Association between muscle strength and advanced fibrosis in non-alcoholic fatty liver disease: a Korean nationwide survey

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Abstract

Background We investigated the association between muscle strength and the prevalence of advanced fibrosis among individuals with non-alcoholic fatty liver disease (NAFLD) using a nationwide cross-sectional survey.

Methods Individuals, 20 to 79 years of age, from the Korean National Health and Nutrition Examination Surveys (KNHANES) from 2014 to 2016 were selected (\(N = 14\,861\)), with sample weights applied. Muscle strength was quantified as the handgrip strength divided by the body mass index (BMI); low muscle strength (LMS) was defined as the lowest quartile (Q\textsubscript{1}) of the handgrip strength/BMI for our sample population. NAFLD was defined as hepatic steatosis index \(>36\). Advanced fibrosis was defined as a fibrosis-4 index score \(\geq 1.30\) (\textit{Fibrosis-4}).

Results The mean age of the study population was 45.6 \(\pm\) 0.2 years, and 42.4\% were male. As muscle strength increased, the mean BMI and age decreased accordingly, and the proportions of diabetes, dyslipidaemia, hypertension, and obesity decreased significantly (\(P < 0.001\) for all). In a crude analysis, the LMS was associated with an increased prevalence of NAFLD (odds ratio [OR] 3.62, 95\% confidence interval [CI] 3.25–4.03, \(P < 0.001\)), which remained significant even after adjustment for age, sex, obesity, insulin resistance, diabetes, hypertension, dyslipidaemia, and high-sensitivity C-reactive protein (OR 1.66, 95\% CI 1.28–2.16, \(P < 0.001\)). In this logistic regression model, the prevalence of NAFLD decreased by 24\% with each quartile increment in muscle strength (OR 0.76, 95\% CI 0.68–0.85, \(P < 0.001\)). Among individuals with NAFLD (\(n = 2092\)), LMS was significantly associated with the presence of advanced fibrosis (\textit{Fibrosis-4}) independently of age, sex, obesity, diabetes, hypertension, dyslipidaemia, and high-sensitivity C-reactive protein (OR 1.66, 95\% CI 1.01–2.49, \(P = 0.015\)), which lost its statistical significance after additional adjustment for insulin resistance.

Conclusions Low muscle strength is independently associated with NAFLD. The significant association between LMS and advanced fibrosis in NAFLD may be mediated through insulin resistance.

Keywords Hepatic steatosis; Hepatic fibrosis; Muscle strength; Sarcopenia; Insulin resistance
Introduction

Sarcopenia is defined as a progressive decrease in muscle mass and function.\textsuperscript{3} Sarcopenia increases the risk for metabolic disease, physical disability, poor quality of life, and mortality.\textsuperscript{2–4} Recently, an independent association between appendicular skeletal muscle mass and histological severity of non-alcoholic fatty liver disease (NAFLD) has been reported.\textsuperscript{5} Insulin resistance (IR), an important pathogenic mechanism of NAFLD,\textsuperscript{6} also increases the risk of sarcopenia via reduction of protein synthesis and increased protein breakdown.\textsuperscript{7,8}

To date, the association between NAFLD and sarcopenia has been principally evaluated from a perspective of low skeletal muscle mass rather than the quality of muscle function.\textsuperscript{5,7} However, recent studies have demonstrated that muscle strength is more important than muscle mass in predicting health outcomes in older adults.\textsuperscript{10,11} Yet there have been few population-based studies on the association between muscle strength and NAFLD.

In the current study, we investigated the association between muscle strength and the prevalence of NAFLD through an analysis of a nationwide representative cross-sectional survey dataset. In addition, the association between muscle strength and advanced fibrosis among individuals with NAFLD was also analysed.

