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EPIDEMIOLOGY • ORIGINAL ARTICLE

Risk of gallstones in patients with obstructive sleep apnea: a nationwide observational cohort study

Chien-Hua Chen[1,2,3,4] · Cheng-Li Lin[5,6] · Chung-Y. Hsu[7] · Chia-Hung Kao[7,8,9]

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Abstract

Purpose To assess the association between obstructive sleep apnea (OSA) and gallstones.

Methods We identified 3827 patients aged ≥ 20 years with OSA between 2000 and 2010 from the Longitudinal Health Insurance Research Database 2000 (LHID2000) as the study cohort. The beneficiaries without OSA were randomly selected and propensity-matched with the study cohort in a 1:1 ratio according to age; sex; occupation; urbanization; comorbidities of hypothyroidism, hyperlipidemia, diabetes, liver cirrhosis, alcohol-related illness, hypertension, chronic obstructive pulmonary disease (COPD), obesity, inflammatory bowel disease, stroke, coronary artery disease (CAD), hepatitis B virus, and hepatitis C virus; and the index year. All patients were followed until the end of 2011 or withdrawal from the National Health Insurance program to determine the incidence of gallstones.

Results The prevalence of OSA was higher in men (67.3%) and in patients younger than 49 years (57.0%; mean age 47.8 ± 15.1 years). The cumulative incidence of gallstones was higher in the OSA cohort than in the non-OSA cohort (log-rank test, $P < 0.001$). Compared with patients without OSA, those with OSA had an increased risk of gallstones (adjusted hazard ratio = 1.53, 95% confidence interval = 1.16–2.03) after adjustment for age, sex, hyperlipidemia, diabetes, hypertension, COPD, stroke, and CAD.

Conclusion The study shows a strong association between OSA and gallstones. Moreover, our findings suggest the requirement for survey and health education for gallstones in OSA and further studies to verify whether the treatment of OSA can reduce the risk of gallstones.

Keywords Obstructive sleep apnea · Gallstones · Comorbidities

Introduction

The disease of gallstones is one of the most common diseases in the gastrointestinal outpatient department, and its global prevalence is 5–15% [1–3]. Gallstones are predominantly found in elderly patients, women, and Western countries. Ultrasonography is the most common diagnostic tool for diagnosing gallstones and offers high accuracy (sensitivity 90% and specificity 88%) [4]. Approximately 2–4% of patients with gallstones will develop biliary colic, with the reported mortality rate being 3–20% after the first attack of acute pancreatitis and being 24% after acute cholangitis [5, 6].

✉ Chia-Hung Kao
d10040@mail.cmuh.org.tw

[1] Digestive Disease Center, Show-Chwan Memorial Hospital, Changhua, Taiwan

[2] Digestive Disease Center, Changbing Show-Chwan Memorial Hospital, Lukang, Changhua County, Taiwan

[3] Department of Food Science and Technology, Hungkuang University, Taichung, Taiwan

[4] Chung Chou University of Science and Technology, Yuanlin, Changhua County, Taiwan

[5] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[6] College of Medicine, China Medical University, Taichung, Taiwan

[7] Graduate Institute of Biomedical Sciences, School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan

[8] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

[9] Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan

Gallstones raise a major public health concern because cholecystectomy, the only definite treatment of symptomatic gallstones, has high medical costs and results in loss of working hours [7]. Furthermore, approximately 1–2% of patients with gallstones were reported to require surgery annually [8].

Obstructive sleep apnea (OSA), characterized by frequent upper airway blockage during sleep, has been recognized as a major linkage between sleep disruption and intermittent hypoxia [9, 10]. The diagnosis of OSA is standardized according to the simultaneous overnight polysomnography recordings during sleep, including electroencephalography, electrooculography, electromyography, oronasal airflow, and oxyhemoglobin saturation [9]. Moreover, OSA-associated daytime sleepiness was reported in 3–7% of men and 2–5% of women [9]. OSA was reported as an independent risk factor for hypertension, cardiovascular disease, stroke, impaired glucose metabolism, and malignancy [11]. However, no study has discussed the association between OSA and gallstones.

OSA can cause sympathetic hyperactivity, insulin resistance, and proinflammatory effects; thus, its pathophysiological mechanisms are similar to those of gallstones [12]. Hence, we conducted a nationwide, population-based cohort study by analyzing data from Taiwan's Longitudinal Health Insurance Research Database (LHID2000) to assess the association between OSA and subsequent gallstones.

