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RESEARCH ARTICLE
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INTERPRETATION ON THE SEVERITY LEVELS OF SLEEP DURATIONAND OBSTRUCTIVE SLEEP APNEA LEADING TO STROKE : A CASE-CONTROL STUDY

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Abstract:

***Background*:** The stroke and obstructive sleep apnea is intertwined in such a manner that obstructive sleep apnea is an independent risk factor for stroke and do explains of 30-40% of risk to stroke. But the proper evidences are still poor. Hence we explore the risk relation between obstructive sleep apnea and stroke by conducting a case-control study over a period of 6 months.

***Methods*:** The study included both case and control groups in which the population suffering from stroke is taken as a case group and the healthy population is taken as a control group. We have used set of questtionnaires(Berlin questionnaire, STOP-Bang questionnaire, Epworth sleepiness scale) for estimating the risk of obstructive sleep apnea within the entire population and the odds ratio is calculated between the groups to estimate the amount of risk. Logistic regression is also performed to estimate the individual variable (hypertension, snoring, BMI, age, gender, neck circumference) riskfor OSA.

***Results*:** Positive association is confirmed between the stroke and obstructive sleep apnea with a 3.68 odds ratio, indicating that a person suffering from OSA is at 3.68- fold risk of developing a stroke. The variables Snoring and BP had a p-value of 0.015 and <0.001. This indicates that this influence is statistically significant. The odds ratio of Snoring was 1.73, which means that the probability of Stroke increases by 1.73 times. The odds ratio of BP was 6.99 showing a 6.99-fold greater risk for stroke occurrence. However, the variable Neck circumference had a p-value of 168 indicating that this influence is not statistically significant but had an Odds ratio of 1.45.

***Limitations*:** The social history of case and control groups was not considered. This and short time period could become a limitation in our study as smoking and substance abuse may contribute to OSA in the population.

***Conclusion*:** Our study have provided an additional insights on explaining the risk of obstructive sleep apnea to the stroke which is also stastically proved. Hence obstructivesleep apnea should also be considered as an important risk factor for the stroke to reducethe stroke occurrence.
Keywords: Obstructive sleep apnea(OSA), stroke, case-control study, snoring, odds ratio, berlin questionnaire, STOP-Bang questionnaire.

Introduction:

Stroke can be simply defined as damage to the brain due to interruption to its blood supply. Stroke is the leading cause of disability and death in India and 2nd leadingcause of death across worldwide. According to a study conducted, the crude prevalence ranged from 40-559 per 100,000 persons in rural and urban parts of India.[1] In urban area, the incidence of stroke is 152 per 100,000 persons.[1] The estimated adjusted prevalence rate of stroke ranges are, 84-262/1,00,000 in rural and 334-424/1,00,000 in urban areas.[2] With such higher prevalence rates, there's an absolute need to focus on the risk factors of stroke so that we can minimize the morbidity of stroke.

Risk factors in the stroke play a major role in the development of stroke within the population as stroke is most prevalent in the population that neglects the risk factors. Many of the stroke's risk factors are lifestyle related like smoking, alcohol consumption, diabetes, dyslipidemia etc.,[3] Unlike the typical risk factors that are categorized into 1. Non-modifiable 2. Modifiable, one must consider the importance ofindependent risk factors like Obstructive sleep apnea (OSA) in the development of stroke within the population.

Though many of the stroke risk factors are lifestyle related i.e., modifiable. Non- Modifiable risk factors also play an important role in the stroke incidence. Age and gender are non-modifiable risk factors for stroke

