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Skeletal muscle mass to visceral fat area ratio as a predictor of nonalcoholic fatty liver disease in lean and overweight men and women with effect modification by sex

Running title: SV ratio and fatty liver

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Conflict of interest

All authors declare that they have no conflict of interest.

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Authors' contributions

YCho, YChang, SR, and CDB planned, designed and implemented the study, including quality assurance and control. SR analyzed the data and designed the study's analytic strategy. HS and SR supervised field activities. YCho and YChang drafted the manuscript. All authors interpreted the results and contributed to critical revisions of the manuscript. All authors approved the final version of this manuscript

Abstract

Background and Aims: The effect of sarcopenic visceral obesity on risk of nonalcoholic fatty liver disease (NAFLD) is uncertain. We investigated whether: a) the skeletal muscle mass to visceral fat area ratio (SV ratio), as a measure of sarcopenic visceral obesity, is a risk factor for NAFLD; and b) the SV ratio adds to conventional adiposity measures to improve prediction of incident NAFLD.

Methods: Adults without NAFLD (n=151,017) were followed up for a median of 3.7 years. Hepatic steatosis was measured using ultrasonography, and liver fibrosis scores were estimated using the Fibrosis-4 index (FIB-4) and the NAFLD Fibrosis Score (NFS). Cox-proportional hazards models were used to determine sex-specific adjusted hazard ratios (aHRs) [95% confidence intervals (CIs)]. The incremental predictive performance was assessed using the area under the receiver operating characteristic curve, net reclassification improvement, and integrated discrimination improvement.

Results: Multivariable-aHRs (95% CIs) for incident NAFLD comparing the lowest versus the highest quintile of SV ratio were 3.77 (3.56–3.99) for men and 11.69 (10.46–13.06) for women (*P*–interaction by sex <0.001). For incident NAFLD with intermediate/high FIB4, aHRs were 2.83 (2.19–3.64) for men, and 7.96 (3.85–16.44) for women (similar results were obtained for NFS). Associations remained significant even after adjustment for body mass index, waist circumference, and time-varying covariates. These associations were also pronounced in non-obese than obese participants (*P*–interaction <0.001). The addition of SV ratio to conventional adiposity measures modestly improved risk prediction for incident NAFLD.

Conclusions: SV ratio was inversely associated with risk of developing NAFLD, with effect-modification by sex and obesity. Low SV ratio is a complementary index to conventional adiposity measures in the evaluation of NAFLD risk.

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease, with an

overall estimated global prevalence of 25%-30% in adults [1]. NAFLD is a multisystem disease that increases the risk of liver-specific complications and extrahepatic diseases, such as cardio-metabolic morbidity and mortality [2-5]. Currently, there is no approved medical therapy for NAFLD [6]. Further research is needed to understand the heterogeneous factors that are involved in the aetiology and pathogenesis of this complex liver condition, in order to give better insight into how best to identify high-risk individuals and design effective treatments for the disease.

Obesity, specifically abdominal obesity, is a well-established risk factor for NAFLD [7, 8]. Visceral fat area (VFA) is an accurate and reproducible measure of abdominal obesity and has a stronger association with metabolic syndrome (MetS) and NAFLD risk than proxy measures of adiposity, such as body mass index (BMI) and waist circumference (WC) [7, 9]. Along with visceral obesity, reduced skeletal muscle mass, an essential component of sarcopenia, has been reported as a novel risk factor for NAFLD [10]. Skeletal muscle is a key tissue, given that glucose disposal is facilitated by insulin, and reduced skeletal muscle mass may induce relative insulin resistance [11, 12]. Visceral adipose tissue is also strongly associated with insulin resistance [40]; thus, the combination of decreased muscle mass and increased visceral fat mass may markedly perturb metabolism and increase NAFLD risk.

Recently, it has been reported that "sarcopenic visceral obesity" i.e. the coexistence of sarcopenia and high visceral adiposity levels, is associated with higher levels of insulin resistance and metabolic impairment; than either the presence of low muscle mass, or obesity as individual risk factors [14, 15]. The skeletal muscle mass to visceral fat area ratio (SV ratio) is a single integrated measure used to describe sarcopenic visceral obesity and the SV ratio is generated by dividing the appendicular skeletal muscle mass (ASM) by VFA [16]. Recent studies have shown a close association between SV ratio and cardiometabolic diseases, including

T2DM, MetS and arterial stiffness, independent of conventional obesity measures [16, 17]. To the best of our knowledge, no cohort studies to date have investigated the effect of SV ratio on the risk of developing incident NAFLD in the general population.

This study aimed to test the hypothesis that people with a low SV ratio, as an indicator of sarcopenic visceral obesity, have a greater risk of incident NAFLD (defined by liver fat) and incident NAFLD with increased risk of liver fibrosis (defined by liver fat and increased liver fibrosis scores) and then that addition of SV ratio to body mass index (BMI) or waist circumference, as conventional adiposity measures, improves risk prediction for incident NAFLD.

MATERIALS AND METHODS

Study population

The present study was performed in a subsample of the Kangbuk Samsung Health Study, a large-scale cohort study of Korean adults who attended health check-ups annually or biennially at the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea [18]. 310,740 participants underwent an initial health check-up, including bioelectrical impedance analyzer (BIA) measurements between 2011 and 2018 and at least one follow-up examination until December 31, 2019. After excluding participants who met the exclusion criteria (**Figure 1**), 151,017 participants were included in the current analysis. All procedures involved in this study of human participants were in accordance with the the Ethical Principles for Medical Research Involving Human Subjects outlined in the 2013 Declaration of Helsinki. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No. KBSMC 2021-04-048), which waived the requirement for informed consent due to the use of anonymized retrospective data that were routinely collected during the health screening process.

Data collection

Health screening examinations, including questionnaires, impedance analyses and liver ultrasounds, were repeated every year or two years during the follow-up visits. Physical activity levels were recorded using the validated Korean version of the International Physical Activity Questionnaire short form and were converted to metabolic equivalents (METs; min/week)[19]. They were classified into one of the following three categories: inactive, minimally active, or health-enhancing physical activity (HEPA), meeting one of the following two standards: (i) vigorous-intensity activity on ≥3 days per week totaling ≥1,500 MET min/week, or (ii) 7 days with any combination of walking, moderate-intensity, or vigorous-intensity activities, achieving at least 3,000 MET min/week[19].

Measurement and definition of SV ratio, a sarcopenic visceral obesity index

A multi-frequency BIA (InBody 720; Biospace Inc., Seoul, Korea) was used to measure body composition after all participants had fasted overnight (≥10 hours) prior to BIA measurement. The BIA technique has been validated for body composition assessment, with a good correlation with those obtained by dual-energy X-ray absorptiometry or abdominal computed tomography (CT), including VFA and appendicular skeletal muscle mass (ASM) [20, 21]. A previous study of 200 Korean adults aged 20–69 years estimated the validity of lean body mass (LBM) and percent body fat (PBF) measurements assessed using BIA and DXA[22]. The correlation coefficients between DXA and BIA for LBM and PBF were high (r=0.951 and r=0.889 for men and r=0.956 and r=0.898 for women, respectively) [22]. In addition, in a study of children with obesity and NAFLD in the United States, total fat mass and skeletal muscle mass determined using BIA and MRI were strongly correlated (r =0.813 and r=0.701, respectively)[23]. It has also been reported that visceral fat mass measured using BIA is highly

correlated with visceral fat mass measured using abdominal CT scan (r=0.759)[24]. In our study, ASM was defined as the sum of the lean tissue mass in the arms and legs and SV ratio (kg/cm^2) was calculated as ASM (kg) divided by VFA (cm^2) [16, 25].

Liver ultrasound measures and definition of fatty liver and its severity

Abdominal ultrasound was performed by experienced radiologists who were unaware of the study's aims. Hepatic steatosis (HS) was diagnosed based on the standard criteria: a diffuse increase in fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma, deep beam attenuation, and bright vessel walls [26]. The inter-observer and intra-observer reliability values for HS diagnosis were substantial (kappa statistic of 0.74) and excellent (kappa statistic of 0.94), respectively [18]. We used the Fibrosis-4 (FIB-4) and NAFLD fibrosis score (NFS), two validated non-invasive indices of advanced fibrosis, to evaluate HS severity [27, 28]. The FIB-4 cut-off points were defined as <1.30 (low risk), 1.30–2.67 (intermediate risk), and ≥2.67 (high risk) for predicting probability of advanced fibrosis [27, 28]. The NFS cut-off points were <−1.455 for a low risk, 0.676 to−1.455 for an intermediate risk, and >0.676 for a high probability of advanced fibrosis [27, 28]. Since the number of the study participants who progressed to high fibrosis score category (FIB-4 ≥2.67 or NFS >0.676) during a median follow-up of 3.7 years was too small to obtain a reliable estimate, we combined the individuals with an intermediate and high risk of HS severity for FIB-4 and NFS scores.

Statistical analysis

No standard cut-off points have been established for SV ratio to define sarcopenic visceral obesity. To assess the relationship between the SV ratio as a continuous factor and NAFLD risk, we modelled the SV ratio as restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the sample distribution to provide a flexible estimate of the

concentration-response relationship between the SV ratio and incident NAFLD. Then, we defined sex-specific quintiles of SV ratio within the study population as follows: 0.09-0.26, 0.26-0.31, 0.31-0.36, 0.36-0.45 and 0.45-8.04 for men; and 0.06-0.18, 0.18-0.22, 0.22-0.25, 0.25-0.30 and 0.30-6.34 for women. The fifth quintile representing the highest SV ratio was used as the reference group. The primary endpoints for the study were a) incident HS, and b) incident HS with intermediate/high probability of advanced fibrosis at follow-up, assessed by two noninvasive fibrosis markers (FIB-4 and NFS levels). The incidence rate was presented as the number of cases per 1000 person-years. Cox-proportional hazard models were used to estimate the adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for incident HS by comparing the highest (reference) to each of the other four SV ratio quintiles.

The models were adjusted incrementally as follows: Model 1 was adjusted for age, center (Seoul or Suwon), year of the screening exam, education level (below college graduate, college graduate or higher, or unknown), alcohol consumption (<10 g/day or ≥10 g/day), smoking (never, former, current smoking and unknown), physical activity (inactive, minimally active, health-enhancing physical activity or unknown), total energy intake (quintiles, or unknown), medication for hyperlipidemia, history of diabetes and history of hypertension. Model 2 was adjusted for all covariates in Model 1, plus BMI as a continuous variable. To incorporate change in SV ratio and change in covariates during the follow-up period, we conducted time-dependent analyses, wherein updated status of SV ratio and other covariates were treated as time-varying covariates.

We performed further analyses to compare the predictive ability of the SV ratio (and its individual components) using Harrell's C-index (the area under the receiver operating characteristic curve [AUROC]) and also calculated net reclassification improvement (NRI), and integrated discrimination improvement (IDI) to quantify the incremental predictive ability

by adding the SV ratio relative to BMI or waist circumference.

Furthermore, to assess whether SV ratio provides additional information beyond BMI, an indicator of overall obesity, we performed stratified analyses based on obesity status (BMI of <25 vs. ≥25 kg/m^2[29]).

All analyses were conducted using STATA version 16.0 (StataCorp LP, College Station, TX, USA), and we defined the *p*-value for statistical significance as a two-sided $p<0.05$.

RESULTS

Baseline Characteristics

The baseline characteristics of 59,699 men and 91,318 women are presented according to SV ratio quintiles (**Table 1, and Supplementary Tables 1-2**). Individuals in the lowest quintile of the SV ratio had the least appendicular skeletal muscle mass with the highest fat mass and greatest visceral fat area. Individuals in the lowest SV ratio (first quintile) tended to be older, consumed more alcohol, and had higher HOMA-IR and hs-CRP levels than those in the fifth quintile. Moreover, there were a higher proportion of subjects with hypertension, hyperlipidemia, and physical inactivity in this quintile compared to the highest SV ratio quintile. There was a modest inverse association between both obesity and abdominal obesity with SV ratio quintile; the correlation coefficients between SV ratio and BMI were –0.53 for women and –0.43 for men, while coefficients between SV ratio and WC were –0.49 for women and –0.43 for men. The baseline characteristics of the participants are presented according to the presence of missing data (Supplementary Table 3–4). Although most baseline characteristics were different between the two groups, main exposure and other anthropometric measures, including body composition, BMI, and waist circumference, after adjusting for age and sex were similar between the two groups.

Development of NAFLD according to SV ratio

During 523145.8 person-years of follow-up, 26,543 cases of incident NAFLD were identified (27.0 per 10^3 person-years for women; and 91.7 per 10^3 person-years for men), and the median follow-up duration was 3.7 years (interquartile range: 2.0–4.8 years; maximum: 7.3 years). In the spline regression models, the NAFLD risk decreased across the range of the SV ratios in men (**Figure 2**). In women, the SV ratio showed an inverted J-shaped association with the incidence of NAFLD, while the overall trend tended to be inverse between the SV ratio and NAFLD risk. SV ratio quintile was inversely associated with the risk of incident NAFLD (*P*–trend <0.001) and this association differed by sex (*P*–interaction <0.001) (**Table 2**). After adjustment for confounders, multivariable-adjusted HRs (95% CIs) for incident NAFLD, comparing the lowest to the highest SV ratio quintile, were 3.42 (3.24–3.61) for men and 11.27 (10.10–12.58) for women. These associations were attenuated after adjusting for BMI, but values remained highly statistically significant. Importantly, all of these associations were similarly observed in time-dependent analyses; wherein, the updated status of SV ratio and other confounders were incorporated as time-varying covariates. These data indicated that change in SV ratio or other key covariates between baseline and follow up, did not materially affect the results. After adjusting for WC instead of BMI, this association persisted (**Supplementary Table 5**).

