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Clinical characteristics in patients with nonalcoholic steatohepatitis in Japan: a retrospective cohort study using the National Health Insurance claims database

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Title: Clinical characteristics in patients with nonalcoholic steatohepatitis in Japan: a retrospective cohort study using the National Health Insurance claims database

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Abstract (275/300 words)

Objectives: To examine the clinical characteristics of patients with nonalcoholic steatohepatitis (NASH) and associated comorbidities.

Design: This retrospective cohort study using the national health insurance claims database.

Setting: Japanese patients with NASH was conducted between April 2015 and March 2020.

Participants: Patients who met the diagnostic definitions for NASH (n = 545) were matched with non-NASH controls (n = 185,264) and randomly selected according to sex, birth year, and residential area.

Interventions: No interventions were made.

Primary and secondary outcome measures: Odds ratios (OR) were estimated for the relationship between patient background, e.g., age, sex, body mass index (BMI), NASH-related comorbidities, and lifestyle-related diseases.

Results: BMI was significantly higher in patients with NASH than in controls (25.75 kg/m^2 vs. 22.90 kg/m^2, p <0.001). NASH was associated with an increased risk for hepatic cirrhosis (OR 28.81 (95% Cl, 21.79–38.08), followed by liver cancer (OR 18.38 (95% Cl 12.56–26.89)), gastroesophageal reflux disease (OR 3.08 (95% Cl 2.53–3.73)), colorectal adenomas (OR 2.54 (95% Cl 1.25–5.16)), colon cancer (OR 2.36 (95% CI 1.70–3.28)), cancer (OR 2.16 (95% Cl 1.79–2.62)), sleep apnea (OR 1.82 (95% Cl 1.20–2.76)), cardiovascular disease (OR 1.40 (95% Cl 1.16–1.69), and osteoporosis (OR 1.25 (95% Cl 1.02–1.53)). There were no significant associations between NASH and risk for depression (OR 1.11 (95% Cl 0.87–1.41)), insomnia (OR 1.12 (95% Cl 0.94–1.34)), or chronic kidney diseases (OR 0.81 (95% Cl 0.58–1.12)).

Conclusions: In the daily medical care of patients, it is necessary to consider sex and age differences and to pay close attention to the risk for liver cancer, but also other lifestyle-related comorbidities associated with NASH.

Strengths and limitations of this study:

- The data used in this study were collected from the NHI and therefore do not cover the whole of Japan.
- Secondary data analysis may lead to systematic limitations.
- It should be recognized that the data are secondary and that some information is missing.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, affecting approximately 20–30% of the global population[1]. NAFLD includes nonalcoholic fatty liver (NAFL), which is pathologically pure steatosis alone, or in which steatosis is accompanied by inflammatory cell infiltration, and nonalcoholic steatohepatitis (NASH), which is accompanied by hepatic steatosis, and inflammatory cell infiltration, as well as ballooning (hepatocellular ballooning) and hepatic fibrosis[2].

Liver tissue biopsy is the gold standard for diagnosing NAFLD[3–6], which is consistent with guidelines published overseas. However, in clinical practice, it is not feasible to perform a liver biopsy with bleeding or pain in all patients with NAFLD. Therefore, the proportion of patients undergoing liver biopsy for a NASH diagnosis in clinical practice is not fully understood. According to Rinella et al[4], the rate of biopsy for the diagnosis of NASH and the rate of prescription of therapeutic drugs recommended by the guidelines are low, and NASH is underdiagnosed[6]. According to an estimate based on a Markov model of the number of patients with NAFL and NASH worldwide, the number of patients with fibrotic NASH at stage III or higher in Japan is predicted to increase to 660,000 in 2016 and 990,000 in 2030[7]. In addition, although the prevalence of NASH has been estimated to be approximately 3–5% of the population[8,9], there is insufficient evidence for the prevalence of NASH in the general population due to selection bias in liver biopsies and diagnostic difficulties.

NASH is strongly associated with metabolic syndrome, obesity, diabetes mellitus, hypertension, and dyslipidemia[1], and the major causes of death are cardiovascular and liver disease-related events[6]. Obesity and diabetes mellitus are risk factors for cardiovascular and liver disease-related events, including decompensated cirrhosis and liver cancer. Overseas guidelines propose the evaluation of liver function by abdominal echography and blood tests in patients with obesity or diabetes mellitus[3]. In the Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Diseases/Nonalcoholic Steatohepatitis 2020 (2nd Edition) of Japan (the NASH/NAFLD guideline)[10], it is recommended that primary care physicians assess liver function in patients with risk factors including obesity, diabetes mellitus, dyslipidemia, and hypertension and identify all cases of NAFLD fibrosis progression (as primary screening). As NASH is often asymptomatic and cirrhosis may already be diagnosed at the time of diagnosis, efficient screening and timing of referral to a gastroenterologist are important. In NASH, liver fibrosis progresses by one stage in approximately 7 years, and progresses faster in patients with comorbid metabolic diseases such as obesity and diabetes mellitus[11]. Therefore, it is recommended that the degree of fibrosis in the NASH group should be regularly evaluated, and, depending on the results, follow-up observation or screening should be performed for liver-related diseases such as liver failure and liver cancer, and non-liver-related diseases such as cerebrocardiovascular events and cancers of other organs[2].

In Japan, which has a universal health insurance system, almost all residents are covered by medical insurance. It is possible to understand the medical situation of local residents by investigating the claims data of medical insurance held by the administration[12]. Japan has several public health insurance systems. Each municipality serves as the payer of the National Health Insurance (NHI), and the municipalities jointly established the "Federation of National Health Insurance Organizations (FNHIO)" to provide insurance services. Each prefecture has one payer.

The University of Occupational and Environmental Health, Japan (UOEH) has been able to use health insurance claims data by closely cooperating with payers in the Kyushu region of Japan. In addition, the Kyushu region has a high incidence of hepatocellular carcinoma, and measures against hepatitis and liver cancer have been emphasized since early in Japan. Therefore, as a case study, we examined the clinical characteristics of patients with NASH using the NHI claims data from the Kyushu region. NHI is the data that enables us to grasp the disease information of persons participating in national health insurance every month. Eguchi et al. [13] showed that the age-specific prevalence of NAFLD was higher in middle-aged men and older women, with differences in the age distribution of NAFLD onset between males and females. To obtain data on the late-stage elderly, in this study, we matched the NHI claims and the health insurance database for persons 75 years of age and older on an individual basis and constructed an original database.

Methods

Study Design and Data Source

Japan's health insurance system is commonly divided into three types: company health insurance for those employed in a business, NHI for residents of each region, and long-term elderly health insurance (LEHI) for those aged 75 years or older. NHI is a mutual assistance program in which enrolled members pay premiums to a financial pool to which the national government and local municipalities add funds. This retrospective cohort study was analyzed using the NHI and LEHI claims databases, comprising inpatient, outpatient, and dispensing service data from domestic payers over April 2015 (through March 2020), provided by the public institution in two prefectures in the Kyushu region of Japan.

The data included the age and gender of each beneficiary, the type of service used, the month during which the service was used, monthly expenditures on the use of the services, and exit information (death or move-out). We prepared a panel database combining basic medical check-up data and claim databases conducted on a patient-by-patient basis to examine the clinical characteristics of patients with NASH. This study was approved by the ethics committee of the University of Occupational and Environmental Health, Japan.

Study population and eligibility criteria

The inclusion criteria were patients of any age with a record of at least one episode of NASH during the study period from April 2015 to March 2020. An episode of NASH was defined as a diagnosis of NASH (ICD-10 K-75.8; other inflammatory liver diseases or K-76.0; other fatty liver). In addition, patients who could be visually confirmed to have "hepatitis," "non-alcoholic," and "NASH" were also included in the analysis. By using ICD-10; K-75.8 and K-76.0, we have known extremely difficult to sort out NASH patients from NAFLD patients. Since definitive diagnosis of NASH is histopathological diagnosis by liver biopsy and it is essential to confirm pathologically characteristic finding, patients diagnosed with NASH after liver biopsy (percutaneous needle biopsy, endoscopic biopsy and endoscopic ultrasound-guided fine-needle aspiration biopsy) indication were selected. Controls that never had a claim associated with NASH were randomly selected from patients who visited a medical facility at least once between April 2015 and March 2020.

Exclusion criteria were claims for any of the following conditions at any time: hepatitis B virus, hepatitis C virus, human immunodeficiency virus, alcoholic liver disease, toxic liver injury, copper metabolism disorder, autoimmune hepatitis, Gaucher's disease, lysosomal acid lipase deficiency, biliary cirrhosis, cholangitis, or iron metabolism disorder. ICD-10 codes were used to identify the patients with these diseases.

A patient was defined as having a comorbidity if they had at least one claim for the relevant ICD-10 code during the analysis period. Fourteen comorbidity categories of interest identified using ICD-10 diagnosis codes (Supplemental Table1) were pre-specified: hypertension, dyslipidemia, type 2 diabetes, osteoporosis, insomnia, depression, hepatic cirrhosis, liver cancer, cancer, colorectal adenomas, chronic kidney disease (CKD), gastroesophageal reflux disease (GERD), cardiovascular disease (CVD), and sleep apnea syndrome (SAS). The prevalence of these predefined comorbidity groups has been reported in all patients with NASH and non-NASH comparators.

According to our definition, each patient classified as having NASH was matched with non-NASH comparators randomly selected from the original database by sex, birth year, and residential area.

Data Collection

Baseline data on all patient characteristics (age, sex), date of death (if data were recorded), prescribed drugs for treating NASH, and NASH-related comorbidities were collected. Age and sex were obtained as of April 2015. The dates of death and prescribed drugs for treating NASH-related comorbidities were obtained at any time during the study period. Height, weight, and laboratory test values were also obtained from patients' available data at any time during the study period. BMI was calculated from the data of height and weight recorded.

Statistical Analyses

We designed a case-control study to compare the occurrence of comorbidities among the NASH and non-NASH groups during the analysis period and to assess the relationship between NASH and comorbidities. Odds ratios of age, sex, life-related diseases (hypertension, dyslipidemia, type 2 diabetes), and NASH-related comorbidities. All analyses were conducted for the two groups: the NASH group, in which patients had at least one record of being diagnosed with NASH, and the non-NASH group, in which the patients had no record of being diagnosed.

We conducted descriptive statistics using multiple logistic regression models to analyze the relationship between NASH and sex, age, lifestyle-related diseases, death, and comorbidities for continuous data (Odd Ratio [OR], 95% confidence interval [95% CI]). Differences between the NASH and non-NASH groups were evaluated using paired-sample t-tests for continuous variables. Statistical significance was set at $p < 0.05$.

All statistical analyses were performed using Stata Ver.17.0 released in April 2021 (Stata Coro, College Station, Texas, USA).

Results

Patient characteristics

Patient background characteristics are shown in Table 1. A total of 545 patients with NASH (209 males and 336 females) were selected from the claims databases, and 185,264 non-NASH controls (80,051 males and 105,213 females) were identified. The median (interquartile range; IQR) age of the NASH and non-NASH groups was 68 (63.00-75.00) and 65 (44.0– 74.0) years, respectively. In the NASH and the non-NASH groups, 4.4% and 3.6% of patients (cases, n = 24; non-NASH controls, n = 6,696) died during the analysis period from April 2015 to March 2020, respectively. Among the NASH group, the most frequently prescribed agents were statins (53.2%), followed by angiotensin receptor blockers (ARBs) (45.9%), and vitamin E (12.1%), and among the non-NASH group, it was ARBs (22.2%), statins (21.4%), and angiotensin-converting-enzyme inhibitor (ACEi) (2.8%).

Table 2 summarizes the values of the patients whose height, weight, BMI, and blood test values could be extracted for each group. A total of 220 patients were identified in the NASH group, and 44,913 patients were identified in the non-NASH group. BMI was significantly higher than in the NASH vs. non-NASH group (25.75 kg/m^2 vs. 22.90 kg/m^2, p <0.001). The laboratory test value (> 5%) was also higher than in the NASH vs. non-NASH group, except for high-density cholesterol (54.0 mg/dL and 61.0 mg/dL, respectively) and low-density lipoprotein cholesterol (109.0 mg/dL and 117.0 md/dL, respectively).

Comorbidities

Table 3 summarizes the NASH-related comorbidities of patients in each group. The prevalence of all NASH-related comorbidities was significantly higher in the NASH group vs. the non-NASH group, except autoimmune hepatitis. The five most prevalent comorbidities were over 50% in the NASH group: dyslipidemia (82.6 %), hypertension (78.7 %), GERD (69.9%), type 2 diabetes (62.2%), and CVD (56.0%). In the non-NASH group, no more than 50% of NASH-related comorbidities were present, with hypertension (46.5%) being the most common comorbidity, followed by dyslipidemia (36.4%).

Age, sex, and life-related disease as risk factors for NASH

The influence of sex, age, and life-rated disease on NASH has been reported previously[14] [15]. Multiple logistic regression models were used to assess the effect of sex, age, and lifestyle-related diseases on the prevalence of NASH. Figure 1 shows the odds ratio (OR) for these factors associated with the prevalence of NASH. Female sex, hypertension, dyslipidemia, and type 2 diabetes had a significantly higher risk than the non-NASH group;

dyslipidemia and type 2 diabetes were very high (4.39 and 5.83, respectively). The association with age was insignificant compared to the non-NASH group.

In a separate multiple logistic regression model examining the association between mortality due to NASH and each of these risk factors, adjusted for sex, age, and lifestyle-related diseases, the ORs for age and type 2 diabetes were significantly higher than in the non-NASH group (Figure 1).

Comorbidities as risk factors for NASH

The OR with NASH and NASH-related comorbidities is shown in Table 4. In a multiple logistic regression model examining the association between NASH and developing comorbidities, compared to non-NASH, hepatic cirrhosis was associated with the greatest risk of NASH (OR 28.81, 95% CI, 21.79–38.08), followed by liver cancer (OR 18.38, 95% CI, 12.56–26.89), GERD (OR 3.08, 95% CI 2.53–3.73), colorectal adenomas (OR 2.54, 95% CI 1.25-5.16), colon cancer (OR 2.36, 95% CI 1.70–3.28), cancer (OR 2.16, 95% CI 1.79–2.62), SAS (OR: 1.82, 95% CI 1.20–2.76), CVD (OR 1.40, 95% CI 1.16–1.69), and osteoporosis (OR 1.25, 95% CI 1.02–1.53). No significant difference in comorbidities was observed for depression (OR 1.11, 95% CI 0.87–1.41), insomnia (OR 1.12, 95% CI 0.94–1.34), and CKD (OR 0.81, 95% CI 0.58–1.12).

There was no significant difference in OR for osteoporosis (OR 1.03, 95% CI 0.94–1.13) in NASH vs. non-NASH, but OR was significantly increased to 6.69 (95% CI 6.47–6.91) in females. OR for CKD was less <1, and it was not significantly elevated with NASH. However, when NASH patients had a history of hypertension, dyslipidemia, or type 2 diabetes, ORs increased significantly to 4.34（95% CI 4.01–4.69）, 1.34 (95% CI 1.28–1.40) and 2.08 (95% CI 1.98–2.18), which has been shown to increase the risk of developing CKD.