The modifiable risk factors like hypertension, diabetes, smoking etc., also helpsin the development of stroke and the incidence of stroke occurs at elder age.[3] Hypertension is the cardinal modifiable risk factor for stroke with an adjusted relative risk of 1.4 (at age 80) and 4.0 (at age 50) and there is a strong, undeviating, linear and continuous relationship between blood pressure and stroke risk.[4] Diabetes Mellitus is one of the modifiable risk factors for stroke with an adjusted relative risk ranging from 1.8 to 6.[4] Elevated body cholesterol level is one of the modifiable risk factors having an adjusted relative risk of 2.0 thereby increasing the stroke risk and other cardiovascular problems.[4] Smoking remains a major risk factor for stroke, nearly doubling the risk with a dose-response relationship between years of smoking and stroke risk. [5-6] Smoking is adjusted for relative risk by 1.8.[4] There is evidence for a J- shaped relationship between alcohol consumption and ischemic stroke risk, with light to moderate alcohol intake (less than or equal to 2 drinks per day in men and less than or equal to 1 drink per day in women) protects against stroke, and excessive alcohol consumption is associated with an increased risk of ischemic stroke.[7-8] Traditional risk factors such as age, sex, hypertension, diabetes, dyslipidemia explains about 60-80% of entire stroke risk. Obstructive sleep apnea is one of the most prevalent diseases within the general population with an adjusted relative risk of 2.24(with 95% Cl) i.e., almost greater or equals to the traditional risk factors.[4] OSA is considered as an independent risk factor for the development of stroke.[9]

Obstructive Sleep Apnea (OSA) is characterized by intermittent hypoxia, autonomic fluctuations and recurrent complete and partial obstructive upper airway events resulting in sleep

fragmentation.[10] According to a study, the global prevalence and burden of obstructive sleep apnea includes 936 million of adults aged 30-69 yearsof age have mild to severe OSA and 425 million of 30-69 years of age have moderate to severe OSA. In this study India stands at 4th place with highest affected individuals in the country. According to their estimation nearly 1 billion adults aged 30-69 years globally could have Obstructive sleep apnea.[11]

The mechanism by which OSA causes stroke has not been fully explained. Certainly, traditional risk factors of stroke that includes hypertension, dyslipidemia, smoking, and diabetes are most prevalent but do not fully explain the stroke risk. OSAinduces acute and chronic pathogenic effects that have been proposed as an intermediateprocess that predispose to stroke. Acutely, OSA causes intermittent and recurrent hypoxia, repetitive awakening and creates intra thoracic pressure causing increased blood pressure and heart rate after apnea, increased sleep fragmentation and an intermittent decrease in cerebral blood flow. As a result of acute effects, there is a downstream cascade of side effects which includes arrhythmia, reactive oxidative stress, endothelial dysfunction, atherosclerosis, changes in cerebral blood flow, hypertension, autonomic dysfunction, hypercoagulability which may predispose to stroke. Other factors such as presence of patent foramen ovale may increase the risk ofstroke in OSA patients.[11]

We have conducted a case-control study to evaluate the risk of obstructive sleep apnea and sleep duration in occurrence of stroke within case and control group. The case group comprises of 263 stroke individuals. The control group number was matched with the case group irrespective of their demographics such as age group, BMI etc., and associated risk factors. This study includes the utilization of 3 questionnaires in which2 of them (Berlin and STOP-Bang questionnaires) were used to estimate the severity ofOSA within the population and the other (Epworth Sleepiness Scale-ESS) used to estimate the daytime sleepiness in the population which is a prime symptom of OSA. It also helped us to understand the sleep duration within the population. ESS states that the score is inversely associated with normal sleep cycle. It implies that sleep disturbance due to OSA may lead to daytime sleepiness by the possible factors such as repeated partial or complete apnea events leading to sleep fragmentation.

Most of the published data in this type of studies included a smaller number ofindividuals within the stroke population keeping the study specified to a particular typeof stroke. Our study population is of wide range on age basis (age group above 20). Thecase group consist of stroke patients irrespective of its type excluding stroke caused by trauma. This differentiates our study from other existing studies, making it unique. We've taken a specific population such that the case group were suffering from OSA.prior to their stroke occurrence which gives us insight upon their increased risk of strokeoccurrence due to Obstructive Sleep Apnea(OSA).

