Nonalcoholic Fatty Liver Disease and Sarcopenia Are Independently Associated With Cardiovascular Risk

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OBJECTIVES: **Nonalcoholic fatty liver disease (NAFLD) and sarcopenia have a close association with an increased risk of atherosclerotic cardiovascular disease (ASCVD). This study investigated the influence of NAFLD and sarcopenia on ASCVD risk.**

METHODS: **Data from the 2008–2011 Korean National Health and Nutrition Examination Surveys database were analyzed (n = 7,191). The sarcopenia index was calculated using dual-energy x-ray absorptiometry. Sarcopenia was defined as the lowest quintile sarcopenia index value (cutoffs = 0.882 for men and 0.582 for women). NAFLD was defined as a comprehensive NAFLD score ≥40. Liver fibrosis was assessed using the fibrosis-4 (FIB-4) index. ASCVD risk was evaluated using American College of Cardiology/American Heart Association guidelines. High probability of ASCVD was defined as ASCVD risk >10%.**

RESULTS: **The prevalence rates of NAFLD and sarcopenia were 31.2% (n = 2,241) and 19.5% (n = 1,400), respectively. The quartile-stratified ASCVD risk scores were positively associated with NAFLD and sarcopenia (all *P* for trend < 0.001). Subjects with both NAFLD and sarcopenia had a higher risk for high probability of ASCVD (odds ratio = 1.83, *P* = 0.014) compared with controls without NAFLD and sarcopenia. Among subjects with NAFLD, FIB-4–defined significant liver fibrosis and sarcopenia additively raised the risk for high probability of ASCVD (odds ratio = 3.56, *P* < 0.001) compared with controls without FIB-4–defined significant liver fibrosis or sarcopenia.**

DISCUSSION: **NAFLD and sarcopenia were significantly associated with an increased risk of ASCVD in the general population. In addition, NAFLD with significant liver fibrosis and sarcopenia were significantly associated with an increased risk of ASCVD in subjects with NAFLD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B435, http://links.lww.com/AJG/B436, and http://links.lww.com/AJG/B437

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common metabolic liver disorders, with an estimated prevalence of ~30% in developed countries (1–5), and its incidence is expected to rise rapidly in the future as the rate of obesity increases, populations age, and sedentary lifestyles prevail (2). Cardiovascular disease (CVD) is significantly linked to severity of liver fibrosis (6,7), and it is the leading cause of mortality in patients with NAFLD (8). This close association between NAFLD and CVD likely stems from the central role the liver plays in glucose and lipid metabolism, independent of other cardiometabolic risk factors such as diabetes, obesity, hypertension, and dyslipidaemia (9–11).

Sarcopenia, which is defined as age-related loss of muscle mass, strength, and function (12), has become a serious medical issue in aging societies. It is known that sarcopenia is significantly associated with an increased risk of cardiovascular events or mortality in patients with metabolic phenotypes such as type 2 diabetes (T2D) or chronic kidney disease (CKD) (13,14). This close association between sarcopenia and cardiovascular events or mortality can probably be explained by the fact that patients with sarcopenia, especially those with chronic medical illnesses, are inevitably subject to increased risk due to decreased physical ability and functional impairment preventing exercise (15,16).

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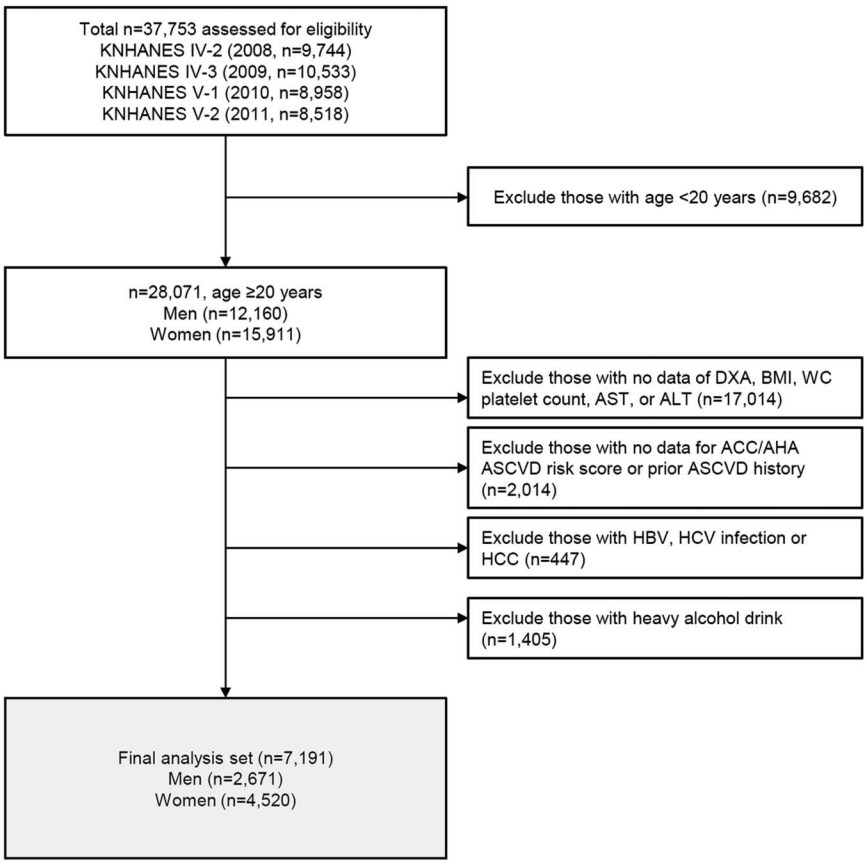

Figure 1. Flow diagram of subject inclusion and exclusion in the Korea National Health and Nutrition Examination Surveys (KNHANES IV and V). Of 37,753 subjects, 7,191 were finally included (2,671 men and 4,520 women). ACC/AHA, American College of Cardiology/American Heart Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; KNHANES, Korea National Health and Nutrition Examination Survey; WC, waist circumference.

Recently, the complex relationship between sarcopenia and NAFLD/nonalcoholic steatohepatitis has been a focus of clinical attention (17,18). A recent study showed a strong relationship between NAFLD and sarcopenia in the general population, suggesting sarcopenia as a novel risk factor for NAFLD (19). A subsequent study further confirmed this significant association, independent of obesity and insulin resistance, which are the common denominators linking NAFLD and sarcopenia (20). In addition, based on the concept that most patients with NAFLD have simple hepatic steatosis with a favorable prognosis (2), another recent study showed that a subgroup of patients with NAFLD and significant liver fibrosis had significantly increased risk for sarcopenia among those with the entire spectrum of NAFLD (21).

Although NAFLD and sarcopenia are independently associated with increased CVD risk, the interactive influence of NAFLD and sarcopenia on CVD risk, supported by the independent association between NAFLD and sarcopenia, has not been fully determined. Thus, we investigated how, independent of other metabolic factors (e.g., central obesity, obesity, hypertension, T2D, CKD, and dyslipidaemia), NAFLD and sarcopenia interactively influence CVD risk in the general population and whether NAFLD with significant liver fibrosis has a similar independent association with CVD risk in the subpopulation with NAFLD, using the data from the Korea National Health and Nutrition Examination Survey (KNHANES).

