Ann Acad Med Singap 2023;52:570-9
https://doi.org/10.47102/annals-acadmedsg.202379

ORIGINAL ARTICLE

Risk of dementia in the elderly with non-alcoholic fatty liver disease: A nested case-control study in the Republic of Korea

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is known to be associated with metabolic syndrome of which diabetes is an important component. Although diabetes is a known risk factor for dementia, studies on the association between NAFLD and dementia still produce conflicting results. This study aimed to determine whether NAFLD would be a risk factor for the development of dementia in an elderly population.

Method: This study included 107,369 subjects aged ≥60 years in the Korean National Health Insurance Service-Senior cohort, entered in 2009 and followed up until 2015. NAFLD was diagnosed by calculating fatty liver index (FLI). Subjects were screened for dementia at baseline using a Korean Dementia Screening Questionnaire, and dementia was diagnosed using ICD-10 codes. Controls were randomly selected at a ratio of 1:5 from individuals who were at risk of becoming the case subjects at the time of selection.

Results: From 107,369 subjects, 65,690 stroke- and dementia-free subjects without chronic hepatitis B or C or excessive alcohol drinking were selected for evaluation. Having NAFLD, determined by FLI, was associated with increased risk of dementia development (adjusted odds ratio [AOR] 1.493; 95% confidence interval [CI] 1.214–1.836). The increased risk of dementia in NAFLD subjects was independent of type 2 diabetes (AOR 1.421; 95% CI 1.013–1.994, in subjects with diabetes: AOR 1.540; 95% CI 1.179–2.010, in subjects without diabetes).

Conclusion: In this population-based nested case-control study, having NAFLD increased the risk of dementia in elderly individuals, independent of accompanying diabetes.

Ann Acad Med Singap 2023;52:570-9

Keywords: dementia, metabolic syndrome, non-alcoholic fatty liver disease, population-based study

CLINICAL IMPACT

What is New

- This nationwide nested case-control study assessed the risk of dementia in elderly subjects.
- Fatty liver index-defined non-alcoholic fatty liver disease (NAFLD) was associated with newly diagnosed dementia in subjects older than 60 years, independent of diabetes mellitus, a known risk factor for dementia.

Clinical Implication

- Dementia and NAFLD are frequent conditions that share underlying metabolic risk factors, and the finding of this study adds evidence that NAFLD is associated with newly developed dementia in elderly subjects.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease affecting about 25% of the general population.[1,2] NAFLD has a broad disease spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH)/liver cirrhosis, resulting in increased risk of developing not only liver-related complications but also extrahepatic morbidities.[3] Common extrahepatic manifestations of NAFLD consist of cardiovascular diseases, non-liver cancers and chronic kidney disease (CKD).[4-6] It has been contemplated that increased extrahepatic complications in NAFLD might be due to metabolic derangements, such as type 2 diabetes or hypertension that are thought to have a strong association with NAFLD.[7,8]

In recent years, several reports have suggested possible links between NAFLD and impaired cognitive functions.[9-11] In a study analysing the correlation between NAFLD and total cerebral brain volume using brain magnetic resonance imaging in the cohort of Framingham Study, it was found that NAFLD is associated with smaller total cerebral brain volume independent of visceral adipose tissue and cardiometabolic risk factors.[12] In addition, a recent cohort study demonstrated that elevated liver enzymes were associated with a higher risk of

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Alzheimer's disease (AD) where NAFLD is the most frequent aetiology of abnormal liver enzyme levels.[13] On the other hand, there are studies reporting the negative association between NAFLD and cognitive function decline or dementia.[14,15]

In this study, we investigated the associations between NAFLD and the risk of dementia in an elderly population, age over 60 years, using the database of the nationwide population-based National Health Insurance Service (NHIS)-Senior cohort (NHIS-Senior) in the Republic of Korea.[16] NHIS-Senior provides nationally representative cohort data of the entire elderly population in South Korea and includes mental health screening as a major variable.

METHOD

Database

NHIS is a single-payer insurance programme that has been providing compulsory national health screening since 1996, covering almost the entire Korean population of 50 million.[17] NHIS-Senior comprises 558,147 individuals over the age of 60 years, that were randomly sampled from the 5 million examinees who received physical health examinations provided by the Korean NHIS in 2002.[18] The information in the NHIS-Senior dataset included all inpatient and outpatient medical claims data, including prescription drug use, diagnostic and treatment codes, and primary and secondary diagnosis codes. Measurements from health check-up examinations, and information on socioeconomic and demographic status were also contained. All individuals included in NHIS-Senior were followed up until 2015 unless there was death or disqualification for National Health Insurance, such as emigration.

