Association Between Non-Alcoholic Fatty Liver Disease and Osteoarthritis

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Abstract

Background: The prevalence of knee osteoarthritis is increasing due to population aging and an increase in obesity. Besides the mechanical stress caused by weight-bearing and age, osteoarthritis is associated with obesity and metabolic syndrome.

Aim: We analyzed the association between non-alcoholic fatty liver disease and knee osteoarthritis.

Methods: This cross-sectional, retrospective study was conducted among adults aged >50 years that were enrolled from the 5th National Health and Nutrition Survey (2010–2012). After excluding those diagnosed with chronic diseases, liver diseases, and a history of excessive alcohol consumption, 2,193 individuals were included. A hepatic steatosis index >36 and <30 was considered to indicate the presence and absence of non-alcoholic fatty liver disease, respectively. Knee osteoarthritis was diagnosed according to the Kellgren–Lawrence grade based on knee radiography findings.

Results: The risk of non-alcoholic fatty liver disease was 3.653 times higher in the mild osteoarthritis group than in the normal group, and 11.969 and 6.331 times higher in patients with moderate osteoarthritis and severe osteoarthritis, respectively.

Conclusions: We found that non-alcoholic fatty liver disease was significantly associated with knee osteoarthritis, and that different odds ratios for non-alcoholic fatty liver disease were observed depending on the severity of the knee osteoarthritis.

1. Introduction

Osteoarthritis (OA) is the third most prevalent disease worldwide among the elderly population, and as life expectancy increases, its prevalence is expected to increase to one-third of the middle-aged adult population by 2030 [1, 2]. OA is considered a chronic disease that affects various tissues in the joints to form bone spurs, thereby causing joint pain, stiffness, and restricted movement, all of which reduce a patients physical activity, and ultimately their quality of life [1, 2].

Non-alcoholic fatty liver disease (NAFLD) is diagnosed when fat deposits are observed in the hepatocytes on imaging or histology in patients with no history of significant alcohol or continuous drug intake, or liver disease due to other causes, including genetic diseases that cause increased fat deposition [3, 4]. NAFLD includes a spectrum of conditions, such as non-alcoholic steatohepatitis and NAFLD associated with cirrhosis [3, 4]. Recent reports have estimated the prevalence of NAFLD and non-alcoholic steatohepatitis to be 6–51% and 3–5%, respectively. The reported prevalence of NAFLD varies due to differences in the study population, diagnostic criteria, and definition of NAFLD used [3, 4]. Nonetheless, the prevalence of NAFLD is increasing worldwide [3, 4].

Several studies have shown that obesity causes OA in the knees and hips. In addition, many studies have revealed an association between metabolic syndrome and knee OA [5]. However, large-scale studies

investigating an association between NAFLD and knee OA are scarce.

OA is not only a disease caused by ageing or physical factors, but also a metabolic disease in which biochemical factors are involved, and these factors may affect both the onset and the course of the disease [6]. It has been reported that mechanisms associated with inflammation, obesity, and metabolic syndrome are the pathological mechanisms underlying knee OA [6–8]; thus, a potential relationship between NAFLD and knee OA can be proposed.

Liver biopsy is the gold standard for the diagnosis of NAFLD. However, it is an invasive procedure with the potential for sample error; it is also expensive, which makes its routine application difficult for all patients [9, 10]. Recently, several predictive indicators have been introduced to simplify NAFLD diagnosis [9, 10]. The hepatic steatosis index (HSI) is such an indicator and predicts NAFLD using only patient sex, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, body mass index (BMI), and diabetic status [9–11]. HSI is a useful and simple tool for diagnosing NAFLD compared to extrapolating the large-scale data available from the National Health and Nutrition Survey. It is calculated as follows: HSI = 8 × (ALT/AST ratio) + BMI (+ 2, if female; + 2, if diabetes mellitus).

Thus, this study aimed to investigate the association between NAFLD—diagnosed based on the HSI—and knee OA using data derived from the National Health and Nutrition Survey.