Methods

Data source

Data in this retrospective cohort study were retrieved from the LHID2000, a subset of the National Health Insurance (NHI) program in Taiwan [13]. The LHID2000 includes the data for 1,000,000 beneficiaries, who were randomly sampled from the NHI program, and represents approximately 5% of all residents of Taiwan. The NHI program, established on March 1, 1995, covers more than 99% of the 23.74 million residents of Taiwan. The NHI program and LHID2000 have been thoroughly detailed in our previous studies [14, 15]. Diseases in the LHID2000 were coded according to the 2001 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claim information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR2). The IRB also specifically waived the consent requirement.

Data sharing statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

Patients

This study identified patients with newly diagnosed OSA (ICD-9-CM 327.23) who were aged ≥ 20 years from the LHID2000 between January 1, 2000, and December 31, 2010. The date of OSA diagnosis was considered the index date. The diagnosis of OSA was ascertained through a record linkage to the registry of Catastrophic Illness Certificate, a part of NHI program in Taiwan. The patients should undergo polysomnography to apply Catastrophic Illness Certificate for waiving copayment, and an apnea–hypopnea index (AHI) threshold of 15 events/h with or without symptoms or 5 events/h accompanying symptoms of daytime sleepiness, fatigue, insomnia, mood disorders, and cognitive impairment, or cardiovascular disease was required for the diagnosis of OSA [16]. However, the severity of OSA was unavailable in the registry of Catastrophic Illness Certificate. The non-OSA cohort included patients without OSA who were randomly selected from the LHID2000 through 1:1 propensity matching with the OSA cohort. The non-OSA cohort was frequency-matched according to age (at every 5-year interval); sex; occupation; urbanization; comorbidities of hypothyroidism (ICD-9-CM 224), hyperlipidemia (ICD-9-CM 272), diabetes (ICD-9-CM 250), liver cirrhosis (ICD-9-CM 571 and A347), alcohol-related illness (ICD-9-CM 9291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), hypertension (ICD-9-CM 401–405), chronic obstructive pulmonary disease (COPD; ICD-9-CM 491, 492, and 496), obesity [(body mass index) BMI ≥ 30 kg/m^2] (ICD-9-CM 278), inflammatory bowel disease (IBD; ICD-9-CM 555 and 556), stroke (ICD-9-CM 430–438), coronary artery disease (CAD; ICD-9-CM 410–414), hepatitis B virus (ICD-9-CM V02.61, 070.20, 070.22, 070.30, and 070.32), and hepatitis C virus (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, and V02.62); and the index year of OSA. Both OSA and non-OSA cohorts excluded patients with a history of gallstones

(ICD-9-CM 574.0, 574.1, 574.2, 574.6, 574.7, 574.8, and 574.9) and those with incomplete information on age or sex at baseline. This diagnosis of gallstones included both asymptomatic and symptomatic stones, and the diagnosis mainly based on combined of clinical symptoms and/or abdominal ultrasonography. We classified white-collar workers as people with long indoor working hours, such as institutional, business, and industrial administration personnel; blue-collar workers as those with long outdoor working hours, such as fishermen, farmers, and industrial laborers; and other occupations as retired, unemployed, or low-income occupations [15]. Furthermore, we classified the levels of urbanization according to the population density (people/km^2). Each patient was examined from the index date until gallstone occurrence, death, withdrawal from the NHI program, or December 31, 2011. Patients would be withdrawn from the NIH program if they emigrated out of Taiwan or died during the follow-up period. Both cause-specific and non-cause-specific deaths would be included in the analysis if the cause of death could be identified. However, the deaths would be censored when the causes could not be identified. The index date of the control patients was randomly assigned according to the month and day corresponding to the index year of the matched patients.

Statistical analysis

We used the chi-squared test to compare and examine the distributions of age, sex, and comorbidities between the OSA and non-OSA cohorts. Student's *t* test was used to compare and determine the mean ages (standard deviations) and follow-up period (SDs) between the two cohorts. We used the Kaplan–Meier method to compare the cumulative incidence of gallstones and survival between the study cohorts; the log-rank test was used to examine the differences. The incidence density rates of gallstones were estimated by dividing the incidence of gallstones by the number of person-years for each risk factor. Furthermore, we stratified the incidence density rates of gallstones by age, sex, and comorbidities. We used univariable and multivariable Cox proportional hazard regression models to assess the OSA-related risk of gallstones. The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox model, after adjustment for age, sex, hyperlipidemia, diabetes, liver cirrhosis, hypertension, COPD, CAD, and IBD. We used SAS Version 9.4 (SAS Institute, Cary, NC, USA) to analyze all data, and two-tailed $P < 0.05$ was considered significant.

