Sleep Medicine 16 (2015) 955–960

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Obstructive sleep apnea is associated with liver disease: a population-based cohort study

Tzu-Chieh Chou [a,b], Wen-Miin Liang [a,c], Chang-Bi Wang [a], Trong-Neng Wu [a,d,*], Liang-Wen Hang [e,f,g,**]

[a] Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan
[b] Department of Health Risk Management, College of Management, China Medical University, Taichung, Taiwan
[c] Graduate Institute of Biostatistics, Biostatistics Center, College of Management, China Medical University, Taichung, Taiwan
[d] Department of Nursing, College of Medicine and Nursing, Hunguang University, Taichung, Taiwan
[e] Department of Respiratory Therapy, College of Health Care, China Medical University, Taichung, Taiwan
[f] Sleep Medicine Center, Department of Pulmonary and Critical Care Medicine, China Medical University Hospital, Taichung, Taiwan
[g] Department of Healthcare Administration, Asia University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 12 February 2015
Accepted 25 February 2015
Available online 14 May 2015

Keywords:
Obstructive sleep apnea
Liver disease
Non-alcoholic fatty liver disease
Cirrhosis
Hepatitis B
Hepatitis C

ABSTRACT

Background: The association between obstructive sleep apnea (OSA) and the risk of liver disease is unclear. Moreover, population-based studies on the risk of liver disease among people with OSA have not yet been conducted. This study aimed to investigate the risk of subsequent development of liver disease among people with OSA.

Methods: Using Taiwan National Health Insurance claims data, this study collected subjects from a cohort of 17,374 people with OSA who were diagnosed between 2000 and 2008. A control group of 69,496 people was selected from the same database and matched by age, gender, urbanization, income, and date of initial admission. All subjects were followed up until 2010. Liver disease incidence and risk were calculated.

Results: The overall risk of liver disease among people with OSA was significantly higher than in the control group (aHR = 5.52, $p < 0.001$). Non-alcoholic fatty liver disease, cirrhosis, and hepatitis C had significant aHRs of 5.29, 7.50, and 7.19 (all at $p < 0.001$), respectively. In contrast, hepatitis B had the smallest aHR of 3.71.

Conclusions: The risk of liver disease was more than five times higher among people with OSA compared with the control group; this was particularly for cirrhosis and hepatitis C. Liver disease is thus a very important health issue among people with OSA.

1. Introduction

Liver diseases, including viral infections, alcoholic, and non-alcoholic causes, are major global health problems. In the Far East, the prevalence of viral and non-alcoholic causes of liver disease is extremely high [1,2]. Fatty liver disease is also a widespread and common global health issue. Particularly in China, population-based surveys have revealed that fatty liver has become a serious public health problem as a result of improved living standards and increased alcohol consumption [3]. Epidemiological studies of fatty liver disease have revealed some important risk factors. Large population-based surveys in the Asia-Pacific region have indicated that the prevalence rates of non-alcoholic fatty liver disease (NAFLD) range from 12 to 24% in population subgroups of age, gender, ethnicity, and geographic location (urban vs rural) [4]. Most important, the major risk factors of NAFLD are obesity and insulin resistance [5]. Non-alcoholic fatty liver disease exists along a continuum with various degrees of severity, such as steatosis without inflammation, non-alcoholic steatohepatitis (NASH), and liver cirrhosis or end-stage NAFLD [6]. Insulin resistance and dyslipidemia are the key promoters of fatty acid deposition in the liver [7,8]. The identified risk factors for the progression of NAFLD are: obesity, being over 45 years of age, having diabetes, hypertriglyceridemia, or hypertension [9,10]. Previous studies have also shown hepatitis B and hepatitis C prevalence in Taiwan to be 13.0% and 4.2%, respectively [11]. The major risks for hepatic viral infection are family history, vertical transmission from mother to child, and age [12].

