Association between metabolic associated fatty liver disease and Osteoarthritis using data from the Korean National Health and Nutrition Examination Survey (KNHANES)

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Research Article

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Abstract

Osteoarthritis of the knee (knee OA) is on the rise due to the aging population and increasing obesity. In addition to mechanical stress attributed to weight and age, osteoarthritis is associated with obesity and metabolic dysregulation. Here, a cross-sectional study targeting retrospectively registered 17,476 adults aged 50 years or older who were enrolled in the National Health and Nutrition Survey (2010–2011) was performed to analyze the association between the newly named metabolic associated fatty liver disease (MAFLD) and knee OA. Fatty liver index (FLI) ≥ 60 confirmed the presence of MAFLD, and FLI < 30 indicated the absence of MAFLD. Knee OA was diagnosed according to the Kellgren–Lawrence scale based on knee radiography results. A complex sample logistic regression analysis was performed. Statistically significant factors were adjusted to estimate probability ratios, and 95% confidence intervals were used to investigate the association between knee OA and MAFLD. The probability of knee OA was 1.479 times higher in the presence of MAFLD than that in the normal group. The results indicate that MAFLD is significantly associated with knee OA, suggesting that these two disorders should be managed simultaneously.

1. Introduction

The prevalence of obesity is increasing worldwide. Obesity is strongly associated with metabolic associated fatty liver disease (MAFLD) (Chalasani et al., 2012, Byrne and Targher, 2015). The newly defined MAFLD includes or modified characteristics that were overlooked in non-alcoholic fatty liver disease (NAFLD) (Eslam et al., 2020b, Eslam et al., 2020a). When the amount of alcohol consumed was >30 g/day for men and >20 g/day for women, they were excluded from the diagnosis of NAFLD as well as other chronic liver diseases, such as viral hepatitis. Instead, the factors of metabolic abnormality was considered to diagnosis MAFLD (Chalasani et al., 2012, Byrne and Targher, 2015).

Upon renaming NAFLD as MAFLD in 2020, the following characteristics were better reflected. First, the term better reflects the close relationship between fatty liver and metabolic conditions, including hyper-nutrition, sedentary lifestyle and type 2 diabetes, hypertension, dyslipidemia, and obesity. Second, the term allows easier recognition of the effects of fatty liver and metabolic status on the natural history of various liver diseases, such as chronic alcoholic hepatitis and chronic viral hepatitis (Eslam et al., 2020b, Eslam et al., 2020a, Fouad et al., 2020).

Knee osteoarthritis (OA) is a musculoskeletal disorder associated with weight bearing and aging. However, knee OA is no longer characterized as a disease with an underlying physical mechanism but can be identified as a disease that shares the mechanism with metabolic diseases (Berenbaum, 2013, Griffin and Guilak, 2008). Hence, knee OA can be explained as the cause and result of metabolic dysfunction such as dyslipidemia, high blood sugar, high blood pressure, and inflammation. Therefore, a number of studies have been conducted to confirm the association between metabolic syndrome and knee OA (Cho et al., 2018, Engström et al., 2009, Niu et al., 2017). Knee OA is associated with the presence or absence of metabolic syndrome and each characteristic of metabolic syndrome. Based on this hypothesis, in this study, we analyzed the relationship between knee OA and MAFLD, which better reflects metabolic abnormality than NAFLD.

When diagnosing MAFLD, there should be evidence of fat accumulation in the liver determined by biopsy, imaging, and blood biomarkers. In addition, the following three criteria should be examined (Valenti and Pelusi, 2020): overweight/obesity, the presence of type 2 diabetes, and the presence of two or more metabolic dysregulation factors. Fatty liver index (FLI) is the only serum biomarker suitable for identifying liver steatosis in large-scale epidemiological studies (Valenti and Pelusi, 2020, Eslam et al., 2020c). In particular, since imaging tests are not possible in large-scale epidemiological investigations conducted at the national level, examination of FLI is the only method to prove fat accumulation in the liver. In this study, we analyzed the association between MAFLD and knee OA, and FLI was used to confirm the fat accumulation in the liver.

