Obesity and Non-Obesity Obstructive Sleep Apnoea Hypertension Syndromes (OOHS & NOOHS): New Clinical Discoveries

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Biological Sciences - Article

Keywords: hypertension, major adverse cardiovascular events, obesity, obstructive sleep apnoea, risk factors

Posted Date: July 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-706703/v1>

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Abstract

Obesity, obstructive sleep apnoea (OSA) and hypertension are common clinical risk factors. Their coexistence is termed Obesity and Non-Obesity OSA Hypertension Syndromes (OOHS & NOOHS) due to high linkage. This study reported the clinical characteristics of OOHS and NOOHS. A total of 163 patients, aged 23–74 years, were randomly enrolled at the outpatients department who were either obese or non-obese, suffered OSA and hypertension. Subjects with a Body Mass Index (BMI) of ≥ 25 (Chinese criteria), of ≥ 27 (criteria of this study), and of ≥ 30 (WHO criteria) were defined as obese or non-obese, respectively. Cases with snoring were classified as mild, moderate and severe OSA by using the Apnoea-Hypopnoea Index where mild is 5–15, moderate is 15–30, and severe is > 30 . Daytime blood pressure (BP) was measured to assess any correlation. Data from those with isolated obesity, OSA, hypertension, and metabolic syndrome were compared. Long-term follow-up was carried out. 7 typical cases with OOHS and NOOHS were assessed and included general patient information, initial diagnosis, medical history, related risk factors, BMI, and BP. 163 cases with OOHS and NOOHS often have similar or different clinical characteristics. Both potentially suffer from major adverse cardiovascular events (MACEs) which are associated with increased BMI, OSA, and increased BP. Long-term follow-up showed the outcomes consistently linked to their lifestyle and adherence to treatment. Our new clinical discoveries suggest that both OOHS and NOOHS are high risk conditions in MACEs. There is an urgent need for early lifestyle interventions and related treatments.

Background

Obesity, OSA and hypertension are common internationally and present major challenges in the field of public health. According to the Report on the Nutrition and Chronic Disease Status of Chinese Residents, more than 50.0% of Chinese residents aged ≥ 18 years were obese, there were only 30.1% obese residents in 2012¹. OSA is a common condition among patients with cardiovascular disease (CVD) affecting at least 9 to 15% of middle-aged adults in 2000², 17% of women and 34% of men in the US³ and 40% to 60% of CVD patients in 2015⁴. There are almost 1.0 billion individuals affected globally and with prevalence exceeding 50% in some countries in 2019⁵. OSA is associated with a 2- to 3-fold increased risk of CVD.³ In fact, OSA is an important and independent risk factor of CVD⁶ and contributes to the increased incidence of MACE, stroke, cardiometabolic risk, cardiovascular morbidity and mortality⁷⁻⁹. In addition, the Survey on the Status of Nutrition and Health of the Chinese People in 2012 showed that $\geq 25.2\%$ of adults in China aged 18 years had hypertension¹.

Epidemiologic data support the link to obesity, OSA, and hypertension. Data also shows that each of obesity, OSA and hypertension is an independent risk factor of both CVD and cerebrovascular diseases. If undiagnosed and untreated, both obesity and OSA may lead to hypertension and other CVD¹⁰⁻¹². There was an obvious correlation of obesity, OSA and hypertension. Nevertheless, it is currently unclear of the incidence of their correlation and little is known how about the exact risk of their correlation to the cardiovascular and cerebrovascular system.

This is a preliminary report on the clinical characteristics of the correlation of obesity, OSA, and hypertension. As new clinical discoveries, this correlation for obesity has been termed as OOHS and that of non-obesity as NOOHS¹³. Data relating to OOHS and NOOHS by different criteria of obesity according to the World Health Organization (WHO) (BMI ≥ 30), China (BMI ≥ 25), and this study (BMI ≥ 27) were also compared.

Results

Clinical characteristics of 7 typical cases with OOHS and NOOHS syndromes were assessed including general information, primary diagnosis, past and family history, “environment-sleep-emotion-exercise-diet” [E(e)SEED] related risk factors, BMI, BP, and others (Tables 1 & 2).

