Adverse muscle composition is linked to poor functional performance and metabolic comorbidities in NAFLD

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Supplementary materials

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

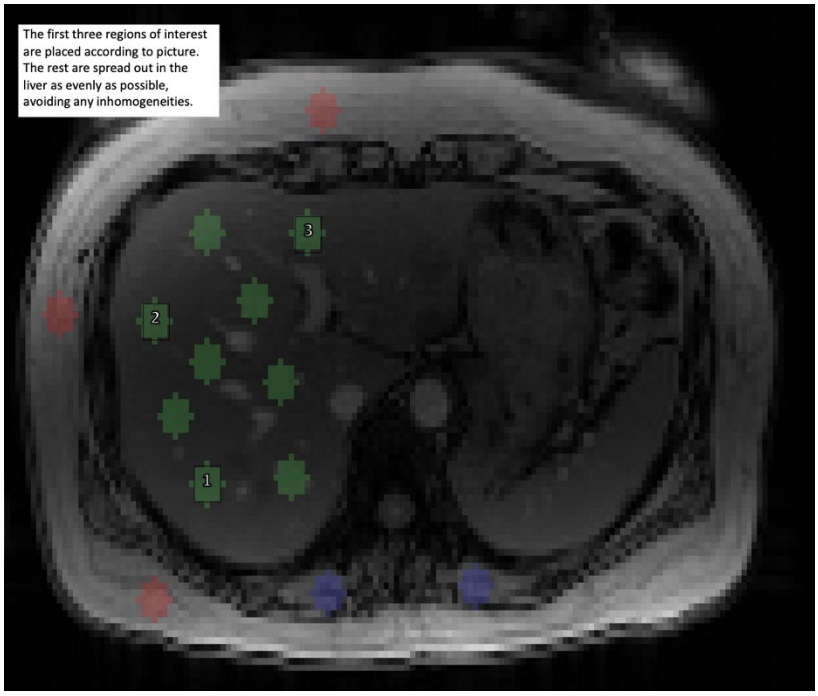
(Cited. http://biobank.ndph.ox.ac.uk/showcase/docs/Gripstrength.pdf, Accessed April 2019)

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 hßolding 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).

MRI scanning protocol and image analysis

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 mm^3, 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 mm^3, and 224×174 matrix; slab five consisted of 72 slices, voxel size 2.23×2.23×3.5 mm^3, and 224×162 matrix; slab six of 64 slices, voxel size 2.23×2.23×4 mm^3, 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].

Translation of current sarcopenia thresholds from DXA to MRI

Methods: To leverage the full dataset (N=9,545) for sarcopenia assessment, sex-specific thresholds for low muscle quantity based on DXA (ALM/height^2 <6.0/7.0 kg/m^2 (females/males)) were translated to MRI (thigh FFMV/height^2) utilizing the subset with DXA and hand grip strength data available (N=4,553). Thresholds were determined by optimizing sensitivity and specificity for detecting individuals with low muscle quantity. Diagnostic performance (area under receiver operator characteristic (AUROC) curve), sensitivity, and specificity for sarcopenia detection were determined using derived FFMV/height^2 thresholds compared to ALM/height^2 thresholds.

Results: The correlation between ALM/height^2 and thigh FFMV/height^2 was 0.93 (95% CI: 0.92-0.93). Resulting thresholds for thigh FFMV/height^2 were 3.0/3.6 L/m^2 (females/males). Sensitivity and specificity for sarcopenia detection using MRI-measured thigh FFMV/height^2 instead of DXA-measured ALM/height^2 were 0.93 and 0.99, respectively. AUROC was 0.96 (95% CI: 0.93-0.98). Applying sarcopenia-detection thresholds based on DXA-based ALM/height^2 and hand grip strength stratified 101 (2.2%) participants from the DXA subset. Applying derived MRI-based thigh FFMV/height^2 and hand grip strength thresholds for sarcopenia detection stratified 241 (2.5%) participants from the whole cohort. Supplemental material includes a comparison between characteristics for the DXA subset and the whole cohort (**Table S1** below).

