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Association between Snoring and High-Risk Carotid Plaque Features

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Abstract

Objectives—Previous studies have demonstrated an association between snoring and carotid disease independent of sleep apnea. The aim of this study was to quantify the association between self-reported snoring and high-risk carotid plaque features on magnetic resonance imaging (MRI) that predict stroke.

Study design—Cross-sectional

Setting—Tertiary care university hospital and affiliated county hospital

Methods—We surveyed 133 subjects with asymptomatic carotid artery disease that had been previously evaluated with high-resolution MRI. The survey captured data on self-reported snoring (exposure) and covariates (age, sex, body mass index, and sleep apnea by the STOP-Bang questionnaire). A subset of patients underwent home sleep apnea testing. High-risk carotid plaque features were identified on the high-resolution MRI and included thin/ruptured fibrous cap and intraplaque hemorrhage (outcomes). We quantified the association between snoring and high-risk carotid plaque features with the chi-square test (unadjusted analysis) and multivariate logistic regression adjusting for the covariates.

Results—Sixty-one (46%) of 133 subjects surveyed responded; 32 (52%) reported snoring. Significantly higher proportions of snorers than nonsnorers had a thin/ruptured fibrous cap (56% vs. 25%, p=0.01) and intraplaque hemorrhage (63% vs. 29%, p<0.01). In multivariate analysis, snoring was associated with thin/ruptured fibrous cap (OR 4.4, 95% CI 1.1–16.6, p=0.04) and

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intraplaque hemorrhage (OR 8.2, 95% CI 2.1–31.6, p<0.01) after adjusting for age, sex, BMI, and sleep apnea.

Conclusion—This pilot study suggests a significant independent association between snoring and high-risk carotid plaque features on MRI. Further study is warranted to confirm these results in a larger cohort of subjects.

Keywords

snoring; sleep apnea; carotid; stroke; atherosclerosis; high-resolution MRI

Introduction

Carotid atherosclerosis is the primary etiologic factor in ischemic stroke, which is a leading cause of disability and death in the United States [1,2]. Several studies have reported an association between snoring and cerebrovascular pathology [3–11]. Most authors have attributed this finding to the overlap of snoring and obstructive sleep apnea (OSA), which is an independent risk factor for stroke [12–18].

Some research suggests that snoring may contribute to carotid disease independent of OSA. A recent meta-analysis demonstrated an increased relative risk of stroke in self-reported habitual snorers [19]. After adjusting for cardiovascular risk factors, Lee et al. found that heavy snoring (>50% of the night) was significantly associated with carotid but not femoral atherosclerosis in subjects with mild OSA [20]. Li et al. found a significant independent association between self-reported severe snoring (≥5 nights per week) and both carotid thickness and the presence of plaque on ultrasound [21]. In a population-based study by Olson et al., snorers without OSA had significantly higher odds of occlusive vascular disease than non-snorers [22].

Though there is evidence to support the association between snoring and carotid disease, the mediators of this association are unclear. Carotid atherosclerosis is an insidious process of lipid deposition, endothelial dysfunction and inflammation that results in vessel wall plaque formation and luminal stenosis [23]. Though degree of stenosis is the clinical measure of disease severity [24], the majority of ischemic cerebrovascular events occur in subjects with mild-to-moderate stenosis [25]. The majority of strokes arise from sudden rupture of the “vulnerable plaque” with consequent atheroembolization. Plaque vulnerability is not defined by size, but by thinning of the fibrous cap overlying the thrombogenic, lipid-rich necrotic core, often preceded by intraplaque hemorrhage [26]. High-resolution magnetic resonance imaging (MRI) has emerged as a tool capable of precisely measuring the carotid plaque composition in order to identify plaques most likely to rupture [27–29]. In a prospective cohort study of subjects with asymptomatic 50% to 79% stenosis, Takaya et al. found that plaques with intraplaque hemorrhage and thin/ruptured fibrous cap were 5 and 17 times more likely to develop subsequent cerebrovascular ischemia, respectively [28].

Plaque rupture results from a combined process of inflammation and biomechanical stress [30,31]. Studies of the impact of biomechanical stressors on vasculature have shown that vibration energy – including that produced by snoring – results in vasoconstriction,

sympathetic activation and endothelial damage [32–38]. In addition, vibration trauma may contribute to mechanical stress on the carotid wall, which predicts of plaque rupture [39,40]. Therefore, it is biologically plausible that snoring may be a risk factor for stroke through a mechanism of vibration trauma that is independent of the hypoxia and sympathetic activation that characterizes OSA.

