Causal Associations between Sarcopenia Traits and Cognitive Impairment: A Mendelian Randomization Study

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Abstract

Observational studies had indicated an association between cognitive impairment and sarcopenia, but high-quality causal effect evidence remained lacking. The purpose of this study is to determine the causal relationship between cognitive impairment and sarcopenia through a bidirectional Mendelian randomization (MR) study. The inverse variance-weighted (IVW) method was employed as the primary analytical approach to assess causal relationships. Additionally, we conducted sensitivity analyses using MR-Egger and weighted median to complement the IVW results. IVW analysis revealed that walking pace showed causal effects on cognitive performance (OR = 2.171, 95% C.I.: 1.696–2.779, P = 7.6×10^{-10}) and fluid intelligence (OR = 6.401, 95% C.I.: 3.573–11.467, P = 4.4×10^{-10}). Similar conclusions were drawn concerning the causal relationship between appendicular lean mass (ALM) with cognitive performance (OR = 1.099, 95% C.I.: 1.074–1.125, P = 1.1×10^{-15}) and fluid intelligence (OR = 1.237, 95% C.I.: 1.173–1.304, P = 3.1×10^{-15}). Furthermore, reverse MR analysis demonstrated that genetically predicted cognitive performance (OR = 1.106, 95% C.I.: 1.080–1.133, P = 2.1×10^{-16}) and fluid intelligence (OR = 1.049, 95% C.I.: 1.034–1.063, P = 1.7×10^{-11}) were causally associated with walking pace, and so as were ALM (OR = 1.163, 95% C.I.: 1.094–1.237, P = 1.4×10^{-6} and OR = 1.066, 95% C.I.: 1.026–1.108, P = 0.0011, respectively). Our Mendelian randomization analysis supported a bidirectional causal effect between sarcopenia traits and cognitive impairment, which suggested the necessity for new therapy and prevention strategies for the corresponding patients. Further investigation is required to explore the individual effects of muscle strength, muscle mass, and physical performance on the cognitive function, as well as to uncover their underlying pathological mechanisms.

Introduction

The inevitable trend of global population aging has brought about a significant burden on health issues worldwide. Among these, age-related cognitive impairment is one of the crucial diseases. It results in mild cognitive impairment, dementia and so on when the cognitive function declining exceeds an expected range, leading to loss of functional abilities and changes in behavioral patterns.

Similar to cognitive impairment, as an age-related condition, sarcopenia also leads to disability and functional loss in the elderly population. Characterized by the loss of skeletal muscle mass and strength, sarcopenia can result in adverse outcomes such as falls, disability, frailty, reduced life quality, or even death. In recent years, more and more researches have been conducted in this field to mitigate the negative impact of sarcopenia among the elderly population.

Many studies have indicated an increased risk of cognitive impairment in the elderly population with sarcopenia. Additionally, some researches also supported a reverse causal relationship between them. However, conclusions drawn from observational studies may be affected by confounding factors. Randomized controlled trials (RCTs) are employed to establish causal relationships between exposures and outcomes, while they come with significant time and financial resource requirements,
which are difficult to conduct. Mendelian randomization (MR), as an optimal alternative to RCTs, could mitigate the influence of confounding variables or reverse causality on causal inference.

The purpose of this study is to determine the bidirectional causal associations between sarcopenia and cognitive impairment by using MR analysis, thereby providing valuable insights for clinical diagnosis, treatment, and prevention.

Methods

Study design

In order to prevent potential impacts of the confounding factors and the reverse causality, a bidirectional Mendelian randomization study design was employed in this research. We utilized the two-sample MR method and different genome-wide association studies (GWASs) summary-level datasets from European ancestry population to explore the causal relationships between sarcopenia related traits and cognitive impairment related characteristics (Fig. 1). This study was conducted in two stages: firstly, we analyzed whether the sarcopenia traits were causally related to cognitive impairment; secondly, we assessed the reverse causal association between genetically determined cognitive impairment and sarcopenia traits.

Data source

We employed three distinct features to represent cognitive status: cognitive performance, fluid intelligence score, and prospective memory result (Fig. 1). Summary statistics related to cognitive performance were obtained from the Social Science Genetic Association Consortium (SSGAC), which encompassed 257,841 samples of European ancestry and measured their cognitive level scores. Summary-level data for fluid intelligence (149,051 samples) and prospective memory (152,605 samples) were sourced from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU).