2. Material And Methods

2.1 Participants and enrollment

We surveyed 17,476 men and women who participated in the National Health and Nutrition Survey conducted from 2010 to 2011. All participants comprised adult men and women over 50 years of age who had undergone an X-ray examination of the knee joint. Of these, 10,759 participants under the age of 50 were excluded. Additionally, 390 patients with missing variables in the diagnostic criteria for MAFLD were excluded. Subjects with an FLI ≥60 were defined as having MAFLD. Subjects with FLI <30 were defined as having no evidence of MAFLD. Therefore, individuals with an FLI between 30 and 60 were excluded from the study. A total of 6,327 subjects were included for the final analysis.

The Korean National Health and Nutrition Examination Survey (KNHANES) was approved by the Centers for Disease Control and Prevention Institutional Review Board (IRB). KNHANES used layered multi-level cluster probability sampling. Our study was also approved by the Wonkwang University Hospital Institutional Review Board (IRB approval number: 2021-03-032).

For KNHANES, data on gender, age, alcohol, and smoking history were collected through a health survey, and data including BMI, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood test results of the patients were analyzed. Health surveys were conducted through patient interviews or self-report, and other parameters were obtained through direct measurements, observations, and sample analysis.

2.2 Knee OA diagnosis

Radiographs of the knees of the subjects were analyzed by a specialist. Experts evaluate the Kellgren–Lawrence rating (Kellgren and Lawrence, 1957). The Kellgren–Lawrence grades were classified as follows: 0, normal; 1, bone tissue formation in ligament attachments, such as the edge of the joint or the tibia vertebrae; 2, narrowing of the clear bone tissue and joint space associated with subchondral bone sclerosis; 3, moderate multiple bone tissues, clear narrowing of the joint space, some sclerosis and possible deformation of the bone contour; 4, large bone tissue, marked narrowing of the joint space, severe sclerosis, and clear deformity of the bone contour. According to the recommended criteria, patients with a Kellgren-Lawrence score of 2 or higher were defined as exhibiting knee OA. In this study, knee OA cases with a Kellgren–Lawrence rating of 0 or 1 were defined as normal, 2 as mild, 3 as moderate, and 4 as severe.

2.3 MAFLD diagnosis

FLI was used to diagnose MAFLD and was calculated as:

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

where TG denotes triglyceride (mg/dL), GGT represents γ-glutamyl transferase (U/L), and WC denotes the waist circumference (cm). The FLI measurement ranges from 0 to 100. Fatty liver disease was ruled out with FLI <30, and the presence of disease was confirmed with an FLI ≥60 by good diagnostic accuracy (area under the receiver operating characteristic [ROC] curve [AUC] = 0.85; 95% CI = 0.81–0.88).

2.4 Anthropometric and biochemical parameters

Anthropometric and biochemical measurements were performed 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). BMI was calculated as weight (kg) divided by the square of the height (m^2). SBP and DBP were measured thrice in the right upper arm at 5-min intervals using a mercury sphygmomanometer (Baumanometer; WA Baum Co., Copiague, NY). The second and third blood pressure measurements were used in this study. Blood samples were randomly collected after an 8-h fasting period. The 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, gamma-glutamyl transferase (-GT), and vitamin D (Vit D) readings were obtained using a Hitachi 7600 automatic analyzer (Hitachi, Tokyo, Japan).