The first aim of this study was to quantify the association between snoring and high-risk carotid plaque features on MRI. We hypothesized that there would be a significant association between self-reported snoring and high-risk carotid plaque as defined by 1) thin or ruptured fibrous cap, and 2) intraplaque hemorrhage, independent of age, sex, body mass index (BMI), and OSA (defined by STOP-Bang score ≥4). In addition, we hypothesized that those who snored more frequently and more loudly would have the highest percentages of high-risk MRI features. The second aim was to pilot objective measurement of OSA in the existing cohort of carotid MRI patients via home sleep apnea testing, in order to assess feasibility of home sleep apnea testing in this retrospective cohort and begin to estimate the objective prevalence and severity of OSA in this cohort.

Methods

Patients and recruitment

Sleep surveys were mailed to 133 subjects who had undergone high-resolution MRI of their carotid arteries. Subjects were part of a longitudinal cohort recruited 1) to identify MRI plaque characteristics predictive of stroke, and 2) to follow the natural history of carotid plaques on imaging [28,41,42]. Subjects with asymptomatic carotid stenosis by duplex ultrasound were recruited from the University of Washington Medical Center (UWMC) and affiliated hospitals. All subjects underwent baseline MRI at the UWMC Vascular Imaging Lab using a previously published protocol [28,43–45]. Images were analyzed by two experienced reviewers blinded to clinical information who identified areas of hemorrhage and categorized fibrous caps as either “thick” versus “thin or ruptured” using published, histologically validated criteria [43,46,47]. Subjects were excluded from the original cohort if they had contraindication to MRI, limited life expectancy, severe chronic illness or chronic disability, age <40 or >80 years, prior carotid surgery or neck radiation, history of transient ischemic attack (TIA) or stroke within the five years preceding the MRI, or pregnancy.

Subjects who had not withdrawn from the original cohort were contacted. Those willing to participate and able to give informed consent were included. This study was approved by the Institutional Review Board of the University of Washington.

Data Collection

Subjects completed the survey on paper or online via REDCap, a secure, web-based research application [48]. Subjects were encouraged to ask for help from a bed partner if available. Patients were asked to indicate on a Likert scale the frequency and severity of snoring at the time of their baseline study MRI (date of MRI provided as a reference). The sleep survey was administered between August 2013 and May 2015, whereas MRIs occurred between January 2000 and April 2015. Because some MRIs occurred years prior to the date of

survey, subjects were also asked to report on their snoring at the present time for use in a secondary analysis. Analysis of present snoring does not preserve the correct temporal relationship between snoring and outcome. However, we theorized that present snoring was likely to be more accurately recalled and could serve as a proxy for past snoring, as snoring is unlikely to change in late adulthood[49–51].

Embedded within the survey were questions required to calculate a STOP-Bang score for each subject. The STOP-Bang is an 8-item validated OSA screening instrument [52,53]. Subjects score one point for each item if they report snoring louder than talking, daytime sleepiness, observed apneas, hypertension, BMI > 35, age > 50, male sex, or neck circumference > 16 inches. A score of ≥4 was chosen *a priori* to identify subjects likely to have OSA, which corresponds to a 97% positive predictive value for having OSA (apnea hypopopnea index, AHI ≥ 5) [53].

Eighteen subjects (30%) did not report neck circumference, which was required to calculate STOP-Bang score. Twelve subjects had scores too high or too low for this missing variable to impact their classification of OSA at the predetermined cut off and as such they were included in the analysis. Due to the importance of STOP-Bang to the analysis, neck circumference was imputed for the remaining six using published data on the relationship between BMI and neck circumference [54]. This imputation resulted in an increase in STOP-Bang score from <4 to ≥4 in one subject. STOP-Bang score was not calculated for five subjects due to multiple missing variables.

Demographic and anthropomorphic data including age, sex, height, weight, blood pressure, and health history had been previously collected as part of the MRI cohort study. This occurred via standardized survey and/or direct measurement at the time of MRI.

Sleep testing

In order to pilot sleep testing for OSA in this cohort, a subset of subjects was administered home sleep apnea test using the Watch-PAT™. This is a validated, FDA-approved home sleep apnea test device that measures arterial tonography and oximitry to identify apneas and hypopneas[55]. The recording software automatically scores the data and provides a report and hypnogram with AHI (hypopneas include a 4% desaturation) and other sleep testing parameters. AHI was chosen as the primary OSA severity variable.

The recruitment goal was 20 subjects. Survey respondents living within one hour of UWMC were contacted by phone and offered home sleep apnea testing. The test was delivered to the subject's home and instruction provided by a member of the research team, who collected the device and downloaded the data when testing was complete.

Analysis

Statistical analysis was conducted with Stata/SE 13 software (StataCorp LP, College Station, Texas). Descriptive summaries for continuous variables are reported as means ± standard deviations, whereas frequencies are reported for categorical variables.