Materials and methods

Study participants

We performed a retrospective analysis of the 2014 to 2016 data from the Korean National Health and Nutrition Examination Surveys (KNHANES). The KNHANES involves a nationwide cross-sectional health examination and survey performed by the Korea Centers for Disease Control and Prevention in the Ministry of Health and Welfare, with details having been previously reported.\textsuperscript{9} Briefly, the KNHANES recruit participants using a stratified multistage probability-based sampling design; sampling weights are assigned to each respondent to ensure that the results are representative of the whole Korean population.

Among a total of 23 080 participants enrolled in the KNHANES between 2014 and 2016, we included 14 861 individuals, 20 to 79 years old, whose handgrip strength (HGS) data were available. The exclusion criteria were as follows: alcohol consumption >210 g/week for men and >140 g/week for women,\textsuperscript{12} and positive serological markers for hepatitis B or C virus. After screening for the exclusion criteria, 13 502 individuals were included in our analysis (Figure 1). The use of the KNHANES 2014 data was approved by the institutional review board (IRB) of the Korea Centers for Disease Control and Prevention (IRB No. 2013-12EXP-03-5C). IRB approval was not required for use of the KNHANES data between 2015 and 2016 under the Bioethics Act. Our study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Metabolic parameters measurement

Diabetes mellitus (DM) was defined as an 8 h fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL) or glycated haemoglobin level ≥48 mmol/mol (6.5%), or use of anti-diabetic medication including insulin.\textsuperscript{12} Hypertension (HTN) was defined as a systolic blood pressure (BP) ≥140 mmHg, or diastolic BP ≥90 mmHg, or taking antihypertensive medications; dyslipidaemia (DL) was defined as non-high-density lipoprotein cholesterol ≥190 mg/dL or taking lipid-lowering medication.\textsuperscript{14} Obesity and abdominal obesity were defined as a body mass index (BMI) ≥25 kg/m\textsuperscript{2} and waist circumference ≥90 and ≥85 cm in men and women, respectively.\textsuperscript{16} Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as [fasting glucose (mg/dL) × fasting insulin (uU/mL)]/405; IR was defined as HOMA-IR ≥2.5.\textsuperscript{17} Elevated high-sensitivity C-reactive protein (hs-CRP) was defined as ≥1 mg/L.\textsuperscript{18}

Assessment of muscle strength

Muscle strength was quantified by the HGS, assessed using a digital grip strength dynamometer (TKK 5401; Takei, Tokyo, Japan), as previously reported.\textsuperscript{19} Briefly, HGS was measured with the individual standing upright, with the elbow in full extension. Participants were instructed to squeeze the dynamometer as strongly as possible, for at least 3 s. Three measures were obtained, with a 1 min rest period between each trial. Following the previous studies, muscle strength was calculated from mean HGS of a dominant arm adjusted by BMI: HGS/BMI.\textsuperscript{20,21} The quartiles of muscle strength were calculated in each gender, with Q\textsubscript{1} and Q\textsubscript{4} being the lowest and highest quartiles of HGS/BMI, respectively. The Q\textsubscript{2} was defined as the group of subjects with low muscle strength (LMS).

Assessment of non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease was defined using previously well-validated fatty liver prediction models: the hepatic steatosis index (HSI),\textsuperscript{22} calculated as 8 × alanine aminotransferase (ALT)/aspartate aminotransferase (AST) + 2, if diabetes; +2 if female). NAFLD was defined as HSI ≥36.\textsuperscript{22} The sensitivity and specificity of HSI for prediction of NAFLD have been reported to be 86% and 66%, respectively, in Caucasians\textsuperscript{23} and 93.1% and 92.4%, respectively, in the Korean population.\textsuperscript{22}
Assessment of advanced fibrosis in non-alcoholic fatty liver disease