Table 1 Demographic characteristics of and comorbidities in patient with and without obstructive sleep apnea (OSA)

Variable	OSA		
	No $N = 3827$	Yes $N = 3827$	*P* value
Gender	*N* (%)	*N* (%)	0.73
Female	1266 (33.1)	1252 (32.7)	
Male	2561 (66.9)	2575 (67.3)	
Stratify age			0.89
≤49	2193 (57.3)	2181 (57.0)	
50–64	1097 (28.7)	1094 (28.6)	
65+	537 (14.0)	552 (14.4)	
Age, mean (SD)[a]	47.7 (15.1)	47.8 (15.1)	0.71
Occupation			
White collar	2322 (60.7)	2299 (60.1)	
Blue collar	1016 (26.6)	1013 (26.5)	
Others[b]	489 (12.8)	515 (13.5)	
Urbanization level[b]			0.99
1 (highest)	1336 (34.9)	1326 (34.7)	
2	1144 (29.9)	1138 (29.7)	
3	708 (18.5)	716 (18.7)	
4 (lowest)	639 (16.7)	647 (16.9)	
Comorbidity			
Hypothyroidism	28 (0.73)	16 (0.42)	0.07
Hyperlipidemia	1121 (29.3)	1146 (30.0)	0.53
Diabetes	359 (9.38)	377 (9.85)	0.49
Cirrhosis	21 (0.55)	15 (0.39)	0.32
Alcohol-related illness	244 (6.38)	257 (6.72)	0.55
Hypertension	1437 (37.6)	1473 (38.5)	0.40
COPD	588 (15.4)	638 (16.7)	0.12
Obesity	199 (5.20)	211 (5.51)	0.54
Inflammatory bowel disease	45 (1.18)	47 (1.23)	0.83
Stroke	161 (4.21)	178 (4.65)	0.34
CAD	775 (20.3)	823 (21.5)	0.18
HBV	222 (5.80)	231 (6.04)	0.66
HCV	70 (1.83)	52 (1.36)	0.10

Chi-square test

[a] Two-sample *t* test

[b] The urbanization level was determined by dividing the population density of the residential area into four levels, with level 1 being the most urbanized and level 4 the least urbanized & Other occupation categories included those who were primarily retired, unemployed, and low-income populations

Results

In this study, the OSA and non-OSA cohorts included 3827 patients each (Table 1). Both cohorts were well-matched for age, sex, and comorbidities. The mean ages of patients in the OSA and non-OSA cohorts were 47.8 ± 15.1 and 47.7 ± 15.1 years, respectively. Most patients were younger than 49 years (57.0%) and were men (67.3%). In both cohorts, the five common comorbidities according to the order of their frequency were hypertension (38.5%), hyperlipidemia (30.0%), CAD (21.5%), COPD (16.7%), and diabetes (9.85%).

Figure 1 shows that the cumulative incidence of gallstones was higher in the OSA cohort than in the non-OSA cohort (log-rank test, $P < 0.001$). The average follow-up duration was

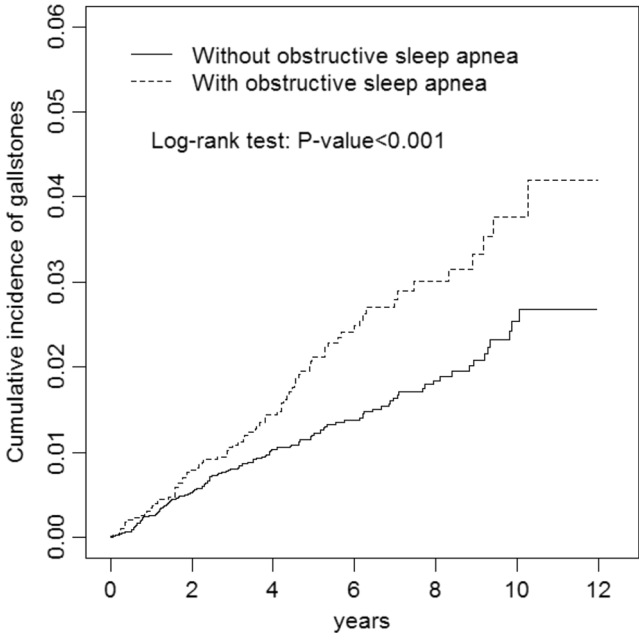

Fig. 1 Cumulative incidence of gallstones in patients with and without obstructive sleep apnea

5.15 ± 2.90 years for the OSA cohort and 5.07 ± 2.87 years for the non-OSA cohort.