Although the pathogenesis of NAFLD is not fully understood, a 'two-hit' hypothesis has been proposed [13]. In this hypothesis, the first hit represents increased fat accumulation in the liver because

* Corresponding author. Department of Nursing, College of Medicine and Nursing, Hunguang University, Taichung, Taiwan. Tel.: +886 4 26318652; fax: +886 4 26310744.
E-mail address: tnwu@sunrise.hk.edu.tw (T.-N. Wu).
** Corresponding author. Department of Respiratory Therapy, College of Health Care, China Medical University, Taichung, Taiwan. Tel.: +886 4 22062121 1781; fax: +886 4 2062121 1784.
E-mail address: lungwen.hang@gmail.com (L.-W. Hang).

http://dx.doi.org/10.1016/j.sleep.2015.02.542
1389-9457/

of peripheral insulin resistance. The nature of the second hit is NASH, which results from the progression of NAFLD. Although the pathogenesis remains unclear, the consequences of oxidative stress, including lipid peroxidation, cell degeneration and necrosis, apoptosis, pro-inflammatory cytokine expression, liver stellate cell activation, and fibrogenesis have all been implicated [14–16]. Oxidative stress also plays an important role in the pathogenesis of viral hepatitis by worsening the severity of fibrosis progression [17].

Obstructive sleep apnea (OSA) is a sleep breathing disorder characterized by recurrent airflow obstruction caused by a total or partial collapse of the upper airways [18]. Untreated OSA can contribute to the development or progression of other disorders that affect multiple daily functions [19]. Obstructive sleep apnea is also associated with systemic or pulmonary hypertension [20,21], cardiac and cerebrovascular morbidity and mortality [18,22], neuropsychological impairment [23], and increased risk of automobile and occupational accidents [24,25]. Moreover, previous studies have postulated a correlation between OSA and liver disease. A meta-analysis by Musso et al., which included 18 cross-sectional studies, showed a two-fold increased risk of liver disease among people with OSA, indicating that OSA is associated with liver disease [26]. Obstructive sleep apnea can induce oxidative stress after intermittent hypoxia (IH) and may damage the liver because of lipid peroxidation [27]. However, studies of NAFLD, cirrhosis, hepatitis B, and hepatitis C infection among people with OSA are limited. It is believed that there are no studies that have utilized a national database in an Asian population. Most studies of people with OSA correlated with liver disease are cross-sectional, hospitalized-based study types; no large-scale, population-based study has been conducted to elucidate the relationship between OSA and liver disease. Given the need for research in this area, and the findings supporting the association of OSA with liver disease, the present retrospective and population-based study attempted to determine the incidence of NAFLD, NASH, hepatitis B, and hepatitis C infection among people with OSA in Taiwan over a 10-year follow-up period, and it investigated the incidence and effects of comorbidities on liver disease.

2. Materials and methods

2.1. Data sources

The National Health Insurance (NHI) database, which was published by the Department of Health of Taiwan, covers the period from 1997 to 2010. The NHI program was started in 1995 to finance health care for all Taiwanese residents. In 2010, the coverage rate was more than 99% of the whole population. The completeness and accuracy of the NHI Research Database (NHIRD) is guaranteed by the Department of Health and the NHI Bureau of Taiwan. This retrospective, population-based cohort study screened all subjects. All sampled individuals were followed up until the end of 2010.

2.2. Ethics statement

The NHIRD is composed of anonymous secondary data released to the public for research purposes. Thus, this study was exempted from a full review by the local ethics review committee.

2.3. Subject collection and study design

From the database, this study selected all people aged >20 years who were diagnosed with OSA (based on ICD-9-CM codes 780.X, 32720, 32721, 32726, and 32729) between January 1, 2000 and December 31, 2008. The first day of OSA diagnosis was assigned as the index day. All were diagnosed with OSA and examined with polysomnography (PSG) within one year before or after the index day.

To avoid confounding effects, the people who had liver disease before the index day were excluded. The control group was selected from the same database, excluding those diagnosed with OSA or liver disease before the index day, and they were matched by age, gender, urbanization status, income, and index day at a ratio of 1:4 (OSA vs control group) during the same time period. Liver disease diagnosis, including NAFLD (ICD-9-CM code: 571.8), cirrhosis (ICD-9-CM codes: 571.2, 571.5, and 571.6), hepatitis B (ICD-9-CM codes: V02.61, 070.20, 070.22, 070.30, and 070.32), and hepatitis C (ICD-9-CM codes: V02.62, 070.41, 070.44, 070.51, and 070.54) were identified among the people with OSA and the control group. To ensure matching accuracy, social indicators for each subject were calculated using age, gender, income, and insurance district. In total, 17,374 people with OSA and 69,496 controls were enrolled in the study. The cohort was followed until their exit from the NHI program, death, or the end of 2010.