Subjects self-reported snoring, specifying frequency and loudness. Frequent snoring was defined as ≥ 5 nights per week [21]. Loud snoring was defined as snoring "louder than talking". Pearson's Chi-squared statistic or the Fisher exact test was used to test the association between any snoring, frequent snoring, and loud snoring with each of the two high-risk MRI plaque characteristics: 1) thin/ruptured fibrous cap and 2) intraplaque hemorrhage.

Multivariate logistic regression with robust standard errors was used to test the association between snoring and plaque characteristic adjusting for age, sex, BMI, and OSA. Subjects with a STOP-Bang score ≥4 were considered to have OSA for the purpose of this analysis.

A separate analysis was performed on the subset of patients in whom objective OSA data were obtained with home sleep apnea testing. Subjects with AHI ≥15 were considered to have OSA. This is a cutoff for moderate or greater OSA, which is associated with increased risk of stroke[15,17,18,56].

Results

Description of sample

Sixty-one (46%) of 133 subjects completed the survey. Forty-seven subjects did not respond, 22 (17%) actively declined, two (2%) were deceased and one (<1%) had advanced dementia.

Respondents were on average 68 years old and mildly overweight (Table 1). The majority was male and hypertensive. Thirty-two respondents (52%) reported snoring at the time of their MRI. Snorers did not differ significantly from nonsnorers with regard to age, sex, time between MRI and survey, BMI, hypertension and past stroke/TIA (Table 1, p>0.05).

Eight (13%) were frequent snorers (≥5 nights/week) and seven (12%) snored louder than talking. Twenty-nine subjects (48%) had OSA defined by a STOP-Bang score ≥ 4. A significantly higher percentage of snorers had OSA (79% vs. 21%, p<0.001). Twenty-four (39%) had help from a bed partner in answering the questions. There was no association between snoring and time between MRI and sleep survey (p > 0.05), but among those who had help from a bed partner, a larger proportion reported snoring than among those who did not have help (75% vs. 38%, p<0.01).

Twenty-five (41%) subjects had a thin/ruptured fibrous cap on MRI whereas 28 (46%) had intraplaque hemorrhage. Mean age was greater for those with thin/ruptured fibrous cap than without (71 vs. 66 years, p=0.03), but did not differ significantly for plaque hemorrhage (p>0.05). Mean BMI and average time between MRI and sleep survey did not differ significantly by either plaque feature (p>0.05).

Association between snoring and MRI plaque features that predict stroke

A significantly greater percentage of snorers than nonsnorers had a thin/ruptured cap and intraplaque hemorrhage (Table 2). When snoring was stratified by frequency, significant differences in MRI features were not seen. Thirty-eight percent of frequent snorers (≥ 5 nights/week) had thin/ruptured cap on MRI; however, this was lower than in those who

snored less frequently (Table 2). A similar pattern was observed for loudness, and also when the stratified snoring variables were tested for association with intraplaque hemorrhage (Table 2). Those with high-risk plaque features had higher percentages of OSA than those without, but these differences were not statistically significant (Table 2). This analysis was repeated for self-reported snoring at the time of the sleep survey and the results did not differ from past snoring at the time of MRI (data not shown).

Multivariate analysis

Multivariate logistic regression analysis was performed to test the association between snoring and each of the two plaque features, adjusting for covariates. Snorers had over four times the odds of having a thin/ruptured cap on MRI than nonsnorers, adjusting for age, sex, BMI and OSA (Table 3). The odds of intraplaque hemorrhage were eight times higher among snorers than nonsnorers, adjusting for age, sex, BMI and OSA (Table 3).

Home sleep apnea test subset

Of the 31 eligible respondents contacted, 18 (58%) agreed to undergo home sleep apnea testing. Of those, 17 completed testing and one was unable to sleep with the device. Subjects tested did not differ significantly from those not tested with regard to either plaque characteristic, demographics, snoring (overall, loudness or frequency), and STOP-Bang score (all $p < 0.05$). Those sleep tested had significantly less time between MRI and sleep survey than those not tested (mean 16 vs. 44 months, $p<0.01$).

Mean AHI was 14 events/hour (SD 13.7, range 2 – 55). Five (29%) subjects had an AHI ≥ 15, indicating moderate or severe OSA. Nine (53%) reported snoring at the time of MRI. One (6%) reported frequent snoring, and two (12%) loud snoring.

When the association between snoring and outcome was tested in the subset, a greater percentage of snorers than nonsnorers had thin/ruptured cap and intraplaque hemorrhage on MRI (Table 4). A higher percentage of those with AHI ≥ 15 had a thin/ruptured cap, but a lower percentage had intraplaque hemorrhage on MRI.