According to the different criteria of obesity, there were different data on OOHS and NOOHS. When BMI ≥ 27 , there were OOHS in 54 cases, male 43 and female 11, aged 28–73yrs and 36–63yrs, respectively. Means of BMI 28.99 (27.08– 33.41 kg/m²) and 28.94 (27.01–32.87 kg/m²) respectively. All patients had OSA from mild, moderate, to severe. Mean BP in males and female was 150.36/98.73 mmHg (110–200/70–136 mmHg), 158.36/97.18 mmHg (122–200/72–116 mmHg) respectively. Cardiovascular and cerebrovascular events including chronic heart failure (CHF), ischaemic heart disease (IHD) (angina pectoris, AP or myocardial infarction, MI), arrhythmia (atrial premature complex, APC; ventricular premature complex, VPC; atrial tachycardia, AT; atrial fibrillation, AF; atrioventricular block, AVB; left bundle branch block, LBBB), and cerebrovascular accident (CVA) were found in both male and female patients (Table 3). Some patients suffered dis-lipidaemia and fatty liver and some patients had significant family history. None of the female patients were neither smokers nor drank alcohol.

In the group of patients with a BMI ≥ 27 , there were 109 cases with NOOH syndrome, 72 were male and 37 were female 37, aged 23–78 years and 38–74 years respectively. The mean BMI was 23.97 (18.03–26.99 kg/m²) and 24.16 (20.70–26.81 kg/m²), respectively. All patients had OSA from mild, moderate, to severe. Mean BP was 149.03/95.34mmHg (185–112/68–126 mmHg), 158.27/94.36 mmHg (198–120/65–118 mmHg) in the males and females respectively. Cardiovascular and cerebrovascular events including CHF, IHD (AP, MI), arrhythmia (APC,VPC, AT, AF) and cerebro-vascular accident (CVA) were also found in both male and female patients (Tables 4 & 5). Fewer cases were associated with dis-lipidaemia and no fatty livers were found. Some had significant family history, especially in females, but none of the patients smoked and drank excess alcohol, and there was no sudden cardiac death in female patients.

In the group of BMI ≥ 25 (Chinese criteria of obesity), there were 93 cases with OOHS syndrome, 71 were male and 22 were female. This indicates that OOHS cases increase greatly in this group. However, according to WHO criteria of BMI ≥ 30 , only 12 cases were male and 3 cases were female, OOHS syndrome cases decrease in this group (Table 6).

Both OOHS and NOOHS are very high risks for the cardiovascular and cerebrovascular system. There were high rates in related MACE which include CHF, IHD (AP, MI), arrhythmia (APC,VPC, AT, AF, AVB, LBBB), and CVA, and similar spectrums as showed in this study (Fig. 1. A, B, C). However, no cases with impaired glucose tolerance (IGT) or type 2 diabetes (T2D) were found in the group of OOHS, but these were found in the NOOHS group. No fatty liver cases were found in the group of NOOHS, but were seen in OOHS syndrome. Both IGT or T2D and fatty liver are related to BMI. It was found that there were often MACE in both OOHS and NOOHS. This infers that increased BMI and also OSA will result in high risk to the cardiovascular and cerebrovascular systems.

The clinical features of OOHS and NOOHS were compared with isolated obesity, OSA, hypertension (iHTN), and MS. Obesity or non-obesity and the severity of OSA strongly link to increased and high risk in both OOH and NOOH syndromes when compared with isolated groups. After 12 years of long-term follow-up, the clinical outcomes of patients with OOHS and NOOHS have been assessed and are shown in Table 7.

Discussion

Obesity, OSA, and hypertension are independent risk factors of for the cardiovascular and cerebrovascular systems. There have been previous studies of obesity, OSA, and hypertension respectively¹⁴. However, none of these studies increased the understanding of the association of obesity or non-obesity, OSA, and hypertension in relation to OOHS and NOOHS. In fact, the co-clinical spectrum of OOHS and NOOHS relating to the cardiovascular and cerebrovascular systems includes arterial hypertension (40-60%), pulmonary hypertension (20-30%), CHD (20-30%), CHF (5-10%), arrhythmia (AVB, sinus arrests, and AF), and CVA (5-10%)¹⁵. These are the wide range of vascular diseases related to OOHS or NOOHS.

Several mechanisms related to obesity, OSA, and hypertension such as sympathetic activation, hyper-leptinaemia, insulin resistance, elevated angiotensin II and aldosterone levels, oxidative and inflammatory stress, endothelial dysfunction, impaired baroreflex function, and perhaps effects on renal function have been reported¹⁶⁻¹⁸. These mechanisms could result in the cardiovascular and cerebrovascular complications resulting from OOHS or NOOHS, but the exact relationship is still unclear. Further work may include using animal models of OOHS and NOOHS to further assess the relationship to obesity and OSA^{19,20}. The genetic basis of OOHS and NOOHS also requires further analysis, one possible candidate is FTO^{21,22}. Factors such as endothelial dysfunction²³, the TASK-1 gene and the gut microbiome may be important^{17,24}.

