Journal of Hepatology, Volume *5*

Supplemental information

Adverse muscle composition is a significant risk factor for all-cause mortality in NAFLD

Jennifer Linge, Patrik Nasr, Arun J. Sanyal, Olof Dahlqvist Leinhard, and Mattias Ekstedt

Adverse muscle composition is a significant risk factor for all-cause mortality in NAFLD

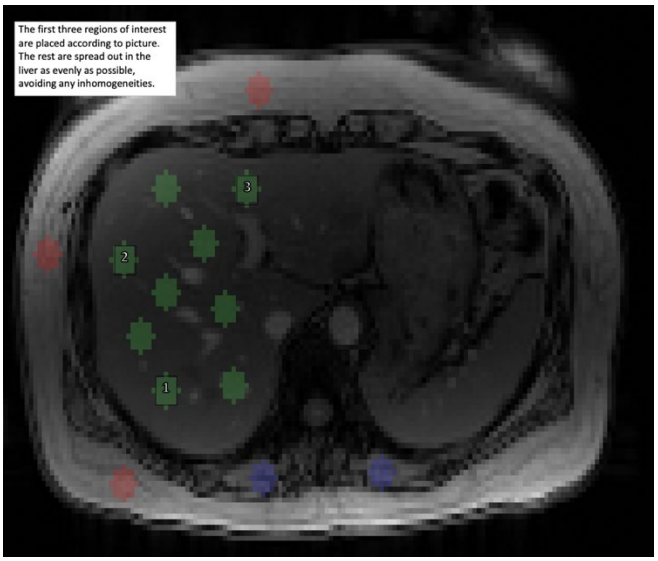
Jennifer Linge, Patrik Nasr, Arun J Sanyal, Olof Dahlqvist Leinhard, Mattias Ekstedt

Table of contents

Supplementary materials and methods

Section S1. MRI scanning protocol, image analysis and UK Biobank field information

The subjects were scanned in supine position in a Siemens MAGNETOM Aera 1.5 T MRI scanner (Siemens, Erlangen, Germany) using the dual-echo Dixon Vibe protocol covering neck to knees. Common parameters for all slabs were: flip angle=10°, TR=6.69 ms, TE=2.39/4.77 ms, and bandwidth=440 Hz. The first slab, over the neck, consisted of 64 slices, voxel size 2.23×2.23×3 mm3, and 224×168 matrix; slabs two to four were acquired during 17-second expiration breath-holds with 44 slices, voxel size 2.23×2.23×4.5 mm3, and 224×174 matrix; slab five consisted of 72 slices, voxel size 2.23×2.23×3.5 mm3, and 224×162 matrix; slab six of 64 slices, voxel size 2.23×2.23×4 mm3, and 224×156 matrix.



For liver proton density fat fraction (PDFF) quantification, nine regions of interest (ROI) were placed while avoiding major vessels and bile ducts (see figure to the right). The liver water, fat and T2* of each ROI were computed by magnitude-based chemical shift technique[1] with a 6-peak lipid model[2]. To correct for T1-bias, caused by differences in water and fat T1, a correction factor was applied to the water signal. The correction factor was computed using the body Dixon images of the first 3,000 scanned UK Biobank participants as reference. The liver ROIs were transferred to, and compared with, the fat Dixon images intensities, which were calibrated using the adipose tissue as an intensity reference[3,4] and corrected using the liver T2*, a process which results in T1 insensitive fat measurements[5].

For whole body measurements, the image analysis consisted of (1) image calibration, (2) fusion of image stacks, (3) image segmentation, and (4) quantification of fat and muscle volumes[4,6-9] and included manual quality control by an analysis engineer. Muscle volumes were calculated as fat-tissue free muscle volumes[4]. MFI was calculated as the average T2*-corrected fat value and converted to proton density fat fraction (PDFF)2.

UK Biobank field information

Liver PDFF, using data from UK Biobank field ID's 22436 ('10P Liver PDFF (proton density fat fraction)') and 24352 (FR liver PDFF mean). Data from field 22436 was used where data was missing for field 24352.

Fat-free muscle volume, using data from UK Biobank field ID's 22409 ('Total thigh fat-free muscle volume'), 22403 ('Anterior thigh fat-free muscle volume (right)'), 22404 ('Posterior thigh fat-free muscle volume (right)'), 22405 ('Anterior thigh fat-free muscle volume (left)'), and 22406 ('Posterior thigh fat-free muscle volume (left)').

Muscle fat infiltration, using data from UK Biobank field ID's 24353 ('Anterior thigh muscle fat infiltration (MFI) (left)') and 24353 ('Anterior thigh muscle fat infiltration (MFI) (right)').

Section S2. Variable definitions

Cancer, any type of cancer reported in an interview with a trained nurse.