In order to control for OSA within this small subset, the association between snoring and plaque characteristics was estimated among the 12 subjects *without* high-risk OSA (all AHI < 15 on home sleep apnea testing). Higher percentages of high-risk plaque features were seen among snorers within this group, but these differences were not statistically significant (Table 5).

Discussion

In this sample of subjects with unique carotid phenotyping, self-reported snoring was significantly associated with two high-risk carotid plaque features on MRI that predict stroke. The odds of high-risk features were four to eight times higher in snorers than in nonsnorers of similar age, sex, BMI and OSA classified by STOP-Bang score. We piloted home sleep apnea testing in a subset in order to directly control for OSA. Within this under-powered pilot subset, the association between snoring and high-risk plaque features among those without high-risk OSA were in the same direction as in the overall sample.

We hypothesized that more severe snoring would be associated with high-risk plaque features. However, when snoring was stratified by frequency and loudness, the most severe snoring groups had percentages of high-risk plaque features that were lower than the less severe snoring groups. This finding could be due to misclassification of snoring severity, as snorers may not be able to accurately report how loud or frequently they snore. To evaluate this possibility post-hoc, we limited analysis to those who had help from a bed partner to classify their snoring and found the same overall pattern of results (data not shown).

Unlike the insidious process of lipid deposition and vessel inflammation that forms carotid plaque, hemorrhage and cap rupture are discrete events. There may be a threshold effect of snoring vibration on these specific features rather than a dose-response relationship. It is also possible that snoring severity may not be best quantified by loudness or time spent snoring. A recent study found that increased carotid thickness was associated with snoring at particular sound frequencies, which may be more important to carotid risk than loudness or duration of snoring [57].

There was not a significant association between high-risk plaque features and OSA whether defined by STOP-Bang ≥ 4 (within the greater cohort) or AHI ≥ 15 (pilot home sleep apnea test group). This study was not designed or powered to test the association between OSA and stroke; that relationship is well-established [58]. Small sample size limited the power to detect a significant association between plaque features and OSA within the sleep test pilot subgroup. However, point estimates obtained from this pilot suggest that a larger study may be worthwhile. Within the greater sample, the lack of association may have been due in part to misclassification of OSA. STOP-Bang score has been validated to classify risk of OSA but there is no cutoff to differentiate between mild and moderate OSA. Therefore, any cutoff will include some subjects with mild OSA, which has a weaker or no association with stroke[56,59]. Alternatively, cap rupture and intraplaque hemorrhage may be more prone to biomechanical stress (snoring vibration) than to oxidative stress (OSA). Though snoring and OSA impact the carotids by different mechanisms, there has been little investigation into the interaction between the two. A recent prospective study in women showed those with untreated versus CPAP-treated OSA had six times the risk of stroke, which was three fold higher than their risk of coronary heart disease [60]. Snoring may have been an unmeasured risk factor that contributed to the markedly elevated stroke risk. This is similar to the findings of Lee et al. who showed that heavy snoring was significantly associated with carotid but not femoral atherosclerosis in subjects *with OSA* [20]. The independent effects of treating snoring versus OSA on long-term stroke risk have not been tested.

This study has important limitations. As noted above, measuring snoring by self-report could have introduced exposure misclassification related to the inherent difficulty in recalling snoring at the time of MRI. To assist with recall as much as possible, subjects were provided with the date of their first MRI and were encouraged to ask for help from a bed partner. We could not go back to the time of baseline MRI and measure snoring objectively. Even if this was possible, objective snoring measured during sleep testing is vulnerable to changes in microphone direction, body position and background noise, and only provides a snapshot of a single night [57,61]. Ideally, objective snoring would be measured reliably and include accurate measures of loudness, pitch, energy, and tissue effect. Currently, self- and bed

partner-reported snoring is the most common and reliable measure used clinically and in the literature, and gives the best estimate of snoring exposure over time [3,4,8,11,62–65]. We collected data on current snoring patterns as a secondary predictor. These data were less prone to recall error, but they rely on the assumption that current snoring reflects past snoring. The overall reported rates of past and present snoring were similar and the results of the analysis of snoring at the two time points did not differ.

While our findings support amassing evidence for a causative relationship between snoring and carotid disease [19–21,37,38,65], other studies have not found a significant relationship between the two[62,66,67]. These studies vary in both how they define snoring and carotid disease. This is the first study to examine the relationship of snoring with specific high-resolution phenotyping of carotid disease highly predictive of stroke. The results of this pilot study provide a foundation for a larger-scale prospective study to further examine the relationships between snoring, OSA, carotid disease, and stroke. This has implications for how stroke risk is evaluated and treated. Snoring interventions may ultimately be indicated to prevent the progression of carotid atherosclerosis and stroke.