Table S1. Cohort characteristics comparing complete dataset (whole cohort) to DXA subset. Values are mean (standard deviation). For liver fat, median (interquartile range) is shown. VCG, virtual control group adjusted. Low hand grip defined as below 16/27 kg (females/males). † Data extracted from baseline assessment (years 2006–2010).

	Whole cohort	Females	Males	DXA subset
N participants	9,545	5,026	4,519	4,553
% females	52.66	100.00	0.00	53.00
Age, years	62.59 (7.49)	61.86 (7.33)	63.41 (7.59)	62.31 (7.51)
Weight, kg	75.52 (14.77)	68.66 (12.91)	83.14 (12.85)	75.46 (14.77)
Height, cm	169.06 (8.93)	162.96 (6.15)	175.84 (6.26)	168.99 (9.05)
BMI, kg/m^2	26.34 (4.33)	25.86 (4.71)	26.87 (3.8)	26.34 (4.33)
Visceral adipose tissue volume (L)	3.68 (2.21)	2.63 (1.51)	4.84 (2.27)	3.69 (2.21)
Abdominal subcutaneous adipose tissue volume (L)	7.01 (3.19)	8.04 (3.41)	5.85 (2.46)	7 (3.15)
Appendicular lean mass/height^2, kg/m^2	7.34 (1.23)	6.55 (0.85)	8.24 (0.94)	7.34 (1.23)
Liver fat, %	2.36 (1.49-4.57)	1.99 (1.34-3.73)	2.85 (1.74-5.59)	2.35 (1.49-4.62)
Muscle composition				
Fat-tissue free muscle volume, L	10.34 (2.56)	8.36 (1.18)	12.54 (1.77)	10.25 (2.56)
Fat-tissue free muscle volume z-score ($FFMV_{VCG}$)	0.00 (0.98)	0.00 (0.99)	0.00 (0.98)	-0.07 (0.97)
Muscle fat infiltration, %	7.40 (1.85)	7.92 (1.83)	6.83 (1.71)	7.44 (1.81)
% Adverse muscle composition (AMC)	10.20 %	9.47 %	11.02 %	10.74 %
% Only high muscle fat	14.76 %	15.44 %	14.01 %	14.78 %
% Only low muscle volume	14.57 %	15.60 %	13.43 %	16.25 %
% Normal muscle composition	60.46 %	59.49 %	61.54 %	58.23 %
Functional performance & metabolic comorbidity				
Sarcopenia	2.52 %	3.20 %	1.77 %	3.34 %
Low hand grip strength	6.34 %	6.65 %	6.00 %	8.02 %
Slow walking pace	4.40 %	4.80 %	3.96 %	4.22 %
No stair climbing	7.87 %	7.62 %	8.14 %	7.29 %
More than one fall last year	4.83 %	5.83 %	3.72 %	4.61 %