In the analyses to evaluate the predictive ability of the SV ratio (and its individual components), a significant but modest increase in category-based NRI and IDI were observed when the SV ratio was added to the BMI-based model or WC-based model (**Table 3, Supplementary Table 6**). The improvement was greater than that observed with the individual components (**Supplementary Table 6**). The predictive performance of the SV ratios was not superior to that of BMI or WC-based on the AUROC **(Supplementary Table 7).** Although in

our study, the predictive performance of BMI, waist circumference, and SV ratio was inadequate to predict incident NAFLD on an individual level **(Supplementary Table 7)**, adding the SV ratio improved the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (**Table 3**). Thus, the SV ratio may be a complementary index to conventional adiposity measures for evaluating NAFLD risk.'

Development of NAFLD with intermediate/high fibrosis score according to SV ratio

During follow-up, 1,329 cases of incident NAFLD with intermediate/high FIB4 score were identified (0.9 per 10^3 person-years for women; and 4.3 per 10^3 person-years for men), while 1,986 cases of incident NAFLD with intermediate/high NFS score were identified (1.3 per 10^3 person-years for women; and 6.5 per 10^3 person-years for men). The risk of incident NAFLD with increased fibrosis scores decreased as SV ratio increased (*P*–trend <0.001) and this association was stronger in women than in men (*P*–interaction <0.001) (**Table 4**), although the age-standardized incidence of NAFLD was much lower in women than in men (**Supplementary Table 8**). Comparing the lowest to the highest SV ratio quintile, the multivariable-adjusted HRs (95% CIs) for incident NAFLD with intermediate/high FIB4 were 2.83 (2.19–3.64) for men and 7.96 (3.85–16.44) for women. These associations were attenuated after adjustment for either BMI or WC (**Supplementary Table 3**) but remained statistically significant. These associations were also consistently observed in time-dependent analyses, again indicating that change in status of SV ratio or other covariates between baseline and follow up did not materially affect the results. The results were also more pronounced when NFS was used instead of the FIB-4 score. Further adjustment for HOMA-IR and hs-CRP also did not materially change the results (**Supplementary Table 9**).

The risk of developing NAFLD with a high fibrosis score, either high FIB-4 or high NFS, was

significantly higher in the lowest SV ratio quintile than in the highest SV ratio quintile among men although a similar tendency was observed among women, this did not reach statistical significance (**Supplementary Table 10**).

Subgroup analysis

The associations between SV ratio quintiles and incident NAFLD differed by obesity status defined as BMI ≥25 kg/m^2 (*p*–interaction <0.001), in which the association was considerably stronger in non-obese individuals than obese individuals (**Table 5**). For men, the HR (95% CI) for NAFLD comparing the lowest to the highest SV ratio quintile was 2.92 (2.73–3.13) for non-obese participants and 1.72 (1.42–2.07) for obese participants. In contrast to men, women with the lowest SV ratio had a markedly increased risk of NAFLD in non-obese subjects (HR: 7.97, 95% CI: 7.10–8.94). In obese women in the lowest SV ratio quintile, there was a trend towards increased risk of incident NAFLD (HR: 1.87, 95% CI: 0.47–7.48).

The inverse association between SV ratio and NAFLD was much stronger in non-obese women than in obese women (*p*–interaction <0.001). Importantly, all of the associations described above were consistently observed when BMI was replaced by WC, as a measure of abdominal obesity (**Supplementary Table 11**). In additional analyses stratified using re-categorization including 'lean,' 'overweight,' and 'obese,' the association between the low SV ratio and risk of NAFLD was most pronounced in lean individuals with BMI of <23 kg/m^2 (**Supplementary Table 12**).

The association between SV ratio and the risk of incident NAFLD with intermediate/high FIB-4 (or NFS score) was statistically significant only in non-obese participants and the associations were consistently observed in in non-obese participants grouped by WC instead of BMI (**Supplementary Tables 13-16**). Due to a small number of outcomes within the highest

(fifth) SV ratio quintile in women with obesity or abdominal obesity, the fourth quintile was used as the reference group**.** Among women, the association between SV ratio and NAFLD tended to be stronger in premenopausal women than in postmenopausal women but without significant interaction by menopausal status (**Supplementary Table 17**).

DISCUSSION

Our novel findings show that in a retrospective cohort study of >150,000 adults with over half a million person-years of follow-up, low SV ratio was an independent risk factor for developing incident NAFLD during the follow-up period (both overall NAFLD, and NAFLD with increased levels of liver fibrosis markers). Interestingly, our data show that the inverse association between SV ratio and NAFLD was stronger in women than in men, and in non-obese than in obese participants, and the association between SV ratio and NAFLD was significantly modified by sex and obesity. Low SV ratio is a complementary index to conventional adiposity measures in the evaluation of NAFLD risk. These associations persisted even after adjustment for either BMI or WC or when adjusted for changes in potential confounders during follow-up, as time-varying covariates. Importantly, the time dependent analyses take account of any potential change in status of SV ratio or other key covariates, between baseline and follow up.

In analyses assessing the incremental predictive ability after adding the SV ratio to conventional adiposity indices (either BMI or WC), the addition of the SV ratio consistently showed a significant, although modest, improvement in the AUROC, NRI and IDI, compared to the base model based on age and conventional adiposity measures. Thus, the SV ratio may be a complementary index that adds to conventional adiposity measures in the evaluation of NAFLD risk and this finding needs to be tested further in other cohorts and in different ethnic

groups.

Recent cross-sectional and longitudinal studies have shown a positive association between low skeletal muscle mass and NAFLD risk [10, 30, 31], focusing on ASM adjusted for proxy indicators of obesity, such as BMI or body weight, without considering visceral adiposity.

SV ratio combines two body composition measures, ASM and VFA, and can be used to identify sarcopenic visceral obesity. Several studies have evaluated the association between SV ratio and NAFLD [25, 32-34]. However, previous studies have had at least one of the following limitations: cross-sectional study design; use of proxy measures for diagnosing NAFLD, such as fatty liver index or hepatic steatosis index (rather than liver biopsy or liver imaging); lack of adjustment for potential confounders, including BMI or WC; or lack of consideration of effect modification by sex or obesity.

In our study, the relative impact of the SV ratio on the risk of NAFLD was more pronounced in women than in men although the absolute incidence of NAFLD was much lower in women than in men. Women, especially pre-menopausal women, tend to have metabolically more favorable fat distribution, such as more fat in the gluteofemoral region and subcutaneous area, while fat is predominantly stored in the visceral area in men.[36, 37] Additionally, the amount of skeletal muscle mass in women was lower than that in men.[38] Proxy measures of overall adiposity, such as BMI, may not be particularly useful as a measure of metabolic risk in women. We suggest that better differentiation between fat and lean mass is needed in women. Measures such as sarcopenic visceral obesity may be helpful as a measure of metabolic risk in women. Further research using detailed phenotyping of fat distribution and measurement of skeletal muscle mass will help understand the differential effect of SV ratio on NAFLD risk between men and women.

Furthermore, in our study, the independent and inverse association between SV ratio and NAFLD risk was much stronger among non-obese participants than among obese participants with the strongest association seen in lean individuals with BMI of <23 kg/m^2. These findings were consistently observed even when the changes in SV ratio, BMI, and other confounders over time were treated as time-varying covariates, suggesting that obesity is an effect modifier of the association between the SV ratio and NAFLD risk. Potential contributory factors include that lean NAFLD subjects who have been identified by BMI might also include people with an unfavorable combination of excess abdominal adipose tissue, decreased protective fat tissue, and low levels of skeletal muscle mass. Indeed, although NAFLD is strongly associated with overall and central obesity, it also occurs in non-obese subjects, with approximately 40% of the global NAFLD population being classified as non-obese [39]. Non-obese subjects with NAFLD also show higher all-cause mortality, and mortality due to CVD and liver disease, than obese NAFLD individuals [39]. Further research using detailed fat distribution phenotyping and skeletal muscle mass measurement will be helpful in understanding the differential effect of SV ratio on risk of NAFLD in men and women, and between non-obese and obese individuals.

Several plausible mechanisms may explain the concurrent roles of skeletal muscle and visceral fat mass in the risk of NAFLD, including insulin resistance, previously described, and inflammation. The skeletal muscle is capable of secreting myokines, such as myostatin and irisin, which are involved in oxidative stress and inflammation [12]. Dysregulation of these myokines may promote liver injury by increasing insulin resistance and oxidative stress [41]. Visceral adipose tissue macrophages produce proinflammatory cytokines, such as interleukin-6 (IL-6), and tumor necrosis factor α, which are correlated with muscle atrophy, and may increase the risk of NAFLD progression [42]. Moreover, cytokines such as IL-6, which are produced by inflamed adipose tissue, may further increase muscle wasting and exacerbate the

situation in chronic inflammatory states [43].

Despite these findings, our study has certain limitations. First, BIA could overestimate fat-free mass (FFM) and underestimate fat mass in obese elderly populations [20]. BIA may also be affected by certain factors, such as fluid status, pregnancy, and malnutrition.[44] The hydration status of the study participants was not determined before the body composition assessment. All participants performed an overnight fast of ≥10 h prior to the BIA measurements because fasting blood samples were collected at this time. Women in our study were supposed to be non-pregnant to be eligible for a comprehensive health screening test that included imaging studies. However, any inaccuracy in the BIA assessment would be universally applicable to all participants in the study. The results of this study might not be generalizable to other adult populations with extreme bodyweight and abnormal hydration status. Second, we used liver ultrasound and liver fibrosis index (NFS and FIB-4) in our analyses. It was neither feasible nor ethical to obtain histological data on liver steatosis and fibrosis from liver biopsies of this occupational cohort of relatively healthy participants. The non-invasive diagnosis of the fatty liver using ultrasonography and liver fibrosis indices has been validated with acceptable accuracy and reproducibility and has been widely used in population-based studies [28, 45]. Third, the relatively short follow-up time (median of 3.7 years) precluded an evaluation of advanced fibrosis (FIB-4 ≥2.67 or NFS >0.676) due to small case numbers. Considering the natural history of fibrosis progression in patients with NAFLD has a long duration of 14.3 (95% CI, 9.1–50.0) years in one stage of fibrosis progression for patients with NAFLD [35], future studies with longer follow-up durations are needed to determine the risk of NAFLD with high fibrosis score, a more severe form of NAFLD, according to the SV ratio. Fourth, in our study, dietary intake was assessed using a 103-item self-administered food frequency questionnaire (FFQ) reflective of usual food intake over the past year that was developed and validated for use in

South Korea [46]. Additionally, seasonings and oils, typically included in Korean diet, are not considered in this FFQ, which tends to underestimate total calorie intake compared to that in dietary records, the reference standard [46]; thus, we cannot exclude measurement errors in the dietary assessments. Fifth, data on myokine and adipokine levels were not available, although dysregulation of the myokines and adipokines may contribute to liver injury by chronic inflammation.[40, 41] Future studies with a detailed assessment of myokine and adipokine levels may help elucidate the mechanism underlying the association between SV ratio and NAFLD. Finally, our study population comprised healthy middle-aged adults of Korean ethnicity, who had good access to health care facilities; therefore, the generalizability of our findings to other ethnic groups needs to be tested.

In conclusion, we have identified that low SV ratio is an independent risk factor for developing NAFLD. Notably, low SV ratio was a stronger risk factor for NAFLD in women than in men and was a much stronger risk factor in non-obese (especially, lean) than in obese participants. This association was independent of BMI, WC, time-varying covariates (that take account of change in status between baseline and follow up), and other potential confounders, such as physical activity, in a large Korean cohort. Low SV ratio is a complementary index that adds to conventional adiposity measures in the evaluation of NAFLD risk. Future studies with consideration of effect modification by sex and obesity are needed to examine whether similar findings exist in other ethnic groups.

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Data Availability Statement

The data are not publicly available outside of the hospital because of Institutional Review Board restrictions (the data were not collected in a way that could be distributed widely). However, the analytical methods are available from the corresponding author upon request.

References

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
2. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62:S47-64.
3. Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. J Hepatol 2020;72:785-801.
4. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut 2021.
5. Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021.
6. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.
7. Jakobsen MU, Berentzen T, Sorensen TI, et al. Abdominal obesity and fatty liver. Epidemiol Rev 2007;29:77-87.
8. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology 2010;51:679-89.
9. Shuster A, Patlas M, Pinthus JH, et al. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol 2012;85:1-10.
10. Cai C, Song X, Chen Y, et al. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Hepatol Int 2020;14:115-126.
11. Klip A, Paquet MR. Glucose transport and glucose transporters in muscle and their metabolic regulation. Diabetes Care 1990;13:228-43.

12. Severinsen MCK, Pedersen BK. Muscle-Organ Crosstalk: The Emerging Roles of Myokines. Endocr Rev 2020;41.
13. Kelley DE. Skeletal muscle fat oxidation: timing and flexibility are everything. J Clin Invest 2005;115:1699-702.
14. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol 2018;14:513-537.
15. Alalwan TA. Phenotypes of Sarcopenic Obesity: Exploring the Effects on Peri-Muscular Fat, the Obesity Paradox, Hormone-Related Responses and the Clinical Implications. Geriatrics (Basel) 2020;5.
16. Kim TN, Park MS, Lim KI, et al. Skeletal muscle mass to visceral fat area ratio is associated with metabolic syndrome and arterial stiffness: The Korean Sarcopenic Obesity Study (KSOS). Diabetes Res Clin Pract 2011;93:285-291.
17. Wang Q, Zheng D, Liu J, et al. Skeletal muscle mass to visceral fat area ratio is an important determinant associated with type 2 diabetes and metabolic syndrome. Diabetes Metab Syndr Obes 2019;12:1399-1407.
18. Chang Y, Ryu S, Sung KC, et al. Alcoholic and non-alcoholic fatty liver disease and associations with coronary artery calcification: evidence from the Kangbuk Samsung Health Study. Gut 2019;68:1667-1675.
19. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-95.
20. Ling CH, de Craen AJ, Slagboom PE, et al. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr 2011;30:610-5.
21. Kyle UG, Genton L, Hans D, et al. Validation of a bioelectrical impedance analysis equation to predict appendicular skeletal muscle mass (ASMM). Clin Nutr 2003;22:537-43.
22. Yang SW, Kim TH, Choi HM. The reproducibility and validity verification for body

composition measuring devices using bioelectrical impedance analysis in Korean adults. J Exerc Rehabil 2018;14:621-627.

