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Elevated Health Care Utilization in Young Males Adult With Obstructive Sleep Apnea

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Running head: Young adult OSA patients

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Abstract

Objective: to explore morbidity and health care utilization (HCU) among young adult males with OSA compared middle-aged OSA patients, over the five-year period preceding diagnosis.

Methods: Case-Control prospective study. 117 young (22–39 years) males with OSA were matched with 117 middle-aged (40–64 years) OSA male for body mass index (BMI), apnea-hypopnea index (AHI), oxygen saturation, arousal and wakening index, and Epworth Sleepiness Scale. Each OSA patient was matched with controls by age, geographic area and physician.

Results: Young adult males with OSA have no increase for specific comorbidity compared to controls. Middle-aged OSA patients have increased risk for cardiovascular diagnosis (CVD) (OR, 95% CI; 2.1, 1.7–3.8). HCU for all five years was $\geq$1.9 times higher among young and middle-aged male OSA patients ($p < 0.002$) than controls. Multiple logistic regression analysis revealed that hyperlipidemia (7.0; 1.7–29.2) in young adults and BMI >37 (5.6; 1.6–20.1) and CVD (2.7; 1.15–6.3) in middle-aged adults, are the only independent determinants for the upper third, “most costly”, OSA patients.

Conclusion: Compared to middle-aged males with OSA in which increased expenditure was related to CVD and BMI, in younger cases utilization was not related to any specific disease.

Key words: Age, Heath Care Utilization, Obstructive sleep apnea, Morbidity

Introduction

Obstructive sleep apnea (OSA) is a common disorder affecting 4% of the middle-aged male population. Untreated OSA may be a burden on the health care system because OSA is a risk factor for chronic conditions such as cardiovascular disease (CVD). Elevated costs and CVD have been documented years prior to diagnosis of OSA.[1,2]

Most information about OSA co-morbidities has been described using cross-sectional population-based studies starting from forty years of age.[3–6] Data regarding health care utilization[1,2,7-12] were obtained from laboratory-based OSA patients mostly above forty years of age. The risk for CVD among OSA patients increases with age.[1,2,4] Clinicians and decision-makers are following the results of the Sleep Heart Health Study that provides data on OSA patients starting from forty years of age.[4-6] Little is known about whether young adult (<40 years of age) males with OSA have different morbidity and health care utilization compared to their controls and middle-aged male OSA patients (40–64 years).

We were motivated to perform this study after the recent call[13] emphasizing the need for early OSA diagnosis and treatment among young adults. Decision-makers are currently less aware of the potential dividends from investments in preventive or early intervention among young adult OSA patients. The purpose of this study was to explore morbidity and health care utilization among young adult males with OSA, over the five-year period preceding diagnosis.

Methods

Setting: Case-control study conducted in two Sleep-Wake Disorders Centers (Soroka University Medical Center and Loewenstein Hospital–Rehabilitation Center) in two districts (South and Center) where >95% and >70% of patients respectively, are enrollees of Clalit Health Care Services (CHS), the largest Health Maintenance Organization (HMO) in Israel.

Informed consent was obtained from all OSA subjects.

Study population: Between January 2001 and April 2003, male OSA patients were consecutively recruited (22 through 64 years, with polysomnographically (PSG) proven OSA). We matched 117 young adult male OSA patients 22 through 39 years with 117 middle-aged male OSA patients 40 through 64 years by body mass index (BMI), apnea-hypopnea index (AHI), oxygen saturation below 90% (T_{90}), arousal and wakening index, ESS.[14] Each OSA patients was matched 1:1 by age, gender, geographic area, and family physician to control subjects selected randomly from CHS database.[2,11]

Excluded are patients and controls with chronic obstructive pulmonary disease (COPD), genetic disorders, cancer, autoimmune disorders, and patients hospitalized >50 days during the five years of data collection.[1,2,11] Patients were not matched to controls for body mass index (BMI) because that information is not included in the CHS database. Due to Ethical considerations we were not able to contact the control subjects, it is possible that an about 5% of the controls might have undiagnosed OSAS.