Discussion

Using NHI claim data and LEHI in the Kyushu region, we constructed an original database and examined the clinical characteristics of patients with NASH for 5 years from April 2015 to March 2020. It has been reported that the prevalence of NAFLD/NASH varies by age and gender[13,15,16] . In a cross-sectional study[13] conducted among 8,352 subjects who underwent health checkups from 2009 to 2010 at three health centers in Japan, the overall prevalence of NAFLD was 29.7%, more than 30% in males aged 30–60 years, and increased with age in females aged 30–60 years old. It is considered that a decrease in estrogen due to aging and menopause affects the progression of NAFLD in females[14]. Similar to NAFLD, there are more middle-aged males and older females in the age distribution of NASH prevalence. In this study, the median age of the NASH patient group was 68 years (IQR, 63.00-75.00), showing an older age and a higher proportion of females than males (38.3% vs. 61.7%). This finding also suggests that the prevalence of NASH is higher in older females.

NAFLD/NASH is strongly associated with obesity[7,13,15]. This study showed that the BMI was significantly higher in the NASH group than in the non-NASH group (25.75 kg/m^2 vs 22.9 kg/m^2, p <0.001). Obesity is the most common manifestation of the metabolic syndrome and is considered the most important risk factor for NAFLD/NASH, which can also be regarded as a liver lesion[17]. The prevalence of NAFLD/NASH in non-obese participants (BMI <23 kg/m^2) was ≤10%. The prevalence of NAFLD/NASH increases with increasing BMI and is approximately 80% in highly obese subjects (BMI >30 kg/m^2)[10]. It has also been reported that hepatic steatosis, inflammatory cell infiltration, and ballooning decreased by 7% or more of body weight loss, and the NAFLD activity score improved[18]. This study also showed that the median BMI was higher than 25 kg/m^2 in the NASH patient group, suggesting the importance of not only liver lesions, but also active lifestyle interventions in daily medical practice for NAFLD/NASH. However, it is essential to change the consciousness of patients for lifestyle interventions, and maintenance of the target achievement rate and adherence becomes an issue. Similar to previous research[19,20], the results of the present study may support the association of NAFLD/NASH with several metabolic comorbidities, including type 2 diabetes, dyslipidemia, hypertension, and CVD. In terms of CKD, patients with NASH were shown to have a higher risk of complications if they had hypertension or type 2 diabetes. Management of these conditions may complicate the treatment of NASH, impacting clinical care outcomes.

According to the NASH/NAFLD guidelines[10], some therapeutic drugs for dyslipidemia, hypertension, and diabetes mellitus have been suggested to be effective for NASH, and aggressive treatment of patients with complications of these lifestyle-related diseases is recommended. Therefore, this survey investigated the proportion of prescriptions for antihyperlipidemic, hypertensive, and antidiabetic drugs. As a result, the proportion of

prescriptions was 53.2% for statins and 45.9% for angiotensin receptor blockers (ARBs) in the NASH group, which was significantly higher than 21.4% for statins and 22.2% for ARBs in the non-NASH group, but the proportion of prescriptions was less than 50%. The NASH/NAFLD guideline[10] recommends the administration of vitamin E for NAFLD/NASH without comorbidities. For patients with diabetes mellitus, pioglitazone, GLP-1 antagonists, and GSLT2 inhibitors have been proposed. In addition, statins have been proposed for patients complicated with dyslipidemia, and ARBs and angiotensin II converting enzyme (ACE) inhibitors have been proposed for patients complicated with hypertension. However, statins are contraindicated for hepatic cirrhosis, and pioglitazone is contraindicated for serious hepatic impairment. In addition, SGLT2 inhibitors are indicated for careful administration in Child-Pugh class C patients, and ARBs are indicated for "careful administration" or "contraindication" in patients with cirrhosis. Caution should be exercised when selecting drugs. At present, there is no drug for which there is sufficient evidence that it improves fibrosis in patients with NASH. These are considered to be the reasons for the lack of aggressive drug treatments. It is anticipated that many clinical studies on drug therapy and development for NASH will be conducted in the future.

The prevalence of lifestyle-related diseases in NAFLD in Japan is reported to be approximately 60–80% for dyslipidemia, 40% for hypertension, and 20–50% for diabetes mellitus[10]. The results of this study focusing on NASH also showed that the complication rates of dyslipidemia, hypertension, GERD, and type 2 diabetes were significantly higher in the NASH group than in the non-NASH group (82.6% vs. 36.4 %, $p < 0.001$; 78.7% vs. 46.5%, $p < 0.001$; 69.9% vs. 28.7%, $p < 0.001$; 62.2% vs. 14.4%, $p < 0.001$), which was higher than the complication rate of lifestyle-related disease of NAFLD. In a study by Terai et al.[21][22] who estimated complications in patients with NAFLD/NASH using the Medical Data Vision (MDV) claims database, the prevalence of dyslipidemia at 67–74 years of age was 57.9%, the prevalence of hypertension was 57.2%, and the prevalence of type 2 diabetes was 32.5%, which was lower than that in the present study (dyslipidemia, 82.6%, hypertension, 78.7%, type 2 diabetes, 62.2%), but the prevalence of CVD was 75.8%, which was higher than that in the present study (56.0%). This is because the MDV used by Terai et al. [21][22] summarizes the health insurance data for acute-care hospitals in Japan but does not include information on health insurance data for general practitioners and core hospitals. This may have contributed to the higher rate of CVD requiring surgery. In the present study, a multivariate analysis was performed for sex, age, and risk factors for lifestyle-related diseases of NASH, and the OR and 95% CI for each factor were obtained. The odds ratio (OR) was ≥1 for factors other than age. Among them, dyslipidemia (OR 4.39, 95% CI 3.41–5.65) and type 2 diabetes (OR 5.83, 95% CI 4.83–7.04) showed an OR of ≥4, indicating that these are major risk factors for the development of NASH. This study also confirmed that the presence of type 2 diabetes increased the risk of death from NASH (OR 1.34, 95% CI 1.26–1.43). These results suggest that more aggressive interventions are needed for patients with dyslipidemia and type 2 diabetes.

NAFLD should be considered a systemic disease that presents with many comorbidities and other lifestyle-related diseases[22]. A multivariate analysis was performed for risk factors for comorbidity of NASH (risk of onset), and OR and 95% Cl for each factor were obtained. We found that cirrhosis (OR 28.81, 95% CI, 21.79–38.08) and liver cancer (OR 18.38, 95% CI, 12.56–26.89) were significant and major risk factors for comorbidity. Cancer development from NAFLD occurs at an annual rate of approximately 0.04%, while hepatocarcinogenesis from NASH cirrhosis occurs at an annual rate of approximately 2–3%[22]. This analysis showed a higher risk factor than that reported in previous studies. In a hospital-based study[23], 68 patients with NASH cirrhosis (mean age, 63 years; 57% male) were observed for an average of 3.4 years, of whom seven patients developed cancer. In addition, the 5-year cumulative rate of Hepatocellular carcinoma (HCC) among patients with NASH was 11.3%, which was lower than the 30.5% rate of Hepatitis C virus cirrhosis in the study group[24] . In a median 3.2-year observational study of 195 patients with NASH cirrhosis (mean age 56.6 years, 44.1% male), 25 (12.8%) subjects developed hepatocarcinogenesis, a lower rate than 20.3% of HCV cirrhosis evident for the control group. In NASH, liver fibrosis progresses by one step every 7 years[11] . The observation period of this study was 5 years, whereas the observation period of Yatsuji et al. [23] and Ascha et al.[25] was approximately 3 years, which may have been related to the difference in cancer incidence; thus, our results are acceptable. The prognosis of NASH cirrhosis worsens with increasing degrees of fibrosis and severity of cirrhosis[26] . Since liver cancer is the most important vital prognostic factor in patients with cirrhosis, it is important to monitor its course in consideration of carcinogenesis.

After liver cancer and cirrhosis, GERD showed the highest OR. In the present study, the complication rate of GERD in the NASH group was as high as 69.9% and was also a high-risk factor. Several cross-sectional and cohort studies have investigated the association between NAFLD and risk of GERD[27–35]. However, the results from such studies have been conflicting so far. Some study showed a higher prevalence of GERD among patients with NAFLD compared to the general population. While other studies have failed to find a significant association between NAFLD and risk of GERD. Obesity is a potential confounding factor in clinical studies on the association between NAFLD and GERD, as it has been established as a common risk factor for both diseases[33,36] . A systematic review and meta-analysis of observation studies of NAFLD with and without obesity in the development of GERD by Xue J et al.[37] showed a significant association between NAFLD and risk of GERD. However, to our knowledge, there is no study has defined a temporal or causal relationship between NAFLD and GERD. As NASH is an advanced from NAFLD, the risk of GERD should be kept in mind in clinical practice.

Limitations

This study had some limitations. First, our results may not be generalizable to all NASH patient groups in Japan. The database only contained data collected from NHI in the Kyushu region and did not cover the whole of Japan.

Second, missing records and insufficient data entries were inevitable. The NHI covers self-employed, unemployed, and retired persons under the age of 75 years. Therefore, to obtain data for the oldest of the older population, we added data on health insurance for persons 75 years and older. However, the medical record of each patient may not trace the patient's full medical history if the patient moved or switched to employer-based health insurance.

Third, the lack of information must be acknowledged. In the present study, NASH and its comorbidities were categorized based on ICD-10 three-character code block categories. A stable version of the ICD-11 was released in 2018 and officially endorsed by all WHO members during the 72nd World Health Assembly in 2019. The original code for NASH in ICD-11 is given, but it has not yet been officially enforced in Japan. In addition, the current state of NASH diagnosis in Japan has not been clarified, and it has been difficult to accurately extract NASH cases from actual medical care in Japan.

Conclusions

To the best of our knowledge, this is the first study to assess the clinical characteristics and predictors of NASH using NHI claims data from the Kyushu region in Japan. In addition, the database we developed combines a large health claims database with specific medical examination data. Therefore, our study is the first to include an overview of NASH-attributable patients in Japan. NASH is expected to become an increasingly common health disorder from a social and epidemiological perspective because of the recent increase in the number of patients and the diversity of diseases and conditions. The results of this study indicated that NASH is associated with a high risk of complications of liver cancer and cirrhosis, and that coexisting lifestyle-related diseases increase the risk of death and the risk of complications of GERD. In the daily medical care of patients with NASH, it is necessary to consider sex and age and to pay close attention not only to liver lesions, but also to various other lifestyle-related neoplasms.

Author contributions: Substantial contribution to study conception, design, and planning of the study: TK, SK, KI, SM1, KF, KM, SM2; substantial contributions to analysis and interpretation of the data: TK, SK, SM1; drafting the article or revising it critically for important intellectual content: KI, TK, SM1; interpretation of results and supervised the project: SM2. All the authors have read and agreed to the published version of the manuscript.

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Data availability statement: The data that support the findings of this study are available from the corresponding author on reasonable request due to privacy or ethical restrictions.

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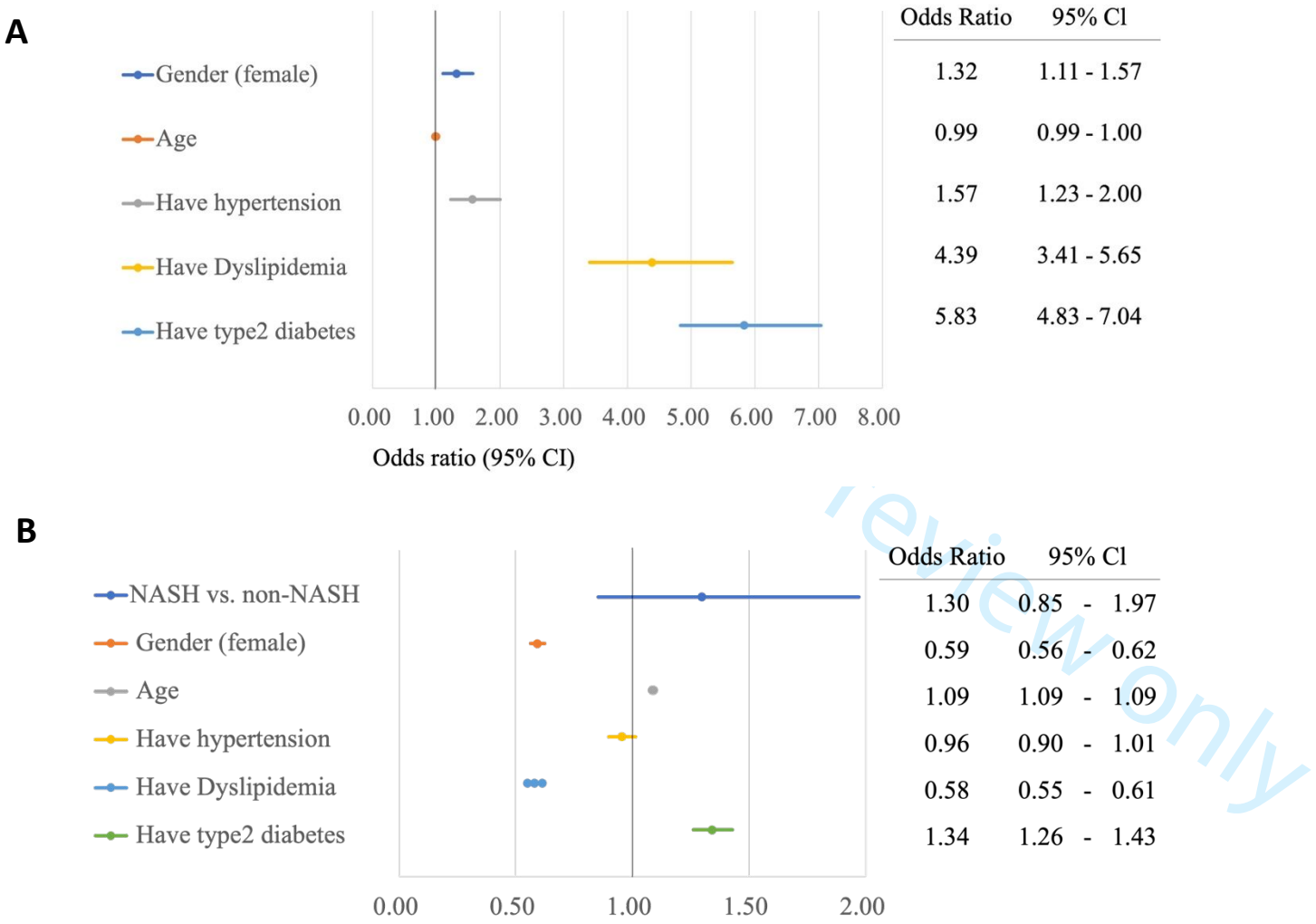

Figure 1. (A) Forest plot of risk adjusted odds ratios of diagnosed with NASH according to patients' background and life-related diseased. (B) Forest plot of risk adjusted odds ratios for mortality based on patients' background and life-related diseases.

