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AGING EFFECT ON SLEEPINESS AND APNEAS SEVERITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME: A META-ANALYSIS STUDY

--Manuscript Draft--

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Abstract:	Purpose Different authors have reported that aging could be associated with changes in Obstructive Sleep Apnea (OSA) related parameters (Apnea/hypopnea index, SpO2, reduction of daytime sleepiness, etc.), type of sleep and pattern of collapse. Regarding

OSA severity in elderly patients, it is commonly believed that the AHI score tends to increase with aging.

Methods

in this paper, we reviewed the literature regarding the studies which compared older (>65 years old) and young (<65 years old) OSA patients regarding the effect of aging on daytime sleepiness (ESS evaluation) and OSA severity (AHI evaluation). A meta-analysis to evaluate the effect of age on daytime sleepiness and OSAS severity was also performed in order to corroborate previously reported experience.

Results

Meta-analysis showed no statistical (p=0,8) differences regarding AHI differences emerged from the comparison of the two groups of patients. Elderly patients (>65 years old) showed less daytime sleepiness, showing a statistical difference in the meta-analysis of data (p=0.004)

Conclusion

Although a direct correlation between aging and AHI values would seem to be present, no significant differences in baseline AHI between young (<65-years-old) and elderly (>65-years-old) patients emerged in this meta-analysis study. The effects of OSAS on daytime sleepiness seem to be much more prominent in young or middle-aged patients than in elderly patients.

Title Page

AGING EFFECT ON SLEEPINESS AND APNEAS SEVERITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME: A META-ANALYSIS STUDY

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Informed consent: Informed consent was obtained from all individual participants included in the study.

ABSTRACT

Purpose: Different authors have reported that aging could be associated with changes in Obstructive Sleep Apnea (OSA) related parameters (Apnea/hypopnea index, SpO2, reduction of daytime sleepiness, etc.), type of sleep and pattern of collapse. Regarding OSA severity in elderly patients, it is commonly believed that the AHI score tends to increase with aging.

Methods: in this paper, we reviewed the literature regarding the studies which compared older (>65 years old) and young (<65 years old) OSA patients regarding the effect of aging on daytime sleepiness (ESS evaluation) and OSA severity (AHI evaluation). A meta-analysis to evaluate the effect of age on daytime sleepiness and OSAS severity was also performed in order to corroborate previously reported experience.

Results: Meta-analysis showed no statistical (p=0,8) differences regarding AHI differences emerged from the comparison of the two groups of patients. Elderly patients (>65 years old) showed less daytime sleepiness, showing a statistical difference in the meta-analysis of data (p=0.004)

Conclusion: Although a direct correlation between aging and AHI values would seem to be present, no significant differences in baseline AHI between young (<65-years-old) and elderly (>65-years-old) patients emerged in this meta-analysis study. The effects of OSAS on daytime sleepiness seem to be much more prominent in young or middle-aged patients than in elderly patients.

INTRODUCTION

Obstructive Sleep Apnea (OSA) syndrome is one of the most common sleep-disorder breathing (SDB) conditions [1-3]. It is characterized by reduction (hypopnea) or complete cessation (apnea) of airflow in the upper airways during the night, in the presence of breathing effort [3].

The incidence of OSA is often underestimated, affecting between 2 and 5% of the middle-aged population [3–5]. However, it has been shown that aging is positively related with an increase in the incidence of OSA [6–10]. Different studies have estimated OSA incidence rates between 5.6 to 13% in people over 65 years of age [3,7–12]. Analyzing 427 elderly people over 65, suffering from OSA, Ancoli et al. [7], showed that 24% of them presented an apnea/hypopnea index (AHI) greater than 5 and that 62% had a respiratory disturbance, with a Respiratory Disorder Index score(RDI)

≥ 10. In another study comprising 5615 men and women between 40 and 98 years of age, sleep apnea was found to be most frequent in subjects aged 60 years or older (20% had an AHI ≥ 15).

The main clinical characteristic of the patients with obstructive sleep apnea syndrome is the presence of an excessive daytime sleepiness[7-10]. Morning headaches, impotence, intellectual deterioration, and restless sleep are other OSA related symptoms but are far less frequent than daytime sleepiness [3-20]. The most important scale for the assessment of daytime sleepiness is the Epworth Sleepiness Scale (ESS) published in 1991 by Murray Johns [21]. It consists of a self-administered questionnaire that investigates specifically and in a very simple manner the extent of daytime sleepiness.

The severity of OSA was classified according to the guidelines of the American Academy of Sleep Medicine through the Apnea-Hypopnea Index (AHI) namely the number of episodes of apneas/hypopnea events per hour of real sleep measured by polysomnographic evaluation [2-10].

Different authors have reported that aging could be associated with changes in OSA related parameters (AHI, SpO_2, reduction of daytime sleepiness, etc.), type of sleep and pattern of collapse[21-27].

A reverse correlation between age and daytime sleepiness in patients suffering from sleep disordered breathing would seem to be present and confirmed by evidence in the literature [10-18,22-25]. Morrell et al. (28) (SDB), studied more than 3000 subjects affected by sleep-disordered breathing (SBD) and observed that although the incidence of SBD increases in elderly patients, the association between sleepiness and SBD reduces with aging ($p = 0.04$).