2.4. Statistical analysis and liver disease risk analysis

Based on symptoms alone, it is difficult to detect liver disease developing in the first year after the index day. Therefore, people diagnosed with liver disease registered in the first year after the index day were excluded. Each subject was followed up for a minimum of two years and a maximum of 11 years. The demographic data and comorbidities of these two cohorts were first analyzed. Cumulative incidence analyses were performed using the Kaplan–Meier method, and the differences between the curves were tested with the log-rank test. The hazards ratios (HRs) of liver disease were measured using the stratified Cox proportional hazards model to determine whether OSA is a risk factor for developing liver disease. The model included age, gender, and comorbidities. All data management and calculation of HRs were performed using the SAS System (version 9.3; SAS Institute, Cary, NC). Cumulative incidence was analyzed using the Statistical Package for the Social Sciences (version 10.0; SPSS Inc, Chicago, IL). Statistical significance was set as a two-tailed p-value of <0.05.

3. Results

3.1. Demographic data

A total of 17,374 people with OSA were selected as the OSA cohort. The control cohort consisted of 69,496 matched subjects without OSA diagnosis. Obstructive sleep apnea predominantly affected males (11,852, 68.2%). Approximately 4314 (24.8%), 3414 (19.7%), 1612 (9.3%), 2156 (12.4%), and 818 (4.7%) people with OSA and 1221 (1.8%), 2616 (3.8%), 1910 (2.8%), 439 (0.6%), and 170 (0.2%) people in the control group had hypertension, diabetes, hyperlipidemia, congestive heart failure, and atrial fibrillation, respectively. All incidences of comorbidities were higher in people with OSA compared with the control group ($p < 0.001$) (Table 1).

3.2. Incidence of liver disease among subjects

Table 2 shows the liver disease incidence in the OSA cohort and the control group. The incidence of liver disease was higher among people with OSA compared with the control group (11.6% vs 3.0%). Non-alcoholic fatty liver disease and cirrhosis also showed higher incidences among people with OSA than the control group (7.0% vs 1.8% and 1.8% vs 0.4% for NAFLD and cirrhosis, respectively). Viral hepatitis showed the same pattern, and hepatitis B and hepatitis C incidences were nearly three-fold and five-fold higher among people with OSA than in the control group, respectively.

Table 1
Comparison of baseline characteristics and comorbidities among people with and without obstructive sleep apnea.

	People with obstructive sleep apnea $N = 17,374$	Control group $N = 69,496$	p^*
Age			0.99
<30	1184 (6.8%)	4759 (6.9%)	
30–59	7106 (40.9%)	28,404 (40.9%)	
≥60	9084 (52.3%)	36,333 (52.3%)	
Gender			1.00
Male	11,852 (68.2%)	47,408 (68.2%)	
Female	5522 (31.8%)	22,088 (31.8%)	
Urbanization area			1.00
Area 1	6086 (35.0%)	24,344 (35.0%)	
Area 2	3861 (22.2%)	15,444 (22.2%)	
Area 3	2941 (16.9%)	11,764 (16.9%)	
Area 4	2530 (14.6%)	10,120 (14.6%)	
Area 5	1956 (11.3%)	7824 (11.3%)	
Income per month (NTD)			1.00
<10,000	7554 (43.5%)	30,216 (43.5%)	
10,000–20,000	5601 (32.2%)	22,404 (32.2%)	
20,001–30,000	1270 (7.3%)	5080 (7.3%)	
30,001–40,000	893 (5.1%)	3572 (5.1%)	
40,001–50,000	949 (5.5%)	3796 (5.5%)	
>50,000	1107 (6.4%)	4428 (6.4%)	
Comorbidities			
Hypertension	4314 (24.8%)	1221 (1.8%)	<0.001
Diabetes	3414 (19.7%)	2616 (3.8%)	<0.001
Hyperlipidemia	1621 (9.3%)	1910 (2.8%)	<0.001
Congestive heart failure	2156 (12.4%)	439 (0.6%)	<0.001
Atrial fibrillation	818 (4.7%)	170 (0.2%)	<0.001

* By chi-squared test.

Table 2
Incidence of all liver diseases, non-alcoholic fatty liver disease, cirrhosis, hepatitis B, and hepatitis C among people with and without obstructive sleep apnea.

