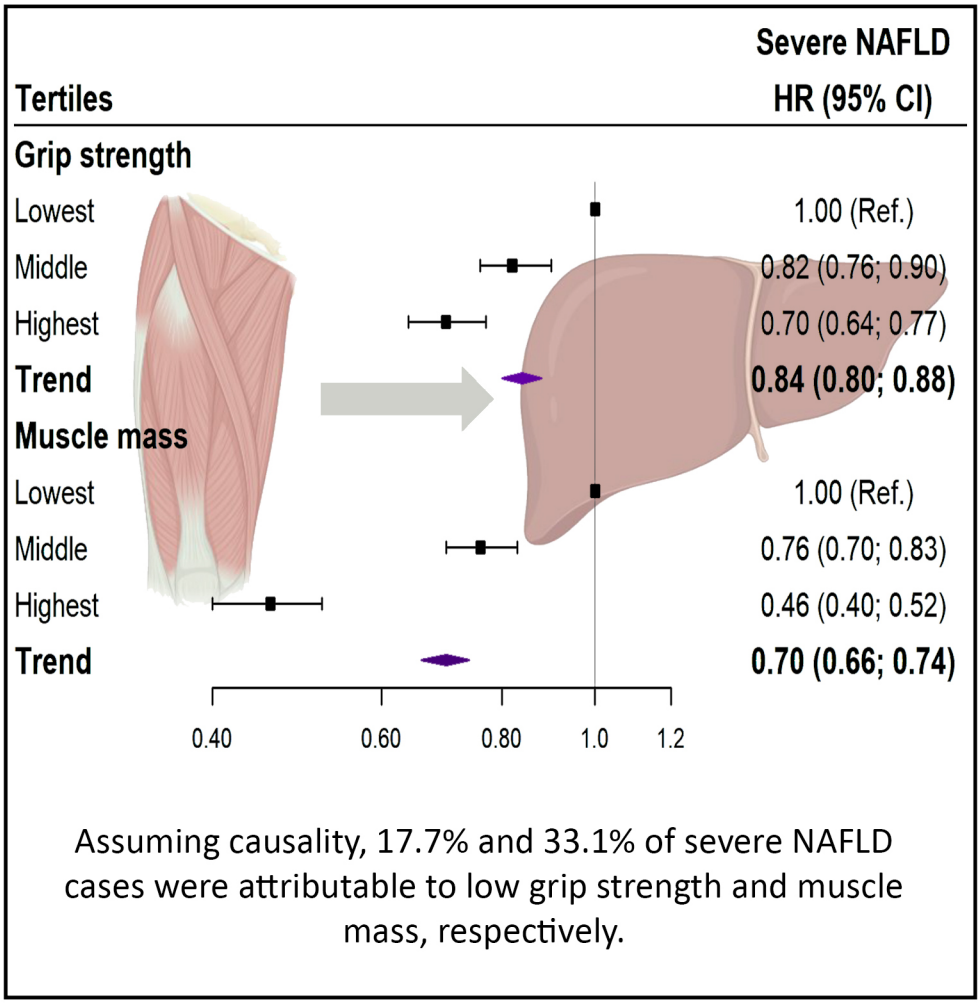


Assuming causality, 17.7% and 33.1% of severe NAFLD cases were attributable to low grip strength and muscle mass, respectively.

# Associations of muscle mass and grip strength with severe NAFLD: a prospective study of 333,295 UK Biobank participants

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## Conflict of interest

PW has received research grants from Roche Diagnostics, AstraZeneca and Boehringer Ingelheim outside the submitted work, and NS has received grant and personal fees from Boehringer Ingelheim, and personal fees from Amgen, AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi outside the submitted work. All other authors declare no conflict of interest.


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## Authorship contribution

F.P-R, F.K.H, C.C-M and J.P.P. contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. F.P-R performed the literature search and the analyses. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission, with final responsibility for publication. F.K.H, C.C-M and J.P.P contributed equally to this work and are joint senior authors. FP-R, F.K.H, C.C-M and J.P.P are the guarantor.

**Abstract**

**Background & Aim –** Cross-sectional studies have shown lower muscle mass and strength as risk factors for non-alcoholic fatty liver disease (NAFLD). However, the evidence from prospective studies is limited. This study examined both the strength and pattern of the associations between these two physical capability markers and severe NAFLD in the UK Biobank study.

**Methods –** 333,295 participants were included in this prospective study. Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer, and the Janssen equation was used to estimate skeletal muscle mass by bioimpedance. Muscle mass was adjusted for body weight and all exposures were sex-standardised. Associations of muscle mass and strength with severe NAFLD (defined as hospital admission or death) were first investigated by tertile of each exposure using Cox proportional hazard models. Nonlinear associations were investigated using penalised cubic splines fitted in the Cox proportional hazard models.

**Results** – After a median follow-up of 10 years (IQR: 9.3 to 10.7 years), 3,311 individuals were diagnosed with severe NAFLD (3,277 hospitalisations and 34 deaths). Compared with the lowest tertile of muscle mass, the risk of NAFLD was lower in the middle (HR: 0.76 [95% CI: 0.70 to 0.83] and the highest tertile (HR: 0.46 [95% CI: 0.40 to 0.52]). Tertiles of grip strength showed a similar pattern. Nonlinearity was only identified for muscle mass ($p<0.001$). One lower tertile of grip strength and muscle mass accounted for 17.7%% and 33.1%% of diagnosed severe cases, respectively.

**Conclusions –** Lower muscle mass and grip strength were associated with higher risk of developing severe NAFLD. Interventions to improve physical capability may be protective, but this needs to be investigated in appropriately designed trials.