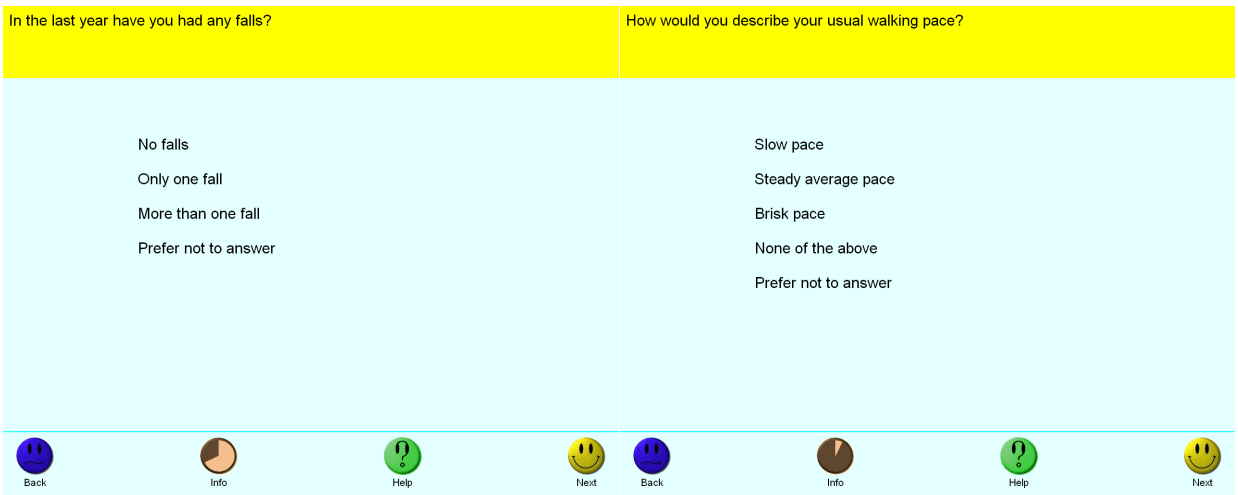
Coronary heart disease (CHD), defined by ICD-10 codes I20–I25, Z95.1. Controls excluded participants with these codes and those with self-reported history of heart attack, angina, or other heart/cardiac problems (N = 82 excluded).

Type 2 diabetes (T2D), diagnosed by a doctor and with age at diagnosis above 30 years. Controls excluded type 1 diabetes and/or gestational diabetes (N = 39 excluded).

Smoking, assessed through touchscreen questionnaire categorized into 'Prefer not to answer', 'Never', 'Previous', and 'Current'. Data-Field: 20116

Alcohol consumption, assessed through touchscreen questionnaires about frequency of intake and average intake of specific beverages ('red wine', 'champagne plus white wine', 'beer plus cider', 'spirits', 'fortified wines', and 'other alcoholic drinks'). Number of alcohol units per week was calculated using the Drinkaware definition (Drinkaware: https://www.drinkaware.co.uk/facts/alcoholic-drinks-and-units/what-is-an-alcohol-unit, Accessed April 2022).

Physical activity calculated according to the guidelines for data processing and analysis of IPAQ. The categorical score was calculated based on the protocol for IPAQ Short Form.
Touchscreen questionnaire screenshot for falls, walking pace, and stair climbing:



At home, during the last 4 weeks, about how many times a DAY do you climb a flight of stairs? (approx 10 steps)

None

1-5 times a day

6-10 times a day

11-15 times a day

16-20 times a day

More than 20 times a day

Do not know

Prefer not to answer

Section S3. Protocol description for recording of hand grip strength in UK Biobank (UK Biobank Field IDs 46, 47)

(*Cited*. https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Gripstrength.pdf, Accessed June 2022)

1. The staff member explains that the first measure will be of grip strength (indicating the Jamar dynamometer device to be used) and that strength in both hands will be measured in turn.
2. The participant is asked to sit upright in a chair and place their forearms on armrests. With dynamometer handle set to the second incremental slot the participant is asked to hold it first in their right hand. For participants with very large hands the handle is moved to the third slot.
3. The participant's elbow of the arm holding the dynamometer is against their side and bent to a 90° angle so that their forearm is pointing forwards with their thumb uppermost. Their wrist is straight so that their hand is either pointing forwards or bent slightly outwards.
4. The staff member supports the dynamometer lightly with one hand and rotates the red peak-hold needle anti-clockwise to zero. They explain to the participant that the adjustable handle of the dynamometer does not move while they are gripping it, but it will measure the strength of their grip. The participant is asked to squeeze the handle of the dynamometer as strongly as they can for about 3 seconds. They are given encouragement while doing so.
5. After 3 seconds the participant is asked to stop, the dynamometer is taken from them and the maximum hand grip strength is read in whole kilogram force units as indicated on the outer aspect of the dial by the red peak-hold needle. This value is entered into the computer (see below).