Methodology:

STUDY DESIGN:

It is a case-control study which includes stroke population as case group in Neurology department of Santhiram Medical College and General Hospital and theHealthy population as control group to study the impact of obstructive sleep apnea and sleep duration in occurrence of stroke.

METHODS OF DATA COLLECTION

The severity levels of OSA were estimated through Berlin Questionnaire, STOP- Bang Questionnaire, Epworth Sleepiness Scale.

SAMPLING TECHNIQUE

For Case group, the subjects for the study should be diagnosed to stroke.

For Control group, the selection of subjects for the study used a simple random sampling technique (probability sampling technique). In this sampling technique, every population has a similar chance to enrol in the study as the subject but they should be undiagnosed to stroke.

STASTICAL ANALYSIS:
This study uses Odds ratios for the estimation of risk associated between case and control groups. Case and control groups are divided into exposed and unexposed based upon their severity levels. Odds ratio was performed between these groups.

Logistic regression was used to determine the risk of stroke between comorbid groups. ROC curve was used to determine the sensitivity of the tools (questionnaires) utilized. Results were derived based upon these statistical analyses

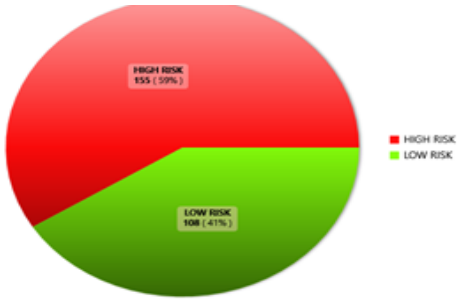
SAMPLING CRITERIA:
We have included stroke patients and healthy population with age group between 20-85 years who are diagnosed with stroke. Patients with cardiac diseases were excluded along with pregnant and lactating women also strokes caused by road traffic accidents.

Results:
This Case-Control study has a sample size of 526 in which the case group and control group have 263 each. The case group included 263 patients of cerebral stroke and the control group also includes 263 healthy population. The subjects of both case and control groups were asked to answer the OSA severity assessment scales (STOP- Bang Questionnaire, Berlin Questionnaire) and Epworth Sleepiness Scale. The case- group had a 62.7% of male population indicating that stroke was more prevalent in the male population compared to female population (37.3%). The control-group was matched similarly with percentage in terms of gender to the case-group.

Table.1.Age Wise distribution in Case and Control Groups:

Age	Male		Female		Total		Percentage (%)	
	Case	Control	Case	Control	Case	Control	Case	Control
21-30	01	04	01	01	02	05	01	02
31-40	12	15	06	10	18	25	07	09
41-50	29	27	12	21	41	48	16	19
51-60	50	43	29	31	79	74	30	28
61-70	45	39	28	17	73	56	28	23
71-80	23	29	17	19	40	48	15	17
81-85	05	05	05	02	10	07	03	02
TOTAL	165	162	98	101	263	263	100	100

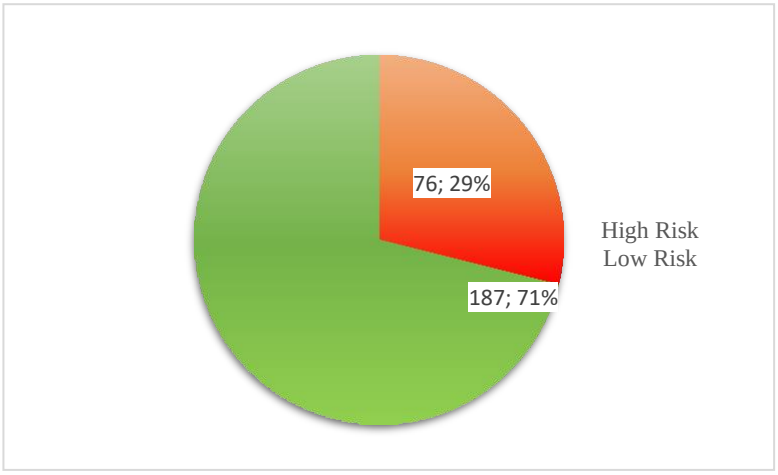
Berlin Questionnaire Results:
Berlin Questionnaire results in Case Group
Based on the scores given for individuals, Berlin questionnaire from case group revealed that 59% of the total cases group population were categorized under high-risk category and 41% of the case group population were grouped under low-risk category.Similarly, the results were interpreted from the control group population and two levels of risk categories were observed (low and high risk) in the control group.