2.5 Sociodemographic and lifestyle variables

The sociodemographic parameters and lifestyle variables (smoking and alcohol history, regular exercise, moderate physical activity, educational level, and household income) of the subjects were evaluated. With respect to smoking and alcohol consumption, participants were classified as current smokers or non-smokers and current drinkers and non-drinkers. The International Physical Activity Questionnaire was used to measure the degree of physical exercise (Craig et al., 2003). A person was considered exercising regularly if he worked out at least five times a week for 30 min per session or performed strenuous physical activity thrice a week for at least 20 min per session. Activities such as slow swimming, doubles tennis, volleyball, badminton, table tennis, and lifting light objects were defined as appropriate physical activities. According to the educational background, participants were categorized into four groups: elementary school graduation, junior high school graduation, high school graduation, and college graduation or higher. Average total household income was investigated. Household income was divided into four stages, namely low, middle-low, middle-high, and high. The quartiles were divided into less than 1 million won per month(low), 1 to 2 million won(middle-low), 2 to 3 million won(middle-high), and more than 3 million won(high).

2.6 Statistical Analysis

Statistical analysis was performed using PASW (SPSS version 26.0, IBM SPSS Inc., Chicago, IL, USA). Statistical significance was set to $P < 0.05$. Since KNHANES data comprise complex survey data, complex sample analysis was performed using weights. The weights were applied according to the guidelines for using raw data collected in KNHANES provided by the Centers for Disease Control and Prevention.

Frequency analysis was performed using a complex sample plan. A composite sample Rao-Scott adjusted chi-square test and a composite sample generalized linear model were used to analyze the relationship between general characteristics, blood test results, and the presence of knee OA and MAFLD (Table 1). A complex sample logistic regression test was used to examine whether the MAFLD-related variables affect osteoarthritis (Table 2). Statistically significant factors were adjusted to estimate the odds ratio (OR) and 95% confidence interval (CI). Data are presented as mean ± standard error (SE) or percentage (%) for categorical variables. Model 1 was unadjusted, and Model 2 was adjusted for age, sex, education, alcohol consumption, and smoking (Table 3).

3. Results

3.1 Patient characteristics

A total of 6,327 subjects met the criteria of this study. The subjects in the knee OA group comprised 24% male and 44.8% female participants. Of the knee OA patients, 27.3% were classified as those who consumed alcohol and 41.5% as non-drinkers ($P < 0.05$). Of the knee OA patients, 22.5% were smokers and 37.7% were non-smokers ($P < 0.05$). Of the knee OA patients, 39.5% had diabetes, and 54.9% were non-diabetic ($P < 0.05$). Of the knee OA patients, 38.9% demonstrated dyslipidemia, and 32.5% were classified into the non-dyslipidemia group ($P < 0.05$). SBP, waist circumference (WC), BMI, and HbA1c, Vit D, and γ-GT levels were all higher in the knee OA group than those in the normal group (Table 1).

3.2 Association between MAFLD-related variables and knee OA

A complex sample logistic regression test was used to analyze the association of knee OA with variables related to MAFLD. After adjusting for age, sex, education, alcohol consumption, and smoking, except with BMI, no association was observed between the MAFLD variables and knee OA (Table 2).

3.3 Relationship between knee OA and MAFLD

To analyze whether MAFLD affects osteoarthritis, a complex sample logistic regression test was used. After adjusting for age, sex, education, alcohol consumption, and smoking, the results showed a 1.475 times higher risk of knee OA with MAFLD (Table 3).

4. Discussion

This study analyzed the relationship between the newly termed MAFLD and knee OA. Among the criteria used to define MAFLD, BP; WC; fasting blood sugar, TG, and HDL levels; and the presence of diabetes were not associated with knee OA. However, BMI was associated with knee OA. Although none of the criteria demonstrated any association with MAFLD, MAFLD was related to knee OA since the odds ratio was 1.475 (95% CI, 1.181–1.842) times higher, suggesting that along with obesity, MAFLD is an important factor that should be addressed simultaneously when discussing knee OA.