Table 2 shows the incidence of and risk factors for gallstones. Compared with patients without OSA, those with OSA were associated with an increased risk of gallstones [adjusted HR (aHR) = 1.53, 95% CI = 1.16–2.03] after adjustment for age, sex, hyperlipidemia, diabetes, hypertension, COPD, stroke, and CAD. Moreover, the risk of gallstones increased at 1-year intervals (aHR = 1.02, 95% CI = 1.00–1.03). Among the comorbidities, only hyperlipidemia (aHR = 1.58, 95% CI = 1.17–2.13) and hypertension (aHR = 1.86, 95% CI = 1.31–2.62) were the independent risk factors for gallstones after multivariable analysis of comorbidities.

Table 3 shows the comparison of the gallstone incidence densities between patients with and without OSA by demographic characteristics and comorbidities. The overall incidence density rates of gallstones in patients with and without OSA were 3.91 and 2.45 per 1000 person-years, respectively. The sex-specific relative risk of gallstones in the OSA cohort was higher than that in the non-OSA cohort for women (aHR = 1.74, 95% CI = 1.12–2.68). The age-specific relative risk of gallstones in the OSA cohort was higher than that in the non-OSA cohort for patients aged ≥ 65 years (aHR = 2.10, 95% CI = 1.18–3.73). The association between OSA and gallstone risk was stronger in patients with blue-collar jobs (aHR = 1.84, 95% CI = 1.11–3.05). Moreover, this association was stronger in patients living in the least urbanized areas (aHR = 2.74, 95% CI = 1.35–5.56). The comorbidity-specific relative risk of gallstones was higher in the OSA cohort than in the non-OSA cohort for patients without comorbidities (aHR = 2.23, 95% CI = 1.27–3.93) or those with comorbidities (aHR = 1.39, 95% CI = 1.01–1.92).

Discussion

Consistent with the literature, OSA was more prevalent in men with a men:women ratio of approximately 2:1 in our cohort [9]. Moreover, the prevalence of OSA was reported to increase with age and reached a plateau after the age of 60 years [17, 18]. In contrast to the literature, most patients with OSA in this study were younger than 49 years (57.0%; mean age, 47.8 ± 15.1 years). The predominance of middle-aged patients in our OSA cohort might reflect more awareness of OSA and medical resource utilization in this population. The prevalence of OSA in elderly patients might have been underestimated in our study. Nevertheless, compared with OSA in middle-aged patients, OSA in elderly patients was reported to be a distinct clinical entity, and its increased risk of adverse outcomes remains controversial [19].

Consistent with the literature, hypertension, hyperlipidemia, CAD, COPD, and diabetes were the common comorbidities associated with OSA this study (Table 1) [9–11]. OSA has been reported to increase the risk of cardiovascular disease through intermittent hypoxia, repetitive arousal from sleep, marked fluctuations in intrathoracic pressure, and increased blood pressure during sleep [20, 21]. The possible pathophysiological mechanisms underlying the association between diabetes and OSA might include decreased insulin sensitivity because of intermittent hypoxia, increased glycolysis and gluconeogenesis caused by increased sympathetic activity, and increased cortisol secretion following each nadir of interrupted sleep cycles [22]. Sometimes, OSA and COPD overlapped although hypoxia in OSA is usually intermittent and in COPD is usually to a greater extent. Hypoxia is the key factor for both COPD and OSA to promote atherogenesis and cardiovascular disease by increasing oxidative stress [23]. Furthermore, OSA can activate sterol-regulatory element-binding protein 1 and stearoyl-coenzyme A desaturase-1 to increase triglyceride synthesis rather than cholesterol biosynthesis [24].

Age, hyperlipidemia, and hypertension remained the independent risk factors for gallstones in multivariable analysis (Table 2). It is postulated that increased biliary cholesterol secretion, decreased 7-α hydroxylase activity, impaired bile salt synthesis, impaired gallbladder emptying, and long-term exposure to lithogenic factors can increase the risk of gallstones during aging [1]. The association between gallstones and hypercholesterolemia remains unclear. However, hypertriglyceridemia is frequently associated with overweight and insulin resistance that result in the cholesterol supersaturation of bile and impaired motility of the gallbladder [25]. The postulated pathogenesis for the association between hypertension and gallstones is that hypertension can increase the sympathetic tone to impair gallbladder emptying, thus increasing the risk of gallstones [26].