**Keywords:** NAFLD; Grip strength; Sarcopenia; Muscle skeletal.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is a non-communicable disease characterised by excessive fat accumulation in the liver in the absence of other aetiologies such as hepatitis (both viral and autoimmune), medication, drugs, and excessive alcohol intake [1, 2]. NAFLD has been recognised as one of the most common forms of chronic liver disease. Globally, 1 out of 4 adults has been diagnosed with NAFLD (25.2%) [2], while in the UK, around 1 out of 3 adults has early stages of the disease [3]. That noted, the prevalence of diagnosed NAFLD in EU countries is far lower than 25%, at least based on available clinical records in several countries [4]. Since NAFLD is closely associated with other chronic conditions that have exponentially incremented in the last years (like type 2 diabetes, obesity, and hypertension) [5], its prevalence will likely rise as well [1, 2]. Therefore, identifying emerging risk factors contributing to the disease might help to identify high-risk individuals and develop prevention or treatment strategies.

Increased body weight, metabolic syndrome – along with its components: central adiposity, hyperglycaemia, dyslipidaemia and hypertension – type 2 diabetes, insulin resistance, older age, and ethnicity (especially South Asians) are the most common and strongest risk factors for NAFLD [1, 2]. However, other emerging risk factors, such as physical inactivity, unhealthy diet, and muscle weakness, have been identified in recent years [6]. In this context, sarcopenia, the age-related decline in muscle strength and quantity, has been found as a risk factor for NAFLD since the early stages of the disease. A causal role for sarcopenia is plausible given the function of skeletal muscle in energy metabolism. In addition, muscle atrophy and weakness are associated with insulin resistance, which is linked to NAFLD [7, 8]. Systemic inflammation, physical inactivity, and nutritional deficiencies are also considered part of both conditions' underlying mechanisms [7, 8].

Previous studies have used mainly cross-sectional data to study the associations of sarcopenia [9, 10] and its components [11-13] with prevalent NAFLD. Although some longitudinal studies have reported a higher risk of incident NAFLD in individuals with low muscle mass [14], the evidence for grip strength from prospective studies is limited. Additionally, previous studies have investigated this association using only categorical data, limiting our understanding of the true patterns of the association. Understanding whether the relationship is linear or nonlinear would inform decisions on whether mass or targeted public health interventions would be most appropriate. Therefore, considering that low muscle mass and strength are prevalent in individuals with NAFLD, especially in those with an advanced stage [15], this study aimed to examine both the strength and pattern of the associations between these two physical capability markers and severe NAFLD in the UK Biobank study.

## Methods

### *General information about UK Biobank*

UK Biobank is a cohort study that enrolled, from the general population, over 500,000 participants aged 37-73 years at baseline (5.5% response rate)[16]. In brief, between 2006 and 2010, participants attended one of 22 assessment research centres across Scotland, England and Wales [17, 18]. All participants completed a touch-screen questionnaire, had physical measurements taken, and provided blood, urine, and saliva samples at baseline. More information about the UK Biobank protocol can be found online (**http://www.ukbiobank.ac.uk).**

### *Physical capability markers*

Grip strength and muscle mass were the physical capability markers included in this prospective study. These markers were selected as they are used in the definition of sarcopenia, and the association between sarcopenia and NAFLD has been previously reported in cross-

sectional studies [9, 10]. Gait speed – used to define severe sarcopenia – was only included in one sensitivity analysis of this study as it was self-reported in UK Biobank as a categorical variable, prohibiting us from examining whether the association was nonlinear. More information about this variable can be found elsewhere [19].

Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. One value was recorded for each hand, and the average of both was expressed in absolute units (kg) and used in subsequent analyses. To estimate skeletal muscle mass, we applied the Janssen equation [20] to total body composition in ohms measured by bioimpedance (BIA, Tanita BC418MA, Tokyo, Japan). The validity of BIA-measured muscle mass was verified using Pearson's correlation coefficient, and a Bland-Altman plot against dual-energy X-ray absorptiometry (DXA) measured muscle mass in a subset of UK Biobank participants as it has been previously reported [19]. Since biological parameters might vary according to the individual's body size, confounding the results, muscle mass was divided for body weight. Grip strength is reported in absolute terms since we previously demonstrated that the association of grip strength with health outcomes did not differ according to whether it was expressed in absolute or relative terms [21]. Finally, both exposures were sex-standardised and extreme values (±2.5 standard deviations [SD] from the median [$n_{\text{both exposures}}$=15,793]) were removed (Supplementary Figure 1).

*Outcome – severe NAFLD*

Severe NAFLD (fatal and non-fatal) was defined as hospitalisation or death due to NAFLD or non-alcoholic steatohepatitis (NASH) and was ascertained from linked hospital and death databases. Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Dates and causes of hospital admissions were identified via record linkage

to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). Details of the linkage procedure can be found at http://content.digital.nhs.uk/services. Hospital admissions data were available until the end of March 2021 in England and Scotland and the end of March 2018 in Wales. Mortality data were available until the end of February 2021. Therefore, follow-up was censored at these dates.

Using the International Classification of Diseases, 10th revision (ICD-10), and the latest Expert Panel Consensus Statement [22], NAFLD (including NASH) was defined for the main analyses of this study as ICD-10 K76.0 (fatty [change of] liver, not elsewhere classified) and K75.8 (other specified inflammatory liver diseases). A broader definition was used for the sensitivity analysis, as shown in the statistical analyses section.