The accumulation of fat in the liver is a symptom and diagnostic factor associated with obesity and metabolic dysfunction (Friedman et al., 2018). The prevalence rate of MAFLD is increasing due to sedentary lifestyles, excessive calorie intake, and nutritional imbalance (Friedman et al., 2018, Loomba and Sanyal, 2013). In addition, its insidious onset and a prolonged course influence the increase in the number of patients diagnosed with fatty liver (Friedman et al., 2018). Previously, fatty liver was classified into alcoholic fatty liver and NAFLD according to alcohol consumption. Additionally, chronic viral hepatitis has been classified as another liver disease (Friedman et al., 2018, Loomba and Sanyal, 2013). However, alcohol consumption, viral hepatitis, or other causes of liver disease are not currently prerequisites for the diagnosis of MAFLD (Eslam et al., 2020b, Eslam et al., 2020a). The criteria for MAFLD, which is the new term of NAFLD, include the presence of steatosis and diabetes as well as increased BMI, WC, BP, and TG, HDL, blood sugar, and high-sensitivity C-reactive protein (hsCRP) levels. The conceptual new MAFLD better reflects metabolic abnormality (Chalasani et al., 2012, Byrne and Targher, 2015).

OA is a complex disease caused by inflammatory mediators secreted by the cartilage, bone, and synovium (Berenbaum, 2013). In knee OA, obesity-related lipid mediators play a potential role in cartilage breakdown, contributing to the pathophysiology of the disease (Masuko et al., 2009). Due to obesity, the abnormal mechanism of adipokines affect the expression of factors involved in the inflammatory response, which exacerbates osteoarthritis (Thijssen et al., 2015). Even with the presence of dyslipidemia, it has an adverse effect due to abnormal fat accumulation, which triggers the onset of osteoarthritis (Zhuo et al., 2012, Sellam, 2013). Hyperglycemia and insulin resistance lead to oxidative stress and the accumulation of glycated reaction products. These products accumulate in the cartilage and cause damage. High blood sugar level causes systemic chronic inflammation, exacerbating osteoarthritis (Yoshimura et al., 2011). High blood pressure induces ischemia in the subchondral joint, blocking the supply of nutrients from the cartilage and reducing bone remodeling (Valenti and Pelusi, 2020).

As the prevalence of obesity increases, the prevalence of knee OA is also increasing (Berenbaum et al., 2013). A load is placed on the knee due to obesity; this mechanical pressure affects knee OA. On the contrary, if the symptoms of knee OA limit physical activity and movement, it can lead to obesity (Berenbaum et al., 2013). In addition to the simple weight-bearing mechanism, between obesity and knee OA, several pathophysiological mechanisms are involved, such as insulin resistance, abnormal lipid metabolism, and blood pressure elevation (Zhuo et al., 2012, Sellam, 2013).

This study used the data of the National Health and Nutrition Survey conducted on a large scale at the national level. Although the representativeness of the group could be better reflected than using data from a multicenter study, imaging tests such as ultrasound or computed tomography used to determine fat accumulation in the liver were not performed. Therefore, FLI, among serum biomarkers, was used for the diagnosis of fatty liver. FLI has been used in several studies as it has proven its effectiveness in diagnosing NAFLD (Bedogni et al., 2006, Fedchuk et al., 2014, Motamed et al., 2016). FLI is an algorithm based on WC, BMI, and TG and γ-GT levels and can be used to predict fatty liver (Bedogni et al., 2006). When MAFLD was redefined in 2020, the Asian Pacific Association for the Study of the live clinical practice guidelines also revealed that FLI is the only serum biomarker available (Eslam et al., 2020c). A large population study has been performed in which participants' abdominal ultrasound data were collected to assess the ability of FLI to detect fatty liver. FLI measurements were used to identify patients with NAFLD with an AUC value of 0.813 (Koehler et al., 2013). FLI is useful for identifying NAFLD in patients with type 2 diabetes. A previous study showed that subjects with type 2 diabetes demonstrated a high prevalence of NAFLD when diagnosed with FLI, even at normal alanine aminotransferase levels (Sviklāne et al., 2018).