The low risk population comprises of 71% of total control group and 29% of population were categorized under high risk.

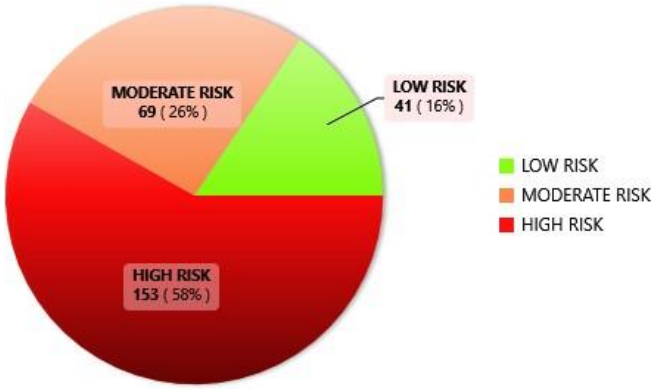
1.1.1. Berlin Questionnaire results in Control Group:

1.2. STOP-Bang Results:



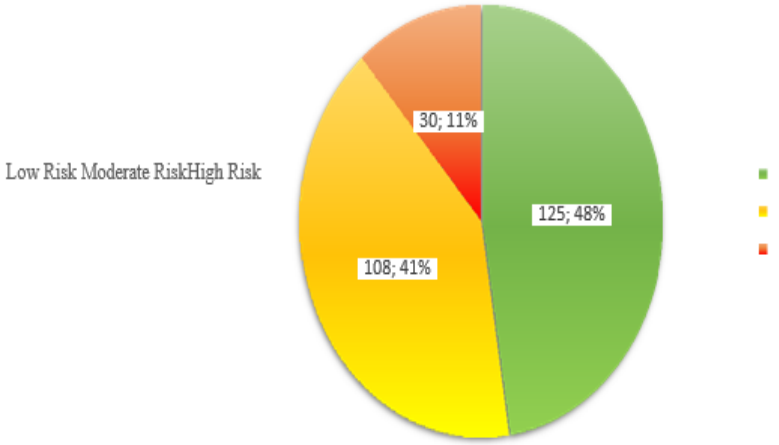
1.2.1. STOP-Bang results in Case group:

Based on the interpretation from STOP-Bang questionnaire 58% of case group population was grouped under high-risk category. The similarity of high risk of OSA



was found in both Berlin and STOP-Bang questionnaires(59%, 58%). Whereas the control-group population had a high risk of only 10% compared to that of case-group.

1.2.2. STOP-Bang results in Control group:



1.3. STATISTICAL ANALYSISOdd's Ratio

1.3.1. Odd's Ratio of population examined through Berlin questionnaire.

Outcome

Exposure		Yes	No	Total
Yes		155	76	231
	Row %	67.10%	32.90%	100.00%
	Col %	58.94%	28.90%	43.92%
No		108	187	295
	Row %	36.61%	63.39%	100.00%
	Col %	41.06%	71.10%	56.08%
Total		263	263	526
	Row %	50.00%	50.00%	100.00%
	Col %	100.00%	100.00%	100.00%

Odds-based Parameters

	Estimate	Lower	Upper
Odds Ratio	3.5313	2.4574	5.0745
MLE Odds Ratio (Mid-P)	3.5223	2.4557	5.0790
Fisher-Exact		2.4188	5.1611

Statistical Tests

	X^2	2 Tailed P
Uncorrected	48.1732	0.00000000
Mantel-Haenszel	48.0817	0.00000000
Corrected	46.9614	0.00000000