This aspect has been confirmed in a recent study reported by Vicini et al.[27] Using a regression analysis they showed a positive correlation between reduction of daytime sleepiness and aging ($p = 0.0001$).

Regarding OSA severity in elderly patients, it is commonly believed that the AHI score tends to increase with aging; however, increase of the AHI with aging is still a debatable topic in the literature. Peppard et al.[29] was one of the first authors to show that AHI increases over time, although this increase was strongly related to weight gain. Lappanen et al [3] studied 1090 patients with OSA and observed in the whole population that AHI, duration of apneas and SpO_2 desaturations presented a statistically significant increase as age increases. However, in more detailed analysis, when patients were divided into different categories according to the severity of OSA , AHI was found to present a statistically significant increase with age only in the moderate OSA category. Diversely, Hoch et al. [30] reported that

AHI did not present statistically significant differences between age groups (60–74 vs ≥70 years) and that AHI did not show a statistically significant increase over time (3-year interval) in either of the age groups. Furthermore, it has been shown in 18-year follow-up study that changes in AHI were not associated with statistically significant differences in age [31].

To clarify these aspects in this paper we reviewed the literature regarding the studies which compared older (>65 years old) and young (<65 years old) OSA patients regarding the effect of aging on daytime sleepiness (ESS evaluation) and OSA severity (AHI evaluation). No review article regarding the effect of aging on daytime sleepiness and changes in OSA severity has been published until now.

A meta-analysis to evaluate the effect of age on daytime sleepiness and OSAS severity was also performed in order to corroborate previously reported experience.

MATERIAL AND METHODS

Literature review - research protocol

A comprehensive review of the English language literature about OSAS patient and aging was performed using PubMed, EMBASE, Cochrane Library and CENTRAL electronic databases.

The research was performed using the following keywords: ‘Sleep apnea and aging’, ‘Sleep apnea in elderly patients’ , ‘sleepiness and aging’, ‘Epworth scale and elderly’, ‘apnea/hypopnea index elderly’ and ‘apnea/hypopnea index and aging’.

Thirty-four records about the topics studied were initially identified by abstract reading.

Two papers were excluded because found to be duplicates during research.

Twenty-six papers were excluded later because: review articles (6 papers), letters to the Editor (2 papers), absence of a patient sub-classification into young (<65 years old) or elderly (>65 years old) (8 papers), absence of data about ESS and/or AHI(10 papers).

The flow-chart of study selection is reported in Fig. 1

Meta-analysis protocol

Data from the studies were first extracted and assessed by the principal investigator (G.I.) and thereafter independently evaluated by two coauthors (A.C. and G.M.) using standardized data forms.

Articles were examined for data resolution with the intent of performing a meta-analysis.

Different methods of meta-analysis were considered in reviewing the literature to seek results that would provide meaningful analysis with the least risk of introducing biases. The quality assessment of studies (QUADAS-2) tool was used to evaluate the relevant study design characteristics of the included studies [32].

Statistical analysis was performed with statistical software (STATA 8.2; StataCorp LP, College Station, Texas). Random effects modelling (standard error estimate = inverse of the sample size) was used to calculate summary effect measures with corresponding 95% confidence intervals (CI), and forest plots were generated. The I^2 statistic was used to assess between-study heterogeneity.

A p value < 0.05 was considered significant.

RESULTS

A graphical display of QUADAS-2 results is shown in Fig. 2. This graphical display shows the possible risk of bias.

Six studies [22-27] were included in the meta-analysis regarding the evaluation of age effect on daytime sleepiness and OSA severity.

Studies considered in the meta-analysis and the OSA parameters of each study are reported in Table 1.

In Table 2 has been reported meta-analysis results.

A total of 1869 patients were considered eligible for the study. Of these , 1447 were identified as age <65 years old and 422 as age > 65years old. Mean age of patients <65 years old was 45.1 years whereas average age of >65 years old patients was 69.1 years

No statistical (p=0,8) differences regarding AHI differences emerged from the comparison of the two groups of patients.

Elderly patients (>65 years old) showed less daytime sleepiness (ESS evaluation) , showing a statistical difference in the meta-analysis of data (p=0.004). (Fig.3A-3B, box plot).

A regression model comparing age of patients and ESS showed a correlation between aging and reduction of daytime sleepiness (p= 0.05).

Regression analysis (Figure 4) comparing the age of patients and AHI scores. No correlation between aging and AHI emerged (p=0.5).

Using random-effects modelling, the summary effect size was -0.01 and did not demonstrate an aging effect on AHI (k = 6 studies; 95% CI, -0.01 to 0.12; p<0.01, I^2 = 75.5%) instead the summary effect size was -0.33 and any correlations between aging and ESS reduction were founf (k = 6 studies; 95% CI, -0.44 to -0.21; p<0.01, I^2 = 89%) (Fig.5A-5B).