Our results revealed a strong association between OSA and gallstones after adjustment for age, sex, hyperlipidemia, diabetes, hypertension, COPD, stroke, and CAD (Table 2). The

Table 2 Hazard ratios of gallstones in association with age, sex, occupation, urbanization level, and comorbidities and medication in univariable and multivariable Cox regression models

Variable	Crude		Adjusted[a]	
	HR	(95% CI)	HR	(95% CI)
OSA	1.60	(1.21, 2.11)**	1.53	(1.16, 2.03)**
Age, years	1.03	(1.02, 1.04)***	1.02	(1.00,1 .03)**
Gender (female vs male)	1.39	(1.06, 1.83)*	1.31	(0.99, 1.73)
Occupation				
White collar	1.00	(Reference)	1.00	(Reference)
Blue collar	1.26	(0.93, 1.71)		
Others[b]	1.13	(0.76, 1.70)		
Urbanization level[b]				
1 (highest)	1.00	(Reference)	1.00	(Reference)
2	0.94	(0.68, 1.31)		
3	0.72	(0.48, 1.08)		
4 (lowest)	0.79	(0.52, 1.20)		
Baseline comorbidities (yes vs no)				
Hypothyroidism	3.33	(0.83, 13.4)		
Hyperlipidemia	2.30	(1.75, 3.02)***	1.58	(1.17, 2.13)**
Diabetes	1.86	(1.25, 2.77)**	0.94	(0.62, 1.44)
Cirrhosis	3.14	(0.78, 12.6)		
Alcohol-related illness	0.98	(0.50, 1.91)		
Hypertension	2.83	(2.14, 3.73)***	1.86	(1.31, 2.62)***
COPD	1.69	(1.23, 2.33)**	1.09	(0.77, 1.54)
Obesity	0.90	(0.42, 1.90)		
Inflammatory bowel disease	1.36	(0.34, 5.46)		
Stroke	2.18	(1.27, 3.75)**	1.13	(0.64, 1.99)
CAD	1.97	(1.47, 2.63)***	0.92	(0.65, 1.29)
HBV	0.66	(0.29, 1.48)		
HCV	1.62	(0.52, 5.08)		

Crude HR, relative hazard ratio; Adjusted HR[a], multivariable analysis of factors, including age, sex, hyperlipidemia, diabetes, hypertension, COPD, stroke, and CAD

[b] The urbanization level was determined by dividing the population density of the residential area into four levels, with level 1 being the most urbanized and level 4 the least urbanized & Other occupation categories included those who were primarily retired, unemployed, and low-income populations

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

age-specific relative risk of gallstones was higher in the OSA cohort than in the non-OSA cohort for patients aged ≥ 65 years. The association between OSA and gallstones risk was stronger in patients with blue-collar jobs. Moreover, the comorbidity-specific relative risk of gallstones was higher in the OSA cohort than in the non-OSA cohort for patients without comorbidities (Table 3). In addition, the risk of gallstones in the OSA cohort increased with the follow-up duration after OSA diagnosis (Fig. 1). These findings support an increased risk of gallstones after OSA diagnosis; however, the causal relationship between OSA and gallstones could not be ascertained in this observational study.

According to our review of relevant literature, this study is the first to report an association between OSA and gallstones. Furthermore, the possible pathophysiological mechanisms underlying the development of gallstones after the diagnosis of OSA are as follows. First, intermittent hypoxia because of respiratory tract obstruction during sleep will cause the activation of the sympathetic tone, which will impair gallbladder contractility [27]. Second, OSA can result in insulin resistance, irrespective of changes in abdominal fat or body weight [28]. Hypoxia can promote proinflammatory cytokine secretion to cause insulin resistance [22]. Contrastingly, hyperinsulinemia can increase the activity of hydroxylmethylglutaryl-coenzyme A reductase and increase the hepatic uptake of low-density lipoprotein cholesterol to increase cholesterol biosynthesis [29, 30]. Moreover, insulin resistance can reduce serum levels of high-density lipoprotein cholesterol to enhance the formation of gallstones [31, 32]. Finally, OSA can cause systemic inflammation by increasing the serum levels of hypoxia-

