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Association between monosodium glutamate intake and sleep disordered breathing among Chinese adults with normal body weight

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Abstract

Background and aims: To assess whether monosodium glutamate (MSG) intake is associated with sleep disordered breathing (SDB).

Methods: Data from 1227 Chinese who participated in the Jiangsu Nutrition Study (JIN) were analyzed. All the participants were examined at two time points (2002 baseline and 2007 follow-up). MSG intake was quantitatively assessed in 2002 and a sleep questionnaire was used to assess snoring, and to construct a SDB probability score in 2007. We define those within the fifth quintile of the score (highest) as having a high probability of SDB.

Results MSG intake was positively associated with snoring and high probability of SDB among participants with normal body weight but not overweight. Comparing extreme quartiles of MSG intake among people with BMI<23, the OR for snoring was 2.02 (95% confidence interval (CI): 1.02, 4.00), and the OR for a high probability of SDB was 3.11 (95% CI: 1.10, 8.84).There was a joint effect between MSG and overweight in relation to SDB.

Conclusion MSG intake may increase the risk of sleep disordered breathing among Chinese adults with normal body weight.

INTRODUCTION

Sleep-disordered breathing (SDB) encompasses a range of breathing abnormalities that occur during sleep, including obstructive sleep apnoea (OSA), central sleep apnoea and periodic breathing [1]. Snoring which may occur independently of OSA is a common manifestation of this disorder and prevalent in the general population worldwide [2, 3]. SDB is related to an increased risk of a range of diseases, including hypertension [4], diabetes [1, 5], metabolic syndrome [6], cardiovascular disease [7] and stroke [2].

Obesity is the most important risk factor for SDB; other possible lifestyle factors relating to SDB are smoking and alcohol drinking [2, 8]. Men have a higher risk of SDB than premenopausal, but not postmenopausal women [2, 8], suggesting that estradiol may be protective.

Monosodium glutamate (MSG) is a widely used flavour enhancer. In 1968, Kwok reported a possible link between MSG and “Chinese restaurant” syndrome including symptoms of numbness, weakness, and heart palpitations [9]. Since then, a range of studies have claimed an association between MSG and health outcomes, including asthma, diabetes, obesity, and allergic rhinitis [10-12]. Glutamate is an excitatory neurotransmitter that is intimately involved with sleep-wake states [13], and has been shown to activate a number of brain areas [14], for example the insular cortex, anterior cingulate gyrus, and amygdala [15] which play a crucial role in the central regulation of the autonomic nervous system. The insular cortex in particular is associated with the regulation of breathing during sleep [15]. The objective of this study was to assess the association of MSG intake with SDB based on a large population-based study in China, the Jiangsu Nutrition Study (JIN).

MATERIALS AND METHODS

Subjects

The JIN cohort study of persons aged 20 years or older and the methods of sampling have been described previously [16]. In 2002, 2849 adults aged 20 and above living in two cities and six rural areas took part in a Chinese National Nutrition and Health Survey. In 2002, information relating to food intake and sleep duration was obtained by questionnaire [17, 18]. In 2007, an attempt to re-contact all original participants was made. Some had either moved to other cities for temporary work or moved to other streets within the urban area. Therefore, of the original 2849 participants, 1682 were identified for follow-up. Overall, 1492 (52.3% of the original cohort) participated in the follow-up interview, and of these190 participants refused clinical evaluation, thus height and weight measurements were obtained from 1282 (45.0%). In addition 210 participants completed the interview at home but missed the measurement in the clinic. For the analysis we excluded those participants who had extreme values of weight change (i.e. > 20 kg, n=11), and those who had known diabetes, stroke, or cancer at baseline (n=40). Four participants also had missing values for MSG intake at baseline. The final sample size examined for weight change consisted of 509 men and 718 women (total n=1227). Compared with the retained participants, those lost to follow-up, were generally younger (45.5 vs 49.3 years) but there were no differences in the mean BMI or energy intake. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by Jiangsu Provincial Centre for Disease Control and Prevention. Informed consent was obtained from each participant.

Data collection and measurements

Participants were interviewed at their homes by health workers using a standard questionnaire in 2002 and 2007 [16]. The health workers were intensively trained in all aspects of data collection.