FLI's cut-off point for accurately identifying NAFLD in China's middle-aged and elderly was 30 (Huang et al., 2015). Patients with FLI <30 can be classified as NAFLD-free. In addition, FLI >60 can confirm the presence of NAFLD (Zelber-Sagi et al., 2013, Bedogni et al., 2006). Therefore, in this study, patients with FLI <30 were classified as MAFLD-negative, and those with ≥60were classified as MAFLD-positive. Additionally, FLI is associated with insulin resistance, coronary heart disease, and early atherosclerosis (Kim et al., 2012, Kim et al., 2015). Furthermore, FLI value has been found to be associated with all-cause, hepatic-related, cardiovascular disease-related, and cancer mortality (Gastaldelli et al., 2009). In a study of the Korean population, the prevalence of NAFLD determined using FLI was significantly higher in subjects with metabolic disorders, including metabolic syndrome. This study found that the analysis of FLI may be useful for the early management of metabolic syndrome and for detecting populations at a high risk of cardiovascular disease (Khang et al., 2019). Since the usefulness of FLI has already been determined, this study further revealed an association FLI with knee OA.

Metabolic abnormality factors other than SBP did not affect knee OA risk, but MAFLD increased knee OA risk by 1.475 times. The results of this study, which showed that MAFLD diagnosed with FLI correlates with knee OA, suggest the necessity of diagnosing and managing MAFLD in knee OA patients.

Treatment of knee OA includes weight loss and pain control, and the goal may be to improve the quality of life and for an easier and smoother routine. The treatment of MAFLD is effective in weight loss, exercise, and diet. These two chronic diseases overlap in terms of management. Considering the relationship so far, improvement of metabolic abnormality will be needed in the management of the two diseases.

The sectional design of the study is a limitation. Therefore, it was not possible to define a causal relationship. Additionally, the most accurate diagnostic method for MAFLD has not been used. Korean criteria for diagnosing MAFLD with FLI should be specified in the future. Further research is needed to compensate for these limitations in the future.

In conclusion, the results of this study suggest that metabolic diseases such as MAFLD should be considered in the management and treatment of knee OA. Our findings suggest that a new multifaceted approach is needed to manage knee OA and MAFLD and that both diseases require comprehensive treatment in terms of metabolic aspects.

Declarations

Funding

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Competing interests

The author declares no competing interests

Availability of data and material

Not applicable.

Code availability

Not applicable

Authors' contributions

A Lum Han:.Study design, data collection, data analysis, and manuscript drafting

Ethics approval

This study followed the ethical standards laid out in the Declaration of Helsinki. The study was approved by the Clinical Trial Screening Committee of Wonkwang University Hospital (institutional review board [IRB] approval number: 2021-03-032).

The name of the IRB is Wonkwang University Hospital Institutional Review Board, which belongs to Wonkwang University 3rd General Hospital, and its address is as follows: Wonkwang University Hospital, Sinyong-dong 344-2, Iksan, Jeollabuk-do.

Consent to participate

Not applicable. The data used were publicly available at the national level, and anonymity was guaranteed. The author also declared that the data will not be used for any purpose other than the research purpose.

Consent for publication

Not applicable. This is because all patient information was investigated anonymously, and the manuscript did not reveal the patient's personal clinical information or the patient's image.

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Tables

Table 1. Differences between general characteristics, knee osteoarthritis, and MAFLD