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References

1. Minino, A., Murphy, S., Xu, J., Kochanek, K. [Accessed Dec 23, 2013] Deaths: final data for 2008. National Vital Statistics Reports. 2011. http://www.ncbi.nlm.nih.gov/pubmed/22808755
2. Mozaffarian D, Benjamin EJ, et al. Writing Group M. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016; 133(4):e38–360. [PubMed: 26673558]
3. Partinen M, Palomaki H. Snoring and cerebral infarction. Lancet. 1985; 2(8468):1325–1326. [PubMed: 2866387]
4. Koskenvuo MKJ, Heikkilä K, Sarna S, Telakivi T, Partinen M. Snoring as a risk factor for ischemic heart disease and stroke in men. British medical journal (Clinical research ed). 1987; 294:643.
5. Spriggs DA, French JM, Murdy JM, Bates D, James OF. Historical risk factors for stroke: a case control study. Age Ageing. 1990; 19(5):280–287. [PubMed: 2251961]
6. Palomaki H. Snoring and the risk of ischemic brain infarction. Stroke; a journal of cerebral circulation. 1991; 22(8):1021–1025.
7. Palomaki HKM, Raininko R, Salonen O, Juvela S, Sarna S. Risk factors for cervical atherosclerosis in patients with transient ischemic attack or minor ischemic stroke disorders. Stroke; a journal of cerebral circulation. 1993; 24:970–5.
8. Smirne S, Palazzi S, Zucconi M, Chierchia S, Ferini-Strambi L. Habitual snoring as a risk factor for acute vascular disease. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 1993; 6(9):1357–1361.
9. Jennum P, Schultz-Larsen K, Davidsen M, Christensen NJ. Snoring and risk of stroke and ischaemic heart disease in a 70 year old population. A 6-year follow-up study. International journal of epidemiology. 1994; 23(6):1159–1164. [PubMed: 7721517]
10. Neau J, Meurice J, Paquereau J, Chavagnat J, Ingrand P, Gil R. Habitual snoring as a risk factor for brain infarction. Acta neurologica Scandinavica. 1995; 92(1):63–68. [PubMed: 7572063]

11. Hu FB, Willett WC, Manson JE, et al. Snoring and risk of cardiovascular disease in women. J Am Coll Cardiol. 2000; 35(2):308–313. [PubMed: 10676674]
12. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol. 2003; 41(9):1429–1437. [PubMed: 12742277]
13. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. The Lancet. 2005; 365(9464):1046–1053.
14. Yaggi H, Concato J, Kernan W, Lichtman J, Brass L, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. NEJM. 2005; 359(19):2034–2041.
15. Munoz R, Duran-Cantolla J, Martinez-Vila E, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke; a journal of cerebral circulation. 2006; 37(9):2317–2321.
16. Parati G, Lombardi C, Narkiewicz K. Sleep apnea: epidemiology, pathophysiology, and relation to cardiovascular risk. American journal of physiology. Regulatory, integrative and comparative physiology. 2007; 293(4):R1671–1683.
17. Bagai K. Obstructive sleep apnea, stroke, and cardiovascular diseases. The neurologist. 2010; 16(6):329–339. [PubMed: 21150380]
18. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. American journal of respiratory and critical care medicine. 2010; 182(2):269–277. [PubMed: 20339144]
19. Li M, Li K, Zhang X-W, Hou W-S, Tang Z-Y. Habitual snoring and risk of stroke: A meta-analysis of prospective studies. International Journal of Cardiology. 2015:185.
20. Lee S, Amis C, Byth K, et al. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep. 2008; 31(9):1207–1213. [PubMed: 18788645]
21. Li Y, Liu J, Wang W, et al. Association of self-reported snoring with carotid artery intima-media thickness and plaque. Journal of sleep research. 2012; 21(1):87–93. [PubMed: 21752134]
22. Olson LGKM, Hensley MJ, Saunders N. A community study of snoring and sleep-disordered breathing. American journal of respiratory and critical care medicine. 1995; 152(2):717–720. [PubMed: 7633732]
23. Ross R. Atherosclerosis--an inflammatory disease. The New England journal of medicine. 1999; 340(2):115–126. [PubMed: 9887164]
24. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. Stroke; a journal of cerebral circulation. 1999; 30(9):1751–1758.
25. Hatsukami TS, Yuan C. MRI in the early identification and classification of high-risk atherosclerotic carotid plaques. Imaging Med. 2010; 2(1):63–75. [PubMed: 20953294]
26. Davies M. Stability and instability: two faces of coronary atherosclerosis. Circulation. 1995; 94(8): 2013–2020.
27. Cai J-M, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation. 2002; 106(11):1368–1373. [PubMed: 12221054]
28. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke; a journal of cerebral circulation. 2006; 37(3):818–823.
29. Fabiano S, Mancino S, Stefanini M, et al. High-resolution multicontrast-weighted MR imaging from human carotid endarterectomy specimens to assess carotid plaque components. Eur Radiol. 2008; 18(12):2912–2921. [PubMed: 18751713]
30. Arroyo L, Lee R. Mechanisms of plaque rupture: mechanical and biologic interactions. Cardiovascular Research. 1999; 41(2):396–375.
31. Michel JB, Virmani R, Arbustini E, Pasterkamp G. Intraplaque haemorrhages as the trigger of plaque vulnerability. Eur Heart J. 2011; 32(16) 1977–1985, 1985a, 1985b, 1985c.
32. Bovenzi M, Griffin MJ, Ruffell CM. Vascular responses to acute vibration in the fingers of normal subjects. Cent Eur J Public Health. 1995; 3(Suppl):15–18. [PubMed: 9150959]