This study was approved by the Institutional Review Board of Yonsei University Health System (3-2019-0167). Informed consent was waived, as the researchers only accessed the database for analysis purposes, and personal information was anonymised to protect individuals' privacy.

Case and control selection

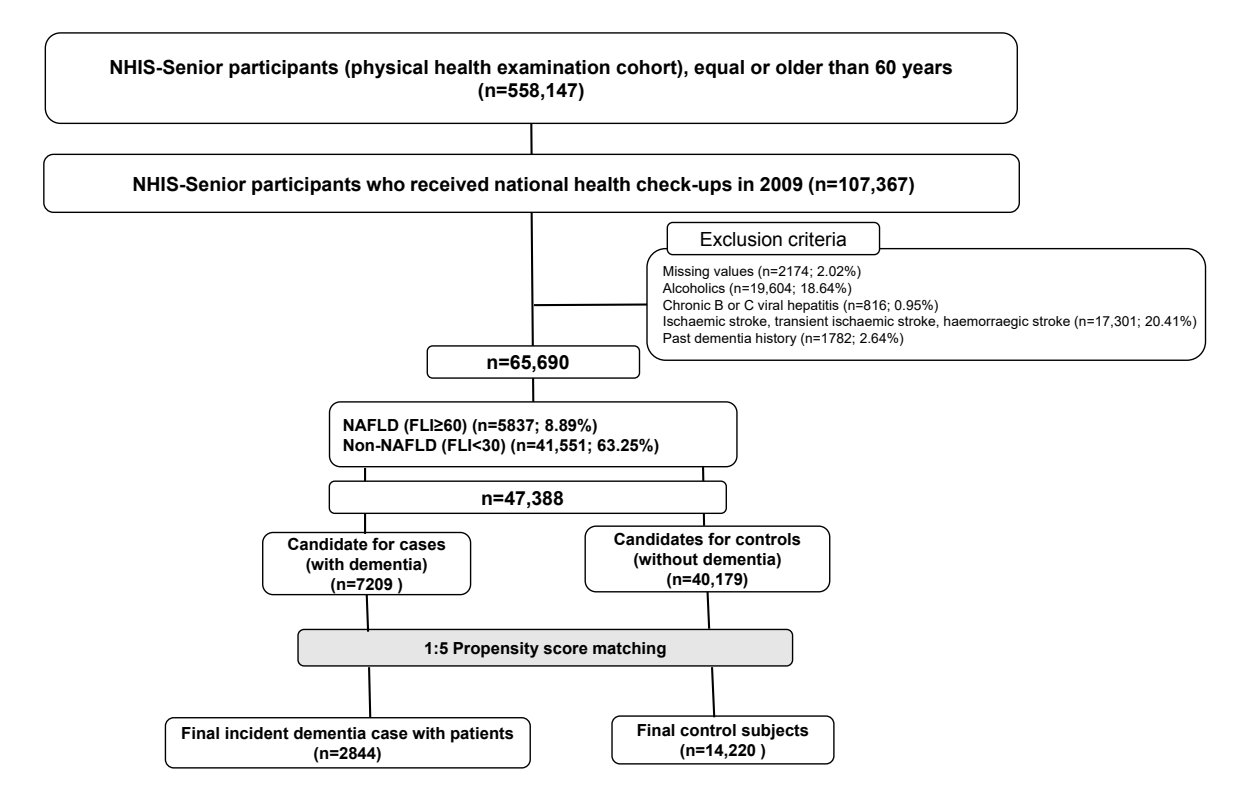
From the Korean NHIS-Senior, a total of 107,367 subjects who had a health check-up in 2009—the year when serum triglyceride (TG) level was included as a parameter in the physical health examination programme—and follow-up data were reviewed until December 2015. those, subjects who met the following criteria were excluded (n=41,677): missing data (n=2174); excessive alcohol drinking (>210 g/week for men and >140 g/week for women)[19] (n=19,604); positive serologic markers of hepatitis B or C (n=816); past history of ischaemic stroke, transient ischaemic stroke, haemorrhagic stroke (n=17,301); having dementia before or at the time of enrolment (n=1782). A total of 65,690 individuals were analysed in our study (Fig. 1). The fatty liver index (FLI) was calculated to define NAFLD. FLI was the relatively easy and accurate index that was calculated from routine measures used in clinical settings, such as body mass index (BMI), waist circumference, TG, and gamma glutamyl transferase (γGT).[20] The accuracy of FLI had been validated in identifying NAFLD with the comparable accuracy with abdominal sonography.[21] FLI was calculated according to the following formula.[20]