PATIENTS AND METHODS

Study subjects

The KNHANES is a nationwide, population-based, cross-sectional health examination and survey that is annually conducted by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention in the Ministry of Health and Welfare to monitor the general health and nutritional status of the general civilian population in South Korea (22). Subjects are randomly selected from 600 randomly selected districts in cities and provinces in South Korea to represent a sample of the Korean population.

As described in Figure 1, of the 37,753 subjects in the KNHANES 2008–2011, we initially selected 28,071 subjects aged ≥20 years (12,160 men and 15,911 women). Of these, 20,880 were excluded, based on the following: (i) insufficient clinical and laboratory information to calculate body mass index (BMI), muscle mass, or degree of liver fibrosis or steatosis, (ii) insufficient data to calculate the risk of atherosclerotic CVD (ASCVD) or history of ASCVD, (3) positive serologic markers of hepatitis B virus, or hepatitis C virus, or hepatocellular carcinoma at enrollment or history of it, or (4) heavy alcohol consumption (>210 g/wk for men and 140 g/wk for women) (21).

Written informed consent was secured from all subjects before the study began, and the KNHANES was conducted following ethical approval by the Institutional Review Board of the Korea

Table 1. Baseline characteristics of the study population

Variables	NAFLD (−) Sarcopenia (−) (n = 4,286, 59.6%)	NAFLD (+) Sarcopenia (−) (n = 1,505, 20.9%)	NALFD (−) Sarcopenia (+) (n = 664, 9.2%)	NAFLD (+) Sarcopenia (+) (n = 736, 10.3%)	*P* value
Demographic variables					
Age, yr	44.5 ± 15.1	50.3 ± 13.8[d]	58.5 ± 15.5[d,e]	60.7 ± 15.8[d,e,f]	<0.001
Male sex	1,337 (31.2)	812 (54.0)	216 (32.5)	306 (41.6)	0.733
ASM, kg	17.6 ± 4.3	21.9 ± 4.9[d]	14.7 ± 3.4[d,e]	17.4 ± 4.0[e,f]	<0.001
Waist circumference, cm	75.4 ± 7.4	89.7 ± 6.8[d]	78.9 ± 6.7[d,e]	91.2 ± 7.5[d,e,f]	<0.001
BMI, kg/m^2	21.8 ± 2.3	26.3 ± 2.5[d]	23.2 ± 2.1[d,e]	27.3 ± 2.9[d,e,f]	<0.001
Sarcopenic index[a]	0.8 ± 0.2	0.8 ± 0.2[d]	0.6 ± 0.1[d,e]	0.6 ± 0.1[d,e]	<0.001
Systolic BP, mm Hg	111.6 ± 16.0	121.6 ± 16.2[d]	121.3 ± 18.9[d]	126.9 ± 16.7[d,e,f]	<0.001
Diastolic BP, mm Hg	71.6 ± 9.9	78.1 ± 10.3[d]	73.7 ± 10.4[d,e]	77.4 ± 10.0[d,f]	<0.001
Hypertension	638 (14.9)	568 (37.7)	244 (36.7)	315 (57.2)	<0.001
Metabolic syndrome	411 (9.6)	953 (63.3)	165 (24.8)	554 (75.3)	<0.001
Diabetes	128 (3.0)	299 (19.9)	37 (5.6)	186 (25.3)	<0.001
Current smoker	617 (14.4)	338 (22.5)	80 (12.0)	9.5 (14.8)	0.460
Central obesity[b]	696 (16.2)	1·047 (69.6)[d]	193 (29.1)[d,e]	578 (78.5)[d,e,f]	<0.001
Obesity[c]	371 (8.7)	1·055 (70.1)[d]	147 (22.1)[d]	590 (80.2)[d,e,f]	<0.001
Exercise	695 (16.2)	259 (17.2)	69 (10.4)[d,e]	77 (10.5)[d,e]	<0.001
Laboratory variables					
Fasting blood glucose, mg/dL	91.1 ± 10.6	108.3 ± 33.8[d]	94.5 ± 14.7[d,e]	109.0 ± 28.4[d,f]	<0.001
Insulin, μIU/mL[a]	8.8 ± 3.2	12.2 ± 5.4[d]	9.1 ± 3.4[e]	12.7 ± 6.4[d,f]	<0.001
HOMA-IR[a]	2.0 ± 0.8	3.3 ± 1.9[d]	2.1 ± 1.0[d,e]	3.4 ± 2.1[d,f]	<0.001
Total cholesterol, mg/dL	181.6 ± 33.0	199.3 ± 36.3[d]	195.5 ± 35.9[d]	203.9 ± 37.9[d,e,f]	<0.001
Triglyceride, mg/dL[a]	93.9 ± 50.7	189.9 ± 113.6[d]	112.1 ± 55.6[d,e]	182.2 ± 98.8[d,f]	<0.001
HDL cholesterol, mg/dL[a]	50.9 ± 10.9	41.6 ± 8.7[d]	48.5 ± 10.5[d,e]	43.0 ± 9.5[d,f]	<0.001
LDL cholesterol, mg/dL[a]	111.4 ± 29.1	122.4 ± 32.5[d]	123.9 ± 32.2[d]	126.7 ± 35.2[d]	<0.001
Serum creatinine, mg/dL	0.8 ± 0.2	0.9 ± 0.2[d]	0.8 ± 0.2[e]	0.9 ± 0.2[d,e,f]	<0.001
eGFR, mL/min/1.73 m^2	98.2 ± 17.2	90.9 ± 16.4[d]	89.3 ± 17.3[e]	85.6 ± 17.3[d,e,f]	<0.001
AST, IU/L[a]	19.3 ± 7.8	24.7 ± 10.8[d]	20.4 ± 5.4[d,e]	25.8 ± 12.0[d,f]	<0.001
ALT, IU/L[a]	15.7 ± 7.6	30.5 ± 20.6[d]	16.4 ± 6.6[e]	29.3 ± 21.4[d,f]	<0.001
Platelet count, 10^9/L[a]	254.9 ± 56.0	256.3 ± 59.3	261.4 ± 60.1	262.8 ± 58.4[d]	0.003
Gamma-GT, IU/L[a]	21.4 ± 36.6	41.4 ± 43.4[d]	23.4 ± 19.3[d,e]	44.4 ± 58.4[d,f]	<0.001
Liver fibrosis					
FIB-4	0.9 ± 0.6	1.0 ± 0.7	1.3 ± 0.7[d,e]	1.2 ± 0.6[d,e]	<0.001
Significant fibrosis by FIB-4	819 (19.1)	340 (22.6)[d]	266 (40.1)[d,e]	372 (37.1)[d,e]	<0.001
Liver steatosis					
CNS	10.0 ± 10.6	69.2 ± 17.5[d]	17.5 ± 11.5[d,e]	72.8 ± 18.0[d,e,f]	<0.001
FLI	13.2 ± 11.8	52.2 ± 19.1[d]	19.1 ± 12.2[d,e]	56.2 ± 20.3[d,e,f]	<0.001

Variables are expressed as mean ± SD or n (%).
ALT, alanine aminotransferase; ASM, appendicular skeletal muscle; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CNS, comprehensive NAFLD score; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; FLI, fatty liver index; GT, glutamyl-transpeptidase; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.
[a]Log transformed.
[b]Central obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women.
[c]Obesity was defined as BMI ≥25 kg/m^2.
[d]$P < 0.05$ by *post hoc* analyses when compared without sarcopenia and NAFLD.
[e]$P < 0.05$ by *post hoc* analyses when compared without sarcopenia, with NAFLD.
[f]$P < 0.05$ by *post hoc* analyses when compared with sarcopenia, without NAFLD.

