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REPLY OPEN ACCESS

Comment on 'Association Between Handgrip Strength and Cardiovascular Disease Risk in MASLD: A Prospective Study From UK Biobank' by T. S. Lim et al.—Authors' Reply

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Dear Editor,

We appreciate the thoughtful comments from Zhao et al. [1] regarding our recent publication [2]. Their insights offer valuable opportunities to clarify aspects of our methodology and further contextualize our findings.

First, with regard to the use of the fibrosis-4 (FIB-4) index to define advanced liver fibrosis, we acknowledge its diagnostic limitations, which were also addressed in the limitations section of our manuscript. We applied FIB-4 not as a diagnostic gold standard, but as a practical, widely used and guideline-endorsed tool for noninvasive risk stratification in population-based studies [3–7]. Although its diagnostic accuracy may vary with factors such as age [8], FIB-4 remains a validated surrogate for liver fibrosis risk, particularly in settings where liver biopsy or elastography is not feasible [9–11]. In our study, FIB-4 was not part of the primary analysis but was used in a subgroup analysis to examine whether the observed association between handgrip strength (HGS) and cardiovascular disease (CVD) risk was maintained irrespective of liver fibrosis severity.

Second, we acknowledge the heterogeneous nature of metabolic dysfunction-associated steatotic liver disease (MASLD), which spans a spectrum of hepatic and cardiometabolic abnormalities including inflammation, fibrosis and comorbidities such as diabetes mellitus, hypertension and dyslipidaemia [12]. Our primary aim was to evaluate the association between HGS and CVD risk in individuals with MASLD, rather than to characterize histologic or metabolic heterogeneity. To account for key clinical differences, we applied exact propensity score matching across major demographic and metabolic variables. Furthermore, covariates such as body mass index, diabetes mellitus, hypertension, dyslipidaemia and physical activity were also included in our multivariable models. After applying propensity score matching and adjusting covariates, the association between lower HGS and increased CVD risk remained consistent, strengthening the credibility of our findings.

Third, Zhao et al. appropriately emphasize the distinction between association and causation. We fully agree with the comment that causality cannot be determined from observational cohort data alone. In this study, we insisted on the associations between low HGS and CVD risks, not causality between the two conditions, and the findings support the hypothesis that reduced muscle strength may serve as a clinically meaningful and potentially modifiable risk marker. We agree that future studies using methods such as Mendelian randomization would be valuable to clarify causal pathways [13].

Fourth, the concern regarding the long follow-up period (median 13.1 years) and potential changes in clinical parameters over time is well taken. We acknowledge that repeated measurements of liver function, HGS and lifestyle factors would offer more temporal precision. However, as with many large-scale cohort studies, our analysis relied on baseline measurements of muscle strength. Although one-time baseline measurement may not fully capture its temporal variation, the consistency of associations across multiple models supports the notion that baseline HGS may serve as a stable proxy for long-term risk—forming the basis of our hypothesis. Future studies incorporating repeated assessments of HGS and related clinical variables would help elucidate dynamic relationships with cardiovascular outcomes.

Lastly, we recognize that the generalizability of our findings may be limited by the predominantly European ancestry of the UK Biobank cohort. Nonetheless, our findings are consistent with prior reports from diverse populations and support the growing body of evidence linking sarcopenia to cardiometabolic health [9, 14, 15].

In conclusion, we appreciate the constructive feedback from Zhao et al. and their recognition of the importance of our research. Our study highlights the relevance of muscle strength as an independent cardiovascular risk indicator in MASLD—one that may help improve risk stratification beyond traditional metabolic parameters. We hope our findings contribute to future efforts to develop more personalized preventive strategies in this increasingly prevalent disease population.

Conflicts of Interest

The authors declare no conflicts of interest.

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