*Covariates*

Age at baseline was determined from dates of birth at baseline assessment. Sex was self-reported at baseline. Deprivation (area-based socioeconomic status) was derived from the postcode of residence, using the Townsend score [23]. Ethnicity was self-reported and categorised as: white, south Asian, black, Chinese, and mixed ethnic background. Self-reported smoking status was categorised as never, former or current smoker. The frequency of alcohol intake was also self-reported at baseline and categorised into 5 categories: daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only and never. The components of the metabolic syndrome (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL and high triglycerides) were defined using baseline data. Central obesity was defined as a waist circumference higher than 88 cm and 102 cm in women and men, respectively. High glycaemia/diabetes was defined as fasting glucose $\geqslant$5.6 mmol/l or self-report of a physician diagnosis of diabetes. High blood pressure/hypertension was defined as a systolic blood pressure $\geqslant$130 mm Hg and/or a diastolic blood pressure $\geqslant$85 mm

Hg or self-report of a physician diagnosis of hypertension. High triglycerides were defined as ⩾1.7 mmol/l and low HDL-cholesterol as <1.3 mmol/l in women and <1.0 mmol/l in men [24-26]. Type of physical activity was self-reported using the International Physical Activity Questionnaire short form [27]. A cumulative dietary risk factor score was applied, ranging from 0 (most healthy) to 9 (least healthy). This score was derived from 9-food items based on current UK guidelines using baseline data and has been described elsewhere [28]. Additional information on the measurements is available on the UK Biobank website (http://www.ukbiobank.ac.uk).

*Ethical Approval*

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). The study protocol is available online (http://www.ukbiobank.ac.uk/). This work was conducted under the UK Biobank application number 7155.

*Statistical analyses*

Descriptive baseline characteristics by tertile of grip strength and muscle mass are presented as means with SD for quantitative variables and as frequencies and percentages for categorical variables.

Associations between grip strength, muscle mass, and severe NAFLD were first investigated using Cox proportional hazard models by tertile of each exposure. Individuals in the lowest tertile were used as the reference group in each case. The results are reported as hazard ratios (HR) and their 95% confidence intervals (95% CIs). Time of follow-up was used as the time-dependent variable.

Nonlinear associations between these two physical capability markers and severe NAFLD were investigated using penalised cubic splines fitted in Cox proportional hazard models. The

penalised spline is a variation of the basis spline, which is less sensitive to knot numbers and placements than restricted cubic splines [29]. For the curves, the mean value of each exposure was used as a reference group. The proportional hazard assumption was checked using Schoenfeld residuals. Using the Expert Panel Consensus Statement [22], participants with other liver disease (ICD-10: B16, B17, B18, B19, E83.1, E83.0B, E88.0A, E88.0B, I82.0, K70, K73.9, K73.2, K74.3, k74.4, K74.5, K75.4, K76.5, K83.0A, K83.0F) or alcohol/drug use disorder (ICD-10: E24.4, F10, F11-F14, F16, F18, F19, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, T51.0, T51.9, X65, Y57.3, Z50.2, Z71.4, Z72.1) at/before baseline (n=10,911) were excluded (a full list of these variables can be found in Supplementary Table 1). In addition, all analyses were conducted using 2-year landmark analyses, excluding all participants who experienced events within the first two years of follow-up (n=196). This approach minimised the effect of reverse causality.

The population attributable fraction (PAF) was calculated to estimate the proportion of severe NAFLD cases that were attributable to the exposures [30]. The PAFs were derived using the adjusted HRs obtained from the nonlinear associations. The potential impact fractions (PIF) of two scenarios were calculated to determine which of the counterfactual scenarios may have had a more substantial public health impact [31]. The first scenario represented a mass population intervention approach that moved the lowest tertile to the middle tertile, and the middle tertile to the highest tertile. The second scenario represented a targeted intervention that moved only people in the lowest tertile to the middle tertile for each exposure.

Analyses were adjusted for confounding factors, including age, sex, deprivation, ethnicity, the individual components of the metabolic syndrome (central obesity, high glycaemia/diabetes, hypertension/high blood pressure, low HDL and high triglyceride), smoking, alcohol intake, physical activity, and a diet score. A directed acyclic graph explained the association between the exposures, the outcome, and covariates is available in Supplementary Figure 2. Four

sensitivity analyses were performed: i) excluding people who self-reported drinking more than 14 units of alcohol/week using the methodology reported by Jani et al. [32]; ii) using the same disease codes to ascertain NAFLD, but applied to primary care records as well as hospitalisation and death records. This more complete ascertainment, which also included less severe cases, was only possible in the 148,814 UK Biobank participants who had been linked to primary care records; iii) widening the definition of NAFLD to include a broader definition that includes K76.8 (other specified diseases of the liver), K76.9 (liver disease, unspecified) as well as unspecified liver diseases: K74.0 (hepatic fibrosis), K74.1 (hepatic sclerosis), K74.2 (hepatic fibrosis with hepatic sclerosis), and K74.6 (other and unspecified cirrhosis of the liver); and iv) using the categorical variable gait speed as exposure for the main outcome included in the analyses.

Finally, to investigate whether the association between the physical capability markers and severe NAFLD (main outcome) differed population subgroup, the analyses were repeated and stratified by age (≥ and < 60 years), sex (male and female), and alcohol intake (never/special occasions and regular drinking).

Stata 17 and R 3.6.1 were used to perform the analyses (using the packages 'forestplot', 'survival', and 'spline'). A p-value below 0.05 was considered statistically significant.

**Results**

After excluding people with missing data, liver disease or alcohol/drug use disorders at/before baseline, and events within the first two years of follow up, 333,295 participants were included in this prospective study (Supplementary Figure 1). The median follow-up was 10.0 years (interquartile range 9.3 to 10.7 years). Over this period, 3,311 participants (3,277 hospitalisations and 34 deaths without prior hospitalisation) were recorded as developing severe NAFLD.

The main baseline characteristics of participants by tertile of grip strength are presented in Table 1. Overall, individuals with a higher grip strength were younger, less likely to be deprived and more likely to be white and drink alcohol 3-4 times a week or almost daily (Table 1). They also had a lower prevalence of central obesity, high glycaemia/diabetes, high blood pressure/hypertension, high triglycerides and low HDL compared to those in the lowest tertile. Participants' characteristics by tertile of muscle mass are shown in Supplementary Table 2.