Section S4. R packages used for statistical analysis and visualizations

survival
survimer
forestmodel
ggplot2
table1
rtf

Supplementary tables

Category	Diagnosis	ICD-10_codes	Excluded at/before imaging	Liver-related events post imaging
Other liver diseases at/before baseline	ALD	K70	YES	Not included
	Viral hepatitis	B16, B17, B18, B19		
	Autoimmune liver disease (AIH, PBC, PSC)	K830, K743, K754		
	Hemochromatosis	E831		
	Wilson's disease	E830		
	Alpha-1-antitrypsin deficiency	E880		
	Budd-Chiari syndrome	I820, K765		
	Chronic hepatitis, unspecified	K739, K732		
	Secondary or unspecified biliary cirrhosis	K744, K745		
Alcohol/drug use disorder at/before baseline	Codes associated with alcohol use disorder	F10	YES	Not included
	Codes associated with somatic consequences of alcohol (except ALD)	E244, G621, I426, K292, G312, G721, K852, K860, T510, T519, Y573, X65, Z502, Z714, Z721		
	Codes associated with drug use disorders except nicotine/caffeine	F11, F12, F13, F14, F16, F18, F19		
Compensated cirrhosis	Cirrhosis, compensated	K746	YES	4
	Esophageal varices, not bleeding	I859, I982		3
	Gastric varices, not bleeding	I864		0
	Esophageal varices, bleeding	I850, I983		0
	Ascites	R18		4
	HE	K746+lactulose		0
	Hepatorenal syndrome	K767		0
	Portal hypertension	K766		3
Liver transplantation	LT status	Z944	YES	1
Liver cancer outcomes	HCC	C220	YES	3
	Liver cancer, unspecified	C229		1
Unspecified codes that might be relevant for some studies	Chronic or unspecified liver failure	K721, K729	YES	1
	Acute or subacute liver failure	K720		0
	Portal vein thrombosis	I819, K751		0
	Hepatic fibrosis or sclerosis or fibrosis with sclerosis	K740, K741, K742		2
Total number of unique participants with liver related events post imaging:				**13**

Table S1 Description of ICD-10 codes used to investigate liver related outcomes in participants with non-alcoholic fatty liver disease (NAFLD).

ICD-10 code chapter	Total	NAFLD	Matched controls
II Neoplasms	76	36	40
IX Diseases of the circulatory system	41	18	23
Covid-19	16	8	8
X Diseases of the respiratory system	6	1	5
XX External causes of morbidity and mortality	4	1	3
VI Diseases of the nervous system	2	1	1
XI Diseases of the digestive system	2	1	1
I Certain infectious and parasitic diseases	1	1	0
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1	1	0
IV Endocrine, nutritional, and metabolic diseases	1	1	0
Total	150	69	81

Table S2 Specific primary causes of death in the matched dataset (N=10,138) broken down between NAFLD and sex-, age-, and BMI-matched controls on ICD-10 code chapter level.

ICD-10 code block	Total	NAFLD	Matched controls
C15-C26 Malignant neoplasms of digestive organs	30	13	17
I20-I25 Ischaemic heart diseases	24	11	13
Covid-19	16	8	8
C30- C39 Malignant neoplasms of respiratory and intrathoracic organs	10	5	5
I60-I69 Cerebrovascular diseases	10	2	8
C69-C72 Malignant neoplasms of eye, brain, and other parts of central nervous system	9	6	3
C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic, and related tissue	8	3	5
C43-C44 Melanoma and other malignant neoplasms of skin	4	2	2
C50-C50 Malignant neoplasm of breast	3	1	2
C76-C80 Malignant neoplasms of ill-defined, secondary, and unspecified sites	3	1	2
J40-J47 Chronic lower respiratory diseases	3	0	3
J80-J84 Other respiratory diseases principally affecting the interstitium	3	1	2
C00-C14 Malignant neoplasms of lip, oral cavity, and pharynx	2	1	1
C51-C58 Malignant neoplasms of female genital organs	2	0	2
C60-C63 Malignant neoplasms of male genital organs	2	1	1
C64-C68 Malignant neoplasms of urinary tract	2	2	0
I10-I15 Hypertensive diseases	2	1	1
I26-I28 Pulmonary heart disease and diseases of pulmonary circulation	2	2	0
K70-K77 Diseases of liver	2	1	1
X60-X84 Intentional self-harm	2	0	2
A30-A49 Other bacterial diseases	1	1	0
C45-C49 Malignant neoplasms of mesothelial and soft tissue	1	1	0
D80-D89 Certain disorders involving the immune mechanism	1	1	0
E70-E90 Metabolic disorders	1	1	0
G10-G14 Systemic atrophies primarily affecting the central nervous system	1	1	0
G70-G73 Diseases of myoneural junction and muscle	1	0	1

I05-I09 Chronic rheumatic heart diseases	1	0	1
I30-I52 Other forms of heart disease	1	1	0
I80-I89 Diseases of veins, lymphatic vessels, and lymph nodes, not elsewhere classified	1	1	0
W00-W19 Falls	1	1	0
Y83-Y84 Surgical and other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure	1	0	1

Table S3 Specific primary causes of death in the matched dataset (N=10,138) broken down between NAFLD and sex-, age-, and BMI-matched controls on ICD-10 code block level.