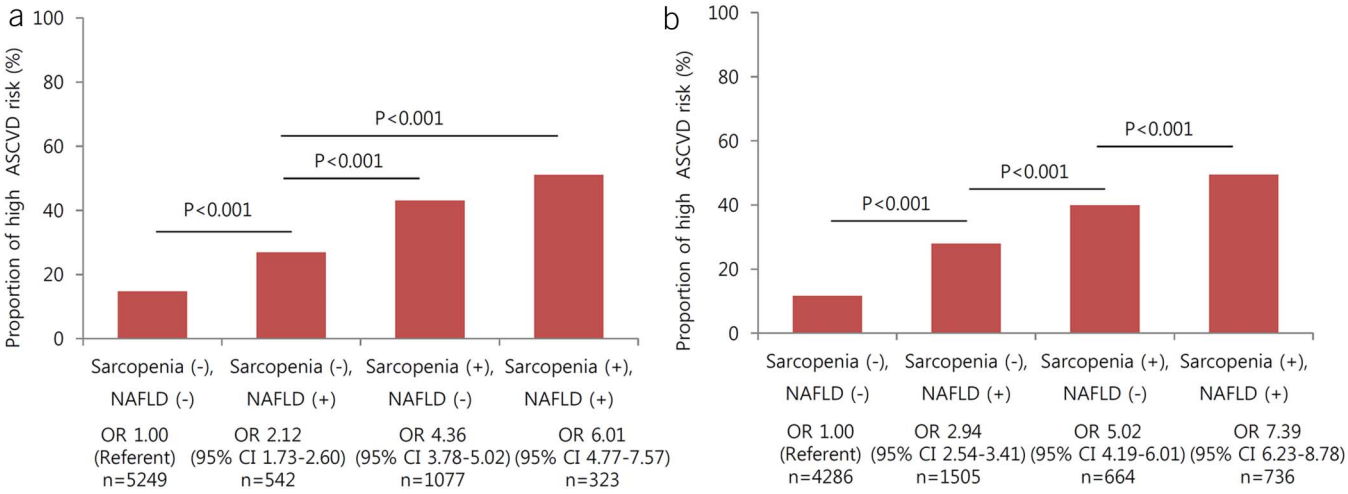

Figure 2. The relative risk for high probability of ASCVD according to NAFLD and sarcopenia status (**a** and **b**). Presence of CNS- (**a**) or FLI-defined (**b**) NAFLD and sarcopenia showed strong positive relationship with quartile-stratified ASCVD risk (all *P* for trend <0.001). Relative risk for high probability of ASCVD was highest in subjects with CNS- (**a**) or FLI-defined (**b**) NAFLD and sarcopenia (all $P < 0.001$). ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CNS, comprehensive NAFLD score; FLI, fatty liver index; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

Centers for Disease Control and Prevention (No: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, and 2011-02CON-06C).

Appendicular skeletal muscle mass and the definition of sarcopenia

As described previously (21), appendicular skeletal muscle mass was measured using dual-energy x-ray absorptiometry (QDR 4500A; Hologic, Bedford, MA). The sarcopenia index was calculated as follows: sarcopenia index = total appendicular skeletal muscle mass (kg)/BMI (kg/m^2). Sarcopenia was defined as the lowest quintile for sex-specific sarcopenia index cutoff values (<0.882 for men and <0.582 for women), based on a modified recommendation from the Foundation for the National Institutes of Health (23).

NAFLD and liver fibrosis

NAFLD was defined using previously validated fatty liver prediction models (see Table 1, Supplementary Digital Content 3, http://links.lww.com/AJG/B437): the comprehensive NAFLD score (CNS) (1) and the fatty liver index (FLI) (24); a CNS ≥40 and a FLI ≥60 and were considered indicative of having NAFLD (1,24). We further assessed fibrotic burden using previously validated liver fibrosis prediction model among subjects with NAFLD (n = 2,236): the fibrosis-4 (FIB-4) index (25) (see Table 1, Supplementary Digital Content 3, http://links.lww.com/AJG/B437).

Assessment of ASCVD risk and cardiometabolic disease components

ASCVD risk was evaluated using the 10-year ASCVD risk score from the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (26). Subjects exhibiting ACC/AHA ASCVD risk > 10% were considered as having high probability of ASCVD. Based on the criteria for the Asian-Pacific region (27), subjects were considered obese when their BMI was ≥25 kg/m^2. Central obesity was defined based on waist circumference criteria from the Korean Society for the Study of Obesity (≥90 cm for men and ≥85 cm for women) (27). T2D was defined based on the use of insulin or oral hypoglycaemic agents, fasting plasma glucose ≥126 mg/dL, or glycated hemoglobin ≥6.5%. Subjects were diagnosed as hypertensive when the systolic pressure was ≥140 mm Hg and the diastolic pressure was ≥90 mm Hg or if antihypertensive medications were currently used. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology collaboration equation (28), and CKD was characterized as eGFR <60 mL/min/1.73 m^2 (29). Hyper low-density lipoprotein (LDL) cholesterolaemia was characterized based on individual LDL cholesterol goals recommended in a 2004 update of the ATP III guidelines or current use of an anti-dyslipidemia drug (e.g., statin) for both sexes (30). Hypo high-density lipoprotein (HDL) cholesterolaemia was defined as HDL <40 mg/dL for men and <50 mg/dL for women. Hypertriglyceridemia was defined as serum triglycerides ≥150 mg/dL or use of triglyceride-lowering agents.

Clinical parameters and biochemical analysis

KNHANES data include medical history, smoking habits and alcohol consumption, exercise level, and disease diagnosis and/or treatment, based on direct interviews and self-reporting, using standardized health questionnaires (21). Smoking status was categorized by self-report as non- or current smoker. Regular exercise was defined as engaging in moderate or vigorous exercise on a regular basis (≥20 min at a time, at least 3 times per week) (31).

After overnight fasting for at least 8 hours, blood specimens collected from each subject were processed and transported in cold storage to the Central Testing Institute (Neodin Medical Institute, Seoul, Korea). All blood samples were analyzed within 24 hours of transportation, as previously described (31). The homeostasis model assessment of insulin resistance (HOMA-IR) was assessed as previously described (32).