$$FLI = (e(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745))/(1 + e(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745)) \times 100$$

Similar to a previous study, the FLI cutoff of <30 was applied to predict the absence of NAFLD (specificity: 87%, negative likelihood ratio: 0.2), and FLI≥60 was used for identifying the presence of NAFLD (sensitivity: 86%, positive likelihood ratio: 0.5).[20]

The primary outcome of interest was the development of dementia, which was identified using the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Among the NHIS-Senior cases, the eligibility criteria for the dementia incidence patients were as follows: (1) first-time diagnosis of dementia (ICD F00-F03 or G30), (2) discharge diagnosis with a primary diagnosis code of dementia or confirmed at least twice in the outpatient department, and (3) no prior diagnosis of cerebrovascular disease (Fig. 1). The date of dementia diagnosis was the first date of outpatient or inpatient records with a primary diagnosis of dementia. The index date was defined as the date 1 year prior to the date of dementia diagnosis. Controls were randomly selected at a ratio of 1:5 from individuals who were at risk of becoming the case subjects at the time when the particular case subjects were selected. The subjects excluded during the case selection were also excluded from the risk set. The case and control subjects were matched based on the duration of follow-up until the age at case selection, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, hypertension, diabetes mellitus (DM), current smoking status, and economic status at index date. Since DM is known as the major risk factor for dementia,[22,23] the case and control subjects were further analysed in a subgroup analysis based on the presence of DM or absence of DM.

Fig. 1. Flow of study population.



FLI: fatty liver index; NAFLD: non-alcoholic fatty liver disease; NHIS-Senior: National Health Insurance Service

Assessment of dementia

The subjects were screened for dementia at baseline using the Korean Dementia Screening Questionnaire (KDSQ). The KDSQ consists of 3 subscales (global memory function, other cognitive function, and instrumental activities of daily living), including 15 items that can detect early changes in cognitive decline.[24] Scores for each item in the KDSQ range from 0 to 2, with a higher score indicating poorer function and a higher frequency. The KDSQ is not affected by age or educational level and has shown a sensitivity of 0.79 and a specificity of 0.80 for dementia. The KDSQ rate positive was defined as the case with the score ≥6.[25] The development of dementia was confirmed by ICD-10 codes for dementia (F00-F03, G30).

Clinical variables and biochemical measurements

We obtained information about baseline comorbidities from inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using the medical billing and prescription drug information registered before the index date. In order to increase the accuracy of diagnoses, the study was conducted based on the condition diagnosed when the patient was discharged from the hospital or diagnosed at least twice in the outpatient department, which was the same as in previous studies using NHIS.[18,26]

Hypertension was defined when blood pressure was 140/90 mmHg or higher, according to the 2020 International Society of Hypertension Global Hypertension Practice Guidelines,[27] or when taking antihypertensive medications. Diabetes was defined as a fasting blood glucose level of 126 mg/dL or currently taking diabetes medications. BMI was calculated as body weight divided by height squared (kg/m^2). An individual's standard income was based on the total amount of national health insurance premiums paid by the insured in the index year in proportion to the individual's income. Smoking status was categorised as non-smokers and past smokers into 1 group, and current smokers into another group. Blood pressure was measured using a mercury sphygmomanometer after resting for at least 10 minutes in a sitting position. Blood samples were collected as measured by a blood laboratory after an overnight fast for 12 hours. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), TG, γGT, total cholesterol, and low-density cholesterol were analysed from blood samples.

