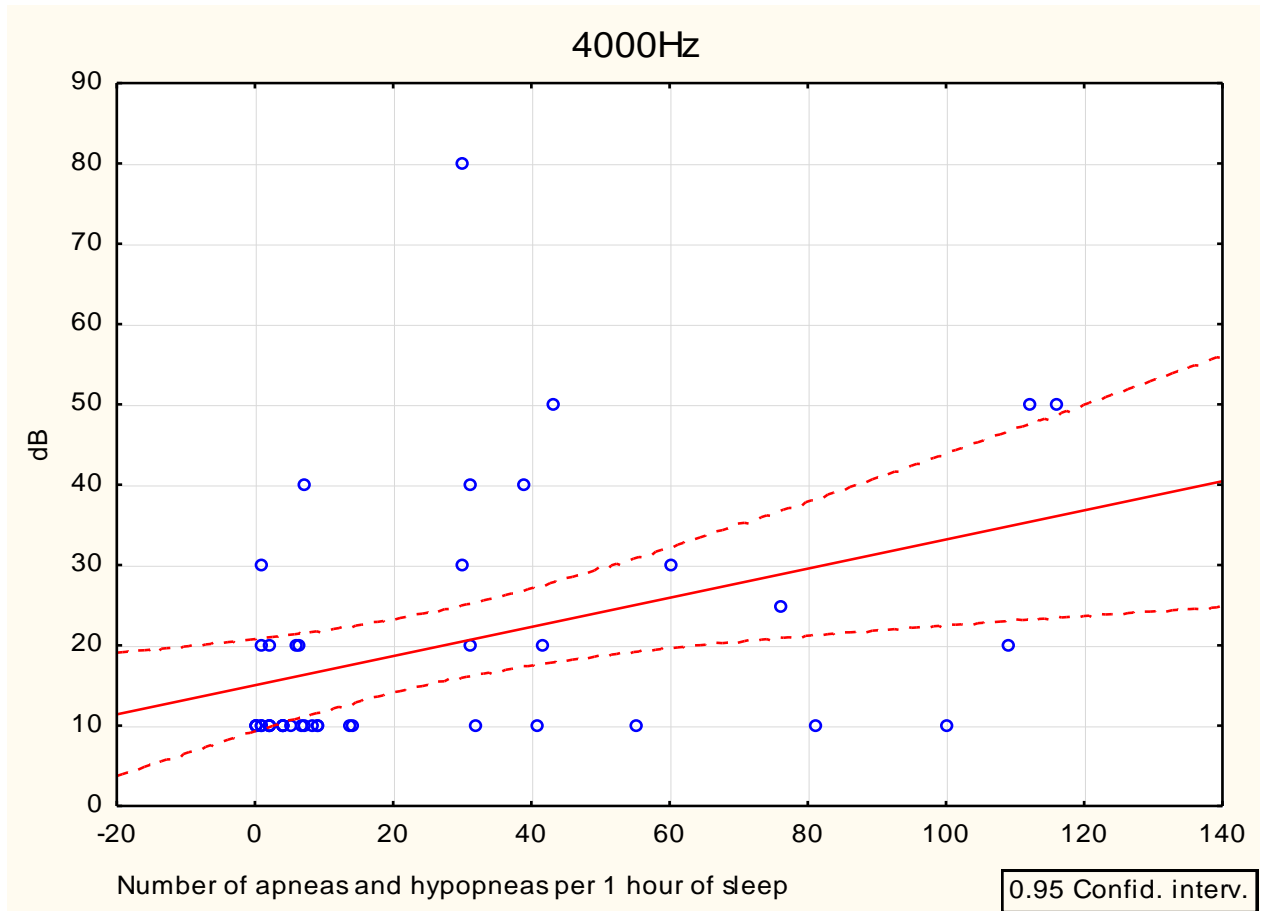
Significantly different means are highlighted.

**Table 3.** Tone audiometry: correlation with age, BMI, T90, ODI and AHI (Spearman correlation).

	1000 Hz	2000 Hz	4000 Hz	8000 Hz
Age	<b>0.4159</b>	<b>0.5470</b>	<b>0.4084</b>	<b>0.5007</b>
	<b>p = 0.006</b>	<b>p &lt; 0.001</b>	<b>p = 0.007</b>	<b>p = 0.001</b>
BMI	<b>0.3668</b>	<b>0.3107</b>	<b>0.4955</b>	<b>0.5054</b>
	<b>p = 0.016</b>	<b>p = 0.037</b>	<b>p = 0.001</b>	<b>p = 0.001</b>
T90	0.1744	0.1871	<b>0.3259</b>	<b>0.4681</b>
	p = 0.263	p = 0.230	<b>p = 0.033</b>	<b>p = 0.002</b>
ODI	0.1129	0.2277	<b>0.3780</b>	<b>0.4521</b>
	p = 0.471	p = 0.142	<b>p = 0.012</b>	<b>p = 0.002</b>
AHI	0.1530	0.2681	<b>0.3941</b>	<b>0.4607</b>
	p = 0.327	p = 0.082	<b>p = 0.009</b>	<b>p = 0.002</b>