23. Orkin S, Yodoshi T, Romantic E, et al. Body composition measured by bioelectrical impedance analysis is a viable alternative to magnetic resonance imaging in children with nonalcoholic fatty liver disease. JPEN J Parenter Enteral Nutr 2021.

24. Ogawa H, Fujitani K, Tsujinaka T, et al. InBody 720 as a new method of evaluating visceral obesity. Hepatogastroenterology 2011;58:42-4.

25. Shida T, Akiyama K, Oh S, et al. Skeletal muscle mass to visceral fat area ratio is an important determinant affecting hepatic conditions of non-alcoholic fatty liver disease. J Gastroenterol 2018;53:535-547.

26. Mathiesen UL, Franzen LE, Aselius H, et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. Dig Liver Dis 2002;34:516-22.

27. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-54.

28. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104-12.

29. World Health Organization, Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia, 2000.

30. Kim G, Lee SE, Lee YB, et al. Relationship Between Relative Skeletal Muscle Mass and Nonalcoholic Fatty Liver Disease: A 7-Year Longitudinal Study. Hepatology 2018;68:1755-1768.

31. Koo BK, Kim D, Joo SK, et al. Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. J Hepatol 2017;66:123-131.

32. Moon JS, Yoon JS, Won KC, et al. The role of skeletal muscle in development of nonalcoholic

Fatty liver disease. Diabetes Metab J 2013;37:278-85.

33. Su X, Xu J, Zheng C. The relationship between non-alcoholic fatty liver and skeletal muscle mass to visceral fat area ratio in women with type 2 diabetes. BMC Endocr Disord 2019;19:76.

34. Shida T, Oshida N, Oh S, et al. Progressive reduction in skeletal muscle mass to visceral fat area ratio is associated with a worsening of the hepatic conditions of non-alcoholic fatty liver disease. Diabetes Metab Syndr Obes 2019;12:495-503.

35. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643-54 e1-9; quiz e39-40.

36. Karpe F, Pinnick KE. Biology of upper-body and lower-body adipose tissue--link to whole-body phenotypes. Nat Rev Endocrinol 2015;11:90-100.

37. Pinnick KE, Nicholson G, Manolopoulos KN, et al. Distinct developmental profile of lower-body adipose tissue defines resistance against obesity-associated metabolic complications. Diabetes 2014;63:3785-97.

38. Stevens J, Katz EG, Huxley RR. Associations between gender, age and waist circumference. Eur J Clin Nutr 2010;64:6-15.

39. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:739-752.

40. Mirza MS. Obesity, Visceral Fat, and NAFLD: Querying the Role of Adipokines in the Progression of Nonalcoholic Fatty Liver Disease. ISRN Gastroenterol 2011;2011:592404.

41. Bhanji RA, Narayanan P, Allen AM, et al. Sarcopenia in hiding: The risk and consequence of underestimating muscle dysfunction in nonalcoholic steatohepatitis. Hepatology 2017;66:2055-2065.

42. Boutari C, Perakakis N, Mantzoros CS. Association of Adipokines with Development and Progression of Nonalcoholic Fatty Liver Disease. Endocrinol Metab (Seoul) 2018;33:33-43.

43. Munoz-Canoves P, Scheele C, Pedersen BK, et al. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J 2013;280:4131-48.

44. Buchholz AC, Bartok C, Schoeller DA. The validity of bioelectrical impedance models in clinical populations. Nutr Clin Pract 2004;19:433-46.

45. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011;54:1082-90.

46. Ahn Y, Kwon E, Shim JE, et al. Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. Eur J Clin Nutr 2007;61:1435-41.

Figure legends

Fig. 1. Flow chart of study participants

Fig. 2. Multivariable-adjusted hazard ratios (95% confidence intervals) for incident non-alcoholic fatty liver disease (NAFLD) using the skeletal muscle mass and visceral fat area ratio (SV ratio) as a continuous factor in A) men and B) women. The curves represent adjusted hazard ratios (solid line) and their 95% confidence intervals (dashed lines) for incident NAFLD on the basis of restricted cubic splines for the SV ratios with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, and 95^{th} percentiles of sex-specific sample distribution. The model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, hyperlipidaemia medication, history of diabetes, history of hypertension, and body mass index.

Fig. 1

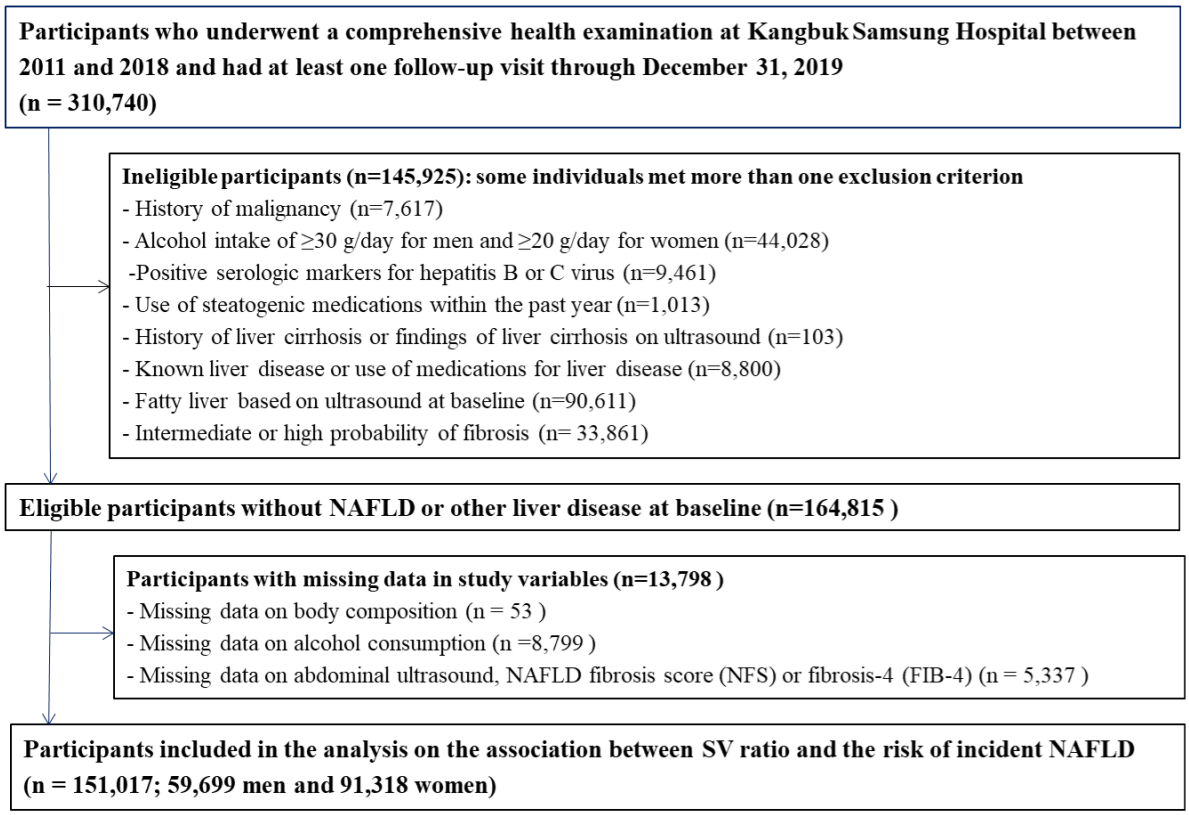

Participants who underwent a comprehensive health examination at Kangbuk Samsung Hospital between 2011 and 2018 and had at least one follow-up visit through December 31, 2019 (n = 310,740)
Ineligible participants (n=145,925): some individuals met more than one exclusion criterion
- History of malignancy (n=7,617)
- Alcohol intake of ≥30 g/day for men and ≥20 g/day for women (n=44,028)
-Positive serologic markers for hepatitis B or C virus (n=9,461)
- Use of steatogenic medications within the past year (n=1,013)
- History of liver cirrhosis or findings of liver cirrhosis on ultrasound (n=103)
- Known liver disease or use of medications for liver disease (n=8,800)
- Fatty liver based on ultrasound at baseline (n=90,611)
- Intermediate or high probability of fibrosis (n= 33,861)
Eligible participants without NAFLD or other liver disease at baseline (n=164,815)
Participants with missing data in study variables (n=13,798)
- Missing data on body composition (n = 53)
- Missing data on alcohol consumption (n =8,799)
- Missing data on abdominal ultrasound, NAFLD fibrosis score (NFS) or fibrosis-4 (FIB-4) (n = 5,337)
Participants included in the analysis on the association between SV ratio and the risk of incident NAFLD (n = 151,017; 59,699 men and 91,318 women)

Fig. 2

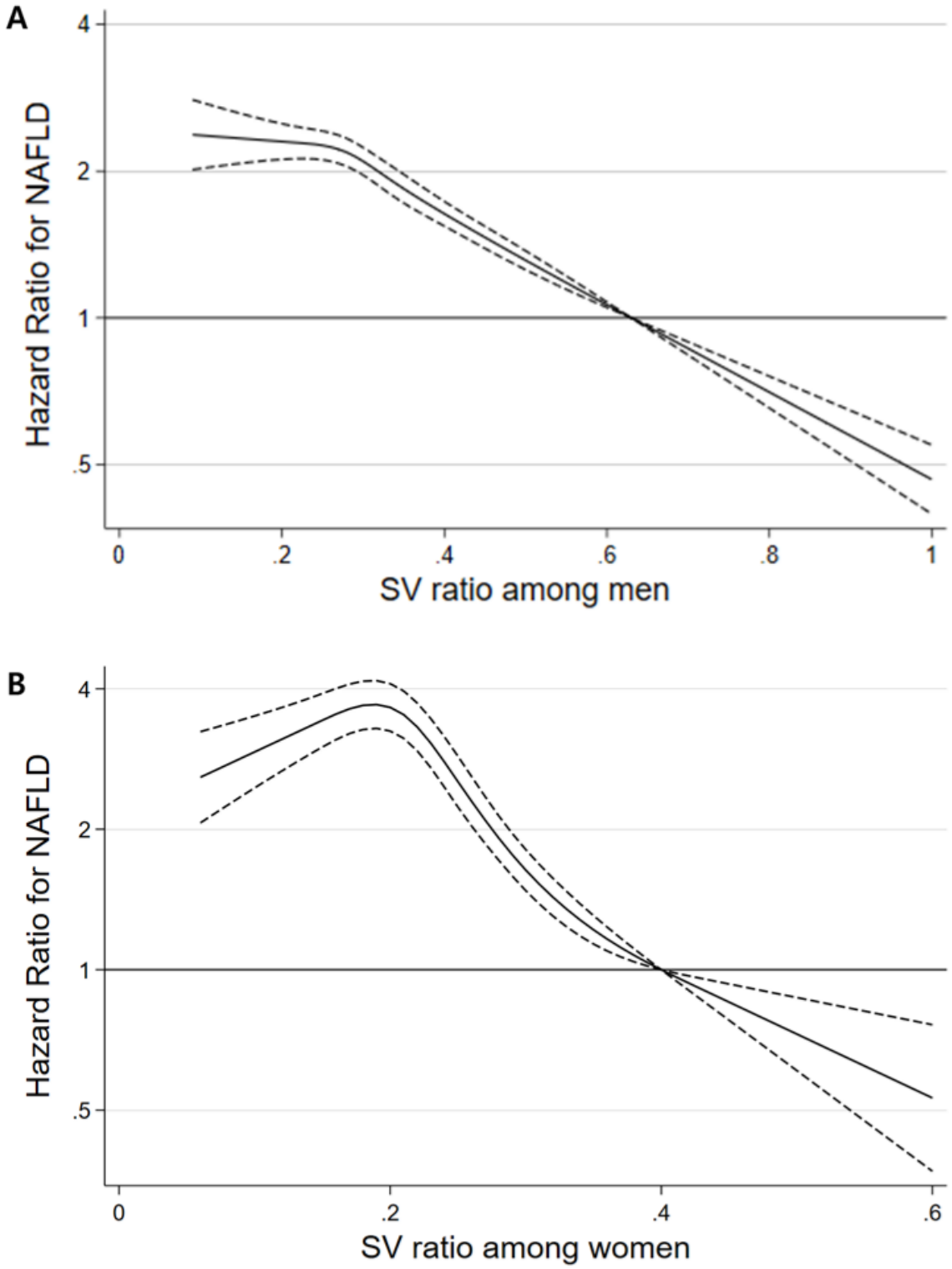

A
Hazard Ratio for NAFLD
4
2
1
.5
0
.2
.4
.6
.8
1
SV ratio among men
B
Hazard Ratio for NAFLD
4
2
1
.5
0
.2
.4
.6
SV ratio among women

Table 1. Estimated [a] mean values (95% CI) and adjusted [a] proportion (95% CI) of baseline characteristics by skeletal muscle mass to visceral fat area ratio quintiles (n=151,017)

