Letter to the Editor

The association between sarcopenia and cirrhosis: a Mendelian randomization analysis

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We read with great interest the study by Kuchay *et al.* (1) which showed sarcopenia was very common in patients with cirrhosis and could have a significant impact on their survival. Kim *et al.* (2) indicated that the presence of sarcopenia was associated with poor prognosis and the development of complications from cirrhosis and could be used for risk assessment. It is difficult to infer causal effects only from observational studies because of confounding. Here, we attempted to answer whether the associations of sarcopenia-related phenotypes with cirrhosis were causal or not by using the Mendelian randomization (MR) design.

MR is a statistical approach based on genome-wide association studies (GWAS) to construct instrumental variables (IVs) and can effectively bring down the confounding bias of environmental or other disease factors, because alleles are randomly assigned to offspring (3). IVs refer to variables that only affect the outcome through risk factors, and MR uses single-nucleotide polymorphisms (SNPs) as IVs to identify risk factors. MR simulate the causal relationships between exposures and outcomes. Here, we leverage data from large-scale genetic association studies to identify genetic proxies for sarcopenia. We used appendicular lean mass, hand grip strength (right & left), low hand grip strength (60 years and older), and usual walking pace as genetically predicted sarcopenia-related traits, and conducted MR analysis of them separately with cirrhosis to investigate whether sarcopenia is genetically associated with cirrhosis.

Summary genetic association estimates for sarcopenia and cirrhosis were obtained from MRCIEU GWAS database. Three sarcopenia-related traits included appendicular lean mass in 450,243 samples [ebi-a-GCST90000025 (4), N=450,243], and hand grip strength (right/left) in 461,089/461,026 samples (ukb-b-10215, N=461,089)/ ukb-b-7478, N=461,026). Low hand grip strength defined by the foundation for the European Working Group on Sarcopenia in Older People (EWGSOP) set up with women and men aged 60 years and older comprised 135,468 samples, including 34,589 cases and 100,879 healthy controls (ebi-a-GCST90007527, N=135,468). Usual walking pace in 459,915 samples (ukb-a-513, N=335,349). And cirrhosis comprised 218,792 samples [finn-b-CIRRHOSIS_BROAD (5), N=218,792]. The GWAS data for cirrhosis were for all-cause cirrhosis. The population used in the study was European. The GWAS data for cirrhosis were for all-cause cirrhosis. The population used in the study was European.

The MR analyses (*Figure 1*) were performed by using the inverse-variance weighted (IVW) method. All summary data used in this study were publicly available and obtained with the consent and ethical approval of the relevant participants. SNPs at $P<5\times10^{-8}$ were selected as instrumental variables. The LD threshold was set to $r^2=0.001$ within a distance of 10,000 kb. Besides, weighted median, MR-Egger and MR-

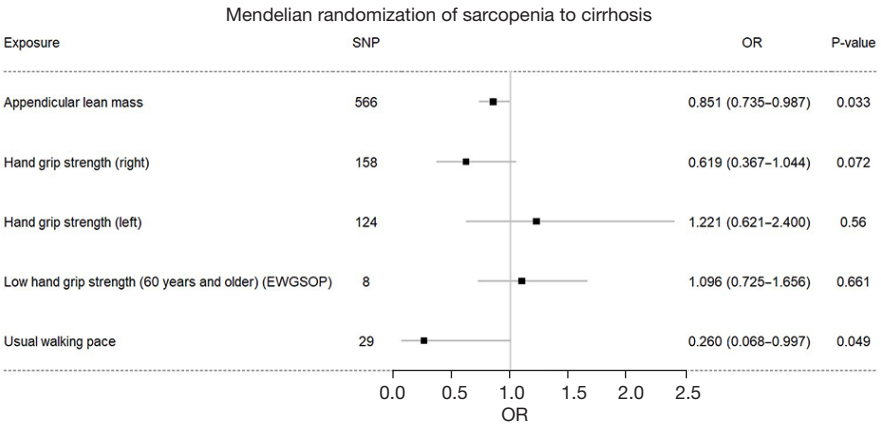

Figure 1 MR estimates using the IVW method of appendicular lean mass, hand grip strength (right & left), low hand grip strength (60 years and older) and usual walking pace on cirrhosis. CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse-variance weighted.

PRESSO methods were adopted as sensitivity analyses.

The IVW method, in conjunction with other methods, suggested that there were consistent evidences that appendicular lean mass was causally associated with cirrhosis [OR =0.851 (95% CI: 0.735–0.987), P=0.033]. The MR leave-one-out sensitivity analysis that removed 1 SNP at a time showed stable results, except for rs2871960. We also found that usual walking pace was causally associated with cirrhosis [OR =0.260 (95% CI: 0.068–0.997), P=0.049]. Overall, the MR leave-one-out sensitivity analysis showed stable results. The higher appendicular lean mass and usual walking pace were protective factors for cirrhosis. Genetically elevated appendicular lean mass and usual walking pace could decrease the risk of cirrhosis. There was no evidence supporting the association of hand grip strength (right&left) and low hand grip strength (60 years and older) with cirrhosis. The MR-PRESSO method also did not detect outliers. There was neither heterogeneity nor horizontal pleiotropy in MR estimates (Cochranes's Q P value >0.05 and MR-Egger intercept P value >0.05). The reverse MR was not supported by sufficient SNPs.

In conclusion, our study revealed a unidirectional effect of sarcopenia on cirrhosis. The associations estimated by the MR analysis have greater accuracy because these estimates are less confounded by socioeconomic, environmental, and behavioral factors, and the timing of causality is reasonable. These findings may be helpful in clarifying clinical implications and guiding clinical decision-making.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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