Among individuals with NAFLD, as defined by the HSI, advanced fibrosis was assessed using the following prediction models: (i) fibrosis-4 index (FIB-4)\(^{24}\) = age (years) \(\times\) AST [U/L]/(platelet [10\(^9\)/L] \(\times\) ALT [U/L])\(^{1/2}\) and (ii) BARD score\(^{25}\) = the sum of the following scores (BMI \(\geq 28\) = 1 point; AST/ALT ratio \(\geq 0.8\) = 2 points; diabetes = 1 point). Advanced fibrosis was defined as either a FIB-4 score \(\geq 1.30\) (Fibrosis\(_{\text{FIB-4}}\))\(^{26}\) or a BARD score \(\geq 2\) (Fibrosis\(_{\text{BARD}}\))\(^{25}\). As the diagnostic performance of FIB-4 for advanced fibrosis is un acceptably low in patients aged \(>65\) or \(<35\) years\(^{27}\), only subjects aged 35–65 years (\(n = 2092\)) were included in analysis for advanced fibrosis.

Statistical analyses

Variables are reported as the mean ± standard error (SE) or the prevalence ± SE (%). Linear regression or logistic linear regression analysis was used to compare the clinical variables according to muscle strength, adjusted for age, sex, obesity, IR, and

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**Figure 1** Flow diagram of participants for the study. Among a total of 23 080 participants in the Korean National Health and Nutrition Examination Surveys (KNHANES) 2014–2016, 13 502 individuals were included in our analysis. Individuals with non-alcoholic fatty liver disease, defined by hepatic steatosis index, aged 35–65 years (\(n = 2092\)), were analysed for advanced fibrosis. HBV, hepatitis B virus; HCV, hepatitis C virus; HGS, handgrip strength.
other metabolic parameters. Sampling weights were applied to all analyses. Statistical analyses were performed using IBM SPSS Statistics (Version 22.0, IBM Corp., Armonk, NY, USA), with a P value < 0.05 considered significant for all tests.

Results

Clinical characteristics according to muscle strength

The mean age of the study population was 45.6 ± 0.2 years, with 42.4% of the sample being male. Mean HGS was 23.7 kg (standard error [SE], 0.2 kg), 29.7 kg (SE, 0.2 kg), 33.4 kg (SE, 0.2 kg), and 37.5 kg (SE, 0.2 kg), and muscle strength (HGS/BMI) was 0.90 (SE, 0.0), 1.19 (SE, 0.0), 1.40 (SE, 0.0), and 1.71 (SE, 0.0) in the Q1, Q2, Q3, and Q4, respectively (P < 0.001; Table 1). As muscle strength increased, mean BMI and mean age were accordingly decreased (P < 0.001 in both; Table 1). Waist circumference, systolic BP, ALT, AST, triglycerides, glycated haemoglobin, hs-CRP level, and HOMA-IR also significantly decreased in order from the Q1 towards the Q4 (P < 0.001 in all; Table 1). As muscle strength increased, the proportions of cardio-metabolic disorders including DM, DL, HTN, and obesity decreased significantly (P < 0.001 in all; Table 1).