	People with obstructive sleep apnea $N = 17,374$	Control group $N = 69,496$	p^*
All liver diseases	2008 (11.6%)	2049 (3.0%)	<0.001
Non-alcoholic fatty liver disease	1217 (7.0%)	1226 (1.8%)	<0.001
Cirrhosis	310 (1.8%)	249 (0.4%)	<0.001
Hepatitis B	255 (1.5%)	352 (0.5%)	<0.001
Hepatitis C	182 (1.1%)	153 (0.2%)	<0.001

* By chi-squared test.

3.3. *Cumulative incidence of liver disease in the obstructive sleep apnea and control groups*

Kaplan–Meier estimates of the cumulative incidences of liver disease for OSA and the control group are shown in Fig. 1. The cumulative incidence of all liver disease in the OSA cohort was significantly higher than in the control group ($p < 0.001$, log-rank test, Fig. 1A). After the 10-year follow-up, the cumulative incidence was almost 10 times higher among people with OSA than in the control group. The greatest difference between the two groups was for NAFLD ($p < 0.0001$, log-rank test, Fig. 1B). Nevertheless, cirrhosis, hepatitis B, and hepatitis C showed smaller, but still significant, differences between people with OSA and the control group (Fig. 1C–E).

After adjusting the Cox multivariable proportional hazards analysis for age, gender, and comorbidities (Table 3), the risk of liver disease among the people with OSA was significantly higher than in the control group (aHR = 5.52, $p < 0.001$), and the risk was similar with NAFLD (aHR = 5.29, $p < 0.001$). Cirrhosis had an aHR of 7.50, whereas hepatitis C had an aHR of 7.19. Hepatitis B had the smallest aHR of 3.71, although all liver diseases showed a significant risk increase among people with OSA (all at $p < 0.001$).

Table 3
Cox proportional-hazards regression estimated hazard ratios (HR) in all liver diseases, non-alcoholic fatty liver disease, cirrhosis, hepatitis B and C among people with and without obstructive sleep apnea.

	Crude HR (95% CI)	p	Adjusted HR (95% CI)*	p
All liver diseases	6.24 (5.82–6.70)	<0.001	5.52 (5.12–5.96)	<0.001
Non-alcoholic fatty liver disease	5.83 (5.34–6.37)	<0.0001	5.29 (4.81–5.81)	<0.001
Cirrhosis	8.84 (7.23–10.80)	<0.0001	7.50 (6.02–9.34)	<0.001
Hepatitis B	3.89 (3.27–4.62)	<0.0001	3.71 (3.09–4.46)	<0.001
Hepatitis C	8.47 (6.55–10.96)	<0.0001	7.19 (5.41–9.55)	<0.001

* Adjusted for age, gender, and comorbidities.

4. Discussion

Liver disease is a common global health problem, especially in the Far East. Studies have shown that the overall prevalence of NAFLD in Taiwan is approximately 11.4–41.0%. The rates were higher in population subgroups – from 66.4% in healthy taxi drivers to 80% in obese individuals who attended weight-reduction programs [28]. Compared with other cross-sectional, hospital-based studies, the present research is probably the first large-scale, population-based cohort study to show an increase in liver disease among people with OSA compared with a control group. In the present study, the risks of NAFLD and cirrhosis were higher among people with OSA compared with the control group (aHR = 5.29 and 7.50, 95% CI 4.81–5.81 and 6.02–9.34, respectively). This study is also the first one to show a significant risk of viral hepatitis among people with OSA compared with the control group (aHR = 3.71 and 7.19, 95% CI 3.09–4.46 and 5.41–9.55 in hepatitis B and hepatitis C, respectively). The use of a large, representative, nationwide, and population-based sample to observe the risk of liver disease among people with OSA increases the validity of the results. The retrospective cohort study design provides a sufficient conclusion that represents the general OSA population.

Previous studies have postulated a relationship between OSA and liver disease since 2005. A study of 83 people with OSA and matched controls suggested a relationship between OSA and the progression of steatosis to steatohepatitis [29]. In a larger study of 218 people with OSA, severe OSA (defined as >50 apneic/hypopneic episodes/h [AHI]) was associated with increased liver enzymes (OR 5.9, $p < 0.02$). People with an AHI >50/h were also more likely to have steatosis, lobular necrosis, and fibrosis by liver biopsy [30]. One study on NASH included 99 people with PSG data: 77 NASH and 22 non-NASH controls. The results suggested that frequent nocturnal hypoxic episodes among people with NAFLD might be a risk factor for developing NASH [31].