Statistical analysis

The baseline characteristics of patients with dementia and the matched cohort were compared with chi-squared tests for categorical variables and Mann-Whitney U tests for continuous variables. To analyse the association between NAFLD and risk of dementia, conditional logistic regression was performed. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were determined. Other matching variables for the nested case-control study design (i.e. confounders that were adjusted for) were... age; gender; cardiovascular disease risk factors, such as BMI, SBP, DBP, fasting blood glucose, hypertension, DM, current smoking status; and economic status. All of the confounders listed above were identified on the index date.

Although we primarily used the nested case-control design in assessing the association between NAFLD and dementia in order to avoid immortal time bias, we also assessed the association between incident NAFLD, which was entered into the models as a time-varying factor, and dementia using Cox proportional hazards regression models. The underlying time scale was the observational period and observation started on the date that participants enrolled in this study. Participants were censored at the date of dementia diagnosis, date of death or end of the study period, defined as the last date of follow-up or 31 December 2018. Covariates adjusted in multivariate analysis were identical to those adjusted in conditional logistic regression analysis from the nested case-control design.

All analyses were two-tailed, and $P<0.05$ was considered significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

From the 107,306 participants in NHIS-Senior, 65,690 subjects who met the inclusion criteria were taken for NAFLD evaluation. Among 65,690 subjects, those with either NAFLD by FLI≥60 or non-NAFLD by FLI<30 were included in the analysis (Fig. 1). The final number of participants with either NAFLD or non-NAFLD was 47,388 after excluding 18,302 subjects with intermediated value evaluated by FLI. From 47,388 subjects, 7209 were diagnosed with dementia. Cases with dementia and the control subjects were matched based on the duration of follow-up until the age at case selection, gender, BMI, SBP, DBP, fasting blood glucose, hypertension, DM, current smoking status and economic status. The final number of cases was 2844, and 14,220 subjects served as the control. The baseline characteristics of the study subjects are presented in Table 1. Compared with the control group, dementia case patients had more elevated AST, γGT levels, combined NAFLD, heart failure and CKD. Naturally, dementia case patients had significantly increased KDSQ positive rates as well as KDSQ scores compared with those of the control subjects (Table 1).

Having NAFLD was significantly associated with increased risk of dementia (AOR 1.493; 95% CI 1.214–1.836) (Table 2). The association between NAFLD and development of dementia with and without DM is shown. The baseline characteristics of the 2 groups are described in Table 3. In the diabetic population, dementia case patients had significantly higher TG level and combined heart failure when other factors were not significantly different. The proportion of those with NAFLD was not different between dementia cases and the control subjects among those with DM. On the other hand, among the non-diabetic population, dementia case had increase AST, rGT levels, combined NAFLD, heart failure, myocardial infarction (MI) and CKD. However, having NAFLD was significantly associated with increased risk of dementia in both the DM group (AOR 1.421; 95% CI 1.013–1.994) and the non-DM group (AOR 1.540; 95% CI 1.179–2.010) (Table 4).

DISCUSSION

In this nationwide longitudinal nested case-control study, we evaluated 2844 dementia cases and 14,220 control cases with matching variables, including age, gender, various metabolic factors and the time of the follow-up at a 1:5 ratio, from NHIS-Senior. NHIS-Senior contains the follow-up data from 554,147 subjects over the age of 60 years, including the data from a validated dementia screening questionnaire. We found that having NAFLD, identified by FLI, a validated composite index of NAFLD, was associated with increased risk of all-cause dementia. The result was independent of having type 2 diabetes although the association tended to be stronger in those without diabetes.

The association observed in our study is in accordance with a recent Swedish cohort study showing increased dementia incidence in those with 65 years or older subjects with ICD code-defined NAFLD after a median follow-up period of 5.5 years.[28] In this study, the control group had significantly lower proportion of metabolic derangements, such as diabetes, dyslipidaemia, hypertension and obesity. After the adjustment of these metabolic factors, NAFLD patients still showed increased HR of dementia. Another cohort study from Korea, that included subjects aged 40–69 years, also indicated the association

Table 1. Baseline characteristics of dementia and matched controls.