Statistical analysis

The characteristics of the study subjects were analyzed according to NAFLD and sarcopenia status using one-way analysis of variance to compare continuous variables and χ^2 tests for categorical variables, followed by *post hoc* analyses using the Bonferroni method. The association between NAFLD/sarcopenia and the

Table 2. ORs and 95% CIs of cardiometabolic and renal risk factors according to the status of NAFLD and sarcopenia

Cardiometabolic and renal risk factors	NAFLD by CNS				NAFLD by FLI			
	NAFLD (−) Sarcopenia (−)	NAFLD (+) Sarcopenia (−)	NAFLD (−) Sarcopenia (+)	NAFLD (+) Sarcopenia (+)	NAFLD (−) Sarcopenia (−)	NAFLD (+) Sarcopenia (−)	NAFLD (−) Sarcopenia (+)	NAFLD (+) Sarcopenia (+)
Central obesity[a]	1.00 (ref.)	33.76 27.57–41.35 $P < 0.001$	1.66 1.35–2.04 $P < 0.001$	34.11 26.49–43.92 $P < 0.001$	1.00 (ref.)	26.95 20.93–34.70 $P < 0.001$	1.64 1.41–1.92 $P < 0.001$	36.70 24.82–54.26 $P < 0.001$
Obesity[b]	1.00 (ref.)	33.86 28.50–40.24 $P < 0.001$	4.38 3.48–5.50 $P < 0.001$	73.56 57.71–93.76 $P < 0.001$	1.00 (ref.)	22.32 17.55–28.38 $P < 0.001$	3.17 2.73–3.69 $P < 0.001$	40.18 27.70–58.28 $P < 0.001$
Hypertension	1.00 (ref.)	3.07 2.64–3.57 $P < 0.001$	1.49 1.21–1.82 $P < 0.001$	3.58 2.97–4.32 $P < 0.001$	1.00 (ref.)	3.49 2.82–4.31 $P < 0.001$	1.47 1.25–1.72 $P < 0.001$	3.99 3.07–5.19 $P < 0.001$
Diabetes	1.00 (ref.)	6.91 5.52–8.64 $P < 0.001$	0.94 0.64–1.39 $P = 0.754$	5.63 4.37–7.26 $P < 0.001$	1.00 (ref.)	3.05 2.35–3.96 $P < 0.001$	1.08 0.86–1.36 $P = 0.489$	2.99 2.25–3.97 $P < 0.001$
CKD[c]	1.00 (ref.)	1.92 1.36–2.73 $P < 0.001$	0.93 0.62–1.42 $P = 0.745$	1.48 1.03–2.13 $P = 0.35$	1.00 (ref.)	2.72 1.73–4.29 $P < 0.001$	0.96 0.69–1.33 $P = 0.797$	1.60 1.01–2.53 $P = 0.047$
Hyper-LDL cholesterolemia[d]	1.00 (ref.)	2.84 2.45–3.30 $P < 0.001$	1.47 1.20–1.81 $P < 0.001$	2.69 2.24–3.23 $P < 0.001$	1.00 (ref.)	1.84 1.49–2.27 $P < 0.001$	1.37 1.17–1.61 $P < 0.001$	1.96 1.53–2.51 $P < 0.001$
Hypo-HDL cholesterolemia[e]	1.00 (ref.)	3.97 3.47–4.54 $P < 0.001$	1.19 1.00–1.41 $P = 0.057$	3.05 2.55–3.64 $P < 0.001$	1.00 (ref.)	3.83 3.13–4.67 $P < 0.001$	1.21 1.05–1.39 $P = 0.009$	2.50 1.95–3.21 $P < 0.001$
Hypertriglyceridemia[f]	1.00 (ref.)	8.40 7.31–9.66 $P < 0.001$	1.35 1.10–1.67 $P = 0.005$	6.61 5.52–7.91 $P < 0.001$	1.00 (ref.)	13.88 11.11–17.35 $P < 0.001$	1.29 1.11–1.51 $P = 0.001$	7.28 5.61–9.45 $P < 0.001$

Adjusted for age, sex, smoking, and exercise.
BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CNS, comprehensive NAFLD score; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.
[a]Central obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women.
[b]Obesity was defined as BMI ≥25 kg/m^2.
[c]CKD was defined if subjects had an eGFR less than 60 mL/min/1.73 m^2.
[d]Hyper-LDL cholesterolemia was characterized as the individual's LDL cholesterol goal recommended by 2004 update of the ATP III guidelines or currently taking anti-dyslipidemia drug.
[e]Hypo-HDL cholesterolemia was defined as serum HDL cholesterol <40 mg/dL for men and <50 mg/dL for women.
[f]Hypertriglyceridemia was defined as serum triglycerides ≥150 mg/dL or taking triglyceride-lowering agents.

ASCVD risk score was evaluated using a χ^2 test after transformation of the variables into quartiles.

The *P* value for the interaction between sarcopenia, fibrosis, and the ASCVD risk was 0.613. As the FIB-4 and the ASCVD risk score contain overlapping variables, the variance inflation factor was used to evaluate multicollinearity in the multivariate analysis. However, there was no evidence of multicollinearity (highest variance inflation factor = 2.231).

Multivariate logistic regression analysis was applied to determine the independent association between NAFLD/sarcopenia and high ASCVD risk (ACC/AHA ASCVD risk >10%) after adjusting for age and sex in model 1. Variables in model 1, exercise, and smoking status were adjusted in model 2. Variables in model 2, hypertension, T2D, obesity, central obesity, HOMA-IR, CKD, hyper-LDL cholesterolaemia, and hypo-HDL cholesterolaemia were adjusted in model 3. In addition, to assess the impact of high ASCVD risk, the adjusted model 3 was applied for each factor including NAFLD, sarcopenia, hypertension, T2D, smoking, exercise, CKD, hyper-LDL cholesterolaemia, and hypo-HDL cholesterolaemia. Then, we selected subjects with NAFLD to evaluate whether NAFLD with liver fibrosis had an independent association with high ASCVD risk in the subpopulation with NAFLD.

As total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, insulin, and the HOMA-IR values were not normally distributed, analyses were performed using log-transformed data to achieve approximately symmetrical distributions. Continuous and categorical variables were expressed as mean ± SD and numbers (%), respectively. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM, Armonk, NY).

RESULTS

Baseline characteristics of the study population

A total of 7,191 subjects were recruited (2,671 men and 4,520 women) (Figure 1). Baseline characteristics according to the status of NAFLD and sarcopenia are shown in Table 1. The

Table 3. OR and 95% CIs of high probability in ASCVD risk (>10%) according to the status of sarcopenia and NAFLD defined by different scores

	NAFLD by CNS				NAFLD by FLI			
Multivariate models	Sarcopenia (−) NAFLD (−)	Sarcopenia (−) NAFLD (+)	Sarcopenia (+) NAFLD (−)	Sarcopenia (+) NAFLD (+)	Sarcopenia (−) NAFLD (−)	Sarcopenia (−) NAFLD (+)	Sarcopenia (+) NAFLD (−)	Sarcopenia (+) NAFLD (+)
Model 1	1.00 (ref.)	4.28 3.31–5.54 $P < 0.001$	1.69 1.22–2.33 $P = 0.002$	3.30 2.49–4.39 $P < 0.001$	1.00 ref.	4.35 3.07–6.16 $P < 0.001$	1.34 1.05–1.72 $P = 0.018$	3.60 2.47–5.25 $P < 0.001$
Model 2	1.00 (ref.)	5.11 3.87–6.75 $P < 0.001$	1.90 1.34–2.69 $P < 0.001$	4.12 3.04–5.59 $P < 0.001$	1.00 ref.	4.44 3.09–6.38 $P < 0.001$	1.51 1.62–1.95 $P = 0.002$	3.87 2.58–5.80 $P < 0.001$
Model 3	1.00 (ref.)	2.18 1.43–3.33 $P < 0.001$	1.63 1.07–2.49 $P = 0.024$	1.83 1.13–2.96 $P = 0.014$	1.00 ref.	2.88 1.75–4.75 $P < 0.001$	1.28 0.92–1.78 $P = 0.141$	2.04 1.17–3.56 $P = 0.012$