Coronary heart disease (prevalent)	4.70 %	2.71 %	6.93 %	4.96 %
Coronary heart disease (incident)	1.72 %	0.78 %	2.77 %	2.35 %
Type 2 diabetes	4.48 %	2.88 %	6.26 %	4.33 %
Biomarker panel [†]				
Glycated haemoglobin (HbA1c), mmol/mol	35.11 (5.00)	34.9 (4.58)	35.35 (5.42)	35.07 (4.96)
Glucose mmol/L	5.01 (1.01)	4.96 (0.84)	5.06 (1.16)	5.00 (1.06)
Albumin, g/L	45.29 (2.51)	45.03 (2.53)	45.56 (2.47)	45.21 (2.49)
Direct bilirubin, umol/L	1.84 (0.79)	1.67 (0.69)	1.99 (0.84)	1.85 (0.81)
Total bilirubin, umol/L	9.33 (4.49)	8.31 (3.83)	10.45 (4.87)	9.39 (4.60)
Gamma glutamyltransferase, U/L	34.14 (33.93)	27.31 (27.95)	41.63 (38.09)	34.52 (35.79)
Alanine aminotransferase, U/L	22.9 (14.06)	19.51 (13.51)	26.62 (13.71)	23.10 (14.66)
Aspartate aminotransferase, U/L	25.84 (11.70)	24.11 (12.98)	27.75 (9.75)	25.99 (13.29)
Cholesterol, mmol/L	5.72 (1.09)	5.88 (1.07)	5.56 (1.10)	5.71 (1.09)
HDL-cholesterol, mmol/L	1.47 (0.37)	1.62 (0.37)	1.30 (0.30)	1.46 (0.37)
LDL direct, mmol/L	3.58 (0.83)	3.62 (0.82)	3.54 (0.84)	3.57 (0.83)
Triglycerides, mmol/L	1.67 (0.98)	1.46 (0.80)	1.89 (1.10)	1.67 (0.99)
C-reactive protein, mg/L	2.17 (3.68)	2.25 (3.70)	2.07 (3.66)	2.15 (3.70)
AST:ALT	1.27 (0.44)	1.37 (0.45)	1.16 (0.40)	1.27 (0.44)
FIB-4	1.32 (0.52)	1.24 (0.48)	1.42 (0.55)	1.32 (0.54)
NAFLD fibrosis score (NFS)	-2.04 (1.00)	-2.17 (1.00)	-1.90 (0.98)	-2.04 (1.00)

Regression modelling of muscle biomarkers and functional performance

Logistic regression modelling was used to investigate the associations between each outcome and muscle volume ($FFMV_{VCG}$) and muscle fat (MFI) as continuous variables. Results showed both $FFMV_{VCG}$ and MFI were significantly associated with low hand grip strength, slow walking pace, CHD and T2D within NAFLD. Differences between variables were found for stair climbing ($FFMV_{VCG}$ significant; MFI nonsignificant) and falls (MFI significant; $FFMV_{VCG}$ nonsignificant). **Table S2** presents summary of results below.

Table S2. Results from logistic regression modelling within the NAFLD population using fat-tissue free muscle volume z-score ($FFMV_{VCG}$) and muscle fat $infiltration_{adj}$ (MFI_{adj} – sex-adjusted MFI) as predictors respectively. Models adjusted for sex, age, BMI and liver fat. VCG, virtual control group adjusted.

	Muscle volume z-score ($FFMV_{VCG}$)		Muscle fat $infiltration_{adj}$ (MFI_{adj})	
	Odds ratio	p-value	Odds ratio	p-value
Low hand grip strength	0.60 (0.46-0.78)	<0.001	1.21 (1.08-1.36)	0.001
Slow walking pace	0.58 (0.45-0.73)	<0.001	1.27 (1.14-1.42)	<0.001
No stair climbing	0.78 (0.62-0.96)	0.023	1.04 (0.93-1.15)	ns
More than 1 fall last year	0.83 (0.64-1.07)	ns	1.16 (1.03-1.30)	0.012
Coronary heart disease	0.68 (0.53-0.88)	0.003	1.22 (1.09-1.36)	<0.001
Type 2 diabetes	0.64 (0.52-0.78)	<0.001	1.30 (1.19-1.43)	<0.001

Medications

Insulin: Participants taking insulin were identified using UK Biobank field IDs 6153 'Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones', 6177 'Medication for cholesterol, blood pressure or diabetes' (gathered through touchscreen questionnaires). Participants reporting using of insulin at any of the visits were considered currently on insulin treatment.

Statins: Participants taking statins were identified by searching UK Biobank field ID 20003 'Treatment/medication code' (gathered through verbal interview with a trained nurse) for the UK brands listed below. Participants with any of the corresponding codes reported were considered currently on statin treatment.