Characteristics	Cases (n=2844)	Controls (n=14,220)	*P* value
Age at case selection, years	72.5 ± 3.6	72.4 ± 3.6	0.548
Male sex, no. (%)	649 (22.8)	3245 (22.8)	>0.999
BMI, kg/m^2	22.9 ± 2.5	22.9 ± 2.4	0.337
NAFLD[a], no. (%)	192 (6.8)	784 (5.5)	**0.009**
Economic status, no. (%)			>0.999
Low	487 (17.1)	2435 (17.1)	
Middle	688 (24.2)	3440 (24.2)	
High	1669 (58.7)	8345 (58.7)	
Current smoker, no. (%)	78 (2.7)	390 (2.7)	>0.999
Hypertension[b] no. (%)	1742 (61.3)	8710 (61.3)	>0.999
SBP, mmHg	128.0 ± 14.5	128.2 ± 13.2	0.385
DBP, mmHg	77.1 ± 9.5	77.2 ± 9.0	0.836
Fasting glucose, mg/dL	96.0 ± 12.5	95.9 ± 12.1	0.751
Total cholesterol, mg/dL	200.2 ± 39.2	200.0 ± 37.5	0.777
LDL cholesterol, mg/dL	121.4 ± 39.3	121.5 ± 40.6	0.916
TG, mg/dL	125.1 ± 72.4	122.3 ± 67.9	0.058
AST, U/L	25.2 ± 12.7	24.6 ± 10.0	**0.032**
ALT, U/L	20.2 ± 14.5	19.7 ± 12.8	0.095
γGT, U/L	23.8 ± 34.9	21.6 ± 22.5	**0.001**
Creatinine, mg/dL	0.96 ± 0.90	0.95 ± 0.94	0.589
Heart failure, no. (%)	345 (12.13)	1220 (8.6)	**<0.001**
CKD or ESRD, no. (%)	33 (1.2)	77 (0.5)	**<0.001**
History of MI, no. (%)	64 (2.3)	251 (1.8)	0.079
Malignancy, no. (%)	217 (7.6)	1088 (7.7)	0.969
Cognitive function[c]			
KDSQ positive rate, no. (%)	83 (27.9)	278 (15.7)	**<0.001**
KDSQ score	2.0 ± 2.1	1.4 ± 1.7	**<0.001**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; ESRD: end-stage renal disease; KDSQ: Korean Dementia Screening Questionnaire; LDL: low-density lipoprotein; MI: myocardial infarction; NALFD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TG: triglyceride; γGT: γ glutamyl transferase
Values are expressed as means ± standard deviation or no. (%).
Bold values represent statistical significance.
Case and control subjects were matched based on the duration of follow-up until the age at case selection, gender, cardiovascular disease risk factors (e.g. BMI, SBP, DBP, fasting blood glucose, hypertension, diabetes mellitus, current smoking status) and economic status.
[a] NAFLD was defined as having fatty liver index ≥60, a fatty liver prediction model based on BMI, waist circumference, TG and γGT.
[b] Hypertension was defined as SBP≥140 mmHg, DBP≥90 mmHg or receiving antihypertensive drugs.
[c] KDSQ includes 5 items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency. The KDSQ rate positive was defined as the case with the score ≥6.

Table 2. Relationship between dementia and non-alcoholic fatty liver disease.

Liver status[a]	Cases (n=2844)	Controls (n=14,220)	Crude	Adjusted[b]
	No. (%)	No. (%)	OR (95% CI)	OR (95% CI)
Non-NAFLD	2652 (93.3)	13,436 (94.5)	1.00	1.00
NAFLD	192 (6.8)	784 (5.5)	1.372 (1.125–1.673)	1.493 (1.214–1.836)

CI: confidence interval; NAFLD: non-alcoholic fatty liver disease; OR: odds ratio
[a] NAFLD was defined as having fatty liver index (FLI) ≥60, a fatty liver prediction model based on body mass index (BMI), waist circumference, triglyceride and γ glutamyl transferase. Non-NAFLD was defined as having FLI<30.
[b] Adjusted for age, gender, BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, hypertension, diabetes mellitus, current smoking status and economic status.

Table 3. Baseline characteristics of dementia and matched controls in diabetes mellitus and non-diabetes mellitus groups at index date[a].