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, exercise, and current smoking.
Model 3: adjusted for age, sex, hypertension, diabetes, obesity, central obesity, HOMA-IR, CKD, hyper-LDL cholesterolemia, and hypo-HDL cholesterolemia.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CNS, comprehensive NAFLD score; FLI, fatty liver index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

prevalence of NAFLD and sarcopenia was 31.2% (2,241 of 7,191) and 19.5% (1,400 of 7,191), respectively. Subjects with both NAFLD and sarcopenia were significantly older and had significantly greater waist circumference, BMI, systolic blood pressure, and total cholesterol levels than those of other groups (all $P < 0.05$), whereas eGFR was significantly lower in subjects with both NAFLD and sarcopenia ($P > 0.001$). In addition, the proportion of central obesity, obesity, and CNS/FLI-defined fatty liver was significantly higher in subjects with both NAFLD and sarcopenia than those of other groups (all $P < 0.05$).

The proportion of cardiometabolic phenotypes including hypertension, metabolic syndrome, T2D, central obesity, and obesity was significantly greater in subjects with either NAFLD or sarcopenia compared with those without NAFLD and sarcopenia and was highest in subjects with both NAFLD and sarcopenia (all $P < 0.05$). Liver-related laboratory results, including alanine aminotransferase levels, were significantly greater in subjects with NAFLD, regardless of sarcopenic status (all $P < 0.05$). Among subjects with NAFLD, fibrotic burden, assessed using FIB-4, was significantly greater when subjects had sarcopenia (mean 1.0 ± 0.7 in subjects without sarcopenia vs 1.2 ± 0.6 in subjects with sarcopenia, $P < 0.001$).

Association between ASCVD risk and the presence of NAFLD/sarcopenia

We assessed the relative risk for high probability of ASCVD according to the presence of NAFLD, as defined by CNS (Figure 2a) and FLI (Figure 2b), stratified by sarcopenia. Subjects with CNS-defined NAFLD had a significantly increased

Table 4. Comparison of ORs and 95% CIs for high probability of ASCVD contributed by NAFLD, the degree of fatty liver, sarcopenia, and cardiometabolic/renal risk factors stratified by obesity status

	Nonobese (n = 5,028)		Obese (n = 2,163)	
Risk factors	OR	*P* value	OR	*P* value
CNS-defined NAFLD	1.45 (1.15–1.86)	<0.001	1.72 (1.22–2.43)	0.002
Degree of fatty liver by CNS	1.39 (1.08–1.79)	0.012	1.67 (1.28–2.18)	<0.001
Degree of fatty liver by FLI	1.43 (1.13–1.80)	0.003	1.60 (1.30–1.98)	<0.001
Sarcopenia	4.32 (3.47–5.37)	<0.001	2.33 (1.82–2.96)	<0.001
Hypertension	8.64 (7.15–10.44)	<0.001	5.71 (4.46–7.30)	<0.001
Diabetes	5.36 (3.90–7.35)	<0.001	5.24 (3.83–7.17)	<0.001
Current smoking	3.15 (2.64–3.77)	<0.001	2.67 (1.97–3.62)	<0.001
Exercise	1.03 (0.80–1.33)	0.815	0.80 (0.57–1.10)	0.169
CKD	8.98 (5.57–14.48)	<0.001	9.21 (5.22–16.23)	<0.001
Hyper-LDL cholesterolemia	2.04 (1.66–2.51)	<0.001	1.76 (1.37–2.25)	<0.001
Hypo-HDL cholesterolemia	1.33 (1.11–1.59)	0.002	0.99 (0.77–1.26)	0.912

Adjusted for age, sex, hypertension, diabetes, CKD, hyper-LDL cholesterolaemia, and hypo-HDL cholesterolaemia.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CNS, comprehensive NAFLD score; FLI, fatty liver index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

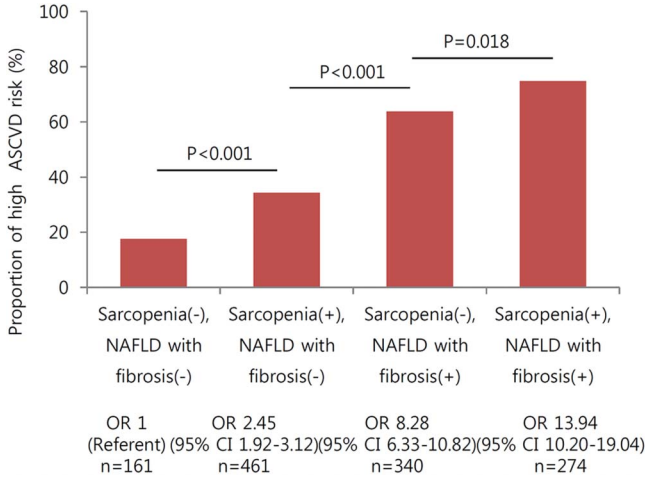

Figure 3. The relative risk for high probability of ASCVD according to FIB-4–defined significant liver fibrosis and sarcopenia. The relative risk for high probability of ASCVD was highest in subjects with FIB-4–defined significant liver fibrosis and sarcopenia (all $P < 0.001$). ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

prevalence of high probability of ASCVD compared with those without CNS-defined NAFLD, independent of sarcopenia (26.9% vs 14.8%; odds ratio [OR] = 2.12, 95% confidence interval [CI] = 1.73–2.60 among subjects without sarcopenia; and 51.1% vs 43.1%; OR = 1.38, 95% CI = 1.08–1.77 among subjects with sarcopenia) (all $P < 0.001$). Compared with subjects without CNS-defined NAFLD and sarcopenia (considered as a control group), the presence of CNS-defined NAFLD and sarcopenia additively increased the relative risk for high probability of ASCVD (OR = 4.36, 95% CI = 1.90–3.32 among subjects with sarcopenia, but without CNS-defined NAFLD; and OR = 6.01, 95% CI = 4.77–7.57 among subjects with both CNS-defined NAFLD and sarcopenia) (all $P < 0.001$). Similar findings were observed, when NAFLD was defined using FLI.

Association between NAFLD/sarcopenia and cardiometabolic/renal risk factors

As varying cardiometabolic and renal risk factors contribute to raise the ASCVD risk, we investigated the association between NAFLD/sarcopenia and cardiometabolic/renal risk factors with minimal adjustment using age, sex, smoking, and exercise (Table 2). When CNS was used to define NAFLD and subjects without NAFLD and sarcopenia were considered as a control group, the relative risk for central obesity (OR = 33.76 vs 1.66), obesity (OR = 33.86 vs 4.38), hypertension (OR = 3.07 vs 1.49), T2D (OR = 6.91 vs 0.94), CKD (OR = 1.92 vs 0.93), hyper-LDL cholesterolaemia (OR = 2.84 vs 1.47), hypo-HDL cholesterolaemia (OR = 3.97 vs 1.19), and hypertriglyceridemia (OR = 8.40 vs 1.35) was raised much more by NAFLD than by sarcopenia (all $P < 0.001$). Subjects with both NAFLD and sarcopenia showed much higher ORs for central obesity (34.11), obesity (73.56), and hypertension (3.58) compared with other groups with either NAFLD or sarcopenia (all $P < 0.001$). When FLI was used to define NAFLD, similar findings were observed.