Brand name	UK Biobank Field ID 20003 coding	Brand name	UK Biobank Field ID 20003 coding
advicor	Not found	lipostat	1140861970
altocor	Not found	livalo	Not found
altoprev	Not found	lovastatin	Not found
atorvastatin	1141146234	mevacor	Not found
baycol	Not found	pitava	Not found
compactin	Not found	pravastatin	1140888648
crestor	1141192414	ptavastatin	Not found
fluvastatin	1140888594	rosuvastatin	1141192410
lescol	1140864592	simvastatin	1140861958
lipex	Not found	vyforin	Not found
lipitor	1141146138	zecor	Not found

Supplementary results

Table S3 Comparison of population characteristics between different muscle composition groups within NAFLD: (1) adverse muscle composition (AMC), (2) low $FFMV_{VCG}$ only, (3) high MFI only, and (4) moderate to high $FFMV_{VCG}$ and low to moderate MFI (normal muscle composition). Factor shows difference in mean between the two groups. p-values shown for unadjusted and adjusted (sex, age, BMI, liver fat) modelling. FFMV, fat-tissue free muscle volume; MFI, muscle fat infiltration; PDFF, proton density fat fraction; VCG, virtual control group adjusted.

Muscle composition groups within NAFLD	Population characteristics	Factor	p-value	p-value (adjusted)
(1) Adverse muscle composition (AMC) vs (4) Normal muscle composition	% Females	0.98	0.822	-
	Age	1.08	<0.001	-
	Weight	1.04	0.006	0.794
	BMI	1.06	<0.001	-
	% With overweight (BMI > 25 kg/m^2)	1.09	0.005	0.999
	Visceral adipose tissue	1.28	<0.001	<0.001
	Abdominal subcutaneous adipose tissue	1.19	<0.001	<0.001
	Fat-tissue free muscle volume	0.84	<0.001	<0.001
	Appendicular lean mass/height^2	0.93	<0.001	<0.001
	Liver fat (PDFF)	1.01	0.772	-
(1) Adverse muscle composition (AMC) vs (2) Only low muscle volume ($FFMV_{VCG}$)	% Females	1.01	0.967	-
	Age	1.04	0.002	-
	Weight	1.12	<0.001	0.243
	BMI	1.12	<0.001	-
	% With overweight (BMI > 25 kg/m^2)	1.37	<0.001	1.000
	Visceral adipose tissue	1.27	<0.001	<0.001
	Abdominal subcutaneous adipose tissue	1.22	<0.001	0.998
	Fat-tissue free muscle volume	1.02	0.517	0.265
	Appendicular lean mass/height^2	1.05	0.066	0.188
	Liver fat (PDFF)	1.12	0.103	-
(1) Adverse muscle composition (AMC) vs (3) Only high muscle fat (MFI)	% Females	0.68	<0.001	-
	Age	1.03	0.003	-
	Weight	0.96	0.011	0.174
	BMI	0.94	<0.001	-
	% With overweight (BMI > 25 kg/m^2)	1.02	0.490	0.997
	Visceral adipose tissue	1.10	0.002	<0.001
	Abdominal subcutaneous adipose tissue	0.90	0.001	<0.001
	Fat-tissue free muscle volume	0.90	<0.001	<0.001
	Appendicular lean mass/height^2	0.90	<0.001	<0.001
	Liver fat (PDFF)	0.89	0.024	-
(2) Only low muscle volume ($FFMV_{VCG}$) vs (4) Normal muscle composition	% Females	0.97	0.807	-
	Age	1.03	0.010	-
	Weight	0.93	<0.001	0.098
	BMI	0.94	<0.001	-
	% With overweight (BMI > 25 kg/m^2)	0.80	<0.001	0.997
	Visceral adipose tissue	1.01	0.848	0.003
	Abdominal subcutaneous adipose tissue	0.98	0.603	<0.001
	Fat-tissue free muscle volume	0.83	<0.001	<0.001
	Appendicular lean mass/height^2	0.88	<0.001	<0.001
	Liver fat (PDFF)	0.91	0.089	-
(2) Only low muscle volume ($FFMV_{VCG}$) vs (3) Only high muscle fat (MFI)	% Females	0.68	<0.001	-
	Age	0.99	0.441	-
	Weight	0.85	<0.001	0.016
	BMI	0.84	<0.001	-
	% With overweight (BMI > 25 kg/m^2)	0.74	<0.001	0.996
	Visceral adipose tissue	0.87	<0.001	0.649
	Abdominal subcutaneous adipose tissue	0.74	<0.001	<0.001