The clinical signs and symptoms of OOHS or NOOHS are obesity, OSA (including poor sleep quality), apnoea and excessive daytime somnolence. There are also associated major adverse cardiovascular events (MACEs) such as hypertension, arrhythmias, and CHF especially in older patients with untreated OSA. The known risk factors are oxidative stress, age, obesity, smoking, OSA, hyper-lipidemia, hypertension, and T2D and these represent the co-founding factors in OOHS or NOOHS. The risk of CVD (including CHD, insulin resistance, stroke, and T2D) increases with BMI. Hence, OOHS and NOOHS should be considered as new high risk factors which increase the risk of MACEs.

OSA-related OOHS or NOOHS may contribute to metabolic syndrome (MS) which in turn is associated with obesity, hypertension, dyslipidemia, sex hormone abnormalities, inflammation, vascular dysfunction, insulin resistance, and sleep deprivation. Both OOHS and NOOHS are common, especially among individuals such as truck drivers and African Americans^{25,26}. There are known gender differences in obesity and OSA²⁷⁻²⁹ and this study confirmed that OOHS or NOOHS is more common in men than in women, the ratio being about 2 to 3:1.

The treatment of OOHS or NOOHS includes to remove the confounding factors and anti-hypertensive treatment. Patients suffering from OOHS are advised to decrease their BMI by lifestyle interventions such

as environment (external & internal), sleep, emotion, exercise and diet intervention [E(e)SEEDi]^{30,31}. Medication is necessary to control hypertension which may otherwise result in MACEs. Treating OSA by continuous positive airway pressure (CPAP) or surgery is potentially useful in patients suffering from OOHS and NOOHS⁹. Nevertheless, one study found that CPAP treatment does not prevent MACEs resulting from OSA⁴.

It has previously been shown that BP decreases in some of patients after the surgical treatment of OSA. Most of the patients with OOHS or NOOHS need medication to lower BP and to control CHF, arrhythmia, CHD, and CVA. There are a number of patients suffering from OOHS or NOOHS with high levels of obesity and OSA who show a decrease in their BP following control of the BMI and OSA. There is evidence that untreated OSA is associated with left ventricular diastolic and systolic failure and in these cases treatment with CPAP improves systolic function^{6,32,33}.

Weight management is clearly very important for patients with OOHS. Weight loss based low calorie diets with behavioural modifications and sometimes bariatric surgery is helpful either as a primary therapy or combination with surgical treatment of OSA. Liraglutide, a glucagon-like peptide-1 analogue, may be beneficial for weight loss in some patients³⁴, especially when combined with lifestyle modification. In addition the safety and efficacy of Lorcaserin, a selective serotonin 2C receptor agonist, has been confirmed by a clinical trial for sustained weight loss in obese patients³⁵.

The diagnosis and treatment of OOHS and NOOHS may help to achieve better clinical control and improve long-term prognosis. The cardioprotective effects of aggressive treatment, and a reduction in important clinical endpoints such as the rates of myocardial infarction and CVA may be beneficial to patients³⁶⁻³⁸. When assessing obesity, OSA, hypertension (iHTN) and MS, we found that each of them is a risk factor of CVD. Despite this OOHS or NOOHS is a higher risk to both the cardiovascular and cerebrovascular system. It was also found that the diagnosis of patients suffering from OOHS or NOOHS is more likely in those patients with a high prevalence of obesity and OSA. It is recommended that more attention should be paid to these cases due to the higher risk to the patients and higher incidence of MACEs.

The coexistence of obesity and OSA may result in a series of dysfunctions in patients with OOHS and easily contribute to MS. Nevertheless, we cannot just define OOHS or NOOHS syndrome as a Pre-MS status. Since all these patients have OSA, it is still unclear whether the threat to the cardiovascular and cerebrovascular is *via* MS or not. In this study, it seems that the risk of OOHS or NOOHS in some patients is associated with MS, but in others it seems to be not associated with MS. It may be dependent on patients other factors such as race, gender, genetic history, BMI (obesity or non-obesity), and the severity of OSA. The positive treatment of OSA by lifestyle interventions, medication, surgery or CPAP is clearly very important.