Outcome variables-Sleep Questionnaire at follow-up

In 2007, each participant was asked for information regarding their sleep. The sleep questionnaire was adopted from a Finnish questionnaire that has been used to screen for sleep disturbances and sleep apnoea [19]. The questionnaire was validated in Europe but not in China. The respondents were asked if their bedfellows had noticed breathing pauses during their sleep and subsequently these were classified as 'witnessed apnoeas'. Additionally, the following three questions were recorded in a five point scale (0 = 'never', 1 = 'seldom', 2 = 'sometimes', 3='often' and 4 = 'very often'): (i) How often do you wake up during the night? (ii) Do you feel excessively sleepy during the daytime? (iii) Do you fall asleep involuntarily during the daytime? Snoring was assessed by question "Do you snore loudly? 1) no 2) yes 3) do not know". A positive answer was defined as snoring and given a score of 2, while a negative answer was given a score of 0. The answers to these questions demonstrated possible sleep disturbances among the study subjects. The sum of the four questions was calculated, in order to detect an SDB probability score (0-14 points). We define those within the fifth quintile of the score (highest) as high probability for SDB (SDB probability score ≥5). In our study population the SDB score was much lower than the Finnish population, thus we decided to use a lower cut-off than the one used by Tumilehto et al [19].

At both baseline and follow up, sleep duration was established by the question "how many hours do you usually sleep each day?".

Dietary intake: In 2002, dietary intake patterns during the previous year were investigated by a series of detailed questions about the usual frequency and quantity of intake of 33 food groups and beverages. The food frequency questionnaire (FFQ) has been validated [20] and reported to be a useful method for the collection of individual food consumption information in face-to-face interviews, but not in self-administered surveys, due to the current educational level of the majority of the Chinese population.

Exposure variable- Baseline MSG intake

To determine the amount of MSG and other seasonings consumed by individuals, each household was specifically asked about their usual monthly consumption of these items. Individual consumption of MSG was calculated according to the total amount of MSG consumed in the household divided by the number of individuals per household and then adjusted for the proportion of the household energy intake energy consumed by each individual. Average total glutamate intake was also calculated by adding the glutamate concentrations of all foods/seasonings consumed by an individual per day. Nutrient (e.g. sodium, potassium, fibre) and vegetable oil intakes were assessed using a 3-day weighed food diary which recorded all foods consumed by each individual, on three consecutive days; this was done to confirm the intakes reported from the FFQ data. We did not consider under- and over-report of energy intake to be an issue, because upon reviewing the food diaries with the subjects, the health workers would clarify any intake value for a particular food that fell below or above the usual value reportedly consumed by the population within the region. Not everyone was asked for dietary information at follow up (FFQ was only used among those 15 years and above) however the household MSG intake was determined, thus mean household MSG intake was calculated. Food consumption data were analyzed using the Chinese Food

Composition Table. In the current analysis, energy and nutrient intake was calculated using a 3-day weighted food diary.

Dietary patterns: Dietary patterns were identified by factor analysis based on food intake measured by the food frequency questionnaire (FFQ), using standard principal component analysis as described elsewhere. [17] In short, four food patterns were obtained - Factor 1 (‘macho’) was characterized by various kinds of animal foods and alcohol, i.e. foods commonly consumed by men; Factor 2 (the ‘traditional’ pattern) loaded heavily on rice, fresh vegetables and inversely on wheat flour; Factor 3 (‘sweet tooth’) contained cake, milk, yoghurt and drinks; and Factor 4 (‘vegetable rich’ pattern) included whole grains, fruits, root vegetables, fresh and pickled vegetables, milk, eggs and fish. The four factors explained 28.5% of the variance in intake.