Figure 1 shows associations between tertiles of the physical capability markers and severe NAFLD. Compared with individuals in the lowest tertile of grip strength, those in the middle or the highest tertile had 0.82 (95% CI: 0.76 to 0.90) and 0.70-times (95% CI: 0.64 to 0.77) lower risk of severe NAFLD, respectively. Similar patterns of association were identified by tertile of muscle mass ($HR_{\text{middle tertile}}$: 0.76 [95% CI: 0.70 to 0.83] and $HR_{\text{highest tertile}}$: 0.46 [95% CI: 0.40 to 0.52]). Overall, the lowest trend was identified for each tertile increment in muscle mass (HR: 0.70 [95% CI: 0.66 to 0.74]). Individual associations of each covariate included in these analyses can be found in Supplementary Tables 3 and 4. When we included gait speed as exposure in a sensitivity analysis, individuals with average or brisk pace had a lower risk of severe NAFLD compared to those who self-reported a slow pace (Supplementary Table 5)

Nonlinear associations between the exposures (grip strength and muscle mass) and severe NAFLD are shown in Figure 2. After adjusting for covariates, higher grip strength and muscle mass were associated with a lower risk of severe NAFLD ($p<0.001$). There was no evidence of nonlinearity between grip strength and severe NAFLD (nonlinear $p=0.466$), but clear evidence for muscle mass (nonlinear $p<0.001$). Similar results and trends were observed when people who self-reported drinking more than >14 units of alcohol per week were excluded from the analyses (Supplementary Figure 3), when a composite of hospital and primary care data was used (Supplementary Figure 4), and when the wider definition of NAFLD was used

(Supplementary Figure 5). Grip strength also showed evidence of nonlinearity using this wider definition (Supplementary Figure 5).

When the analyses were stratified by age, sex and alcohol intake (Figure 3), a significant interaction was identified between grip strength and alcohol intake (p-interaction=0.021). In terms of muscle mass, the associations were apparent in all subgroups. However, a significant interaction was only observed for alcohol intake (p-interaction= 0.013).

Finally, assuming causality, a lower tertile of grip strength accounted for 17.7% (95% CI: 16.4 to 19.1) of severe NAFLD cases, while a lower tertile of muscle mass accounted for 33.1% (95% CI: 31.8 to 34.4). A mass intervention that moved the two lowest tertiles to the middle and highest tertiles, respectively, would prevent 12.2% (95% CI: 10.5 to 14.1) of severe NAFLD cases for grip strength and 23.4% (95% CI: 21.4 to 25.3) of severe NAFLD cases for muscle mass. In contrast, a targeted intervention that moved only the lowest tertile of each exposure to the middle tertile could potentially prevent 6.6% (95% CI: 5.46 to 7.78) and 13.8% (95% CI: 12.6 to 15.0) of severe cases, respectively. The tertile distributions of grip strength and muscle mass of these scenarios are shown in Supplementary Figures 6 and 7.

**Discussion**

We demonstrated that lower muscle mass and grip strength were associated with a higher risk of severe NAFLD. These associations were independent of confounding factors, present in all subgroups studied, and remained in the sensitivity analyses. The relationship of grip strength was mainly linear, while that of muscle mass was nonlinear. Assuming causality, our PIF analyses demonstrated that interventions on grip strength were proportional to the number of participants targeted. Still, those on muscle mass might be more efficient to target those with the lowest muscle mass (13.8% cases for 1/3 of the population) compared with those on the general public (23.4% cases for 2/3 of the population).

Our findings have identified a prospective relationship between both muscle strength and quantity and severe NAFLD. Given the prospective nature of our study – and the consistency of the results using a 2-year landmark analysis as well as different outcome definitions – the observed associations are unlikely to be due to reverse causation. Furthermore, statistical adjustment provided confidence that the associations did not merely reflect confounding by any of the individual components of the metabolic syndrome (diabetes/high glycaemia, low HDL, high triglycerides, hypertension/high blood pressure, and central obesity) – which are commonly associated with NAFLD. While the biological mechanism between muscle loss and severe NALFD is yet to be explored, it could be related to the reduction in myokines such as interleukin-6 and irisin, which could exacerbate steatosis and inflammation [33, 34]. Furthermore, muscle is a crucial cellular target of insulin. The loss in muscle quantity could trigger insulin resistance, resulting in lipolysis and generation of free fatty acids, contributing to the development and/or progression of NAFLD [35]. There are other possible behavioural mediators linking muscle loss and NAFLD. For instance, weaker muscle or general loss of functional capability was found to predict lower intention to engage in physical activity [36], which could then predispose to severe NAFLD.

This is the first European cohort study exploring both grip strength and muscle mass associations with severe NAFLD. So far, two previous cohort studies have examined muscle mass. Kim et al., over seven years of prospective follow-up of 12,624 South Korean adults without NAFLD at baseline, demonstrated that individuals in the middle and highest tertiles of muscle mass – defined as total appendicular skeletal muscle mass/bodyweight × 100% – had 27% and 56% lower risk of incident NAFLD compared with those in the lowest tertile [14]. Similar to our study, Kim et al. identified a significant interaction by sex (p interaction <0.001) but not by age (p interaction =0.228)[14]. However, they used a different age cut-off to estimate this interaction (≥ and < 50 years) and their analyses were not adjusted for alcohol intake or

diet, which are two important confounders. Likewise, in a 10-years retrospective study involving 4,398 adults, Lee et al. demonstrated that compared with individuals with higher levels of muscle mass (tertile 1), those with lower levels (tertile 2 and 3) had a higher likelihood of incident NAFLD, mainly in nonobese individuals (odds ratio $_{\text{tertile 2}}$ [OR]: 1.38 [95% CI: 1.04 to 1.84]; OR $_{\text{tertile 3}}$: 1.81 [95% CI: 1.34 to 2.45]) [37]. However, Lee et al. did not use the time to event analysis and did not adjust for deprivation or diet. Consequently, even if these two studies have reported this relationship, prospective data in this field is still limited and research investigating the association between grip strength and incident NAFLD from prospective studies is lacking. Therefore, our study not only answers our research question but also provides a unique opportunity to fill gaps in the current literature investigating for the first time both the linear and nonlinear associations between these two exposures and severe NAFLD using an exhaustive list of potential confounders.