2 Methods

2.1 Participants and enrollment

A total of 25,534 men and women participated in the 5th National Health and Nutrition Survey (2010–2012). Of these, 9,798 individuals were aged > 50 years; among them, 4,250 were selected for this study after excluding individuals diagnosed with chronic diseases (hypertension, diabetes, dyslipidemia, cancer), liver diseases (hepatitis B, hepatitis C, cirrhosis), and those with a history of excessive alcohol consumption (defined as > 20 g/d for men and > 10 g/d for women). Individuals with an HSI < 30 were defined as not presenting with NAFLD and those with an HSI > 36 were defined as having evidence of NAFLD. Thus, individuals with an HSI between 30–36 were excluded from the study. For the final analysis, a total of 2,193 subjects were included (Fig. 1).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. The Korean National Health and Nutrition Examination Survey (KNHANES) was approved by the Institutional Review Board (IRB) of the Korea Centers for Disease Control and Prevention. The KNHANES used layered multi-level cluster probability sampling. Our study was also approved by the relevant Hospital Institutional Review Board (IRB approval number: 2020-04-002).

For the KNHANES, data on sex, age, history of alcohol consumption and smoking were collected using a health survey, and the patients' BMI, height, weight, systolic blood pressure (SBP), diastolic blood

pressure (DBP), and blood test parameters were investigated. The health survey was conducted by patient interview or self-reporting in writing, while the other parameters were obtained by direct measurement, observation, and specimen analysis. Adult men and women over 50 years of age, who underwent X-ray examination of the knee joint were also included in this study.

2.2 Assessment of OA

Subjects were assessed using a Kellgren–Lawrence grade after knee radiography. The Kellgren–Lawrence class was classified as follows [12]: 0, normal; 1, formation of osteophytes on the joint margins or in ligamentous attachments, such as the tibial spines; 2, definite osteophytes and narrowing of joint space associated with sclerosis of the subchondral bone; 3, moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of the bone contour; and 4, large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of the bone contour [12]. Based on X-ray examination of the knee joints, patients with a Kellgren–Lawrence score of 2 or more were defined as exhibiting OA [12]. Cases of OA with a Kellgren–Lawrence grade of 0 or 1 were defined as normal, 2 as mild, 3 as moderate, and 4 as severe in this study.

2.3 Assessment of anthropometric and biochemical parameters

Anthropometric and biochemical measurements were obtained by trained inspectors. Height (cm) and weight (kg) were measured using a Seca 225 instrument (Seca, Hamburg, Germany) and a GL-6000-20 scale (G-tech, Seoul, Korea), with an accuracy of up to 0.1 cm and 0.1 kg, respectively. BMI was calculated as weight (kg)/height squared (m2). SBP and DBP were measured three times at the right upper arm, with 5-minute intervals between measurements, using a mercury sphygmomanometer (Baumanometer; WA Baum Co., Copiague, NY); in this study, the second and third blood pressure measurements were used. Blood samples were randomly collected after an 8-hour fast. These samples were immediately processed, refrigerated, and transferred to a central laboratory (Neodin Medical Institute, Seoul, Korea). Fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, AST, ALT, creatinine, hematocrit (HCT), and vitamin D (Vit D) levels were measured using a Hitachi 7600 automated analyzer (Hitachi, Tokyo, Japan).

2.4 Assessment of lifestyle habits

The subjects' sociodemographic parameters and lifestyle variables (history of smoking and alcohol consumption, regular exercise, moderate physical activity, education level, household income) were evaluated. Regarding smoking history, participants were classified as current smokers or non-smokers. Alcohol intake was determined by calculating the amount of alcohol per week in grams. The International Physical Activity Questionnaire was used to measure the degree of physical exercise. A person was considered to exercise regularly if they worked out at least 5 times a week for 30 minutes per session or engaged in strenuous physical activity three times a week for at least 20 minutes per session. Moderate physical activity corresponded to activities, such as slow swimming, doubles tennis, volleyball,

badminton, table tennis, and lifting light items. The level of education was considered, and the participants were divided into four groups based on academic background: elementary school graduation, junior high school graduation, high school graduation, and college graduation and above. Household income was divided into four levels.