Nocturnal IH can increase systemic oxidative stress and serum lipid peroxidation [27], which is implicated in the pathogenesis of NAFLD, NASH, and its progression to advanced stages of hepatic fibrosis [32]. Aside from studies demonstrating a higher prevalence of NAFLD in people with sleep-related breathing disorders [33], a recent study has indicated that a significant correlation exists between OSA and the presence and severity of NAFLD. Obstructive sleep apnea syndrome was found to be highly common, especially in severe NAFLD cases. The incidences of NAFLD in mild, moderate, and severe OSA were 59%, 58.3%, and 78.2%, respectively. The most highly correlated parameter to the severity of NAFLD was found to be the duration of hypoxia, so the authors suggested that nocturnal hypoxemia is a key pathophysiologic factor in the development of NAFLD [34].

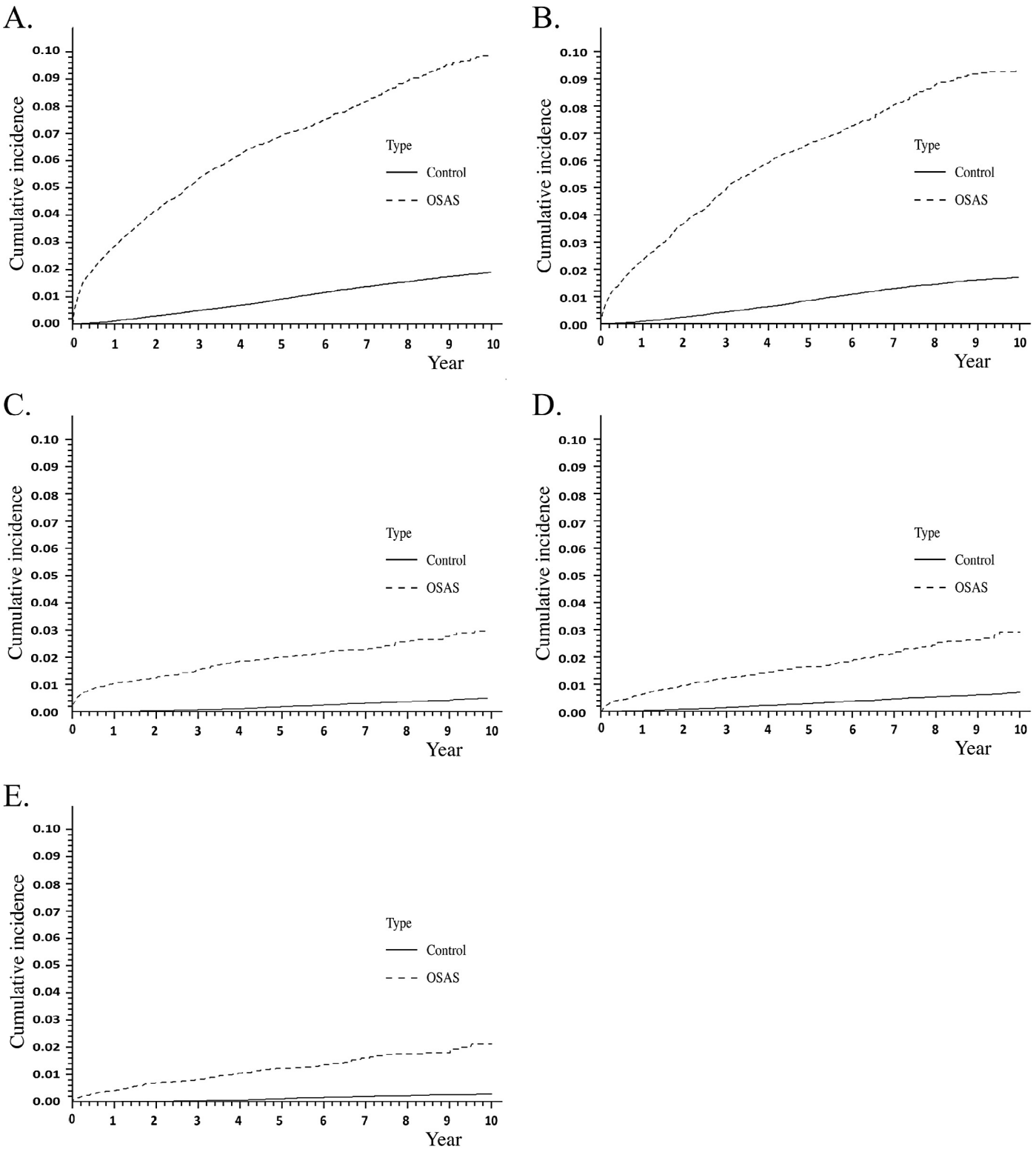

Fig. 1. The estimated cumulative incidence of liver disease among people with and without obstructive sleep apnea by Kaplan–Meier analysis. (A) All liver diseases. (B) Non-alcoholic fatty liver disease. (C) Cirrhosis. (D) Hepatitis B. (E) Hepatitis C.

Data from studies on animal and human models that mimic conditions of IH and sleep fragmentation in OSA have demonstrated the adverse effects of OSA on insulin resistance, glucose intolerance, and diabetes risk [35]. Intermittent hypoxia has also been shown to induce insulin resistance, which is independent of obesity, in healthy humans [36]. Insulin resistance is strongly linked to the excessive deposition of triacylglycerol in hepatocytes, which is the hallmark for NAFLD diagnosis [37]. However, the causal relationship between insulin resistance and NAFLD remains debatable [38]. Given that lab tests showing insulin and glucose levels in subjects were unavailable, the present study was unable to include this information in the analysis. In an effort to consider the effects of insulin

resistance and glucose intolerance, diabetes was included as a comorbidity in this study. Moreover, all crude HRs showed that people with comorbidities such as hypertension, diabetes, hyperlipidemia, congestive heart failure, and atrial fibrillation had significantly higher risk for the development of liver diseases (5.19, 2.89, 2.15, 6.73, and 6.70, respectively). In the multivariate analysis, obviously decreased HRs were found for all comorbidities (aHRs of 1.26, 1.46, 1.13, 1.48, and 1.79, respectively), but they still remained statistically significant ($p < 0.05$) for all comorbidities except hyperlipidemia ($p = 0.19$). These results emphasize the importance of comorbidities in developing liver diseases in the present study group. Nevertheless, during the observation period