Sarcopenia, or a decline in its components, is frequently observed in individuals with liver disease. In fact, around 70% of patients with advanced liver disease have sarcopenia [38]. In this context, and assuming causality, it is not surprising that a lower tertile of grip strength and muscle mass accounted for 17.7% and 33.1% of the severe NAFLD cases. Due to this high prevalence, previous studies and guidelines have recommended assessing muscle wasting, sarcopenia, and frailty by clinicians managing patients with liver disease [37-39]. Additionally – as sarcopenia and its components predict major complications, mortality and worse quality of life – the Japan Society of Hepatology created specific guidelines for assessing sarcopenia in people with liver disease in 2015. These guidelines propose different cut-offs to define sarcopenia and its components in this group [39]. The latter takes relevance considering that the definition of sarcopenia used, particularly how muscle mass is defined, might significantly impact findings on the association between sarcopenia and NAFLD [40]. Therefore, future studies should address the best classification for sarcopenia (especially muscle mass) and

consider other elements that affect muscle quality, such as myosteatosis: fat infiltration in the muscle [41].

*Strengths and limitations*

The use of UK Biobank enabled us to study both exposures in a single, large, and well characterised general population cohort of middle-aged and older adults and adjust for a large range of potential confounder factors, including the common drivers of NAFLD. Furthermore, we were able to assess whether the associations were linear or not and whether they were consistent across subgroups, addressing the limitations of most previous studies. However, this study is not exempt from limitations. Firstly, UK Biobank is not representative of the UK population regarding characteristics, lifestyle, and prevalent diseases. Therefore, whilst risk estimates can be generalised [42], summary statistics such as prevalence and incidence should not [43]. Secondly, our primary analyses used data from hospital admission and death records. The latter includes the advanced or severe cases of NAFLD primarily. However, we carried out a sensitivity analysis using a composite of hospital and primary care data in fewer participants to address this potential limitation. Using these data, the patterns of associations were the same. Thirdly, muscle mass was measured using BIA. Although DXA is the most common method to measure muscle mass, only 5,000 participants were assessed using this approach in the UK Biobank study. Therefore, BIA allowed maximising statistical power in our study. Muscle mass estimated using BIA has been shown to have good agreement with DXA, as shown previously ($r=0.868$, $p <0.001$) [19]. Fourthly, in spite of including a long list of confounding factors in the analyses, unmeasured or residual confounding is possible. Fifthly, gait speed was not measured in the UK Biobank study. Walking pace is usually used as a proxy and it has shown to be strongly associated with different health outcomes [44, 45]. However, it was not recorded as a continuous variable and, since we were interested in both the linear and nonlinear associations of physical capability markers used to define sarcopenia, the latter

was just included as a sensitivity analysis in the Supplementary material. Sixthly, alcohol intake was self-reported at baseline. Therefore, we might have had some recall and misclassification bias in this variable, and the consumption might change during the follow-up due to an indication of liver damage. We tried to avoid such potential reverse causation using a 2-year landmark analysis. Finally, although few prospective studies have investigated the association between the exposures and severe NAFLD, the observational nature of our study does not allow us to infer causality from the results. Consequently, the potential causal link between physical capability markers and NAFLD should be studied in future trials [46].

*Conclusion*

In conclusion, using prospective data from UK Biobank, we have shown that lower muscle mass and grip strength were associated with a higher risk of severe NAFLD. Considering that NAFLD is an increasingly common liver disease and that linearity was observed in the majority of the associations in our study, improving muscle mass and strength levels across the population might impact this increasing public health problem.

**Abbreviations**

| | |
|---|---|
| BIA | : bioimpedance |
| CI | : confidence intervals |
| DXA | : dual-energy X-ray absorptiometry |
| HES | : Health Episode Statistics |
| HR | : hazard ratio |
| ICD | : international Classification of Diseases |
| IQR | : interquartile range |
| NAFLD | : non-alcoholic fatty liver disease |
| NHS | : National Health Service |
| PHE | : Public Health England |
| SD | : standard deviations |
| SMR01 | : Scottish Morbidity Records |

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**Data statement**

All UK Biobank information is available online on the webpage www.ukbiobank.co.uk Data access are available through applications. This research was conducted using the application number 7155.



**Transparency**

The lead author, (the manuscript's guarantor), affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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**Table 1. Characteristics of the population by tertiles of grip strength**