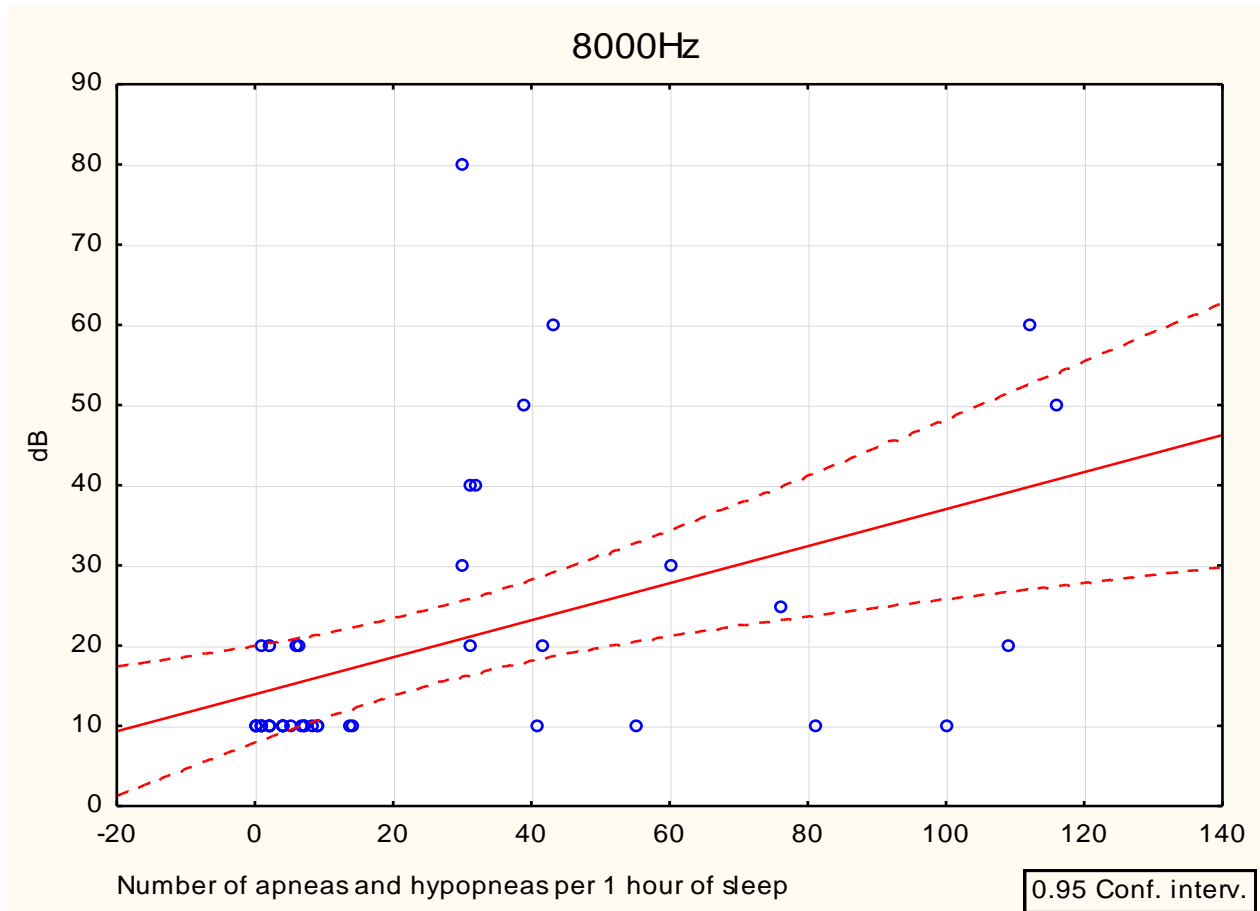
BMI, body mass index; T90, proportion of time peripheral blood oxygen saturation below 90% relative to time in bed; ODI, oxygen desaturation index; AHI, apnea-hypopnea-index; Hz, Hertz. Statistically significant correlations are highlighted.

Fig. 1. Correlation between AHI and PTA at frequency 4000 Hz, correlated with age  
(Spearman correlation statistic).



AHI, apnea/hypopnea index; PTA, pure tone audiometry, dB, decibel, Hz, Hertz.

Fig. 2. Correlation between AHI and PTA - at a frequency 8000, correlated with age, body mass index, oxygen desaturation index, oxygen saturation below 90% (Spearman correlation statistic).



AHI, apnea/hypopnea index; PTA, pure tone audiometry, dB, decibel, Hz, Hertz.