after the index day of this study, when comparing the OSA group with the control group with any liver disease, the incidences of comorbidities for hypertension, diabetes, and hyperlipidemia were 20.6% vs 1.7%, 16.4% vs 7.8%, and 9.0% vs 5.9%, respectively. As compared with the baseline status of comorbidities (when comparing the OSA group with the control group for hypertension, diabetes, and hyperlipidemia, 24.8% vs 1.8%, 19.7% vs 3.8%, and 9.3% vs 2.8%, respectively) (Table 1), a slight decrease in incidences of comorbidities among people with OSA and a slight increase in incidences of comorbidities in the control group were detected after the index day. This could lead to liver diseases occurring more frequently in the control group than in the OSA group. However, in this study, it was still found that an obvious risk of liver diseases occurred in people with OSA, indicating that the conclusion drawn from this study could actually be more conservative.

Some investigations have focused on antiviral drug use, such as interferon alpha, in people with hepatitis C and have made correlations with sleep disturbances [39].

Nevertheless, limited studies have discussed the relationship between OSA and viral hepatitis. Hypoxemia with reoxygenation may be analogous to ischemia–reperfusion, and reoxygenation may cause additional damage through the further production of free radical species that may cause different manifestations, especially in the hepatitides [40]. Other studies have postulated that hypoxemia-induced factors play an important role in the pathogenesis of viral hepatitis, including hepatitis B, hepatitis C, and hepatitis E [41]. Previous investigations have illustrated that disrupted sleep appears to have a serious impact on immune function. In healthy humans and animals, sleep disruption or deprivation could lead to changes in immunological reactions [42]. Sleep deprivation or restriction has been demonstrated to inhibit the response of antibodies to vaccination against hepatitis A and hepatitis B [43,44]. People with OSA have poor sleep quality because of frequent sleep interruption and apnea-related arousals [45]. Proinflammatory markers, including tumor necrosis factor-a, interleukin (IL)-6, IL-8, and C-reactive protein, are increased among people with OSA [46]. Although the present study could not provide direct historical observation of liver disease in both groups, the results for viral hepatitis have given insight into the response to infections in the context of sleep disorders, especially OSA. Using a prospective cohort study design on a topic related to viral hepatitis incidence among people with OSA and the influence of OSA on viral hepatitis is warranted for future study.