2.5 Statistical analysis

Statistical analysis was performed using the PASW (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Since the data from the National Health and Nutrition Survey is complex survey data, a complex sample analysis was performed using weights. Weights were applied according to the guidelines for using raw data of the National Health and Nutrition Survey provided by the Korea Centers for Disease Control and Prevention.

Overall, frequency analysis was performed using a complex sample plan. A complex sample Rao-Scott-adjusted chi-square test and a complex sample generalized linear model were used to compare general characteristics, blood test results, and presence of knee arthritis and NAFLD (Table 1). A complex sample logistic regression test was used to correlate NAFLD with general traits, blood test results, and knee OA.

Table 1
Differences between general characteristics, knee osteoarthritis, and NAFLD

		NAFLD (n = 2,193)		*P*-value
		NO	YES	
Sex	Male	893 (58.0)	183 (37.9)	< 0.0001
	Female	731 (42.0)	386 (62.1)	
Educational level	Elementary	705 (41.9)	231 (36.6)	0.097
	Junior high	272 (17.6)	115 (24.0)	
	High	394 (25.0)	132 (22.6)	
	College	218 (13.1)	81 (14.2)	
Household income	Low	515 (28.7)	110 (16.6)	0.001
	Middle-low	400 (24.5)	152 (27.2)	
	Middle-high	329 (22.5)	156 (27.4)	
	High	364 (23.0)	141 (26.4)	
Moderate physical activity	N	1433 (87.9)	497 (86.4)	0.777
	Y	154 (9.7)	63 (11.1)	
Regular exercise	N	965 (59.7)	357 (59.1)	0.978
	Y	621 (37.7)	203 (38.4)	
Smoking	N	1178 (68.1)	493 (82.1)	< 0.0001
	Y	415 (29.8)	67 (15.3)	
Knee osteoarthritis severity	Normal	1204 (76.5)	366 (69.9)	0.004
	Mild	200 (10.7)	80 (11.6)	
	Moderate	147 (8.8)	92 (14.7)	
	Severe	73 (4.1)	31 (3.8)	
Age (years)		61.54 ± 0.32	56.83 ± 0.32	< 0.0001
SBP (mmHg)		121.83 ± 0.63	125 ± 0.87	0.003
DBP (mmHg)		76.18 ± 0.38	80.87 ± 0.5	< 0.0001

Abbreviations: NAFLD: Non-alcoholic fatty liver disease; HbA1c; SBP, Systolic blood pressure; DBP, diastolic blood pressure; hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; HCT, hematocrit.

	NAFLD (n = 2,193)		*P*-value
	NO	YES	
HbA1c (%)	5.63 ± 0.02	6.07 ± 0.06	< 0.0001
FPG (mg/dL)	93.65 ± 0.41	104.64 ± 1.27	< 0.0001
AST (IU/L)	24.42 ± 0.49	26.23 ± 0.89	0.071
ALT (IU/L)	16.54 ± 0.25	34.17 ± 1.39	< 0.0001
TC (mg/dL)	191.45 ± 1.02	209.34 ± 1.95	< 0.0001
HDL-C (mg/dL)	52.1 ± 0.44	46.84 ± 0.62	< 0.0001
TG (mg/dL)	125.23 ± 4.71	169.85 ± 6.70	< 0.0001
LDL-C (mg/dL)	111.88 ± 2.28	131.01 ± 3.55	< 0.0001
Vit D (ng/mL)	19.51 ± 0.28	17.72 ± 0.33	< 0.0001
HCT (%)	41.54 ± 0.13	42.9 ± 0.24	< 0.0001
Creatinine (mg/dL)	0.84 ± 0.01	0.8 ± 0.01	0.001

Abbreviations: NAFLD: Non-alcoholic fatty liver disease; HbA1c; SBP, Systolic blood pressure; DBP, diastolic blood pressure; hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; HCT, hematocrit.