		Knee osteoarthritis (n = 6,327)		P-value
		NO (n = 3, 934)	YES (n = 2,393)	
Sex	Male	1989(76)	742(24)	<0.0001
	Female	1945(55.2)	1651(44.8)	
Educational level	Elementary	1506(52.2)	1508(47.8)	<0.0001
	Junior high	719(71.3)	351(28.7)	
	High	1059(77.7)	355(22.3)	
	College	575(84.2)	81(14.2)	
Household income	Low	934(64.2)	626(35.8)	0.397
	Middle-low	944(63.3)	620(36.7)	
	Middle-high	1010(66.1)	577(33.9)	
	High	1004(66.8)	531(33.2)	
Moderate physical activity	N	3486(65.6)	2066(34.4)	0.192
	Y	373(62.3)	254(37.7)	
Regular exercise	N	2354(65)	1434(35)	0.540
	Y	1503(65.9)	883(34.1)	
Smoking	N	3106(62.3)	2073(37.7)	<0.0001
	Y	756(77.5)	252(22.5)	
Alcohol	N	1968(58.5)	1513(41.5)	<0.0001
	Y	1881(72.7)	803(27.3)	
Diabetes	N	14(45.1)	14(54.9)	0.010
	Y	517(60.5)	389(39.5)	
Dyslipidemia	N	2884(67.5)	1582(32.5)	<0.0001
	Y	738(61.1)	498(38.9)	
MAFLD	N	3218(65.9)	1830(34.1)	0.901
	Y	508(65.6)	334(34.4)	
Age		59.64±0.19	67.1±0.25	<0.0001
SBP		125.35±0.41	130.82±0.48	<0.0001
DBP		78.57±0.24	77.29±0.29	<0.0001

WC	82.85±0.21	85.21±0.26	<0.0001
BMI	23.59±0.06	24.72±0.09	<0.0001
FPG	102.6±0.55	103.93±0.68	0.121
HbA1c	6.09±0.03	6.25±0.04	0.001
TC	194.43±0.79	196.38±0.96	0.095
HDL-C	48.19±0.29	47.62±0.35	0.167
TG	149.69±2.65	146.98±2.62	0.453
LDL-C	117.01±1.21	120.6±1.85	0.117
Vit D	18.88±0.21	19.43±0.31	0.039
γ-GT	43.17±1.49	33.6±1.22	<0.0001

Abbreviations: MAFLD, metabolic associated fatty liver disease; SBP, Systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; FPG, fasting plasma glucose; HbA1c; hemoglobin A1c; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; Vit D, vitamin D; γ-GT, gamma-glutamyl transferase

Values are presented as number (%) or the mean ± standard deviation.

The P-value was determined through the complex sample Rao-Scott adjusted chi-square test and complex sample generalized linear model T-test.

Table 2. Association between MAFLD-related variables and knee osteoarthritis

	Model 1		Model 2	
	OR(95% CI)	P-value	OR(95% CI)	P-value
SBP	1.036(1.031–1.041)	<0.0001	1.005(0.999–1.011)	0.107
DBP	0.947(0.938–0.955)	<0.0001	1.002(0.992–1.013)	0.670
WC	0.982(0.967–0.997)	0.017	0.985(0.968–1.002)	0.081
FPG	0.998(0.995–1.002)	0.363	1.000(0.997–1.004)	0.938
TG	1.000(0.999–1.000)	0.359	1.000(0.999–1.001)	0.817
HDL-C	1.002(0.995–1.009)	0.656	1.005(0.997–1.013)	0.195
BMI	1.208(1.156–1.262)	<0.0001	1.228(1.166–1.295)	<0.0001
Diabetes	0.509(0.211–1.230)	0.942	0.574(0.200–1.649)	0.368

Abbreviations: MAFLD, metabolic associated fatty liver disease; SBP, Systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride

Model 1: adjusted for age, sex

Model 2: adjusted for age, sex, education, alcohol, smoking

The P-value was determined through the complex sample logistic regression test.

Table 3. Relationship between knee osteoarthritis and MAFLD

	Model 1		Model 2	
	OR(95% CI)	P-value	OR(95% CI)	P-value
MAFLD	1.000(0.818–1.222)	0.996	1.475(1.181–1.842)	0.001

Abbreviations: MAFLD, metabolic associated fatty liver disease

Model 1: adjusted for age, sex

Model 2: adjusted for age, sex, education, alcohol, smoking

The ORs and 95% CI are determined through the complex sample logistic regression test.