Further understanding and investigation of the mechanisms of OOHS and NOOHS are needed possibly by using animal models and related studies. Previous studies found that activation of I κ B kinase- β (IKK- β) and the

proinflammatory protein nuclear factor κ B (NF- κ B) is a primary pathogenic link between obesity and hypertension³⁹. There are pathogenic genetic variants in melanocortin 2 receptor accessory protein 2 (MRAP2) among individuals with severe obesity⁴⁰, and loss-of-function MRAP2 variants are pathogenic for monogenic obesity and hypertension⁴¹. Hence, these genetic variants and related risk factors (obesity, OSA, and hypertension) could be potential targets to improve human health due to the causal effect of blood pressure and obesity on lifespan⁴².

It may be time to renew the criteria of obesity from BMI ≥ 25 to BMI ≥ 27 in China, but BMI ≥ 30 in the WHO. The mortality resulting from OOHS and NOOHS is still unknown. As special types of C-type hypertension^{13,43}, the prognosis of OOHS and NOOHS depends on the data from long-term follow-up and large-scale clinical trials⁴⁴.

However, this study is just a preliminary report on OOHS and NOOHS, there is a need to find and understand more clinical data on the subject. Second, the patient numbers are still small, and long-term follow-up is needed to observe further the clinical outcomes, e.g. MACEs, other endpoint events and overall prognosis. Finally an understanding is needed about whether or not patients suffering from OOHS and NOOHS will develop cardiovascular disease, diabetes, and cancer (CDC) strips^{13,45}. Animal models of OOHS and NOOHS are need to better understand the mechanisms and vital pathogenic genes involved in the syndromes.

All in all, our results indicate that obesity, OSA, and hypertension are not only independent risk factors but also common and major challenges in clinical practice. In this preliminary study on the clinical characteristics, our new clinical discoveries suggest that both OOHS and NOOHS are high risk conditions and may result in MACEs. They both need early lifestyle intervention and treatment.

Methods

Data Collection

A total of 163 patients aged 23-74 years were randomly enrolled at the outpatients department with obesity or non-obesity, prevalence of self-reported chronic snoring or OSA, and hypertension from October, 2003 to December, 2017. Individuals with a BMI ≥ 25 (China), ≥ 27 (this study) and ≥ 30 (WHO) were defined as obese or non-obese (BMI 18-23), respectively. Subjects were divided into two groups (obese and non-obese) by BMI. Patients with snoring were determined mild, moderate, and severe OSA, respectively, by apnoea-hypopnea index (AHI) i.e. the number of apnoeic and hyponoeic events per hour in the range of 5-15, 15-30, and >30 . Daytime blood pressure (BP) was measured for determination of the correlation between obese or non-obese, OSA, and hypertension. Data from patients with OOHS and NOOHS (according to different criteria of BMI) and from those with isolated obesity, OSA, hypertension, and metabolic syndrome (MS) were compared.

Informed consent

Written informed consent was given by all patients included in this study. The study protocol was approved by the Institutional Review Board for Human Subjects Research at Nanchang University (Hospital of Nanchang University,

Jiangxi Academy of Medical Science). The research study was performed in accordance with the principles of the Declaration of Helsinki. There were no potential sources of bias.

Investigations

All of the patients underwent physical and biochemical examinations including routine U&E, liver function, fasting blood glucose, blood lipids, blood viscosity, uric acid, myocardial enzymes, troponin I, oral administration glucose tolerance test or post-prandial 2-hour blood sugar, hepatitis B, prostatic antigen. Other related auxiliary examinations included chest X-ray, routine electrocardiogram, exercise test and 24-hour ambulatory electrocardiogram, ambulatory blood pressure monitoring, colour Doppler ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI), coronary angiography, mammography where relevant).

Statistical analysis

The results of original records were used. Data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS version 17.0, SPSS Inc., Chicago, IL, USA) with t-test for comparisons between two groups. A *P*-value of <0.05 was considered statistically significant.

Declarations

Sources of Funding

There are ethical approval and no funding was received for this work.

Data Availability

Source data for Fig. 1 is available online. All other source data is available upon reasonable request from the corresponding author.

Acknowledgments

The reviewers and editors are gratefully acknowledged for critical review. And the authors acknowledge the contribution of the all staffs who participated in this study.