Association between high probability of ASCVD and the presence of NAFLD/sarcopenia

The association between high probability of ASCVD and the presence of NAFLD/sarcopenia after multistep adjustments is shown in Table 3. When CNS was used to define NAFLD and the relative risk for high probability of ASCVD was assessed after sufficient adjustment (model 3), subjects with sarcopenia, but without NAFLD, were found to have a significantly higher OR for high probability of ASCVD (OR = 1.63, $P = 0.024$) compared with that in subjects without NAFLD and sarcopenia (used as a control group). In addition, subjects with NAFLD but without sarcopenia or those with both NAFLD and sarcopenia showed significantly higher ORs for high probability of ASCVD (OR = 2.18 in subjects with NAFLD but without sarcopenia, $P < 0.001$; and OR = 1.83 in subjects with both NAFLD and sarcopenia, $P = 0.014$). When FLI was used to define NAFLD, similar findings were observed (OR = 2.88 in subjects with NAFLD but without

Table 5. OR and 95% CIs of high probability of ASCVD according to the status of sarcopenia and FIB-4–defined significant liver fibrosis defined by different scores among subjects with NAFLD

Multivariate models	Sarcopenia (−) NAFLD with significant liver fibrosis (−)	Sarcopenia (+) NAFLD with significant liver fibrosis (−)	Sarcopenia (−) NAFLD with significant liver fibrosis (+)	Sarcopenia (+) NAFLD with significant liver fibrosis (+)
Model 1	1.00 (ref.)	1.10 0.78–1.55 $P = 0.579$	1.35 0.93–1.95 $P = 0.111$	1.71 1.13–2.59 $P = 0.011$
Model 2	1.00 (ref.)	1.29 0.90–1.84 $P = 0.164$	1.57 1.07–2.31 $P = 0.023$	1.91 1.25–2.91 $P = 0.003$
Model 3	1.00 (ref.)	1.53 0.98–2.39 $P = 0.063$	2.38 1.48–3.84 $P < 0.001$	3.56 2.11–6.02 $P < 0.001$

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, exercise, and current smoking.
Model 3: adjusted for age, sex, hypertension, diabetes, obesity, central obesity, HOMA-IR, CKD, hyper-LDL cholesterolaemia, and hypo-HDL cholesterolaemia.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; FIB-4, fibrosis-4 index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

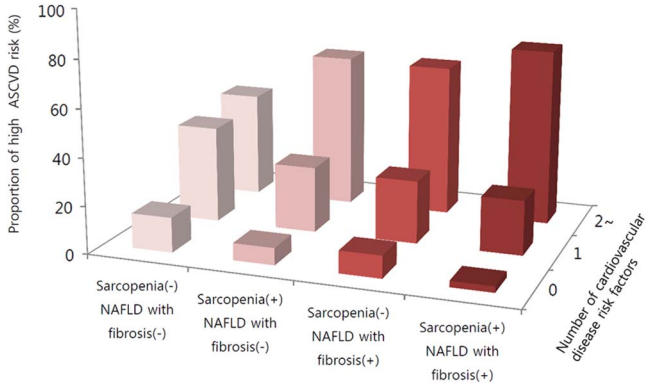

Figure 4. Proportion of subjects with CNS-defined NAFLD with individual ASCVD risk components according to FIB-4–defined significant liver fibrosis. Risk factors included hypertension, diabetes, hyper-LDL cholesterolaemia, central obesity, and CKD. The number of cardiovascular risk factors was significantly greater in subjects with sarcopenia with liver fibrosis than in subjects without sarcopenia without liver fibrosis (all P for trend < 0.001). ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CNS, comprehensive NAFLD score; FIB-4, fibrosis-4 index; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

sarcopenia, $P < 0.001$; and OR = 2.04 in subjects with both NAFLD and sarcopenia, $P = 0.012$).

Association of NAFLD, sarcopenia, and cardiometabolic/renal risk factors with high probability of ASCVD

The adjusted relative risks of CNS-defined NAFLD, the degree of fatty liver by CNS and FLI, sarcopenia, and other cardiometabolic/renal factors for high probability of ASCVD were analyzed in nonobese and obese subjects (Table 4). NAFLD modestly raised the risk for high probability of ASCVD, regardless of obesity (OR = 1.45 in nonobese subjects and OR = 1.72 in obese subjects; all $P < 0.05$), whereas the contribution of sarcopenia to risk of high probability of ASCVD was greater in nonobese subjects than in obese subjects (OR = 4.32 in nonobese subjects and OR = 2.33 in obese subjects; all $P < 0.001$). The degree of fatty liver by CNS and FLI also showed a significant positive association with the risk for high probability of ASCVD, irrespective of obesity (OR = 1.39–1.43 in nonobese subjects and OR = 1.60–1.67 in obese subjects; all $P < 0.05$). Other major risk factors such as hypertension, T2D, current smoking, and CKD had relatively higher ORs for risk for high probability of ASCVD compared with those of NAFLD and sarcopenia. Similar findings were observed when FLI was used to define NAFLD (data not shown).

Association between quartile-stratified ASCVD risk and significant liver fibrosis stratified by sarcopenia among subjects with NAFLD

Because fibrosis progression is significantly associated with an increased risk of liver-related events among subjects with NAFLD (2), we selected subjects with CNS-defined NAFLD for further statistical analysis (n = 2,236). FIB-4–defined significant liver fibrosis and sarcopenia additively increased the relative risk for high probability of ASCVD among subjects with CNS-defined NAFLD (OR = 13.94, 95% CI = 10.20–19.04) ($P < 0.05$) (Figure 3). When FLI was used to define NAFLD, similar findings were observed (data not shown).

Association between high probability of ASCVD and NAFLD with significant liver fibrosis/sarcopenia among subjects with NAFLD

The association between high probability of ASCVD and NAFLD with significant liver fibrosis/sarcopenia among subjects with NAFLD according to multistep adjustments is shown in Table 5. When CNS was used to define NAFLD and the relative risk for high probability of ASCVD was assessed after sufficient adjustment (model 3), sarcopenia alone did not raise the risk for high probability of ASCVD among subjects with NAFLD (OR = 1.53, $P = 0.063$). However, FIB-4–defined significant liver fibrosis and sarcopenia additively raised the OR for risk of high probability of ASCVD among subjects with NAFLD (OR = 2.38, $P < 0.001$ in subjects with significant liver fibrosis but without sarcopenia, and OR = 3.56, $P < 0.001$ in subjects with both significant liver fibrosis and sarcopenia). When 118 subjects with common malignancies in South Korea (39 stomach cancer, 5 colon cancer, 32 breast cancer, 37 cervical cancer, and 6 lung cancer) were further excluded, similar findings were obtained (see Table 2, Supplementary Digital Content 3, http://links.lww.com/AJG/B437).