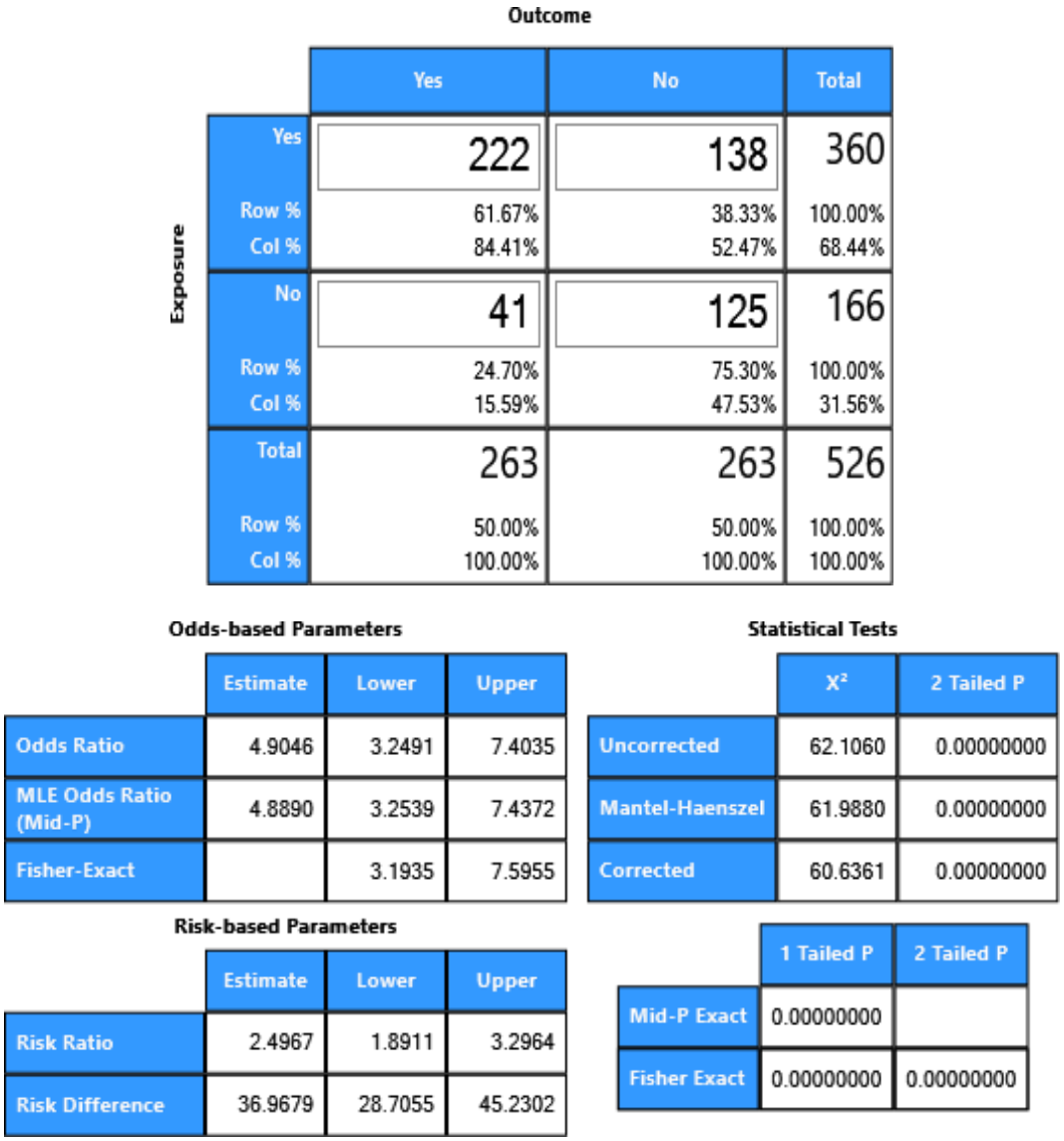
Risk-based Parameters

	Estimate	Lower	Upper
Risk Ratio	1.8328	1.5382	2.1838
Risk Difference	30.4894	22.3081	38.6707

	1 Tailed P	2 Tailed P
Mid-P Exact	0.00000000	
Fisher Exact	0.00000000	0.00000000

The case and control population were divided into Exposed and Un-exposed groups based on their severity levels. Odd's ratio analysis was performed between these groups. According to the results obtained through examining population through Berlin questionnaire, the population suffering from OSA had a 3.53 times chance of developing Stroke.

