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Deciphering the Genetic Link: The Influence of Sarcopenia on Cognitive Performance through Mendelian Randomization

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Abstract: *This study aimed to use Mendelian randomization (MR) to investigate the potential causal relationship between sarcopenia and cognitive performance.31 independent single nucleotide polymorphisms (SNPs) were identified as instrumental variables of sarcopenia. Inverse variance weighted MR analysis revealed a significant negative association between genetically predicted sarcopenia and cognitive performance (β=-0.040, 95% CI: -0.070 to -0.010, p<0.01). However, MR-Egger regression did not support a causal effect. Mendelian randomization analysis results showed a weak causal relationship between sarcopenia and cognitive performance.*

Keywords: *Mendelian randomization, sarcopenia, cognitive performance*

1. Introduction

Aging is accompanied by numerous physical and cognitive changes, among which sarcopenia and cognitive impairment stand out because of their significant impact on the quality of life of the elderly [1]. Sarcopenia, the progressive and generalized loss of skeletal muscle mass and strength, has been widely recognized as a predictor of adverse outcomes such as falls, disability, and mortality [2]. Similarly, cognitive impairment, ranging from mild cognitive deficits to severe dementia, poses substantial challenges for individuals, families, and healthcare systems [3]. Recent research suggests a compelling interconnection between sarcopenia and cognitive performance, suggesting a complex relationship that warrants comprehensive investigation.

An increasing body of literature has underscored the relationship between sarcopenia and cognitive impairment. Kwon et al. highlighted that sarcopenia-related indices such as grip strength, gait speed, and Appendicular Skeletal Muscle (ASM) are significantly associated with cognitive impairment in both men and women [4]. This connection underscores the bidirectional nature of the impact, where not only does sarcopenia contribute to cognitive decline, but cognitive impairment can also exacerbate the progression of sarcopenia.[5]

Conversely, an analysis conducted by Fhon et al. revealed that elderly individuals with cognitive impairment who suffer falls are at a heightened risk of developing sarcopenia [6]. This finding indicates that the physical manifestations of cognitive decline, such as decreased coordination and attention, may precipitate conditions that exacerbate sarcopenia.

Despite a growing consensus on the sarcopenia-cognition link, discrepancies exist within the research community. A notable study by Inhwan et al. found no association between sarcopenia and cognitive impairment among women aged > 75 years, even after adjusting for potential underlying causes [7]. This inconsistency may point to sex differences, age-related factors, or even methodological variances in diagnosing sarcopenia and assessing cognitive function.

However, the general trend suggested a significant correlation between the two conditions. Tessier's research supports this, establishing sarcopenia as independently associated with cognitive impairment and advocating for future cohort studies to elucidate the causal relationship more clearly [8].

The relationship between sarcopenia and cognitive performance is a complex and multifaceted area of study underscored by a growing body of literature that reveals a significant association between these two conditions [9]. While the evidence strongly suggests a link, conflicting findings indicate the need for further research to fully understand the nuances of this relationship. As the global population continues

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to age, unraveling the intricacies of this relationship will be vital for improving health outcomes and quality of life of the elderly.

Mendelian randomization (MR) is a statistical technique that uses genetic variants as instrumental variables (IVs) to determine whether an observational association between a risk factor and outcome is consistent with a causal effect [10]. In a 2-sample MR analysis, the causal effect was estimated by comparing exposure and outcome in different samples [11]. This method is particularly useful when it is challenging to measure exposure and outcome in the same set of individuals [11]. To our knowledge, MR has not been used previously to explore causal effects in the context of Sarcopenia and Cognitive Performance risk. This study aimed to investigate the potential causal association between gout and Cognitive Performance using a 2-sample MR analysis.

2. Methods

The objective of this Mendelian randomization (MR) analysis was to explore the causal relationship between sarcopenia and cognitive performance. We employed a two-sample MR approach, which leverages genetic variants as instrumental variables (IVs), to infer causality between sarcopenia and cognitive performance.