Table 3 Comparison of incidence and hazard ratios of gallstones stratified by gender, sex, and comorbidities between patients with and without obstructive sleep apnea (OSA)

Variables	OSA							
	No			Yes				
	Event	PY	Rate[a]	Event	PY	Rate[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
All	133	54,379	2.45	78	19,974	3.91	1.60 (1.21, 2.11)**	1.53 (1.16, 2.03)**
Gender								
Female	51	17,829	2.86	34	6479	5.25	1.84 (1.19, 2.83)**	1.74 (1.12, 2.68)*
Male	82	36,549	2.24	44	13,495	3.26	1.45 (1.01, 2.10)*	1.41 (0.98, 2.04)
Stratify age								
≤49	53	33,292	1.59	30	11,911	2.52	1.58 (1.01, 2.48)*	1.53 (0.98, 2.40)
50–64	54	14,510	3.72	27	5516	4.89	1.31 (0.82, 2.08)	1.25 (0.79, 1.99)
65+	26	6577	3.95	21	2547	8.25	2.08 (1.17, 3.70)*	2.10 (1.18, 3.73)*
Occupation								
White collar	76	33,606	2.26	44	12,123	3.63	1.61 (1.11, 2.33)*	1.57 (1.08, 2.27)*
Blue collar	36	13,660	2.64	26	5157	5.04	1.91 (1.15, 3.16)*	1.84 (1.11, 3.05)*
Others[d]	21	7112	2.95	8	2694	2.97	1.01 (0.45, 2.27)	0.89 (0.39, 2.02)
Urbanization level[d]								
1 (highest)	59	19,383	3.04	25	7140	3.50	1.15 (0.72, 1.84)	1.10 (0.69, 1.75)
2	39	15,730	2.48	25	5701	4.39	1.77 (1.07, 2.93)*	1.68 (1.02, 2.78)*
3	20	10,244	1.95	12	3775	3.18	1.62 (0.79, 3.31)	1.62 (0.79, 3.32)
4 (lowest)	15	9022	1.66	16	3358	4.76	2.86 (1.41, 5.78)**	2.74 (1.35, 5.56)**
Comorbidity[c]								
No	28	23,725	1.18	21	8003	2.62	2.22 (1.26, 3.91)**	2.23 (1.27, 3.93)**
Yes	105	30,654	3.43	57	11,971	4.76	1.39 (1.01, 1.92)*	1.39 (1.01, 1.92)*

PY, person-years; Rate[a], incidence rate per 1000 person-years; Crude HR, relative hazard ratio; Adjusted HR[b], multivariable analysis of factors including age, sex, hyperlipidemia, diabetes, hypertension, COPD, stroke, and CAD; Comorbidity[c], only having one of the comorbidities (hypothyroidism, hyperlipidemia, diabetes, cirrhosis, alcohol-related illness, hypertension, COPD, obesity, inflammatory bowel disease, stroke, CAD, hepatitis B virus, and hepatitis C virus) classified as the comorbidity group

[d] The urbanization level was determined by dividing the population density of the residential area into four levels, with level 1 being the most urbanized and level 4 the least urbanized & Other occupation categories included those who were primarily retired, unemployed, and low-income populations

*$P < 0.05$, **$P < 0.01$

inducible factor 1 and nuclear factor-kβ through intermittent hypoxia and insulin resistance pathways [12]. Systemic inflammation can promote the formation of gallstones by increasing biliary cholesterol secretion to enhance bile supersaturation [33].

The study has some advantages. First, this is the first population-based cohort study to investigate the association between OSA and gallstones. Moreover, the LHID2000, a longitudinal database with a 12-year observation period for 1,000,000 residents of Taiwan, demonstrates the association between OSA and subsequent gallstones. Second, the monopolized NHI program of Taiwan reports an association between OSA and gallstones based on the actual situation in Taiwan because it provides health care for approximately 99.5% of the residents.