| | Total | Lowest | Middle | Highest |
|---|---|---|---|---|
| **Socio-demographics** | | | | |
| Total n (%) | 333,295 (100) | 112,626 (33.8) | 116,532 (35.0) | 104,137 (31.2) |
| Baseline age (years), mean (SD) | 56.6 (8.0) | 59.2 (7.4) | 56.9 (7.8) | 53.6 (7.9) |
| Sex (female), n (%) | 183,430 (55.0) | 59,856 (53.2) | 67,533 (58.0) | 56,041 (53.8) |
| Deprivation index, mean (SD) | -1.4 (3.0) | -1.2 (3.1) | -1.5 (3.0) | -1.6 (2.9) |
| Deprivation, n (%) | | | | |
| Lower | 114,480 (34.4) | 35,504 (31.5) | 41,063 (35.3) | 37,913 (36.4) |
| Middle | 113,168 (33.9) | 37,559 (33.4) | 39,901 (34.2) | 35,708 (34.3) |
| Higher | 105,647 (31.7) | 39,563 (35.1) | 35,568 (30.5) | 30,516 (29.3) |
| Ethnicity, n (%) | | | | |
| White | 316,476 (95.0) | 105,200 (93.4) | 111,546 (95.7) | 99,730 (95.8) |
| Mixed | 4,666 (1.4) | 1,751 (1.6) | 1,505 (1.3) | 1,410 (1.4) |
| South Asian | 6,344 (1.9) | 3,848 (3.4) | 1,659 (1.4) | 837 (0.8) |
| Black | 4,905 (1.5) | 1,442 (1.3) | 1,517 (1.3) | 1,946 (1.8) |
| Chinese | 904 (0.2) | 385 (0.3) | 305 (0.3) | 214 (0.2) |
| **Lifestyle** | | | | |
| Smoking status, n (%) | | | | |
| Never | 184,776 (55.5) | 61,785 (54.9) | 64,697 (55.5) | 58,294 (56.0) |
| Previous | 116,797 (35.0) | 40,390 (35.9) | 40,982 (35.2) | 35,425 (34.0) |
| Current | 31,722 (9.5) | 10,451 (9.2) | 10,853 (9.3) | 10,418 (10.0) |
| Alcohol frequency intake, n (%) | | | | |
| Daily or almost daily | 67,601 (20.3) | 21,567 (19.2) | 24,094 (20.7) | 21,940 (21.1) |
| 3-4 times a week | 78,496 (23.6) | 24,143 (21.4) | 27,725 (23.8) | 26,628 (25.6) |
| Once or twice a week | 87,165 (26.2) | 28,556 (25.4) | 30,630 (26.3) | 27,979 (26.9) |
| 1-3 times a month | 37,148 (11.1) | 12,235 (10.9) | 13,058 (11.2) | 11,855 (11.4) |
| Special occasions only | 37,574 (11.3) | 14,676 (13.0) | 12,933 (11.1) | 9,965 (9.5) |
| Never | 25,311 (7.5) | 11,449 (10.1) | 8,092 (6.9) | 5,770 (5.5) |
| Diet score, mean (SD) | 4.6 (1.6) | 4.6 (1.6) | 4.5 (1.6) | 4.6 (1.6) |
| Diet score, n (%) | | | | |
| Lower quintile | 86,277 (25.9) | 28,730 (25.5) | 31,209 (26.8) | 26,338 (25.3) |
| 2 quintile | 74,643 (22.4) | 25,064 (22.2) | 26,254 (22.5) | 23,325 (22.4) |
| 3 quintile | 75,455 (22.6) | 25,631 (22.8) | 26,257 (22.5) | 23,567 (22.6) |
| 4 quintile | 56,610 (17.0) | 19,501 (17.3) | 19,229 (16.5) | 17,800 (17.2) |
| Higher quintile | 40,310 (12.1) | 13,700 (12.2) | 13,583 (11.7) | 13,027 (12.5) |
| **Type of physical activity** | | | | |
| Walking for pleasure (not as a means of transport) | 240,592 (72.2) | 78,661 (69.8) | 85,525 (73.4) | 76,406 (73.4) |
| Other exercises (eg: swimming, cycling, keep fit, bowling) | 40,949 (12.3) | 13,139 (11.7) | 13,933 (12.0) | 13,877 (13.3) |
| Strenuous sports | 2,511 (0.7) | 582 (0.5) | 875 (0.7) | 1,054 (1.0) |

| | | | | |
|---|---|---|---|---|
| Light DIY (e.g.: pruning, watering the lawn) | 21,783 (6.5) | 8,388 (7.4) | 7,393 (6.3) | 6,002 (5.8) |
| Heavy DIY (e.g.: weeding, lawn mowing, carpentry, digging) | 8,305 (2.5) | 3,011 (2.7) | 2,794 (2.4) | 2,500 (2.4) |
| None of the above | 18,881 (5.7) | 8,675 (7.7) | 5,945 (5.1) | 4,261 (4.0) |
| Prefer not to answer | 274 (0.1) | 170 (0.2) | 67 (0.1) | 37 (0.1) |
| **Components of the metabolic syndrome** | | | | |
| Central obesity (yes), n (%) | 111,726 (33.5) | 40,846 (36.3) | 37,707 (32.4) | 33,173 (31.9) |
| High glycaemia/diabetes (yes), n (%) | 49,904 (15.0) | 19,695 (17.5) | 17,025 (14.6) | 13,184 (12.7) |
| High blood pressure /hypertension (yes), n (%) | 236,504 (71.0) | 83,014 (73.7) | 82,343 (70.7) | 71,147 (68.3) |
| Low HDL (yes), n (%) | 66,806 (20.0) | 24,222 (21.5) | 22,438 (19.2) | 20,146 (19.4) |
| High triglycerides (yes), n (%) | 133,652 (40.1) | 48,320 (42.9) | 45,753 (39.3) | 39,579 (38.0) |

Descriptive characteristics by tertile of grip strength are presented as means with SD for quantitative variables and as frequencies and percentages for categorical variables. n: number; SD: standard deviation.

**Figure 1. Association between tertiles of physical capability markers and severe NAFLD**

Associations between grip strength, muscle mass and severe NAFLD were investigated by tertile of each exposure using Cox proportional hazard models. Individuals in the lowest tertile were used as the reference group in each case. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up and those with liver disease or alcohol/drug use disorder at baseline. Analyses were adjusted for age, sex, deprivation, ethnicity, components of the metabolic syndrome (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL and high triglyceride), smoking, alcohol intake, physical activity and diet score. A p-value below 0.05 was considered statistically significant.