DISCUSSION

Elderly patients with OSA could show changes in OSA related parameters (AHI, ODI SpO2, etc), OSA symptoms, time of sleep and pattern/type of collapse [2-12]. Aging is associated with a lengthening of the upper airway and descent of the hyoid bone [32-33]. The response of the genioglossus muscle to negative pressure is also reduced in older people compared to younger peopl and less negative pressure is required to collapse the upper airway, independent of BMI in older people [33-37]. Besides, as recently reported by Vicini et al., the number of obstruction sites and collapse pattern may change over time due to changes in pharyngeal anatomy, redistribution of body fat and/or the increased laxity of the oro/hypo-pharyngeal muscular structures, that are known to occur with aging [27]. These changes in the structure and function of the upper airway could have the effect of increasing pharyngeal collapsibility, and the subsequent number of apnoeas or hypopnoeas in older people.

Therefore, is there a correlation between aging, reduction of daytime sleepiness and worsening of the AHI value in OSA patients?

The effect of age on AHI has been previously investigated by different authors, however there is no concordant information available in the literature regarding the effect of age on the severity of OSA disease. Besides, most of the published articles are descriptive reviews without data analysis [2-12, 24-26].

Some authors reported a significant positive correlation between aging and AHI [22,24,27]. In the study of Zhao et al [26] there were significant differences between the <60-years-old and >60-years-old groups in baseline AHI (p=0.001). Comparing aging and AHI, using regression analysis, Vicini et al [27] showed an increase in AHI as patients' age increased (p = 0.03). However, the mean AHI of elderly and young patients (37.7 vs 31.7) was not statistically different (p = 0.07).

In the study of Chung et al [22] a total of 757 OSA patients were subdivided into young and older patients according to their age ,under or over 65 years old. There was no significant difference in AHI among the groups (p = 0.4), despite the longest episode of apnea (p<0.01), mean duration of apnea events (p<0.01) and mean duration of apnea-hypopnea events (p<0.01) were longer in the elderly group compared to young patients. Similar data were reported in another important study on this topic, which comprised 697 OSA patients [23]. The authors observed that there was no significant difference in AHI between younger and older patients with OSA.

The elderly group had a significant higher mean duration of apnea-hypopnea events (P < 0.001) and longer duration of hypoxemia during the total sleep time (p =0.004) and in Non-REM sleep (P = 0.021) than the younger group. They also presented a significantly lower oxygen saturation in REM (P = 0.013) and NREM sleep (P = 0.027) than younger patients (Table 2).

Other evidence suggests that the age-related variation in AHI depends on the OSA severity classes as shown by Leppänen et al [3] in an analysis of the polygraphic data of 1090 OSA patients. They reported that AHI increased with age only in the moderate OSA category (p=0.022), although the duration of apneas increased in mild and severe OSA categories (p≤0.038). Furthermore, the duration of hypopneas increased with age in mild and moderate OSA categories (p≤0.038), and the duration of desaturations (p≤0.013) in all OSA severity categories. Therefore, it could be speculated that the progression of OSA with increasing age manifests as an elevated severity of individual obstruction events with only a minor effect on the number of these events.

Finally some authors postulated that the increase in AHI with aging may be related to the increase in weight in elderly people [3,20-25]. Peppard et al.[29] demonstrated, with a 4-year follow-up, that apnea–hypopnea index (AHI) increases over time but that this increase was strongly related to weight gain [3]. Furthermore, Redline et al. [38] reported that, although long-term change in AHI varies non-uniformly with age, older male patients with a higher body mass index (BMI) have the highest rate of increase in the number of apneas and hypopneas over time.

Chung et al et al [22] confirmed this evidence and showed that in elderly OSA patients, there was a significant correlation between AHI and BMI (r = 0.28, p < 0.01), and that BMI was a significant determinant of AHI (r= 0.30, p < 0.01).

Our meta-analysis results would seem to confirm the absence of differences in AHI values between young (<65 years old) and elderly (>65 years old) patients. In the statistical analysis no difference regarding the AHI values between younger patients and elderly patients emerged (p=0,8).

Using random-effects modelling, the summary estimating not aging effect on AHI (k = 6 studies; 95% CI, -0.01 to 0.12; p=0.001.

A reverse correlation between age and daytime sleepiness in patients suffering from sleep disordered breathing would seem to be present and confirmed by findings in the literature.

Gottlieb et al. [39] also demonstrated that elderly adults had lower mean scores on the ESS than middle aged adults (7.5 vs. 7.9). Similary, in Chung et al ‘s study [22]. The elderly showed a mean ESS score of 7.8, and the middle-aged patients achieved higher ESS scores of 10.6.

Regression analysis showed ESS reduction with aging ($p = 0.0001$) in the study reported by Vicini et al[27].

According to the above evidence it would seem that daytime sleepiness was significantly less severe in the elderly group than in the other groups, even though nocturnal sleep was more severely impaired in the elderly group.

Our meta-analysis results would seem to confirm this data. Elderly patients (>65 years old) showed a lower level of daytime sleepiness (ESS evaluation) with a statistical difference in the meta-analysis of data (p=0.004). Using random-effects modelling, the summary estimating not aging effect on ESS (p=0.001).