Characteristics	SV ratio (kg/cm^2) quintiles					*p*–trend
	Q1	Q2	Q3	Q4	Q5	
Number of participants	30,205	30,209	30,198	30,205	30,200	
Age (years)	40.2 (40.1-40.2)	37.8 (37.7-37.9)	36.7 (36.6-36.8)	35.9 (35.8-35.9)	34.6 (34.6-34.7)	<0.001
Male (%)	38.3 (37.8-38.9)	39.2 (38.7-39.8)	39.7 (39.1-40.2)	40.0 (39.4-40.5)	40.4 (39.9-41.0)	<0.001
Alcohol intake (%)[b]	26.4 (25.9-26.8)	24.5 (24.1-25.0)	23.2 (22.7-23.6)	22.9 (22.5-23.4)	21.9 (21.4-22.3)	<0.001
Current smoker (%)	11.4 (11.1-11.7)	11.7 (11.4-12.1)	11.4 (11.1-11.8)	11.5 (11.2-11.9)	12.5 (12.1-12.8)	0.001
HEPA (%)	11.4 (11.1-11.8)	12.0 (11.6-12.3)	12.6 (12.2-12.9)	14.2 (13.8-14.6)	16.2 (15.8-16.6)	<0.001
Education level (%)[c]	82.7 (82.3-83.1)	86.4 (86.0-86.8)	87.8 (87.4-88.2)	87.7 (87.4-88.1)	87.1 (86.7-87.5)	<0.001
History of diabetes (%)	0.6 (0.5-0.6)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.5 (0.4-0.5)	0.6 (0.5-0.7)	0.764
History of hypertension (%)	4.4 (4.2-4.6)	3.3 (3.1-3.5)	3.0 (2.8-3.2)	2.9 (2.7-3.1)	2.5 (2.3-2.7)	<0.001
History of CVD (%)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.342
Anti-lipid medication use (%)	1.4 (1.3-1.5)	1.1 (0.9-1.2)	0.9 (0.7-1.0)	0.7 (0.6-0.8)	0.6 (0.5-0.7)	<0.001
Obesity (%)[d]	36.6 (36.1-37.2)	15.7 (15.3-16.1)	8.6 (8.3-8.9)	4.2 (3.9-4.4)	1.1 (1.0-1.2)	<0.001
Abdominal obesity (%)[e]	28.0 (27.5-28.5)	11.5 (11.1-11.8)	5.5 (5.2-5.7)	2.1 (1.9-2.2)	0.4 (0.3-0.4)	<0.001
Body mass index (kg/m^2)	24.2 (24.2-24.3)	22.7 (22.7-22.8)	21.9 (21.8-21.9)	21.1 (21.1-21.1)	19.9 (19.9-19.9)	<0.001
Waist circumference (cm)	82.8 (82.7-82.8)	79.3 (79.3-79.4)	77.2 (77.1-77.3)	75.2 (75.1-75.3)	71.8 (71.8-71.9)	<0.001
Glucose (mg/dl)	92.2 (92.1-92.3)	91.5 (91.5-91.6)	91.2 (91.1-91.3)	90.8 (90.7-90.9)	90.2 (90.1-90.3)	<0.001
HbA1c (%)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	0.682
SBP (mmHg)	107.1 (107-107.2)	105.1 (105-105.2)	104.2 (104.1-104.3)	103.6 (103.5-103.7)	102.5 (102.4-102.6)	<0.001
DBP (mmHg)	68.4 (68.3-68.5)	67.3 (67.2-67.3)	66.8 (66.7-66.9)	66.5 (66.4-66.6)	66.0 (65.9-66.1)	<0.001
Total cholesterol (mg/dl)	195.5 (195.1-195.8)	190.2 (189.9-190.6)	187.0 (186.6-187.3)	184.3 (183.9-184.6)	180.5 (180.1-180.8)	<0.001
LDL-C (mg/dl)	123.5 (123.2-123.8)	118.0 (117.7-118.3)	114.7 (114.4-115.0)	111.3 (111-111.6)	106.0 (105.7-106.3)	<0.001
HDL-C (mg/dl)	60.6 (60.5-60.8)	62.1 (61.9-62.2)	63.4 (63.2-63.6)	65.3 (65.2-65.5)	68.0 (67.9-68.2)	<0.001
Triglycerides (mg/dl)	100.1 (99.5-100.6)	93.0 (92.5-93.6)	88.2 (87.7-88.7)	83.1 (82.6-83.6)	75.4 (74.9-75.9)	<0.001
ALT (U/L)	19.0 (18.9-19.1)	17.7 (17.6-17.8)	16.9 (16.0.8-17)	16.2 (16.1-16.3)	15.4 (15.3-15.5)	<0.001
AST (U/L)	19.3 (19.2-19.3)	18.8 (18.7-18.9)	18.6 (18.5-18.6)	18.5 (18.5-18.6)	18.6 (18.6-18.7)	<0.001
GTP (U/L)	24.7 (24.5-24.9)	21.6 (21.4-21.8)	20.2 (20.0-20.4)	19.0 (18.8-19.2)	17.7 (17.5-17.9)	<0.001

hs-CRP (mg/L)	1.25 (1.17-1.33)	0.91 (0.84-0.99)	0.85 (0.78-0.93)	0.83 (0.75-0.91)	0.78 (0.70-0.85)	<0.001
HOMA-IR	1.56 (1.56-1.57)	1.36 (1.35-1.37)	1.25 (1.24-1.26)	1.14 (1.14-1.15)	1.00 (0.99-1.00)	<0.001
Total energy intake (kcal/d)[f]	1,374 (1,366-1,382)	1,382 (1,374-1,390)	1,373 (1,365-1,381)	1,375 (1,367-1,383)	1,395 (1,387-1,403)	0.002
ASM (kg)	18.4 (18.4-18.5)	18.8 (18.8-18.8)	19.0 (19.0-19.0)	19.1 (19.1-19.2)	19.3 (19.2-19.3)	<0.001
Visceral fat area (cm^2)	96.5 (96.4-96.7)	77.4 (77.3-77.5)	67.0 (66.9-67.1)	57.1 (57.0-57.3)	41.9 (41.8-42.1)	<0.001
Fat mass (kg)	21.0 (20.9-21.0)	17.5 (17.4-17.5)	15.4 (15.4-15.5)	13.5 (13.5-13.6)	10.7 (10.7-10.7)	<0.001

[a]Adjusted for age and sex; [b] ≥10 g/day; [c] ≥ College graduate; [d] BMI ≥ 25kg/m^2; [e] waist circumference ≥90 cm for men ≥85 cm for women; [f] among 103,890 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake)

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63.

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40.

Abbreviations: ALT, alanine aminotransferase; ASM, appendicular skeletal muscle mass; AST, aspartate transaminase; CI, confidence intervals; CVD, cardiovascular disease; HbA1c, HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physically active; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; SV ratio, skeletal muscle mass to visceral fat area ratio.

Table 2. Development of non-alcoholic fatty liver disease by skeletal muscle mass to visceral fat area ratio quintiles

SV ratio (kg/cm^2) quintiles	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)		HR (95% CI)[b] in a model with time-dependent variables
					Model 1	Model 2	
Men							
Q1 (< 0.26)	34,429	4,937	143.4	3.42(3.24-3.61)	3.77 (3.56-3.99)	1.92 (1.8-2.05)	2.46 (2.30-2.63)
Q2 (0.26-0.30)	36,754	4,275	116.3	2.75(2.60-2.90)	2.97 (2.81-3.15)	1.84 (1.74-1.96)	2.29 (2.15-2.44)
Q3 (0.31-0.35)	38,362	3,628	94.6	2.23(2.10-2.36)	2.36 (2.23-2.50)	1.66 (1.56-1.76)	2.00 (1.88-2.13)
Q4 (0.36-0.44)	39,930	2,961	74.2	1.74(1.65-1.85)	1.81 (1.70-1.92)	1.44 (1.35-1.53)	1.64 (1.54-1.75)
Q5 (≥ 0.45)	42,393	1,800	42.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
p–trend				<0.001	<0.001	<0.001	<0.001
Per 0.1 decrease in SV ratio				1.41(1.39-1.43)	1.45 (1.43-1.48)	1.21 (1.19-1.23)	1.28 (1.26-1.31)
Women							
Q1 (< 0.19)	59,022	3,928	66.6	11.27 (10.10-12.58)	11.69 (10.46-13.06)	3.37 (2.99-3.8)	3.65 (3.18-4.19)
Q2 (0.19-0.22)	66,574	2,406	36.1	6.44 (5.76-7.21)	6.73 (6.01-7.53)	3.19 (2.84-3.57)	3.76 (3.28-4.31)
Q3 (0.23-0.26)	67,680	1,433	21.2	3.87 (3.45-4.35)	4.02 (3.58-4.51)	2.46 (2.19-2.77)	2.50 (2.17-2.87)
Q4 (0.27-0.31)	68,393	819	12.0	2.24 (1.98-2.54)	2.31 (2.04-2.61)	1.74 (1.54-1.98)	1.74 (1.50-2.02)
Q5 (≥ 0.32)	69,611	356	5.1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
p–trend				<0.001	<0.001	<0.001	<0.001
Per 0.1 decrease in SV ratio				3.46 (3.32-3.60)	3.55 (3.40-3.70)	1.68 (1.60-1.76)	1.53 (1.47-1.60)

[a] Estimated from Cox proportional hazard models. Multivariable model 1 was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes, and history of hypertension; model 2: model 1 plus adjustment for body mass index.

[b] Estimated from Cox proportional hazard models with quintiles of SV ratio, smoking, alcohol consumption, physical activity, total energy intake, BMI, medication for hyperlipidaemia, history of diabetes, and history of hypertension as time-dependent categorical variables and baseline age, center, year of screening exam, education level as time-fixed variables.

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40
Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years; SV ratio, skeletal muscle mass to visceral fat area ratio.

Table 3. Comparison of the discriminatory power of the skeletal muscle mass to visceral fat area ratios in the detection of non-alcoholic fatty liver disease

	AUROC (95% CI)		NRI[c]		IDI	
	Harrel's C (95% CI)	*P* value	Index	*P* value	Index	*P* value
Addition of SV ratio to BMI						
Men						
Base model (age and BMI)[a]	0.643 (0.638–0.647)	reference		reference		reference
+ SV ratio	0.650 (0.646–0.654)	< 0.001	0.03994	< 0.001	0.00636	< 0.001
Women						
Base model (age and BMI)[a]	0.779 (0.774–0.783)	reference		reference		reference
+ SV ratio	0.782 (0.778–0.787)	< 0.001	0.00757	0.013	0.00041	0.073
Addition of SV ratio to waist circumference						
Men						
Base model (age and waist circumference)[b]	0.649 (0.644–0.653)	reference		reference		reference
+ SV ratio	0.656 (0.652–0.660)	< 0.001	0.04078	< 0.001	0.00537	< 0.001
Women						
Base model (age and waist circumference)[b]	0.769 (0.765–0.774)	reference		reference		reference
+ SV ratio	0.778 (0.774–0.783)	< 0.001	0.02538	< 0.001	0.00371	< 0.001

[a] Base model adjusted for age and BMI.
[b] Base model adjusted for age and waist circumference.
[c] Risk cut-offs of 10% and 30% were used.
Abbreviations: AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SV ratio, skeletal muscle mass and visceral fat area ratio.

Table 4. Development of hepatic steatosis (HS) plus intermediate / high probability of advanced fibrosis by skeletal muscle mass to visceral fat area ratio quintiles

SV ratio (kg/cm^2) quintiles	HS plus intermediate-to-high FIB-4				HS plus intermediate-to-high NFS			
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men								
Q1 (< 0.26)	46,789	368	7.9	2.83 (2.19-3.64)	46,297	570	12.3	3.98 (3.21-4.93)
Q2 (0.26-0.30)	47,295	223	4.7	2.20 (1.70-2.84)	46,950	386	8.2	3.23 (2.60-4.00)
Q3 (0.31-0.35)	47,094	186	3.9	2.01 (1.56-2.61)	46,972	251	5.3	2.20 (1.76-2.75)
Q4 (0.36-0.44)	46,728	153	3.3	1.71 (1.31-2.23)	46,628	195	4.2	1.70 (1.35-2.14)
Q5 (≥ 0.45)	46,344	86	1.9	1.00 (reference)	46,292	114	2.5	1.00 (reference)
p–trend				<0.001				<0.001
Per 0.1 decrease in SV ratio				1.36 (1.27-1.45)				1.55 (1.46-1.65)
Women								
Q1 (< 0.19)	67,879	177	2.6	7.96 (3.85-16.44)	67,702	274	4.0	12.69 (6.88-23.41)
Q2 (0.19-0.22)	72,083	65	0.9	4.60 (2.20-9.61)	72,014	105	1.5	6.27 (3.36-11.69)
Q3 (0.23-0.26)	70,823	35	0.5	3.01 (1.39-6.49)	70,759	54	0.8	3.74 (1.95-7.16)
Q4 (0.27-0.31)	70,163	28	0.4	2.84 (1.29-6.23)	70,176	26	0.4	2.01 (0.99-4.07)
Q5 (≥ 0.32)	70,365	8	0.1	1.00 (reference)	70,350	11	0.2	1.00 (reference)
p–trend				<0.001				<0.001
Per 0.1 decrease in SV ratio				2.57 (2.01-3.28)				3.95 (3.21-4.87)

[a] Estimated from Cox proportional hazard models with adjustment for age, center, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidemia, history of diabetes (only for HS plus intermediate-to-high FIB-4) and history of hypertension.
The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63
The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40
Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Table 5. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by overall obesity