Data resources included: PSG results,[15,16] obstructive apnea was defined as an episode of complete cessation of breathing of ≥10 seconds with continuing inspiratory effort; airflow was measured by thermistor. A hypopnea was scored when continuing inspiratory effort was accompanied by a reduction of at least 50% in airflow, resulting in either an arousal or oxygen desaturation of at least 4%. Apnea hypopnea index (AHI) was calculated per hour of sleep. Oxygen desaturation index was calculated as the number of desaturation events (SaO_2 decreased more than 4%) per hour of sleep. The percentage of time with a mean SaO_2 below 90% was calculated and expressed as T_{90}. Sleeping habits, clinical history, ESS, and Functional Outcomes of Sleep Questionnaire (FOSQ)[17] were collected as previously described.[2] Language was not a barrier to completing the questionnaires, as the questionnaire had been validated in Hebrew.[2] We reviewed the accumulated diagnoses of CVD along with their respective International Classification of Diseases, Ninth Revision (ICD-9) codes including hypertension [401–405], ischemic heart disease [410–414], cardiac arrhythmia, congestive heart failure, valvular cardiac disease, cerebrovascular accident [426–438], and peripheral vascular disease [443]. A definition of CVD diagnosis[2] includes at least one of the following ICD-9 codes: 410–414, 426–438, and 443. In addition, we included medical conditions which increase the risk of CVD, i.e., hyperlipidemia [272] and diabetes mellitus [250]. Participant's mailing address was used as a proxy for socioeconomic status.[18]

Health care utilization was obtained from databases of CHS.[2,11,19-21] All costs were combined for the five years prior to the PSG diagnosis and similar time periods were used for the control subjects. Health care utilization included hospitalization (days and costs), emergency department visits (number and costs), visits to specialists (type of specialty, number of visits, cost; OSA consultations did not include the last otolaryngology surgeon or pulmonologist visits prior to PSG study). and prescriptions supplied (number, category,[22] cost), according to the price list published by the Israeli Ministry of Health in 2005 (4.5 NIS = 1 $US). Cost of the PSG study was not included.

Statistical analysis

Health care utilization was analyzed according to previous recommendations[23] using SPSS software (v 14.0). We applied the following design: young adult (22–39 years) males with OSA, young paired male adults, and middle-aged male OSA patients (40–64 years).[4–6] To confirm that the middle-aged male OSA group is typical, we included additional group of middle-aged male pair-matched controls. Costs are not normally distributed among OSA patients[11]. Therefore, we arbitrarily divided OSA group by cost, the "most costly" (upper 33.3%) male OSA patients and "least costly" (remaining 66.6%) patients. The multiple logistic regression model was fitted to establish the determinants of the "most costly" OSA patients (dependent variable). Independent variables included age, body mass index (BMI), partner complaints, ICD-9 codes, supplied drugs, smoking history, PSG findings, ESS, and FOSQ. Statistical significance was accepted when $p \leq 0.05$ with Bonferroni correction for multiple comparisons.

Results

1508 males underwent PSG studies during study period; of those, 112 were enrollees of other HMOs and/or were severely sick patients. 93 (6.7%) patients refused to participate in the study and 243 (18.6%) were ≥ 65 years of age and did not meet the inclusion criteria. Following PSG, 138 subjects did not meet the inclusion criteria of OSA diagnosis (<AHI 5); finally, 922 male OSA patients (AHI $\geq$ 5) were eligible for this study. Of those, all 117 (12.7%) young adult males with OSA were population-matched with middle-aged OSA patients randomly selected using SPSS software from 805 eligible middle-aged patients.

Subjects: The characteristics of our male OSA patients are shown in Table 1. Mean age difference between both groups was 20 years ($p < 0.0001$). No significant differences were found in arousal and wakening index, AHI, T_{90}, ESS, BMI, and FOSQ scores of young and middle-aged adults. In both groups ESS score inversely correlates with FOSQ score ($r = -0.29$, $p = 0.013$ and $r = -0.46$, $p < 0.0001$, in young adult and middle-aged OSA patients, respectively). The number of married middle-aged OSA patients is 27% greater ($p < 0.0001$); middle-aged patients have fewer years of education ($p < 0.05$). Both young and middle-aged adults males with OSA reported a similar ($p = 0.6$) weight gain of about 5 kg in the 12 months prior to PSG study and a similar prevalence of habitual snoring of 95%. More young adult males with OSA are current smokers (48%, $p < 0.024$). 60% of the bed partners of both male OSA groups reported significant sleep disturbances due to the patient's habitual loud snoring. About half of the partners who complained about snoring slept in separate bedrooms.