References

1. Ma, L. Y. et al. [China cardiovascular diseases report 2018: an updated summary](#). *J Geriatr Cardiol* **17**,1-8 (2020).
2. Ferini-Strambi, L., Fantini, M. L. & Castronovo, C. Epidemiology of obstructive sleep apnea syndrome. *Minerva Med* **95**, 187-202 (2004).

3. Gottlieb, D. J. & Punjabi, N. M. [Diagnosis and Management of Obstructive Sleep Apnea: A Review](#). *JAMA* **323**, 1389-1400 (2020).
4. McEvoy, R. D. et al. SAVE Investigators and Coordinators. [CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea](#). *N Engl J Med* **375**, 919-931 (2016).
5. Benjafield, A. V. et al. [Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis](#). *Lancet Respir Med* **7**, 687-698 (2019).
6. Lattimore JD, Celermajor DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. *J Am Coll Cardiol* **41**, 1429-1437 (2003).
7. [Coughlin, S. R., Mawdsley, L., Mugarza, J. A., Calverley, P. M. A. & Wilding, J. P. H.](#) Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* **25**, 735-741 (2004).
8. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. [Obstructive sleep apnea as a risk factor for stroke and death](#). *N Engl J Med* **353**, 2034-2041 (2005).
9. Drager, L. F., Togeiro, S. M., Polotsky, V. Y. & Lorenzi-Filho, G. [Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome](#). *J Am Coll Cardiol* **62**, 569-576 (2013).
10. Gami, A. S. et al. [Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 ad](#)
11. Cadby, G. et al. [Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large](#)
12. Yu, J. et al. [Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis](#). *JAMA* **318**, 156-166 (2017).
13. Hu, C. S., Wu, Q. H., Hu, D. Y. & Tkebuchava, T. [Novel strategies halt cardiovascular, diabetes, and cancer strips](#)
14. Wolk, R., Shamsuzzaman, A. S. & Somers, V. K. Obesity, sleep apnea, and hypertension. *Hypertension* **42**, 1067-1
15. Schulz, R. et al. Vaskuläre Folgeerkrankungen bei obstruktiver Schlafapnoe [Obstructive sleep apnea-related ca
16. Ryan, S. [Mechanisms of cardiovascular disease in obstructive sleep apnoea](#). *J Thorac Dis* **10**, S4201-S4211 (2018).
17. Durgan, D. J. [Obstructive Sleep Apnea-Induced Hypertension: Role of the Gut Microbiota](#). *Curr Hypertens Rep* **19**, 35 (2017).
18. Farré, N., Farré, R. & Gozal, D. [Sleep Apnea Morbidity: A Consequence of Microbial-Immune Cross-Talk?](#) *Chest* **154**, 754-759 (2018).

19. Rocchini, A. P., Moorehead, C., Wentz, E. & Deremer, S. Obesity-induced hypertension in the dog. *Hypertension*
20. Kimoff, R. J. et al. Canine model of obstructive sleep apnea: model description and preliminary application. *J App*
21. Frayling, T. M. et al. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. *Science* **316**, 889-894 (2007).
22. Locke, A. E. et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197-206 (2015).
23. Bhattacharjee R, Kim J, Alotaibi WH, Kheirandish-Gozal L, Capdevila OS, Gozal D. Endothelial dysfunction in children without hypertension: potential contributions of obesity and obstructive sleep apnea. *Chest* **141**, 682-691 (2012).
24. Shi, T. et al. Genetic variants of rs1275988 and rs2586886 in TWIK-related acid-sensitive K⁺ channel-1 gene may be potential risk factors for obese patients with obstructive sleep apnea. *Chin Med J (Engl)* **132**, 2059-2065 (2019).
25. Moreno, C. R. et al. High risk for obstructive sleep apnea in truck drivers estimated by the Berlin questionnaire: prevalence and associated factors. *Chronobiol Int* **21**, 871-879 (2004).
26. Johnson, D. A. et al. Association Between Sleep Apnea and Blood Pressure Control Among Blacks. *Circulation* **139**, 1275-1284 (2019).
27. Broström, A. et al. Gender differences in respiratory disturbance, sleep and daytime sleepiness in hypertensive patients with different degrees of obesity. *Eur J Cardiovasc Nurs* **12**, 140-149 (2013).
28. Quintana-Gallego, E. et al. Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. *Respir Med* **98**, 984-989 (2004).
29. Temple, K. A. et al. Sex Differences in the Impact of Obstructive Sleep Apnea on Glucose Metabolism. *Front End*
30. Hu, C. Grants supporting research in China. *Eur Heart J* **39**, 2342-2344 (2018).
31. Hu, C. S. & Tkebuchava, T. SEEDi^{1.0-3.0} strategies for major noncommunicable diseases in China. *J Integr Med* **15**, 265-269 (2017).
32. Sin, D. D. et al. Relationship of systolic BP to obstructive sleep apnea in patients with heart failure. *Chest* **123**, 15
33. Li, J. et al. Self-reported Snoring Patterns Predict Stroke Events in High-Risk Patients With OSA: Post Hoc Analyses of the SAVE Study. *Chest* **158**, 2146-2154 (2020).
34. Pi-Sunyer, X. et al. SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med* **373**, 11-22 (2015).

