CORRESPONDENCE

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The causal association between sarcopenia and colorectal cancer: a Mendelian Randomization analysis

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A recent study by Kim et al. [1] published in the *Korean Journal of Internal Medicine* reported that sarcopenia was an important risk factor for colorectal neoplasia in a single-center population using logistic regression analysis, but sarcopenia was assessed using appendicular skeletal muscle mass only. In addition, Sun et al. [2] found that sarcopenia may be an important cancer risk factor for colorectal cancer (CRC) in a cohort of Asian populations using multivariate Cox regression analysis. To infer a causal association between sarcopenia and CRC, our study performed a bi-directional, two-sample Mendelian Randomization (MR) analysis in a large-scale European population.

The genome-wide association studies (GWAS) summary data of sarcopenia-related phenotypes and CRC were obtained from IEU OpenGwas project [3]. The CRC data comprised 377,673 samples, including 5,657 cases and 372,016 healthy controls. Sarcopenia-related phenotypes included hand grip strength (right/left) in 335,842/335,821 samples, usual walking pace in 459,915 samples and appendicular lean mass in 450,243 samples, where hand grip strength (right/left) and usual walking pace represent the muscle function of sarcopenia. In this study, we used the inverse variance weighted method as the primary approach of MR analysis to exclude potentially pleiotropic single-nucleotide polymorphisms (SNPs) through traits. MR analysis uses genetic variation as an instrumental variable to estimate causal effects and results are not affected by confounding factors. MR-egger regression was used to test the pleiotropy and leave-one-out sensitivity analysis was used to test the stability. SNPs 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. Forest plots were used to visualize the results of MR.

The MR analyses (Fig. 1) showed that appendicular lean mass was associated with CRC (odds ratio, 1.002; 95% confidence interval, 1.001–1.003; $p = 0.005$). Six hundred twenty-seven SNPs were used as instrumental variables. The intercept of MR-egger analysis had no significant deviation from 0 (intercept = 1.32×10^{-5}), indicating that there was no evidence of horizontal pleiotropy. In leave-one-out analysis, all error lines on the same side of 0 means the results were stable (Fig. 2). There were no strong evidences supporting associations of hand grip strength (right/left) and usual walking pace with CRC. The reverse MR analysis suggested the genetic predisposition to CRC could not affect sarcopenia-related phenotypes.

In conclusion, we investigated the impacts of sarcopenia on CRC using large-scale GWAS summary data. MR analyses

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Exposure	Outcome	NSNP	*p*	OR (95% CI)
Appendicular lean mass	Colorectal cancer	627	0.005	1.002 (1.001–1.003)
Hand grip strength (right)	Colorectal cancer	97	0.728	1.001 (0.995–1.007)
Hand grip strength (left)	Colorectal cancer	82	0.695	1.001 (0.995–1.007)
Usual walking pace	Colorectal cancer	56	0.964	1.000 (0.989–1.012)
Colorectal cancer	Appendicular lean mass	9	0.849	0.904 (0.321–2.545)
Colorectal cancer	Hand grip strength (right)	8	0.235	1.480 (0.775–2.827)
Colorectal cancer	Hand grip strength(left)	8	0.552	1.326 (0.524–3.357)
Colorectal cancer	Usual walking pace	8	0.801	1.067 (0.646–1.763)

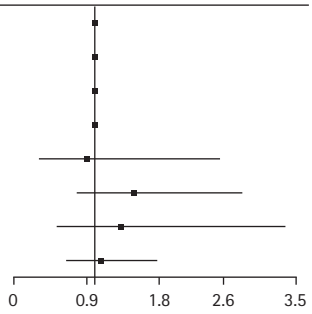

Figure 1. Mendelian randomization (MR) between sarcopenia-related phenotypes and colorectal cancer. On the X-axis, odds ratio (OR) are shown and data are represented as OR and 95% confidence internal (CI). NSNP, number of SNPs.