	Fat-tissue free muscle volume	0.88	<0.001	<0.001
	Appendicular lean mass/height^2	0.85	<0.001	<0.001
	Liver fat (PDFF)	0.80	<0.001	-
(3) Only high muscle fat (MFI) vs (4) Normal muscle composition	% Females	1.44	<0.001	-
	Age	1.04	<0.001	-
	Weight	1.09	<0.001	0.150
	BMI	1.12	<0.001	-
	% With overweight (BMI > 25 kg/m^2)	1.07	0.004	0.996
	Visceral adipose tissue	1.16	<0.001	<0.001
	Abdominal subcutaneous adipose tissue	1.32	<0.001	0.161
	Fat-tissue free muscle volume	0.94	<0.001	0.002
	Appendicular lean mass/height^2	1.04	0.022	0.079
	Liver fat (PDFF)	1.13	0.001	-

Table S4 Comparison between different muscle composition groups within NAFLD: (1) adverse muscle composition (AMC), (2) low $FFMV_{VCG}$ only, (3) high MFI only, and (4) moderate to high $FFMV_{VCG}$ and low to moderate MFI (normal muscle composition). Factor shows difference in prevalence of outcomes between the two groups. p-values shown for unadjusted and adjusted (sex, age, BMI, liver fat) modelling. FFMV, fat-tissue free muscle volume; MFI, muscle fat inifiltration; VCG, virtual control group adjusted. Low hand grip defined as below 16/27 kg (females/males).

Muscle composition groups within NAFLD	**Functional performance & metabolic comorbidity**	**Factor**	**p-value**	**p-value (adjusted)**
(1) Adverse muscle composition (AMC) vs (4) Normal muscle composition	Low hand grip strength	2.24	0.006	0.026
	Slow walking pace	3.87	<0.001	<0.001
	No stair climbing	1.86	0.007	0.191
	More than one fall last year	2.70	<0.001	0.001
	Coronary heart disease (prevalent)	3.84	<0.001	<0.001
	Coronary heart disease (incident)	1.86	0.122	0.390
	Type 2 diabetes	3.31	<0.001	<0.001
(1) Adverse muscle composition (AMC) vs (2) Only low muscle volume ($FFMV_{VCG}$)	Low hand grip strength	1.27	0.527	0.623
	Slow walking pace	2.19	0.027	0.538
	No stair climbing	1.66	0.129	0.421
	More than one fall last year	3.70	0.012	0.023
	Coronary heart disease (prevalent)	2.58	0.005	0.076
	Coronary heart disease (incident)	4.93	0.116	0.225
	Type 2 diabetes	1.41	0.143	0.670
(1) Adverse muscle composition (AMC) vs (3) Only high muscle fat (MFI)	Low hand grip strength	1.38	0.310	0.354
	Slow walking pace	1.08	0.754	0.076
	No stair climbing	1.47	0.134	0.301
	More than one fall last year	1.69	0.073	0.019
	Coronary heart disease (prevalent)	2.79	<0.001	0.001
	Coronary heart disease (incident)	2.37	0.106	0.180
	Type 2 diabetes	1.25	0.198	0.139
(2) Only low muscle volume ($FFMV_{VCG}$) vs (4) Normal muscle composition	Low hand grip strength	1.76	0.114	0.182
	Slow walking pace	1.76	0.130	0.028
	No stair climbing	1.12	0.729	0.920
	More than one fall last year	0.73	0.547	0.629
	Coronary heart disease (prevalent)	1.49	0.275	0.357
	Coronary heart disease (incident)	0.38	0.356	0.391
	Type 2 diabetes	2.35	0.001	<0.001
(2) Only low muscle volume ($FFMV_{VCG}$) vs (3) Only high muscle fat (MFI)	Low hand grip strength	1.09	0.847	0.803
	Slow walking pace	0.49	0.034	0.541
	No stair climbing	0.88	0.690	0.975
	More than one fall last year	0.46	0.139	0.380
	Coronary heart disease (prevalent)	1.08	0.834	0.451
	Coronary heart disease (incident)	0.48	0.507	0.654
	Type 2 diabetes	0.89	0.620	0.460
(3) Only high muscle fat (MFI) vs (4) Normal muscle composition	Low hand grip strength	1.62	0.072	0.190
	Slow walking pace	3.59	<0.001	0.021
	No stair climbing	1.27	0.265	0.854
	More than one fall last year	1.60	0.094	0.447
	Coronary heart disease (prevalent)	1.38	0.248	0.922
	Coronary heart disease (incident)	0.79	0.663	0.497
	Type 2 diabetes	2.64	<0.001	<0.001