Figures

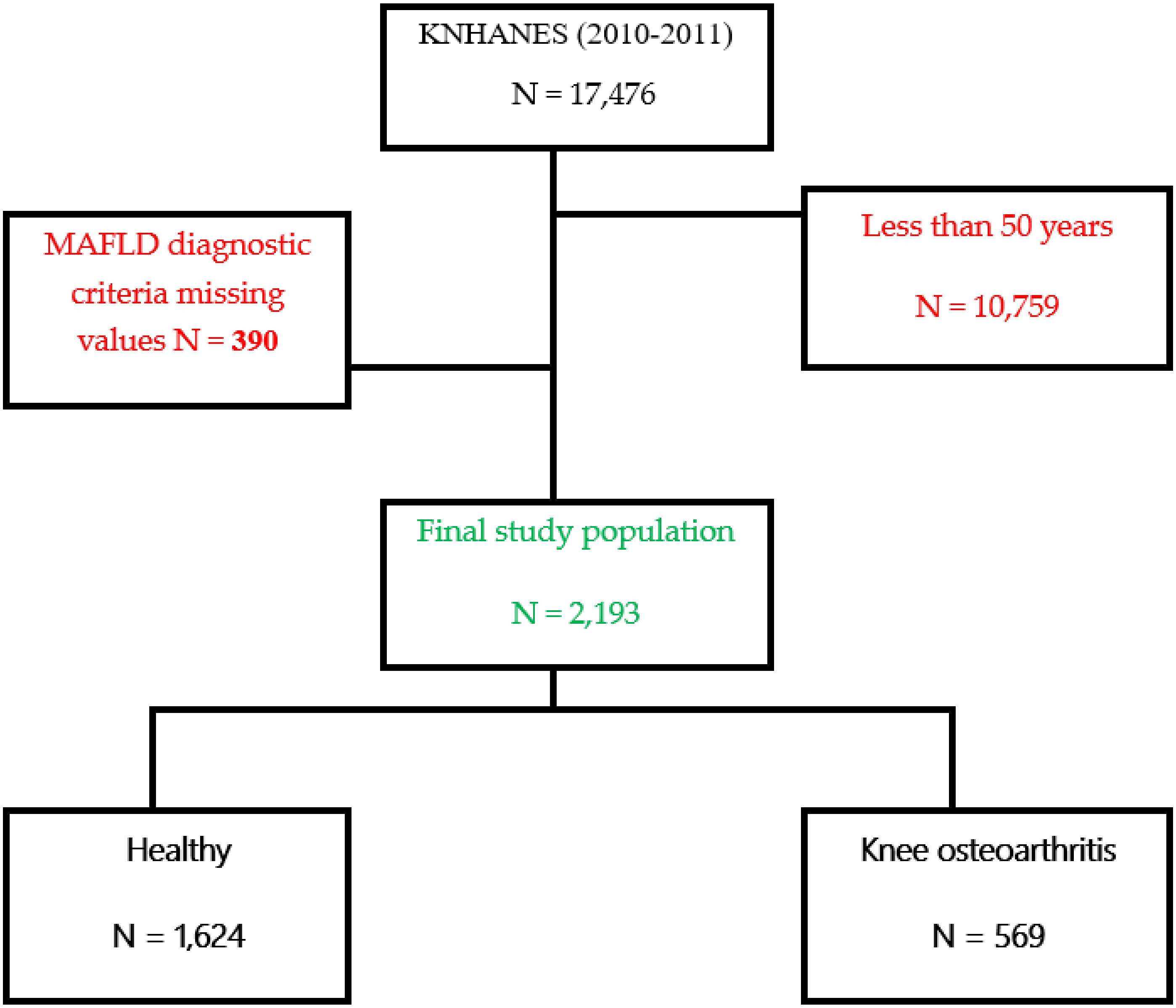

Figure 1

Flow diagram of subjects in this study. KNHANES, Korean National Health and Nutrition Examination Survey; MAFLD, metabolic associated fatty liver disease