Co-morbidity: Compared to their controls, similar risk was found regarding diagnosis of CVD, Hyperlipidemia, Diabetes, Asthma, and depression among young adults with OSA. Only a few subjects (number ranged from 0 to 12) in both young adult groups were found to have these illnesses. However, middle-aged OSA subjects (number ranged from 7 to 45) compared to their controls had more Hyperlipidemia, Diabetes, Asthma, or increased risk for CVD (OR, 95% CI, 2.1; 1.7–3.8).

Health care utilization: Compared to controls, the five-year total costs (Table 2) were 1.98 and 1.9 times as high in young and middle-aged OSA patients, respectively ($p < 0.002$). Only one young adult and one middle-aged adult had zero health care expenditures during the five-year observation period. Except for hospitalization costs for visits in the Emergency Department, Consultations and supplied Drugs were all significantly higher in both OSA groups compared to controls (Table 2).

Consultations: Compared to controls, the total number of visits to specialists during the five years prior to PSG diagnosis revealed that young adult males with OSA had more consultations with otolaryngology surgeons (ENT) and pulmonologists (1.3± 0.1 vs. 0.3 ±0.07, $p < 0.0001$) and (0.09 ± 0.03 vs. 0.02± 0.01, $p < 0.05$). There were 32% more repeated (≥2) ENT consultations among young adults with male OSA compared to 5.2% of their controls ($p < 0.0001$). Relative to controls, middle-aged male adults with OSA had more consultations with ENTs (0.4 ±0.1 vs. 1.4± 0.1, $p < 0.0001$), pulmonologists (0.02±0.01 vs. 0.4±0.1, $p < 0.0001$), and other specialists (e.g., dermatologist, cardiologist, orthopedist, neurologist, gastroenterologist), $p < 0.01$. Significantly more repeated (≥2) consultations were found among all consultants except for orthopedics, urology, and general surgery.

Supplied drugs: Compared to controls, the total five-year costs for drugs among young and middle-aged male OSA patients were 2.9 and 3.3 times as high ($p = 0.056$ and < 0.001), respectively (Table 2). The mean total numbers of supplied drugs for the five years prior to PSG diagnosis are summarized in Table 3. Included are the pharmacological categories in which significant differences were found in one of the studied groups. The main drug category supplied to young and middle-aged male adults with OSA were for respiratory category and CVD, respectively. No differences were found in the number (Table 3) and/or costs of supplied CVD drugs to young male OSA patients relative to their controls (\$8.8±3.5 vs. \$1.7±0.8, respectively, p = 0.1). Cost for the Cholesterol and Triglyceride Reducer drugs sub-category was \$0.60 and \$2.70 in controls and young adult males with OSA, respectively, and in middle-aged adults \$6.70 and \$36.00, respectively. Drugs for the Obstructive Airway Diseases sub-category comprised <30% of the respiratory system category, in all four groups. Hypnotic and Sedative drugs were supplied similarly (<14%) and the Antipsychotic sub-category drugs were supplied from the Psycholeptics and Psychoanaleptics category, among young adult male OSA patients and controls, 68% and 33% (p<0.01), respectively. The Psycholeptics and Psychoanaleptics category drugs were supplied significantly more to middle-aged adult males with OSA (Table 3).

Characteristics of the upper third, most costly, male OSA patients: When dividing the young adult OSA group by cost, the upper 33.3% (n=39) of patients who were the "most costly" consumed 82% of all costs and had a mean consumption per person five years prior to PSG diagnosis of \$1876±349 vs. the low costly (66.6%) patients with \$206±17.7 (p < 0.0001). The "most costly" subjects consumed 9.1-fold more health care resources than the "least costly" patients. The "most costly" young adult male OSA subjects were diagnosed more frequently with Hyperlipidemia (p < 0.002), but had similar T_{90}, ESS, BMI, FOSQ, AHI, arousal and wakening index compared to the "least costly" subjects. For example, AHI was 33.9±4.5 vs. 28.8±2.7 events/hr (p =

0.6) and arousal and wakening index was 37.5±6.2 vs. 26.9±4.2 events/hr ($p = 0.3$) in the "most costly" vs. "least costly" patients, respectively.