SV ratio (kg/cm^2) quintiles	No obesity				Obesity				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men									
Q1 (< 0.26)	20,065	2,203	109.8	2.92 (2.73-3.13)	14,363	2,734	190.3	1.72 (1.42-2.07)	<0.001
Q2 (0.26-0.30)	27,067	2,716	100.3	2.63 (2.47-2.80)	9,686	1,559	161.0	1.42 (1.17-1.72)	
Q3 (0.31-0.35)	31,908	2,664	83.5	2.15 (2.02-2.28)	6,455	964	149.4	1.31 (1.08-1.59)	
Q4 (0.36-0.44)	36,326	2,526	69.5	1.75 (1.64-1.86)	3,604	435	120.7	1.05 (0.85-1.28)	
Q5 (≥ 0.45)	41,404	1,686	40.7	1.00 (reference)	988	114	115.4	1.00 (reference)	
p–trend				<0.001				<0.001	
Per 0.1 decrease in SV ratio				1.34 (1.32-1.36)				1.31 (1.26-1.37)	0.308
Women									
Q1 (< 0.19)	45,524	2,141	47.0	7.97 (7.10-8.94)	13,498	1,787	132.4	1.87 (0.47-7.48)	<0.001
Q2 (0.19-0.22)	62,913	2,034	32.3	5.93 (5.29-6.65)	3,661	372	101.6	1.49 (0.37-5.99)	
Q3 (0.23-0.26)	66,588	1,328	19.9	3.75 (3.33-4.22)	1,092	105	96.2	1.39 (0.34-5.62)	
Q4 (0.27-0.31)	68,134	789	11.6	2.22 (1.96-2.52)	259	30	115.8	1.69 (0.40-7.09)	
Q5 (≥ 0.32)	69,580	354	5.1	1.00 (reference)	30	2	66.5	1.00 (reference)	
p–trend				<0.001				<0.001	
Per 0.1 decrease in SV ratio				2.77 (2.65-2.90)				1.50 (1.32-1.69)	<0.001

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes (only for HS plus intermediate-to-high FIB-4), and history of hypertension

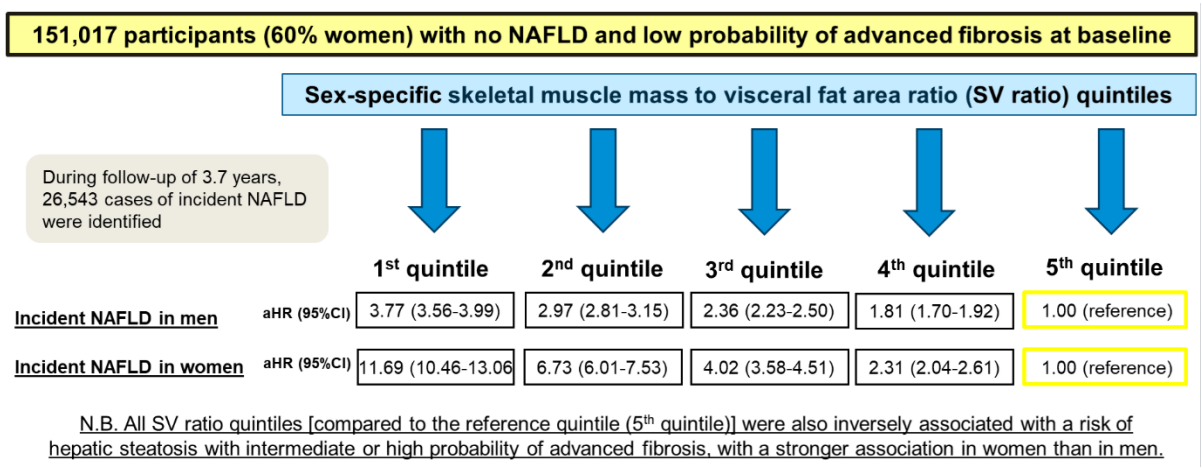
[b] *P for interaction*

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Graphical Abstract



Skeletal muscle mass to visceral fat area ratio as a predictor of nonalcoholic fatty liver disease in lean and overweight men and women with effect modification by sex

Running title: SV ratio and fatty liver

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Supplementary Tables

Supplementary Table 1. Estimated mean values (95% CI) and adjusted proportion (95% CI) of baseline characteristics according to skeletal muscle mass to visceral fat area ratio quintiles among men (N=59,699)

Supplementary Table 2. Estimated mean values (95% CI) and adjusted proportion (95% CI) of baseline characteristics by skeletal muscle mass to visceral fat area ratio quintiles among women (N=91,318)

Supplementary Table 3. Baseline characteristics according to missing data for study variables among eligible participants without NAFLD or other liver diseases at baseline (N=164,815)

Supplementary Table 4. Age-and sex-adjusted anthropometry and body composition characteristics according to the missing data (N=164,815)

Supplementary Table 5. Hazard ratios (95% CI) of non-alcoholic fatty liver disease, and NAFLD with intermediate-to-high probability of advanced fibrosis according to skeletal muscle mass to visceral fat area ratio quintiles after further adjustment for waist circumference as continuous variable instead of body mass index

Supplementary Table 6. Comparison of the discriminatory power of the visceral fat area, skeletal mass appendix, skeletal muscle mass, and visceral fat area ratios for detecting non-alcoholic fatty liver

disease (base model adjusted for age and either BMI or waist circumference)

Supplementary Table 7. Overall accuracy for non-alcoholic fatty liver disease by adiposity indices

Supplementary Table 8. Age-standardized incidence density of hepatic steatosis (HS) and HS plus intermediate/high probability of advanced fibrosis by sex

Supplementary Table 9. Hazard ratiosa (95% CI) of non-alcoholic fatty liver disease, and NAFLD with intermediate-to-high probability of advanced fibrosis according to skeletal muscle mass to visceral fat area ratio quintiles after further adjustment for HOMA-IR and hs-CRP

Supplementary Table 10. Development of hepatic steatosis (HS) and a high probability of advanced fibrosis by skeletal muscle mass to visceral fat area ratio quintiles

Supplementary Table 11. Hazard ratiosa (95% confidence intervals) of non-alcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by abdominal obesity

Supplementary Table 12. Hazard ratios (95% confidence intervals) of nonalcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by BMI categories

Supplementary Table 13. Hazard ratiosa (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on Fiborsis-4 score according to skeletal muscle mass to visceral fat area quintiles by overall obesity

Supplementary Table 14. Hazard ratiosa (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on Fiborsis-4 score according to skeletal muscle mass to visceral fat area quintiles by abdominal obesity

Supplementary Table 15. Hazard ratiosa (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on non-alcoholic fatty liver disease fibrosis score (NFS) according to skeletal muscle mass to visceral fat area quintiles by overall obesity

Supplementary Table 16. Hazard ratiosa (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on non-alcoholic fatty liver disease fibrosis score (NFS) according to skeletal muscle mass to visceral fat area quintiles by

abdominal obesity

Supplementary Table 17. Hazard ratiosa (95% confidence intervals) of non-alcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by menopausal status

Supplementary Table 1. Estimated[a] mean values (95% CI) and adjusted[a] proportion (95% CI) of baseline characteristics according to skeletal muscle mass to visceral fat area ratio quintiles among men (N=59,699)

Characteristics	SV ratio quintiles (kg/cm^2)					*p*– trend
	Q1(0. 09-0.26)	Q2(0.26-0.31)	Q3(0.31-0.36)	Q4(0.36-0.45)	Q5(0.45-8.04)	
Number of participants	11,940	11,943	11,937	11,942	11,937	
Age (years)	40.9 (40.8-41.0)	37.8 (37.7-37.9)	36.7 (36.6-36.8)	36.2 (36.1-36.3)	35.6 (35.5-35.7)	<0.001
Seoul center(%)	68.8 (67.9-69.7)	61.0 (60.2-61.9)	53.8 (52.9-54.7)	45.8 (44.9-46.7)	35.8 (34.9-36.6)	<0.001
Alcohol intake (%) [b]	48.2 (47.3-49.1)	47.1 (46.2-48.0)	44.0 (43.1-44.9)	42.7 (41.8-43.5)	39.9 (39.1-40.8)	<0.001
Current smoker (%)	26.4 (25.6-27.2)	27.3 (26.5-28.1)	26.8 (26.0-27.6)	26.6 (25.8-27.4)	28.4 (27.6-29.3)	0.016
HEPA (%)	14.0 (13.4-14.6)	14.8 (14.1-15.4)	15.6 (14.9-16.2)	17.5 (16.8-18.2)	20.4 (19.7-21.2)	<0.001
Education level (%) [c]	92.9 (92.5-93.4)	92.8 (92.3-93.2)	92.0 (91.5-92.5)	90.3 (89.8-90.9)	88.3 (87.7-88.9)	<0.001
History of diabetes (%)	0.9 (0.8-1.0)	1.0 (0.8-1.2)	0.9 (0.7-1.1)	0.8 (0.7-1.0)	1.2 (1.0-1.4)	0.142
History of hypertension (%)	7.8 (7.3-8.2)	6.3 (5.8-6.7)	5.8 (5.3-6.2)	5.6 (5.2-6.0)	4.8 (4.4-5.2)	<0.001
History of CVD (%)	0.9 (0.7-1.1)	0.7 (0.6-0.9)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.6-0.9)	0.662
Anti-lipid medication use (%)	2.1 (1.9-2.3)	1.7 (1.5-2.0)	1.4 (1.2-1.6)	1.2 (0.9-1.4)	1.0 (0.8-1.2)	<0.001
Obesity (%) [d]	50.3 (49.4-51.2)	29.8 (29.0-30.6)	18.7 (18.0-19.4)	9.8 (9.3-10.3)	2.6 (2.4-2.9)	<0.001
Abdominal obesity (%)[e]	34.3 (33.4-35.2)	17.3 (16.6-18.0)	10.2 (9.7-10.7)	4.1 (3.8-4.5)	0.7 (0.6-0.9)	<0.001
Body mass index (kg/m^2)	25.1 (25.1-25.1)	24.0 (24.0-24.1)	23.3 (23.3-23.4)	22.6 (22.6-22.7)	21.3 (21.3-21.4)	<0.001
Waist circumference (cm)	87.1 (87.0-87.2)	84.5 (84.4-84.6)	82.8 (82.7-82.9)	80.9 (80.8-81.0)	77.1 (77.0-77.2)	<0.001
Glucose (mg/dl)	93.9 (93.7-94.1)	93.8 (93.6-94.0)	93.4 (93.3-93.6)	93.3 (93.1-93.5)	92.6 (92.4-92.8)	<0.001
HbA1c (%)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	0.008
SBP(mmHg)	113.4 (113.2-113.6)	112.0 (111.8-112.2)	111.3 (111.1-111.5)	110.4 (110.2-110.6)	108.9 (108.7-109.1)	<0.001
DBP(mmHg)	72.8 (72.7-73.0)	71.9 (71.7-72.0)	71.4 (71.3-71.6)	70.7 (70.6-70.9)	69.7 (69.5-69.8)	<0.001
Total cholesterol (mg/dl)	200.1 (199.5-200.7)	196.3 (195.7-196.8)	193.5 (192.9-194.0)	189.8 (189.2-190.3)	183.7 (183.1-184.3)	<0.001
LDL-C(mg/dl)	131.1 (130.5-131.6)	127.9 (127.4-128.4)	125.8 (125.3-126.3)	122.3 (121.8-122.8)	115.7 (115.2-116.2)	
HDL-C (mg/dl)	54.5 (54.2-54.7)	55.3 (55.1-55.5)	56.1 (55.9-56.3)	57.8 (57.6-58.1)	61.2 (61.0-61.4)	<0.001
Triglycerides (mg/dl)	119.1 (118.0-120.1)	113.5 (112.4-114.5)	108.3 (107.3-109.4)	102.9 (101.8-103.9)	90.6 (89.6-91.7)	<0.001
GTP(U/L)	36.3 (35.8-36.8)	31.8 (31.4-32.3)	29.5 (29.0-29.9)	26.9 (26.4-27.3)	23.2 (22.8-23.7)	<0.001
ALT (U/L)	25.0 (24.8-25.2)	23.4 (23.2-23.6)	22.0 (21.8-22.2)	20.6 (20.4-20.8)	18.6 (18.4-18.8)	<0.001
AST (U/L)	21.6 (21.5-21.7)	21.0 (20.9-21.2)	20.6 (20.5-20.7)	20.2 (20.1-20.3)	20.0 (19.9-20.1)	<0.001

hs-CRP (mg/L)	1.21 (1.09-1.34)	1.04 (0.92-1.16)	1.03 (0.91-1.15)	0.91 (0.79-1.03)	1.01 (0.89-1.13)	<0.001
HOMA-IR	1.52 (1.51-1.54)	1.38 (1.37-1.40)	1.30 (1.29-1.32)	1.21 (1.20-1.22)	1.05 (1.04-1.07)	<0.001
Total energy intake (kcal/d) [f]	1517 (1503-1530)	1526 (1513-1539)	1527 (1514-1539)	1533 (1520-1545)	1536 (1523-1549)	0.167
ASM (kg)	23.1 (23.1-23.2)	23.8 (23.8-23.9)	24.0 (24.0-24.1)	24.1 (24.1-24.2)	24.0 (24.0-24.1)	<0.001
Visceral fat area (cm^2)	100.6 (100.4-100.8)	83.2 (83.0-83.4)	72.0 (71.8-72.2)	60.5 (60.3-60.7)	42.1 (41.9-42.2)	<0.001
Fat mass (kg)	19.9 (19.9-20.0)	16.9 (16.8-17.0)	15.1 (15.1-15.2)	13.2 (13.2-13.3)	10.0 (9.9-10.0)	<0.001

[a]Adjusted for age

[b] ≥10 g/day; [c] ≥ College graduate; [d] BMI ≥ 25kg/m^2; [e] waist circumference ≥90 cm; [f] among 40,152 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake)

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63.