35. Bohula, E. A. et al. CAMELLIA–TIMI 61 Steering Committee and Investigators. Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients. *N Engl J Med* **379**, 1107-1117 (2018).

36. Wolk, R. & Somers, V. K. Obesity-related cardiovascular disease: implications of obstructive sleep apnea. *Diabetes Obes Metab* **8**, 250-260 (2006).

37. Sánchez-de-la-Torre, M. et al. Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* **8**, 359-367 (2020).

38. Ou, Q. et al. SAVE investigators. The Effects of Long-term CPAP on Weight Change in Patients With Comorbid OSA and Cardiovascular Disease: Data From the SAVE Trial. *Chest* **155**, 720-729 (2019).

39. Purkayastha, S., Zhang, G. & Cai, D. [Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKK-beta and NF-kappaB](#). *Nat Med* **17**, 883-887 (2011).

40. Asai, M. et al. [Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity](#). *Science* **341**, 275-278 (2013).

41. Baron, M. et al. [Loss-of-function mutations in MRAP2 are pathogenic in hyperphagic obesity with hyperglycemia and hypertension](#). *Nat Med* **25**, 1733-1738 (2019).

42. Sakaue, S. et al. [Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan](#). *Nat Med* **26**, 542-548 (2020).

43. Hu, C. S. C-type Hypertension. *Eur Heart J* **40**, 715 (2019).

44. MacKay, S. et al. Effect of Multilevel Upper Airway Surgery vs Medical Management on the Apnea-Hypopnea Index and Patient-Reported Daytime Sleepiness Among Patients With Moderate or Severe Obstructive Sleep Apnea: The SAMS Randomized Clinical Trial. *JAMA* **324**, 1168-1179 (2020).

45. Hu, C. S., Wu, Q. H. & Hu, D. Y. Cardiovascular, diabetes, and cancer strips: evidences, mechanisms, and classifications. *J Thorac Dis* **6**, 1319-1328 (2014).

Tables

Table 1. Clinical characteristics of typical OOHS Cases.

Items	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.
	OOHS with gastric ulcer	OOHS with gout, fatty liver, and infection	OOHS with family history of obesity	OOHS with family history of hypertension	OOHS with family history of hypertension and stroke
General information	Male, 39 years old, married, engaged in engineering management	Male, 42 years old, married, principal of primary school	Male, 42 years old, married, tricycle driver	Male, 50 years old, married, engaged in entertainment	Male, 52 years old, married, truck driver
Chief complaint	Palpitation and chest tightness after tired for more than 2 years	Arthralgia for 3-4 years	Easy to starve for half a year (physical examination when accompanying his father to see a doctor)	Blood pressure rises for half a year	Numbness and swelling in the back of the brain for half a month
Past history	Gastric ulcer with bleeding	History of gout (oral colchicine), fatty liver	A history of hyperthyroidism and treatment more than ten years ago	Obesity	Hypertension for 5-6 years, has been taking anti-hypertension agents
Family history	Both parents were healthy	His father died of stomach cancer and his mother has bronchiectasis	His father had hypertension, his mother, grandmother, uncle and young brother were obese, his uncle died of cancer	His father, uncle, aunt and younger brother all had hypertension, and his mother was healthy	Both parents died of hypertension and stroke
Environment	Living in a city	Living in a town	Living in a city	Living in a city	Living in a town
Sleep	OSA (+++), often stay up late (surfing the internet or watching TV), to sleep until after 24 o'clock, or even 2-3 o'clock in the morning	OSA (++)	OSA (+++), does not stay up late	OSA (+++), often stay up late, to sleep until after 24 o'clock	OSA (+++), good sleep
Emotion	Good	No or less anxiety or depress	No anxiety or depression	No anxiety or depress	Good emotion
Exercise	Less exercise, driving to work, taking the elevator (less climbing)	Less exercise, driving to work, taking the elevator (less climbing)	Manual work (riding tricycle)	Walk for half an hour every night	Less physical activity, truck driver for more than 20 years
Diet	Chewing betel nut for more than 2 years, smoking (10 cigarettes/day),	Smoking (more than 20 cigarettes/day), drinking (more	No smoking, less drinking	Smoking (20 cigarettes/day, more than 25 years), drinking	Smoking (20 cigarettes/day, over 20 years), drinking liquor