The presence of sarcopenia is determined by three most commonly used body characteristics: hand grip strength, walking pace, and appendicular lean mass (ALM). The GWAS data for these three traits were derived from the UK Biobank (UKB). In brief, the UK Biobank is a large prospective cohort study that includes genetic and health information of approximately 500,000 individuals aged between 40 and 69 years from the United Kingdom who participated in this research. Table S1 summarizes the data sources for this study. All the data presented in Table S1 have received approval from the relevant review boards, and the involved participants have provided informed consent.

Instrumental variables selection

Instrumental variables (IVs) selection should adhere to the following three well-established assumptions:

1. The instrumental variables must be strongly associated with the exposure of interest;
2. The instrumental variables should be unrelated to confounding factors;
3. The instrumental variables affect the outcome solely through its association with the exposure, without any direct effect on the outcome.
We selected single nucleotide polymorphisms (SNPs) significantly associated with the exposure factor at the genome-wide significance as instrumental variables ($P < 5 \times 10^{-8}$). For some exposures, where a limited number of SNPs were identified as significant at the genome-wide level ($n < 3$), we also adopted a more relaxed threshold to screen for instrumental variables ($P < 5 \times 10^{-6}$). Evaluation of linkage disequilibrium (LD) between SNPs was performed using a reference population of 1000 Genomes European panel. Independent SNPs, defined as those with an $R^2$ value less than 0.001 and a clumping window size greater than 10,000 kb, were used as instrumental variables. In addition, to ensure that the potential instrumental variables have sufficient power to detect the causal effects of exposures on the outcomes, we calculated the F-statistic of the potential instrumental variables using the formula $F = R^2(n-k-1)/k(1-R^2)^2$. Here, $n$ represented the sample size, $k$ represented the number of instrumental variables, and $R^2$ was computed using the formula $R^2 = 2 \times EAF_i \times (1 – EAF_i) \times \beta_i^2$, where $EAF_i$ denoted the allele frequency and $\beta$ represented the estimated effect of the gene on the exposure. If the F-statistic of the instrumental variables was greater than 10, the likelihood of weak instrument bias was minimal.

**Statistical analysis**

Mendelian Randomization (MR) analysis used genetic variables as instrumental variables to estimate the causal effects of exposure factors on outcomes. In this study, the Inverse Variance Weighted (IVW) method was the primary analytical approach used to assess the causal relationships between cognitive impairment and sarcopenia traits. IVW-MR used a meta-analysis approach combined with the Wald estimates for each SNP to obtain an overall estimate of the effect for exposures on outcomes. Heterogeneity among the selected instrumental variables is assessed using Cochran's Q test. In the presence of significant heterogeneity ($P < 0.05$), a random-effects IVW model was applied; otherwise, a fixed-effects IVW model was used. Sensitivity analyses, including MR-Egger and weighted median methods, were conducted to complement and validate the results from IVW-MR analysis. The MR-Egger regression is based on the assumption of instrument strength independent of direct effect (InSIDE), enabling the assessment of pleiotropy through the intercept term. If the intercept term equals zero, it suggests the absence of horizontal pleiotropy and the results of MR-Egger regression are consistent with IVW. The weighted median method allows up to 50% of selected genetic instruments to be invalid. The MR-Egger intercept test was used to monitor whether the MR analysis was influenced by horizontal pleiotropy. Furthermore, we performed Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) analysis to identify and remove pleiotropic SNPs, followed by a subsequent MR analysis to assess the robustness of the results. A significance level of $P < 0.05$ was considered statistically significant. In case of multiple comparisons, Bonferroni-corrected $P < 0.0056 (0.05/9)$ were considered statistically significant associations, and $P$ values between 0.0056 and 0.05 were considered suggestive association. All analyses were conducted using the TwoSample-MR and MR-PRESSO packages in the R software (version 4.2.1).

**Ethics statement**
Ethical approval and informed consent were obtained from the original GWAS. The MR analysis in this study received approval from the Ethics Review Committee of Zhengzhou University Affiliated Zhengzhou Central Hospital, Henan, China.