Other lifestyle factors: Cigarette smoking was assessed by asking the frequency of daily cigarette smoking. Information on passive smoking was asked. Eating out was assessed by asking whether individuals ate out on a frequent basis and was coded as yes or no. Alcohol consumption was assessed by asking the frequency and amount of alcohol consumed. Questions on daily commuting were grouped into three categories - (1) using motorized transportation, or no work (0 minute of walking or cycling), (2) walking or bicycling 1-29 minutes, and (3) walking or bicycling for ≥ 30 minutes. Daily leisure time physical activity was grouped into three categories: 0, 1-29, and ≥ 30 minutes. Time spent on sedentary activities each day (viewing television, operating computer, playing video games and reading during leisure time) was classified into four categories: <1, 1-1.9, 2-2.9, and ≥3 hours. Education was recoded into either ‘Low’ (illiteracy, primary school); ‘Medium’ (junior middle school); or, ‘High’ (high middle school or higher), based on six categories of education levels in the questionnaire.

Occupation was recoded into 'Manual' or 'Non-manual' based on a question with 12 occupational categories. Antihypertensive medication use (yes/no) was asked at baseline and follow-up.

Anthropometric measurements: In both 2002 and 2007, anthropometric measurements were obtained using standard protocols and techniques. Body weight was measured in light indoor clothing without shoes to the nearest 100 grams. Height was measured without shoes to the nearest mm using a stadiometer. Overweight was defined as BMI $\geq$23 Kg/m^2 .Waist circumference was measured to the nearest mm midway between the inferior margin of the last rib and the crest of the ilium, in the mid-axillary line in a horizontal plane. Blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the subject, who was seated for 5 min before the measurement. The mean of these two measurements was used in the analyses. Hypertension was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg, or using antihypertensive drugs.

Statistics

MSG intake was recoded into quartiles. Chi square tests were used to compare the difference between categorical variables, and ANOVA was used to compare differences in continuous variables between groups. Multilevel logistic regression was used to determine the association between MSG intake (quartiles) and snoring and high probability for SDB adjusted for age, education, occupation, active commuting, leisure time physical activity, smoking, passive smoking, alcohol drinking, eating out, overweight, and energy intake. These multivariate models were adjusted for household cluster using the xtmelogit command. We tested for linear trend across categories of

MSG intake by assigning each participant the median value for the category and modelling this value as a continuous variable. Food patterns were also put into the multivariate models to control for the residual confounding. Hypertension was not adjusted in the multivariate analysis because of its collinearity with overweight. All the analyses were performed using STATA 11 (Stata Corporation, College Station). Multiplicative interaction between MSG intake and sex/hypertension was tested using the likelihood ratio test by adding the product of MSG intake and sex/hypertension in the multivariate model. Statistical significance was considered to be when $p < 0.05$ (two sided).

RESULTS

The mean intake of MSG for the entire population was 3.8 g/day (SD, 4.3). Of the 1227 participants, 72 reported no use of MSG and the median intakes across the quartiles were 0.8, 2.0, 3.7 and 6.9 g/d, respectively. Table 1 shows the cross-sectional associations between MSG intake, nutrients and specific food items or food groups. MSG intake was positively associated with fat intake ($P < 0.001$) but inversely associated with carbohydrate intake ($P < 0.001$). No significant difference in energy and protein intake was found across MSG intake quartiles. Total glutamate was the same in quartiles one to three but was on average 37% greater in quartile four ($P < 0.001$). At baseline, the overall prevalence of overweight/obesity (BMI ≥ 23 kg/m2) was 51.3%. MSG intake was inversely related to BMI and central obesity at baseline.

Of the sample, 36% reported snoring (52.4% in men, 25.7% in women), and 3.6% had witnessed apnoea (5.5% in men, 2.3% in women). Across the quartiles of MSG intake, the prevalence of snoring increased from 46.5% to 54.0% in men (p=0.110), 18.1% to 28.2% in women (p=0.024), 27.5% to 42.0% in gender combined (p<0.001). Both the mean SDB probability score and the percentage of high SDB probability score increased with increased MSG intake. No association between MSG intake and witnessed apnoea was found. At baseline, high MSG intake was associated with short sleep duration (Table 2).