Group	Diabetes mellitus			Non-diabetes mellitus		
Characteristics	Cases (n=746)	Control (n=3730)	*P* value	Cases (n=2098)	Control (n=10,490)	*P* value
Age at case selection, years	72.0 ± 3.2	72.0 ± 3.2	0.736	72.6 ± 3.7	72.6 ± 3.7	0.614
Male sex, no. (%)	144 (19.3)	720 (19.3)	>9.999	505 (24.1)	2525 (24.1)	>9.999
BMI, kg/m^2	23.5 ± 2.3	23.5 ± 2.3	0.659	22.7 ± 2.5	22.7 ± 2.4	0.385
NAFLD[b]	77 (10.3)	325 (8.7)	0.161	115 (5.5)	459 (4.4)	**0.027**
Economic status, no. (%)			>9.999			>9.999
Low	119 (16.0)	595 (16.0)		368 (17.5)	1840 (17.5)	
Middle	161 (21.6)	805 (21.6)		527 (25.1)	2635 (25.1)	
High	466 (62.5)	2330 (62.5)		1203(57.4)	6015 (57.4)	
Current smoker, no. (%)	735 (98.5)	3675 (98.5)	>9.999	67 (3.2)	335 (3.2)	>9.999
Hypertension[c], no. (%)	593 (79.5)	2965 (79.5)	>9.999	1149 (54.8)	5745 (54.8)	>9.999
SBP, mmHg	128.6 ± 13.8	128.6 ± 13.2	0.937	127.8 ± 14.7	128.1 ± 13.3	0.341
DBP, mmHg	76.8 ± 9.5	76.8 ± 8.9	0.953	77.3 ± 9.5	77.3 ± 9.0	0.836
Fasting glucose, mg/dL	101.7 ± 16.2	101.6 ± 15.9	0.861	94.0 ± 10.1	93.9 ± 9.6	0.772
Total cholesterol, mg/dL	196.9 ± 41.4	196.7 ± 38.4	0.911	201.4 ± 38.3	201.1 ± 37.1	0.787
LDL cholesterol, mg/dL	117.5 ± 46.1	117.9 ± 39.4	0.820	122.8 ± 36.4	122.8 ± 41.0	0.969
TG, mg/dL	135.6 ± 88.2	126.8 ± 71.2	**0.011**	121.3 ± 65.4	120.7 ± 66.6	0.680
AST, U/L	24.8 ± 8.7	24.6 ± 10.7	0.720	25.3 ± 13.9	24.6 ± 9.8	**0.030**
ALT, U/L	21.0 ± 10.7	21.0 ± 15.6	0.912	19.9 ± 15.7	19.2 ± 11.6	0.059
γGT, U/L	25.0 ± 27.5	23.4 ± 26.4	0.133	23.4 ± 37.2	20.9 ± 20.9	**0.003**
Creatinine, mg/dL	0.99 ± 0.95	0.97 ± 0.98	0.375	0.96 ± 0.90	0.94 ± 0.94	**0.029**
Heart failure, no. (%)	119 (15.9)	408 (10.9)	**<0.001**	226 (10.8)	812 (7.7)	**<0.001**
CKD or ESRD, no. (%)	11 (1.5)	45 (1.2)	0.548	22 (1.0)	32 (0.3)	**<0.001**
History of MI, no. (%)	24 (3.2)	116 (3.1)	0.878	40 (1.9)	135 (1.3)	**0.027**
Malignancy, no. (%)	60 (8.0)	330 (8.9)	0.477	157 (7.5)	758 (7.2)	0.678

Table 3. Baseline characteristics of dementia and matched controls in diabetes mellitus and non-diabetes mellitus groups at index date.[a] (Cont'd)

Group	Diabetes mellitus			Non-diabetes mellitus		
Characteristics	Cases (n=746)	Control (n=3730)	*P* value	Cases (n=2098)	Control (n=10,490)	*P* value
Cognitive function[d]						
KDSQ positive rate, no. (%)	27 (29.7)	79 (16.0)	**0.002**	56 (27.0)	199 (15.5)	**<0.001**
KDSQ score	2.1 ± 2.1	1.5 ± 1.7	**0.011**	2.0 ± 2.1	1.4 ± 1.7	**<0.001**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; ESRD: end-stage renal disease; KDSQ: Korean Dementia Screening Questionnaire; LDL: low-density lipoprotein; MI: myocardial infarction; NALFD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TG: triglyceride; γGT: γ glutamyl transferase
Values are expressed as means ± standard deviation or no. (%).
Bold values represent statistical significance.
Case and control subjects were matched based on the duration of follow-up until the age at case selection, gender, cardiovascular disease risk factors (e.g. BMI, SBP, DBP, fasting blood glucose, hypertension, diabetes mellitus, current smoking status) and economic status.
[a] The index date was defined as the date 1 year prior to the date of dementia diagnosis.
[b] NAFLD was defined as having fatty liver index ≥60, a fatty liver prediction model based on BMI, waist circumference, TG and γGT.
[c] Hypertension was defined as SBP≥140 mmHg, DBP≥90 mmHg or receiving antihypertensive drugs.
[d] KDSQ includes 5 items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency. The KDSQ rate positive was defined as the case with the score ≥6.