NASH, nonalcoholic steatohepatitis; CI, confidence interval

Table1. Baseline patient demographics and characteristics for NASH and non-NASH group

		NASH group N=545		non-NASH group N=185,264		*p*-value
Age years; Median (IQR)		68	(63.00-75.00)	65	(44.00-74.00)	<0.001
Gender n (%)						
	Male	209	(38.3%)	80,051	(43.2%)	0.022
	Female	336	(61.7%)	105,213	(56.8%)	
Death n (%)		24	(4.4%)	6,696	(3.6%)	0.300
Prescribed drugs for treatment of NASH during analysis period						
Type 2 diabetes	Pioglitazone	16	(2.9%)	1,600	(0.9%)	<0.001
	GLP1 agonist	18	(3.3%)	794	(0.4%)	<0.001
	SGLT2	61	(11.2%)	2,851	(1.5%)	<0.001
Dyslipidemia	Statins	290	(53.2%)	39,692	(21.4%)	<0.001
Hypertension	ARB	250	(45.9%)	41,202	(22.2%)	<0.001
	ACEi	34	(6.2%)	5,220	(2.8%)	<0.001
None	Vitamin E	66	(12.1%)	5,057	(2.7%)	<0.001

NASH, nonalcoholic steatohepatitis; IQR, Interquartile range; GLP1, Glucagon-like peptide-1; SGLT2, Sodium-glucose cotransporter 2; ARB, Angiotensin II receptor blocker; ACEi, Angiotensin converting enzyme inhibitor.

Table2. Characteristics of the patients with specific health examination data in analyzed NASH and non-NASH group

	NASH group N=220		non-NASH group N=44,913		*p*-value
Degree of obesity; Median (IQR)					
Body weight, kg	63.90	(55.35-71.50)	56.00	(48.90-64.00)	<0.001
Hight, cm	156.75	(150.75-163.80)	156.00	(149.80-163.40)	0.400
Body mass index, kg/m^2	25.75	(23.40-28.10)	22.90	(20.80-25.20)	<0.001
Laboratory test values; Median (IQR)					
AST, U/L	31.00	(23.00-52.00)	22.00	(19.00-26.00)	<0.001
ALT, U/L	31.50	(21.00-55.50)	17.00	(13.00-23.00)	<0.001
γ-GTP, U/L	42.00	(27.00-77.00)	22.00	(16.00-34.00)	<0.001
SBP, mmHg	130.00	(121.00-140.00)	129.00	(119.00-140.00)	0.220
DBP, mmHg	75.00	(70.00-81.50)	74.00	(67.00-80.00)	0.020
HbA1c, %	6.00	(5.70-6.50)	5.70	(5.40-6.00)	<0.001
TG, mg/dL	127.50	(90.50-171.00)	95.00	(70.00-134.00)	<0.001
HDL, mg/dL	54.00	(44.50-63.00)	61.00	(51.00-73.00)	<0.001
LDL, mg/dL	109.00	(91.00-127.50)	117.00	(99.00-138.00)	<0.001

NASH, nonalcoholic steatohepatitis; IQR, Interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-Guanosine Triphosphate; SBT, Systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglyceride; HDL; high-density lipoprotein cholesteryl; LDL, low-density lipoprotein cholesterol.

Table 3. NASH-related comorbidities identified in the analyzed population.

Combination or disease, n (%)	NASH group N=545		non-NASH group N=185,264		*p*-value
Dyslipidemia	450	(82.6%)	67,463	(36.4%)	<0.001
Hypertension	429	(78.7%)	86,101	(46.5%)	<0.001
Gastroesophageal reflux disease	381	(69.9%)	53,156	(28.7%)	<0.001
Type2 diabetes	339	(62.2%)	26,732	(14.4%)	<0.001
Cardiovascular disease	305	(56.0%)	54,293	(29.3%)	<0.001
Insomnia	225	(41.3%)	48,487	(26.2%)	<0.001
Osteoporosis	188	(34.5%)	38,149	(20.6%)	<0.001
Cancer	166	(30.5%)	22,310	(12.0%)	<0.001
Hepatic cirrhosis	71	(13.0%)	632	(0.3%)	<0.001
Depression	80	(14.7%)	18,038	(9.7%)	<0.001
Chronic renal failure	42	(7.7%)	9,136	(4.9%)	0.005
Liver cancer	34	(6.2%)	428	(0.2%)	<0.001
Sleep apnea syndrome	24	(4.4%)	2,368	(1.3%)	<0.001
Colorectal adenomas	8	(1.5%)	634	(0.3%)	<0.001

NASH, nonalcoholic steatohepatitis; GLP1, Glucagon-like peptide-1; SGLT2 Sodium-glucose cotransporter 2; ARB, Angiotensin II receptor blocker; ACEi, Angiotensin converting enzyme inhibitor

Table 4. Risk adjusted odds ratio with NASH onset and NASH-related comorbidities relationship.

	Hepatic cirrhosis		Liver cancer		Gastroesophageal reflux diseases		Colorectal adenomas		Colon cancer		Cancer	
	OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)	
NASH vs. non-NASH	28.81	(21.79-38.08)	18.38	(12.56-26.89)	3.08	(2.53-3.73)	2.54	(1.25-5.16)	2.36	(1.70-3.28)	2.16	(1.79-2.62)
Gender (female)	0.70	(0.60-0.81)	0.45	(0.37-0.55)	0.92	(0.90-0.94)	0.41	(0.35-0.49)	0.62	(0.59-0.66)	0.57	(0.55-0.59)
Age	1.04	(1.03-1.04)	1.06	(1.05-1.07)	1.04	(1.04-1.04)	1.02	(1.02-1.03)	1.05	(1.05-1.05)	1.05	(1.05-1.05)
Hypertension	1.78	(1.45-2.19)	1.31	(1.03-1.67)	1.90	(1.85-1.95)	1.54	(1.25-1.90)	1.36	(1.25-1.47)	1.22	(1.17-1.26)
Dyslipidemia	0.73	(0.62-0.86)	0.86	(0.70-1.04)	1.72	(1.68-1.76)	1.72	(1.45-2.05)	1.1	(1.03-1.18)	1.08	(1.04-1.11)
Type 2 diabetes	2.15	(1.82-2.54)	2.56	(2.10-3.13)	1.58	(1.54-1.63)	1.46	(1.23-1.74)	1.62	(1.51-1.74)	1.69	(1.63-1.75)
	Sleep apnea syndrome		Cardiovascular diseases		Osteoporosis		Depression		Insomnia		Chronic kidney diseases	
	OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)	
NASH vs. non-NASH	1.82	(1.20-2.76)	1.40	(1.16-1.69)	1.25	(1.02-1.53)	1.11	(0.87-1.41)	1.12	(0.94-1.34)	0.81	(0.58-1.12)
Gender (female)	0.34	(0.31-0.37)	0.74	(0.72-0.76)	6.68	(6.47-6.91)	1.43	(1.38-1.48)	1.35	(1.31-1.38)	0.58	(0.56-0.61)
Age	1.00	(1.00-1.00)	1.07	(1.07-1.07)	1.08	(1.07-1.08)	1.02	(1.02-1.02)	1.04	(1.03-1.04)	1.06	(1.05-1.06)
Hypertension	3.19	(2.80-3.62)	2.99	(2.90-3.07)	1.50	(1.45-1.55)	1.32	(1.27-1.38)	1.78	(1.73-1.83)	4.33	(4.00-4.68)
Dyslipidemia	2.02	(1.84-2.22)	2.08	(2.03-2.13)	1.68	(1.64-1.73)	1.24	(1.19-1.28)	1.38	(1.34-1.41)	1.35	(1.29-1.41)
Type 2 diabetes	1.57	(1.43-1.72)	1.78	(1.72-1.83)	1.23	(1.18-1.27)	1.22	(1.17-1.27)	1.32	(1.29-1.36)	2.08	(1.99-2.18)

NASH, nonalcoholic steatohepatitis; OR, odds ratio; Cl, confidence interval;

Supplementary Information

Supplemental Table 1. ICD-10 codes for definition of comorbidity complexes

Comorbidity	ICD-10 codes
Hypertension	I10 - I15
Dyslipidemia	E780 - E785
Type 2 diabetes	E11
Osteoporosis	M80 - M82
Insomnia	G470
Depression	F30 - F39
Hepatic cirrhosis	K743 - K746
Liver cancer	C22
Colon cancer	C18
Cancer	C00 - C96, D00 - D48, D370 - D386, D390 - D392, D397, D399, D410 - D414, D417, D419, D440 - D449
Colorectal adenomas	D126
Chronic kidney disease	N18
Gastroesophageal reflux disease	K21
Cardiovascular disease	I20 - I25, I60 - I69
Sleep apnea syndrome	G473

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Title: Clinical characteristics in patients with nonalcoholic steatohepatitis in Japan: a 5-year large-scale claim database analysis

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ABSTRACT (288/300 words)

Objectives: To examine the clinical characteristics of patients with nonalcoholic steatohepatitis (NASH) and associated comorbidities.

Design: A case-control study using the national health insurance and the long-term elderly health insurance claims database.

Setting: Eligible patients diagnosed with NASH (ICD-10 K-75.8, other inflammatory liver disease or K-76.0, other fatty liver) between April 2015 and March 2020 were included.

Participants: Patients who met the diagnostic definitions for NASH (n = 545) were matched with non-NASH controls (n = 185,264) and randomly selected according to sex, birth year, and residential area.

Interventions: No interventions were made.

Primary and secondary outcome measures: Odds ratios (OR) were estimated for the relationship between patient background, e.g., age, sex, body mass index (BMI), NASH-related comorbidities, and lifestyle-related diseases.

Results: In total, 545 NASH (38.3% male) and 185,264 non-NASH controls (43.2% male) were identified. The median age in the NASH and non-NASH was 68 (IQR 63.0–75.0) and 65 (IQR 44.0 –74.0) years, respectively. BMI was significantly higher in patients with NASH than in controls (25.75 kg/m^2 vs. 22.90 kg/m^2, p <0.001). Individuals with female hypertension, dyslipidemia, and type 2 diabetes were at a higher risk for NASH prevalence. NASH was also associated with an increased risk of hepatic cirrhosis (OR 28.81 (95% CI, 21.8 –38.08), followed by liver cancer (OR 18.38 (95% CI 12.56–26.89)). There were no significant associations between NASH and risk for depression (OR 1.11 (95% Cl 0.87–1.41)), insomnia (OR 1.12 (95% Cl 0.94–1.34)), or chronic kidney diseases (OR 0.81 (95% Cl 0.58–1.12)).

Conclusions: In the daily medical care of patients, it is necessary to consider sex and age differences and to pay close attention to the risk for liver cancer, but also other lifestyle-related comorbidities associated with NASH.

Strengths and limitations of this study:

- In this study, analysis was performed using claim data covering a wide range of age groups, including elderly patients.
- To extract patients with NASH with high purity, data extraction was limited to patients with a history of liver biopsies.
- A long-term observation period of 5 years was established.

- Japan has several public health insurance systems, but the data used in this study were collected from the NHI and therefore did not cover the whole of Japan.
- It should be recognized that the data are secondary use and that some information is missing.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease, affecting approximately 20–30% of the global population[1]. NAFLD includes nonalcoholic fatty liver (NAFL), which is pathologically pure steatosis alone, or in which steatosis is accompanied by inflammatory cell infiltration, and nonalcoholic steatohepatitis (NASH), which is accompanied by hepatic steatosis, inflammatory cell infiltration, ballooning (hepatocellular ballooning) and hepatic fibrosis[2].

Liver tissue biopsy is the gold standard for diagnosing NAFLD[3–6], which is consistent with guidelines published overseas. However, in clinical practice, performing a liver biopsy with bleeding or pain in all patients with NAFLD is not feasible. Therefore, the proportion of patients undergoing liver biopsy for a NASH diagnosis in clinical practice is not fully understood. According to Rinella et al[4], the biopsy rate for NASH diagnosis and the therapeutic drugs prescription rate recommended by the guidelines are low, and NASH is underdiagnosed[6]. According to an estimate based on a Markov model of the number of patients with NAFL and NASH worldwide, the number of patients with fibrotic NASH at stage III or higher in Japan is predicted to increase to 660,000 in 2016 and 990,000 in 2030[7]. Moreover, although NASH prevalence has been estimated to be approximately 3–5% of the population[8,9], there is insufficient evidence for NASH prevalence in the general population due to selection bias in liver biopsies and diagnostic difficulties.

NASH is strongly associated with metabolic syndrome, obesity, diabetes mellitus (DM), hypertension, and dyslipidemia[1], and the major causes of death are cardiovascular and liver disease-related events[6]. Obesity and DM are risk factors for cardiovascular and liver disease-related events, including decompensated cirrhosis and liver cancer. Overseas guidelines propose evaluating liver function by abdominal echography and blood tests in patients with obesity or [3]. In the Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Diseases/Nonalcoholic Steatohepatitis 2020 (2nd Edition) of Japan (the NASH/NAFLD guideline)[10], it is recommended that primary care physicians assess liver function in patients with risk factors including obesity, DM, dyslipidemia, and hypertension and identify all cases of NAFLD fibrosis progression (as primary screening). As NASH is often asymptomatic and cirrhosis may already be diagnosed at the time of diagnosis, efficient screening and timing of referral to a gastroenterologist are important. In NASH, liver fibrosis progresses by one stage in approximately 7 years and progresses faster in patients with comorbid metabolic diseases such as obesity and DM[11]. Therefore, it is recommended that the degree of fibrosis in the NASH group should be regularly evaluated, and, depending on the results, follow-up observation or screening should be performed for liver-related diseases such as liver failure and liver cancer, and non-liver-related diseases such as cerebrocardiovascular events and cancers of other organs[2].

Japan, with a universal health insurance system, has almost all residents covered by medical insurance. Understanding the medical situation of local residents is possible by investigating the claims data of medical insurance held by the administration[12]. Each municipality serves as the payer of the National Health Insurance (NHI), and the municipalities jointly established the "Federation of National Health Insurance Organizations (FNHIO)" to provide insurance services. Each prefecture has one payer.

The University of Occupational and Environmental Health, Japan (UOEH) has used health insurance claims data by closely cooperating with payers in NHI; the data enables us to grasp the disease information of persons participating in national health insurance every month. Eguchi et al. [13] showed that the age-specific NAFLD prevalence was higher in middle-aged men and older women, with differences in the age distribution of NAFLD onset between males and females. To obtain data on the late-stage elderly, in this study, we matched the NHI claims and the health insurance database for persons aged ≥75 years individually and constructed an original database.

METHODS

Study Design and Data Source

Japan's health insurance system is commonly divided into three types: company health insurance for those employed in a business, NHI for residents of each region, and long-term elderly health insurance (LEHI) for those aged ≥75 years. NHI is a mutual assistance program in which enrolled members pay premiums to a financial pool to which the national government and local municipalities add funds. This case-control study was analyzed using the NHI and LEHI claims databases, comprising inpatient, outpatient, and dispensing service data from domestic payers over April 2015 (through March 2020), provided by the public institution in Japan.

The data included the age and gender of each beneficiary, the type of service used, the month during which the service was used, monthly expenditures on the use of the services, and exit information (death or move-out). We prepared a panel database combining basic medical check-up data and claim databases conducted on a patient-by-patient basis to examine the clinical characteristics of patients with NASH. This study was approved by the ethics committee of the University of Occupational and Environmental Health, Japan (R4-026).

Study population and eligibility criteria

The inclusion criteria were patients of any age with a record of at least one episode of NASH during the study period from April 2015 to March 2020. An episode of NASH was defined as NASH diagnosis (ICD-10 K-75.8; other inflammatory liver diseases or K-76.0; other fatty liver). Furthermore, patients whose disease name string could be confirmed as "hepatitis," "non-alcoholic," and "NASH" in the claims data were also included in the analysis. Using ICD-10; K-75.8 and K-76.0, we have learned that differentiating patients with NASH from patients with NAFLD is extremely difficult. Since definitive diagnosis of NASH is histopathological diagnosis by liver biopsy and it is essential to confirm pathologically characteristic finding, patients diagnosed with NASH after liver biopsy (percutaneous needle biopsy, endoscopic biopsy and endoscopic ultrasound-guided fine-needle aspiration biopsy) indication were selected. Controls that never had a claim associated with NASH were randomly selected from patients who visited a medical facility at least once between April 2015 and March 2020.