Abbreviations: ALT, alanine aminotransferase; ASM, appendicular skeletal muscle mass; AST, aspartate transaminase; CI, confidence intervals; CVD, cardiovascular disease; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physically active; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 2. Estimated[a] mean values (95% CI) and adjusted[a] proportion (95% CI) of baseline characteristics by skeletal muscle mass to visceral fat area ratio quintiles among women (N=91,318)

Characteristics	SV ratio quintiles (kg/cm^2)					*p*– trend
	Q1 (0.06-0.18)	Q2 (0.18-0.22)	Q3 (0.22-0.25)	Q4 (0.25-0.30)	Q5 (0.30-6.34)	
Number of participants	18,265	18,266	18,261	18,263	18,263	
Age (years)	39.7 (39.6-39.8)	37.8 (37.7-37.9)	36.7 (36.6-36.8)	35.7 (35.6-35.8)	34.0 (33.9-34.1)	<0.001
Seoul center (%)	47.1 (46.3-47.8)	49.0 (48.3-49.7)	52.5 (51.8-53.2)	55.4 (54.7-56.1)	63.3 (62.6-64.0)	<0.001
Alcohol intake (%) [b]	11.9 (11.4-12.4)	10.1 (9.6-10.5)	9.8 (9.4-10.2)	10.1 (9.7-10.5)	9.7 (9.3-10.1)	<0.001
Current smoker (%)	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.2 (1.0-1.4)	1.4 (1.3-1.6)	1.7 (1.5-1.9)	0.001
HEPA (%)	9.7 (9.3-10.1)	10.0 (9.6-10.4)	10.5 (10.1-11.0)	12.1 (11.6-12.5)	13.7 (13.2-14.3)	<0.001
Education level (%) [c]	75.7 (75.1-76.4)	82.1 (81.6-82.7)	85.0 (84.5-85.5)	86.0 (85.5-86.5)	86.4 (85.9-86.9)	<0.001
History of diabetes (%)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.2 (0.1-0.3)	0.2 (0.2-0.3)	0.004
History of hypertension (%)	2.0 (1.9-2.2)	1.4 (1.2-1.6)	1.2 (1.1-1.4)	1.2 (1.0-1.4)	1.0 (0.8-1.1)	<0.001
History of CVD (%)	0.5 (0.4-0.5)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.4 (0.3-0.5)	0.321
Anti-lipid medication use (%)	0.9 (0.8-1.0)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	<0.001
Obesity (%) [d]	27.5 (26.9-28.2)	6.4 (6.0-6.8)	1.9 (1.7-2.1)	0.4 (0.4-0.5)	0.0 (0.0-0.1)	<0.001
Abdominal obesity (%)[e]	23.7 (23.1-24.4)	7.6 (7.2-8.0)	2.3 (2.1-2.5)	0.7 (0.6-0.8)	0.2 (0.1-0.2)	<0.001
Body mass index (kg/m^2)	23.7 (23.6-23.7)	21.9 (21.9-21.9)	20.9 (20.9-20.9)	20.1 (20.1-20.1)	19.0 (19.0-19.1)	<0.001
Waist circumference (cm)	79.9 (79.8-80.0)	76.0 (75.9-76.0)	73.5 (73.4-73.6)	71.4 (71.3-71.5)	68.4 (68.3-68.5)	<0.001
Glucose (mg/dl)	91.1 (91.0-91.2)	90.1 (90.0-90.2)	89.7 (89.6-89.8)	89.2 (89.1-89.4)	88.6 (88.5-88.7)	<0.001
HbA1c (%)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	5.5 (5.5-5.5)	0.002
Total cholesterol (mg/dl)	192.4 (192.0-192.9)	186.2 (185.8-186.6)	182.7 (182.2-183.1)	180.7 (180.3-181.1)	178.4 (178.0-178.9)	<0.001
SBP(mmHg)	103 (102.9-103.2)	100.5 (100.4-100.7)	99.6 (99.4-99.7)	99.1 (99.0-99.3)	98.5 (98.3-98.6)	<0.001
DBP(mmHg)	65.5 (65.4-65.6)	64.2 (64.1-64.4)	63.8 (63.7-63.9)	63.7 (63.6-63.9)	63.6 (63.4-63.7)	<0.001
LDL-C(mg/dl)	118.6 (118.2-119.0)	111.5 (111.1-111.8)	107.4 (107.0-107.7)	104.2 (103.8-104.6)	99.8 (99.4-100.2)	<0.001
HDL-C (mg/dl)	64.7 (64.4-64.9)	66.5 (66.3-66.7)	68.1 (67.9-68.4)	70.3 (70.0-70.5)	72.5 (72.3-72.8)	<0.001
Triglycerides (mg/dl)	87.5 (87.0-88.0)	79.8 (79.3-80.3)	75.1 (74.6-75.6)	70.2 (69.7-70.7)	65.3 (64.8-65.8)	<0.001
GTP(U/L)	17.1 (16.9-17.2)	14.9 (14.7-15.0)	14.2 (14.0-14.3)	13.9 (13.7-14.1)	14.1 (13.9-14.2)	<0.001
ALT (U/L)	15.1 (15.0-15.2)	13.9 (13.8-14.0)	13.4 (13.3-13.5)	13.4 (13.2-13.5)	13.4 (13.3-13.6)	<0.001
AST (U/L)	17.8 (17.7-17.8)	17.3 (17.2-17.4)	17.2 (17.2-17.3)	17.4 (17.3-17.5)	17.8 (17.7-17.9)	<0.001
hs-CRP (mg/L)	1.28 (1.17-1.38)	0.83 (0.73-0.93)	0.73 (0.63-0.83)	0.78 (0.68-0.88)	0.62 (0.51-0.72)	<0.001

HOMA-IR	1.59 (1.58-1.60)	1.34 (1.33-1.35)	1.22 (1.21-1.23)	1.10 (1.09-1.11)	0.96 (0.95-0.97)	<0.001
Total energy intake (kcal/d) [f]	1285 (1274-1295)	1290 (1279-1300)	1275 (1264-1285)	1275 (1265-1285)	1309 (1298-1319)	0.001
ASM (kg)	15.4 (15.3-15.4)	15.5 (15.5-15.6)	15.7 (15.6-15.7)	15.8 (15.8-15.9)	16.2 (16.2-16.2)	<0.001
Visceral fat area (cm^2)	93.9 (93.7-94.0)	73.5 (73.4-73.7)	63.7 (63.5-63.9)	55.0 (54.8-55.1)	42.0 (41.8-42.2)	<0.001
Fat mass (kg)	21.7 (21.6-21.7)	17.8 (17.8-17.9)	15.7 (15.6-15.7)	13.7 (13.7-13.8)	11.2 (11.1-11.2)	<0.001

[a]Adjusted for age

[b] ≥10 g/day; [c] ≥ College graduate; [d] BMI ≥ 25kg/m^2; [e] waist circumference ≥85 cm; [f] among 63,738 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake)

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40.

Abbreviations: ALT, alanine aminotransferase; ASM, appendicular skeletal muscle mass; AST, aspartate transaminase; CI, confidence intervals; CVD, cardiovascular disease; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physically active; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 3. Baseline characteristics according to missing data for study variables among eligible participants without NAFLD or other liver diseases at baseline (N=164,815)

Characteristics	Participants with No missing data (included in the final analysis)	Missing data (not included)
Number	151,017	13,798
Age (years) [a]	37.0 (6.6)	40.7 (8.6)
Male (%)	39.5	26.4
Alcohol intake (%)[c]	23.8	22.4
Current smoker (%)	11.7	8.7
High education level (%)[d]	86.3	80.2
HEPA (%)[e]	13.2	14.8
History of diabetes (%)	0.6	1.1
History of hypertension (%)	3.3	4.6
History of CVD (%)	0.6	1.1
Anti-lipid medication use (%)	1.0	2.1
Systolic BP (mmHg) [a]	104.5 (11.2)	104.2 (11.9)
Diastolic BP (mmHg) [a]	67.0 (8.7)	66.7 (9.0)
Glucose (mg/dL) [a]	91.2 (9.0)	92.1 (9.6)
Total cholesterol (mg/dL) [a]	187.5 (31.4)	190.5 (33.2)
LDL-C (mg/dL) [a]	114.7 (29.4)	118.6 (30.9)
HDL-C (mg/dL) [a]	63.9 (15.5)	83.5 (35.0)
Triglycerides (mg/dL) [b]	76 (57–104)	75 (57–104)
ALT (U/L) [b]	14 (11–20)	14 (11–19)
AST (U/L) [b]	18 (15–21)	17 (14–21)
GGT (U/L) [b]	15 (11–23)	14 (11–21)
hsCRP (mg/L) [b]	0.3 (0.2–0.6)	0.4 (0.2–0.8)
HOMA-IR [b]	1.12 (0.78–1.58)	1.16 (0.80–1.65)
Total calorie intake (kcal/day) [b, f]	1321 (972-1696)	1258 (892-1656)

Data are expressed as [a] mean (standard deviation), [b] median (interquartile range), or percentage.
[c] ≥10 g/day
[d] ≥ college graduate; [e] defined as physical activity that meets either of two criteria: (i) vigorous-intensity activity on three or more days per week accumulating ≥1,500 metabolic equivalents (MET) min/week; or (ii) seven days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving at least 3,000 MET-min/week
[f] Among 111,535 participants with plausible estimated energy intake levels (within three standard deviations of the log-transformed mean energy intake)
Abbreviations: ALT, alanine aminotransferase; ASM, appendicular skeletal muscle mass; AST, aspartate transaminase; CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physically active; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein

Supplementary Table 4. Age-and sex-adjusted anthropometry and body composition characteristics according to the missing data (N=164,815)

Characteristics	Participants with No missing data (included in the final analysis)	Missing data (not included)
Number	151,017	13,798
Body mass index (kg/m^2)	22.0 (21.9–22.0)	22.1 (22.0–22.1)
Waist circumference (cm)	77.2 (77.2–77.2)	77.2 (77.1–77.3)
ASM (kg)	18.8 (18.8–18.8)	18.9 (18.9–18.9)
Visceral fat area (cm^2)	68.2 (68.1–68.3)	69.5 (69.1–69.8)
Fat mass (kg)	15.6 (15.6–15.7)	15.8 (15.8–15.9)
SV ratio	0.31 (0.30–0.31)	0.31 (0.31–0.31)

Adjusted for age and sex;
Abbreviations: ASM, appendicular skeletal muscle mass; CI, confidence intervals; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 5. Hazard ratios[a] (95% CI) of non-alcoholic fatty liver disease, and NAFLD with intermediate-to-high probability of advanced fibrosis according to skeletal muscle mass to visceral fat area ratio quintiles after further adjustment for waist circumference as continuous variable instead of body mass index

SV ratio (kg/cm^2) quintiles	**NAFLD**	**NAFLD+ intermediate-to-high Fib4**	**NAFLD+ intermediate-to-high NFS**
Men			
Q1 (0.09-0.26)	1.91 (1.79-2.04)	1.62 (1.23-2.15)	1.34 (1.06-1.69)
Q2 (0.26-0.31)	1.81 (1.71-1.92)	1.46 (1.11-1.91)	1.46 (1.17-1.83)
Q3 (0.31-0.36)	1.62 (1.53-1.72)	1.47 (1.12-1.92)	1.20 (0.95-1.50)
Q4 (0.36-0.45)	1.41 (1.33-1.50)	1.39 (1.06-1.82)	1.15 (0.91-1.45)
Q5 (0.45-8.04)	1.00 (reference)	1.00 (reference)	1.00 (reference)
p–trend	<0.001	0.005	0.004
Per 0.1 decrease in SV ratio	1.2 (1.18-1.22)	1.17 (1.08-1.26)	1.11 (1.04-1.18)
Women			
Q1 (0.06-0.18)	3.80 (3.38-4.28)	3.43 (1.61-7.31)	3.23 (1.71-6.12)
Q2 (0.18-0.22)	3.27 (2.92-3.67)	2.68 (1.27-5.67)	2.63 (1.40-4.96)
Q3 (0.22-0.25)	2.46 (2.18-2.76)	2.07 (0.95-4.50)	2.07 (1.08-3.98)
Q4 (0.25-0.30)	1.71 (1.51-1.94)	2.26 (1.03-4.97)	1.35 (0.66-2.75)
Q5 (0.30-6.34)	1.00 (reference)	1.00 (reference)	1.00 (reference)
p–trend	<0.001	<0.001	<0.001
Per 0.1 decrease in SV ratio	1.85 (1.77-1.94)	1.54 (1.19-2.01)	1.64 (1.31-2.04)

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes (not for HS plus intermediate-to-high **NFS**), history of hypertension and waist circumference.

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63.

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40.

Abbreviations: FIB-4, Fibrosis-4 score; NFS, non-alcoholic fatty liver disease fibrosis score; CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 6. Comparison of the discriminatory power of the visceral fat area, skeletal mass appendix, skeletal muscle mass, and visceral fat area ratios for detecting non-alcoholic fatty liver disease (base model adjusted for age and either BMI or waist circumference)

	AUROC (95% CI)		NRI[c]		IDI	
	Harrel's C (95% CI)	*P* value	Index	*P* value	Index	*P* value
Men						
Base model (age and BMI)[a]	0.643 (0.638–0.647)	Reference		Reference		Reference
+ Visceral fat area	0.649 (0.645–0.653)	< 0.001	0.00989	< 0.001	0.00459	< 0.001
+ Appendicular skeletal muscle mass	0.646 (0.642–0.650)	< 0.001	0.00586	0.009	0.00200	< 0.001
+ SV ratio	0.650 (0.646–0.654)	< 0.001	0.03994	< 0.001	0.00636	< 0.001
Base model (age and waist circumference)[b]	0.649 (0.644–0.653)	Reference		Reference		Reference
+ Visceral fat area	0.654 (0.655–0.658)	< 0.001	0.00816	0.001	0.00300	< 0.001
+ Appendicular skeletal muscle mass	0.653 (0.649–0.657)	< 0.001	0.01095	< 0.001	0.00391	< 0.001
+ SV ratio	0.656 (0.652–0.660)	< 0.001	0.04078	< 0.001	0.00537	< 0.001
Women						
Base model (age and BMI)[a]	0.779 (0.774–0.783)	Reference		Reference		Reference
+ Visceral fat area	0.781 (0.777–0.786)	< 0.001	–0.00077	0.658	0.00002	0.824
+ Appendicular skeletal muscle mass	0.780 (0.775–0.785)	< 0.001	–0.00047	0.782	0.00013	0.085
+ SV ratio	0.782 (0.778–0.787)	< 0.001	0.00757	0.013	0.00041	0.073
Base model (age and waist circumference)[b]	0.769 (0.765–0.774)	Reference		Reference		Reference
+ Visceral fat area	0.779 (0.774–0.783)	< 0.001	0.01756	< 0.001	0.00323	< 0.001
+ Appendicular skeletal muscle mass	0.770 (0.765–0.775)	< 0.001	0.00564	0.004	0.00006	0.555
+ SV ratio	0.778 (0.774–0.783)	< 0.001	0.02538	< 0.001	0.00371	< 0.001

[a] Base model adjusted for age and BMI.
[b] Base model adjusted for age and waist circumference.