Table 4. Relationship between dementia and non-alcoholic fatty liver disease according to diabetes mellitus.

	With diabetes mellitus				Without diabetes mellitus			
	Cases (n=746)	Controls (n=3730)	Adjusted*	*P* value	Cases (n=2098)	Controls (n=10,490)	Adjusted*	*P* value
	No. (%)	No. (%)	OR (95% CI)		No. (%)	No. (%)	OR (95% CI)	
Non-NAFLD	669 (89.68)	3405 (91.3)	1.00	0.042	1983 (94.5)	10,031 (95.6)	1.00	0.002
NAFLDa	77 (10.3)	325 (8.7)	1.421 (1.013–1.994)		115 (5.5)	459 (4.4)	1.540 (1.179–2.010)	

CI: confidence interval; NAFLD: non-alcoholic fatty liver disease; OR: odds ratio
[a] NAFLD was defined as having fatty liver index (FLI) ≥60, a fatty liver prediction model based on body mass index (BMI), waist circumference, triglyceride and γ glutamyl transferase.
* Adjusted for age, gender, BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, hypertension, diabetes mellitus, current smoking status and economic status.
In the Cox proportional hazards regression model, NAFLD was the risk factor for dementia, compared to non-NAFLD in the overall, DM, and non-DM population (adjusted hazard ratio [HR] 1.239 [95% CI 1.129–1.360], 1.229 [95% CI 1.070–1.412], 1.227 [95% CI 1.080–1.395]), respectively (Table 5).

between dementia and NAFLD identified by the hepatic steatosis index from calculation using ALT/AST ratio, BMI, gender and diabetes.[29] The control group from the Korean study also showed significantly lower metabolic disorders, and the multivariable analysis adjusting these metabolic factors still produced increased HR of dementia development in NAFLD patients. However, the association between NAFLD and dementia is still under dispute, and some studies claimed the lack of association. A study using primary data from Germany suggested that ICD code-defined NAFLD/NASH patients failed to demonstrate increased risk of dementia compared with those without NAFLD/NASH diagnosis.[14] In this German study, the NAFLD/NASH group and the control group showed no significant differences in the proportion of metabolic derangements such as diabetes, hyperlipidaemia and hypertension. Another study from Sweden compared biopsy-proven NAFLD with the control group and suggested no association between NAFLD and dementia.[30] As the investigators of this Swedish study discussed in the article, there were insufficient clinical and biochemical information on the control group. Since NAFLD is highly prevalent and tends to be underdiagnosed, the control group could have not been truly the control group. In addition, the German study defined NAFLD/NASH by ICD code, having the possibility that those who failed to be assessed for NAFLD/NASH might have been included in the control group, affecting the dementia event outcome. Considering that defining exposed (NAFLD) and unexposed (non-NAFLD) groups is an important process in an observational study evaluating the association

Table 5. Hazard ratios for dementia risk factors in the Cox regression model.

Overall		
	HR (95% CI)	***P***
Age	**1.101 (1.096–1.106)**	**<0.001**
Male sex	**0.782 (0.740–0.827)**	**<0.001**
BMI	**0.961 (0.951–0.970)**	**<0.001**
Hypertension	**1.154 (1.097–1.213)**	**<0.001**
Diabetes	**1.177 (1.118–1.239)**	**<0.001**
High economic status	**0.934 (0.880–0.990)**	**0.0228**
Smoking	**1.142 (1.043–1.251)**	**0.0043**
NAFLD[a]	**1.493 (1.214–1.836)**	**0.001**
Subjects with type 2 diabetes		
Age	**1.094 (1.085–1.102)**	**<0.001**
Male sex	**0.799 (0.728–0.876)**	**<0.001**
BMI	**0.966 (0.951–0.981)**	**<0.001**
Hypertension	**1.144 (1.043–1.255)**	**0.0044**
High economic status	**0.900 (0.816–0.992)**	**0.0343**
Smoking	**1.203 (1.028–1.406)**	**0.0343**
NAFLD[a]	**1.094 (1.085–1.102)**	**<0.001**
Subjects without diabetes		
Age	**1.104 (1.098–1.110)**	**0.0017**
Male sex	**0.773 (0.721–0.828)**	**<0.001**
BMI	**0.957 (0.946–0.969)**	**<0.001**
Hypertension	**1.158 (1.090–1.230)**	**<0.0001**
Smoking	**1.122 (1.002–1.255)**	**0.0452**
NAFLD[a]	**1.104 (1.098–1.110)**	**<0.001**