| Table 1 Clinical characteristics according to muscle strength quartiles |
|-----------------------------|----------------|----------------|----------------|----------------|
|                             | Total           | Q1             | Q2             | Q3             | Q4             |
| Unweighted N                | 13 502          | 3193           | 3354           | 3456           | 3499           |
| HGS (kg)b                   | 31.8 ± 0.1      | 23.7 ± 0.2     | 29.7 ± 0.2     | 33.4 ± 0.2     | 37.5 ± 0.2     |
| HGS/BMI                     | 1.35 ± 0.0      | 0.90 ± 0.0     | 1.19 ± 0.0     | 1.40 ± 0.0     | 1.71 ± 0.0     |
| Age (years)                 | 45.6 ± 0.2      | 54.1 ± 0.5     | 48.2 ± 0.4     | 43.7 ± 0.3     | 39.7 ± 0.3     |
| BMI (kg/m²)                 | 23.8 ± 0.0      | 26.2 ± 0.1     | 24.8 ± 0.1     | 23.6 ± 0.1     | 21.8 ± 0.1     |
| Waist circumference (cm)    | 82.0 ± 0.1      | 88.4 ± 0.2     | 84.4 ± 0.2     | 81.2 ± 0.2     | 76.7 ± 0.2     |
| Systolic BP (mmHg)          | 116.5 ± 0.2     | 121.9 ± 0.4    | 118.6 ± 0.3    | 115.4 ± 0.3    | 112.3 ± 0.3    |
| Diastolic BP (mmHg)         | 75.3 ± 0.1      | 75.5 ± 0.2     | 76.1 ± 0.2     | 75.6 ± 0.2     | 74.3 ± 0.2     |
| AST (IU/L)                  | 22.0 ± 0.2      | 24.4 ± 0.3     | 23.0 ± 0.3     | 21.4 ± 0.2     | 20.2 ± 0.2     |
| ALT (IU/L)                  | 22.0 ± 0.2      | 26.5 ± 0.6     | 24.2 ± 0.5     | 21.2 ± 0.3     | 18.2 ± 0.2     |
| Total cholesterol (mg/dL)   | 190.6 ± 0.4     | 192.1 ± 0.9    | 193.5 ± 0.8    | 191.3 ± 0.7    | 186.7 ± 0.7    |
| HDL (mg/dL)                 | 51.0 ± 0.1      | 47.6 ± 0.2     | 45.7 ± 0.3     | 51.0 ± 0.2     | 54.2 ± 0.2     |
| TG (mg/dL)                  | 138.2 ± 1.4     | 153.1 ± 2.6    | 150.5 ± 2.7    | 140.9 ± 2.6    | 117.0 ± 2.8    |
| LDL (mg/dL)                 | 116.0 ± 0.5     | 117.9 ± 1.0    | 118.4 ± 1.1    | 116.5 ± 0.9    | 111.8 ± 1.0    |
| HbA1c (%)                   | 5.6 ± 0.0       | 5.9 ± 0.0      | 5.7 ± 0.0      | 5.6 ± 0.0      | 5.5 ± 0.0      |
| HOMA-IR                     | 2.2 ± 0.0       | 3.2 ± 0.2      | 2.5 ± 0.1      | 2.0 ± 0.1      | 1.5 ± 0.0      |
| hs-CRP (mg/L)               | 1.2 ± 0.0       | 1.7 ± 0.1      | 1.3 ± 0.1      | 1.1 ± 0.0      | 0.8 ± 0.0      |
| Diabetes mellitus (%)       | 10.7 ± 0.3      | 21.9 ± 0.9     | 12.8 ± 0.7     | 8.7 ± 0.6      | 3.6 ± 0.3      |
| Dyslipidaemia (%)           | 16.5 ± 0.4      | 23.0 ± 1.0     | 20.9 ± 0.8     | 15.8 ± 0.8     | 9.6 ± 0.6      |
| Hypertension (%)            | 24.1 ± 0.5      | 41.2 ± 1.2     | 29.6 ± 0.9     | 19.9 ± 0.9     | 12.4 ± 0.6     |
| Obesity (%)                 | 33.6 ± 0.5      | 59.9 ± 1.1     | 44.8 ± 1.1     | 29.3 ± 0.9     | 11.6 ± 0.7     |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HGS, handgrip strength; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Q, quartile; Q1, the lowest quartile; Q4, the highest quartile; TG, triglycerides.

Muscle strength was calculated from mean HGS divided by BMI. Values are presented as mean or prevalence ± standard error.

*From logistic and linear regression without any adjustment.

Handgrip strength of dominant arm.

Association between non-alcoholic fatty liver disease and low muscle strength

The prevalence of NAFLD was 45.0% (SE, 1.1%), 30.5% (SE, 1.0%), 20.3% (SE, 0.9%), and 7.5% (SE 0.5%) in the Q1, Q2, Q3, and Q4, respectively (P for trend < 0.001; Figure 2A); LMS, defined as Q1, was associated with an increased prevalence of NAFLD (odds ratio [OR] 3.62, 95% confidence interval [CI] 3.25–4.03, P < 0.001). After adjustment for age, sex, obesity, DM, HTN, DL, and elevated hs-CRP level, the association between LMS and NAFLD remained significant (OR 1.92, 95% CI 1.61–2.29, P < 0.001; Model 3 in Table 2). Even after additional adjustment for IR, LMS was associated with 1.66 times higher prevalence of NAFLD (OR 1.66, 95% CI 1.28–2.16, P < 0.001; Model 4 in Table 2).