How can the lower daytime sleepiness in the elderly be explained? : although this aspect is not yet clear, it seems that the perception of sleepiness in the elderly may be confounded by their different expectations or to their acceptance of an increased fragmentation of sleep. Daytime napping could be a factor in reducing the symptom of sleepiness. Older people are less likely to be employed full-time and therefore have more opportunities for napping, whereas younger people in full-time employment may have less opportunity for a given level of nocturnal sleep disruption (due to SDB or other causes). Such life style modifications are likely to reduce the impact of nocturnal sleep disturbances on the symptom of sleepiness in elderly OSA patients.[2-12,20-25]

One of the limitations of this study could be the limited number of papers considered in the final analysis. However, considering the high number of patients analyzed in the meta-analysis we believe that the results observed are reliable.

Finally, obesity could play an important role in elderly patients with OSAS and BMI could be a significant variable in determining the severity of OSAS in the elderly patients

Analysis of the differences in BMI between the two groups of patients analyzed in this meta-analysis did not show statistical difference. This data shows that the BMI difference was not a study bias.

CONCLUSION

The authors performed this meta-analysis study in order to identify any differences in the severity of OSA in patients under and over 65 years of age.

Although a direct correlation between aging and AHI values would seem to be present, no significant differences in baseline AHI between young (<65-years-old) and elderly (>65-years-old) patients emerged in this meta-analysis study.

The effects of OSAS on daytime sleepiness seem to be much more prominent in young or middle-aged patients than in elderly patients.

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LEGEND

Figure 1; Flow-chart of study selection.

Figure 2; QUADAS-2: graphical display shows the possible risk of bias.

Figure 3; 3A:Box plot of AHI difference between <65 and >65 years old patients; 3B: Box plot of ESS difference between <65 and >65 years old patients.

Figure 4; Regression model comparing the age of patients and AHI scores showed no correlation between aging and AHI increase (p= 0.5).

Figure 5; 5A:Random-effects modelling of aging effect on AHI; 5B: Random-effects modelling of aging effect on ESS.

Figure1

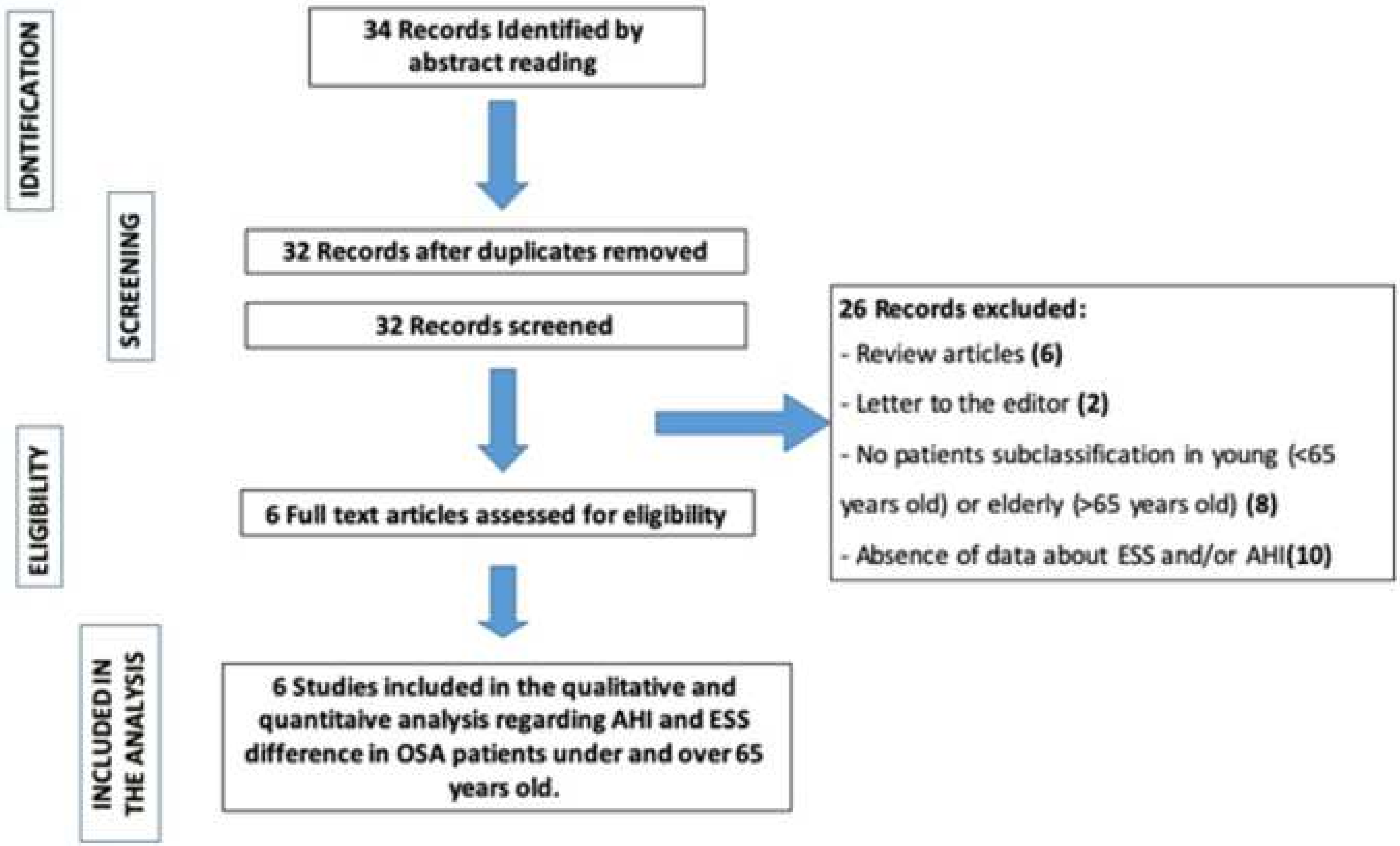
IDNTIFICATION
SCREENING
ELIGIBILITY
INCLUDED IN THE ANALYSIS
34 Records Identified by abstract reading
32 Records after duplicates removed
32 Records screened
26 Records excluded:
- Review articles (6)
- Letter to the editor (2)
- No patients subclassification in young (<65 years old) or elderly (>65 years old) (8)
- Absence of data about ESS and/or AHI(10)
6 Full text articles assessed for eligibility
6 Studies included in the qualitative and quantitaive analysis regarding AHI and ESS difference in OSA patients under and over 65 years old.