Variable	Unit	Whole cohort (N=40,174)			Excluding cancer (N=35,628)			Women (N=20,823)			Men (N=19,351)			Younger participants (N=20,084)			Older participants (N=20,090)		
		cHR	95% CI	p-value	cHR	95% CI	p-value	cHR	95% CI	p-value	cHR	95% CI	p-value	cHR	95% CI	p-value	cHR	95% CI	p-value
NAFLD	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	1.07	[0.83; 1.37]	0.621	1.08	[0.81; 1.43]	0.609	0.94	[0.59; 1.50]	0.796	1.05	[0.78; 1.42]	0.728	0.95	[0.56; 1.64]	0.864	1.08	[0.81; 1.43]	0.590
Low muscle volume z-score	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	2.14	[1.80; 2.55]	**<0.001**	2.11	[1.73; 2.58]	**<0.001**	1.88	[1.40; 2.54]	**<0.001**	2.30	[1.85; 2.86]	**<0.001**	1.64	[1.09; 2.46]	**0.017**	1.79	[1.47; 2.18]	**<0.001**
High muscle fat infiltration (MFI)	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	2.14	[1.80; 2.55]	**<0.001**	2.60	[2.13; 3.16]	**<0.001**	2.01	[1.50; 2.69]	**<0.001**	2.62	[2.11; 3.24]	**<0.001**	2.11	[1.44; 3.09]	**<0.001**	1.83	[1.50; 2.22]	**<0.001**
Adverse muscle composition	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	3.11	[2.55; 3.80]	**<0.001**	3.14	[2.50; 3.95]	**<0.001**	2.80	[1.98; 3.96]	**<0.001**	3.21	[2.52; 4.09]	**<0.001**	2.98	[1.78; 4.96]	**<0.001**	2.30	[1.85; 2.85]	**<0.001**
Liver PDFF	%	1.02	[1.00; 1.03]	0.098	1.02	[1.00; 1.04]	**0.024**	1.02	[0.99; 1.05]	0.122	1.00	[0.97; 1.02]	0.908	1.05	[1.02; 1.08]	**0.002**	1.00	[0.98; 1.02]	0.980
Muscle volum z-score	SD	0.63	[0.58; 0.69]	**<0.001**	0.63	[0.57; 0.70]	**<0.001**	0.71	[0.61; 0.83]	**<0.001**	0.60	[0.54; 0.67]	**<0.001**	0.79	[0.66; 0.95]	**0.012**	0.69	[0.62; 0.77]	**<0.001**
Muscle fat infiltration	%	1.18	[1.14; 1.22]	**<0.001**	1.19	[1.15; 1.24]	**<0.001**	1.21	[1.14; 1.27]	**<0.001**	1.23	[1.19; 1.28]	**<0.001**	1.20	[1.11; 1.29]	**<0.001**	1.11	[1.07; 1.16]	**<0.001**

Table S4 Cox proportional-hazard ratios (**crude**) of all-cause mortality for different strata of the UK Biobank data: (1) whole cohort, (2) whole cohort excluding participants with a previous cancer 1diagnosis at imaging, (3) women only, (4) men only, (5) younger participants (below median age of 64.7 years), and (6) older participants (above median age of 64.7 years). For categorical variables: non-alcoholic fatty liver disease (NAFLD) [yes/no], low muscle volume z-score [yes/no], high muscle fat infiltration [yes/no], adverse muscle composition (MC) and continuous variables: liver proton density fat fraction (PDFF) [%], muscle volume z-score [SD], muscle fat infiltration (MFI) [%]. CI, confidence interval; Ref, reference.

Variable	Unit	Whole cohort (N=40,174) Adjusted: sex, age, BMI			Excluding cancer (N=35,628) Adjusted: sex, age, BMI			Women (N=20,823) Adjusted: age, BMI			Men (N=19,351) Adjusted: age, BMI			Younger participants (N=20,084) Adjusted: sex, age, BMI			Older participants (N=20,090) Adjusted: sex, age, BMI		
		aHR	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**	**aHR**	**95% CI**	**p-value**
NAFLD	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	0.93	[0.71; 1.21]	0.567	0.89	[0.66; 1.21]	0.461	0.81	[0.49; 1.32]	0.397	0.99	[0.72; 1.35]	0.938	0.73	[0.41; 1.29]	0.277	1.00	[0.74; 1.35]	0.988
Low muscle volume z-score	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	1.54	[1.29; 1.84]	**<0.001**	1.52	[1.24; 1.87]	**<0.001**	1.50	[1.10; 2.03]	**0.009**	1.55	[1.24; 1.93]	**<0.001**	1.51	[1.00; 2.27]	**0.048**	1.53	[1.25; 1.87]	**<0.001**
High muscle fat infiltration (MFI)	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	1.63	[1.35; 1.99]	**<0.001**	1.72	[1.38; 2.15]	**<0.001**	1.57	[1.12; 2.19]	**0.008**	1.65	[1.29; 2.10]	**<0.001**	1.56	[1.01; 2.41]	**0.045**	1.66	[1.33; 2.06]	**<0.001**
Adverse muscle composition	no	Ref			Ref			Ref			Ref			Ref			Ref		
	yes	1.94	[1.57; 2.39]	**<0.001**	1.88	[1.48; 2.39]	**<0.001**	2.02	[1.41; 2.91]	**<0.001**	1.86	[1.44; 2.41]	**<0.001**	2.23	[1.32; 3.77]	**0.003**	1.89	[1.50; 2.37]	**<0.001**
Liver PDFF	%	1.00	[0.98; 1.02]	0.864	1.01	[0.98; 1.03]	0.559	1.02	[0.99; 1.06]	0.232	0.99	[0.96; 1.02]	0.548	1.03	[0.99; 1.07]	0.140	0.99	[0.96; 1.02]	0.458
Muscle volum z-score	SD	0.78	[0.70; 0.85]	**<0.001**	0.77	[0.69; 0.86]	**<0.001**	0.83	[0.71; 0.98]	**0.025**	0.75	[0.66; 0.85]	**<0.001**	0.84	[0.70; 1.02]	0.073	0.76	[0.68; 0.85]	**<0.001**
Muscle fat infiltration	%	1.16	[1.11; 1.21]	**<0.001**	1.15	[1.10; 1.22]	**<0.001**	1.21	[1.14; 1.27]	**<0.001**	1.14	[1.08; 1.21]	**<0.001**	1.20	[1.11; 1.29]	**<0.001**	1.15	[1.10; 1.21]	**<0.001**