Exclusion criteria were claims for any of the following conditions at any time: hepatitis B virus, hepatitis C virus, human immunodeficiency virus, alcoholic liver disease, toxic liver injury, copper metabolism disorder, autoimmune hepatitis, Gaucher's disease, lysosomal acid lipase deficiency, biliary cirrhosis, cholangitis, or iron metabolism disorder. ICD-10 codes were used to identify the patients with these diseases. It should be noted that given the expert opinion that a liver biopsy may be performed for a definitive diagnosis of

autoimmune hepatitis to extract a purer sample in patients with NASH, patients with autoimmune hepatitis were excluded.

A patient was defined as having a comorbidity if they had at least one claim for the relevant ICD-10 code during the analysis period. Fourteen comorbidity categories of interest identified using ICD-10 diagnosis codes (Supplemental Table1) were pre-specified: hypertension, dyslipidemia, type 2 diabetes (T2D), osteoporosis, insomnia, depression, hepatic cirrhosis, liver cancer, cancer, colorectal adenomas, chronic kidney disease (CKD), gastroesophageal reflux disease (GERD), cardiovascular disease (CVD), and sleep apnea syndrome (SAS). The prevalence of these predefined comorbidity groups has been reported in all patients with NASH and non-NASH comparators.

According to our definition, each patient classified as having NASH was compared with non-NASH comparators randomly selected from the original database by sex, birth year, and residential area (Supplemental Figure 1).

Data Collection

Baseline data on all patient characteristics (age, sex), date of death (if data were recorded), prescribed drugs for treating NASH, and NASH-related comorbidities were collected. Age and sex were obtained as of April 2015. The dates of death and prescribed drugs for treating NASH-related comorbidities were obtained at any time during the study period. Height, weight, and laboratory test values were also obtained from patients' available data at any time during the study period. BMI was calculated from the data of height and weight recorded.

Information on the pathological classification of NASH could not be obtained due to the unavailability of medical examination test results in the NHI and LEHI claims databases.

Statistical Analyses

We designed a case-control study to compare the occurrence of comorbidities among the NASH and non-NASH groups during the analysis period and to assess the relationship between NASH and comorbidities. Odds ratios of age, sex, life-related diseases (hypertension, dyslipidemia, T2D), and NASH-related comorbidities. All analyses were conducted for the two groups: the NASH group, in which patients had at least one record of being diagnosed with NASH, and the non-NASH group, in which the patients had no record of being diagnosed.

Descriptive statistics were conducted using logistic regression models to analyze the relationship between NASH and sex, age, lifestyle-related diseases, death, and comorbidities (Odd Ratio [OR], 95% confidence interval [95% CI]). Differences between the NASH and non-

NASH groups were evaluated using Pearson's chi-squared test for categorical variables and independent t-tests for continuous variables. Statistical significance was set at $p < 0.05$.

All statistical analyses were performed using Stata Ver.17.0 released in April 2021 (Stata Coro, College Station, Texas, USA).

Patient and public involvement

Patients and members of the public were not involved in the conducting of the study.

RESULTS

Patient characteristics

Patient background characteristics are shown in Supplemental Table 2. In total of 545 patients with NASH (209 males and 336 females) were selected from the claims databases, and 185,264 non-NASH controls (80,051 males and 105,213 females) were identified. The median (interquartile range; IQR) age of the NASH and non-NASH groups was 68 (63.0-75.0) and 65 (44.0– 74.0) years, respectively. Among the NASH group, the most frequently prescribed agents were statins (53.2%), followed by angiotensin receptor blockers (ARBs) (45.9%), and vitamin E (12.1%), and among the non-NASH group, it was ARBs (22.2%), statins (21.4%), and angiotensin-converting-enzyme inhibitor (ACEi) (2.8%).

Table 1 summarizes the values of the patients whose height, weight, BMI, and blood test values could be extracted for each group. In total, 220 patients were identified in the NASH group, and 44,913 patients were identified in the non-NASH group. BMI was significantly higher than in the NASH vs. non-NASH group (25.8 kg/m^2 vs. 22.9 kg/m^2, p <0.001). The laboratory test value (> 5%) was also higher than in the NASH vs. non-NASH group, except for high-density cholesterol (54.0 mg/dL and 61.0 mg/dL, respectively) and low-density lipoprotein cholesterol (109.0 mg/dL and 117.0 md/dL, respectively).

Table 1. Characteristics of the patients with specific health examination data in analyzed NASH and non-NASH groups

	NASH group N=220		non-NASH group N=44,913		*p*-value
Degree of obesity; Median (IQR)					
Body weight, kg	63.9	(55.4-71.5)	56.0	(48.9-64.0)	<0.001
Height, cm	156.8	(150.8-163.8)	156.0	(149.8-163.4)	0.400
Body mass index, kg/m^2	25.8	(23.4-28.1)	22.9	(20.8-25.2)	<0.001
Laboratory test values; Median (IQR)					
AST, U/L	31.0	(23.0-52.0)	22.0	(19.0-26.0)	<0.001
ALT, U/L	31.5	(21.0-55.5)	17.0	(13.0-23.0)	<0.001
γ-GTP, U/L	42.0	(27.0-77.0)	22.0	(16.0-34.0)	<0.001
SBP, mmHg	130.0	(121.0-140.0)	129.0	(119.0-140.0)	0.220
DBP, mmHg	75.0	(70.0-81.5)	74.0	(67.0-80.0)	0.020
HbA1c, %	6.0	(5.7-6.5)	5.7	(5.4-6.0)	<0.001
TG, mg/dL	127.5	(90.5-171.0)	95.0	(70.0-134.0)	<0.001
HDL, mg/dL	54.0	(44.5-63.0)	61.0	(51.0-73.0)	<0.001
LDL, mg/dL	109.0	(91.0-127.5)	117.0	(99.0-138.0)	<0.001

NASH, nonalcoholic steatohepatitis; IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-guanosine triphosphate; SBT, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglyceride; HDL; high-density lipoprotein cholesteryl; LDL, low-density lipoprotein cholesterol.

Comorbidities

Table 2 summarizes the NASH-related comorbidities of patients in each group. The prevalence of all NASH-related comorbidities was significantly higher in the NASH group vs. the non-NASH group, except autoimmune hepatitis. The five most prevalent comorbidities were over 50% in the NASH group: dyslipidemia (82.6 %), hypertension (78.7 %), GERD (69.9%), T2D (62.2%), and CVD (56.0%). In the non-NASH group, no more than 50% of NASH-related comorbidities were present, with hypertension (46.5%) being the most common comorbidity, followed by dyslipidemia (36.4%).

Table 2. NASH-related comorbidities identified in the analyzed population.

Combination or disease, n (%)	NASH group N=545		non-NASH group N=185,264		*p*-value
Dyslipidemia	450	(82.6%)	67,463	(36.4%)	<0.001
Hypertension	429	(78.7%)	86,101	(46.5%)	<0.001
Gastroesophageal reflux disease	381	(69.9%)	53,156	(28.7%)	<0.001
Type2 diabetes	339	(62.2%)	26,732	(14.4%)	<0.001
Cardiovascular disease	305	(56.0%)	54,293	(29.3%)	<0.001
Insomnia	225	(41.3%)	48,487	(26.2%)	<0.001
Osteoporosis	188	(34.5%)	38,149	(20.6%)	<0.001
Cancer	166	(30.5%)	22,310	(12.0%)	<0.001
Hepatic cirrhosis	71	(13.0%)	632	(0.3%)	<0.001
Depression	80	(14.7%)	18,038	(9.7%)	<0.001
Chronic renal failure	42	(7.7%)	9,136	(4.9%)	0.005
Liver cancer	34	(6.2%)	428	(0.2%)	<0.001
Sleep apnea syndrome	24	(4.4%)	2,368	(1.3%)	<0.001
Colorectal adenomas	8	(1.5%)	634	(0.3%)	<0.001

NASH, nonalcoholic steatohepatitis; GLP1, glucagon-like peptide-1; SGLT2 sodium-glucose cotransporter 2; ARB, angiotensin II receptor blocker; ACEi, angiotensin converting enzyme inhibitor

Age, sex, and life-related disease as risk factors for NASH

The influence of sex, age, and life-rated disease on NASH has been reported previously[14]. Multiple logistic regression models were used to assess the effect of sex, age, and lifestyle-related diseases on NASH prevalence. Figure 1 shows the odds ratio (OR) for these factors associated with NASH prevalence. Females sex, hypertension, dyslipidemia, and T2D had a significantly higher risk than the non-NASH group; dyslipidemia and T2D were very high (4.39 and 5.83, respectively). The association with age was insignificant compared to the non-NASH group.

In a separate multiple logistic regression model examining the association between mortality due to NASH and each risk factor, adjusted for sex, age, and lifestyle-related diseases, the ORs for age and T2D were significantly higher than in the non-NASH group (Figure 2).

Comorbidities as risk factors for NASH

The OR with NASH and NASH-related comorbidities, adjusted for sex, age, and lifestyle-related diseases, is shown in Supplemental Table 3. In a multiple logistic regression model examining the association between NASH and developing comorbidities, compared to non-NASH, NASH was associated with the greatest risk of hepatic cirrhosis (OR 28.81, 95% CI, 21.79–38.08), followed by liver cancer (OR 18.38, 95% CI, 12.56–26.89), GERD (OR 3.08, 95% CI 2.53–3.73), colorectal adenomas (OR 2.54, 95% CI 1.25-5.16), colon cancer (OR 2.36, 95% CI 1.70–3.28), cancer (OR 2.16, 95% CI 1.79–2.62), SAS (OR: 1.82, 95% CI 1.20–2.76), CVD (OR 1.40, 95% CI 1.16–1.69), and osteoporosis (OR 1.25, 95% CI 1.02–1.53). No significant difference in comorbidities was observed for depression (OR 1.11, 95% CI 0.87–1.41), insomnia (OR 1.12, 95% CI 0.94–1.34), and CKD (OR 0.81, 95% CI 0.58–1.12).

There was no significant difference in OR for osteoporosis (OR 1.03, 95% CI 0.94–1.13) in NASH vs. non-NASH, but OR was significantly increased to 6.68 (95% CI 6.47–6.91) in females. OR for CKD was less <1, and it was not significantly elevated with NASH. However, when patients with NASH had a history of hypertension, dyslipidemia, or T2D, ORs increased significantly to 4.33（95% CI 4.00–4.68）, 1.35 (95% CI 1.29–1.41) and 2.08 (95% CI 1.99–2.18), which has been shown to increase the risk of developing CKD.

DISCUSSION

Using NHI claims data and LEHI, we constructed an original database and examined the clinical characteristics of patients with NASH for 5 years from April 2015 to March 2020. It has been reported that NAFLD/NASH prevalence varies by age and gender[13,15,16] . In a cross-sectional study[13] conducted among 8,352 participants who underwent health checkups from 2009 to 2010 at three health centers in Japan, NAFLD overall prevalence was 29.7%, more than 30% in males aged 30–60 years, and increased with age in females aged 30–60 years old. It is considered that a decrease in estrogen due to aging and menopause affects NAFLD progression in females[14]. Similar to NAFLD, there are more middle-aged males and older females in the age distribution of NASH prevalence. In this study, the median age of the NASH group was 68 years (IQR, 63.0-75.0), showing an older age and a higher proportion of females than males (38.3% vs. 61.7%). This finding also suggests that NASH prevalence is higher in older females.

NAFLD/NASH is strongly associated with obesity[7,13,15]. This study showed that the BMI was significantly higher in the NASH group than in the non-NASH group (25.8 kg/m^2 vs 22.9 kg/m^2, p <0.001). Obesity is the most common manifestation of the metabolic syndrome and the most important risk factor for NAFLD/NASH, which can also be regarded as a liver lesion[17]. World Health Organization (WHO) diagnostic criteria define BMI 25 kg/m^2 or more as overweight and BMI 30 kg/m^2 or more as obese. In Japan, the definition of obesity as judged by the Japan Society for Study of Obesity is set as a BMI of 25 kg/m^2 or more, which is lower than the WHO criteria. One of the reasons for this is that it is known that Japanese people are more likely to develop fatty liver if their BMI is less than 25 kg/m^2 but are not obese and develop fatty liver at a high rate after their BMI exceeds 25 kg/m^2. NAFLD/NASH prevalence in non-obese participants (BMI <23 kg/m^2) was ≤10%. NAFLD/NASH prevalence increases with increasing BMI and is approximately 80% in highly obese participants (BMI >30 kg/m^2)[10]. It has also been reported that hepatic steatosis, inflammatory cell infiltration, and ballooning decreased by 7% or more of body weight loss, and the NAFLD activity score improved[18]. This study also showed that the median BMI was higher than 25 kg/m^2 in the NASH patient group, suggesting the importance of liver lesions and active lifestyle interventions in daily medical practice for NAFLD/NASH. However, it is essential to change the consciousness of patients for lifestyle interventions, and maintenance of the target achievement rate and adherence becomes an issue. Similar to previous research[19,20], the results of the present study may support NAFLD/NASH association with several metabolic comorbidities, including T2D, dyslipidemia, hypertension, and CVD. Regarding CKD, patients with NASH were shown to have a higher risk of complications if they had hypertension or T2D. Management of these conditions may complicate the treatment of NASH, impacting clinical care outcomes.

According to the NASH/NAFLD guidelines[10], some therapeutic drugs for dyslipidemia, hypertension, and DM have been suggested to be effective for NASH, and aggressive treatment of patients with complications of these lifestyle-related diseases is recommended. Therefore,

this survey investigated the proportion of prescriptions for antihyperlipidemic, hypertensive, and antidiabetic drugs. As a result, the proportion of prescriptions was 53.2% for statins and 45.9% for angiotensin receptor blockers (ARBs) in the NASH group, which was significantly higher than 21.4% for statins and 22.2% for ARBs in the non-NASH group, but the proportion of prescriptions was less than 50%. Premature mortality in NASH is related to both hepatic (cirrhosis and hepatocellular carcinoma) and extra-hepatic complications, largely CVD. Many therapeutic agents have been tested but are still nonapproved, specifically for NASH. Also, presently, there is no drug with sufficient evidence of improving fibrosis in patients with NASH. It is anticipated that many clinical studies on drug therapy and development for NASH will be conducted in the future.