Risk cut-offs of 10% and 30% were used.
Abbreviations: AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence intervals; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SV ratio, skeletal muscle mass; visceral fat area ratio.

Supplementary Table 7. Overall accuracy for non-alcoholic fatty liver disease by adiposity indices

	AUROCs (95% CI)[a]	
	Men	Women
BMI	0.640 (0.636–0.644)	0.769 (0.765–0.774)
Waist circumference	0.647 (0.643–0.651)	0.759 (0.754–0.764)
SV ratio	0.619 (0.614–0.623)	0.729 (0.724–0.734)

[a] Values are presented as AUROCs with 95% CIs for NAFLD.
Abbreviations: ASM, appendicular skeletal muscle mass; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; SV ratio, skeletal muscle mass and visceral fat area ratio; BMI, body mass index.

Supplementary Table 8. Age-standardized incidence density of hepatic steatosis (HS) and HS plus intermediate/high probability of advanced fibrosis by sex

	Age-standardized incidence density (/ 10^3 PY)		
	For HS	For HS plus intermediate-to-high FIB-4	For HS plus intermediate-to-high NFS
Men	90.5 (89.1–91.8)	4.0 (3.8–4.3)	6.1 (5.8–6.4)
Women	27.1 (26.6–27.7)	0.9 (0.8–1.0)	1.4 (1.3–1.5)

Supplementary Table 9. Hazard ratios[a] (95% CI) of non-alcoholic fatty liver disease, and NAFLD with intermediate-to-high probability of advanced fibrosis according to skeletal muscle mass to visceral fat area ratio quintiles after further adjustment for HOMA-IR and hs-CRP

SV ratio (kg/cm^2) quintiles	**NAFLD**	**NAFLD+ intermediate-to-high Fib4**	**NAFLD+ intermediate-to-high NFS**
Men			
Q1 (0.09-0.26)	1.03 (0.81-1.32)	1.47 (1.10-1.96)	3.84 (3.08-4.78)
Q2 (0.26-0.31)	1.29 (1.02-1.62)	1.40 (1.07-1.85)	3.23 (2.59-4.02)
Q3 (0.31-0.36)	1.10 (0.87-1.39)	1.43 (1.09-1.88)	2.21 (1.76-2.77)
Q4 (0.36-0.45)	1.12 (0.89-1.42)	1.39 (1.06-1.82)	1.74 (1.38-2.21)
Q5 (0.45-8.04)	1.00 (reference)	1.00 (reference)	1.00 (reference)
p–trend	0.861	0.061	<0.001
Per 0.1 decrease in SV ratio	1.04 (0.98-1.1)	1.13 (1.05-1.22)	1.53 (1.44-1.63)
Women			
Q1 (0.06-0.18)	2.48 (1.26-4.88)	3.33 (1.47-7.51)	12.42 (6.53-23.63)
Q2 (0.18-0.22)	2.44 (1.26-4.73)	2.92 (1.31-6.48)	6.37 (3.31-12.23)
Q3 (0.22-0.25)	2.13 (1.08-4.21)	2.41 (1.06-5.46)	3.95 (2.01-7.79)
Q4 (0.25-0.30)	1.38 (0.66-2.91)	2.45 (1.06-5.66)	1.96 (0.93-4.11)
Q5 (0.30-6.34)	1.00 (reference)	1.00 (reference)	1.00 (reference)
p–trend	0.002	0.005	<0.001
Per 0.1 decrease in SV ratio	1.29 (1.03-1.62)	1.44 (1.09-1.90)	3.87 (3.11-4.82)

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes (not for HS plus intermediate-to-high **NFS**), history of hypertension, HOMA-IR and hs-CRP.

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63.

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40.

Abbreviations: FIB-4, Fibrosis-4 score; NFS, non-alcoholic fatty liver disease fibrosis score; CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 10. Development of hepatic steatosis (HS) and a high probability of advanced fibrosis by skeletal muscle mass to visceral fat area ratio quintiles

SV ratio (kg/cm^2) quintiles	HS plus high FIB-4				HS plus high NFS			
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)
Men								
Q1 (< 0.26)	47,466	28	0.6	3.37 (1.47–7.75)	47,476	31	0.7	12.61 (3.76–42.31)
Q2 (0.26–0.30)	47,684	23	0.5	2.93 (1.29–6.66)	47,687	21	0.4	8.00 (2.36–27.10)
Q3 (0.31–0.35)	47,421	21	0.4	2.70 (1.18-6.14)	47,428	18	0.4	6.53 (1.91–22.27)
Q4 (0.36–0.44)	46,958	18	0.4	2.27 (0.98–5.22)	46,962	18	0.4	6.22 (1.83–21.15)
Q5 (≥ 0.45)	46,489	8	0.2	3.37 (1.47–7.75)	46,497	3	0.1	1.00 (reference)
p–trend				0.005				<0.001
Per 0.1 decrease in SV ratio				1.36 (1.10–1.67)				1.89 (1.45–2.47)
Women								
Q1 (< 0.19)	68,204	8	0.1	3.31 (0.37–29.29)	68,204	7	0.1	4.63 (0.54–40.07)
Q2 (0.19–0.22)	72,203	4	0.1	2.45 (0.27–22.28)	72,205	3	0.0	2.13 (0.22–20.72)
Q3 (0.23–0.26)	70,883	–	–	–	70,883	–	–	–
Q4 (0.27–0.31)	70,215	1	0.0	0.85 (0.05–13.70)	70,220	–	–	–
Q5 (≥ 0.32)	70,371	1	0.0	1.00 (reference)	70,371	1	0.0	1.00 (reference)
p–trend				0.073				<0.001
Per 0.1 decrease in SV ratio				1.76 (0.65–4.73)				2.99 (0.87–10.28)

[a] Estimated from Cox proportional hazard models with adjustment for age, center, year of screening examination, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidemia, history of diabetes (only for HS plus intermediate-to-high FIB-4), and history of hypertension.

The mean SV ratio in each quintile among men was Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5 = 0.63.

The mean SV ratios in each quintile among women were Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5 = 0.40.

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 11. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by abdominal obesity

SV ratio (kg/cm^2) quintiles	No abdominal obesity				Abdominal Obesity				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men									
Q1 (< 0.26)	24,913	2,983	119.7	3.13 (2.94-3.33)	9,514	1,953	205.3	1.66 (1.2-2.3)	<0.001
Q2 (0.26-0.30)	31,185	3,301	105.9	2.71 (2.55-2.87)	5,569	974	174.9	1.38 (0.99-1.91)	
Q3 (0.31-0.35)	34,872	3,077	88.2	2.21 (2.09-2.35)	3,486	551	158.1	1.23 (0.88-1.72)	
Q4 (0.36-0.44)	38,427	2,748	71.5	1.75 (1.65-1.86)	1,492	213	142.7	1.11 (0.78-1.57)	
Q5 (≥ 0.45)	42,101	1,762	41.9	1.00 (reference)	288	37	128.3	1.00 (reference)	
p–trend				<0.001				<0.001	
Per 0.1 decrease in SV ratio				0.77 (0.76-0.78)				0.87 (0.84-0.90)	0.099
Women									
Q1 (< 0.19)	46,466	2,375	51.1	8.83 (7.87-9.9)	12,299	1,542	125.4	2.46 (1.02-5.92)	<0.001
Q2 (0.19-0.22)	61,833	2,001	32.4	6.03 (5.38-6.76)	4,606	401	87.1	1.79 (0.74-4.33)	
Q3 (0.23-0.26)	66,033	1,330	20.1	3.84 (3.41-4.32)	1,449	101	69.7	1.41 (0.57-3.46)	
Q4 (0.27-0.31)	67,795	789	11.6	2.26 (1.99-2.56)	459	29	63.1	1.3 (0.5-3.36)	
Q5 (≥ 0.32)	69,403	351	5.1	1.00 (reference)	106	5	47.0	1.00 (reference)	
p–trend				<0.001				<0.001	
Per 0.1 decrease in SV ratio				0.34 (0.33-0.36)				0.53 (0.47-0.60)	<0.001

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes, and history of hypertension

[b] *P for interaction*

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations:CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 12. Hazard ratios (95% confidence intervals) of nonalcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by BMI categories

SV ratio (kg/cm^2) quintiles	Lean (BMI <23 kg/m^2)		Overweight (BMI 23-24.9 kg/m^2)		Obesity (BMI ≥25 kg/m^2)		*P value*[b]
	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men							
Q1 (< 0.26)	84.5	2.52 (2.29–2.78)	128.6	2.00 (1.80–2.23)	190.3	1.68 (1.39–2.03)	<0.001
Q2 (0.26–0.30)	80.3	2.40 (2.20–2.61)	118.1	1.82 (1.64–2.02)	161.0	1.40 (1.16–1.70)	
Q3 (0.31–0.35)	67.1	1.98 (1.83–2.15)	103.8	1.57 (1.42–1.75)	149.4	1.30 (1.07–1.57)	
Q4 (0.36–0.44)	60.0	1.74 (1.61–1.88)	87.1	1.30 (1.17–1.45)	120.7	1.04 (0.85–1.28)	
Q5 (≥ 0.45)	35.4	1.00 (reference)	67.1	1.00 (reference)	115.4	1.00 (reference)	
p–trend		<0.001		<0.001		<0.001	
Per 0.1 decrease in SV ratio		1.27 (1.25–1.30)		1.26 (1.22–1.30)		1.30 (1.24–1.35)	0.550
Women							
Q1 (< 0.19)	34.6	6.03 (5.31–6.84)	68.4	1.76 (1.13–2.74)	132.4	1.80 (0.45–7.19)	<0.001
Q2 (0.19–0.22)	24.5	4.68 (4.14–5.28)	63.2	1.74 (1.12–2.71)	101.6	1.44 (0.36–5.79)	
Q3 (0.23–0.26)	17.3	3.40 (3.01–3.85)	46.7	1.30 (0.83–2.05)	96.2	1.34 (0.33–5.43)	
Q4 (0.27–0.31)	10.3	2.07 (1.81–2.36)	47.2	1.33 (0.83–2.14)	115.8	1.64 (0.39–6.86)	
Q5 (≥ 0.32)	4.8	1.00 (reference)	34.6	1.00 (reference)	66.5	1.00 (reference)	
p–trend		<0.001		<0.001		<0.001	
Per 0.1 decrease in SV ratio		2.39 (2.26–2.52)		1.35 (1.22–1.49)		1.46 (1.29–1.65)	<0.001

[a] Estimated from Cox proportional hazard models. The multivariable model was adjusted for age, center, year of screening examination, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidemia, history of diabetes (only for HS plus intermediate-to-high FIB-4), and history of hypertension.

[b] *P for interaction by BMI categories*

The mean SV ratio in each quintile among men was Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5 = 0.63.

The mean SV ratios in each quintile among women were Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5 = 0.40.

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 13. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on **Fiborsis-4** score according to skeletal muscle mass to visceral fat area quintiles by **overall obesity**

SV ratio (kg/cm^2) quintiles	No obesity				Obesity				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men									
Q1 (< 0.26)	25,471	204	8.0	2.57 (1.93-3.43)	21,318	164	7.7	0.68 (0.37-1.27)	<0.001
Q2 (0.26-0.30)	33,718	146	4.3	2.06 (1.54-2.74)	13,576	77	5.7	0.62 (0.33-1.16)	
Q3 (0.31-0.35)	38,316	134	3.5	1.90 (1.43-2.54)	8,779	52	5.9	0.67 (0.35-1.28)	
Q4 (0.36-0.44)	42,093	122	2.9	1.66 (1.24-2.22)	4,635	31	6.7	0.76 (0.38-1.51)	
Q5 (≥ 0.45)	45,068	75	1.7	1.00 (reference)	1,276	11	8.6	1.00 (reference)	
p–trend				<0.001				0.450	
Per 0.1 decrease in SV ratio				1.30 (1.20-1.40)				1.00 (0.89-1.13)	<0.001
Women									
Q1 (< 0.19)	50,334	118	2.3	2.33 (1.50-3.63)	17,545	59	3.4	0.69 (0.09-5.00)	0.631
Q2 (0.19-0.22)	67,568	55	0.8	1.48 (0.93-2.36)	4,515	10	2.2	0.66 (0.08-5.21)	
Q3 (0.23-0.26)	69,488	34	0.5	1.07 (0.65-1.78)	1,335	1	0.7	0.23 (0.01-3.76)	
Q4 (0.27-0.31)	69,838	27	0.4	1.00 (reference)	324	1	3.1	1.00 (reference)	
Q5 (≥ 0.32)	70,328	8	0.1	0.36 (0.17-0.80)	37	-	-	-	
p–trend				<0.001				0.549	
Per 0.1 decrease in SV ratio				2.22 (1.71-2.88)				1.05 (0.53-2.08)	0.034

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes and history of hypertension

[b] *P for interaction*

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 14. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on **Fiborsis-4** score according to skeletal muscle mass to visceral fat area quintiles by **abdominal obesity**