33. Bovenzi M, Lindsell CJ, Griffin MJ. Duration of acute exposures to vibration and finger circulation. Scand J Work Environ Health. 1998; 24(2):130–137. [PubMed: 9630061]
34. Bovenzi M, Lindsell CJ, Griffin MJ. Magnitude of acute exposures to vibration and finger circulation. Scand J Work Environ Health. 1999; 25(3):278–284. [PubMed: 10450780]
35. Bovenzi MLC, Griffin MJ. Response of finger circulation to energy equivalent combinations of magnitude and duration of vibration. Occupational and environmental medicine. 2001; 58(3):185–193. [PubMed: 11171932]
36. Curry BD, Govindaraju SR, Bain JL, et al. Evidence for frequency-dependent arterial damage in vibrated rat tails. Anat Rec A Discov Mol Cell Evol Biol. 2005; 284(2):511–521. [PubMed: 15791580]
37. Cho JG, Witting PK, Verma M, et al. Tissue vibration induces carotid artery endothelial dysfunction: a mechanism linking snoring and carotid atherosclerosis? Sleep. 2011; 34(6):751–757. [PubMed: 21629363]
38. Amatoury J, Howitt L, Wheatley JR, Avolio AP, Amis TC. Snoring-related energy transmission to the carotid artery in rabbits. J Appl Physiol (1985). 2006; 100(5):1547–1553. [PubMed: 16455812]
39. Tang D, Teng Z, Canton G, et al. Sites of rupture in human atherosclerotic carotid plaques are associated with high structural stresses: an in vivo MRI-based 3D fluid-structure interaction study. Stroke; a journal of cerebral circulation. 2009; 40(10):3258–3263.
40. Tang D, Teng Z, Canton G, et al. Local critical stress correlates better than global maximum stress with plaque morphological features linked to atherosclerotic plaque vulnerability: an in vivo multi-patient study. Biomed Eng Online. 2009; 8(15):15. [PubMed: 19650901]
41. Saam T, Underhill HR, Chu B, et al. Prevalence of American Heart Association type VI carotid atherosclerotic lesions identified by magnetic resonance imaging for different levels of stenosis as measured by duplex ultrasound. J Am Coll Cardiol. 2008; 51(10):1014–1021. [PubMed: 18325441]
42. Sun J, Canton G, Balu N, et al. Blood Pressure Is a Major Modifiable Risk Factor Implicated in Pathogenesis of Intraplaque Hemorrhage: An In Vivo Magnetic Resonance Imaging Study. Arterioscler Thromb Vasc Biol. 2016; 36(4):743–749. [PubMed: 26848155]
43. Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. Arterioscler Thromb Vasc Biol. 2005; 25(1):234–239. [PubMed: 15528475]
44. Balu N, Yarnykh VL, Chu B, Wang J, Hatsukami TS, Yuan C. Carotid plaque assessment using fast 3D isotropic resolution black-blood MRI. Magn Reson Med. 2011; 65:627–637. [PubMed: 20941742]
45. Wang J, Bornert P, Zhao H, et al. Simultaneous noncontrast angiography and intraplaque hemorrhage (SNAP) imaging for carotid atherosclerotic disease evaluation. Magn Reson Med. 2013; 69:337–345. [PubMed: 22442116]
46. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation. 2000; 102(9):959–964. [PubMed: 10961958]
47. Chu B, Kampschulte A, Ferguson MS, et al. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. Stroke; a journal of cerebral circulation. 2004; 35(5):1079–1084.
48. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009; 42(2):377–381. [PubMed: 18929686]
49. Fisher D, Pillar G, Malhotra A, Peled N, Lavie P. Long-term follow-up of untreated patients with sleep apnoea syndrome. Respiratory Medicine. 2002; 96(5):337–343. [PubMed: 12113384]
50. Ancoli-Israel S, Gehrman P, Kripke DF, et al. Long-term follow-up of sleep disordered breathing in older adults. Sleep medicine. 2001:2.
51. Berger G, Berger R, Oksenberg A. Progression of snoring and obstructive sleep apnoea: the role of increasing weight and time. The European respiratory journal. 2009; 33(2):338–345. [PubMed: 19010989]

52. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008; 108(5):812–821. [PubMed: 18431116]
53. Farney RJ, Walker BS, Farney RM, Snow GL, Walker JM. The STOP-Bang equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2011; 7(5):459–465B. [PubMed: 22003340]
54. Ben-Noun L, Sohar E, Loar A. Neck circumference as a simple screening measure for identifying overweight and obese patients. Obes Res. 2001; 9(8):470–477. [PubMed: 11500527]
55. Yalamanchali S, Farajian V, Hamilton C, Pott TR, Samuelson CG, Friedman M. Diagnosis of Obstructive Sleep Apnea by Peripheral Arterial Tonometry. JAMA otolaryngology-- head & neck surgery. 2013; 139(12):1343–1350. [PubMed: 24158564]
56. Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2014; 10(4):355–362. [PubMed: 24733978]
57. Lee GS, Lee LA, Wang CY, et al. The Frequency and Energy of Snoring Sounds Are Associated with Common Carotid Artery Intima-Media Thickness in Obstructive Sleep Apnea Patients. Sci Rep. 2016; 6:30559. [PubMed: 27469245]
58. Li M, Hou W-S, Zhang X-W, Tang Z-Y. Obstructive sleep apnea and risk of stroke: A meta-analysis of prospective studies. International Journal of Cardiology. 2014; 172(2):466–469. [PubMed: 24452224]
59. Palomaki H, Kaste M, Raininko R, Salonen O, Juvela S, Sarna S. Risk factors for cervical atherosclerosis in patients with transient ischemic attack or minor ischemic stroke disorders. Stroke; a journal of cerebral circulation. 1993; 24:970–975.
60. Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nunez N, Caballero-Martinez I, Catalan-Serra P, Almeida-Gonzalez CV. Role of sleep apnea and continuous positive airway pressure therapy in the incidence of stroke or coronary heart disease in women. American journal of respiratory and critical care medicine. 2014; 189(12):1544–1550. [PubMed: 24673616]
61. Maimon N, Hanly P. Does snoring intensity correlate with the severity of obstructive sleep apnea? Journal of clinical sleep medicine. 2010; 6(5):475–478. [PubMed: 20957849]
62. Mason RH, Mehta Z, Fonseca AC, Stradling JR, Rothwell PM. Snoring and severity of symptomatic and asymptomatic carotid stenosis: a population-based study. Sleep. 2012; 35(8): 1147–1151. [PubMed: 22851810]
63. Olson L, King M, Hensley M, Saunders N. A community study of snoring and sleep-disordered breathing. American journal of respiratory and critical care medicine. 1995; 152(2):717–720. [PubMed: 7633732]
64. Rich J, Raviv A, Raviv N, Brietzke SE. An epidemiologic study of snoring and all-cause mortality. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011; 145(2):341–346. [PubMed: 21493281]
65. Nagayoshi M, Tanigawa T, Yamagishi K, et al. Self-Reported Snoring Frequency and Incidence of Cardiovascular Disease: The Circulatory Risk in Communities Study (CIRCS). Journal of Epidemiology. 2012; 22(4):295–301. [PubMed: 22447210]
66. Yeboah J, Redline S, Johnson C, et al. Association between sleep apnea, snoring, incident cardiovascular events and all-cause mortality in an adult population: MESA. Atherosclerosis. 2011; 219(2):963–968. [PubMed: 22078131]
67. Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR. Snoring is not associated with all-cause mortality, incident cardiovascular disease, or stroke in the Busselton Health Study. Sleep. 2012; 35(9):1235–1240. [PubMed: 22942501]

Table 1

Characteristics of respondents overall and by self-reported snoring status (N=61)

	Snoring		All Respondents	
	No N=29	Yes N=32	N=61	
Variable	**Mean (SD) or %**	**Mean (SD) or %**	**Mean (SD) or N (%)**	**Missing N (%)**
Age at MRI (years)	68 (8)	68 (8)	68 (8)	0
Body mass index (kg/m^2)	25.1 (4.2)	26.6 (4.7)	25.9 (4.5)	0
Time to survey (months)	51 (52)	57 (48)	54 (50)	0
Male	42	58	43 (70)	0
Hypertension	43	57	49 (80)	3 (5)
Past stroke/TIA	30	70	10 (16)	2 (3)
Sleep apnea *	21	79	29 (48)	5 (8)
Help from partner	25	75	24 (39)	0
Frequent snoring **	0	100	8 (13)	4 (7)
Loud snoring **	0	100	7 (12)	3 (5)

TIA = transient ischemic attack; CPAP = continuous positive airway pressure

* Sleep apnea values include imputed data for five subjects.