Given a strong association between age and muscle strength, the prevalence of NAFLD according to muscle strength was investigated using a 10 year age stratification (Supporting Information, Table S1). We compared the prevalence of NAFLD in each quartile of muscle strength across each 10 year age strata in our sample group: 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years. The prevalence of NAFLD in the LMS group (Q1) was significantly higher in all age strata groups than in the other groups (Q2, Q3, and Q4; P < 0.001 in all) (Figure 2B).
The quantitative association between muscle strength and non-alcoholic fatty liver disease

A dose–response relationship was observed between muscle strength and NAFLD (Figure 2A); the prevalence of NAFLD significantly decreased as the quartiles of muscle strength increased, compared with that in the Q₁ (Table 3; \( P < 0.001 \) in all quartiles). For every 1 quartile (1Q) increment in muscle strength, the prevalence of NAFLD decreased by 51% (OR per 1Q increment 0.49, 95% CI 0.47–0.51, \( P < 0.001 \)). The

The quantitative association between muscle strength and non-alcoholic fatty liver disease

Figure 2 Prevalence of non-alcoholic fatty liver disease (NAFLD) according to muscle strength. (A) The prevalence of NAFLD according to muscle strength quartiles in the entire study population. (B) The prevalence of NAFLD in 10 year age strata according to the presence of low muscle strength. *Significantly lower compared with the Q₁ (\( P < 0.05 \)). †Significantly higher compared with the rest of the groups (Q₂, Q₃, and Q₄).
prevalence of NAFLD was significantly lower even in the Q4 group (i.e., the second lowest muscle strength group) compared with the Q1 group (OR for NAFLD 0.54, 95% CI 0.47–0.61, P < 0.001). After adjustment for age, sex, obesity, DM, HTN, DL, elevated hs-CRP level, and IR, this quantitative association between muscle strength and the prevalence of NAFLD remained significant (Model 4 in Table 3). In Model 4, the prevalence of NAFLD decreased by 24% per 1Q increment in muscle strength (OR per 1Q increment 0.76, 95% CI 0.68–0.85, P < 0.001).

### Association between muscle strength and advanced fibrosis

To investigate the association between muscle strength and advanced fibrosis, only individuals with NAFLD were selected (n = 2092). For these patients with NAFLD, both FIB-4 and BARD scores were calculated to detect advanced fibrosis. The prevalence of advanced fibrosis in each quartile (Q1–Q4) showed a decreasing trend as muscle strength increased (Figure 3): FibrosisFIB4, 18.0% (SE 1.6%), 11.2% (SE 1.4%), 8.0% (SE, 1.4%), and 2.6% (SE, 1.0%) (P < 0.001); FibrosisBARD, 63.9% (SE, 2.3%), 50.3% (SE, 2.4%), 42.4% (SE, 2.6%), and 29.7% (SE, 4.6%) (P < 0.001).

Low muscle strength was found to be significantly associated with an increased risk of advanced fibrosis (FibrosisFIB4, OR 2.29, 95% CI 1.68–3.13, P < 0.001; FibrosisBARD, OR 2.22, 95% CI 1.76–2.81, P < 0.001), which remained statistically significant after adjustment for age, sex, and obesity (FibrosisFIB4, OR 1.50, 95% CI 1.06–2.12, P = 0.023; FibrosisBARD, OR 1.57, 95% CI 1.21–2.04, P = 0.001; Model 4 in Table 4). Additional adjustment for DM, HTN, DL, and elevated hs-CRP level did not attenuate the significant association between LMS and advanced fibrosis (FibrosisFIB4, OR 1.66, 95% CI 1.01–2.49, P = 0.015; FibrosisBARD, OR 1.81, 95% CI 1.30–2.51, P < 0.001; Model 3 in Table 4). However, adding IR to multivariable-adjusted analysis weakened the association between LMS and advanced fibrosis; statistical significance was maintained for FibrosisBARD but not for FibrosisFIB4 (Model 4 in Table 4).