In multivariate analyses adjusting for age, gender, overweight/obesity, lifestyle factors as well as dietary factors including dietary patterns (Table 3), baseline MSG intake was positively associated with snoring at follow up. Comparing the extreme quartiles of MSG intake, the OR for snoring was 1.91(95% CI: 1.16, 3.17), and the OR for a high probability of SDB was 2.40(1.22, 4.58). A positive association between total glutamate intake and snoring and a high probability of SDB was found (data not shown). Overweight/obesity was positively associated with both snoring and SDB in multivariate analysis (data not shown). Stratified analyses showed a significant positive association between MSG intake and snoring and high probability of SDB among participants with normal BMI. Across the quartiles of MSG intake, among participants with normal BMI, the OR's were 1, 1.10 (0.56, 2.20), 2.19(1.10, 4.36) and 2.02(1.02, 4.00) for snoring; 1, 1.31(0.49, 3.52), 1.65(0.58, 4.63), and 3.11(1.10, 8.84) for a high probability of SDB. These associations were not statistically significant among participants with BMI≥23.

A joint effect between MSG intake and overweight in relation to snoring and a high probability of SDB was also found (Figure 1). In this case, overweight was positively associated with snoring and a high probability of SDB.

No significant interaction between MSG intake and sex or hypertension was found (data not shown). Among those who reported taking hypertensive medication (n=215), there was no association between MSG intake and snoring or high probability for SDB (data not shown).

DISCUSSION

In this study, we found a positive association between the intake of MSG at baseline and snoring and SDB at follow up among Chinese adults with normal body weight. There was a significant additive interaction between overweight and MSG intake in relation to snoring and SDB. There was a similar association between total glutamate intake and snoring and SDB. To our knowledge, this is the first population study to report an association between MSG intake and SDB.

The prevalence of snoring (36%) in our sample is consistent with that of other studies in China, although because of age related differences in the cohorts studied, and the increase in snoring with increasing age, direct comparison is not possible. In the Guangzhou Biobank Cohort Study, 80.0% of the Chinese participants aged 50-85 years reported snoring [7], while the prevalence of snoring was 23% among men living in Hong Kong with a mean age of 41 years [3]. The prevalence of OSA in the Chinese population is lower than Western populations [3]. In our study, the proportion of 'witnessed apnoea' is much lower than in Finland [19].

Apart from anatomical abnormalities of the upper airway, and severe obesity, there are other factors that may also play a role in the genesis of SDB including upper airway dilator muscle dysfunction, lung capacity and instability in breathing control [21]. MSG has been shown to induce activation of vagal pathways via glutamate receptors in the proximal gastrointestinal tract, and to modify gut motility [22]. Gastroesophageal reflux disease (GERD) has been found to be associated with OSA [23] A study in Shanghai showed that the prevalence of GERD in adults, defined as heartburn and/or regurgitation of any frequency during the previous week, was 6.2% [24]. Several large population studies in China found an association between GERD and sleep disorders [25]. Heartburn is a common complaint in relation to the "Chinese Restaurant Syndrome" [26] and given the effects of MSG on gastro-intestinal motility it possible that increased reflux is a mediating factor. Interestingly ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, has been found to be effective in the treatment of GERD [27].

An association between MSG intake and chronic rhinitis has been described in a single case report [28]. We do not have information on rhinitis in this study, but the prevalence of allergic rhinitis in the study area is about 10% [29]. Whether rhinitis mediates the effect of MSG on SDB remains to be determined.

The relationship between body weight, MSG and SDB is complex. Consistent with current knowledge, overweight/obesity was positively associated with SDB in our sample. We found a strong positive association between MSG and SDB in lean individuals. Using the group with normal weight and low MSG intake as reference, those who were overweight and had high intake of MSG had in general a higher risk of SDB. However, in stratified analysis, using overweight and low MSG intake as reference, the association between MSG intake and SDB among overweight group became marginally significant (p for trend=0.141). This discrepancy may suggest that unmeasured confounding factors exist. An inverse association between MSG intake and BMI/central obesity at baseline was also noted and this suggests the relationship between MSG and SDB may occur through other mechanisms and not be dependent on the presence (or absence) of obesity. Despite the difference in reported prevalence of snoring between genders, there was no interaction between gender and MSG intake.