SV ratio (kg/cm^2) quintiles	No abdominal obesity				Abdominal Obesity				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men									
Q1 (< 0.26)	32,306	248	7.7	2.47 (1.88-3.23)	14,480	120	8.3	0.98 (0.31-3.08)	0.388
Q2 (0.26-0.30)	39,215	182	4.6	2.13 (1.63-2.78)	8,080	41	5.1	0.67 (0.21-2.17)	
Q3 (0.31-0.35)	42,172	159	3.8	1.94 (1.48-2.54)	4,917	27	5.5	0.72 (0.22-2.38)	
Q4 (0.36-0.44)	44,652	141	3.2	1.69 (1.29-2.22)	2,066	12	5.8	0.72 (0.20-2.54)	
Q5 (≥ 0.45)	45,953	83	1.8	1.00 (reference)	386	3	7.8	1.00 (reference)	
p–trend				<0.001				0.104	
Per 0.1 decrease in SV ratio				0.77 (0.72-0.83)				0.77 (0.60-0.98)	0.997
Women									
Q1 (< 0.19)	51,704	128	2.5	2.68 (1.72-4.18)	15,893	48	3.0	2.46 (1.02-5.92)	0.018
Q2 (0.19-0.22)	66,370	52	0.8	1.48 (0.92-2.38)	5,567	13	2.3	1.79 (0.74-4.33)	
Q3 (0.23-0.26)	68,937	34	0.5	1.12 (0.67-1.87)	1,681	1	0.6	1.41 (0.57-3.46)	
Q4 (0.27-0.31)	69,504	26	0.4	1.00 (reference)	517	2	3.9	1.00 (reference)	
Q5 (≥ 0.32)	70,148	8	0.1	0.38 (0.17-0.83)	116	-	-	-	
p–trend				<0.001				0.955	
Per 0.1 decrease in SV ratio				0.41 (0.32-0.53)				1.14 (0.61-2.14)	0.002

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes, and history of hypertension

[b] *P for interaction*

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 15. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on non-alcoholic fatty liver disease fibrosis score (**NFS**) according to skeletal muscle mass to visceral fat area quintiles by **overall obesity**

SV ratio (kg/cm^2) quintiles	No obesity				Obesity				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men									
Q1 (< 0.26)	25,428	226	8.9	2.43 (1.88-3.14)	20,868	344	16.5	0.94 (0.59-1.50)	0.006
Q2 (0.26-0.30)	33,598	205	6.1	2.43 (1.90-3.13)	13,353	181	13.6	0.90 (0.56-1.44)	
Q3 (0.31-0.35)	38,294	155	4.0	1.81 (1.40-2.34)	8,677	96	11.1	0.76 (0.46-1.24)	
Q4 (0.36-0.44)	42,048	144	3.4	1.57 (1.21-2.04)	4,580	51	11.1	0.73 (0.43-1.24)	
Q5 (≥ 0.45)	45,027	95	2.1	1.00 (reference)	1,265	19	15.0	1.00 (reference)	
p–trend				<0.001				0.087	
Per 0.1 decrease in SV ratio				1.30 (1.21-1.39)				1.13 (1.00-1.27)	0.308
Women									
Q1 (< 0.19)	50,317	129	2.6	4.08 (2.59-6.43)	17,385	145	8.3	0.67 (0.21-2.12)	0.033
Q2 (0.19-0.22)	67,541	76	1.1	2.65 (1.66-4.23)	4,472	29	6.5	0.67 (0.20-2.22)	
Q3 (0.23-0.26)	69,433	49	0.7	1.91 (1.17-3.14)	1,326	5	3.8	0.40 (0.10-1.69)	
Q4 (0.27-0.31)	69,857	23	0.3	1.00 (reference)	319	3	9.4	1.00 (reference)	
Q5 (≥ 0.32)	70,314	11	0.2	0.56 (0.27-1.16)	37	-	-	-	
p–trend				<0.001				0.665	
Per 0.1 decrease in SV ratio				2.59 (2.06-3.26)				1.16 (0.75-1.82)	0.001

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, and history of hypertension

[b] *P for interaction*

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 16. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease with intermediate-to-high probability of advanced fibrosis based on non-alcoholic fatty liver disease fibrosis score (**NFS**) according to skeletal muscle mass to visceral fat area quintiles by **abdominal obesity**

SV ratio (kg/cm^2) quintiles	No abdominal obesity				Abdominal Obesity				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Men									
Q1 (< 0.26)	32,168	316	9.8	2.69 (2.12-3.41)	14,126	254	18.0	0.96 (0.45-2.04)	0.051
Q2 (0.26-0.30)	39,019	273	7.0	2.66 (2.11-3.35)	7,931	113	14.2	0.81 (0.38-1.73)	
Q3 (0.31-0.35)	42,101	196	4.7	1.94 (1.53-2.46)	4,865	55	11.3	0.63 (0.29-1.38)	
Q4 (0.36-0.44)	44,587	170	3.8	1.61 (1.26-2.05)	2,031	25	12.3	0.63 (0.27-1.46)	
Q5 (≥ 0.45)	45,912	107	2.3	1.00 (reference)	377	7	18.6	1.00 (reference)	
p–trend				<0.001				0.004	
Per 0.1 decrease in SV ratio				0.74 (0.70-0.79)				0.74 (0.63-0.88)	0.956
Women									
Q1 (< 0.19)	51,654	159	3.1	5.65 (3.55-8.99)	15,764	115	7.3	0.69 (0.25-1.89)	0.001
Q2 (0.19-0.22)	66,336	76	1.1	2.98 (1.84-4.84)	5,531	29	5.2	0.66 (0.23-1.87)	
Q3 (0.23-0.26)	68,879	48	0.7	2.08 (1.24-3.47)	1,674	6	3.6	0.45 (0.13-1.60)	
Q4 (0.27-0.31)	69,525	21	0.3	1.00 (reference)	511	4	7.8	1.00 (reference)	
Q5 (≥ 0.32)	70,133	11	0.2	0.61 (0.29-1.27)	116	-	-	-	
p–trend				<0.001				0.563	
Per 0.1 decrease in SV ratio				0.30 (0.24-0.38)				0.84 (0.55-1.30)	<0.001

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, and history of hypertension

[b] *P for interaction*

The mean SV ratio in each quintile among men: Q1, 0.23; Q2, 0.29; Q3, 0.33; Q4, 0.40 and Q5, 0.63

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations: CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Supplementary Table 17. Hazard ratios[a] (95% confidence intervals) of non-alcoholic fatty liver disease according to skeletal muscle mass to visceral fat area quintiles by menopausal status

SV ratio (kg/cm^2) quintiles	Pre-menopause (N= 87,940)				Post-menopause (N=3,378)				*P value*[b]
	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Multivariable-adjusted HR[a] (95% CI)	
Q1 (< 0.19)	54,018	3,553	65.8	11.86 (10.6-13.26)	5,004	375	74.9	5.66 (2.80-11.44)	<0.001
Q2 (0.19-0.22)	64,734	2,308	35.7	6.61 (5.90-7.40)	1,840	98	53.3	5.13 (2.49-10.55)	
Q3 (0.23-0.26)	66,145	1,396	21.1	3.99 (3.54-4.49)	1,535	37	24.1	2.79 (1.30-5.98)	
Q4 (0.27-0.31)	67,156	801	11.9	2.30 (2.03-2.61)	1,237	18	14.5	1.75 (0.76-4.02)	
Q5 (≥ 0.32)	68,570	348	5.1	1.00 (reference)	1,041	8	7.7	1.00 (reference)	
p–trend				<0.001				<0.001	
Per 0.1 decrease in SV ratio				3.66 (3.51-3.82)				2.08 (1.76-2.47)	<0.001

[a] Estimated from Cox proportional hazard models. Multivariable model was adjusted for age, centre, year of screening exam, alcohol consumption, smoking, physical activity, total energy intake, education level, medication for hyperlipidaemia, history of diabetes, and history of hypertension

[b] *P for interaction*

The mean SV ratio in each quintile among women: Q1, 0.17; Q2, 0.21; Q3, 0.25; Q4, 0.29 and Q5, 0.40

Abbreviations:CI, confidence interval; HR, hazard ratio; SV ratio, skeletal muscle mass to visceral fat area ratio.

Response

31 March 2022

Prof. Gyongyi Szabo (Editor in Chief); Kymberly Watt (Associate Editor)
Hepatology Communications

Dear Prof. Gyongyi Szabo and Kymberly Watt,

Thank you for your constructive suggestions regarding our manuscript (HEP4-22-0037.R1) titled '**Skeletal muscle mass to visceral fat area ratio as a predictor for nonalcoholic fatty liver disease in lean and overweight men and women with effect modification by sex.'** We have revised the manuscript according to the reviewers' recommendations and comments as requested. As recommended, we amended our manuscript while reorganizing the Discussion section.

In addition to the revised version of the manuscript, we have uploaded a version with the changes marked in red, reflecting the modifications to the manuscript as well as our point-by-point responses to the reviewers' comments, which detail the changes made in response to these comments.

We are pleased to submit the revised version of the manuscript for publication in ***Hepatology Communications***.

The authors declare no conflicts of interest related to this manuscript, including financial conflicts. This paper has not been submitted for publication elsewhere and is not under consideration by any other journal.

Thank you for your consideration of our manuscript. Please feel free to contact me if you have any questions related to our manuscript. I look forward to hearing from you.

Sincerely,

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Reviewer(s)' Comments to Author:

Reviewer: 1

I agree with the reviewer that the discussion needs reorganization as described.

Response:

Thank you for valuable comments. We agree that our Discussion section needs to be reorganized and we amended our manuscript as your suggestions. Our point-by-point responses are provided below.

consider moving the paragraph " There are several plausible mechanisms that may explain the concurrent roles of skeletal 8 muscle and visceral fat mass in the pathophysiology of NAFLD. Skeletal muscle is a key 9 tissue, given that glucose disposal is facilitated by insulin, and reduced skeletal muscle mass..." to the introduction.

Response:

Thank you. As recommended, we moved the paragraph to the Introduction section and revised the mechanism section below.

Introduction, page 5, last part of 2nd paragraph;

> 'Skeletal muscle is a key tissue, given that glucose disposal is facilitated by insulin, and reduced skeletal muscle mass may induce relative insulin resistance [11, 12]. Visceral adipose tissue is also strongly associated with insulin resistance [40]; thus, the combination of decreased muscle mass and increased visceral fat mass may markedly perturb metabolism and increase NAFLD risk.'

Discussion, page 16, last paragraph to page 17, 1st paragraph;

> 'Several plausible mechanisms may explain the concurrent roles of skeletal muscle and visceral fat mass in the risk of NAFLD, including insulin resistance, previously described, and inflammation. The skeletal muscle is capable of secreting myokines, such as myostatin and irisin, which are involved in oxidative stress and inflammation [12]. Dysregulation of these myokines may promote liver injury by increasing insulin

resistance and oxidative stress [41]. Visceral adipose tissue macrophages produce proinflammatory cytokines, such as interleukin-6 (IL-6), and tumor necrosis factor α, which are correlated with muscle atrophy, and may increase the risk of NAFLD progression [42]. Moreover, cytokines such as IL-6, which are produced by inflamed adipose tissue, may further increase muscle wasting and exacerbate the situation in chronic inflammatory states [43].'

"Since the number of the study participants who progressed to high fibrosis score category 3 (FIB-4 ≥2.67 or NFS >0.676) during a median follow-up of 3.7 years was too small to obtain 4 a reliable estimate, we combined the individuals with an intermediate and high risk of HS 5 severity for FIB-4 and NFS scores, possibly indicating the development of NAFLD with 6 worsening of fibrosis score rather than NAFLD with advanced fibrosis".. to the methods section.

Response:

Thank you. As recommended, we moved the paragraph to the Method section.

Materials and Methods, page 8, last part of 2nd paragraph;

'Since the number of the study participants who progressed to high fibrosis score category (FIB-4 ≥2.67 or NFS >0.676) during a median follow-up of 3.7 years was too small to obtain a reliable estimate, we combined the individuals with an intermediate and high risk of HS severity for FIB-4 and NFS scores.'

and.. "Considering the 7 natural history of fibrosis progression in patients with NAFLD has a long duration of 14.3 8 (95% CI, 9.1–50.0) years in one stage of fibrosis progression for patients with NAFLD 35, future studies with longer follow-up durations are needed to determine the risk of NAFLD with high fibrosis score, a more severe form of NAFLD, according to the SV ratio."... to the limitations paragraph

Response:

Thank you. As recommended, we moved the paragraph to the Limitation section.

Discussion (limitation), page 17, last part to page 18, 1st sentence;

‘Third, the relatively short follow-up time (median of 3.7 years) precluded an evaluation of advanced fibrosis (FIB-4 ≥2.67 or NFS >0.676) due to small case numbers. Considering the natural history of fibrosis progression in patients with NAFLD has a long duration of 14.3 (95% CI, 9.1–50.0) years in one stage of fibrosis progression for patients with NAFLD [35], future studies with longer follow-up durations are needed to determine the risk of NAFLD with high fibrosis score, a more severe form of NAFLD, according to the SV ratio.’

Reviewer: 2

The authors have addressed each of the many individual criticisms I submitted in my initial review and this version of the paper is much strengthened and the methods are more granular. With that said, the organization of the discussion needs to be re-worked with the change in title and the new focus on lean and overweight individuals and also sex-based differences.

Response:

Thank you for constructive comment. As recommended for the previous revision, we have changed the title to ‘**Skeletal muscle mass to visceral fat area ratio as a predictor for nonalcoholic fatty liver disease in lean and overweight men and women with effect modification by sex**”. We have now added information on effect-modification to the Abstract. We have revised our Discussion to emphasize differences between lean and overweight individuals and also effect-modification by sex. We have also reorganized the Discussion section.