Similarly, the proportion of subjects with 2 or more ASCVD risk components was greatly increased in subgroups with FIB-4–defined significant liver fibrosis (Figure 4), regardless of sarcopenia (P for trend < 0.001). When FLI was used to define NAFLD, similar findings were observed (data not shown).

Association between high probability of ASCVD and with significant liver fibrosis/sarcopenia in the general population

Based on subgroup analyses in subjects with NAFLD, we further investigated the association between high probability of ASCVD and NAFLD with significant liver fibrosis/sarcopenia in the general population according to multistep adjustments (models 1, 2, and 3) (Table 6). When CNS and FIB-4 were used to define NAFLD and significant liver fibrosis, respectively, and the relative risk for high probability of ASCVD was assessed after sufficient adjustment (model 3), the relative risks were highest in subjects with NAFLD with significant liver fibrosis compared with subjects with NAFLD, but without significant liver fibrosis or those without NAFLD, regardless of sarcopenia status (OR = 2.27, $P < 0.001$ in subjects without sarcopenia, and OR = 2.95, $P < 0.001$ in subjects with sarcopenia). In addition, subjects with sarcopenia, but without NAFLD (n = 664, OR = 2.36), and those with NAFLD with significant liver fibrosis, but without sarcopenia (n = 340, OR = 2.27), showed similar relative risk for high probability of ASCVD compared with those without NAFLD and sarcopenia (n = 4,286). When other models were used to define NAFLD, similar findings were observed (data not shown). When 118 subjects with common malignancies in South Korea (39 stomach cancer, 5 colon cancer, 32 breast cancer, 37 cervical cancer, and 6 lung cancer) were further excluded, similar findings were obtained (see Table 3, Supplementary Digital Content 3, http://links.lww.com/AJG/B437).

DISCUSSION

This study used nationwide, population-based, cross-sectional data to demonstrate a significant association between ASCVD and the presence of NAFLD and/or sarcopenia and significantly increased unadjusted risk of ASCVD in subjects with NAFLD and/or sarcopenia compared with the risk in those without

Table 6. ORs and 95% CIs for high probability of ASCVD according to CNS-defined NAFLD with or without FIB-4–defined significant liver fibrosis in subjects with sarcopenia and subjects without sarcopenia

	Sarcopenia (−)			Sarcopenia (+)		
Multivariate models	No NAFLD (n = 4,286)	NAFLD without significant liver fibrosis (n = 1,165)	NAFLD with significant liver fibrosis (n = 340)	No NAFLD (n = 664)	NAFLD without significant liver fibrosis (n = 463)	NAFLD with significant liver fibrosis (n = 273)
Model 1	1.00 (ref.)	3.00 2.29–3.92 $P < 0.001$	3.14 2.27–4.35 $P < 0.001$	2.29 1.75–3.00 $P < 0.001$	2.67 1.96–3.63 $P < 0.001$	3.67 2.57–5.26 $P < 0.001$
Model 2	1.00 (ref.)	2.97 2.25–3.92 $P < 0.001$	3.57 2.55–5.00 $P < 0.001$	2.46 1.86–3.25 $P < 0.001$	3.01 2.19–4.14 $P < 0.001$	3.88 2.70–5.59 $P < 0.001$
Model 3	1.00 (ref.)	1.41 0.96–2.09 $P = 0.080$	2.27 1.45–3.55 $P < 0.001$	2.36 1.70–3.26 $P < 0.001$	1.60 1.02–2.52 $P = 0.041$	2.95 1.81–4.83 $P < 0.001$

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, exercise, and current smoking.
Model 3: adjusted for age, sex, hypertension, diabetes, obesity, central obesity, HOMA-IR, CKD, hyper-LDL cholesterolaemia, and hypo-HDL cholesterolaemia.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CNS, comprehensive NAFLD score; FIB-4, fibrosis-4 index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

NAFLD and sarcopenia when subjects with metabolically unhealthy conditions (central obesity, obesity, hypertension, T2D, CKD, and dyslipidaemia) were selected. After appropriate extensive adjustment, we found an approximately 2-fold increased adjusted risk of ASCVD in patients with NAFLD and/or sarcopenia (OR 1.83–2.18 using CNS-defined NAFLD and 2.04–2.88 using FLI-defined NAFLD). Furthermore, when subjects with CNS-defined NAFLD were selected, the risk of ASCVD was highest in subjects who had both sarcopenia and NAFLD with significant liver fibrosis, followed by those with sarcopenia or NAFLD with significant liver fibrosis, and lowest in those without sarcopenia and NAFLD with significant liver fibrosis, even after appropriate adjustment. Although the mechanisms underpinning this association between ASCVD and NAFLD and/or sarcopenia in the general population and between ASCVD and NAFLD with significant liver fibrosis and/or sarcopenia in subjects with NAFLD could not be assessed, all these might indicate that sarcopenia, NAFLD, or NAFLD with liver fibrosis has detrimental effect on atherothrombotic risk, respectively or synergistically. Even after excluding subjects with the common malignancies in South Korea, similar findings were obtained.

The current study has several strengths. First, the selected cohort was large (n > 7,000) to ensure statistical reliability and to investigate the independent association between atherothrombotic risk and sarcopenia, NAFLD, or NAFLD with liver fibrosis. Furthermore, the proportion of sarcopenic subjects in the cohort (19.5%) was similar to that in previous Asian studies (33). This might indicate that subjects with sarcopenia in the current population-based cohort were selected appropriately and that our results may be applicable to most Asian populations, although validation is required for other ethnic groups. In addition, the prevalence of subjects with NAFLD (31.2%) was similar to that of other Asian countries (34). This suggests that our study population based on a nationwide representative cohort was selected in an appropriate manner and was representative of the real world.

Second, we tried to determine the impact of coexisting NAFLD with/without significant liver fibrosis and NAFLD on ASCVD risk in this study. It is well known that NAFLD is a significant risk factor for cardiovascular events (8). Sarcopenia may also affect cardiovascular outcomes via enhanced atrial stiffness, chronic inflammation, or physical inactivity, despite some contradictory reports (35–39). In addition, recent studies suggested the presence of a potential link between NAFLD and sarcopenia (20,21). However, to our knowledge, this is the first study to demonstrate independent associations of ASCVD risk with sarcopenia and NAFLD. In addition, the synergistic unfavorable influence of coexisting NAFLD and sarcopenia (approximately 10% in our population) on ASCVD risk was identified. Because subjects with NAFLD and sarcopenia are most likely to be older and have more vascular risk factors such as hypertension, T2D, metabolic syndrome, central obesity, insulin resistance, and dyslipidaemia, the relationships among sarcopenia, NAFLD, and the increased ASCVD risk might be easily explained. For example, compared with controls without sarcopenia and NAFLD, subjects with both had a 74-fold higher risk of obesity; this was significantly higher than that in subjects with NAFLD alone (34-fold) or those with sarcopenia alone (4-fold), although this association was somewhat attenuated after adjusting for potential confounders.