Table S5 Cox proportional-hazard ratios (**adjusted for sex and/or age, and BMI**) of all-cause mortality for different strata of the UK Biobank data: (1) whole cohort, (2) whole cohort excluding participants with a previous cancer diagnosis at imaging, (3) women only, (4) men only, (5) younger participants (below median age of 64.7 years), and (6) older participants (above median age of 64.7 years). For categorical variables: non-alcoholic fatty liver disease (NAFLD) [yes/no], low muscle volume z-score [yes/no], high muscle fat infiltration [yes/no], adverse muscle composition (MC) and continuous variables: liver proton density fat fraction (PDFF) [%], muscle volume z-score [SD], muscle fat infiltration (MFI) [%]. CI, confidence interval; Ref, reference.

Variable	Unit	Unadjusted			Model 1 (+ sex, age, BMI)			Model 2 (+ low hand grip strength, smoking, alcohol)			Model 3 (+ previous cancer, coronary heart disease, type 2 diabetes)		
		HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value
Adverse muscle composition	no	Ref			Ref			Ref			Ref		
	yes	2.84	[1.70;4.75]	**<0.001**	1.83	[1.08;3.12]	**0.0251**	1.82	[1.06;3.14]	**0.0302**	1.72	[1.00;2.98]	0.0514
Sex	female				Ref			Ref			Ref		
	male				2.07	[1.22;3.50]	**0.0067**	2.31	[1.31;4.05]	**0.0036**	2.31	[1.31;4.08]	**0.0039**
Age	years				1.11	[1.07;1.16]	**<0.001**	1.11	[1.06;1.16]	**<0.001**	1.10	[1.06;1.15]	**<0.001**
BMI	kg/m^2				1.05	[1.00;1.10]	0.0721	1.04	[0.99;1.09]	0.1411	1.04	[0.99;1.09]	0.1546
Low hand grip strength	no							Ref			Ref		
	yes							1.33	[0.67;2.66]	0.4171	1.41	[0.71;2.81]	0.3294
Physical activity	moderate							Ref			Ref		
	low							1.40	[0.81;2.43]	0.2308	1.39	[0.80;2.41]	0.2411
	high							1.16	[0.62;2.15]	0.6445	1.17	[0.63;2.17]	0.6199
Smoking status	no							Ref			Ref		
	previous							1.18	[0.72;1.93]	0.5192	1.17	[0.71;1.92]	0.5368
	current							0.66	[0.09;4.81]	0.6781	0.65	[0.09;4.80]	0.6749
Alcohol consumption	g/day							0.99	[0.95;1.02]	0.4206	0.99	[0.95;1.02]	0.4468
Cancer	no										Ref		
	yes										1.90	[1.08;3.37]	**0.0267**
Coronary heart disease	no										Ref		
	yes										1.14	[0.56;2.36]	0.7133
Type 2 diabetes	no										Ref		
	yes										1.20	[0.67;2.16]	0.5345

Table S6 Cox proportional-hazard ratios of all-cause mortality ***within NAFLD (N=5,069)*** for adverse muscle composition (MC) [yes/no] including unadjusted hazard ratios (HRs) and subsequent adjustments for sex, age, BMI (Model 1); low hand grip strength, smoking status, alcohol consumption (Model 2); previous cancer, coronary heart disease, type 2 diabetes diagnosis (Model 3). BMI, body mass index; CI, confidence interval; Ref, reference.