In the current study, HOMA-IR was available only in 671 subjects with NAFLD. In a stratified analysis according to IR, the association between LMS and FibrosisFIB4 was more prominent in subjects with HOMA-IR <x003C; 2.5 (unweighted N = 279; OR 3.05, 95% CI 1.27–7.30, P = 0.013) than in those with HOMA-IR ≥ 2.5 (unweighted N = 392, OR 1.84, 95% CI 0.92–3.68, P = 0.085), and the same trend held true for FibrosisBARD (Table 5). Stratified analyses according to abdominal obesity, obesity, sex, or age did not reveal any differences in the association between LMS and advanced fibrosis (Table 5).
Discussion

In the current study, muscle strength was inversely associated with the prevalence of NAFLD, irrespective of age. LMS was an independent risk factor for NAFLD regardless of age, sex, obesity, DM, HTN, DL, hs-CRP level, and IR with the odds of NAFLD among individuals with LMS reaching 1.66. Moreover, there was a dose–response relationship between muscle strength and the prevalence of NAFLD; even individuals in the second lowest muscle strength group (Q$_2$) had a significantly lower risk of NAFLD than those with LMS. Among those with NAFLD, LMS showed a significant association with advanced fibrosis independent of age, sex, and other metabolic derangements. However, additional adjustment for IR attenuated this association; LMS was not associated with FibrosisFIB4 after adjustment for IR.

Sarcopenia is a syndrome characterized by loss of skeletal muscle mass and strength with an increased risk of adverse outcomes. Among subjects with non-alcoholic fatty liver disease, low muscle strength was defined as the lowest quartile (Q$_1$) of muscle strength (handgrip strength/body mass index).

Table 4 Risk of advanced fibrosis stratified by low muscle strength in subjects with non-alcoholic fatty liver disease

|                | Fibrosis$_{FIB4}$ | Fibrosis$_{BARD}$ |
|----------------|------------------|------------------|
|                | OR    | 95% CI | P    | OR    | 95% CI | P    |
| Unadjusted     | 2.29  | 1.68–3.13 | <0.001 | 2.22  | 1.76–2.81 | <0.001 |
| Model 1        | 1.56  | 1.11–2.20 | 0.011 | 1.90  | 1.48–2.44 | <0.001 |
| Model 2        | 1.50  | 1.06–2.12 | 0.023 | 1.57  | 1.21–2.04 | 0.001 |
| Model 3        | 1.66  | 1.01–2.49 | 0.015 | 1.81  | 1.30–2.51 | <0.001 |
| Model 4        | 1.35  | 0.75–2.45 | 0.314 | 1.68  | 1.07–2.62 | 0.024 |

CI, confidence interval; Fibrosis$_{FIB4}$, BARD score ≥2; Fibrosis$_{FIB4}$, fibrosis-4 index >1.30; OR, odds ratio.

Low muscle strength was defined as the lowest quartile of muscle strength (handgrip strength/body mass index). Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, and obesity; Model 3, with additional adjustment for the presence of diabetes mellitus, hypertension, dyslipidaemia, and elevated high-sensitivity C-reactive protein in addition to Model 2; Model 4, with additional adjustment for insulin resistance (Homeostatic Model Assessment of Insulin Resistance ≥2.5) in addition to Model 3.