2.1 Selection of Genetic Instruments

Genetic instruments for sarcopenia were meticulously chosen based on publicly available summary statistics datasets from genome-wide association studies (GWAS). Specifically, datasets originated from three GWAS encompassing diverse populations: European cohorts comprising two separate samples (GCST90007526: n = 48,596 European ancestry cases and 207,927 European ancestry controls, and GCST90000025:450,243 European ancestry individuals) [12,13]. From these GWASs, 31 independent single nucleotide polymorphisms (SNPs) strongly associated with sarcopenia served as instrumental variables. Summary statistics were sourced from a comprehensive meta-analysis of GWAS datasets focused on cognitive performance, encompassing 269,867 individuals of European ancestry [14]. These datasets were thoroughly genotyped and imputed, covering 9,295,118 SNPs [14].

2.2 Statistical Analysis

Using a two-sample MR framework, the genetic effects of sarcopenia on the risk of cognitive performance were estimated [15]. This involved the utilization of summary-level data, specifically beta coefficients and standard errors, corresponding to the 31 sarcopenia-associated SNPs from the sarcopenia GWASs as exposure and the same SNPs from the cognitive performance GWASs as outcome [15]. In the primary analysis, owing to the large number of independent SNPs reaching a genome-wide significance threshold ($p < 5\times e^{-8}$), a more stringent significance threshold ($p < 1\times e^{-40}$) was first adopted to select the initial genetic instruments for sarcopenia. If a significant association was found, sensitivity analysis using genome-wide significant instruments was performed. For palindromic instruments or instruments that are absent from the mediator and/or outcome datasets, proxies in high linkage disequilibrium (LD) ($r2 \geq 0.8$) with the initial instruments and significantly associated with the exposure were identified. The inverse-variance weighted (IVW) method, alongside robust sensitivity analyses including MR-Egger regression, was employed to account for potential pleiotropy and ensure the validity of IV assumptions [16]. Using this methodology, our MR analysis aimed to provide insights into the potential causal association between sarcopenia and cognitive performance, adhering to the principles of Mendelian randomization and instrumental variable estimation.

In accordance with the principles of Mendelian randomization (MR), the present study utilized a three-step approach to estimate the uncompounded causal association between sarcopenia and cognitive performance. First, we assessed the independent association of 31 single nucleotide polymorphisms (SNPs) with sarcopenia. Subsequently, we examined the association between each SNP and cognitive performance. Finally, these findings were consolidated to estimate the causal relationship between sarcopenia and cognitive performance using MR analysis, specifically employing the 2-sample MR method.

2.3 Heterogeneity and Sensitivity Analysis

To evaluate the presence of heterogeneity among the single nucleotide polymorphisms (SNPs) used

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as instrumental variables, Cochran's Q statistic was employed as a measure of disparity [17]. Additionally, a "leave-one-out" analysis was conducted to explore the potential impact of individual SNPs on the observed causal association.

Furthermore, a subgroup analysis was performed using only instrumental variable (IV) SNPs that exhibited genome-wide significance. This subgroup analysis aimed to enhance the robustness and reliability of the Mendelian randomization (MR) analysis results.

3. Results

3.1 Screening of SNPs

Our SNP selection analysis revealed a subset of instrumental variables associated with muscular dystrophy based on their significant p-values. Among the identified SNPs, 31 variants were strongly associated with muscular dystrophy phenotypes (Fig 1). However, the p-values revealed that these SNPs were not correlated with cognitive performance in our study cohort. This unexpected finding suggests the specificity of the identified genetic markers for muscular dystrophy traits independent of their effects on cognitive functioning.