Table S5 Comparison for the biomarker panel between different muscle composition groups within NAFLD: (1) adverse muscle composition (AMC), (2) low $FFMV_{VCG}$ only, (3) high MFI only, and (4) moderate to high $FFMV_{VCG}$ and low to moderate MFI (normal muscle composition). Factor shows difference in mean of outcomes between the two groups. p-values shown for unadjusted and adjusted (sex, age, BMI, liver fat) modelling. † Data extracted from baseline assessment (years 2006-2010). FFMV, fat-tissue free muscle volume; MFI, muscle fat infiltration; VCG, virtual control group adjusted

Muscle composition groups within NAFLD	**Biomarker panel†**	**Factor**	**p-value**	**p-value (adjusted)**
(1) Adverse muscle composition (AMC) vs (4) Normal muscle composition	Glycated haemoglobin (HbA1c)	1.08	<0.001	0.001
	Glucose	1.08	0.002	0.026
	Albumin	0.98	0.001	0.034
	Direct bilirubin	0.99	0.884	0.980
	Total bilirubin	0.95	0.252	0.374
	Gamma glutamyltransferase	1.16	0.070	0.111
	Alanine aminotransferase	0.94	0.197	0.235
	Aspartate aminotransferase	0.97	0.425	0.178
	Cholesterol	0.98	0.354	0.563
	HDL-cholesterol	1.02	0.254	0.275
	LDL direct	0.97	0.129	0.267
	Triglycerides	1.04	0.443	0.289
	C-reactive protein	1.31	0.021	0.072
	AST:ALT	1.04	0.175	0.327
	FIB-4	1.04	0.331	0.031
	NAFLD fibrosis score (NFS)	0.86	0.003	0.262
(1) Adverse muscle composition (AMC) vs (2) Only low muscle volume ($FFMV_{VCG}$)	Glycated haemoglobin (HbA1c)	1.04	0.058	0.381
	Glucose	1.05	0.164	0.456
	Albumin	0.98	0.007	0.132
	Direct bilirubin	1.04	0.460	0.334
	Total bilirubin	1.04	0.547	0.305
	Gamma glutamyltransferase	1.10	0.369	0.580
	Alanine aminotransferase	1.06	0.463	0.617
	Aspartate aminotransferase	1.04	0.380	0.685
	Cholesterol	1.00	1.000	0.740
	HDL-cholesterol	1.00	0.941	0.838
	LDL direct	1.00	0.942	0.745
	Triglycerides	1.05	0.429	0.454
	C-reactive protein	1.22	0.205	0.771
	AST:ALT	1.02	0.569	0.456
	FIB-4	1.08	0.141	0.567
	NAFLD fibrosis score (NFS)	0.80	0.001	0.667
(1) Adverse muscle composition (AMC) vs (3) Only high muscle fat (MFI)	Glycated haemoglobin (HbA1c)	1.01	0.588	0.751
	Glucose	1.00	0.969	0.906
	Albumin	1.01	0.069	0.366
	Direct bilirubin	1.05	0.249	0.983
	Total bilirubin	1.03	0.514	0.542
	Gamma glutamyltransferase	1.04	0.677	0.836
	Alanine aminotransferase	0.94	0.279	0.129
	Aspartate aminotransferase	0.95	0.146	0.050
	Cholesterol	1.00	0.815	0.673
	HDL-cholesterol	1.00	0.925	0.259
	LDL direct	0.98	0.424	0.853
	Triglycerides	1.05	0.329	0.446