The present study is a large, population-based, retrospective cohort study. Nevertheless, it has some limitations that should be addressed. First, the NHIRD does not contain personal information, such as lifestyle, body mass index, or smoking/alcohol use, which may contribute to NAFLD risk. The indices of OSA severity and apnea/hypopnea, as well as the frequency and degree of IH, were also unavailable in the database. Second, misclassification of OSA may occur in the NHIRD. Thus, this study enrolled people with OSA with nocturnal PSG evidence and definite diagnoses to minimize possible bias. Third, liver function tests, liver biopsies, or ultrasonographic data were unavailable. These data can be used to determine the factors that best correlate with the presence of NAFLD, which may add to the knowledge of underlying mechanisms linking NAFLD to OSA. Fourth, while previous studies have reported an overall prevalence rate of ≥2–4% in the general population [47], OSA was found to be occurring in approximately 0.9% of the subjects in the database. Therefore, it seems very likely that OSA is being underdiagnosed in Taiwan. This scenario leads to the possibility of many undiagnosed people with OSA in the general Taiwanese population, which may dilute the association detected in this study. Moreover, a lack of clinical and basic personal information could limit the interpretation of data and conclusions that can be drawn from this study. For instance, the high risk of liver disease among people with OSA warrants further verification using other population-based databases.

5. Conclusions

In conclusion, the risk of liver disease was more than five times higher among people with OSA compared with the control group in this large population-based study, particularly for cirrhosis and hepatitis C. A more than five-fold increased risk of NAFLD and an almost four-fold increased risk of hepatitis B infection among people with OSA were observed, indicating that liver disease is a relevant and very important health issue among people with OSA. Further evaluation of this population is warranted to ensure earlier diagnosis and treatment of these health issues. Given that the data analysis was limited by a lack of direct evidence for some potentially confounding variables, a prospective cohort study on liver disease among people with OSA is warranted in the future. Moreover, future studies should clarify the multi-factorial nature of liver disease development among people with OSA with sufficient basic characteristics; it would also be of interest to assess if therapies for OSA, such as continuous positive airway pressure, can decrease morbidity and mortality in the context of liver disease.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.02.542.

Acknowledgements

The authors would like to thank Mr. Chi-Fung Chen and Ms. Wan-Ting Huang for their assistance in the preparation of the manuscript. This work was supported by grants from China Medical University and Hospital (grant number: CMU 100-SR-66 and CMU 100-TS-09).

References

[1] Amarapurkar D, Kamani P, Patel N, et al. Prevalence of non-alcoholic fatty liver disease: population based study. Ann Hepatol 2007;6(3):161–3.
[2] Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45(4):529–38.
[3] Yan H, Luo JY, Zhou XY. Epidemiological analysis of alcoholic and nonalcoholic fatty liver in Shanxi and Gansu province. Weichang Bingxue he Ganbing Xue Zazhi 2007;16:347–50.
[4] Chen CH, Huang MH, Yang JC, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. J Clin Gastroenterol 2006;40(8):745–52.
[5] Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132(2):112–17.
[6] Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 2004;114(2):147–52.
[7] Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. J Clin Gastroenterol 2006;40(Suppl. 1):S5–10.
[8] McCullough AJ. Pathophysiology of nonalcoholic steatohepatitis. J Clin Gastroenterol 2006;40(Suppl. 1):S17–29.