A complex sample logistic regression analysis was performed (Table 2) and statistically significant factors were adjusted to estimate the odds ratio (OR) and 95% confidence interval (CI) to investigate the potential association between the incidence of knee OA and NAFLD. All data are expressed as mean ± standard error (SE) or percentage (%) for categorical variables. *P*-values less than 0.05 were considered statistically significant.

Table 2
General characteristics and relationship between knee osteoarthritis and NAFLD

		NAFLD		*P*-value
		OR	CI	
Sex	Male	1.000	-	
	Female	2.264	(1.764–2.906)	< 0.0001
Educational level	Elementary ≧	1.000	-	
	Junior high	1.562	(1.117–2.184)	0.009
	High	1.031	(0.757–1.406)	0.844
	College ≦	1.238	(0.865–1.772)	0.243
Household income	Low	1.000	-	
	Middle-low	1.921	(1.302–2.835)	0.001
	Middle-high	2.103	(1.47–3.009)	< 0.0001
	High	1.985	(1.381–2.854)	< 0.0001
Moderate physical activity	N	1.000	-	
	Y	1.166	(0.783–1.738)	0.857
Regular exercise	N	1.000	-	
	Y	1.028	(0.800–1.321)	0.828
Smoking	N	2.342	(1.647–3.332)	< 0.0001
	Y	1.000	-	
Knee osteoarthritis severity	Normal	1.000	-	
	Mild	1.194	(0.839–1.699)	0.323
	Moderate	1.833	(1.298–2.590)	0.001
	Severe	1.005	(0.595–1.700)	0.984
Age		0.931	(0.918–0.944)	< 0.0001
SBP (mmHg)		1.010	(1.003–1.017)	0.004
DBP (mmHg)		1.044	(1.030–1.059)	< 0.0001

Abbreviations: NAFLD: Non-alcoholic fatty liver disease; HbA1c, hemoglobin A1C; SBP, Systolic blood pressure; DBP, diastolic blood pressure; hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; HCT, hematocrit.

	NAFLD		*P*-value
	OR	CI	
HbA1c (%)	3.420	(2.227–5.252)	< 0.0001
FPG (mg/dL)	1.045	(1.033–1.058)	< 0.0001
AST (IU/L)	1.008	(0.999–1.017)	0.084
ALT (IU/L)	1.126	(1.096–1.156)	< 0.0001
TC (mg/dL)	1.014	(1.011–1.018)	< 0.0001
HDL-C (mg/dL)	0.963	(0.952–0.975)	< 0.0001
TG (mg/dL)	1.003	(1.000–1.005)	0.040
LDL-C (mg/dL)	0.963	(0.952–0.975)	0.040
Vit D (ng/mL)	0.958	(0.940–0.976)	< 0.0001
HCT (%)	1.089	(1.053–1.126)	< 0.0001
Creatinine (mg/dL)	0.284	(0.130–0.619)	0.002

Abbreviations: NAFLD: Non-alcoholic fatty liver disease; HbA1c, hemoglobin A1C; SBP, Systolic blood pressure; DBP, diastolic blood pressure; hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; HCT, hematocrit.

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, SBP, DBP, FPG, HbA1c, TC, HDL-C, TG, LDL-C, Vit D, HCT, and creatinine (Table 3).

Table 3
Relationship between knee osteoarthritis and NAFLD

		NAFLD	
		Model 1	Model 2
Knee osteoarthritis severity	Normal	-	-
	Mild	1.956 (1.523–2.511)	3.653 (1.851–7.211)
	Moderate	2.981 (2.382–3.730)	11.969 (5.056–28.331)
	Severe	3.882 (2.848–5.290)	6.331 (1.555–25.775)

Abbreviations: NAFLD: Non-alcoholic fatty liver disease; HbA1c, hemoglobin A1C; SBP, Systolic blood pressure; DBP, diastolic blood pressure; hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; HCT, hematocrit.