The main limitation of this study is the use of self-reported sleep data instead of the more valid polysomnographic method to confirm the diagnosis of SDB. However, questionnaires have previously been found to be useful and are widely accepted in detecting and screening for SDB in large epidemiological studies [19]. Although the measurement of sleep data was only done in the follow up and a causal relationship cannot be established, a high proportion of those with snoring or SDB could be expected to be new cases as the development of snoring and SDB is higher before the age 65 years. Another limitation is the measurement of MSG consumption was determined by the total amount of MSG consumed in the household divided by the number of individuals per household and then adjusted for the proportion of the household energy intake energy. This method may under or overestimate MSG intake, although in a large epidemiological study, this would be the most practical way of measuring MSG consumption. Other limitations include the inability to account for a change in MSG consumption during the 5 year follow-up period. Data from the China Health and Nutrition Survey (CHNS) showed that since 2000 the MSG intake in China has decreased: the median intake of MSG was 5.4, 5.9, 4.7, 4.7 g in 1997, 2000, 2004, and 2006 respectively among those high MSG consumers (fifth quintile of MSG intake) [30]. This trend could be due to the public awareness of the effects of MSG intake on health outcomes. The association between MSG intake and SDB in our study will be underestimated if those with high intake of MSG decreased their intake during the follow up. The high rate of lost to follow up may introduce bias and limit the power to generalize the findings.

Nevertheless, the strength of the observation that a high MSG intake is positively associated with SDB in a large population study in Chinese adults with normal body weight, and the joint effect of MSG intake and overweight in relation to snoring and high probability for SDB is of potential public health importance and warrants further examination.

Authorship

ZS had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ZS devised the study concept; ZS, BY, YD, and HZ acquired the data; ZS conducted the statistical analysis and drafted the manuscript; GAW, BY, YD, TKG, GH, RA, HZ, and AWT critically revised the manuscript for important intellectual content.

Guarantor: Shi Z

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DISCLOSURE STATEMENT

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Reference:

[1] Shaw JE, Punjabi NM, Wilding JP, Alberti K, Zimmet PZ. Sleep-disordered breathing and type 2 diabetes - A report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract. 2008;81:2-12.

[2] Punjabi NM. The Epidemiology of Adult Obstructive Sleep Apnea. Proc Am Thorac Soc. 2008;5:136-43.

[3] Ip MSM, Lam B, Lauder IJ, Tsang KWT, Chung KF, Mok YW, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest. 2001;119:62-9.

[4] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342:1378-84.

[5] Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: A prospective study. Am J Epidemiol. 2002;155:387-93.

[6] Angelico F, del Ben M, Augelletti T, de Vita R, Roma R, Violi F, et al. Obstructive sleep apnoea syndrome and the metabolic syndrome in an internal medicine setting. Eur J Intern Med. 2010;21:191-5.

[7] Thomas GN, Jiang CQ, Lao XQ, McGhee SM, Zhang WS, Schooling CM, et al. Snoring and vascular risk factors and disease in a low-risk Chinese population: The Guangzhou Biobank Cohort Study. Sleep. 2006;29:896-900.

[8] Young T, Peppard PE, Gottlieb DJ. Epidemiology of Obstructive Sleep Apnea: A Population Health Perspective. Am J Respir Crit Care Med. 2002;165:1217-39.

[9] Kwok RHM. Chinese-restaurant syndrome. N Engl J Med. 1968;278:796.

[10] Beyreuther K, Biesalski HK, Fernstrom JD, Grimm P, Hammes WP, Heinemann U, et al. Consensus meeting: monosodium glutamate - an update. Eur J Clin Nutr. 2007;61:304-13.

[11] Williams AN, Woessner KM. Monosodium glutamate 'allergy': menace or myth? Clin Exp Allergy. 2009;39:640-6.

[12] He K, Zhao L, Daviglus ML, Dyer AR, Van Horn L, Garside D, et al. Association of Monosodium Glutamate Intake With Overweight in Chinese Adults: The INTERMAP Study. Obesity. 2008;16:1875-80.

[13] Burgess C, Lai D, Siegel J, Peever J. An endogenous glutamatergic drive onto somatic motoneurons contributes to the stereotypical pattern of muscle tone across the sleep-wake cycle. J Neurosci. 2008;28:4649-60.