Third, one may argue that the influence of NAFLD on ASCVD might have been biased because most subjects with NAFLD might have had simple hepatic steatosis, which has an extremely favorable prognosis. Thus, we selected only subjects who were suspected of having NAFLD to determine whether the presence of significant liver fibrosis in subjects with NAFLD might have a significant association with ASCVD risk, based on the concept that liver fibrosis can be considered the sequela of the inflammatory process of NAFLD, and is the single most important factor as well as a clinically relevant issue that correlates with poor outcomes, such as progression to liver cirrhosis and the development of hepatocellular carcinoma in subjects with chronic liver diseases (8,40). In the subgroup with NAFLD, around 20% of

subjects had significant liver fibrosis, which showed an independent association with the increased ASCVD risk, together with sarcopenia. In addition, the concomitant presence of sarcopenia and significant liver fibrosis in this subgroup showed the highest ASCVD risk.

Last, variables related to demographic characteristics, laboratory findings, and metabolic factors were sufficiently adjusted. In addition, we showed that the unfavorable influence of NAFLD, sarcopenia, or NAFLD with significant liver fibrosis on the increased risk of ASCVD was similarly maintained in subgroups with metabolically unhealthy conditions. All these might reinforce the independent correlation between NAFLD/sarcopenia and ASCVD in the general population and between significant liver fibrosis/sarcopenia and ASCVD in subjects with NAFLD.

We are also aware of several issues that remained unresolved in the current study. First, although we used well-validated liver fibrosis (41,42) and steatosis prediction models (1,24), liver imaging and histological information was not available because of the high cost of ultrasonographic examination and the ethical concerns regarding screening of a large national population-based cohort. KNHANES participants who gave informed consent only had serum tests. To validate our results, we recruited 68 patients with NAFLD who underwent liver biopsy with available bioimpedance analysis results to assess skeletal muscle mass and laboratory test results to calculate ASCVD in our institute from January 2017 to July 2019. When liver fibrosis was stratified as F0-2 vs F3-4 and sarcopenic status was defined according to a cutoff of 1.74 for men and 1.25 for women, a stepwise increase in the ASCVD risk was again detected. This is similar to the results from the KNHANES data set (P for trend = 0.003, Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B435). In addition, because KNHANSE was based on questionnaire for cancer diagnosis, subjects with hepatocellular carcinoma were excluded, not based on ultrasound.

Second, because of the cross-sectional nature of the study design, we could not assess the longitudinal dynamic association between status changes in NAFLD and the amount of muscle mass and changing ASCVD risk. We were also unable to show the effects of therapeutic interventions, such as lifestyle modification, exercise, weight loss, medications, nutritional support, or protein supplements, on improvement of NAFLD, sarcopenia, and ASCVD risk. Nevertheless, our results showed the need for screening the population with NAFLD or sarcopenia to identify subjects with a high risk of ASCVD requiring intensive medical therapy. Actually, based on the US Preventive Services Task Force recommendations (43), our data indicated that over 50% of subjects with NAFLD and sarcopenia might need to start a statin or aspirin.

Third, we used a pooled cohort risk equation to assess ASCVD risk and did not examine the risk of real clinical events during follow-up. The 10-year ASCVD risk with primary prevention has been estimated by the ACC/AHA in their blood cholesterol guideline. However, because the equation for calculating ASCVD risk might have been overestimated in the Asian study population, our findings should be interpreted cautiously (44). In addition, although we excluded subjects with previous ASCVD history, it was still possible that subjects with unrecognized cerebral infarction or hidden coronary artery disease might have been included in this study because silent brain infarction or myocardial infarction can be detected in up to 40% of an aged population with vascular risk (45,46).

Fourth, the overall predictive value of FIB-4 for assessing the fibrotic burden in the liver of subjects with NAFLD might be suboptimal (47). In addition, because the proportion of FIB-4–defined significant liver fibrosis (FIB-4 $>$ 2.67) was small among subjects with CNS-defined NAFLD (n = 39), we could not analyze the influence of significant liver fibrosis. Nevertheless, the synergistic influence of sarcopenia and FIB-4–defined significant liver fibrosis on the ASCVD risk was maintained (see Figure 2, Supplementary Digital Content 2, http://links.lww.com/AJG/B436).

Finally, several serum markers, such as HbA1c, were available only for a small proportion of subjects (27.8% [621 of 2,236]). Thus, the incremental influence on the final results, not simply the presence of diabetes, could not be assessed. In addition, detailed information regarding antihypertensive and antidiabetic drugs was not available, preventing analysis of their influence. Furthermore, although we excluded subjects with known chronic liver diseases (such as viral hepatitis and alcoholic liver disease), subjects with other types of chronic liver diseases (such as Wilson disease, autoimmune liver disease, or primary biliary hepatopathy) might have been included in the study, which may have biased the final results.

In conclusion, this nationwide survey of a representative sample of Korean individuals demonstrated that NAFLD and sarcopenia are significantly associated with increased ASCVD risk in the general population and that NAFLD with significant liver fibrosis and sarcopenia are significantly associated with increased ASCVD risk in subjects with NAFLD, independent of other metabolic and clinical factors, indicating that physicians need to evaluate the status of liver and skeletal muscle to identify subjects with high cardiovascular risk and provide appropriate therapeutic interventions to reduce the risk of cardiovascular events by improving NAFLD and sarcopenia. Prospective, well-designed, longitudinal studies are warranted to elucidate the complex relationship between NAFLD, sarcopenia, and cardiovascular risk.

CONFLICTS OF INTEREST

Guarantor of the article: Yong-ho Lee, MD, PhD, Young Dae Kim, MD, PhD, and Seung Up Kim, MD, PhD.

Specific author contributions: Conception and design: E.H., Y.h.L., Y.D.K., and S.U.K. Development of methodology: E.H., Y.h.L., Y.D.K., and S.U.K. Analysis and interpretation of data: E.H., Y.h.L., Y.D.K., and S.U.K. Writing, review, and/or revision of the manuscript: E.H., Y.h.L., Y.D.K., B.K.K., J.Y.P., D.Y.K., S.H.A., B.W.L., E.S.K., B.S.C., K.H.H., H.S.N., J.H.H., and S.U.K. Administrative, technical, or material support: E.H., Y.h.L., Y.D.K., and S.U.K. Study supervision: Y.h.L., Y.D.S., and S.U.K.

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LIVER

Study Highlights

WHAT IS KNOWN

- ✓ CVD is significantly linked to severity of liver fibrosis, and it is the leading cause of mortality in patients with NAFLD.
- ✓ Sarcopenia is significantly associated with an increased risk of cardiovascular events or mortality in patients with metabolic phenotypes such as T2D or CKD.
- ✓ A strong relationship between NAFLD and sarcopenia in the general population suggests sarcopenia as a novel risk factor for NAFLD.

WHAT IS NEW HERE

- ✓ After appropriate extensive adjustment, we found an approximately 2-fold increased adjusted risk of ASCVD in subjects with NAFLD and/or sarcopenia compared with those without NAFLD.
- ✓ Among subjects with NAFLD selected, the risk of ASCVD was highest in subjects who had both sarcopenia and NAFLD with significant liver fibrosis, independent of other metabolic and clinical factors.
- ✓ NAFLD, sarcopenia, and cardiovascular risk are independently associated with each other.

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