

# Sarcopenia and risk of nonalcoholic fatty liver disease: A meta-analysis

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## Abstract

**Background/Aim:** The association between sarcopenia and nonalcoholic fatty liver disease (NAFLD) has been suggested by recent epidemiological studies, although the results have been inconsistent. This meta-analysis was conducted to summarize all available data and estimate the risk of NAFLD among patients with sarcopenia.

**Materials and Methods:** A comprehensive literature review was conducted using MEDLINE and EMBASE databases through November 2016 to identify all studies that compared the risk of NAFLD among patients with sarcopenia versus those without sarcopenia. Effect estimates from each study were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird.

**Results:** Five cross-sectional studies with 27,804 participants met the eligibility criteria and were included in the meta-analysis. The risk of NAFLD in patients with sarcopenia was significantly higher than those without sarcopenia with the pooled odds ratio of 1.54 (95% confidence interval, 1.05–2.26). The statistical heterogeneity was high with an  $I^2$  of 83%.

**Conclusions:** A significantly increased risk of NAFLD among patients with sarcopenia was observed in this study.

**Keywords:** Low muscle mass, meta-analysis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, sarcopenia

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## INTRODUCTION

Sarcopenia is a condition characterized by loss of muscle mass, power, strength, and performance.<sup>[1,2]</sup> Low muscle mass is defined as a decrease in appendicular muscle mass of two standard deviations below the mean for healthy adults.<sup>[3]</sup> An epidemiologic study estimated that sarcopenia may affect up to 57% of men and 60% of women over the

age of 80 years.<sup>[4]</sup> Sarcopenia is associated with increased mortality, functional impairment, disability, and fall.<sup>[5]</sup> The etiology of sarcopenia is usually multifactorial in nature, including chronic inflammation, insulin resistance, nutritional deficiencies, and endocrine abnormality.<sup>[5]</sup>

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by abnormal fat accumulation in the liver

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without a history of significant alcohol consumption. It has been increasingly known as the liver manifestation of metabolic syndrome.<sup>[6]</sup> Prevalence of NAFLD is increasing worldwide as a result of the obesity epidemic.<sup>[6,7]</sup> Risk factors of NAFLD include metabolic syndrome components, hyperuricemia, lack of sleep, and sedentary lifestyle/physical inactivity.<sup>[8-11]</sup>

Interestingly, NAFLD and sarcopenia share several abnormal pathophysiologic processes such as insulin resistance and chronic inflammation. In fact, previous epidemiologic studies have suggested an association between sarcopenia and the development of NAFLD even though the results were inconsistent.<sup>[12-18]</sup> This systematic review and meta-analysis was conducted to summarize all available evidence with the aim to better characterize this relationship.

## MATERIALS AND METHODS

### Information sources and search strategy

A systematic literature search was conducted using EMBASE and MEDLINE databases from inception to November 2016 to identify all original studies that investigated the association between sarcopenia and NAFLD. The systematic literature review was independently conducted by three investigators (K.W., P.P., and P.U.) using the search strategy that included the terms for “sarcopenia” and “nonalcoholic fatty liver disease,” as described in online supplementary data 1. A manual search for additional potentially relevant studies using references of the included articles was also performed. No language limitation was applied. This study was conducted in accordance with the PRISMA (Preferred reporting Items for Systematic Reviews and Meta-Analysis) statement which is provided as online supplementary data 2.

### Selection criteria

Eligible studies were case-control, cross-sectional, or cohort studies that investigated the association between sarcopenia and NAFLD. They had to provide the effect estimates [odds ratios (OR), relative risks (RR), hazard ratios (HR), or standardized incidence ratio (SIR)] with 95% confidence intervals (CI). Inclusion was not restricted by study size. When more than one article using the same database/cohort was available, the study with the most comprehensive data/analyses was included.

Retrieved articles were independently reviewed for their eligibility by the same three investigators. Discrepancy was resolved by conference with all investigators. Newcastle–Ottawa quality assessment scale was used to

appraise the quality of study in three areas including the recruitment of cases and controls, the comparability between the two groups, and the ascertainment of the outcome of interest for cohort study and the exposure for case-control study.<sup>[19]</sup> The modified Newcastle–Ottawa scale, as described by Herzog *et al.*, was used for this cross-sectional study.<sup>[20]</sup>

### Data abstraction

A structured data collection form was used to extract the following data from each study: title of the study, publication year, name of the first author, year of the study, country where the study was conducted, number of participants, demographic data of participants, definition of sarcopenia, methods used to identify and verify sarcopenia and NAFLD, adjusted effect estimates with 95% CI, and covariates that were adjusted in the multivariable analysis.