[14] Kitamura A, Sato W, Uneyama H, Torii K, Niijima A. Effects of intragastric infusion of inosine monophosphate and L: -glutamate on vagal gastric afferent activity and subsequent autonomic reflexes. J Physiol Sci. 2011;61:65-71.

[15] Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J Am Soc Hypertens. 2010;4:174-82.

[16] Shi Z, Luscombe-Marsh ND, Wittert GA, Yuan B, Dai Y, Pan X, et al. Monosodium glutamate is not associated with obesity or a greater prevalence of weight gain over 5 years: findings from the Jiangsu Nutrition Study of Chinese adults. Br J Nutr. 2010;104:457-63.

[17] Shi Z, Hu X, Yuan B, Hu G, Pan X, Dai Y, et al. Vegetable rich food pattern is related to obesity in China. Int J Obes (Lond). 2008 32:975-84.

[18] Shi Z, McEvoy M, Luu J, Attia J. Dietary fat and sleep duration in Chinese men and women. Int J Obes. 2008;32:1835-40.

[19] Tuomilehto H, Peltonen M, Partinen M, Seppä J, Saaristo T, Korpi-Hyövälti E, et al. Sleep-disordered breathing is related to an increased risk for type 2 diabetes in middle-aged men, but not in women- the FIN-D2D survey. Diabetes Obes Metab. 2008;10:468-75.

[20] Zhao W, Hasegawa K, Chen J. The use of food-frequency questionnaires for various purposes in China. Public Health Nutr. 2002;5:829-33.

[21] Owens RL, Eckert DJ, Yeh SY, Malhotra A. Upper airway function in the pathogenesis of obstructive sleep apnea: a review of the current literature. Curr Opin Pulm Med. 2008;14:519-24.

[22] Toyomasu Y, Mochiki E, Yanai M, Ogata K, Tabe Y, Ando H, et al. Intragastric monosodium L-glutamate stimulates motility of upper gut via vagus nerve in conscious dogs. Am J Physiol Regul Integr Comp Physiol. 2010;298:R1125-35.

[23] Jung HK, Choung RS, Talley NJ. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications. J Neurogastroenterol Motil. 2010;16:22-9.

[24] Ma XQ, Cao Y, Wang R, Yan X, Zhao Y, Zou D, et al. Prevalence of, and factors associated with, gastroesophageal reflux disease: a population-based study in Shanghai, China. Dis Esophagus. 2009;22:317-22.

[25] Chen MJ, Wu MS, Lin JT, Chang KY, Chiu HM, Liao WC, et al. Gastroesophageal reflux disease and sleep quality in a Chinese population. J Formos Med Assoc. 2009;108:53-60.

[26] Lacy BE, Weiser K, Chertoff J, Fass R, Pandolfino JE, Richter JE, et al. The Diagnosis of Gastroesophageal Reflux Disease. Am J Med. 2010;123:583-92.

[27] Keywood C, Wakefield M, Tack J. A proof-of-concept study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in gastro-oesophageal reflux disease. Gut. 2009;58:1192-9.

[28] Asero R, Bottazzi G. Chronic rhinitis with nasal polyposis associated with sodium glutamate intolerance. Int Arch Allergy Immunol. 2007;144:159-61.

[29] Han DM, Zhang L, Huang D, Wu YF, Dong Z, Xu G, et al. Self-reported prevalence of allergic rhinitis in eleven cities in China. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2007;42:378-84.

[30] He K, Du S, Xun P, Sharma S, Wang H, Zhai F, et al. Consumption of monosodium glutamate in relation to incidence of overweight in Chinese adults: China Health and Nutrition Survey (CHNS). Am J Clin Nutr. 2011;93:1328-36.

Figure legend

Figure 1: Joint effects of MSG intake and overweight in relation to a) snoring b) high probability for SDB. OR adjusted for variables in model 2 of Table 3. * $p<0.05$, ** $p<0.01$.