** Frequent snoring defined as ≥ 5 nights/week; loud snoring defined as louder than talking.

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Table 2

Association between demographic and sleep characteristics of respondents and plaque features that predict stroke (N=61)

	Thin/ruptured Fibrous Cap					Intraplaque Hemorrhage				
	No N=36		Yes N=25			No N=33		Yes N=28		
Variable	**Mean (SD)**		**Mean (SD)**		**p**	**Mean (SD)**		**Range**		**p**
Age at MRI (years)	66 (1)		71 (2)		**0.03**	67 (1)		69 (2)		0.4
Body mass index (kg/m^2)	25.9 (4.8)		24.0 (5.2)		0.1	25.6 (5.1)		24.4 (5.0)		0.4
Time to survey (months)										
Variable	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**
Sex										
Female	13	72	5	28	0.2	14	78	4	22	**0.02**
Male	23	53	20	47		19	44	24	56	
Hypertension										
No	5	56	4	44	0.8	6	66	3	33	0.3
Yes	29	59	20	41		24	49	25	51	
Past stroke/TIA										
No	32	65	17	35	**0.04**	29	59	20	41	0.1
Yes	3	30	7	70		3	30	7	70	
Snoring										
No	22	76	7	24	**0.01**	21	72	8	28	**<0.01**
Yes	14	44	18	56		12	38	20	63	
Snoring frequency										
Nonsnorer	22	76	7	24	0.09	21	72	8	28	0.07
< 5 nights/week	9	45	11	55		8	40	12	60	
≥ 5 nights/week	5	62	3	38		4	50	4	50	
Snoring loudness										
Nonsnorer	22	76	7	24	**<0.01**	21	72	8	28	**0.01**
≤ talking	8	36	14	64		7	32	15	68	

	Thin/ruptured Fibrous Cap					Intraplaque Hemorrhage				
	No N=36		Yes N=25			No N=33		Yes N=28		
Variable	**Mean (SD)**		**Mean (SD)**		**p**	**Mean (SD)**		**Range**		**p**
> talking	6	86	1	14		5	71	2	29	
Sleep apnea										
No	20	74	7	26	0.08	16	59	11	41	0.6
Yes	15	52	14	48		15	52	14	48	

SD = standard deviation MRI = magnetic resonance imaging; TIA = transient ischemic attack; OSA = obstructive sleep apnea;

Table 3

Multivariate logistic regression analysis of the association between self-reported snoring and MRI plaque features that predict stroke (adjusted for age, sex, BMI, and OSA)

	Thin/ruptured Fibrous Cap			Intraplaque Hemorrhage		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Snoring	4.2	1.3–12.3	0.01	4.4	1.5–13.0	<0.01
Snoring and age	4.1	1.4–13.1	0.01	4.4	1.5–13.0	<0.01
Snoring and sex	3.8	1.2–11.4	0.02	4.0	1.3–12.3	0.02
Snoring and BMI	4.8	1.5–24.8	0.01	4.9	1.6–14.7	<0.01
Snoring and OSA	4.2	1.1–16.2	0.04	6.1	1.4–26.4	0.01
Snoring, age, sex, BMI, OSA	4.4	1.1–16.6	0.04	8.2	2.1–31.6	<0.01

MRI = magnetic resonance imaging; BMI = body mass index; OSA = obstructive sleep apnea; OR = odds ratio

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Table 4

Fisher's exact test of association between snoring and plaque features that predict stroke within subjects who underwent home sleep apnea testing (N=17)

	Thin/ruptured Fibrous Cap					Intraplaque Hemorrhage				
	No N=9		Yes N=8			No N=8		Yes N=9		
Variable	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**
Snoring										
No	5	63	3	37	0.4	5	63	3	37	0.2
Yes	4	44	5	56		3	33	6	67	
Sleep apnea (AHI>15)										
No	7	58	5	42	0.4	5	42	7	58	0.4
Yes	2	40	3	60		3	60	2	40	

AHI = apnea hypopnea index

Table 5

Fisher's exact test of association between snoring and plaque features that predict stroke among subjects with AHI < 15 on home sleep apnea testing (N=12)

	Thin/ruptured Fibrous Cap					Intraplaque Hemorrhage				
	No N=7		Yes N=5			No N=5		Yes N=7		
Variable	**n**	**%**	**n**	**%**	**p**	**n**	**%**	**n**	**%**	**p**
Snoring										
No	4	67	2	33	0.5	4	67	2	33	0.1
Yes	3	50	3	50		1	17	5	83	

AHI = apnea hypopnea index