The prevalence of lifestyle-related diseases in NAFLD in Japan is reported to be approximately 60–80% for dyslipidemia, 40% for hypertension, and 20–50% for DM[10]. The results of this study focusing on NASH also showed that the complication rates of dyslipidemia, hypertension, GERD, and T2D were significantly higher in the NASH group than in the non-NASH group (82.6% vs. 36.4 %, $p < 0.001$; 78.7% vs. 46.5%, $p < 0.001$; 69.9% vs. 28.7%, $p < 0.001$; 62.2% vs. 14.4%, $p < 0.001$), which was higher than the complication rate of lifestyle-related disease of NAFLD. In a study by Terai et al.[21], who estimated complications in patients with NAFLD/NASH using the Medical Data Vision (MDV) claims database, dyslipidemia prevalence at 67–74 years was 57.9%, hypertension prevalence was 57.2%, and T2D prevalence was 32.5%, which was lower than that in the present study (dyslipidemia, 82.6%, hypertension, 78.7%, T2D, 62.2%). However, CVD prevalence was 75.8%, which was higher than that in the present study (56.0%). This is because the MDV used by Terai et al. [21] summarizes the health insurance data for acute-care hospitals in Japan but does not include information on health insurance data for general practitioners and core hospitals. This may have contributed to the higher rate of CVD requiring surgery. In the present study, a multivariate analysis was performed for sex, age, and risk factors for lifestyle-related diseases of NASH, and the OR and 95% CI for each factor were obtained. The odds ratio (OR) was ≥1 for factors other than age. Among them, dyslipidemia (OR 4.39, 95% CI 3.41–5.65) and T2D (OR 5.83, 95% CI 4.83–7.04) showed an OR of ≥4, indicating that these are major risk factors for the development of NASH. This study also confirmed that T2D increased the risk of death from NASH (OR 1.34, 95% CI 1.26–1.43). These results suggest that more aggressive interventions are needed for patients with dyslipidemia and T2D.

NAFLD should be considered a systemic disease that presents with many comorbidities and other lifestyle-related diseases[22]. A multivariate analysis was performed for risk factors for comorbidity of NASH (risk of onset), and OR and 95% Cl for each factor were obtained. We found that cirrhosis (OR 28.81, 95% CI, 21.79–38.08) and liver cancer (OR 18.38, 95% CI, 12.56–26.89) were significant and major risk factors for comorbidity. Cancer development from NAFLD occurs at an annual rate of approximately 0.04%, while hepatocarcinogenesis

from NASH cirrhosis occurs at an annual rate of approximately 2–3%[22]. This analysis showed a higher risk factor than that reported in previous studies. In a hospital-based study[23], 68 patients with NASH cirrhosis (mean age, 63 years; 57% male) were observed for an average of 3.4 years, of whom seven patients developed cancer. Furthermore, the 5-year cumulative rate of Hepatocellular carcinoma (HCC) among patients with NASH was 11.3%, which was lower than the 30.5% rate of Hepatitis C virus cirrhosis in the study group[24]. In a median 3.2-year observational study of 195 patients with NASH cirrhosis (mean age 56.6 years, 44.1% male), 25 (12.8%) participants developed hepatocarcinogenesis, a lower rate than 20.3% of HCV cirrhosis evident for the control group. In NASH, liver fibrosis progresses by one step every 7 years[11] . The observation period of this study was 5 years, whereas the observation period of Yatsuji et al.[23] and Ascha et al.[25] was approximately 3 years, which may have been related to the difference in cancer incidence; thus, our results are acceptable. The prognosis of NASH cirrhosis worsens with increasing degrees of fibrosis and severity of cirrhosis[26] . Since liver cancer is the most important vital prognostic factor in patients with cirrhosis, it is important to monitor its course in consideration of carcinogenesis.

After liver cancer and cirrhosis, GERD showed the highest OR. In the present study, the complication rate of GERD in the NASH group was as high as 69.9% and was also a high-risk factor. Several cross-sectional and cohort studies have investigated the association between NAFLD and GERD risk[27–35]. However, the results from such studies have been conflicting so far. Some study showed a higher prevalence of GERD among patients with NAFLD compared to the general population. While other studies have failed to find a significant association between NAFLD and GERD risk. Obesity is a potential confounding factor in clinical studies on the association between NAFLD and GERD, as it has been established as a common risk factor for both diseases[33,36] . A systematic review and meta-analysis of observation studies of NAFLD with and without obesity in the development of GERD by Xue J et al.[37] showed a significant association between NAFLD and GERD risk. However, to our knowledge, no study has defined a temporal or causal relationship between NAFLD and GERD. As NASH is advanced from NAFLD, GERD risk should be considered in clinical practice.

Limitations

This study had some limitations. First, our results may not be generalizable to all patients with NASH in Japan. Japan has several public health insurance systems. The database used only contained data collected from NHI and did not cover the whole of Japan. Moreover, missing records and insufficient data entries were inevitable. The NHI covers self-employed, unemployed, and retired persons aged< 75 years. Therefore, to obtain data for the oldest of the older population, we added data on health insurance for persons aged< 75 years. However, each

patient's medical record may not trace the patient's full medical history if the patient moved or switched to employer-based health insurance.

Secondly, the lack of information must be acknowledged. Here, NASH and its comorbidities were categorized based on ICD-10 three-character code block categories. A stable version of the ICD-11 was released in 2018 and officially endorsed by all WHO members during the 72nd World Health Assembly in 2019. The original code for NASH in ICD-11 is given but has not yet been officially enforced in Japan. Furthermore, the current state of NASH diagnosis in Japan has not been clarified, and it has been difficult to accurately extract NASH cases from actual medical care in Japan.

This study showed that NASH is significantly involved in the development of intrahepatic lesions such as cirrhosis and liver cancer. However, to better understand the complex etiology of NASH, it may be necessary to investigate its relationship with extrahepatic primary cancers, such as extra-hepatic cancer.

Conclusions

The database we developed combines a large health claims database with specific medical examination data. Therefore, our study is the first to include an overview of NASH-attributable patients in Japan. NASH is expected to become an increasingly common health disorder from a social and epidemiological perspective because of the recent increase in the number of patients and the diversity of diseases and conditions. The results of this study indicated that NASH is associated with a high risk of complications of liver cancer and cirrhosis, and that coexisting lifestyle-related diseases increase the risk of death and the risk of complications of GERD. In the daily medical care of patients with NASH, it is necessary to consider sex and age and pay close attention to liver lesions and various other lifestyle-related neoplasms.

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Figure legends

Fig 1. Forest plot of risk adjusted odds ratios of diagnosed with NASH according to patients' background and life-related diseased.

NASH, nonalcoholic steatohepatitis; CI, confidence interval

Fig 2. Forest plot of risk adjusted odds ratios for mortality based on patients' background and life-related diseases.

NASH, nonalcoholic steatohepatitis; CI, confidence interval

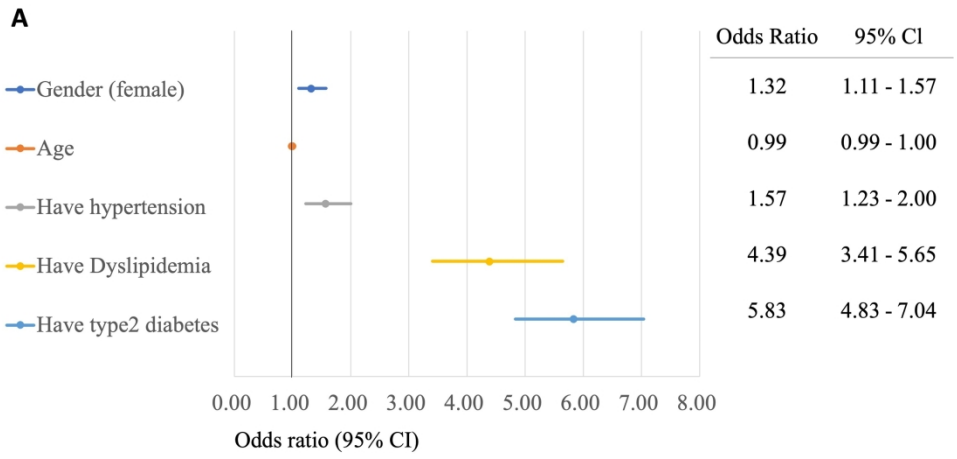


Fig 1. Forest plot of risk adjusted odds ratios of diagnosed with NASH according to patients' background and life-related diseased.
NASH, nonalcoholic steatohepatitis; CI, confidence interval

250x118mm (300 x 300 DPI)

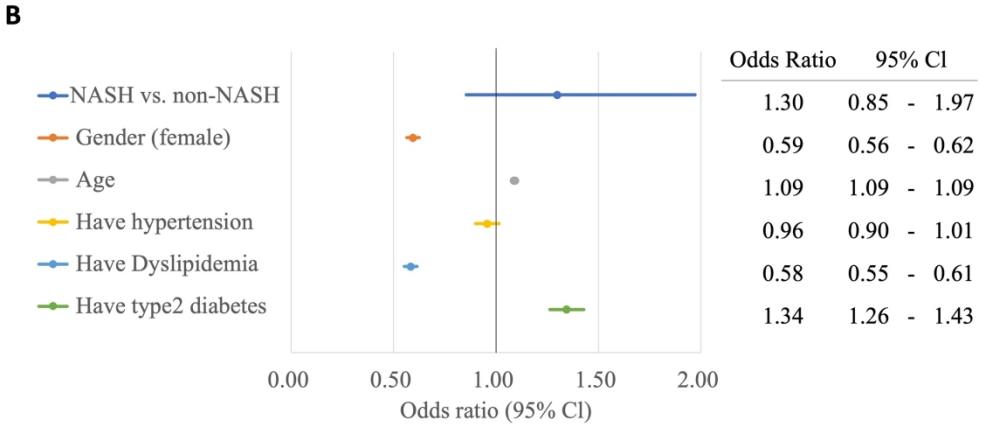


Fig 2. Forest plot of risk adjusted odds ratios for mortality based on patients' background and life-related diseases.
NASH, nonalcoholic steatohepatitis; CI, confidence interval

239x113mm (300 x 300 DPI)

Supplementary Information

Supplemental Table 1. ICD-10 codes for definition of comorbidity complexes

Comorbidity	ICD-10 codes
Hypertension	I10 - I15
Dyslipidemia	E780 - E785
Type 2 diabetes	E11
Osteoporosis	M80 - M82
Insomnia	G470
Depression	F30 - F39
Hepatic cirrhosis	K743 - K746
Liver cancer	C22
Colon cancer	C18
Cancer	C00 - C96, D00 - D48, D370 - D386, D390 - D392, D397, D399, D410 - D414, D417, D419, D440 - D449
Colorectal adenomas	D126
Chronic kidney disease	N18
Gastroesophageal reflux disease	K21
Cardiovascular disease	I20 - I25, I60 - I69
Sleep apnea syndrome	G473

Supplemental Table 2. Baseline patient demographics and characteristics for NASH and non-NASH group

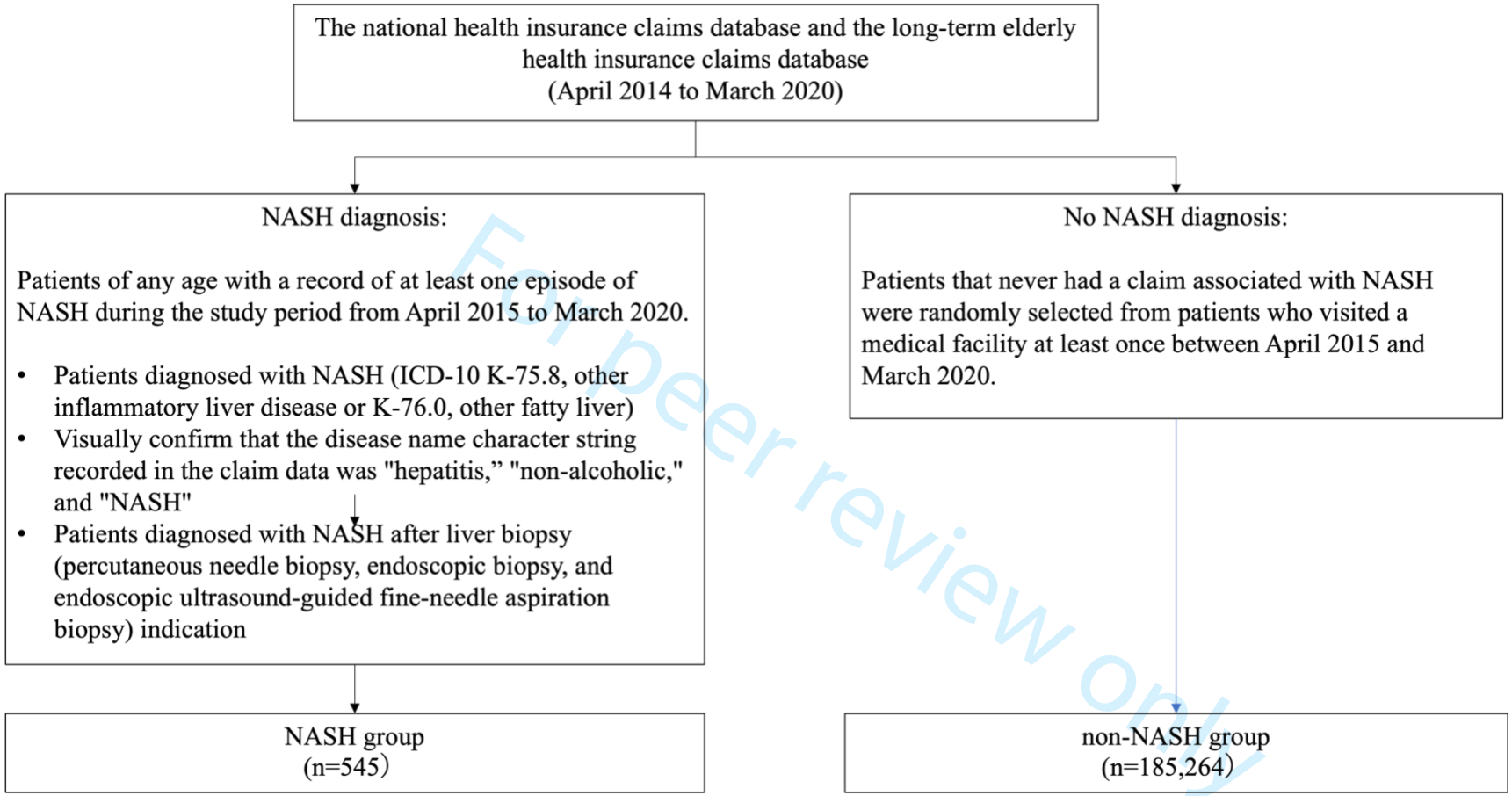
		NASH group N=545		non-NASH group N=185,264		*p*-value
Age years; Median (IQR)		68	(63.00-75.00)	65	(44.00-74.00)	<0.001
Gender n (%)						
	Male	209	(38.3%)	80,051	(43.2%)	0.022
	Female	336	(61.7%)	105,213	(56.8%)	
Death n (%)		24	(4.4%)	6,696	(3.6%)	0.300
Prescribed drugs for treatment of NASH during analysis period						
Type 2 diabetes	Pioglitazone	16	(2.9%)	1,600	(0.9%)	<0.001
	GLP1 agonist	18	(3.3%)	794	(0.4%)	<0.001
	SGLT2	61	(11.2%)	2,851	(1.5%)	<0.001
Dyslipidemia	Statins	290	(53.2%)	39,692	(21.4%)	<0.001
Hypertension	ARB	250	(45.9%)	41,202	(22.2%)	<0.001
	ACEi	34	(6.2%)	5,220	(2.8%)	<0.001
None	Vitamin E	66	(12.1%)	5,057	(2.7%)	<0.001

NASH, nonalcoholic steatohepatitis; IQR, Interquartile range; GLP1, Glucagon-like peptide-1; SGLT2, Sodium-glucose cotransporter 2; ARB, Angiotensin II receptor blocker; ACEi, Angiotensin converting enzyme inhibitor.