	C-reactive protein	0.90	0.326	0.742
	AST:ALT	1.04	0.228	0.173
	FIB-4	0.99	0.757	0.015
	NAFLD fibrosis score (NFS)	1.10	0.137	0.059
(2) Only low muscle volume ($FFMV_{VCG}$) vs (4) Normal muscle composition	Glycated haemoglobin (HbA1c)	1.03	0.068	0.071
	Glucose	1.03	0.322	0.291
	Albumin	1.00	0.680	0.969
	Direct bilirubin	0.95	0.314	0.250
	Total bilirubin	0.91	0.088	0.043
	Gamma glutamyltransferase	1.05	0.630	0.468
	Alanine aminotransferase	0.89	0.048	0.099
	Aspartate aminotransferase	0.93	0.083	0.094
	Cholesterol	0.98	0.427	0.364
	HDL-cholesterol	1.03	0.288	0.478
	LDL direct	0.97	0.166	0.172
	Triglycerides	0.98	0.774	0.982
	C-reactive protein	1.07	0.633	0.217
	AST:ALT	1.02	0.628	0.966
	FIB-4	0.96	0.353	0.009
	NAFLD fibrosis score (NFS)	1.08	0.138	0.127
(2) Only low muscle volume ($FFMV_{VCG}$) vs (3) Only high muscle fat (MFI)	Glycated haemoglobin (HbA1c)	0.97	0.109	0.509
	Glucose	0.96	0.137	0.374
	Albumin	1.03	<0.001	0.018
	Direct bilirubin	1.01	0.840	0.300
	Total bilirubin	1.00	0.934	0.108
	Gamma glutamyltransferase	0.94	0.538	0.681
	Alanine aminotransferase	0.89	0.079	0.069
	Aspartate aminotransferase	0.91	0.025	0.036
	Cholesterol	1.00	0.837	0.996
	HDL-cholesterol	1.00	0.870	0.461
	LDL direct	0.98	0.434	0.615
	Triglycerides	1.00	0.996	0.882
	C-reactive protein	0.74	0.024	0.977
	AST:ALT	1.02	0.660	0.713
	FIB-4	0.92	0.058	0.007
	NAFLD fibrosis score (NFS)	1.37	<0.001	0.038
(3) Only high muscle fat (MFI) vs (4) Normal muscle composition	Glycated haemoglobin (HbA1c)	1.07	<0.001	0.001
	Glucose	1.08	<0.001	0.006
	Albumin	0.97	<0.001	<0.001
	Direct bilirubin	0.94	0.080	0.956
	Total bilirubin	0.92	0.022	0.802
	Gamma glutamyltransferase	1.12	0.102	0.113
	Alanine aminotransferase	1.00	0.927	0.569
	Aspartate aminotransferase	1.03	0.308	0.339
	Cholesterol	0.99	0.419	0.225
	HDL-cholesterol	1.02	0.212	0.863
	LDL direct	0.99	0.452	0.294
	Triglycerides	0.98	0.690	0.799
	C-reactive protein	1.46	<0.001	0.093
	AST:ALT	1.00	0.995	0.540
	FIB-4	1.05	0.105	0.534
	NAFLD fibrosis score (NFS)	0.79	<0.001	0.265

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