Variable	Unit	Unadjusted			Model 1 (+ sex, age, BMI)			Model 2 (+ low hand grip strength, smoking, alcohol)			Model 3 (+ previous cancer, coronary heart disease, type 2 diabetes)		
		HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value
Muscle fat infiltration	%	1.15	[1.07;1.24]	**<0.001**	1.13	[1.03;1.24]	**0.0097**	1.14	[1.02;1.26]	**0.0171**	1.13	[1.01;1.26]	**0.0263**
Sex	female				Ref			Ref			Ref		
	male				2.52	[1.46;4.35]	**<0.001**	2.83	[1.57;5.10]	**<0.001**	2.82	[1.55;5.12]	**<0.001**
Age	years				1.11	[1.07;1.16]	**<0.001**	1.10	[1.06;1.15]	**<0.001**	1.10	[1.05;1.14]	**<0.001**
BMI	kg/m^2				1.02	[0.97;1.08]	0.4518	1.01	[0.95;1.07]	0.7091	1.01	[0.96;1.07]	0.6631
Low hand grip strength	no							Ref			Ref		
	yes							1.39	[0.70;2.75]	0.3479	1.45	[0.73;2.87]	0.2914
Physical activity	moderate							Ref			Ref		
	low							1.38	[0.80;2.39]	0.2523	1.36	[0.79;2.37]	0.2687
	high							1.15	[0.62;2.14]	0.6546	1.16	[0.62;2.15]	0.6388
Smoking status	no							Ref			Ref		
	previous							1.19	[0.73;1.96]	0.4837	1.19	[0.72;1.95]	0.4975
	current							0.64	[0.09;4.72]	0.6642	0.63	[0.09;4.67]	0.6551
Alcohol consumption	g/day							0.99	[0.95;1.02]	0.4460	0.99	[0.95;1.02]	0.4742
Cancer	no										Ref		
	yes										1.95	[1.10;3.44]	**0.0214**
Coronary heart disease	no										Ref		
	yes										1.18	[0.57;2.41]	0.6571
Type 2 diabetes	no										Ref		
	yes										1.15	[0.64;2.08]	0.6394

Table S7 Cox proportional-hazard ratios of all-cause mortality ***within NAFLD (N=5,069)*** for adverse muscle fat infiltration (MFI) [%] including unadjusted hazard ratios (HRs) and subsequent adjustments for sex, age, BMI (Model 1); low hand grip strength, smoking status, alcohol consumption (Model 2); previous cancer, coronary heart disease, type 2 diabetes diagnosis (Model 3). BMI, body mass index; CI, confidence interval; Ref, reference.

Variable	Unit	Unadjusted			Model 1 (+ sex, age, BMI)			Model 2 (+ low hand grip strength, smoking, alcohol)			Model 3 (+ previous cancer, coronary heart disease, type 2 diabetes)		
		HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value
Muscle volume z-score	%	0.70	[0.55;0.88]	**0.0028**	0.74	[0.56;0.96]	**0.0248**	0.75	[0.57;0.99]	**0.0442**	0.77	[0.58;1.02]	0.0688
Sex	female				Ref			Ref			Ref		
	male				2.01	[1.18;3.40]	**0.0098**	2.24	[1.27;3.94]	**0.0054**	2.24	[1.26;3.98]	**0.0058**
Age	years				1.11	[1.07;1.16]	**<0.001**	1.11	[1.06;1.15]	**<0.001**	1.10	[1.06;1.15]	**<0.001**
BMI	kg/m^2				1.09	[1.03;1.14]	**0.0021**	1.08	[1.02;1.14]	**0.0091**	1.07	[1.01;1.14]	**0.0151**
Low hand grip strength	no							Ref			Ref		
	yes							1.35	[0.68;2.69]	0.3880	1.41	[0.71;2.80]	0.3264
Physical activity	moderate							Ref			Ref		
	low							1.19	[0.72;1.95]	0.5005	1.37	[0.79;2.37]	0.2674
	high							0.67	[0.09;4.91]	0.6927	1.17	[0.63;2.17]	0.6171
Smoking status	no							Ref			Ref		
	previous							1.37	[0.79;2.38]	0.2628	1.18	[0.72;1.93]	0.5221
	current							1.16	[0.63;2.15]	0.6384	0.66	[0.09;4.85]	0.6829
Alcohol consumption	g/day							0.99	[0.95;1.02]	0.4491	0.99	[0.95;1.02]	0.4623
Cancer	no										Ref		
	yes										1.92	[1.09;3.40]	**0.0242**
Coronary heart disease	no										Ref		
	yes										1.18	[0.58;2.42]	0.6526
Type 2 diabetes	no										Ref		
	yes										1.19	[0.66;2.13]	0.5691

Table S8 Cox proportional-hazard ratios of all-cause mortality ***within NAFLD (N=5,069)*** for muscle volume z-score [SD] including unadjusted hazard ratios (HRs) and subsequent adjustments for sex, age, BMI (Model 1); low hand grip strength, smoking status, alcohol consumption (Model 2); previous cancer, coronary heart disease, type 2 diabetes diagnosis (Model 3). BMI, body mass index; CI, confidence interval; Ref, reference.