**Figure 2. Association between physical capability markers and severe NAFLD**

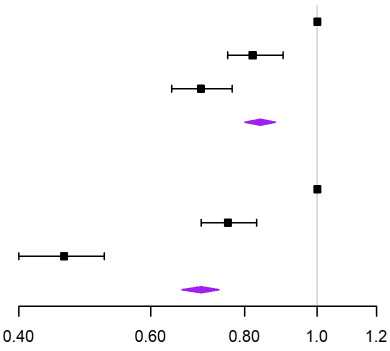
Nonlinear associations between grip strength, muscle mass, and severe NAFLD were investigated using penalised cubic splines fitted in Cox proportional hazard models. For the curves, the mean value of each exposure was used as a reference group. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up and those with liver disease or alcohol/drug use disorder at baseline. Analyses were adjusted for age, sex, deprivation, ethnicity, components of the metabolic syndrome (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL and high triglyceride), smoking, alcohol intake, physical activity and diet score. A p-value below 0.05 was considered statistically significant.

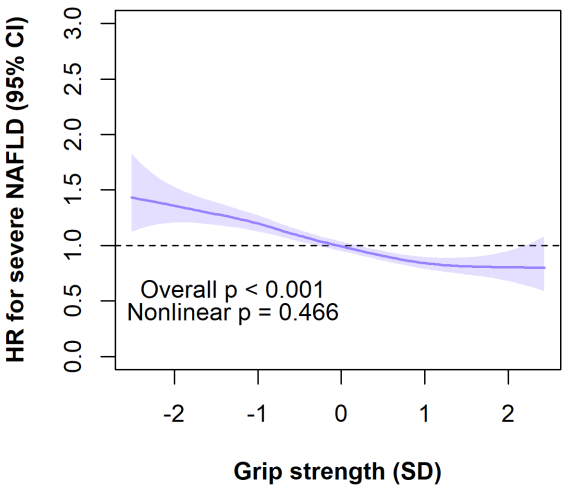
**Figure 3. Association between physical capability markers and severe NAFLD by subgroup**

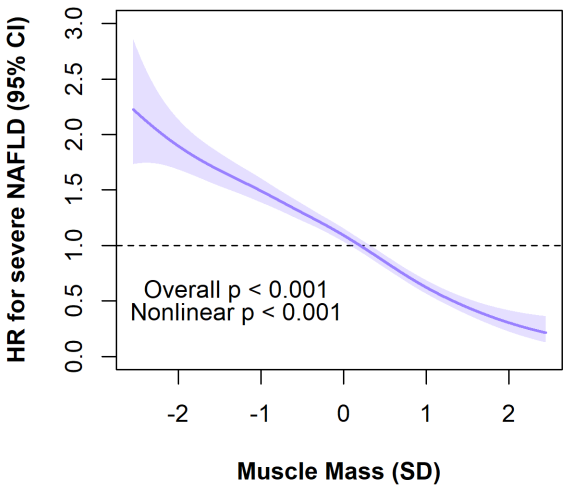
Nonlinear associations between grip strength, muscle mass, and severe NAFLD were investigated using penalised cubic splines fitted in Cox proportional hazard models. For the

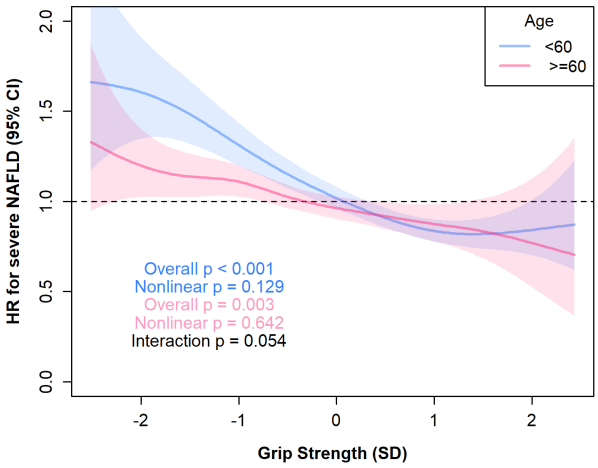
curves, the mean value of each exposure was used as a reference group. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up and those with liver disease or alcohol/drug use disorder at baseline. Analyses were adjusted for age, sex, deprivation, ethnicity, components of the metabolic syndrome (central obesity, high glycaemia/diabetes, high blood pressure/hypertension, low HDL and high triglyceride), smoking, alcohol intake, physical activity and diet score when these were not included as a subgroup. A p-value below 0.05 was considered statistically significant.

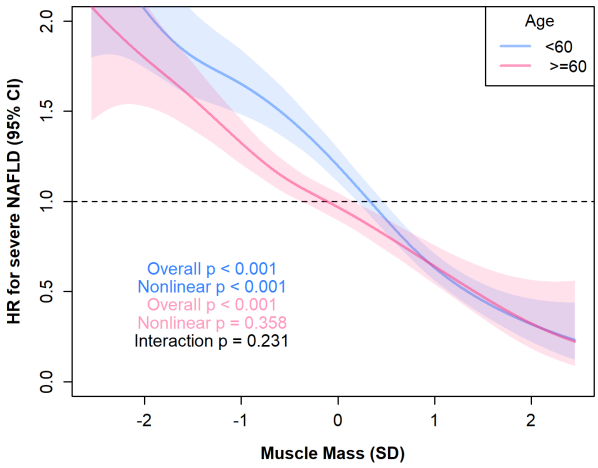
| Tertiles | Total n | Events | Severe NAFLD HR (95% CI) | p-value |
|---|---|---|---|---|
| **Grip strength** | | | | |
| Lowest | 112,626 | 1,419 | 1.00 (Ref.) | |
| Middle | 116,532 | 1,080 | 0.82 (0.76; 0.90) | <0.001 |
| Highest | 104,137 | 812 | 0.70 (0.64; 0.77) | <0.001 |
| **Trend** | | | **0.84 (0.80; 0.88)** | **<0.001** |
| **Muscle mass** | | | | |
| Lowest | 109,990 | 1,990 | 1.00 (Ref.) | |
| Middle | 111,601 | 936 | 0.76 (0.70; 0.83) | <0.001 |
| Highest | 111,704 | 385 | 0.46 (0.40; 0.52) | <0.001 |
| **Trend** | | | **0.70 (0.66; 0.74)** | **<0.001** |