The "most costly" middle-aged male OSA subjects consume 78% of all costs and had a mean consumption per person per five years of $4296±677 vs. $398±32.6 in the "least costly" patients ($p < 0.0001$). The "most costly" male OSA patients consumed 10.8-fold more health care resources than the "least costly" patients. The "most costly" subjects have more co-morbidities i.e., 2 times more CVD ($p = 0.006$), 1.9 times more Hyperlipidemia ($p = 0.005$), 4 times more Diabetes ($p = 0.019$); the univariate odds ratios are exhibited in Table 4B. FOSQ score was 77.4±2.8 vs. 65.2±4 (units) among the "most" vs. "least costly" patients, respectively ($p = 0.03$). The "most costly" middle-aged OSA patients had a significantly greater arousal and awakening index of 44.8±5.8 vs. 22.7±4.7 (events/hr,) ($p = 0.003$) and T_{90} of 19.3±4.4% vs. 8.9±2.4% ($p = 0.014$) relative to "least costly" patients, respectively. However, AHI was similar ($p = 0.77$) between "most costly" vs. "least costly" patients, 31.1±3.5 vs. 32.4±3 (events/hr), respectively.

The univariate and multivariate odds ratios of determinants of the "most costly" male OSA patients are presented in Table 4A and B. After adjusting for age, AHI, and BMI, multiple logistic regression analysis revealed that hyperlipidemia (OR, 95% CI, 7.0; 1.8–29.2) is the only independent determinant for "most costly" young adult males with OSA.

After adjusting for age and AHI, multiple logistic regression analysis revealed that BMI (OR, 95% CI, 5.6; 1.6–20.1) and CVD diagnosis (OR, 95% CI, 2.7; 1.15–6.3) are the independent determinants for "most costly" middle-aged adults with OSA.

Discussion

Young and middle-aged adults with OSA are high consumers of health care services. The "most costly" patients consume more than 78% of all OSA group costs. Young male adults with OSA have high health care utilization due to nonspecific co-morbidity.

Studied subjects: This is the first report comparing health care utilization between young and middle-aged adult males with OSA, stratified by age, in which severity of OSA and BMI have been controlled. Only 15% of the subjects referred for PSG evaluation were young adults. Of those, 12.7% (n=117) were classified as mild typical OSA or beyond. Similar rates of OSA in young adults have been reported.[24-26] It is well known that age *per se* is a continuous and cumulative risk factor for CVD and health care utilization among male OSA patients.[1,2,7-12] However, most information was reported for male OSA patients $\geq$40 years of age. Age definition of "young adults" varies. We adapted the stratification methodology of the Sleep Heart Health Study,[4–6] which selected 40 years-of-age as the lower boundary of their inclusion criteria. But there is no particular reason to suspect that there is a discontinuity or structural break in the relationship between age and health care expenditure at age 40. It is possible that this stratification directed the attention of clinicians and decision-makers from early diagnosis of young adult males with OSA.[13] This study fills the gap in the information needed to prioritize diagnosis in this age category.

Associated morbidity: OSA is already prevalent in the third decade of life these patients are generally referred to a sleep clinic for OSA diagnosis due to characteristic symptoms which will start bothering the subject or his bed partner.[13] Patients who ultimately present for evaluation of OSA have been treated for years for secondary manifestations[28,29] e.g., minor mental disorders[30] and nonspecific respiratory system symptoms. Our information on supplied drugs is an indirect supportive index of secondary and nonspecific manifestations of OSA, especially drugs from the Respiratory system, Antibacterials for Systemic Use, and Psycholeptics and Psychoanaleptics categories. We did not fined indices for the presence of CVD among young adult male with OSA using health care utilization parameters. It is reasonable that the changes in the cardiovascular system are sub clinical and, as hypothesized[13] will be manifested later in life. In some of these individuals, the nonspecific manifestations and CVD may be ameliorated with CPAP treatment.[31] Therefore, we support the need for early OSA diagnosis among young adults.[13]

The only difference between OSA sub-groups was the presence of CVD in the middle-aged patients.[1,2,27,28] In our study the risk for co-morbidities (CVD, hyperlipidemia, and diabetes) among adults with OSA increases considerably with age.[1-6,31-34] Delaying diagnosis and treatment to the fifth and sixth decades may be too late, especially for young adults who may develop irreversible CVD.[13]

Health care utilization: Several factors may complicate attempts to obtain unbiased estimates of health care expenditures. For example, medical care expenditures may exhibit a large number of observations clustered at zero, with the rest of the observations being positive and highly skewed.[35] The usual solution to the problem is to estimate a two-part or Heckman sample selection model.[36] All of this is relevant to our study; however, our OSA subjects are dominated by people who have non-zero health care expenditures (only one middle-aged adult and one young adult had zero health care expenditures); positive and highly skewed utilization were minimized using the exclusion criteria i.e., patients hospitalized more than 50 days during the five years of data collection.[1,2]