Figure2

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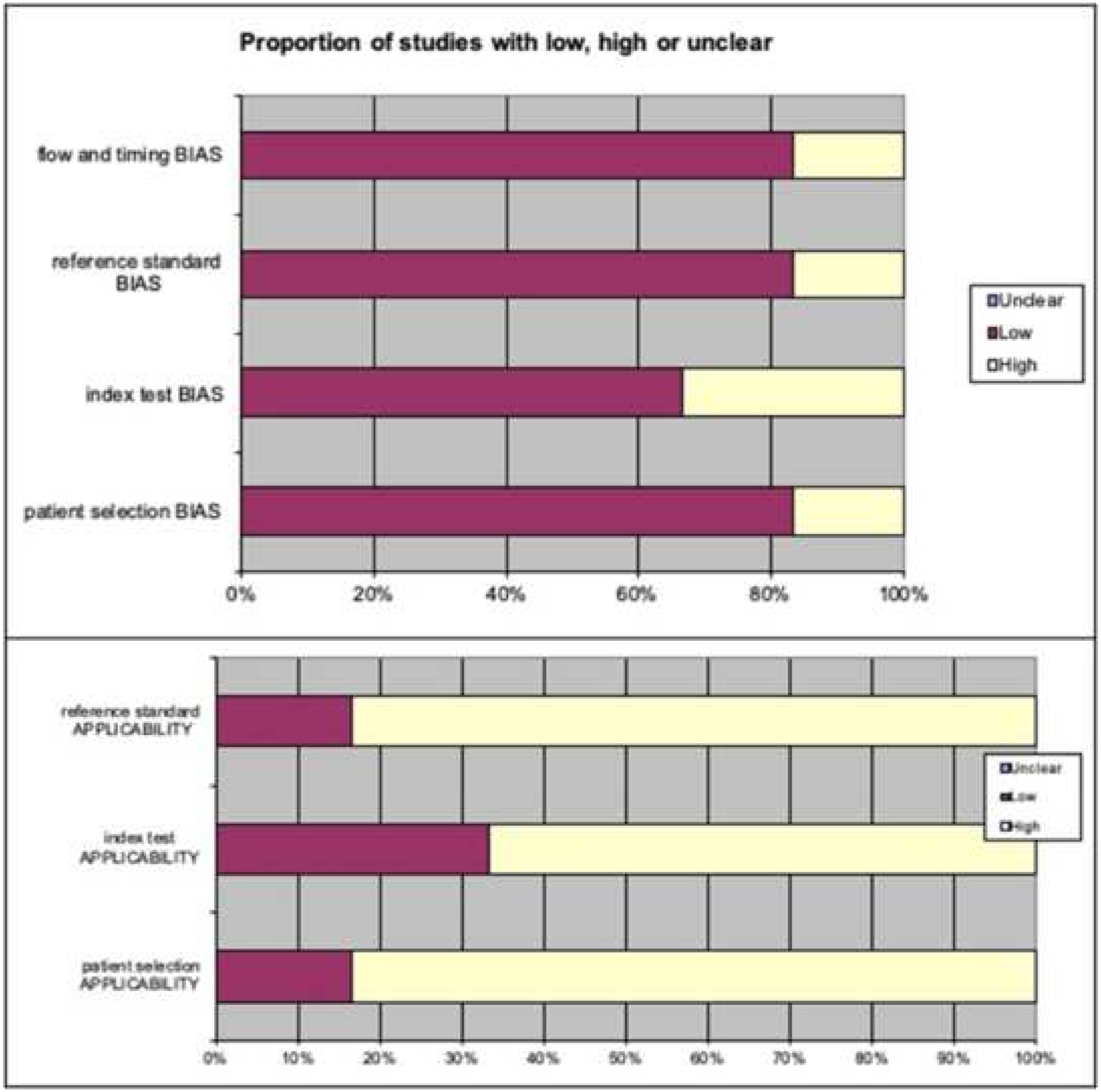