Supplemental Table 3. Risk adjusted odds ratio with NASH onset and NASH-related comorbidities relationship.

	Hepatic cirrhosis		Liver cancer		Gastroesophageal reflux diseases		Colorectal adenomas		Colon cancer		Cancer	
	OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)	
NASH vs. non-NASH	28.81	(21.79-38.08)	18.38	(12.56-26.89)	3.08	(2.53-3.73)	2.54	(1.25-5.16)	2.36	(1.70-3.28)	2.16	(1.79-2.62)
Gender (female)	0.70	(0.60-0.81)	0.45	(0.37-0.55)	0.92	(0.90-0.94)	0.41	(0.35-0.49)	0.62	(0.59-0.66)	0.57	(0.55-0.59)
Age	1.04	(1.03-1.04)	1.06	(1.05-1.07)	1.04	(1.04-1.04)	1.02	(1.02-1.03)	1.05	(1.05-1.05)	1.05	(1.05-1.05)
Hypertension	1.78	(1.45-2.19)	1.31	(1.03-1.67)	1.90	(1.85-1.95)	1.54	(1.25-1.90)	1.36	(1.25-1.47)	1.22	(1.17-1.26)
Dyslipidemia	0.73	(0.62-0.86)	0.86	(0.70-1.04)	1.72	(1.68-1.76)	1.72	(1.45-2.05)	1.1	(1.03-1.18)	1.08	(1.04-1.11)
Type 2 diabetes	2.15	(1.82-2.54)	2.56	(2.10-3.13)	1.58	(1.54-1.63)	1.46	(1.23-1.74)	1.62	(1.51-1.74)	1.69	(1.63-1.75)
	Sleep apnea syndrome		Cardiovascular diseases		Osteoporosis		Depression		Insomnia		Chronic kidney diseases	
	OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)	
NASH vs. non-NASH	1.82	(1.20-2.76)	1.40	(1.16-1.69)	1.25	(1.02-1.53)	1.11	(0.87-1.41)	1.12	(0.94-1.34)	0.81	(0.58-1.12)
Gender (female)	0.34	(0.31-0.37)	0.74	(0.72-0.76)	6.68	(6.47-6.91)	1.43	(1.38-1.48)	1.35	(1.31-1.38)	0.58	(0.56-0.61)
Age	1.00	(1.00-1.00)	1.07	(1.07-1.07)	1.08	(1.07-1.08)	1.02	(1.02-1.02)	1.04	(1.03-1.04)	1.06	(1.05-1.06)
Hypertension	3.19	(2.80-3.62)	2.99	(2.90-3.07)	1.50	(1.45-1.55)	1.32	(1.27-1.38)	1.78	(1.73-1.83)	4.33	(4.00-4.68)
Dyslipidemia	2.02	(1.84-2.22)	2.08	(2.03-2.13)	1.68	(1.64-1.73)	1.24	(1.19-1.28)	1.38	(1.34-1.41)	1.35	(1.29-1.41)
Type 2 diabetes	1.57	(1.43-1.72)	1.78	(1.72-1.83)	1.23	(1.18-1.27)	1.22	(1.17-1.27)	1.32	(1.29-1.36)	2.08	(1.99-2.18)

NASH, nonalcoholic steatohepatitis; OR, odds ratio; Cl, confidence interval



Supplemental Figure 1. Flowchart of case-control selection of patients with NASH from the national health insurance and the long-term elderly health insurance claims database in Japan.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	3
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6		
Objectives	3	State specific objectives, including any prespecified hypotheses	6		
Methods					
Study Design	4	Present key elements of study design early in the paper	7		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	7-8	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7-8	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7-8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8		

Bias	9	Describe any efforts to address potential sources of bias	8		
Study size	10	Explain how the study size was arrived at	7		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-8		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	8-9		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	7

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	7
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	10	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	10
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	10		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	10		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10-11		
Discussion					
Key results	18	Summarise key results with reference to study objectives	12		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	12-15		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	17

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Clinical characteristics in patients with nonalcoholic steatohepatitis in Japan: a case-control study using a 5-year large-scale claims database.

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Title: Clinical characteristics in patients with nonalcoholic steatohepatitis in Japan: a case-control study using a 5-year large-scale claims database

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ABSTRACT (294/300 words)

Objectives: To examine the clinical characteristics of patients with nonalcoholic steatohepatitis (NASH) and associated comorbidities.

Design: A case-control study using the national health insurance and the long-term elderly health insurance claims database.

Setting: Eligible patients diagnosed with NASH (ICD-10 K-75.8, other inflammatory liver disease or K-76.0, other fatty liver) between April 2015 and March 2020 were included.

Participants: Patients who met the diagnostic definitions for NASH (n = 545) were matched with non-NASH controls (n = 185,264) and randomly selected according to sex, birth year, and residential area.

Interventions: No interventions were made.

Primary and secondary outcome measures: Odds ratios (ORs) were estimated for the relationship between patient background, such as age and sex, body mass index (BMI), NASH-related comorbidities, and lifestyle-related diseases.

Results: In total, 545 patients with NASH (38.3% male) and 185,264 non-NASH controls (43.2% male) were identified, with median ages of 68 (IQR 63.0–75.0) and 65 (IQR 44.0 – 74.0) years, respectively. BMI was significantly higher in patients with NASH than in controls (25.75 kg/m^2 vs. 22.90 kg/m^2, p <0.001). The proportions of females, patients with hypertension, patients with dyslipidemia, and patients with type 2 diabetes were higher in the NASH group. In addition, NASH was associated with an increased risk of hepatic cirrhosis (OR 28.81 (95% CI, 21.8 –38.08)), followed by liver cancer (OR 18.38 (95% CI 12.56–26.89)). There was no significant association between NASH and risk for depression (OR 1.11 (95% Cl 0.87–1.41)), insomnia (OR 1.12 (95% Cl 0.94–1.34)), or chronic kidney diseases (OR 0.81 (95% Cl 0.58–1.12)).

Conclusions: In the daily medical care of patients, it is necessary to consider sex and age differences and to pay close attention to the risk of liver cancer, as well as other lifestyle-related comorbidities associated with NASH.

Strengths and limitations of this study:

- In this study, analysis was performed using claims data covering a wide range of age groups, including elderly patients.
- Data extraction was limited to patients with a history of liver biopsies, which may have been considered to include a group with more severe NASH.
- A long-term observation period of 5 years was established.

- Japan has several public health insurance systems, but the data used in this study were obtained from the NHI claims database and therefore did not cover the whole of Japan.
- Secondary data were used in this study, and some of them were missing.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common type of liver disease, affecting approximately 20–30% of the global population [1] . NAFLD includes nonalcoholic fatty liver (NAFL), which is pathologically pure steatosis alone or a situation in which steatosis is accompanied by inflammatory cell infiltration, and nonalcoholic steatohepatitis (NASH), which is accompanied by hepatic steatosis, inflammatory cell infiltration, ballooning (hepatocellular ballooning) and hepatic fibrosis [2].

Liver tissue biopsy is the gold standard for diagnosing NAFLD [3-6], which is consistent with guidelines published overseas. However, in clinical practice, performing a liver biopsy with bleeding or pain in all patients with NAFLD is not feasible. Therefore, the proportion of patients undergoing liver biopsy for a NASH diagnosis in clinical practice is not fully understood. According to Rinella et al. [4], the biopsy rate for NASH diagnosis and the therapeutic drugs prescription rate recommended by the guidelines are low, and NASH is underdiagnosed [6]. According to an estimate based on a Markov model of the number of patients with NAFL and NASH worldwide, the number of patients with fibrotic NASH at stage III or higher in Japan was predicted to increase to 660,000 in 2016 and 990,000 by 2030[7]. Moreover, although NASH prevalence has been estimated to be approximately 3–5% of the population [8,9], there is insufficient evidence for NASH prevalence in the general population due to selection bias in liver biopsies and diagnostic difficulties.

NASH is strongly associated with metabolic syndrome, obesity, diabetes mellitus (DM), hypertension, and dyslipidemia [1], and the major causes of death are cardiovascular and liver disease-related events[6]. Obesity and DM are risk factors for cardiovascular and liver disease-related events, including decompensated cirrhosis and liver cancer. Overseas guidelines propose evaluating liver function by abdominal echography and blood tests in patients with obesity or DM [3]. In the Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Diseases/Nonalcoholic Steatohepatitis 2020 (2nd Edition) of Japan (the NASH/NAFLD guideline) [10], it is recommended that primary care physicians assess liver function in patients with risk factors including obesity, DM, dyslipidemia, and hypertension and identify all cases of NAFLD fibrosis progression (as primary screening). As NASH is often asymptomatic and cirrhosis may already be present at the time of diagnosis, efficient screening and timing of referral to a gastroenterologist are important. In NASH, liver fibrosis progresses by one stage in approximately 7 years and progresses faster in patients with comorbid metabolic diseases such as obesity and DM [11]. Therefore, it is recommended that the degree of fibrosis in the NASH group should be regularly evaluated, and, depending on the results, follow-up observation or screening should be performed for liver-related diseases such as liver failure and liver cancer, and non-liver-related diseases such as cerebrocardiovascular events and cancers of other organs [2].

Japan, with a universal health insurance system, has almost all residents covered by medical insurance. Understanding the medical situation of local residents is possible by investigating the claims data of medical insurance provided by the administration [12]. Each municipality serves as a payer of the National Health Insurance (NHI), and the municipalities jointly established the "Federation of National Health Insurance Organizations (FNHIO)" to provide insurance services. Each prefecture has one payer.

The University of Occupational and Environmental Health, Japan (UOEH) has used health insurance claims data by closely cooperating with payers in the NHI; the data enables the understanding of the disease information of NHI beneficiaries every month. Eguchi et al. [13] showed that age-specific NAFLD prevalence was higher in middle-aged males and older females, with differences in the age distribution of NAFLD onset between both sexes. To obtain data on the late-stage elderly, in this study, we matched the NHI claims and the health insurance database for persons aged ≥75 years individually and constructed an original database.

METHODS

Study design and data source

Japan's health insurance system is commonly divided into three types: company health insurance for those employed in a business, NHI for residents of each region, and long-term elderly health insurance (LEHI) for those aged ≥75 years. NHI is a mutual assistance program in which enrolled members pay premiums to a financial pool to which the national government and local municipalities add funds. This case-control study was analyzed using the NHI and LEHI claims databases, comprising inpatient, outpatient, and dispensing service data from domestic payers over April 2015 (through March 2020), provided by the public institution in Japan.

The data included the age and sex of each beneficiary, the type of service used, the month during which the service was used, monthly expenditures on the use of the services, and exit information (death or move-out). We prepared a panel database combining basic medical check-up data and claims databases conducted on a patient-by-patient basis to examine the clinical characteristics of patients with NASH. This study was approved by the ethics committee of the University of Occupational and Environmental Health, Japan (R4-026).

Study population and eligibility criteria

The inclusion criterion was patients of any age with a record of at least one episode of NASH during the study period from April 2015 to March 2020. An episode of NASH was defined as NASH diagnosis (ICD-10 K-75.8; other inflammatory liver diseases or K-76.0; other fatty liver). Furthermore, patients whose disease name string could be confirmed as "hepatitis," "non-alcoholic," and "NASH" in the claims data were also included in the analysis. Using ICD-10; K-75.8 and K-76.0, we have learned that differentiating patients with NASH from patients with NAFLD is extremely difficult. Since a definitive diagnosis of NASH is histopathological diagnosis by liver biopsy and it is essential to confirm pathologically characteristic finding, patients diagnosed with NASH after liver biopsy (percutaneous needle biopsy, endoscopic biopsy and endoscopic ultrasound-guided fine-needle aspiration biopsy) indication were selected. Controls that never had a claim associated with NASH were randomly selected from patients who visited a medical facility at least once between April 2015 and March 2020.

The exclusion criterion was claims for any of the following conditions at any time: hepatitis B virus, hepatitis C virus, human immunodeficiency virus, alcoholic liver disease, toxic liver injury, copper metabolism disorder, autoimmune hepatitis, Gaucher's disease, lysosomal acid lipase deficiency, biliary cirrhosis, cholangitis, or iron metabolism disorder. ICD-10 codes were used to identify the patients with these diseases. It should be noted that, given the expert opinion that a liver biopsy may be performed for a definitive diagnosis of

autoimmune hepatitis to extract a purer sample in patients with NASH, patients with autoimmune hepatitis were excluded.

A patient was defined as having a comorbidity if they had at least one claim for the relevant ICD-10 code during the analysis period. Fourteen comorbidities of interest identified using ICD-10 diagnosis codes (Supplemental Table1) were pre-specified: hypertension, dyslipidemia, type 2 diabetes (T2D), osteoporosis, insomnia, depression, hepatic cirrhosis, liver cancer, cancer, colorectal adenomas, chronic kidney disease (CKD), gastroesophageal reflux disease (GERD), cardiovascular disease (CVD), and sleep apnea syndrome (SAS). The prevalence of these predefined comorbidities has been reported in all patients with NASH and non-NASH comparators.

According to our definition, each patient classified as having NASH was compared with non-NASH comparators randomly selected from the original database by sex, birth year, and residential area (Supplemental Figure 1).

Data collection

Baseline data on all patient characteristics (age, sex), date of death (if data were recorded), prescribed drugs for treating NASH, and NASH-related comorbidities were collected. Age and sex were obtained as of April 2015. The dates of death and prescribed drugs for treating NASH-related comorbidities were obtained at any time during the study period. Height, weight, and laboratory test values were also obtained from patients' available data at any time during the study period. Body mass index (BMI) was calculated from the data of height and weight recorded.

Information on the pathological classification of NASH could not be obtained due to the unavailability of medical examination test results in the NHI and LEHI claims databases.

Statistical analyses

We designed a case-control study to compare the occurrence of comorbidities between the NASH and non-NASH groups during the analysis period and to assess the relationship between NASH and comorbidities. Odds ratios (ORs) for age, sex, life-related diseases (hypertension, dyslipidemia, T2D), and NASH-related comorbidities were evaluated. All analyses were conducted for the two groups: the NASH group, in which patients had at least one record of being diagnosed with NASH, and the non-NASH group, in which the patients had no record of being diagnosed.

Descriptive statistics were conducted using logistic regression models to analyze the relationship of NASH with sex, age, lifestyle-related diseases, death, and comorbidities, along

with their ORs and 95% confidence intervals (CIs). Differences between the NASH and non-NASH groups were evaluated using Pearson's chi-squared test for categorical variables and independent t-tests for continuous variables. Statistical significance was set at $p < 0.05$.

All statistical analyses were performed using Stata Ver.17.0 released in April 2021 (Stata Coro, College Station, Texas, USA).

Patient and public involvement

Patients and members of the public were not involved in the conducting of the study.

RESULTS

Patient characteristics

Patient background characteristics are shown in Supplemental Table 2. In total, 545 patients with NASH (209 males and 336 females) were selected from the claims databases, and 185,264 non-NASH controls (80,051 males and 105,213 females) were identified, with median (interquartile range; IQR) ages of 68 (63.0-75.0) and 65 (44.0– 74.0) years, respectively. Among the NASH group, the most frequently prescribed agents were statins (53.2%), followed by angiotensin receptor blockers (ARBs) (45.9%), and vitamin E (12.1%), and among the non-NASH group, they were ARBs (22.2%), statins (21.4%), and angiotensin-converting-enzyme inhibitor (ACEi) (2.8%).