To ensure accuracy, this data extraction process was independently performed by two investigators (K.W. and P.P.) and was reviewed by the senior investigator (P.U.).

### Statistical analysis

Data analysis was performed using the Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Adjusted point estimates from each study were combined by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study in the pooled analysis based on its variance.<sup>[21]</sup> As the outcome interest was relatively uncommon, we planned to use RR and HR of cohort study as an estimate for OR to calculate the pooled effect estimates with OR of case-control study and cross-sectional study. In light of the high likelihood of between-study variance because of different study designs, populations, and definition of hyperuricemia, random-effect model was used. Cochran's Q-test and  $I^2$  statistic were used to determine the between-study heterogeneity. A value of  $I^2$  of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity.<sup>[22]</sup>

## RESULTS

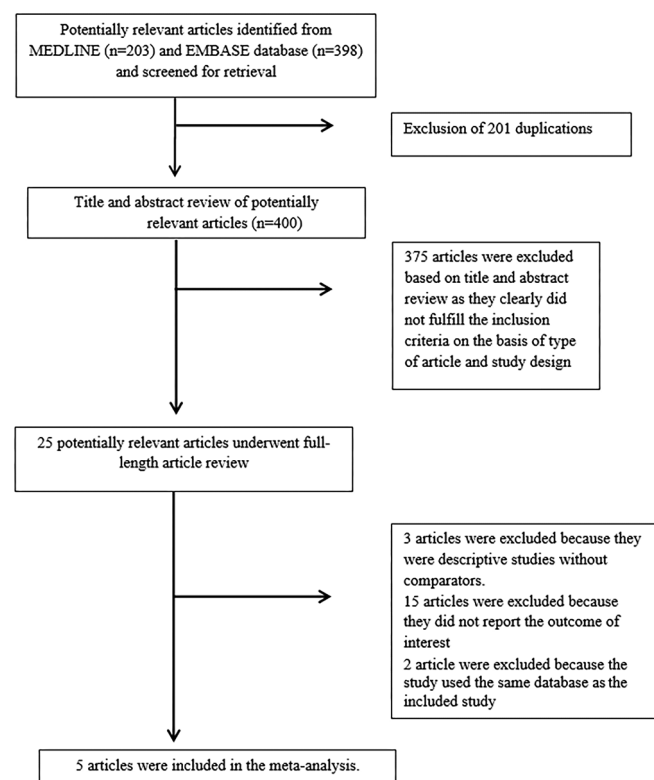
Six hundred and one potentially eligible articles were identified using our search strategy (203 articles from Medline and 398 articles from EMBASE). After the exclusion of duplicated 201 articles, 400 articles underwent title and abstract review. Three hundred and seventy-five articles were excluded at this stage because they were case reports, correspondences, review articles, *in-vitro* studies, animal studies, or interventional

studies, leaving 25 articles for full-text review. Fifteen of them were excluded after the full-length review as they did not report the outcome of interest whereas three articles were excluded since they were descriptive studies without comparative analysis. Seven studies met the eligibility criteria. However, three studies utilized the same database.<sup>[16,17,23]</sup> To avoid duplication of participants, the most comprehensive study was included in the analysis.<sup>[16]</sup> Finally, five cross-sectional studies with 27,804 participants were included in the meta-analysis.<sup>[12,13,15,16,18]</sup> The literature retrieval, review, and selection process are shown in Figure 1. The characteristics and quality assessment of the studies are presented in Table 1. It should be noted that the inter-rater agreement for the quality assessment using the Newcastle–Ottawa scale was high with the kappa statistics of 0.80.

We found a significantly increased risk of NAFLD among individuals with sarcopenia with the pooled OR of 1.54 (95% CI, 1.05–2.26), as shown in Figure 2. The heterogeneity between studies of the overall analysis was high with an  $I^2$  of 83%.

### Evaluation for publication bias

Funnel plot was used to evaluate publication bias [Figure 3]. The graph is asymmetric and suggests that publication bias in favor of positive studies might have been present.



**Figure 1:** Literature review process

## DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis that summarized all available studies regarding the association between sarcopenia and NAFLD. We found an approximately 1.5-fold increased risk of NAFLD among patients with sarcopenia compared to those without sarcopenia.

The exact pathogenesis of this association is yet to be elucidated. There are several possible explanations.