1.3.2. Odd's Ratio of population examined through STOP-Bang questionnaire



Outcome

Exposure		Yes	No	Total
Yes		222	138	360
	Row %	61.67%	38.33%	100.00%
	Col %	84.41%	52.47%	68.44%
No		41	125	166
	Row %	24.70%	75.30%	100.00%
	Col %	15.59%	47.53%	31.56%
Total		263	263	526
	Row %	50.00%	50.00%	100.00%
	Col %	100.00%	100.00%	100.00%

Odds-based Parameters

	Estimate	Lower	Upper
Odds Ratio	4.9046	3.2491	7.4035
MLE Odds Ratio (Mid-P)	4.8890	3.2539	7.4372
Fisher-Exact		3.1935	7.5955

Statistical Tests

	X^2	2 Tailed P
Uncorrected	62.1060	0.00000000
Mantel-Haenszel	61.9880	0.00000000
Corrected	60.6361	0.00000000

Risk-based Parameters

	Estimate	Lower	Upper
Risk Ratio	2.4967	1.8911	3.2964
Risk Difference	36.9679	28.7055	45.2302

	1 Tailed P	2 Tailed P
Mid-P Exact	0.00000000	
Fisher Exact	0.00000000	0.00000000

Similarly, the results obtained from examining the population through STOP-Bang questionnaire had an Odd's ratio of 4.90.

1.3.3. Summary of the odds ratio results obtained

Summary Results

Odds Ratio	Estimate	Lower	Upper
Crude (Cross Product)	3.6889	2.8518	4.7716
Crude (MLE)	3.6840	2.8511	4.7732
Fisher-Exact		2.8287	4.8127
Adjusted (MH)	4.0917	3.1191	5.3675
Adjusted (MLE)	4.0768	3.0876	5.4067

Risk Ratio	Estimate	Lower	Upper
Crude	1.9736	1.7066	2.2825
Adjusted	2.0796	1.7841	2.4240

Chi Square	X^2	1 Tailed P	2 Tailed P
Uncorrected (MH)	109.0554		0.0000000000
Corrected (MH)	107.7214		0.0000000000

The Crude (Cross Product) of both the result obtained was 3.68 (2.85,4.77). This indicates that a person suffering from OSA is at 3.68-fold risk of developing a stroke.

1.4. LOGISTIC REGRESSION

Logistic regression analysis was performed to examine the influenceof Snoring, BP, BMI, Age >50y, Neck circumference, Gender and ESS Analysis to predict Stroke.

1.4.1. Chi-Squared Test

Chi^2	df	p
176.42	7	<.001

Chi Squared test shows that the model as a whole is significant ($Chi^2(7) = 176.42$, $p < .001$, $n = 526$).

Table - Logistic Regression

Variables	Coefficient B	Standard error	z	p	Odds Ratio	95% conf. interval
Snoring	0.55	0.22	2.44	.015	1.73	1.11 - 2.68
BP	1.95	0.23	8.58	<.001	6.99	4.48 - 10.91
BMI						0.61 - 2.43
	0.2	0.35	0.56	.573	1.22	
				<.001	0.43	0.28 - 0.67
Age >50y	-0.84	0.23	3.73			
Neck Circumference	0.37	0.27	1.38	.168	1.45	0.86 - 2.44
Gender	0.05	0.22	0.23	.819	1.05	0.69 - 1.61
ESS Analysis	0.16	0.22	0.71	.48	1.17	0.75 - 1.82
Constant	-1.58	0.47	3.38	.001		

Logistic Regression showed that when the variable is BP, there is 6.99-fold riskof developing stroke. Whereas Snoring and Neck Circumference had an Odd's ratio of 1.73 and 1.45 respectively.