Figure3

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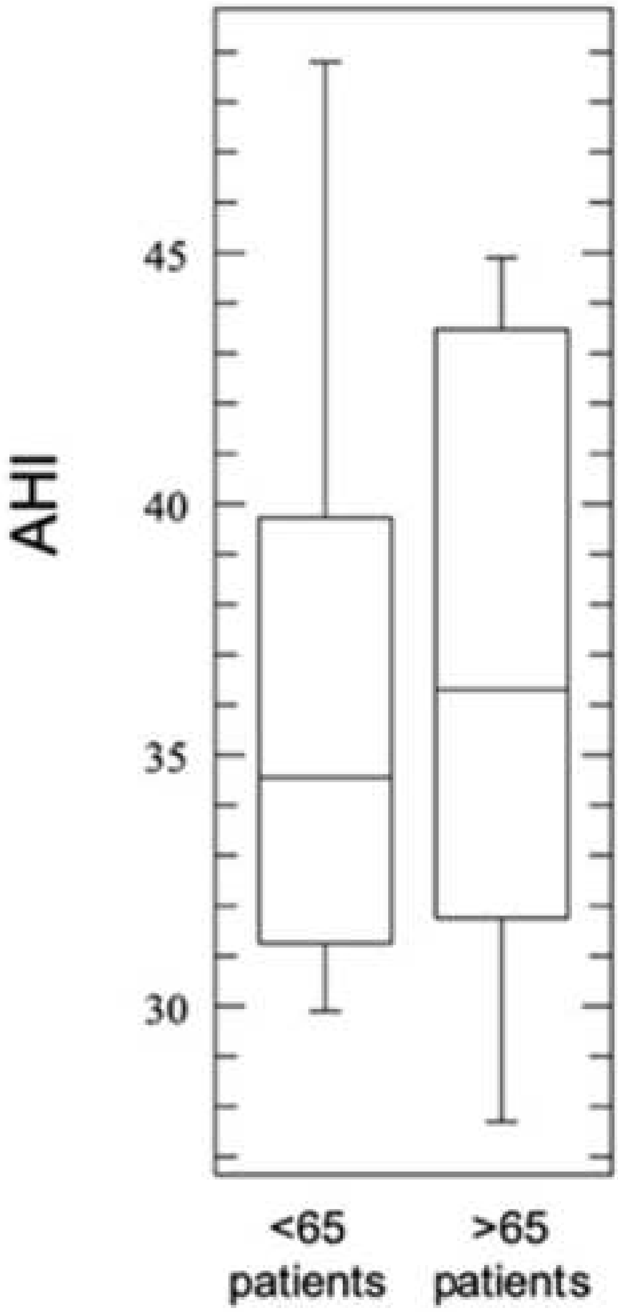


