Letter to the Editor

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# Sarcopenia and risk of cardio-cerebrovascular disease: A two-sample Mendelian randomization study

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**SUMMARY** Based on the association between sarcopenia and the risk of developing cardio-cerebrovascular disease (CCVD) established by a meta-analysis by Fang *et al*.(*Biosci Trends. 2023; 17:293-301*), we have used Mendelian randomization (MR) analysis to test the authenticity and accuracy of such an association. In this MR study, appendicular lean mass, handgrip strength, and walking pace were used as sarcopenia-related traits, with cardiovascular diseases and stroke set as outcomes of CCVD. MR analysis was performed using inverse-variance weighting, the MR Egger, weighted median, simple mode, and weighted mode. No heterogeneity or horizontal pleiotropy in MR estimates was observed (Cochran's Q *P* value > 0.05, MR-PRESSO global test *P* value > 0.05, and MR-Egger intercept *P* value > 0.05). Results of that analysis proved a causal relationship between sarcopenia-related traits and cardio-cerebrovascular disease, with a causal association between appendicular lean mass and cardiovascular diseases and an inverse causal relationship between appendicular lean mass and stroke. However, such a relationship was absent in the case of handgrip strength and the risk of cardiovascular diseases as well as in the case of walking pace and lacunar/ischemic stroke. Therefore, the effect of sarcopenia on CCVD should be carefully explained.

***Keywords*** causal relationship, Mendelian randomization, sarcopenia, cardio-cerebrovascular disease

To the Editor,

We read with great interest where a systematic review and meta-analysis by Fang *et al*. (*1*) suggested that sarcopenia is significantly associated with an elevated risk of developing cardio-cerebrovascular disease (CCVD). However, the causal relationship between sarcopenia and CCVD needs to be further determined; due to the observational studies that were analyzed, residual confounders are difficult to isolate and the limitations of the race and size of the study population are not known. Mendelian randomization (MR) analysis uses genetic variation as an instrumental variable to estimate causal effects, and results are not affected by confounding factors (*2*). Here, we leveraged data from large-scale genetic association studies in European populations and applied two-sample MR analyses to investigate the causal relationship between sarcopenia-related traits (appendicular lean mass, hand grip strength, and walking pace) (*3*) and CCVD (cardiovascular diseases and stroke).

GWAS data on sarcopenia-related traits from the UK Biobank (UKB) were available for appendicular lean mass, hand grip strength (right), and walking pace. We used summary-level genetic data for cardiovascular diseases from the FinnGen biobank, including 218,792 European participants and 16,380,466 single-nucleotide polymorphisms (SNPs). GWAS data on stroke from the FinnGen biobank were available for 180,862 European participants and 16,380,350 SNPs. GWAS data on hard cardiovascular diseases, lacunar stroke, and ischemic stroke were also analyzed at the same time. All GWAS summary statistics can be downloaded from the IEU OpenGWAS project (*https://gwas.mrcieu.ac.uk/*).

The MR analysis was performed using inverse-variance weighting, the MR Egger, weighted median, simple mode, and weighted mode. Cochran's Q statistic, the MR-Egger intercept test, and MR pleiotropy residual sum and outlier (MR-PRESSO) were performed, allowing estimation of heterogeneity and horizontal pleiotropy. Single-nucleotide polymorphisms at $P < 5 \times 10^{-8}$ were selected as instrumental variables. The linkage disequilibrium threshold was set to $r^2 = 0.001$ within a distance of 10,000 kb.