First, skeletal muscle is a major insulin-responsive target organ.<sup>[23-25]</sup> Thus, loss of skeletal muscle will promote insulin resistance and reduce energy expenditures, which could eventually lead to metabolic syndrome and NAFLD.<sup>[26]</sup> Interestingly, studies have also demonstrated that decreased insulin sensitivity (or impairment in insulin signaling) can promote skeletal muscle loss via reduction of the synthesis of muscle protein and mitochondrial dysfunction,<sup>[27]</sup> causing the vicious cycle between insulin insensitivity and sarcopenia.

Second, myokines secreted by skeletal muscles such as irisin, interleukin-6, myostatin, adipocytokines and adiponectin are involved in the regulation of glucose and fatty acid metabolism in the liver.<sup>[28-32]</sup> The imbalance of myokine levels associated with loss of muscle mass could possibly lead to disturbance of glucose and fatty acid metabolism and abnormal hepatic fat accumulation.

Third, it is also possible that the relationship between sarcopenia and NAFLD is not causal. The apparent association could be a result of the same underlying factors that could predispose patients to both NAFLD and sarcopenia. For example, it has been demonstrated that oxidative stress and proinflammatory cytokines of chronic inflammation, such as tumor necrotic factor- $\alpha$  and c-reactive protein, could promote catabolic state, resulting in loss of skeletal muscle.<sup>[27,33]</sup> Similarly, chronic inflammation plays a vital role in the pathogenesis of NAFLD (two-hit hypothesis).<sup>[34]</sup> Prolonged deficiency of vitamin D has been shown to be associated with a reduction in type 2 muscle fibers.<sup>[35]</sup> Vitamin D deficiency is also associated with an increased risk of NAFLD, possibly due to increased inflammatory cytokines.<sup>[36,37]</sup>

The systematic literature review process of this study was comprehensive and the quality of included studies was high as reflected by the high Newcastle–Ottawa scores. However, we acknowledge that this study had

**Table 1: Characteristics of the studies**

	Choi <i>et al.</i> [12]	Hong <i>et al.</i> [13]	Lee <i>et al.</i> [16]	Shen <i>et al.</i> [18]	Koo <i>et al.</i> [15]
Country	South Korea	South Korea	South Korea	United States	South Korea
Study design	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Year	2014	2014	2015	2016	2016
Number of participants	1,926	452	15,132	9,985	309
Participants	Participants were females with diabetes who were recruited from Huh's Diabetes Center from 2006 to 2010	Participants were healthy adults aged >20 years who were recruited from study centers from September 2007 to August 2008 as a part of Korean Sarcopenic Obesity Study. Participants were then evaluated for sarcopenia and NAFLD	This study utilized the database of KNHANES that surveyed adults aged >20 years across Korea from 2008 to 2011. Those without data on ASM were excluded	This study utilized the database of NHANES III that surveyed subjects across United States. Only those who underwent ultrasonography and	Participants were prospectively recruited from Boramae medical center
Mean age of participants in years	58	53.5	50.5	44.5	53.0
Percentage of female	100	63.1	62.9	55.6	53.1
Diagnosis of sarcopenia	SMI in the lowest quartile	Men: SMI <39.8% Women: SMI <34.1% SMI was measured using DXA	Men: SMI <32.2% Women: SMI <25.5% SMI was measured using DXA	Total SMM adjusted for height <sup>2</sup> Men ≤10.75 kg/m <sup>2</sup> Women ≤6.75 kg/m <sup>2</sup> SMM was measured using MRI and bioelectrical impedance formula	Men: ASM/weight <29.0% Women: ASM/weight <22.9% ASM was measured using BIA
Diagnosis of NAFLD	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation	CT scan demonstrated liver attenuation index <5 Hounsfield unit without other causes of hepatic fat accumulation	Fatty liver prediction model	Ultrasonographic evidence of hepatic steatosis with no other causes of secondary hepatic fat accumulation	Liver biopsy shows hepatic steatosis and without other causes of hepatic fat accumulation
Adjusted OR or HR or IRR	OR 2.25 (1.66, 3.04)	OR 5.16 (1.63, 16.33)	OR 1.19 (1.02, 1.39)	OR 1.00 (0.79, 1.27)	Assessed by ASM% OR 1.53 (0.5, 4.65)
Confounder adjustment	Age, hemoglobin A1c, waist, TG, systolic blood pressure, HDL-C, insulin tolerance test	Age, sex, smoking, physical activity, HOMA-IR, hs-CRP, vitamin D	Age, sex, regular exercise, HOMA-IR, smoking, HTN, BMI	Age, sex, ethnicities, obesity, insulin resistance, physical activity, HTN, dyslipidemia	Age, sex, BMI, smoking, HTN, DM, TG, PLT, albumin, HOMA-IR
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3