Fig. 3A

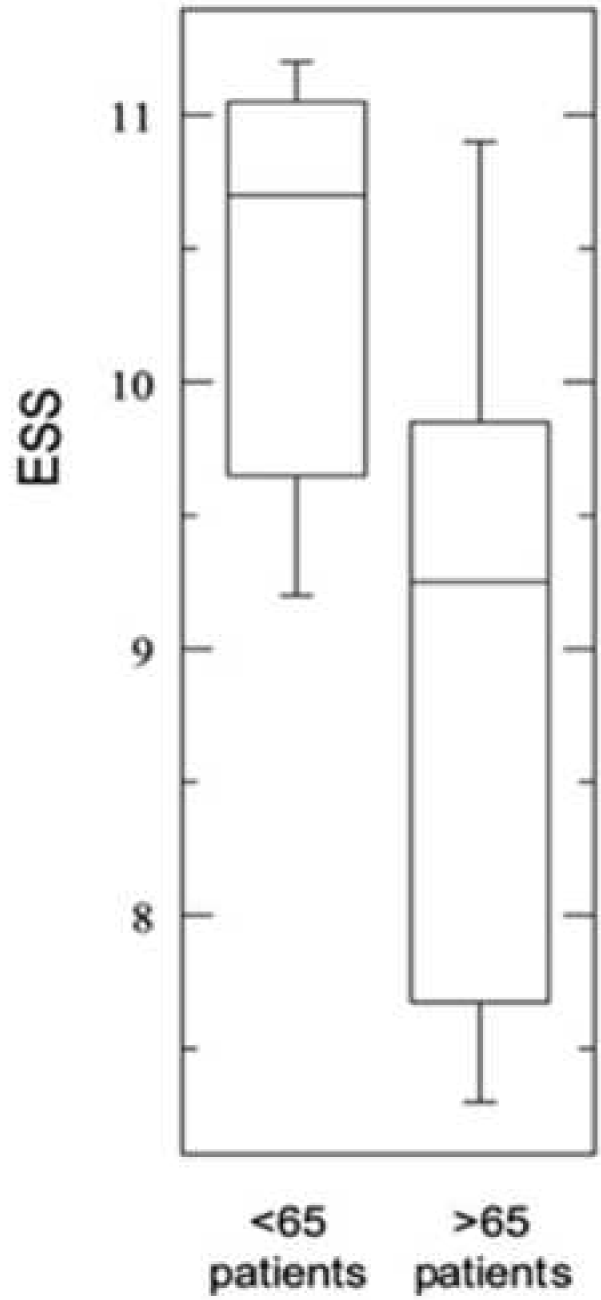
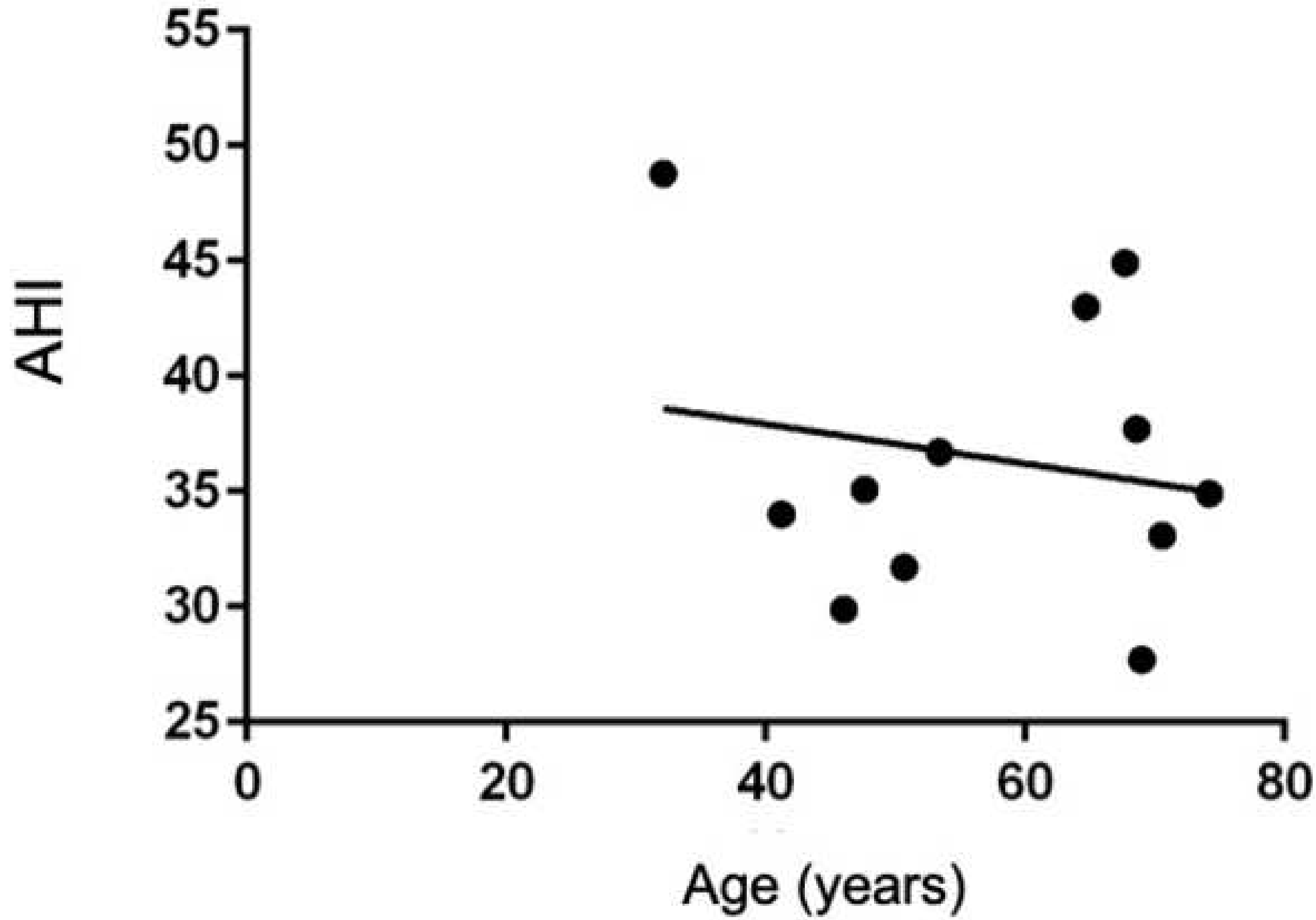


Fig. 3B



55
50
45
40
35
30
25
AHI
0
20
40
60
80
Age (years)