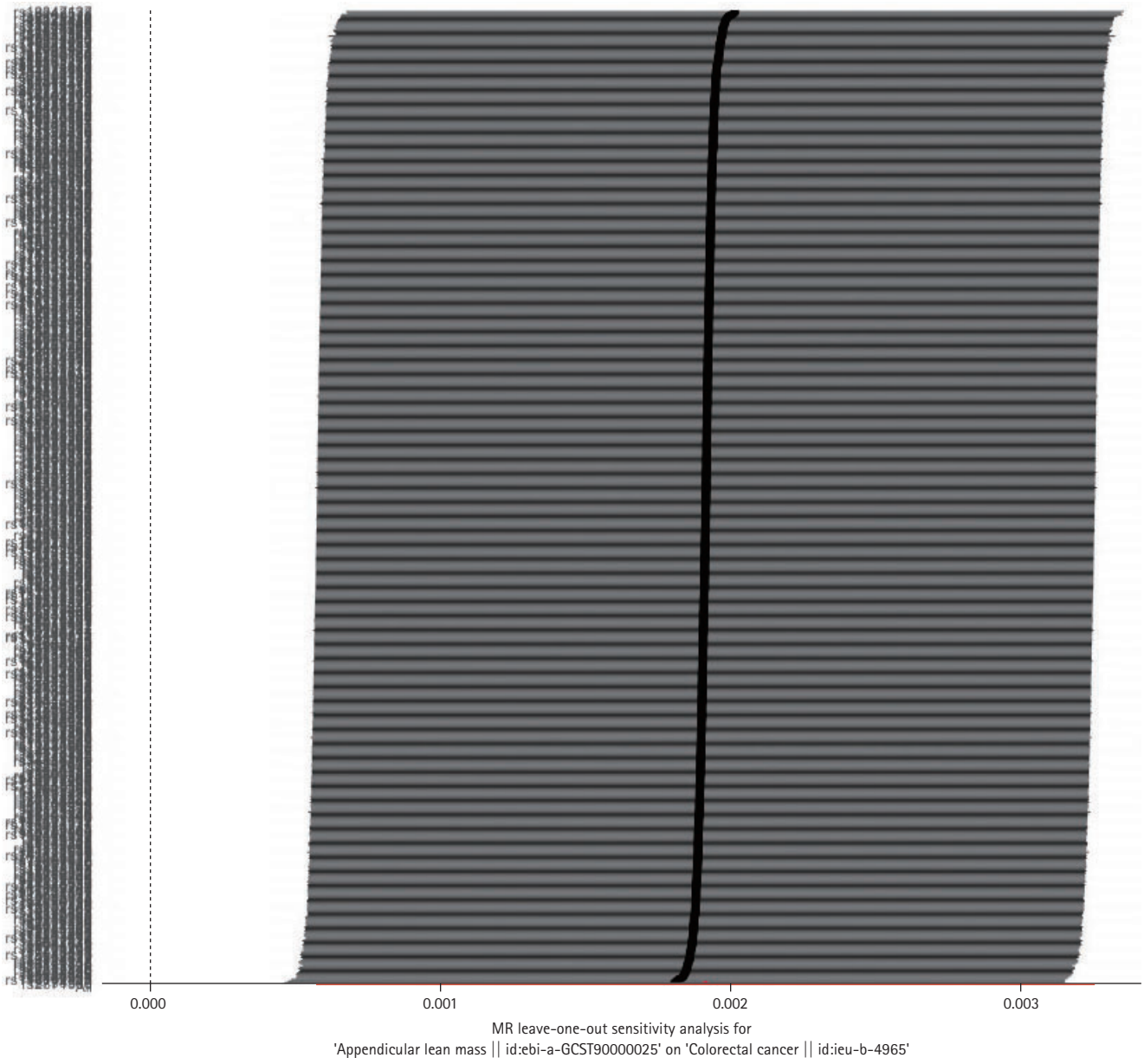

Figure 2. Leave-one-out sensitivity analysis for appendicular lean mass on colorectal cancer. MR, Mendelian Randomization.

indicated the potential causal association between appendicular lean mass and CRC and revealed that the more appendicular lean mass is a risk factor for CRC.

This conclusion contradicts the conclusion of Kim et al. [1], probably because the causal associations could vary among different populations. In addition, our study found four genes GTPBP3, FST, SLC18B1 and AFAP1 that are involved in both sarcopenia and CRC using weighted gene co-expression network analysis, which is a powerful tool to explore the relationships between genes and phenotypic traits. The findings may help shed light on the clinical implications and guide clinical decision-making.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Kim MC, Kim KO, Kang MK. Prevalence and associated risk of advanced colorectal neoplasia in adults with sarcopenia. Korean J Intern Med 2022;37:294-303.
2. Sun MY, Chang CL, Lu CY, Wu SY, Zhang JQ. Sarcopenia as an independent risk factor for specific cancers: a propensity score-matched Asian population-based cohort study. Nutrients 2022;14:1910.
3. Elsworth BL, Lyon MS, Alexander T, Liu Y, Hemani G. The MRC IEU OpenGWAS data infrastructure. BioRxiv 2020 Aug 10 [Epub]. https://doi.org/10.1101/2020.08.10.244293.

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