Table 1 Baseline Sample Characteristics According to MSG Intake Quartiles among Chinese Adults [a]

	Q1 (low), 0.8 g/day (median) N = 307	Q2, 2.0 g/day N =307	Q3, 3.7 g/day N =307	Q4 (high), 6.9 g/day N =306	*P* [b]
Energy (kJ/day) [c]	9706(142)	9898(142)	9643(142)	9765(146)	0.638
Fat (g/day) [d]	73.9(1.4)	81.3(1.4)	84.5(1.4)	86.7(1.4)	<0.001
Protein (g/day) [d]	72.1(0.8)	72.2(0.8)	72.6(0.8)	72.4(0.8)	0.974
Carbohydrate (g/day) [d]	336.5(3.4)	321.0(3.4)	310.4(3.4)	300.6(3.4)	<0.001
Fiber (g/day) [d]	16.0(0.5)	11.8(0.5)	9.0(0.5)	9.5(0.5)	<0.001
Glutamate (g/day) [d]	14.2(0.3)	14.0(0.3)	13.9(0.3)	19.2(0.3)	<0.001
Vegetables (g/day) [c]	259(9)	256(9)	259(9)	264(9)	0.946
Fruits (g/day) [c]	57(5)	57(5)	54(5)	59(5)	0.914
Alcohol intake (g/day)	1.8(0.3)	1.7(0.3)	1.7(0.3)	1.9(0.3)	0.954
Men (%)	33.2	35.2	44.0	53.6	<0.001
Age (years)	48.2(0.8)	50.0(0.7)	49.6(0.8)	48.2(0.7)	0.200
Urban (%)	24.8	16.9	4.2	6.5	<0.001
Weight (kg) [c]	60.3(0.5)	60.4(0.5)	59.5(0.5)	58.5(0.5)	0.045
Waist circumference (cm) [c]	79.8(0.5)	79.3(0.5)	78.4(0.5)	76.9(0.5)	0.001
Central obesity (%) [e]	36.6	32.9	27.8	21.2	<0.001

Obesity (%) (BMI≥28 kg/m^2)	12.4	10.1	8.1	5.2	0.016
Overweight/obesity (%)(BMI≥23 kg/m^2)	53.4	53.8	55.1	43.1	0.011
BMI (kg/m^2) [c]	23.6(0.2)	23.6(0.2)	23.4(0.2)	22.9(0.2)	0.016
Hypertension (%)	30.9	32.3	31.6	26.1	0.339
Low Education (%)	58.0	55.1	53.4	46.1	0.005
Manual job (%)	56.4	53.1	50.8	47.4	0.154
Active commuting (%)					
None	37.1	39.4	39.1	46.4	
1-29 minutes/day	46.3	48.2	51.5	48.7	<0.001
≥30 minutes/day	16.6	12.4	9.5	4.9	
No leisure time physical activity	89.9	90.2	92.2	94.4	0.130
Sedentary activity ≥3 hr/day (%)	9.1	11.7	9.5	17.0	<0.001
Smoker (%)	23.1	21.2	28.7	36.0	<0.001
Alcohol drinker (%)	19.2	19.9	26.1	34.0	<0.001

Abbreviations: BMI, body mass index; MSG, Monosodium Glutamate. Q1-4, quartiles 1-4.

[a] values are mean (SE), or percentage (%).

[b] p values were generated by chi-squared test for categorical variables and ANOVA test for continuous exposures.

[c] Adjusted for age and sex.

[d] Adjusted for age and sex and energy intake.

[e] Defined as waist circumference: men ≥90 cm, women ≥80 cm.

Table 2 Association between Baseline MSG Intake (Quartiles) and Sleep Related Measurements among Chinese Adults in Jiangsu Nutrition Study (n=1227)

	MSG intake quartiles in 2002				
	Q1(0.8 g/day)[a]	Q2 (2.0 g/day)	Q3(3.7 g/day)	Q4(6.9 g/day)	*P* [b]
Sleep categories (baseline) (h/d) (%)					
7-8	68.8	63.2	70.7	71.2	
<7	9.2	13.2	12.5	17.1	0.001
≥9	22.0	23.7	16.8	11.8	
Sleep categories at follow up (h/d) (%)					
7-8	71.7	62.4	65.9	72.2	
<7	16.6	20.9	20.7	16.3	0.123
≥9	11.7	16.7	13.4	11.4	
Snoring (%)					
Men	46.5	46.3	59.7	54.0	0.110
Women	18.1	27.4	30.8	28.2	0.024
Both genders	27.5	34.1	43.5	42.0	<0.001
Witnessed apnoea (%)	2.3	4.6	3.6	3.9	0.488
High probability for SDB (%)	15.1	19.1	20.7	25.9	0.010
Mean probability for SDB score					
mean	2.2	2.4	2.7	3.1	<0.001
SD	2.3	2.4	2.1	2.2	