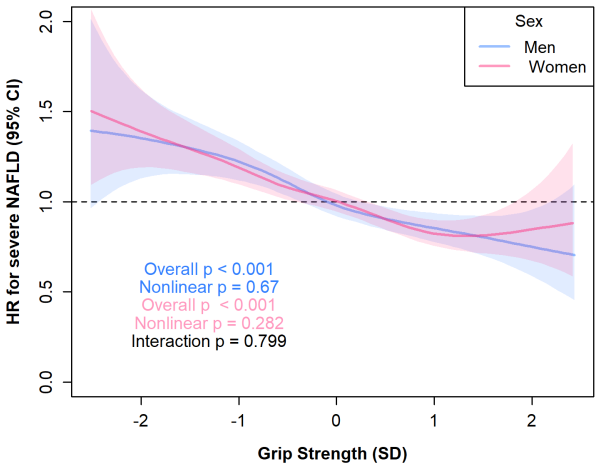


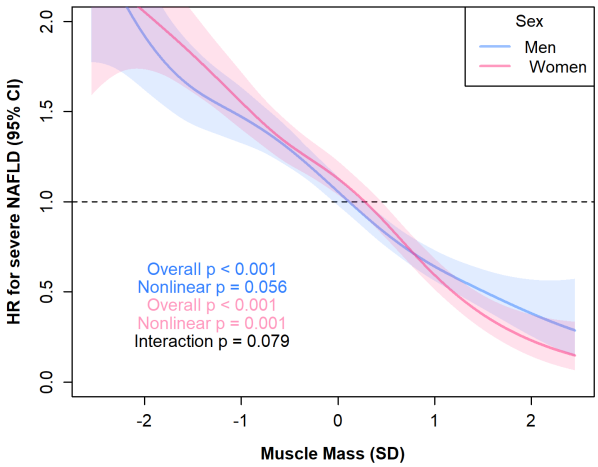

HR for severe NAFLD (95% CI)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Overall p < 0.001
Nonlinear p = 0.466
-2
-1
0
1
2
Grip strength (SD)

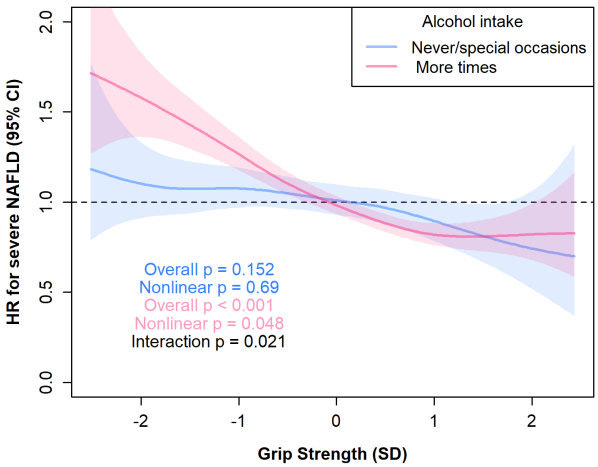

HR for severe NAFLD (95% CI)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Overall p < 0.001
Nonlinear p < 0.001
-2
-1
0
1
2
Muscle Mass (SD)

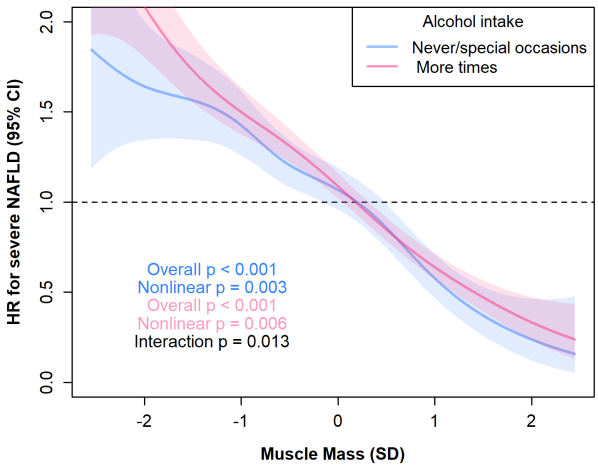

Age
<60
>=60
HR for severe NAFLD (95% CI)
Grip Strength (SD)
Overall p < 0.001
Nonlinear p = 0.129
Overall p = 0.003
Nonlinear p = 0.642
Interaction p = 0.054


Age
<60
>=60
HR for severe NAFLD (95% CI)
Muscle Mass (SD)
Overall p < 0.001
Nonlinear p < 0.001
Overall p < 0.001
Nonlinear p = 0.358
Interaction p = 0.231


Sex
Men
Women
HR for severe NAFLD (95% CI)
Grip Strength (SD)
Overall p < 0.001
Nonlinear p = 0.67
Overall p < 0.001
Nonlinear p = 0.282
Interaction p = 0.799


Sex
Men
Women
HR for severe NAFLD (95% CI)
Muscle Mass (SD)
Overall p < 0.001
Nonlinear p = 0.056
Overall p < 0.001
Nonlinear p = 0.001
Interaction p = 0.079


Alcohol intake
Never/special occasions
More times
HR for severe NAFLD (95% CI)
Grip Strength (SD)
Overall p = 0.152
Nonlinear p = 0.69
Overall p < 0.001
Nonlinear p = 0.048
Interaction p = 0.021


Alcohol intake
Never/special occasions
More times
HR for severe NAFLD (95% CI)
Muscle Mass (SD)
Overall p < 0.001
Nonlinear p = 0.003
Overall p < 0.001
Nonlinear p = 0.006
Interaction p = 0.013