**Result**

Table S2 summarizes all the SNPs selected in this MR study. Due to the limited number of SNPs extracted when considering prospective memory as an exposure factor, we employed a more relaxed P-value threshold ($P < 5 \times 10^{-6}$) to extract IVs. Other instrumental variable selection criteria were based on a genome-wide significance level ($P < 5 \times 10^{-8}$). Except for the SNPs obtained when setting prospective memory as the exposure factor, the F-statistics for all SNPs in this study were greater than 10, indicating the absence of substantial statistical bias due to weak instrumental variables.

For each MR analysis, Cochrane’s Q test was conducted to assess heterogeneity, and significant heterogeneity was observed in each group of MR analysis (Table S3). Therefore, we employed a random-effects IVW model for the MR analysis. In the assessment of horizontal pleiotropy, there was evidence of horizontal pleiotropy in the instrument variables obtained for the effect estimation of low hand grip strength on cognitive performance ($\text{intercept} = 0.0163$, $P = 0.0323$), while no other instances of horizontal pleiotropy were identified (Table S3).

We first investigated the causal effects of sarcopenia traits on cognitive impairment (Fig. 2). In the IVW analysis ($OR = 0.914$, 95% CI: 0.838–0.998, $P = 0.0448$), MR-Egger analysis ($OR = 0.697$, 95% CI: 0.551–0.881, $P = 0.0099$), and Weighted median analysis ($OR = 0.942$, 95% CI: 0.892–0.995, $P = 0.0308$), low hand grip strength demonstrated a suggestive causal effect on cognitive performance (Fig. 2 and Table S4). As for effects of walking pace and ALM on cognitive performance, both IVW analysis ($OR = 2.171$, 95% CI: 1.696–2.779, $P = 7.6 \times 10^{-10}$ and $OR = 1.099$, 95% CI: 1.074–1.125, $P = 1.1 \times 10^{-15}$) and Weighted median analysis ($OR = 1.561$, 95% CI: 1.283–1.901, $P = 8.8 \times 10^{-6}$ and $OR = 1.067$, 95% CI: 1.043–1.091, $P = 2.4 \times 10^{-8}$) showed statistically significant associations, while the MR-Egger results ($OR = 3.131$, 95% CI: 1.148–8.538, $P = 0.0299$ and $OR = 1.074$, 95% CI: 1.017–1.134, $P = 0.0105$) indicated suggestive associations (Fig. 2 and Table S4). After excluding outlier SNPs using the MR-PRESSO method (Table S5), we conducted a MR analysis again. The causal effect of low hand grip strength on cognitive performance which was initially suggestive associated, became significantly associated after outlier SNPs removal. There were no substantial changes in the remaining results (Table S6), indicating the robustness of our MR findings. When the outcome variables were set as fluid intelligence and prospective memory, low grip strength did not demonstrate a statistically significant association ($P > 0.05$). Apart from the MR-Egger analysis ($OR = 16.803$, 95% CI: 1.544–182.881, $P = 0.0243$), which indicated suggestive association, walking pace exhibited a significant causal effect on fluid intelligence ($P < 0.0056$). Meanwhile, ALM consistently showed a significant causal effect on fluid intelligence in all three analytical methods ($P < 0.0056$). The analyses of sarcopenia traits on prospective memory did not reveal
conclusive causal effects, except the IVW analysis for ALM on prospective memory (OR = 0.9873, 95% CI: 0.9786–0.9961, P = 0.0048).

Subsequently, we investigated potential reverse causal relationships (Fig. 3). The IVW analysis did not detect significant causal effects for cognitive performance (OR = 0.878, 95% CI: 0.794–0.971, P = 0.0112), fluid intelligence (OR = 0.971, 95% CI: 0.919–1.027, P = 0.3076), and prospective memory (OR = 1.223, 95% CI: 0.918–1.630, P = 0.1681) on low hand grip strength (Fig. 3). The same results were observed in the sensitivity analysis (Table S7). In the IVW analysis, cognitive performance (OR = 1.106, 95% CI: 1.080–1.133, P = 2.1E-16) and fluid intelligence (OR = 1.049, 95% CI: 1.034–1.063, P = 1.7×10^{-11}) exhibited significant positive causal effects on walking pace, and these findings were supported by sensitivity analysis (Table S5). Cognitive performance (OR = 1.163, 95% CI: 1.094–1.237, P = 1.4×10^{-6}) and fluid intelligence (OR = 1.066, 95% CI: 1.026–1.108, P = 0.0011) showed similar results on ALM (Fig. 3 and Table S7). However, the MR analysis of prospective memory did not support its causal association with the three sarcopenia traits (Fig. 3 and Table S7). The exclusion of outlier SNPs did not substantially alter the results shown above (Table S8).