Supplementary figures

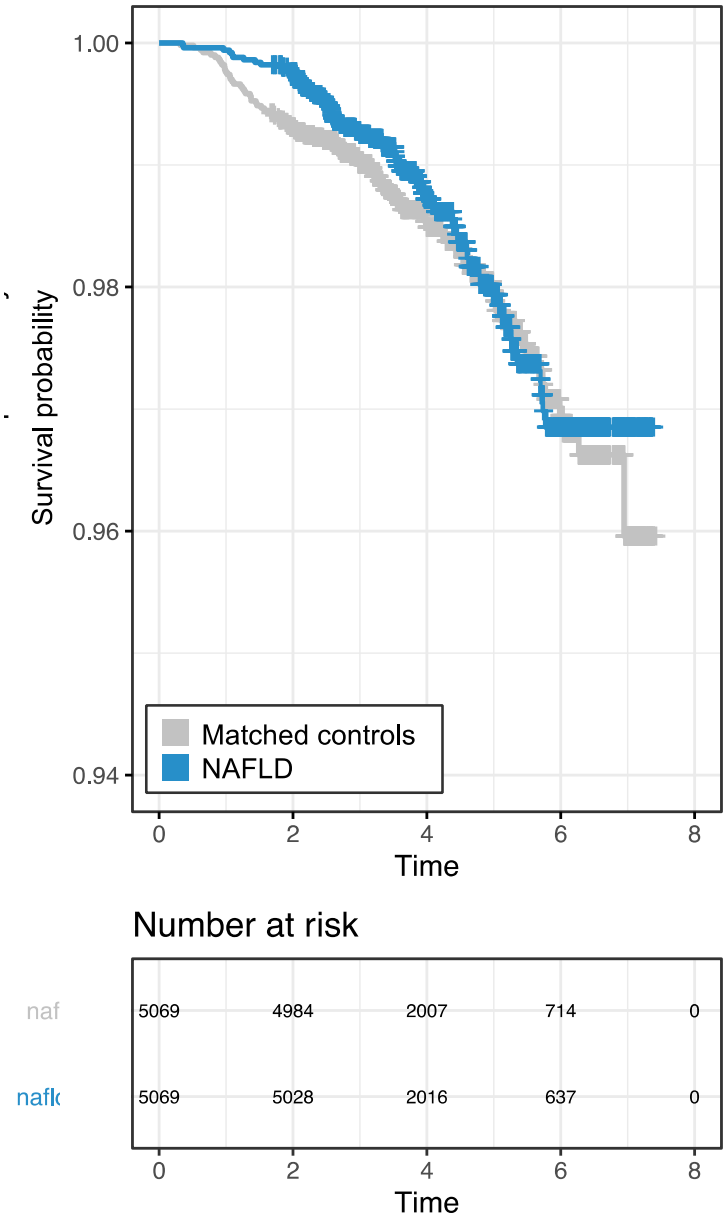


Figure S1 Kaplan-Meier survival curves for all-cause mortality comparing NAFLD (blue) [N=5,069] and sex-, age- and BMI-matched controls (grey) [N=5,069] including counts participants at risk over time. Corresponding to the left panel in Figure 3.