	drinking (150-200g/ day)	than 500g/day), getting drunk once every 2-3 days		more than half a catty of liquor/day before 40 years old	(300-500g/day), abstinence for 4-5 years
Blood pressure	150/120 mmHg (Right), 152/122 mmHg (Left)	162/106 mmHg (Right), 152/106 mmHg (Left)	152/126 mmHg (Right), 154/126 mmHg (Left)	186/136 mmHg (Right), 186/128 mmHg (Left)	206/126 mmHg (Right), 202/120 mmHg (Left)
BMI	83kg/1.74m ²	82kg/1.69m ²	93kg/1.70m ² =32.1, Waist 100 cm	93kg/1.80m ² , Waist 98 cm	100kg/1.75m ² , Waist 98 cm
Others	-	Uric acid increased, triglyceride increased, fasting blood glucose 6.8, postprandial blood glucose 7.3, WBC 12.6	Fatty liver	Fatty liver	Heart rate 50 beats/min, frequent premature beats, hyperlipidemia, fatty liver, diabetes

Table 2. Clinical characteristics of typical NOOHS Cases.

Items	Case 1. NOOHS with AS and coronary heart disease	Case 2. NOOHS
General information	Male, 44 years old, married, farmer	Male, 35 years old, married, plumber & electricity maintenance worker
Chief complaint	Palpitation, tachycardia and upper limb numbness for more than 10 years	Dizziness for 4 days with retching
Past history	Coronary heart disease	Hepatolithiasis for 5-6 years
Family history	Both parents were healthy	His father died (cause unknown), his mother was healthy, his two brothers and three sisters had no hypertension
Environment	Living in the countryside	Living in a city
Sleep	OSA (+++), don't stay up late, have more dreams	OSA (+++), don't stay up late, poor sleep
Emotion	Emotion not so good	Hot tempered
Exercise	Farming, manual labor	Manual work, pipeline and electricity maintenance
Diet	Smoking (20 cigarettes/day for 6-7 years), drinking (150-200g/day)	No smoking, drinking liquor (150g "Duihua" for dinner every day, more than 10 years)
Blood pressure	174/96 mmHg (Right), 186/116 mmHg (Left)	160/110 mmHg (Right), 146/126 mmHg (Left)
BMI	67kg/1.65m ²	69kg/1.68m ² , Waist 82.5 cm
Others	-	-

Table 3. Comparison of clinical data of obesity OOHS according to different criteria of obesity.

OOHS	OOHS ≥ 25 (Male, CN)	OOHS ≥ 25 (Female, CN)	OOHS ≥ 27 (Male, this study)	OOHS ≥ 27 (Female, this study)	OOHS ≥ 30 (Male, WHO)	OOHS ≥ 30 (Female, WHO)
Cases (n)	71	22	43	11	12	3
Age (yrs)	51.39(28-73)	54.64(36-74)	50.81(28-73)	53.82(36-63)	44.08(28-67)	51.00(47-56)
BMI	27.80 (25.06-33.41)	27.47 (25.02-32.87)	28.99 (27.08-33.41)	28.94 (27.01-32.87)	31.42 (30.08-33.41)	31.52 (30.04-32.87)
OSA	+ to +++	+ to +++	+ to +++	+ to +++	+ to +++	+ to +++
Blood Pressure (mmHg)	149.31/98.03 (200-110/70-136)	159.23/94.55 (200-122/65-116)	150.36/98.73 (200-110/70-136)	158.36/97.18 (200-122/72-116)	152.58/104.58 (180-130/80-130)	159.33/97.33 (200-122/92-100)
Family history (CVD)	21	3	13	1	6	1
Others (Smoking, etc)	24	0	13	0	5	0

* + to +++: slight to heavy;

There were significant differences in BMI and blood pressure between OOHS groups and control groups (both blood pressure and BMI were in normal range).