Since costs are not normally distributed among OSA patients, a small group[11] of OSA patients who were the "most ill" and "most costly" consumed more than 70% of all health care resources used by OSA patients. In this study the "most costly" male OSA patients consumed ≥ 9 times more health care resources compared to the "least costly" young and middle-aged male OSA patients who consumed more than 78% of all costs during the five years. Is there any relationship between age and health care expenditure in the young adult OSA males? i.e., are 20 year olds much the same as 39 year olds when it comes to total health care expenditure? We found that age did not predict costs among the "most costly" OSA males. However, it was demonstrated that the risk for CVD and probably its related costs increases with age among OSA patients >40 years of age.[4-6]

Hyperlipidemia was the only determinant found to increase the odds of being included among the "most costly" young adult males with OSA, suggesting that these patients are at greater risk for irreversible arteriosclerotic processes.[13] However, it is possible that since the number of subjects (n=39) in the "most costly" subgroup is small, this may result in statistical under-power. The relationship between hyperlipidemia and excess health service use needs to be interpreted with caution in further studies. Among all young male OSA patients, the high utilization is due to respiratory tract diseases as indicated by significantly more visits to ENT surgeons and pulmonologists, in addition to supplying more respiratory category drugs. This finding is valid even after excluding the Obstructive Airway Diseases category that was dispersed equally among all studied groups.

Mechanisms linking OSA with CVD are complex and multifactorial, i.e., AHI,[5] hemodynamics, neural, metabolic, endothelial, coagulatory, or inflammatory consequences of nocturnal respiratory events, oxidant stress, and low socioeconomic status.[11,37] None of the PSG objective findings of OSA severity (AHI, T_{90}, arousal and awakening index) or BMI adds to the prediction of "most costly" young adult male OSA patients or CVD, supporting earlier reports.[1,2,11,38] Our patients with AHI >20 and >30 have similar health care utilization. AHI is probably an imperfect linear measure of OSA severity and obesity is not necessarily a cause for health-care consumption.[39] Health care utilization does not reflect OSA severity. Many of our OSA patients require treatment and these patients probably had an AHI above the CVD threshold.[2] In addition, factors directly responsible for CVD, such as inflammatory mediators and oxidant stress,[37] are genetically determined responses to the OSA stimulus. We were not permitted to contact the controls to obtain their BMI because of legislation protecting patient confidentiality.[2,11] This is a limitation when analyzing utilization in a health care system in which legislation protecting patient confidentiality exists. High BMI ($\geq$ 38 kg/m^2) and CVD increase the odds of being included among the "most costly" middle-aged OSA patients. The presence of CVD as a risk factor in the "most costly" middle-aged OSA patients in our study is in accordance with previous reports.[1,2,11]

Our data represent a health care system similar to others such as that in Canada.[1,7-10,12] Our results reflect the "true" consumption of health care resources because there is no economic incentive to refer patients to PSG studies.[2,11,19-21,28] In our health care system, cost per visit to a specialist is fixed regardless the length of visit. Further studies are needed to explore whether differences exists between the OSA groups and controls with respect to encounter intensity (i.e., dose, strength, length of visit). We could not determine whether increased exposure to the health care system increased the "risk for elevated health care utilization",[21] we were not permitted to contact controls or patients to obtain additional information, because of legislation protecting patient confidentiality.[2,11,19-21] Finally, the ability of patients to pursue medical help may be influenced by socioeconomic status; we minimized this effect by selecting controls from the same geographic location.[2]

Conclusion: Compared to middle-aged males with OSA in whom increased expenditure was related to CVD and BMI, in younger cases, utilization was not related to any specific disease.