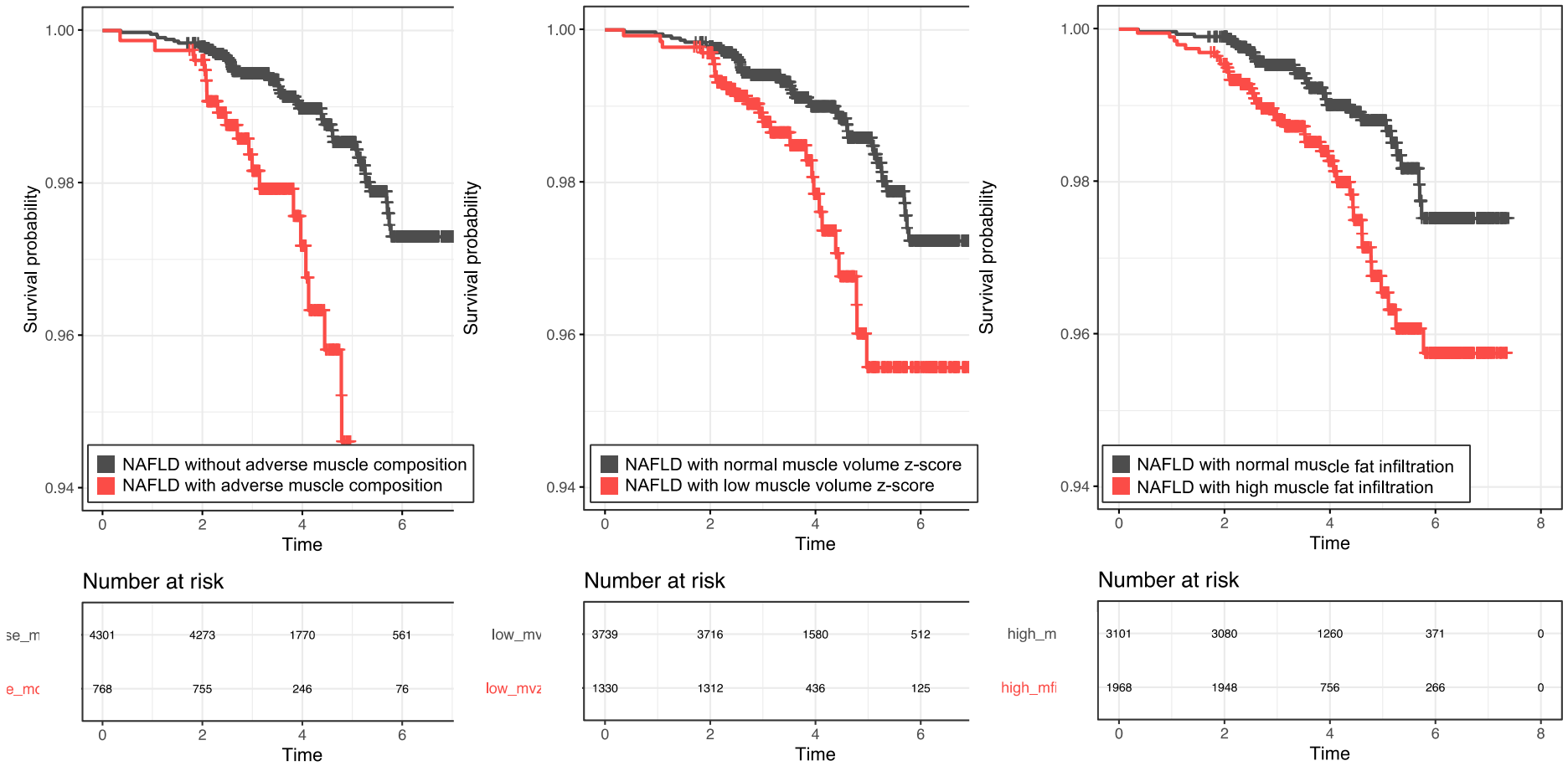


Figure S2 Kaplan-Meier survival curves comparing NAFLD participants with adverse muscle composition (low muscle volume and high muscle fat) [yes/no], low muscle volume (muscle volume z-score < -0.68 SD) [yes/no], high muscle fat (muscle fat infiltration (MFI) > 8.82% for female participants and 7.69% for male participants, respectively) [yes/no]including counts of participants at risk over time. Corresponding to Figure 4.

Supplementary references

1. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative Assessment of Liver Fat with Magnetic Resonance Imaging and Spectroscopy. JMRI 2011;34(4):spcone. 10.1002/jmri.22775
2. Hamilton G, Yokoo T, Bydder M, Cruite I, Schroeder ME, Sirlin CB, Middleton MS. In Vivo Characterization of the Liver Fat 1H MR Spectrum. NMR Biomed 2011;24(7):784–90. 10.1002/nbm.1622
3. Romu T, Borga M, OD Leinhard. MANA-Multi Scale Adaptive Normalized Averaging. In: Proceedings of the 2011 IEEE International Symposium on Biomedical Imaging. 2011;361-4. 10.1109/ISBI.2011.5872424
4. OD Leinhard, A Johansson, J Rydell, Smedby Ö, Nyström F, Lundberg P, Borga M. Quantitative Abdominal Fat Estimation Using MRI Pattern Recognition. In: Proceedings of the 19th International Conference on Pattern Recognition (ICPR) 08-11 Dec, 2008; Tampa, FL. 10.1109/ICPR.2008.4761764
5. Peterson P, Romu T, Brorson H, Dahlqvist Leinhard O, Månsson S. Fat Quantification in Skeletal Muscle Using Multigradient-Echo Imaging: Comparison of Fat and Water References. JMRI 2016;43:203–12. 10.1002/jmri.24972
6. Karlsson A, Rosander J, Romu T, Tallberg J, Grönqvist A, Borga M, Dahlqvist Leinhard O. Automatic and Quantitative Assessment of Regional Muscle Volume by Multi-Atlas Segmentation Using Whole-Body Water–Fat MRI. JMRI 2015;41(6):1558-69. 10.1002/jmri.24726
7. West J, Romu T, Thorell S, Lindblom H, Berin E, Spetz Holm A, Lindh Åstrand L, Karlsson A, Borga M, Hammar M, Dahlqvist Leinhard O. Precision of MRI-based body composition measurements of postmenopausal women. PLoS One 2018;13(2):e0192495. 10.1371/journal.pone.0192495
8. West J, Dahlqvist Leinhard O, Romu T, et al. Feasibility of MR-based body composition analysis in large scale population studies. PLoS ONE 2016; 11:e0163332. 10.1371/journal.pone.0163332
9. Borga M, Thomas EL, Romu T, et al. Validation of a fast method for quantification of intra-abdominal and subcutaneous adipose tissue for large scale human studies. NMR Biomed 2015;28:1747-1753. 10.1002/nbm.3432