BMI: body mass index; CI: confidence interval; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease
[a] NAFLD was defined as having fatty liver index (FLI) ≥60, a fatty liver prediction model based on BMI, waist circumference, triglyceride and γ glutamyl transferase. Non-NAFLD was defined as having FLI<30.
Bold values represent statistical significance.

between a risk factor and an outcome of interest, the underdiagnosed NAFLD subjects that might have been included in the control group could have altered the outcome result. To our best knowledge, all the currently published observational studies on the association between NAFLD and dementia used event-based cohort design where the event being having NAFLD and the outcome being occurrence of dementia.[14,28-31] On the other hand, we applied the nested case-control method, the case being dementia event, in an effort to minimise immortal time bias. However, case-control observational studies also have some limitations, particularly selection bias.[32] Nevertheless, it has been generally believed that when cases and controls are selected from the same source, the likelihood of selection bias tends to be diminished. In our study, the case and control subjects were selected from a population-based cohort.

We used NHIS-Senior, which comprises individuals over the age of 60 years that were randomly sampled from the 5 million examinees who received physical health examinations provided by the Korean NHIS.[18] Unlike the general

NHIS cohort, individuals included in NHIS-Senior were screened for dementia using KDSQ, the primary screening tool for cognitive dysfunction.[24] Those with the possibility of having dementia with KDSQ positive rate are to be further evaluated and diagnosed for dementia.

Apart from the possible sampling bias mentioned above, this study has several other limitations that need to be further addressed in future studies. Although NHIS-Senior is convenient and useful for clinical research, information on the results of specific medical evaluations other than those related to health examinations cannot be assessed. Moreover, NAFLD could only be operationally defined using FLI. However, it has been validated that FLI could identify NAFLD comparable with ultrasonography.[21] In the clinical milieu where NAFLD often fails to receive medical attention, defining NAFLD using a validated prediction model would compensate for the underestimation of the disease. Another limitation is that we could not fully control other possible dementia risk factors, such as educational level, accompanying hearing loss, depression, physical activity level and medication that might affect cognitive functions. In addition, pathophysiological mechanisms between NAFLD and dementia cannot be demonstrated in this observational study. There are studies demonstrating that NAFLD patients have increased risk of carotid atherosclerosis as well as increased carotid intima media thickness that may result in cognitive impairments.[33-35] Another previous investigation suggested that NAFLD and dementia may have a common aetiological mechanism of oxidative stress and inflammation.[36] Among the subtypes of dementia, studies on the pathogenesis of AD produced a growing body of evidence linking AD and insulin resistance, which is the major pathogenesis behind NAFLD.[37,38] A study on the protein–protein interaction analysis of AD and NAFLD identified that both disease entities shared 189 genes related with carbohydrate metabolism, fatty acid metabolism and interleukin-17 signalling pathways.[39] Moreover, brain amyloid burden is known to be an important pathology of AD, and it has been reported that liver dysfunction resulted in decreased peripheral amyloid-β clearance.[40,41] In our study, 79.6% of dementia patients had AD. When NAFLD was associated with AD only, it also demonstrated a significant risk (data not shown). Further studies on the pathophysiology are needed to give solutions for NAFLD and dementia.

CONCLUSION

This nationwide study used a database where dementia was screened out using a dementia screening questionnaire (KDSQ) and evaluated whether having NAFLD was associated with the occurrence of dementia in individuals with age over 60. Our results support that NAFLD was associated with an increased risk of dementia, independent of accompanying DM.

Acknowledgement

This study used data from the Korean National Health Insurance Service (NHIS) (NHIS-2019-2-272) and made clear that all results were not related to NHIS.

Financial support

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2021R1H1A2093347).

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