Figure5

Click here to access/download;Figure;Fig.5.tif

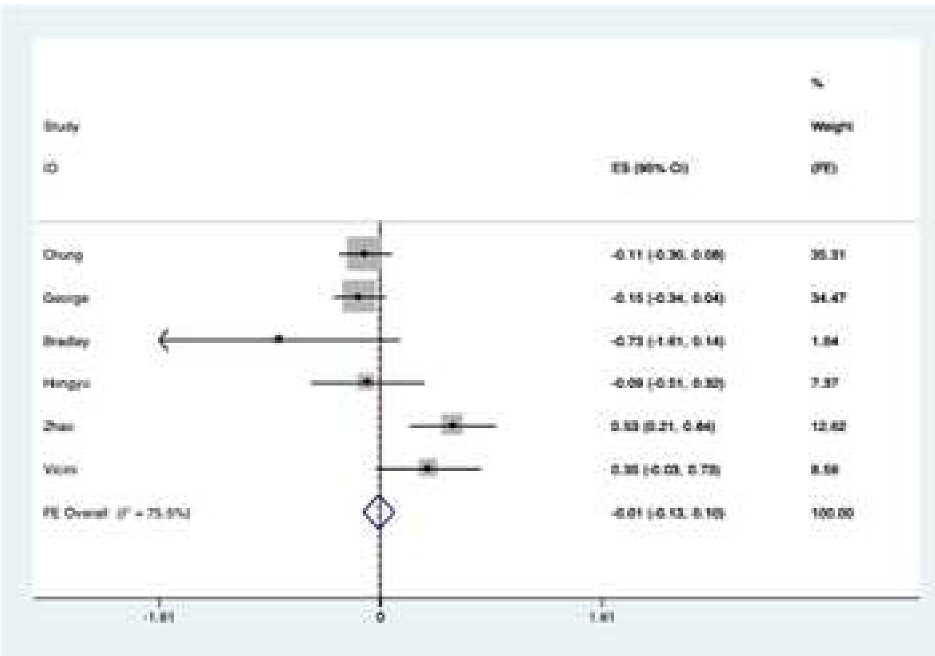


Fig. 5A

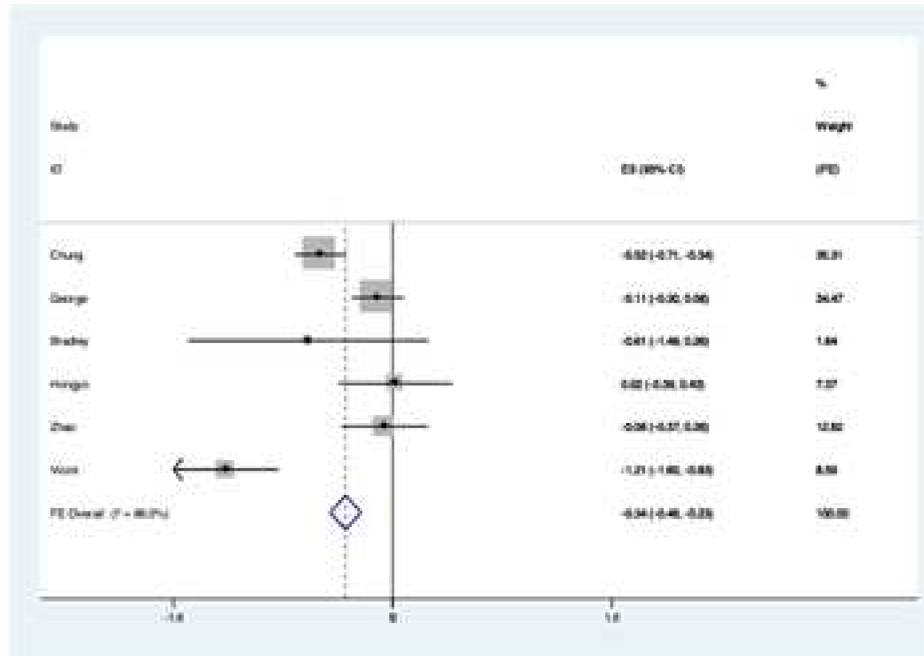


Fig. 5B

TABLE 1: OSA related parameters by age: literature review.

Author	**Year**	**Total patients of the study**	**Age of patients**	**Number of patients according to age sub-classification**	**Midle age**	**AHI**	**ESS**	**BMI**
Chung et al (22)	2009	757	<65	627	46	29,8	10,7	25.9
			>65	130	69	27,7	7,8	24.2
George et al (23)	2012	697	<65	568	47.62	35,1	11,2	33.31
			>65	129	70.54	33,1	10,9	32.18
Edwards et al (24)	2014	20	<60	10	32.1	48,8	10.8	34.9
			>60	10	64.7	43	9.2	31.3
Hongyo et al (25)	2017	90	<65	44	53.4	36,7	9,2	28.1
			>65	46	74.2	34,9	9,3	24.5
Zhao et al (26)	2018	200	<60	148	41.2	34	9,8	28
			>60	52	67.7	44,9	9,5	27.6
Vicini et al (27)	2018	105	<65	50	50.7	31,7	11	26.9
			>65	55	68.6	37,7	7,3	28.4

TABLE 2: Meta-analysis; difference regarding AHI and ESS between patients with and without Laryngopharyngeal reflux disease

	AHI <65	**AHI >65**	**p**	**ESS <65**	**ESS >65**	**p**	**BMI <65**	**BMI >65**	**p**
Mean	36.0	36.9	**0.8**	10.5	9.00	**0.04**	29.5	28.0	**0.4**
SD	6.72	6.40		0.779	1.29		3.68	3.33	
Min-max	29.8 - 48.8	27.7 - 44.9		9.20 - 11.2	7.30 - 10.9		25.9 - 34.9	24.2 - 32.2	
Median	34.5	36.3		10.8	9.25		28.1	28.0	

cover letter