3 Results

3.1 Patient characteristics

A total of 2,193 subjects were recruited for this study. In the NAFLD group, 37.9% participants were men and 62.1% were women. Of individuals with NAFLD, 15.9% were current smokers and 81.7% were non-smokers, and this difference was statistically significant ($P < 0.05$). The prevalence of NAFLD was high in cases of mild and moderate OA. SBP, DBP, FPG, HbA1c, TC, TG, LDL cholesterol, and ALT were all higher in the NAFLD group than in the normal group. Levels of HDL cholesterol and Vit D were lower in the NAFLD group than in the normal group (Table 1).

3.2 Risk factors associated with NAFLD in univariate analysis among OA patients

A complex sample logistic regression test was used to identify variables, among general characteristics that were associated with NAFLD. With regard to sex, women had a 2.3-times higher risk of developing fatty liver than men. The risk of NAFLD in patients with mild and moderate knee arthritis was 1.194 times and 1.833 times higher than the control participants (Table 2).

Table 3 shows the results of the complex sample logistic regression test. The risk of fatty liver was 3.882 times higher in the severe OA group than in the normal group after adjusting for only age and sex. When all the significant variables in Table 2 were corrected and analyzed, the risk of NAFLD was 3.653 times higher in the mild OA group than in the normal group, but the risk was 11.969 times and 6.331 times higher in the moderate OA and severe OA groups, respectively (Table 3).

4. Discussion

OA has long been regarded a unique consequence of the tearing and abrasion processes that lead to cartilage breakdown. Cartilage loss occurs if there is excessive mechanical stress on the joint, and the creation of osteophytes is considered a reactive process of the bone to protect and stabilize the altered joint [13]. OA is a complex disease that is not purely mechanical or simply caused by inflammation; it not only involves the cartilage but also various other tissues, such as the synovium, subchondral bone, capsule, meniscus, muscle, and tendon [14]. In particular, recent research focused on the activities of hormones and cytokines related to inflammation has revealed that in addition to these mechanisms, metabolic pathways also play a large role in the development of OA [8, 15–17]. Obesity is an important risk factor for OA alongside aging and injury, and the potential involvement of obesity-related mechanisms is revealed by OA affecting not only the weight-bearing joints but also the joints of the hand [15, 18]. OA is a complex disease caused by inflammatory mediators released from cartilages, bones, and synovia [16]. In OA, lipid mediators play a potential role in cartilage degradation, contributing to its pathophysiology [17]. In a prospective population-based study, the incidence of knee OA in participants with metabolic symptoms was attributed to an increased BMI [8]. By analyzing the direct and indirect obesity-related factors associated with the development of OA in mice and other animal models, it has

been proposed that a complex interaction between genetic and environmental factors related to obesity contributes to the incidence and severity of OA [19]. Adipose tissue and obesity-related dyslipidemia have been shown to play a central role in obesity-induced OA. Adipose tissue shows signs of inflammation and secretes pro-inflammatory adipokines, in addition to higher levels of cytokines, including TNF-α, IL-6, and vascular endothelial growth factor. This local inflammatory response leads to a low degree of systemic inflammation. In addition, obesity-related dyslipidemia, defined by increased levels of triglycerides, free fatty acids, and oxidative LDLs, can aggravate inflammatory symptoms and increase the production of matrix metalloproteinase in the joint tissue, contributing to the pathogenesis of OA [20].

The basic hypothesis proposed by earlier studies is that obesity is closely related to knee OA. More specifically, in addition to their involvement in energy storage, adipocytes are endocrine cells that secrete hormones and inflammatory cytokines [21–23]. Importantly, the metabolic action of adipose tissue is also further emphasized by its location in the body, as the worse effects are attributed to visceral fat, liver fat, and white fat cells [24–26], which create a framework that is detrimental in chronic diseases [21–23, 27].

In particular, NAFLD adversely affects the prognosis of metabolic diseases [28–30]; thus we designed the study based on this hypothesis. NAFLD is the outcome of obesity, insulin resistance, and metabolic syndrome. However, NAFLD is also responsible for the same conditions [31, 32]. In fact, the pathophysiological mechanisms of NAFLD may lead to the occurrence of extra-hepatic complications, including type 2 diabetes mellitus, cardiovascular disease, and chronic kidney disease [32]. Thus, it can be assumed that NAFLD also affects the occurrence of knee OA and alternatively, knee OA may be associated with the occurrence of NAFLD.