Table 1 summarizes the height, weight, BMI, and blood test values of patients whose data could be extracted for each group. In total, 220 patients were identified in the NASH group, and 44,913 patients were identified in the non-NASH group. BMI was significantly higher than in the NASH vs. non-NASH group (25.8 kg/m^2 vs. 22.9 kg/m^2, p <0.001). The laboratory test value (> 5%) was also higher than in the NASH vs. non-NASH group, except for high-density cholesterol (54.0 mg/dL and 61.0 mg/dL, respectively) and low-density lipoprotein cholesterol (109.0 mg/dL and 117.0 md/dL, respectively).

Table 1. Characteristics of the patients with specific health examination data in analyzed NASH and non-NASH groups.

	NASH group N=220		non-NASH group N=44,913		*p*-value
Degree of obesity; Median (IQR)					
Body weight, kg	63.9	(55.4-71.5)	56.0	(48.9-64.0)	<0.001
Height, cm	156.8	(150.8-163.8)	156.0	(149.8-163.4)	0.400
Body mass index, kg/m^2	25.8	(23.4-28.1)	22.9	(20.8-25.2)	<0.001
Laboratory test values; Median (IQR)					
AST, U/L	31.0	(23.0-52.0)	22.0	(19.0-26.0)	<0.001
ALT, U/L	31.5	(21.0-55.5)	17.0	(13.0-23.0)	<0.001
γ-GTP, U/L	42.0	(27.0-77.0)	22.0	(16.0-34.0)	<0.001
SBP, mmHg	130.0	(121.0-140.0)	129.0	(119.0-140.0)	0.220
DBP, mmHg	75.0	(70.0-81.5)	74.0	(67.0-80.0)	0.020
HbA1c, %	6.0	(5.7-6.5)	5.7	(5.4-6.0)	<0.001
TG, mg/dL	127.5	(90.5-171.0)	95.0	(70.0-134.0)	<0.001
HDL, mg/dL	54.0	(44.5-63.0)	61.0	(51.0-73.0)	<0.001
LDL, mg/dL	109.0	(91.0-127.5)	117.0	(99.0-138.0)	<0.001

NASH, nonalcoholic steatohepatitis; IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-guanosine triphosphate; SBT, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglyceride; HDL; high-density lipoprotein cholesteryl; LDL, low-density lipoprotein cholesterol.

Comorbidities

Table 2 summarizes NASH-related comorbidities of patients in each group. The prevalence rates of all NASH-related comorbidities were significantly higher in the NASH vs. the non-NASH group, except that of autoimmune hepatitis. The five most prevalent comorbidities had rates above 50% in the NASH group: dyslipidemia (82.6 %), hypertension (78.7 %), GERD (69.9%), T2D (62.2%), and CVD (56.0%). In the non-NASH group, the rates were not higher than 50%: hypertension (46.5%) being the most common comorbidity, followed by dyslipidemia (36.4%).

Table 2. NASH-related comorbidities identified in the analyzed population.

Combination or disease, n (%)	NASH group N=545		non-NASH group N=185,264		*p*-value
Dyslipidemia	450	(82.6%)	67,463	(36.4%)	<0.001
Hypertension	429	(78.7%)	86,101	(46.5%)	<0.001
Gastroesophageal reflux disease	381	(69.9%)	53,156	(28.7%)	<0.001
Type2 diabetes	339	(62.2%)	26,732	(14.4%)	<0.001
Cardiovascular disease	305	(56.0%)	54,293	(29.3%)	<0.001
Insomnia	225	(41.3%)	48,487	(26.2%)	<0.001
Osteoporosis	188	(34.5%)	38,149	(20.6%)	<0.001
Cancer	166	(30.5%)	22,310	(12.0%)	<0.001
Hepatic cirrhosis	71	(13.0%)	632	(0.3%)	<0.001
Depression	80	(14.7%)	18,038	(9.7%)	<0.001
Chronic renal failure	42	(7.7%)	9,136	(4.9%)	0.005
Liver cancer	34	(6.2%)	428	(0.2%)	<0.001
Sleep apnea syndrome	24	(4.4%)	2,368	(1.3%)	<0.001
Colorectal adenomas	8	(1.5%)	634	(0.3%)	<0.001

NASH, nonalcoholic steatohepatitis; GLP1, glucagon-like peptide-1; SGLT2 sodium-glucose cotransporter 2; ARB, angiotensin II receptor blocker; ACEi, angiotensin converting enzyme inhibitor

Age, sex, and life-related disease as risk factors for NASH

The influence of sex, age, and life-rated disease on NASH has been reported previously [14]. Multiple logistic regression models were used to assess the effect of sex, age, and lifestyle-related diseases on NASH prevalence. Figure 1 shows the ORs for factors associated with NASH prevalence. Significantly higher risks were observed among females, patients with hypertension, patients with dyslipidemia, and patients with T2D, compared with the non-NASH group; the ORs for dyslipidemia and T2D were very high (4.39 and 5.83, respectively). The association with age was insignificant, compared with that in the non-NASH group.

In a separate multiple logistic regression model examining the association between mortality due to NASH and each risk factor, adjusted for sex, age, and lifestyle-related diseases, the ORs for age and T2D were significantly higher than those in the non-NASH group (Figure 2).

Comorbidities as risk factors for NASH

The ORs for NASH and NASH-related comorbidities, adjusted for sex, age, and lifestyle-related diseases, are shown in Supplemental Table 3. In a multiple logistic regression model examining the association between NASH and developing comorbidities, compared with non-NASH, the risk of developing hepatic cirrhosis was the greatest (OR 28.81, 95% CI, 21.79–38.08), followed by that for liver cancer (OR 18.38, 95% CI, 12.56–26.89), GERD (OR 3.08, 95% CI 2.53–3.73), colorectal adenomas (OR 2.54, 95% CI 1.25-5.16), colon cancer (OR 2.36, 95% CI 1.70–3.28), cancer (OR 2.16, 95% CI 1.79–2.62), SAS (OR 1.82, 95% CI 1.20–2.76), CVD (OR 1.40, 95% CI 1.16–1.69), and osteoporosis (OR 1.25, 95% CI 1.02–1.53). No significant difference in comorbidities was observed for depression (OR 1.11, 95% CI 0.87–1.41), insomnia (OR 1.12, 95% CI 0.94–1.34), and CKD (OR 0.81, 95% CI 0.58–1.12).

There was no significant difference in the OR for osteoporosis (OR 1.03, 95% CI 0.94–1.13) between the NASH and non-NASH groups; however, the OR significantly increased to 6.68 (95% CI 6.47–6.91) in females. The OR for CKD was less <1, and it was not significantly elevated in the NASH group. However, when patients with NASH had a history of hypertension, dyslipidemia, or T2D, the ORs increased significantly to 4.33 (95% CI 4.00–4.68), 1.35 (95% CI 1.29–1.41) and 2.08 (95% CI 1.99–2.18), respectively, which has been shown to increase the risk of developing CKD.

DISCUSSION

Using the NHI and LEHI claims databases, we constructed an original database and examined the clinical characteristics of patients with NASH for 5 years from April 2015 to March 2020. It has been reported that NAFLD/NASH prevalence varies by age and sex [13,15,16]. In a cross-sectional study [13] conducted among 8,352 participants who underwent health checkups from 2009 to 2010 at three health centers in Japan, NAFLD prevalence was 29.7% overall, more than 30% in males aged 30–60 years, and increased with age in females aged 30–60 years old. It is considered that decreased estrogen levels due to aging and menopause affect NAFLD progression in females [14]. Similar to that of NAFLD prevalence, there are more middle-aged males and older females in the age distribution of NASH prevalence. In this study, the median age of the NASH group was 68 years (IQR, 63.0-75.0), showing an older age and a higher proportion of females than males (38.3% vs. 61.7%). This finding also suggests that NASH prevalence is higher in older females.

NAFLD or NASH is strongly associated with obesity [7,13,15]. This study showed that BMI was significantly higher in the NASH group than in the non-NASH group (25.8 kg/m^2 vs 22.9 kg/m^2, p <0.001). Obesity is the most common manifestation of metabolic syndrome and the most important risk factor for NAFLD/NASH, which can also be regarded as a liver lesion [17]. The World Health Organization (WHO) diagnostic criteria define BMI ≥25 kg/m^2 as overweight and BMI ≥30 kg/m^2 as obesity. In Japan, the definition of obesity as judged by the Japan Society for Study of Obesity is BMI ≥25 kg/m^2, which is lower than the WHO value. This is because Japanese people are more likely to develop fatty liver if their BMI is less than 25 kg/m^2 and develop fatty liver at a high rate after their BMI exceeds 25 kg/m^2. A previous study reported NAFLD/NASH prevalence in non-obese participants (BMI <23 kg/m^2) to be ≤10% and that in highly obese participants (BMI >30 kg/m^2) to be approximately 80%[10]. It has also been reported body weight loss ≥7% led to a decrease in the prevalence rates of hepatic steatosis, inflammatory cell infiltration, and ballooning decreased by 7% or more of body weight loss, and improved NAFLD activity score [18]. The present study also showed that the median BMI was >25 kg/m^2 in the NASH group, suggesting the importance of liver lesions and active lifestyle interventions in daily medical practice for NAFLD/NASH. However, it is essential to improve the consciousness of the patients for lifestyle interventions, and maintenance of the target achievement rate and adherence may become an issue. Similar to previous research [19,20], the results of the present study may support NAFLD/NASH association with several metabolic comorbidities, including T2D, dyslipidemia, hypertension, and CVD. Regarding CKD, patients with NASH were shown to have a higher risk of complications if they had hypertension or T2D. Management of these conditions may complicate the treatment of NASH, impacting clinical care outcomes.

According to the NASH/NAFLD guidelines [10], some therapeutic drugs for dyslipidemia, hypertension, and DM have been suggested to be effective for NASH, and

aggressive treatment of patients with complications of these lifestyle-related diseases is recommended. Therefore, this survey investigated the proportion of prescriptions for antihyperlipidemic, hypertensive, and antidiabetic drugs. As a result, the proportion of prescriptions was 53.2% for statins and 45.9% for ARBs in the NASH group, which was significantly higher than 21.4% and 22.2%, respectively, in the non-NASH group, less than 50%. Premature mortality in NASH is related to both hepatic (cirrhosis and hepatocellular carcinoma) and extra-hepatic complications, largely CVD. Many therapeutic agents have been tested but are still nonapproved, specifically for NASH. Moreover, presently, there is no drug with sufficient evidence of improving fibrosis in patients with NASH. Many clinical studies on drug therapy and development for NASH are expected to be conducted in the future.

The prevalence of lifestyle-related diseases in NAFLD in Japan is reported to be approximately 60–80% for dyslipidemia, 40% for hypertension and 20–50% for DM [10]. The results of this study focusing on NASH also showed that the complication rates of dyslipidemia, hypertension, GERD, and T2D were significantly higher in the NASH group than in the non-NASH group (82.6% vs. 36.4 %, $p < 0.001$; 78.7% vs. 46.5%, $p < 0.001$; 69.9% vs. 28.7%, $p < 0.001$; 62.2% vs. 14.4%, $p < 0.001$), higher than those of lifestyle-related diseases in NAFLD. In a study by Terai et al. [21], who estimated complications in patients with NAFLD/NASH using the Medical Data Vision claims database, dyslipidemia prevalence in the 67–74 years group was 57.9%, hypertension prevalence was 57.2%, and T2D prevalence was 32.5%, lower than the rates reported in the present study (82.6%, 78.7%, and 62.2%, respectively). However, CVD prevalence was 75.8%, higher than that in the present study (56.0%). This is because the database used by Terai et al. [21] summarizes the health insurance data for acute-care hospitals in Japan but does not include information on health insurance data for general practitioners and core hospitals. This may have contributed to the higher proportion of CVD cases requiring surgery. In the present study, a multivariate analysis was performed for sex, age, and risk factors for lifestyle-related diseases in NASH. The OR was ≥1 for factors other than age. Among them, dyslipidemia (OR 4.39, 95% CI 3.41–5.65) and T2D (OR 5.83, 95% CI 4.83–7.04) showed an OR ≥4, indicating that these are major risk factors for NASH. In addition, T2D increased the risk of death from NASH (OR 1.34, 95% CI 1.26–1.43). These results suggest that more aggressive interventions are needed for patients with dyslipidemia and T2D.

NAFLD should be considered a systemic disease that presents with many comorbidities and other lifestyle-related diseases [22]. A multivariate analysis was performed for risk factors for comorbidity of NASH (risk of onset). Cirrhosis (OR 28.81, 95% CI, 21.79–38.08) and liver cancer (OR 18.38, 95% CI, 12.56–26.89) were significant and major risk factors for comorbidity. Cancer development from NAFLD occurs at an annual rate of approximately 0.04%, while hepatocarcinogenesis from NASH cirrhosis occurs at an annual rate of approximately 2–3% [22]. Our analysis showed a higher risk factor than that reported in previous studies. In a hospital-based study [23], 68 patients with NASH cirrhosis (mean age,

63 years; 57% male) were observed for an average of 3.4 years, of whom seven patients developed cancer. Furthermore, the 5-year cumulative rate of hepatocellular carcinoma among patients with NASH was 11.3%, which was lower than the 30.5% rate of hepatitis C virus cirrhosis in the study group [24]. In a median 3.2-year observational study of 195 patients with NASH cirrhosis (mean age 56.6 years, 44.1% male), 25 (12.8%) participants developed hepatocarcinogenesis, a lower rate than 20.3% of hepatitis C virus cirrhosis evident for the control group. In NASH, liver fibrosis progresses by one step every 7 years [11]. The observation period of this study was 5 years, whereas the observation period of Yatsuji et al. [23] and Ascha et al. [25] was approximately 3 years, which may have been related to the difference in cancer incidence; thus, our results are acceptable. The prognosis of NASH cirrhosis worsens with increasing degrees of fibrosis and severity of cirrhosis [26]. Since liver cancer is the most important vital prognostic factor in patients with cirrhosis, it is important to monitor its course in consideration of carcinogenesis.

After liver cancer and cirrhosis, GERD showed the highest OR. In the present study, the complication rate of GERD in the NASH group was as high as 69.9% and was also a high-risk factor. Several cross-sectional and cohort studies have investigated the association between NAFLD and GERD risk [27-35]. However, their results have been conflicting so far. Some studies have shown a higher prevalence of GERD among patients with NAFLD, compared with the general population, while other studies have failed to find a significant association between NAFLD and GERD risk. Obesity is a potential confounding factor in clinical studies on the association between NAFLD and GERD, as it has been established as a common risk factor for both diseases [33, 36]. A systematic review and meta-analysis of observation studies of NAFLD patients with and without obesity in the development of GERD by Xue J et al. [37] showed a significant association between NAFLD and GERD risk. However, to our knowledge, no study has defined a temporal or causal relationship between NAFLD and GERD. As NASH is advanced from NAFLD, GERD risk should be considered in clinical practice.

Limitations

First, our results may not be generalizable to all patients with NASH in Japan. Japan has several public health insurance systems; however, the database used only contained data from the NHI and did not cover the whole of Japan. Moreover, missing records and insufficient data entries were inevitable. The NHI covers self-employed, unemployed, and retired persons aged <75 years. Therefore, to obtain data for the oldest of the older population, we added data on health insurance for persons aged <75 years. However, each patient's medical record may not trace the patient's full medical history if the patient moved or switched to employer-based health insurance.