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Table 1. **Demographics and characteristics of male OSA patients.**

	Young adult (<40 years)	Middle-aged (40–64 years)
n	117	117
Age (years)	33.8±4	53.1±6.4#
Married (yes)	61.5% (48)	89% (65)#
Years of Education	13.4±2.7	12.4±3.1*
Sleep efficiency (%)	86±10	83±16.1
Arousal and wakening index (events/hr)	31.7±23.4	32±22.8
AHI (events/hr)	30.5±25	32±25.5
T_{90} (%)	13.1±23.9	12.7±22.2
ESS (score)	9±5.7	8.8±5.4
BMI (kg/m^2)	30.2±6.2	30.7±5.1
CVD (n)	1	24#
HPL (n)	12	45#
Diabetes (n)	3	12*

AHI – Apnea-Hypopnea Index, BMI – Body Mass Index, CVD – Cardiovascular Disease, ESS – Epworth Sleepiness Scale, HPL – Hyperlipidemia, T_{90} – percent sleeping time in which oxygen saturation was below 90%.
Values are mean ± SD. * < 0.05; # < 0.0001

Table 2. **Cost elements for male OSA patients *vs.* matched control subjects in the five years prior to diagnosis.**

	Young adult males			Middle-aged males		
Parameter	Control	OSA	P value	Control	OSA	P value
Hospitalization						
Costs ($US/person/5 years)	144.7±44.6	299.5±115.8	0.7	575±197.1	886.5±221.3	0.161
Median (min, max)	0 (0–2,832)	0 (0–12,036)		0 (0–18,408)	0 (0–19,116)	
Days/person/5 years	0.4±0.1	0.8±0.3	0.7	1.6±0.6	2.5±0.6	0.161
Median (min, max)	0 (0–8)	0 (0–34)		0 (0–52)	0 (0–54)	
Emergency department						
Costs ($US/person/5 years)	88.7±12.2	132.7±16.8	0.020	86.2±19.1	126.1±22.6	0.049
Median (min, max)	0 (0–665.3)	111 (0–887.1)		0 (0–1,996)	0 (0–1,996)	
Visits/person/5 years	0.8±0.1	1.2±0.2	0.024	0.8±0.2	1.1±0.2	0.046
Median (min, max)	0 (0–6)	1 (0–8)		0 (0–18)	0 (0–18)	
Consultations						
Costs ($US/person/5 years)	95.1±10.5	165.4±14#	<0.0001	114±14.2	285.4±25.3	<0.0001
Median (min, max)	39.3 (0–472)	118 (0–787)		79 (0–904)	197 (0–1,967)	
Visits/person/5 years	2.4±0.3	4.2±0.4#	<0.0001	2.9±0.4	7.3±0.6	<0.0001
Median (min, max)	1 (0–12)	3 (0–20)		2 (0–23)	5 (0–50)	
<u>Drugs</u>						
Costs ($US/person/5 years)	57.1±10.1	165.1±45.4#	0.056	120.3±24.6	400±68	<0.001
	17 (0–815)	37 (0–3,322)		38 (0–2,347)	158 (0–5,126)	
Total Costs	386±55	763±137#	0.004	895.3±218.2	1698±282.2	0.002
($US/person/5 years)	162 (0–3,030)	303 (3–12,825)		236 (0–19,305)	559 (0–24,196)	

Values are presented as mean ± SEM (median, range) summing costs and health care utilization per patient during the five years prior to OSA diagnosis. Comparison between OSA patients and matched controls was performed by Wilcoxon test. Comparison between young adult and middle-aged OSA patients was performed by Mann-Whitney test (# $p < 0.0001$).

Table 3. **Mean number of supplied drugs in the five years prior to OSA diagnosis**.

	Young adult males			Middle-aged males		
Parameter	**Mean number of supplied drugs (Median, range)**	**Difference (95% CI)**	**P value**	**Mean number of supplied drugs (Median, range)**	**Difference (95% CI)**	**P value**
Respiratory system (R)	6.5±1.1 (3, 0–85)	3±1.3 (0.4–5.6)	0.002	7.8±1.2 (4, 0–110)	4.8±1.2 (2.3–7.2)	<0.0001
Antibacterials for Systemic Use (J01)	3.4±0.7 (2, 0–73)	1±0.7* (-0.5–2.5)	0.06	4.4±0.5 (3, 0–31)	2.1±0.5 (1.1–3.2)	<0.0001
Cardiovascular System (C) (See below)	3.4±1.4 (0, 0–140)	3±1.5# (0.1–6)	0.2	19±3.5 (1, 0–209)	12.9±4 (5.1–21)	<0.0001
Psycholeptics and Psychoanaleptics (N05, N06)	3±1.1 (0, 0–70)	2.8±1.1# (0.7–5)	0.04	3.9±1.1 (0, 0–85)	2.9±1.1 (0.7–5.1)	0.001
Analgesics (N02)	2.5±0.8 (1, 0–92)	1.4±0.9# (-0.3–3.1)	0.12	5.2±0.9 (2, 0–51)	2.7±0.9 (0.9–4.5)	0.002
Anti-inflammatory and Anti-rheumatic Products (M01)	0.8±0.1 (0, 0–6)	0.22±0.1# (-0.05–0.5)	0.2	2.6±0.4 (2, 0–25)	1±0.5 (0.06–1.9)	0.008
Peptic Ulcer and Gastroesophageal Reflux Disease (A02B)	0.4±0.14 (0, 0–14)	-0.5±0.5# (-1.5–0.5)	0.83	4.1±1 (0, 0–63)	3.2±0.9 (1.4–4.9)	<0.0001
Drugs Used in Diabetes (A10)	0.33±0.33 (0, 0–39)	0.34±0.34* (-0.33–1.01)	0.6	3.7±1.5 (0, 0–115)	3.2±1.4 (0.4–5.9)	0.03