Results of analysis (Figure 1) revealed a causal relationship between sarcopenia-related traits and cardio-cerebrovascular disease. Findings indicated an inverse causal relationship between appendicular lean mass and stroke as well as a causal association between

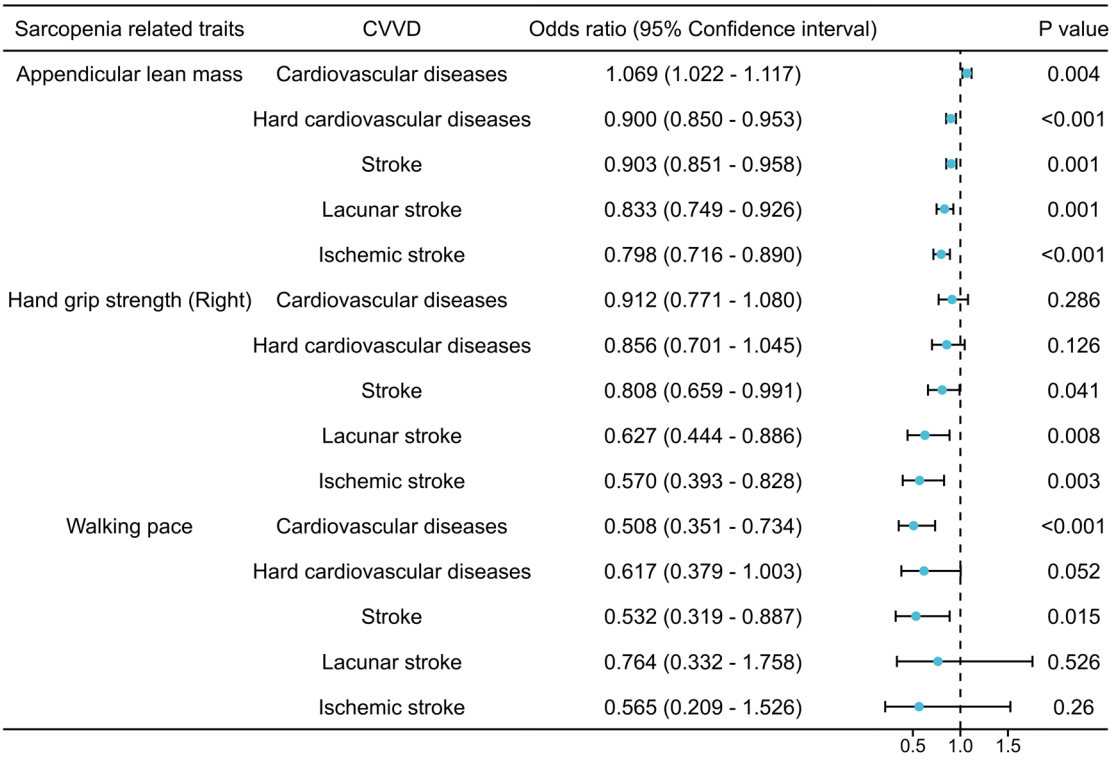


**Figure 1. Mendelian randomization analysis of sarcopenia-related traits and CCVD (cardiovascular diseases, hard cardiovascular diseases, stroke, lacunar stroke, and ischemic stroke) with inverse-variance weighting**ns.

appendicular lean mass and cardiovascular diseases. Notably, hand grip strength (right) was not associated with the risk of cardiovascular diseases but was inversely associated with stroke. Moreover, walking pace was inversely associated with both cardiovascular diseases and stroke but it was not significantly associated with their respective subtypes (lacunar stroke and ischemic stroke). In other words, sarcopenia-related traits, except hand grip strength, have a causal relationship with the risk of cardiovascular diseases. In addition, there was a significant inverse causal relationship between sarcopenia-related traits and stroke. There was neither heterogeneity or horizontal pleiotropy in MR estimates (Cochrane's Q *P* value > 0.05, MR-PRESSO global test *P* value > 0.05, and MR-Egger intercept *P* value > 0.05). Detailed information is presented in Supplemental material (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=170*).

In conclusion, this MR study provided evidence for the causal relationship between sarcopenia and CCVD even though such a relationship is absent in the case of handgrip strength and the risk of cardiovascular diseases as well as in the case of walking pace and lacunar/ischemic stroke. Therefore, the effect of sarcopenia on CCVD should be carefully explained.

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*Conflict of Interest*: The authors have no conflicts of interest to disclose.

## References

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