Second, the lack of information must be acknowledged. NASH and its comorbidities were categorized based on ICD-10 three-character code block categories. A stable version of the ICD-11 was released in 2018 and officially endorsed by all WHO members during the 72nd World Health Assembly in 2019. The original code for NASH in ICD-11 is given but has not yet been officially enforced in Japan. Third, the current state of NASH diagnosis in Japan has not been clarified, and it was difficult to accurately extract NASH cases from actual medical care data in Japan. Furthermore, the study results suggest that the prevalence of NASH is higher in older females. However, there is a possibility of selection bias (e.g., those who visited a healthcare provider, had a blood test, or agreed to undergo a liver biopsy). There are also limitations in drawing firm conclusions about the exact age and sex distributions, given that they are not necessarily representative of all Japanese patients.

This study showed that NASH is significantly involved in the development of intrahepatic lesions such as cirrhosis and liver cancer. To better understand the complex etiology of NASH, it may be necessary to investigate its relationship with extrahepatic primary cancers, such as extra-hepatic cancer.

Conclusions

The database we developed combines a large health claims database with specific medical examination data. Therefore, our study is the first to include an overview of NASH-attributable patients in Japan. NASH is expected to become an increasingly common health disorder from social and epidemiological perspectives because of the recent increase in prevalence and the diversity of diseases and conditions. The results of this study indicated that NASH is associated with high risks of complications of liver cancer and cirrhosis, and that coexisting lifestyle-related diseases increase the risk of death and the risk of complications of GERD. In the daily medical care of patients with NASH, it is necessary to consider sex and age and pay close attention to liver lesions and various other lifestyle-related neoplasms.

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Figure legends

Fig 1. Forest plot of risk adjusted odds ratios of diagnosed with NASH according to patients' background and life-related diseased.

NASH, nonalcoholic steatohepatitis; CI, confidence interval

Fig 2. Forest plot of risk adjusted odds ratios for mortality based on patients' background and life-related diseases.

NASH, nonalcoholic steatohepatitis; CI, confidence interval

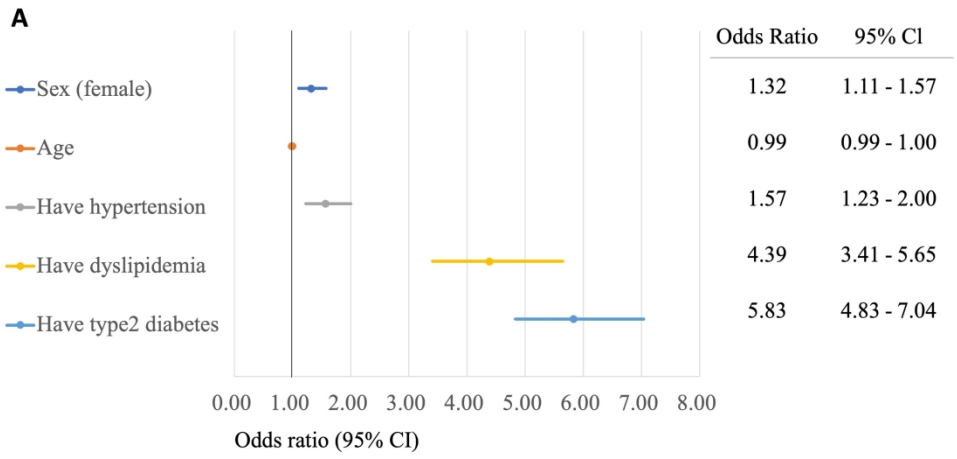


Fig1. Forest plot of risk adjusted odds ratios of diagnosed with NASH according to patients' background and life-related diseased.
NASH, nonalcoholic steatohepatitis; CI, confidence interval

250x118mm (300 x 300 DPI)

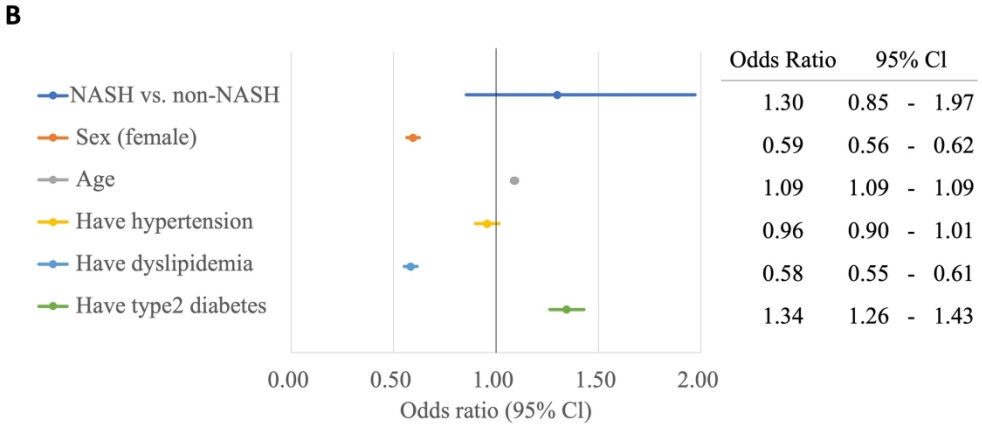


Fig 2. Forest plot of risk adjusted odds ratios for mortality based on patients' background and life-related diseases.
NASH, nonalcoholic steatohepatitis; CI, confidence interval

239x113mm (300 x 300 DPI)

Supplementary Information

Supplemental Table 1. ICD-10 codes for definition of comorbidity complexes

Comorbidity	ICD-10 codes
Hypertension	I10 - I15
Dyslipidemia	E780 - E785
Type 2 diabetes	E11
Osteoporosis	M80 - M82
Insomnia	G470
Depression	F30 - F39
Hepatic cirrhosis	K743 - K746
Liver cancer	C22
Colon cancer	C18
Cancer	C00 - C96, D00 - D48, D370 - D386, D390 - D392, D397, D399, D410 - D414, D417, D419, D440 - D449
Colorectal adenomas	D126
Chronic kidney disease	N18
Gastroesophageal reflux disease	K21
Cardiovascular disease	I20 - I25, I60 - I69
Sleep apnea syndrome	G473

Supplemental Table 2. Baseline patient demographics and characteristics for NASH and non-NASH group

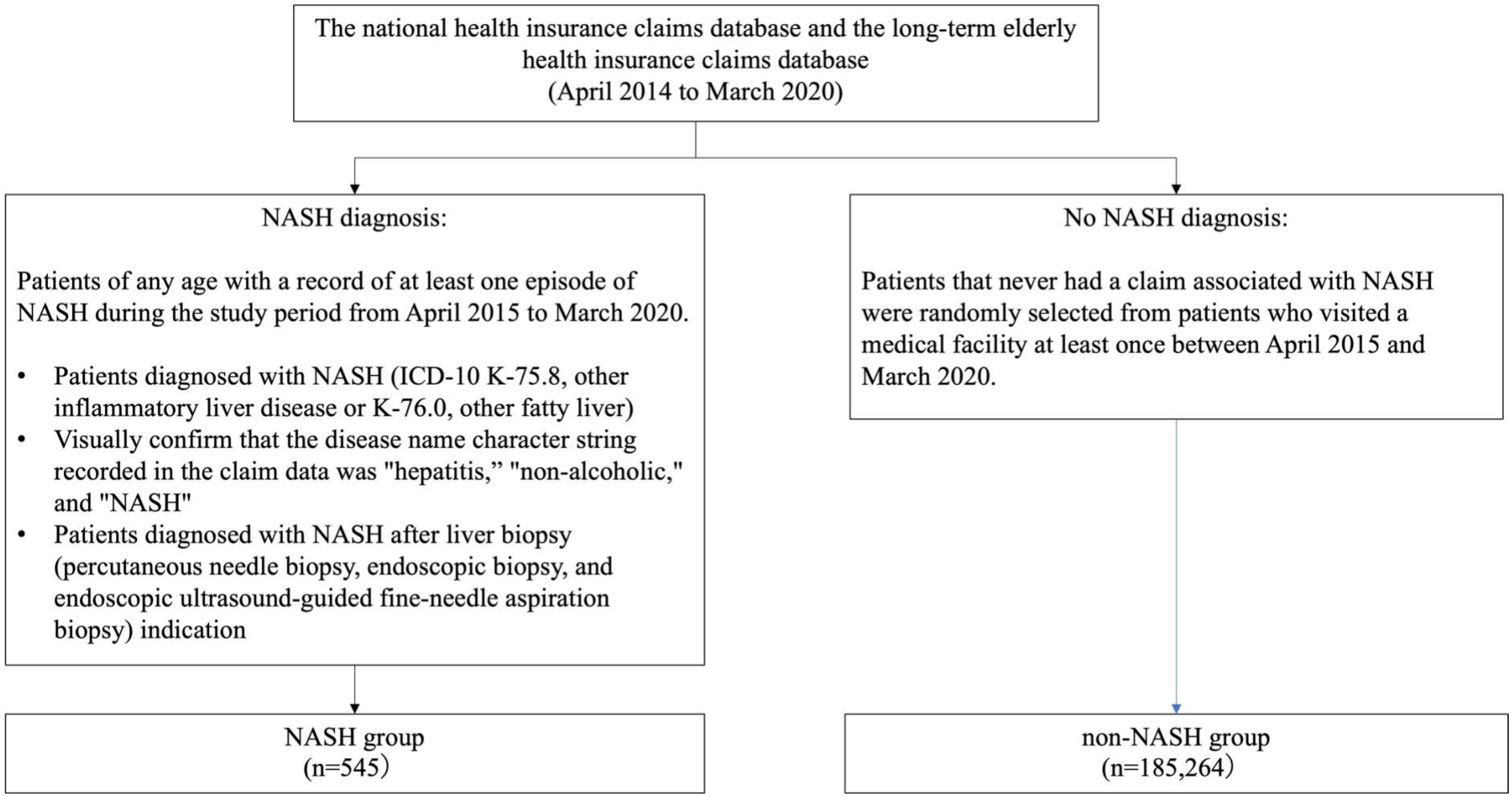
		NASH group N=545		non-NASH group N=185,264		*p*-value
Age years; Median (IQR)		68	(63.00-75.00)	65	(44.00-74.00)	<0.001
Gender n (%)						
	Male	209	(38.3%)	80,051	(43.2%)	0.022
	Female	336	(61.7%)	105,213	(56.8%)	
Death n (%)		24	(4.4%)	6,696	(3.6%)	0.300
Prescribed drugs for treatment of NASH during analysis period						
Type 2 diabetes	Pioglitazone	16	(2.9%)	1,600	(0.9%)	<0.001
	GLP1 agonist	18	(3.3%)	794	(0.4%)	<0.001
	SGLT2	61	(11.2%)	2,851	(1.5%)	<0.001
Dyslipidemia	Statins	290	(53.2%)	39,692	(21.4%)	<0.001
Hypertension	ARB	250	(45.9%)	41,202	(22.2%)	<0.001
	ACEi	34	(6.2%)	5,220	(2.8%)	<0.001
None	Vitamin E	66	(12.1%)	5,057	(2.7%)	<0.001

NASH, nonalcoholic steatohepatitis; IQR, Interquartile range; GLP1, Glucagon-like peptide-1; SGLT2, Sodium-glucose cotransporter 2; ARB, Angiotensin II receptor blocker; ACEi, Angiotensin converting enzyme inhibitor.

Supplemental Table 3. Risk adjusted odds ratio with NASH onset and NASH-related comorbidities relationship.

	Hepatic cirrhosis		Liver cancer		Gastroesophageal reflux diseases		Colorectal adenomas		Colon cancer		Cancer	
	OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)	
NASH vs. non-NASH	28.81	(21.79-38.08)	18.38	(12.56-26.89)	3.08	(2.53-3.73)	2.54	(1.25-5.16)	2.36	(1.70-3.28)	2.16	(1.79-2.62)
Gender (female)	0.70	(0.60-0.81)	0.45	(0.37-0.55)	0.92	(0.90-0.94)	0.41	(0.35-0.49)	0.62	(0.59-0.66)	0.57	(0.55-0.59)
Age	1.04	(1.03-1.04)	1.06	(1.05-1.07)	1.04	(1.04-1.04)	1.02	(1.02-1.03)	1.05	(1.05-1.05)	1.05	(1.05-1.05)
Hypertension	1.78	(1.45-2.19)	1.31	(1.03-1.67)	1.90	(1.85-1.95)	1.54	(1.25-1.90)	1.36	(1.25-1.47)	1.22	(1.17-1.26)
Dyslipidemia	0.73	(0.62-0.86)	0.86	(0.70-1.04)	1.72	(1.68-1.76)	1.72	(1.45-2.05)	1.1	(1.03-1.18)	1.08	(1.04-1.11)
Type 2 diabetes	2.15	(1.82-2.54)	2.56	(2.10-3.13)	1.58	(1.54-1.63)	1.46	(1.23-1.74)	1.62	(1.51-1.74)	1.69	(1.63-1.75)
	Sleep apnea syndrome		Cardiovascular diseases		Osteoporosis		Depression		Insomnia		Chronic kidney diseases	
	OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)		OR (95%Cl)	
NASH vs. non-NASH	1.82	(1.20-2.76)	1.40	(1.16-1.69)	1.25	(1.02-1.53)	1.11	(0.87-1.41)	1.12	(0.94-1.34)	0.81	(0.58-1.12)
Gender (female)	0.34	(0.31-0.37)	0.74	(0.72-0.76)	6.68	(6.47-6.91)	1.43	(1.38-1.48)	1.35	(1.31-1.38)	0.58	(0.56-0.61)
Age	1.00	(1.00-1.00)	1.07	(1.07-1.07)	1.08	(1.07-1.08)	1.02	(1.02-1.02)	1.04	(1.03-1.04)	1.06	(1.05-1.06)
Hypertension	3.19	(2.80-3.62)	2.99	(2.90-3.07)	1.50	(1.45-1.55)	1.32	(1.27-1.38)	1.78	(1.73-1.83)	4.33	(4.00-4.68)
Dyslipidemia	2.02	(1.84-2.22)	2.08	(2.03-2.13)	1.68	(1.64-1.73)	1.24	(1.19-1.28)	1.38	(1.34-1.41)	1.35	(1.29-1.41)
Type 2 diabetes	1.57	(1.43-1.72)	1.78	(1.72-1.83)	1.23	(1.18-1.27)	1.22	(1.17-1.27)	1.32	(1.29-1.36)	2.08	(1.99-2.18)

NASH, nonalcoholic steatohepatitis; OR, odds ratio; Cl, confidence interval



Supplemental Figure 1. Flowchart of case-control selection of patients with NASH from the national health insurance and the long-term elderly health insurance claims database in Japan.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	3
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6		
Objectives	3	State specific objectives, including any prespecified hypotheses	6		
Methods					
Study Design	4	Present key elements of study design early in the paper	7		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	7-8	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7-8	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7-8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8		

Bias	9	Describe any efforts to address potential sources of bias	8		
Study size	10	Explain how the study size was arrived at	7		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-8		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	8-9		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	7

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	7
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	10	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	10
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	10		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	10		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10-11		
Discussion					
Key results	18	Summarise key results with reference to study objectives	12		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	12-15		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	17

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.