Abbreviations: MSG, Monosodium Glutamate; SDB, sleep disordered breathing; SD, standard deviation. Q1-4, quartiles 1-4.

[a] Median MSG intake with quartile.

[b] *P* values were generated by chi-squared test for categorical variables and ANOVA test for continuous exposures.

Table 3 Odds ratio (95%CI) for Snoring and SDB According to Monosodium Glutamate Intake Quartiles Among Chinese Adults in Jiangsu Nutrition Study (n=1227)

	MSG intake quartiles in 2002							
	Q1 (0.8 g/day)[a]	Q2(2.0 g/day)		Q3 (3.7 g/day)		Q4 (6.9 g/day)		*P* [b]
	OR	OR	95%CI	OR	95%CI	OR	95%CI	
Snoring in 2007								
BMI<23								
Model 1 [c]	1.00	1.16	0.60, 2.23	2.48	1.31, 4.69	2.28	1.22, 4.25	0.005
Model 2 [d]	1.00	1.10	0.56, 2.20	2.19	1.10, 4.36	2.02	1.02, 4.00	0.030
BMI≥23								
Model 1 [c]	1.00	1.63	0.92, 2.89	1.76	0.99, 3.11	1.56	0.84, 2.91	0.251
Model 2 [d]	1.00	1.82	1.00, 3.32	1.81	0.97, 3.38	1.53	0.77, 3.03	0.434
All sample								
Model 1 [c]	1.00	1.45	0.93, 2.25	2.06	1.33, 3.20	1.77	1.13, 2.76	0.019
Model 2 [d]	1.00	1.64	1.02, 2.62	2.16	1.32, 3.52	1.91	1.16, 3.17	0.036
High probability for SDB in 2007								
BMI<23								
Model 1 [c]	1.00	1.37	0.53, 3.51	1.83	0.72, 4.66	3.17	1.24, 8.07	0.010
Model 2 [d]	1.00	1.31	0.49, 3.52	1.65	0.58, 4.63	3.11	1.10, 8.84	0.020
BMI≥23								
Model 1 [c]	1.00	1.36	0.64, 2.90	1.24	0.57, 2.66	2.00	0.88, 4.53	0.121
Model 2 [d]	1.00	1.16	0.53, 2.55	1.06	0.46, 2.43	1.92	0.79, 4.66	0.141
All sample								
Model 1 [c]	1	1.40	0.81, 2.43	1.61	0.92, 2.81	2.54	1.44, 4.49	0.005

Model 2 [d]	1	1.22	0.66, 2.26	1.26	0.66, 2.42	2.4	1.22, 4.68	0.007

Abbreviations: BMI, body mass index; CI, confidence interval; MSG, Monosodium Glutamate; OR, odds ratio; SDB, sleep disordered breathing; Q1-4, quartiles 1-4.

[a] Median MSG intake with quartile.

[b] *P* value from a linear trend test.

[c] Model 1 adjusted for age and sex

[d] Model 2 adjusted for age, sex, smoking (yes/no), alcohol drinking (yes/no), passive smoking (yes/no) , active commuting (no, 1-29 minutes/day, ≥30 minutes/day), leisure time physical activity (no, 1-29 minutes/day, >30 minutes/day), sedentary activity(<1 hrs/day, 1-1.9 hrs/day, 2-2.9 hrs/day,≥3 hrs/day), education (low, medium, high), and occupation (manual/non-manual), central obesity (defined as waist circumference: men ≥90 cm, women ≥80 cm), eating out, total energy intake, and dietary patterns (see ref 17). For the analyses in all sample, model 2 also adjusted for overweight (BMI≥23, yes/no).