The study has some disadvantages. First, the LHID2000 could not provide data on lifestyle, dietary habits, environment, BMI, or waist circumference. However, we have substituted the diagnosis of COPD and alcohol-related illness with the habits of smoking and alcohol consumption, respectively. Furthermore, neither occupation nor urbanization level was associated with gallstones in this study. The association between obesity and gallstones remained debated since abdominal circumference, rather than BMI, was supposed to be related to the development of gallstones [34]. By the contrast, OSA can interact with obesity bilaterally as OSA leads to obesity and weight reduction can lessen the severity of OSA [35]. However, the relative small case number of obesity in our OSA cohort (211/3827, 5.51%) might also explain the insignificance of obesity in contributing to the development of gallstones and might reflect that the cause of OSA varied with ethnicity. Metabolic syndrome is a cluster of metabolic disorders, including increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol

or triglyceride levels. The information of BMI and/or waist circumference was inherently unavailable due to our government's law of Personal Data Protection; therefore, we could not assess the association between OSA and metabolic syndrome, BMI, or waist circumference. However, we already used related comorbidities such as hyperlipidemia, diabetes, alcohol-related illness, hypertension, and obesity to do the adjustment to avoid the possible bias. Non-alcoholic fatty liver disease (NAFLD), diagnosed with abdominal ultrasonography with exclusion of known etiology of liver disease, shares some common mechanisms of pathogenesis with gallstones, and it can increase supply of free fatty acid or decrease oxidation of free fatty acid to cause cholesterol supersaturation in bile [3]. However, the code of NAFLD in ICD-9-CM was inherently not comprehensive, and it might be an epiphenomenon of gallstones, rather than an independent risk factor. Therefore, we did not analyze its contribution to the development of gallstones. Second, we could not individually review the medical records to validate the medical coding. However, the Taiwanese government officially administers the NHI program and has stated that all insurance claims should abide by the standard diagnosis criteria for medical reimbursement to avoid statutory sanctions and financial penalties. Furthermore, multivariable Cox proportional hazards regression revealed a consistent association between OSA and gallstones. Third, the prevalence of OSA might be underestimated if patients, particularly for elderly patients, are not aware of seeking medical consultation for OSA. However, the association between OSA and gallstones might also be underestimated in such circumstances. Finally, the definite pathophysiology and casual relationship between OSA and gallstones could not be ascertained in this observational study. Moreover, we could not assess the association between the risk of gallstones and the severity of obstructive sleep apnea.

In conclusion, our population-based cohort study shows a strong association between OSA and gallstones. Furthermore, our findings suggest that surveys and health education for gallstones should be required in OSA and further studies should verify whether the treatment of OSA can reduce the risk of gallstones.

Author contributions Conceptualization: CHC, CHK
Methodology: CHC, CLL, CHK
Software: CLL, CHK
Validation: CHC, CLL, CHK
Formal analysis: CHC, CLL, CHK
Investigation: CHC, CHK
Resources: CHC, CHK
Data curation: CHC, CLL, CHK
Writing (original draft preparation): all authors
Writing (review and editing): all authors
Visualization: all authors
Supervision: CHC, CHK
Project administration: CYH, CHK
Funding acquisition: CYH, CHK

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claim information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR2). The IRB also specifically waived the consent requirement.

Informed consent For this type of study, formal consent is not required.

Abbreviations OSA, obstructive sleep apnea; LHID2000, Longitudinal Health Insurance Research Database 2000; COPD, chronic obstructive pulmonary disease; BMI, body mass index; IBD, inflammatory bowel disease; CAD, coronary artery disease; HBV, hepatitis B virus; HCV, hepatitis C virus infection; CI, confidence interval; aHR, adjusted hazard ratio; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, Ninth Edition, Clinical Modification; AHI, apnea–hypopnea index; NAFLD, non-alcoholic fatty liver disease

References

1. Shaffer EA (2006) Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol 20:981–996
2. Chen CY, Lu CL, Huang YS, Tam TN, Chao Y, Chang FY, Lee SD (1998) Age is one of the risk factors in developing gallstone disease in Taiwan. Age Ageing 27:437–441
3. Chen CH, Huang MH, Yang JC, Nien CK, Etheredge GD, Yang CC, Yeh YH, Wu HS, Der-Aur Chou*, Yueh SK Prevalence and risk factors of gallstone disease in an adult population of Taiwan: an epidemiological survey. J Gastroenterol Hepatol 2006;21:1737–43
4. Ross M, Brown M, McLaughlin K, Atkinson P, Thompson J, Powelson S, Clark S, Lang E (2011) Emergency physician-performed ultrasound to diagnose cholelithiasis: a systematic review. Acad Emerg Med 18:227–235
5. Yadav D, Lowenfels AB (2006) Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas 33: 323–330
6. Salek J, Livote E, Sideridis K, Bank S (2009) Analysis of risk factors predictive of early mortality and urgent ERCP in acute cholangitis. J Clin Gastroenterol 43:171–175
7. Gurusamy KS, Davidson BR (2014) Gallstones. BMJ 348:g2669
8. Ransohoff DF, Gracie WA, Wolfenson LB, Neuhauser D (1983) Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 99:199–204
9. Punjabi NM (2008) The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 5:136–143