Supplied medications are the mean ± SEM (median, range) number of drugs per patient per five years. Presented are all pharmacological groups in which differences were found [Difference – mean difference (95% CI) between cases and controls in the number of times per five years the drug was prescribed]. Cardiovascular categories include:[10] Cardiac Therapy and Selective Calcium Channel Blockers with Direct

Cardiac Effect (C01, C08D); Antiadrenergic Agents, Centrally Acting and Antiadrenergic Agents, Peripherally Acting (C02A,C02C); Arteriolar Smooth Muscle, Agents Acting On (C02D); Low Ceiling Diuretics, Thiazides and Low Ceiling Diuretics, Excluding Thiazides and Potassium Sparing Agents and Diuretics and Potassium Sparing Agents in Combination (C03A, C03B,C03D, C03E); High Ceiling Diuretics (C03C); Peripheral Vasodilators (C04); Vasoprotectives (C05); Beta Blocking Agents (C07); Selective Calcium Channel Blockers with Mainly Vascular Effects (C08C); ACE-Inhibitors, Plain and ACE-Inhibitors, Combinations (C09A,C09B); Angiotensin II Antagonists and Angiotensin II Antagonists, Combinations (C09C,C09D); Cholesterol and Triglyceride Reducers (C10A). Comparison between OSA patients and controls was performed by Wilcoxon test. Comparison between young adult and middle-aged OSA patients was preformed by Mann-Whitney test (* $p<0.05$, # $p<0.0001$).

Table 4. **Determinants of upper third most costly male OSA patients.**

a) Young adult males OSA patients.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (+1 yr)	1.04 (0.95–1.2)	0.390	1.02 (0.91–1.13)	0.773
AHI (+1 event/hr)	1.01 (0.99–1.02)	0.298	1.003 (0.98–1.02)	0.778
BMI (+1 kg/m^2)	1.04 (0.98–1.1)	0.190	1.01 (0.93–1.1)	0.816
HPL (1 – yes/0 – no)	7.5 (1.9–29.6)	0.004	7.0 (1.7–29.2)	0.008

b) Middle-aged males OSA patients.

	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (+1 yr)	1.05 (0.99–1.1)	0.137	1.03 (0.96–1.1)	0.361
AHI (+1 event/hr)	0.998 (0.98–1.01)	0.798	0.993 (0.97–1.01)	0.433
BMI (kg/m^2) (1 ≥38/0 < 38)	5.03 (1.6–16)	0.006	5.6 (1.6–20.1)	0.008
CVD (1 – yes/0 – no)	3.05 (1.36–6.8)	0.007	2.7 (1.15–6.3)	0.023
HPL (1 – yes/0 – no)	3.1 (1.4–6.9)	0.006	Not included	
Diabetes (1 – yes/0 – no)	4.8 (1.3–17.02)	0.016	Not included	
T_{90} (%) (1 ≥10%/0 < 10%)	3.33 (1.3–8.7)	0.014	Not included	

Univariate and multiple logistic regression models were used to calculate odds ratios (ORs) with 95% confidence intervals (CI) and establish the primary determinants of most costly OSA patients.

AHI – Apnea-Hypopnea Index, BMI – body mass index, CVD – Cardiovascular Disease, HPL – Hyperlipidemia, T_{90} – percent sleeping time in which oxygen saturation was below 90%.