[9] Clark JM, Diehl AM. Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. JAMA 2003;289(22):3000–4.
[10] Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37(4):917–23.
[11] Li WC, Lee YY, Chen IC, et al. Association between the hepatitis B and C viruses and metabolic diseases in patients stratified by age. Liver Int 2013;33(8):1194–202.
[12] Wang CS, Chang TT, Yao WJ, et al. Comparison of hepatitis B virus and hepatitis C virus prevalence and risk factors in a community-based study. Am J Trop Med Hyg 2002;66(4):389–93.
[13] Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002;123(1):134–40.
[14] Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121(1):91–100.
[15] Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7(12):677–85.
[16] Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology 2003;37(5):1202–19.
[17] Poli G. Pathogenesis of liver fibrosis: role of oxidative stress. Mol Aspects Med 2000;21(3):49–98.
[18] Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009;6(8):e1000132.
[19] Cartwright RD, Knight S. Silent partners: the wives of sleep apneic patients. Sleep 1987;10(3):244–8.
[20] Blankfield RP, Hudgel DW, Tapolyai AA, et al. Bilateral leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea. Arch Intern Med 2000;160(15):2357–62.
[21] Sajkov D, Wang T, Saunders NA, et al. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2002;165(2):152–8.
[22] Sun H, Shi J, Li M, et al. Impact of continuous positive airway pressure treatment on left ventricular ejection fraction in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. PLoS ONE 2013;8(5):e62298.
[23] Engleman HM, Kingshott RN, Martin SE, et al. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). Sleep 2000;23(Suppl. 4):S102–8.
[24] George CF, Smiley A. Sleep apnea and automobile crashes. Sleep 1999;22(6):790–5.
[25] Ulfberg J, Carter N, Edling C. Sleep-disordered breathing and occupational accidents. Scand J Work Environ Health 2000;26(3):237–42.
[26] Musso G, Cassader M, Olivetti C, et al. Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. Obes Rev 2013;14:417–31.
[27] Jun J, Savransky V, Nanayakkara A, et al. Intermittent hypoxia has organ-specific effects on oxidative stress. Am J Physiol Regul Integr Comp Physiol 2008;295(4):R1274–81.
[28] Lin TJ, Lin CL, Wang CS, et al. Prevalence of HFE mutations and relation to serum iron status in patients with chronic hepatitis C and patients with nonalcoholic fatty liver disease in Taiwan. World J Gastroenterol 2005;11(25):3905–8.
[29] Tatsumi K, Saibara T. Effects of obstructive sleep apnea syndrome on hepatic steatosis and nonalcoholic steatohepatitis. Hepatol Res 2005;33(2):100–4.
[30] Tanne F, Gagnadoux F, Chazouilleres O, et al. Chronic liver injury during obstructive sleep apnea. Hepatology 2005;41(6):1290–6.
[31] Mishra P, Nugent C, Afendy A, et al. Apnoeic-hypopnoeic episodes during obstructive sleep apnoea are associated with histological nonalcoholic steatohepatitis. Liver Int 2008;28(8):1080–6.
[32] Edmison J, McCullough AJ. Pathogenesis of non-alcoholic steatohepatitis: human data. Clin Liver Dis 2007;11(1):75–104, ix.
[33] Singh H, Pollock R, Uhanova J, et al. Symptoms of obstructive sleep apnea in patients with nonalcoholic fatty liver disease. Dig Dis Sci 2005;50(12):2338–43.
[34] Turkay C, Ozol D, Kasapoglu B, et al. Influence of obstructive sleep apnea on fatty liver disease: role of chronic intermittent hypoxia. Respir Care 2012;57(2):244–9.
[35] Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? Front Neurol 2012;3:126.
[36] Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol 2009;106(5):1538–44.
[37] Abdelmalek MF, Diehl AM. Nonalcoholic fatty liver disease as a complication of insulin resistance. Med Clin North Am 2007;91(6):1125–49.
[38] Postic C, Girard J. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. J Clin Invest 2008;118(3):829–38.
[39] Sockalingam S, Abbey SE, Alosaimi F, et al. A review of sleep disturbance in hepatitis C. J Clin Gastroenterol 2010;44(1):38–45.
[40] Samarasinghe DA, Tapner M, Farrell GC. Role of oxidative stress in hypoxia-reoxygenation injury to cultured rat hepatic sinusoidal endothelial cells. Hepatology 2000;31(1):160–5.
[41] Nath B, Szabo G. Hypoxia and hypoxia inducible factors: diverse roles in liver diseases. Hepatology 2012;55(2):622–33.
[42] Gomez-Gonzalez B, Dominguez-Salazar E, Hurtado-Alvarado G, et al. Role of sleep in the regulation of the immune system and the pituitary hormones. Ann N Y Acad Sci 2012;1261:97–106.
[43] Lange T, Perras B, Fehm HL, et al. Sleep enhances the human antibody response to hepatitis A vaccination. Psychosom Med 2003;65(5):831–5.
[44] Prather AA, Hall M, Fury JM, et al. Sleep and antibody response to hepatitis B vaccination. Sleep 2012;35(8):1063–9.
[45] Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. Eur Respir J 1995;8(7):1161–78.
[46] Arnardottir ES, Mackiewicz M, Gislason T, et al. Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep 2009;32(4):447–70.
[47] Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230–5.