**Discussion**

The bidirectional MR analysis in this study was performed using summary-level data from GWASs. We investigated the potential causal relationships between sarcopenia traits (grip strength, walking pace and ALM) and cognitive impairment (cognitive performance, fluid intelligence score, and prospective memory result). Our findings (as Fig. 1 showed) indicated bidirectional causal relationships between genetically predicted walking pace and ALM with cognitive performance and fluid intelligence, whereas low hand grip strength showed suggestive bidirectional associations with cognitive performance. Furthermore, this study supported a suggestive positive causal effect of walking pace and ALM on prospective memory. To the best of our knowledge, this is the first study to explore bidirectional causal relationships between cognitive impairment and three sarcopenia traits using GWAS summary statistics and MR analysis.

Aging is a challenging issue that modern society have to confront, and plays an important role in both sarcopenia and cognitive impairment. Previous evidences demonstrated the association between these two conditions, populations with sarcopenia have a higher risk of cognitive impairment. In addition, this correlation is independent of factors such as gender, region, and race. In our study, the MR analysis supported a causal effect of sarcopenia-related traits on cognitive impairment, aligning generally with previous research findings. Our results complemented previous observational studies, with a strength that the MR study design helped to mitigate the impact of confounding factors on the results.

Observational studies have suggested an increased risk of cognitive impairment associated with decreased handgrip strength. However, our MR analysis did not support a definite causal effect of low hand grip strength on cognitive impairment (P > 0.0056). Only after removing outlier SNPs using the MR-PRESSO method, a causal association between low handgrip strength and cognitive performance achieved statistical significance (P < 0.0056). Handgrip strength serves as a primary indicator of muscle
strength. The updated definition by European Working Group on Sarcopenia in Older People (EWGSOP) considers muscle strength as a fundamental characteristic of sarcopenia, and the loss of functional performance indicates the severity of sarcopenia. We proposed that the reduction in muscle strength might merely represent a mild manifestation of sarcopenia, which explained the lack of robust causal relationship with cognitive impairment in our MR analysis. Of note, although studies supported the independent effects of the muscle strength, muscle mass, and physical performance, sarcopenia was a comprehensive diagnosis that includes the three components. It was hard to draw a causal inference regarding the association between sarcopenia and cognitive impairment by analyzing any single trait mentioned above. Combining our analysis results with previous viewpoints, we leaned towards the notion that the reduction in muscle mass and physical performance might contribute more to the increased risk of cognitive impairment, while the causal effect of low muscle strength on cognitive impairment remains uncertain.

In the individual phenotype analyses, the causal effects of walking pace and ALM on prospective memory were not completely determined (suggestive association), although a statistically significant causal effect of ALM on prospective memory determined by IVW analysis (P = 0.0048) was observed, as evidenced by both unadjusted and MR-PRESSO corrected results. It was noteworthy that the prospective memory test specifically involved image-based information, which differed from cognitive performance and fluid intelligence. This distinction may offer a plausible explanation for the divergent results obtained in MR analyses for different phenotypes.

Peng et al. and Oudbier et al. discussed the potential bidirectional causal relationship between sarcopenia and cognitive impairment in their publications. To the best of our knowledge, there are limited observational studies on the reverse causal effect of cognitive function on the sarcopenia risk. The findings of this MR study suggested reverse causal effects of cognitive performance and fluid intelligence on walking pace and ALM, while the reverse MR analysis for prospective memory did not show conclusive results due to insufficient statistical power. Additionally, consistent with the forward MR analysis, reverse MR analysis for cognitive impairment did not reveal significant causal effects on low hand grip strength even after outlier SNPs were removed. Nevertheless, overall, this study still supported the reverse causal effect of genetically predicted cognitive impairment on sarcopenia.

