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Reply to: "Rationale of adding muscle volume to muscle fat infiltration in the definition of an adverse muscle composition is unclear"

To the Editor:

We thank Dr. Leclerq and colleagues for their interest in our paper and for taking the time to express their concerns.[1] The discussion of potential sarcopenia biomarkers is important; herein, we reply to authors' concerns.

In their letter, the authors suggest that the addition of muscle quantity (muscle volume) to muscle fat for sarcopenia assessment is questionable and that muscle quantity should instead be replaced by hand grip strength. To clarify, our conclusion[2] suggests the *addition* of cut-offs for muscle fat to the current sarcopenia landscape. While we do recommend the *inclusion* of cut-offs for muscle fat, we are not recommending the *exclusion* of functional measures for sarcopenia assessment.

Our work investigated muscle composition within NAFLD to sub-phenotype a heterogeneous population and provide data that may help in risk-stratification. To put this into context, NAFLD was compared to controls without fatty liver and high alcohol consumption. That muscle fat infiltration (MFI) was significantly higher in NAFLD *vs.* controls (as correctly observed by the authors) is likely driven by the higher level of adiposity within NAFLD (BMI 30.1 *vs.* 25.4 kg/m^2): the association of MFI between NAFLD and controls was non-significant (p = 0.453), as was the difference in prevalence of 'only high muscle fat' (p = 0.185) and adverse muscle composition (AMC) (p = 0.657) when adjusted for sex, age and BMI (Table 1, original manuscript).

Follow-up analysis (as suggested) comparing NAFLD to sex and BMI-matched controls showed that the difference in i) MFI was non-significant (mean [SD] 8.0 (2.1)% *vs.* 7.8 (2.0)%, β = 0.02, p = 0.780), ii) the prevalence of high MFI (including AMC) and AMC alone was non-significant (37.8% *vs.* 34.1%, β = -0.04, p = 0.658 and 14.0% *vs.* 14.7%, β = -0.16, p = 0.177, respectively) and iii) the prevalence or incidence of coronary heart disease (CHD) was non-significant (7.8% *vs.* 6.5%, β = 0.14, p = 0.405 and 2.2% *vs.* 1.9%, β = 0.10 p = 0.734, respectively) (p values adjusted for sex, age, BMI). These results further support what can already be read from Table 1 in the original manuscript: that higher MFI and prevalence of AMC in this NAFLD population is probably driven by obesity.

However, we fully agree that muscle fat could be very useful to identify vulnerable patients with NAFLD. In our paper, we investigated the association of muscle composition with functional performance and metabolic comorbidity. Literature tells us that functional measures are effective in identifying vulnerable individuals[3] with the advantage of being simple to acquire, but with the drawbacks of low precision for tracking of disease progression and not being muscle disease specific. A follow-up analysis showed that the combination of muscle fat and hand grip strength (as suggested) did not out-perform the combination of muscle fat and muscle volume z-score (AMC): using the same thresholds to identify high MFI and the thresholds recommended by EWGSOP2[4] to identify low hand grip strength only stratified 40 (3%) participants with NAFLD (compared with 169 (14.0%) stratified using AMC) with a slightly lower CHD prevalence (17.5% *vs.* 19.5%) and a slightly higher prevalence of type 2 diabetes (T2D) (25.0% *vs.* 23.7%) compared to AMC.

It is worth noting that we have not used the recommended thresholds corresponding to low muscle mass for AMC identification as these are highly BMI dependent (despite previously suggested normalizations [*i.e.* division by height^2, weight or BMI][5]). That muscle quantity has been measured differently between studies and that different, ineffective, body size-normalizations have been applied have likely confounded previously published associations between muscle quantity and adverse outcomes. Follow-up (univariate) analyses within NAFLD showed that while muscle volume z-score was significantly associated with CHD (odds ratio [OR] 0.69; 95% CI 0.54–0.89; p = 0.004), muscle volume or muscle volume/height^2 was not (OR 0.91; 95% CI 0.78–1.06; p = 0.226 and OR 0.75; 95% CI 0.43–1.27; p = 0.292) (sex and age adjusted). Further, our original results already indicate that measuring muscle volume does have predictive value alongside muscle fat: Among those with *high* muscle fat, those with low muscle volume z-score had a 2.8x higher prevalence of CHD (p <0.001) and among those with *low* muscle fat, those with low muscle volume z-score had a 2.4x higher prevalence of T2D (p <0.01) (Fig. 3, Table S3, original manuscript).

Today, methods to assess muscle volume are under rapid development and close to completely automatic solutions are available.[6] As muscle fat assessment requires tomographic imaging (MRI or CT) and muscle quantity can be extracted from the same images we do not see a convincing case of excluding muscle quantity for the benefit of hand grip strength – especially since muscle volume (independently of muscle fat) does seem to have predictive value for adverse outcomes within NAFLD. However, as the authors suggest replacing muscle volume with hand grip strength, a follow-up analysis within NAFLD with high MFI was performed which showed that while muscle volume z-score was significantly associated with CHD, hand grip strength was not. In addition, hand grip strength did not attenuate the predictive performance of muscle volume z-score (Table 1).

We share the belief in muscle fat as an important biomarker for sarcopenia assessment in NAFLD/NASH. However, our data suggest that muscle volume should not be excluded for the benefit of hand grip strength. Muscle volume can be obtained from the same tomographic images used to assess muscle fat and independently adds to the predictive performance.

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Table 1. Associations of CHD with muscle volume z-score (sex and BMI invariant) and hand grip strength within UK Biobank participants with NAFLD and high muscle fat (above the 75th percentile (sex-specific)).

	CHD prediction (univariate)				CHD prediction (multivariate)		
		Odds ratio	*p* value			Odds ratio	*p* value
M1	Muscle volume z-score (cont.)	0.65 (0.46-0.93)	0.018	M5	Muscle volume z-score (cont.)	0.68 (0.47-0.98)	0.040
M2	Hand grip strength (cont.)	0.97 (0.93-1.01)	0.194		Hand grip strength (cont.)	0.98 (0.94-1.03)	0.470
M3	Low muscle volume z-score	2.66 (1.45-4.97)	0.002	M6	Low muscle volume z-score	2.72 (1.47-5.15)	0.002
M4	Low hand grip strength	1.51 (0.56-3.58)	0.379		Low hand grip strength	1.39 (0.51-3.41)	0.491

CHD, coronary heart disease; M1-M6, Model 1-Model 6; NAFLD, non-alcoholic fatty liver disease. Models are logistic or linear regression models adjusted for sex and age.

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Conflict of interest
JL and ODL are employees and stockholders of AMRA Medical.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
JL drafted the manuscript. ME and ODL have critically revised the manuscript. All authors have approved the final version of the manuscript.

Supplementary data
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