Table 5 Stratified association between advanced fibrosis and low muscle strength in subjects with non-alcoholic fatty liver disease

|                | Fibrosis$_{FIB4}$ | Fibrosis$_{BARD}$ |
|----------------|------------------|------------------|
|                | OR    | 95% CI | P    | OR    | 95% CI | P    |
| HOMA-IR        |       |        |      |       |        |      |
| <2.5           | 3.05  | 1.27–7.30 | 0.013 | 4.21  | 2.04–8.70 | <0.001 |
| ≥2.5           | 1.84  | 0.92–3.68 | 0.085 | 1.71  | 1.09–2.67 | 0.019 |
| Abdominal obesity |     |        |      |       |        |      |
| No             | 1.95  | 0.98–3.87 | 0.057 | 2.17  | 1.31–3.60 | 0.003 |
| Yes            | 2.42  | 1.72–3.41 | <0.001 | 1.85  | 1.41–2.42 | <0.001 |
| Obesity        |       |        |      |       |        |      |
| No             | 2.42  | 0.86–6.81 | 0.092 | 2.40  | 1.01–5.43 | 0.036 |
| Yes            | 2.20  | 1.58–3.06 | <0.001 | 1.90  | 1.49–2.43 | <0.001 |
| Sex            |       |        |      |       |        |      |
| Male           | 2.43  | 1.51–3.90 | <0.001 | 1.74  | 1.26–2.41 | 0.001 |
| Female         | 2.05  | 1.35–3.10 | 0.001 | 2.73  | 1.88–3.97 | <0.001 |
| Age (years)    |       |        |      |       |        |      |
| <50            | 2.58  | 1.12–5.93 | 0.026 | 1.94  | 1.36–2.76 | <0.001 |
| ≥50            | 1.60  | 1.12–2.28 | 0.010 | 2.11  | 1.52–2.94 | <0.001 |

CI, confidence interval; Fibrosis$_{FIB4}$, BARD score ≥2; Fibrosis$_{FIB4}$, fibrosis-4 index >1.30; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; OR, odds ratio.

Low muscle strength was defined as the lowest quartile of muscle strength (handgrip strength/body mass index). Each stratified analysis was performed using logistic regression without adjustment.
metabolic outcomes.\textsuperscript{28} Recently, LMS has become more widely recognized as a principal determinant of sarcopenia than low muscle mass, based on recent evidence that muscle strength may be more important to predict fracture, falling,\textsuperscript{29} cardiovascular disease, and all-cause mortality.\textsuperscript{30} The most updated guideline from the European Working Group on Sarcopenia in Older People\textsuperscript{31} defined LMS as the key characteristic of sarcopenia. Diagnosis of sarcopenia can be made when LMS coexists with low muscle quantity, and the European Working Group on Sarcopenia in Older People recommends grip strength for a proxy measure of whole-body strength. Grip strength measurement is also a quick and easy-to-obtain test and has been well validated as a tool to predict all causes of death.\textsuperscript{30}

Several mechanisms may influence an inverse association between sarcopenia and NAFLD, including IR, inflammation, myokines, and decreased physical activity.\textsuperscript{28} In the current study, HOMA-IR and hs-CRP levels, as well as the prevalence of NAFLD, significantly increased as muscle strength decreased. Although obesity has been considered as the main pathophysiological factor leading to metabolic syndrome, including NAFLD, non-obese individuals may also develop NAFLD.\textsuperscript{32} Skeletal muscle is the primary target organ of insulin-mediated glucose disposal, and therefore, sarcopenia itself, independent of obesity, may aggravate IR.\textsuperscript{33} In the current study, the significant association between LMS and Fibrosis\textsuperscript{Fib} lost its statistical significance after adjustment for IR, implicating that IR plays an important role in the relationship between LMS and advanced fibrosis in NAFLD. Interestingly, the stratified analysis showed that there was an association between LMS and advanced fibrosis in patients without IR compared with those with IR. Although IR plays a main pathogenic role in developing both NAFLD\textsuperscript{34,35} and sarcopenia,\textsuperscript{33} the latter may increase the severity of NAFLD through IR-independent mechanisms such as systemic inflammation.\textsuperscript{36,37}