In epidemiology, sarcopenia and cognitive impairment share many risk factors, such as cerebrovascular diseases, depression, hypertension, diabetes, and so on. In terms of pathological mechanisms, inflammatory cytokines may play a crucial role in the development of both conditions. Additionally, insulin resistance, disturbances in protein synthesis and degradation metabolism, and mitochondrial dysfunction may also be involved in the pathological process of muscle loss and cognitive impairment. Further researches are necessary to elucidate the pathological mechanisms between sarcopenia and cognitive dysfunction.
This study held certain clinical significance. Consistent with the findings of observational studies, our results supported the necessity of being vigilant about the potential occurrence of cognitive impairment and taking preventive measures in elderly patients clinically diagnosed with sarcopenia. Previous studies have indicated that engaging in muscle-strengthening exercises among the elderly may contribute to improving cognitive function. Similarly, for patients experiencing cognitive impairment, monitoring changes in their muscle mass might be essential to promptly implement interventions and avoid a vicious cycle. There is currently still a lack of drugs or psychological therapies for the treatment of dementia. However, physical interventions during the mild cognitive impairment stage could potentially alter the progression of developing dementia.

Some limitations of the study still needed to be treated with caution. Firstly, all the GWASs data used in this research were derived from European populations, making it difficult to extrapolate the findings to other ethnicities. Secondly, due to the utilization of GWAS summary data, stratified analyses based on factors such as age and gender were not feasible. Additionally, the traits related to sarcopenia used in our MR analysis did not precisely align with the diagnostic criteria for sarcopenia recommended by guidelines, which introduced certain degree of bias as the definition of sarcopenia could significantly impact the results. Despite employing pleiotropy tests and the MR-PRESSO procedure to mitigate directional pleiotropy, residual bias remains difficult to avoid.

In conclusion, this study provided new evidence for causal relationships between sarcopenia and cognitive impairment through MR analysis. The research findings supported the idea that physical performance and muscle mass are the primary influencing factors rather than muscle strength. Additionally, cognitive performance may potentially have a reverse causal effect on sarcopenia. Nevertheless, further confirmation of these conclusions is required through prospective RCTs. Additional researches are needed to explore the underlying mechanisms involved in this relationship.

**Abbreviations**

ALM, appendicular lean mass; C.I., confidence interval; EAF, effect allele frequency; EWGSOP, European Working Group on Sarcopenia in Older People; GWAS, Genome-wide Association Study; InSIDE, instrument strength independent of direct effect; IV, instrumental variable; IVW, inverse variance weighted; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; MRC-IEU, Medical Research Council Integrative Epidemiology Unit; OR, odds ratio; RCT, randomized controlled trial; SNP, single nucleotide polymorphism; SSGAC, the Social Science Genetic Association Consortium; UKB, United Kingdom Biobank.

**Declarations**

**Data availability**
The data used in this study were all publicly available. GWAS summary statistics for cognitive performance were obtained from the SSGAC. GWAS summary statistics for fluid intelligence and prospective memory were sourced from the MRC-IEU. GWAS summary statistics for sarcopenia traits were derived from the UKB.

**Author contributions**

XLS and HFZ conceived the study design. HFZ and HW were involved in data analysis. HFZ and YXX were involved in the figure preparation. XLS and HFZ were major contributors in writing the manuscript. All authors read and approved the final manuscript.

**Acknowledgement**

Not applicable.

**Competing interests**

The authors declared no competing interests.

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Not applicable.

**References**


Figures
Figure 1

The summary of this bidirectional MR study. The solid lines represent significant associations, the dashed lines represent suggestive associations, and the arrows indicate the directions of causality. IV, instrumental variable; SNP, single nucleotide polymorphism; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVW, inverse variance weighted.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure</th>
<th>SNPs</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive performance</td>
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</table>

Figure 2

Causal effects of sarcopenia traits on cognitive impairment derived from inverse variance weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; C.I., confidence interval.
<table>
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<tr>
<th>Outcome</th>
<th>Exposure</th>
<th>SNPs</th>
<th>OR (95%CI)</th>
<th>P</th>
</tr>
</thead>
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<td>Low hand grip strength</td>
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<td>0.878 (0.794 - 0.971)</td>
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</tbody>
</table>

**Figure 3**

Causal effects of genetically predicted cognitive impairment on sarcopenia traits derived from inverse variance weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; C.I., confidence interval

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.xlsx