Liver biopsy is the most accurate approach to make a definitive diagnosis of NAFLD [28, 29]. Nonetheless, imaging studies, such as liver ultrasound and computed tomography, are commonly used to diagnose NAFLD in clinical trials [28, 29]. However, liver imaging tests could not be easily performed for patients in the KNHANES, which was a study targeting Korean nationals. Thus, we adopted a simple diagnostic tool, the HSI, which can be easily calculated using routine laboratory tests. To evaluate the effectiveness of the HSI, a cross-sectional study was conducted in 10,704 subjects who underwent health screening [10]. At values of < 30.0 or > 36.0, HSI detected NAFLD with a specificity of 92.4% [10]. Additionally, NAFLD was excluded with a sensitivity of 93.1% [10]. Furthermore, several studies have reported that HSI is a valid tool for diagnosing NAFLD [33–35]. In patients with type 1 diabetes, an HSI $>$ 36 was significantly associated with metabolic syndrome and nephropathy [34]. Several biomarkers, including HSI, can predict liver steatosis and are associated with homeostatic Model Assessment of Insulin Resistance [35].

Previous studies have shown that several metabolic components are closely associated with the development of OA. These include blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, and blood sugar [36, 37]. Hypertension, hypercholesterolemia, and high blood glucose were associated with unilateral and bilateral knee OA in 979 women as noted in our previous study, following an analysis using

the Kellgren–Lawrence system [36]. Several factors associated with metabolic syndrome have been inversely related to the minimum joint space width and minimum joint space area [37]. Conversely, another study also showed that OA was not associated with metabolic syndrome; after adjusting for BMI, neither metabolic syndrome or its components were associated with the incidence of OA, rather only with blood pressure [38]. A study investigating the association between OA and metabolic syndrome in Korea also provided evidence supporting the importance of metabolic mechanisms in OA incidence in a large population, using data from the National Health and Nutrition Survey [39].

A key finding of our study is the association between knee OA and NAFLD. Additionally, we noted that the risk of NAFLD differed according to the severity of knee OA—the risk of NAFLD was 6.331 times higher in the moderate OA group than in the normal group.

However, in patients with severe OA, the risk of NAFLD was not higher than that in patients with moderate OA. The reasons for this lack of association could not be determined from this study. This warrants confirmation in a large-scale study in the future.

A limitation of this study is that it had a cross-sectional design; thus, it was not possible to define causal relationships. Further, the most accurate diagnostic method for NAFLD was not used. In the future, further research is needed to supplement these limitations.

In conclusion, the results of this study suggest that metabolic diseases, such as NAFLD, should be considered in the management and therapy of knee OA. Our findings can be used as the rationale for a new multi-faceted approach for treating knee OA.

Abbreviations

KNHANES, Korean National Health and Nutrition Examination Survey; OA, Osteoarthritis; NAFLD, Non-alcoholic fatty liver disease; HIS, hepatic steatosis index; HbA1c, hemoglobin A1C; SBP, Systolic blood pressure; DBP, diastolic blood pressure; hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; HCT, hematocrit

Declarations

Ethics approval and consent to participate: The study was approved by the Clinical

Trial Screening Committee of Wonkwang University Hospital (approval number: 2020-04-002). As this was a secondary analysis, informed consent was not required.

Consent for publication: Not applicable.

Availability of data and material: Not applicable. But if there is a special request, it is possible after obtaining approval from the relevant agency.

Competing interests: None.

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Author's contribution: A Lum Han have made substantial contributions to the conception of the work; have drafted the work or substantively revised it.

Youngjon Kim have made interpretation of data.