Table 4. Comparison of clinical data of obesity (BMI $\geq$ 27) or non-obesity (BMI<27)-obstructive sleep apnoea-hyperte

OOHS & NOOHS	OOHS (Male)	OOHS (Female)	NOOHS (Male)	NOOHS (Female)
Cases (n=)	43	11	72	37
Ages (years)	50.81(28-73)	53.82 (36-63)	54.61(23-78)	57.57 (38-74)
BMI	28.99 (27.08-33.41)	28.94 (27.01-32.87)	23.97 (18.03-26.99)	24.16 (20.70-26.81)
OSA	+ to +++	+ to +++	+ to +++	+ to +++
Blood Pressure (mmHg)	150.36/98.73 (200-110/70-136)	158.36/97.18 (200-122/72-116)	149.03/95.34 (185-112/68-126)	158.27/94.36 (198-120/65-118)
Family history (CVD)	13	1	18	13
Total CVE	31	≥ 16	52	≥ 31

* CVE include hypertension emergency, coronary heart disease, arrhythmia or sudden cardiac death, acute or chronic heart failure, CVA; + to +++: slight to heavy.

The blood pressure level of each group was significantly different from that of control groups (the blood pressure level was in the normal range).

Table 5. Cardio-cerebrovascular events and pathologies in patients with OOHS or NOOHS (BMI $\geq$ 27 or <27).

OOHS & NOOHS	OOHS (Male)	OOHS (Female)	NOOHS (Male)	NOOHS (Female)
CCVE (n=)	43	11	72	37
Hypertension Emergency	Yes	Yes	Yes	Yes
CHD AP/ACS/AMI	7	4	12	8
Arrhythmia	4	6	10	10
Acute / Chronic HF	8	3	9	5
CVA	12	2	21	8
Sudden Cardiac Death (SCD)	0	1	0	1
Others				
Dyslipidemia	>10	>3	>5	>1
Fatty Liver	4	2	0	0
IGT or T2DM	0	0	5	1
	13	0	26	0

* There were significant MACE in patients with OOHS and NOOHS regardless of gender, suggesting that OSA is a more important risk factor.

Table 6. Comparison of clinical features of OOHS and NOOHS with isolated hypertension (iHTN) and metabolic synd

Cases	Obesity	OSA	iHTN	OOHS	NOOHS	MS
History (genetic or secondary)	Both	Unclear	Both	Both	Both	Both
Clinical features	A	B	C	A + B + C	B + C	A + C
Diagnosis	BMI	PNG	BP	All	All	BMI + BP + BS
Treatment	Life style	CPAP	Pharmacotherapy	All	All	All
Prognosis	Risk	Risk	Risk	High risk	High risk	High risk

Notes: BMI: body mass index; PNG: sleep polysomnography; CPAP: continuous positive airway pressure. A. BMI ≥27; B. Sleep disorders; C. BP > 140/90mmHg. Life-style treatments were exercise and diet.

Table 7. Analysis of patients with OOHS and NOOHS by long-term follow-up.

	OOHSn=54	NOOHSn=109
Final outcomes	About 1/4 lost contact (died or others)	About 1/4 lost contact (died or others)
Secondary endpoint events	About 1/4 got better after improved lifestyle About 1/4 keeping stable condition after adhering to drug treatment About 1/4 getting worse (e.g. rising blood pressure or developing type 2 diabetes or cancer) A few cases recovered after surgery for OSA.	About 1/4 got better after improved their lifestyle About 1/4 in stable condition after adhering to drug treatment About 1/4 got worse (e.g. rising blood pressure or developing type 2 diabetes or cancer)

Notes: When patients with OOHS or NOOHS also suffer from type 2 diabetes and/or cancer, it means that they may develop cardiovascular, diabetes, and cancer (CDC) strips.

Figures

Figure 1

A. Healthy subject with normal BMI, no obstructive sleep apnoea (OSA), no hypertension; B. Subject with obesity-OSA-hypertension (OOHS); C. Subject with non-obesity-OSA-hypertension (NOOHS). We usually call obesity as “a shaped, but not sounded killer”, OSA as “a sounded, but not shaped killer”, hypertension as “not shaped and sounded killer”. Obviously, OOHS is not only “a shaped and sounded killer” at night, but also “a shaped and not sounded killer” at daytime. OOHS which marks the coexistence of obesity, OSA, and hypertension is a “synthetic killer”, and a very high risk factor of coronary heart disease (CHD), acute myocardial infarction (AMI), CVA, and T2D.