Although several pharmacotherapeutic agents, such as vitamin E,\textsuperscript{38} thiazolidinedione,\textsuperscript{39} glucagon like peptide-1 analogues,\textsuperscript{40} and farnesoid X receptor agonists,\textsuperscript{41} have shown positive results on the treatment of non-alcoholic steatohepatitis, currently, there are no approved medications for NAFLD. The mainstay treatment is lifestyle intervention, focusing on weight loss. However, the achievement of the treatment goal (viz. a weight reduction of $>$10% of body weight)\textsuperscript{42} to regress fibrosis is difficult to obtain for most patients with NAFLD. Considering the paucity in the effective treatment for NAFLD and the substantial NAFLD-related morbidities, resistance training can be a promising treatment strategy against non-alcoholic steatohepatitis and advanced fibrosis. Resistance training has been shown to improve hepatic steatosis\textsuperscript{43,44} and inflammation\textsuperscript{45} in patients with NAFLD, independently of weight loss. Resistance training may increase glycolysis and improve insulin sensitivity through hypertrophy of type II muscle fibres,\textsuperscript{46} increasing glucose transporter 4 expression,\textsuperscript{37} up-regulation of AMP-activated protein kinase and caveolins in type II muscle fibres,\textsuperscript{48} and increasing myokines that are beneficial to hepatic steatosis.\textsuperscript{39,50} Irisin has been reported to have a protective effect on hepatic steatosis,\textsuperscript{50} and its level significantly increased after 8 weeks of initiating exercise in the resistance training group compared with that in the aerobic exercise group.\textsuperscript{39}

There are several limitations in our study. First, data from liver imaging, such as ultrasonography and magnetic resonance imaging, as well as histological information, were not available in the current, population-based study. Because only liver biopsy can distinguish steatohepatitis from simple steatosis, liver biopsy is considered a gold standard method but is hard to perform in primary centres due to its invasiveness and expensiveness. In addition, only a relatively small number of NAFLD subjects (671/2092, 32%) were subjected to HOMA-IR tests, which might account for the lack of statistical significance in the association between LMS and advanced fibrosis adjusted for IR. Second, because of the cross-sectional nature of the current study, causality cannot be determined between LMS and incident NAFLD or advanced fibrosis. Therefore, further prospective longitudinal cohort studies should be conducted to validate whether LMS is the real culprit of NAFLD and advanced fibrosis. Finally, because of insufficient muscle mass data in the current KNHANES analysis, we could not confirm whether the association between LMS and NAFLD persists independently of muscle mass. Although a previous study investigated the association between muscle mass and liver fibrosis using the KNHANES data between 2008 and 2011,\textsuperscript{9} it measured only muscle mass using dual-energy X-ray absorptiometry but not muscle strength. On the contrary, we used the KNHANES data between 2014 and 2016, which measured sarcopenia through the other way.

Collectively, we demonstrated the association between LMS and NAFLD or advanced fibrosis from the nationwide survey representing Korean population. LMS was significantly associated with an increased prevalence of NAFLD independently of age and BMI and was also closely associated with increased IR and higher prevalence of metabolic diseases. The association between LMS and advanced fibrosis in NAFLD subjects was found to be independent of metabolic diseases, such as DM, DL, and obesity, which seemed to be mediated through IR. Considering the cross-sectional nature of the current study, further investigations using a large-scale, histologically confirmed NAFLD cohort are warranted to draw a definite conclusion on the association between LMS and advanced fibrosis in NAFLD. Given that a substantial number of NAFLD subjects are non-obese and there has been no approved pharmacotherapy, our study suggests the therapeutic role of resistance training, especially in lean subjects with NAFLD.
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Author contributions

S.K. and B.K.K. designed the study and collected and analysed the data. S.K., M.K.M., W.K., and B.K.K. interpreted the data and wrote the manuscript. W.K. and B.K.K. critically reviewed and approved the final version of the manuscript.

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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Prevalence of nonalcoholic fatty liver disease according to muscle strength quartiles in 10-year age strata

Conflict of interest

None declared.

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