A Lum Han approved the submitted version (and any substantially modified version that involves the author's contribution to the study);

A Lum Han and Youngjon Kim have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

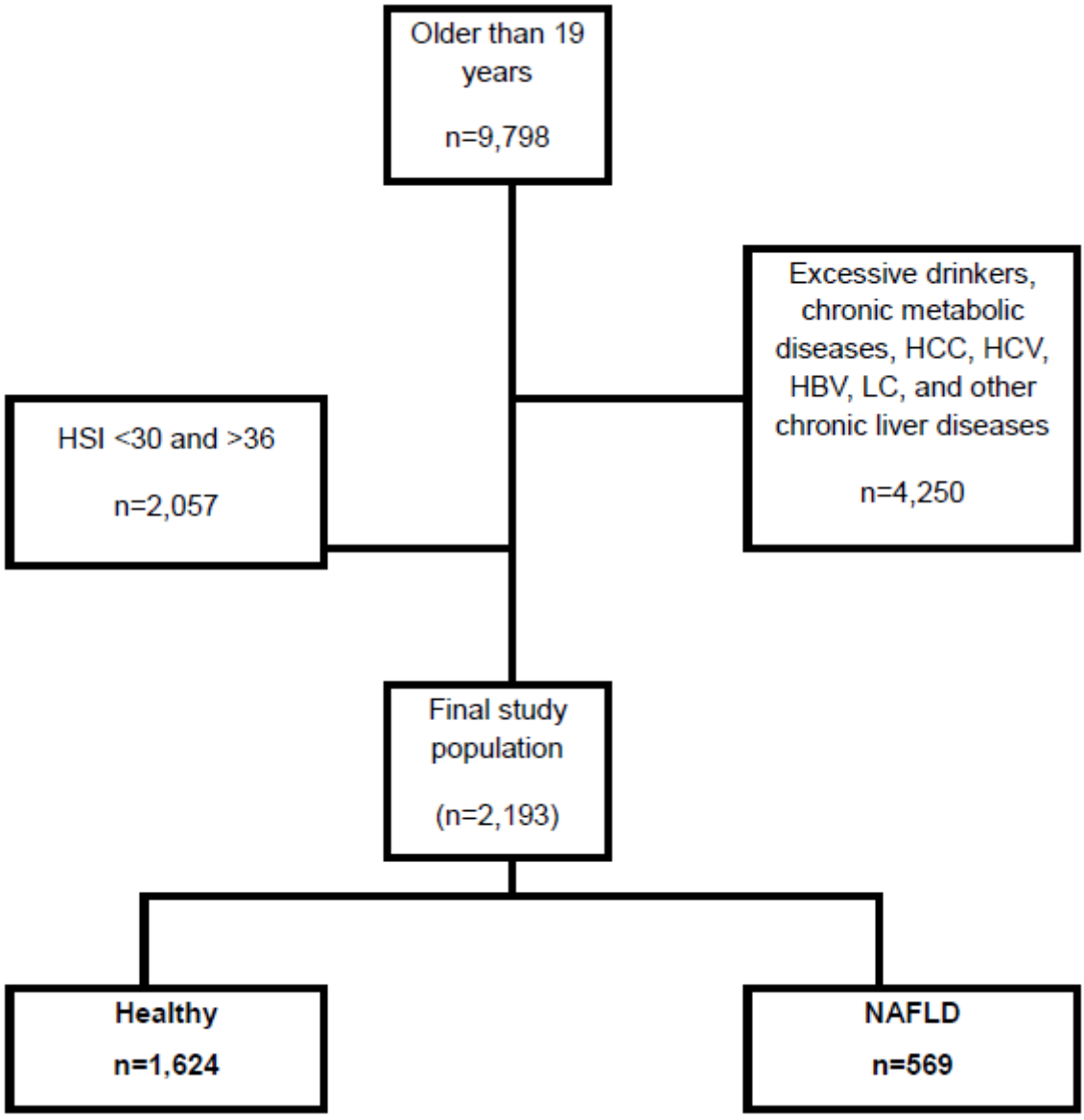

Figure 1

Flow diagram of subjects in this study. HCC, hepatic cellular carcinoma; HCV, hepatitis virus C; HBV, hepatitis virus B; LC, liver cirrhosis; NAFLD, non-alcoholic fatty liver disease; HSI, hepatic steatosis index