2. Conclusion:

The case group had a high severity towards OSA (58%) of which 75% was of male population. The case group, had a higher incidence of OSA (60% high- risk) compared to the control group. Incidence of abnormal sleep duration was equal in both groups. Population having Snoring and Hypertension had an increased probability of developing OSA compared to other co-morbid groups. Snoring and Hypertension were found to have potential in causing stroke, withan odd's ratio of 1.73 and 6.99 respectively. According to the results obtained, people suffering from OSA and abnormal sleep duration were at a 3.68-fold riskto develop a cerebral stroke.

References:

1. Mathur P, Rangamani S, Kulothungan V, Huliyappa D, Bhalla BB, Urs V. National Stroke Registry Programme in India for Surveillance and Research: Design and Methodology. Neuroepidemiology. 2020;54(6):454-461. doi: 10.1159/000510482. Epub 2020 Oct 19. PMID: 33075771.
2. Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India. J Stroke. 2013 Sep;15(3):128-34. doi: 10.5853/jos.2013.15.3.128. Epub 2013 Sep 27. PMID: 24396806; PMCID: PMC3859004.
3. Smajlović D. Strokes in young adults: epidemiology and prevention. Vasc Health Risk Manag. 2015 Feb 24; 11:157-64. doi: 10.2147/VHRM.S53203. PMID: 25750539; PMCID: PMC4348138.
4. Johnson KG, Johnson DC. When will it be time? Evaluation of OSA in stroke and TIA patients. Sleep Med. 2019 Jul; 59:94-95. doi: 10.1016/j.sleep.2018.10.016. Epub 2018 Oct 29. PMID: 30503686.
5. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB,Bravata DM, Dai S,

Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012 Jan 3;125(1):188-97. doi: 10.1161/CIR.0b013e3182456d46. Erratum in: Circulation. 2012 Jun 5;125(22): e1001. PMID: 22215894.

6. Carroll C, Hobart J, Fox C, Teare L, Gibson J. Stroke in Devon: knowledgewas good, but action was poor. J Neurol Neurosurg Psychiatry. 2004 Apr;75(4):567-71. doi: 10.1136/jnnp.2003.018382. PMID: 15026498;PMCID: PMC1739039.
7. Ho EL, Josephson SA, Lee HS, Smith WS. Cerebrovascular complications of methamphetamine abuse. Neurocrit Care. 2009;10(3):295-305. doi: 10.1007/s12028-008-9177-5. Epub 2009 Jan 9. PMID: 19132558.
8. Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. Stroke. 2008 Sep;39(9):2439-43. doi: 10.1161/STROKEAHA.107.510073. Epub 2008 Aug 14. PMID: 18703815; PMCID: PMC3564048.
9. Ponsaing LB, Lindberg U, Rostrup E, Iversen HK, Larsson HBW, Jennum P. Impaired cerebrovascular reactivity in obstructive sleep apnea: a case- control study. Sleep Med. 2018 Mar; 43:7-13. doi: 10.1016/j.sleep.2017.10.010. Epub 2017 Nov 15. PMID: 29482816
10. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N,Mehra R, Bozkurt B, Ndumele CE, Somers VK. Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement from the American Heart Association. Circulation. 2021 Jul 20;144(3): e56-e67. doi: 10.1161/CIR.0000000000000988. Epub 2021 Jun 21. Erratum in: Circulation. 2022 Mar 22;145(12): e775. PMID: 34148375.
11. Lyons OD, Ryan CM. Sleep Apnea and Stroke. Can J Cardiol. 2015 Jul;31(7):918-27. doi: 10.1016/j.cjca.2015.03.014. Epub 2015 Mar 14. PMID: 26112