NAFLD: Nonalcoholic fatty liver disease, NHANES III: Third National Health and Nutritional Examination Survey, HTN: Hypertension, DXA: Dual energy X-ray absorptiometry, BIA: Bioelectrical impedance analysis, SMI: Skeletal muscle index, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insulin resistance, BMI: Body mass index, KNHANES: Korean National Health and Nutrition Examination Survey, ASM: Appendicular skeletal muscle mass, DM: Diabetes mellitus, hs-CRP: High-sensitivity C-reactive protein, PLT: Platelet, SMM: Skeletal muscle mass

some limitations and the results should be interpreted with caution.

First, the methods used to diagnose sarcopenia varied across studies. Only three studies used dual energy X-ray absorptiometry which is considered as the gold standard for muscle mass measurement.<sup>[12,13,16]</sup> Other studies used bioelectrical impedance analysis to estimate the skeletal muscle mass which may have a lower accuracy.<sup>[15,18]</sup> Second, all the included studies were cross-sectional in nature. Therefore, the temporal relationship between sarcopenia and NAFLD could not be established. Third, the statistical heterogeneity

of this meta-analysis was high. We believe that the difference in underlying populations as well as the methods used to diagnose NAFLD and sarcopenia was responsible for this between-study variation. Fourth, publication bias in favor of positive study may have been present in this meta-analysis.

## CONCLUSION

This study demonstrated a significantly increased risk of NAFLD among patients with sarcopenia. However, it is unclear whether this association is causal or is a result of shared predisposing factors.



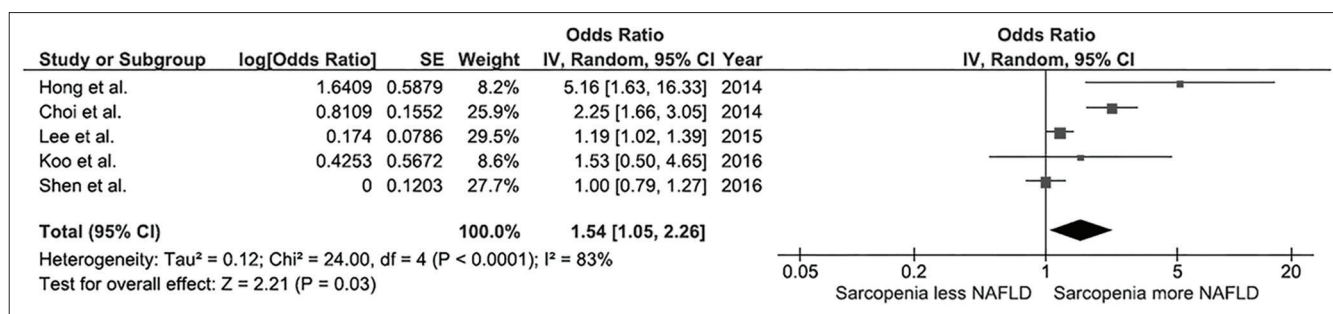


Figure 2: Forest plot

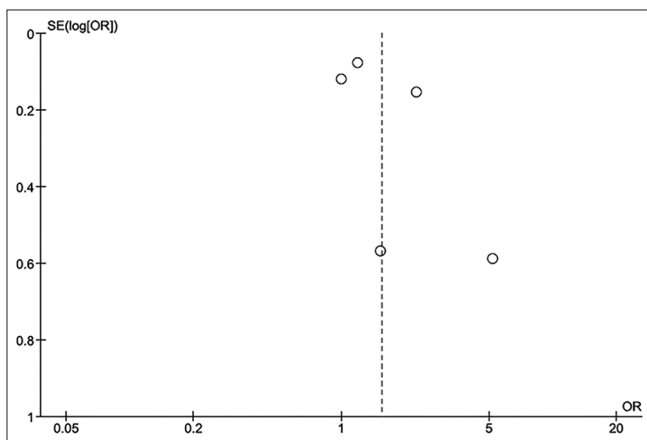


Figure 3: Funnel plot

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### Authors' contributions

All authors had access to the data and a role in writing the manuscript.

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### Conflicts of interest

There are no conflicts of interest.

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