10. Gozal D, Farre R, Nieto FJ (2016) Obstructive sleep apnea and cancer: epidemiologic links and theoretical biological constructs. Sleep Med Rev 27:43–55
11. Marshall NS, Wong KKH, Cullen SRJ, Knuiman MW, Grunstein RR (2014) Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study Cohort. J Clin Sleep Med 10:355–362
12. Unnikrishnan D, Jun J, Polotsky V (2015) Inflammation in sleep apnea: an update. Rev Endocr Metab Disord 16:25–34
13. Database NHIR. Taiwan, http://nhird.nhri.org.tw/en/index.html (cited in 2015)
14. Chen CH, Lin CL, Kao CH (2016) Gastroesophageal reflux disease with proton pump inhibitor use is associated with an increased risk of osteoporosis: a nationwide population-based analysis. Osteoporos Int 27:2117–2126
15. Chen CH, Lin CL, Kao CH (2016) Association between gallbladder stone disease and prostate cancer: a nationwide population-based study. Oncotarget 7:64380
16. Qaseem A, Dallas P, Owens DK, Starkey M, Holty Jon-Erik C, Shekelle P (2014) Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 161:210–220
17. O'Connor GT, Lind BK, Lee ET, Nieto FJ, Redline S, Samet JM et al (2003) Predictors of sleep-apnea-disordered breathing with race and ethnicity: the Sleep Heart Health Study. Sleep 26(74):79
18. Duran J, Esnaola S, Rubio R, Iztueta A (2001) Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 tp 70 yr. Am J Respir Crit Care Med 163:685–689
19. Launois SH, Pepin JL, Levy P (2007) Sleep apnea in the elderly: a specific entity? Sleep Med Rev 11:87–97
20. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH (2008) Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med 177:1150–1155
21. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T, American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, American Heart Association Stroke Council, American Heart Association Council on Cardiovascular Nursing, American College of Cardiology Foundation (2008) Sleep apnea and cardiovascular disease. Circulation 118:1080–1111
22. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE (2004) Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 160:521–530
23. López-Acevedo MN, Torres-Palacios A, Ocasio-Tascón ME, Campos-Santiago Z, Rodríguez-Cintrón W (2009) Overlap syndrome: an indication for sleep studies? Sleep Breath 13:409–413
24. Drager LF, Jun J, Polotsky VY (2010) Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis. Curr Opin Endocrinol Diabetes Obes 17:161–165
25. Smelt AH (2010) Triglycerides and gallstone formation. Clin Chim Acta 411:1625–1631
26. Liew PL, Wang W, Lee YC, Huang MT, Lin YC, Lee WJ (2007) Gallbladder disease among obese patients in Taiwan. Obes Surg 17: 383–390
27. Somer VK, Dyken ME, Clary MP, Abboud FM (1995) Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96: 1897–1904
28. Iftikhar IH, Hoyos CM, Phillips CL, Magalang UJ (2015) Meta-analyses of the association of sleep apnea with insulin resistance, and the effects of CPAP on HOMA-IR, adiponectin, and visceral adipose fat. J Clin Sleep Med 11:475–485
29. Ness GC, Zhao Z, Wiggins L (1994) Insulin and glucagon modulate hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity by affecting immunoreactive protein levels. J Biol Chem 269: 29168–29172
30. Chait A, Bierman EL, Albers JJ (1979) Low-density lipoprotein receptor activity in cultured human skin fibroblasts: mechanism of insulin-induced stimulation. J Clin Invest 64:1309–1319
31. Petitti DB, Friedman GD, Klatsky AL (1981) Association of a history of gallbladder disease with a reduced concentration of high-density- lipoprotein cholesterol. N Engl J Med 304:1396–1398
32. Ko CW, Beresford SAA, Schulte SJ, Lee SP (2008) Insulin resistance and incident gallbladder disease in pregnancy. Clin Gastroenterol Hepatol 6:76–81
33. Maurer KJ, Carey MC, Fox JG (2009) Roles of infection, inflammation, and the immune system in cholesterol gallstone formation. Gastroenterology 136:425–440
34. Camilleri M, Malhi H, Acosta A (2017) Gastrointestinal complications of obesity. Gastroenterology 152:1656–1670
35. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK (2010) Interactions between obesity and obstructive sleep apnea. Chest 137:711–719