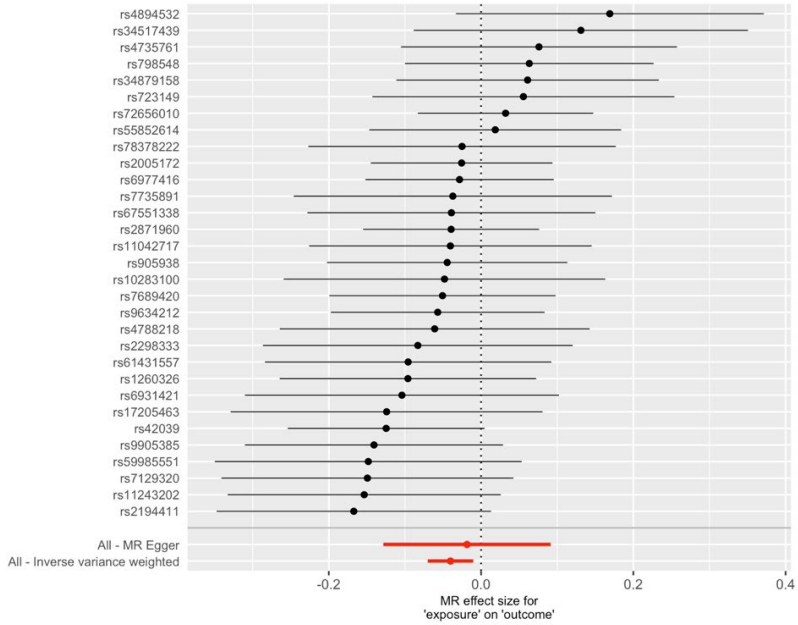

Figure 1: Forrest plot of the causal effects of sarcopenia-associated single nucleotide polymorphisms on cognitive performance. MR, Mendelian randomization.

3.2 Mendelian randomization results

A total of 31 effective instrumental variables were included in this study, covering three dimensions closely related to sarcopenia: muscle mass, muscle strength, and muscle function. Through association analysis between these instrumental variables and cognitive performance indicators (such as memory, executive function, and attention), we employed several Mendelian randomization techniques, including Inverse Variance Weighting (IVW) and MR-Egger regression estimates.

Table 1: The MR estimates from each method of the causal effect of sarcopenia on cognitive performance.

Method	Number of SNPs	β	Standard error	Association P value	Cochran Q statistic	Heterogeneity P value
Inverse variance weighted	31	-0.040	0.015	0.008	24.747	0.737
MR-Egger	31	-0.018	0.056	0.744	24.585	0.699

The results obtained using the Inverse Variance Weighting method indicated that genetic variations associated with sarcopenia significantly affected cognitive performance (beta = -0.040, 95% CI: -0.070

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to -0.010, P=0.008), suggesting a significant negative correlation between sarcopenia and a decline in cognitive performance. MR-Egger regression analysis showed no significant directional pleiotropy (intercept =-0.0008, P for intercept = 0.690), and the weighted median estimate did not support this finding (Beta = -0.18, 95% CI: -0.128 to -0.091, P=0.744) (Table 1, Fig 2).

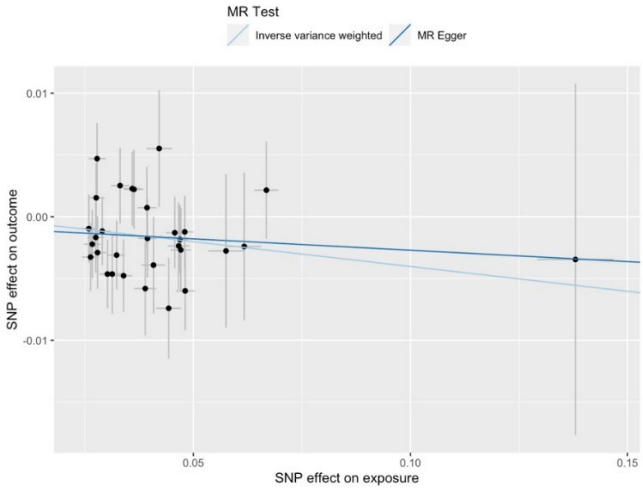

Figure 2: Scatter plots of genetic associations with sarcopenia against the genetic associations with cognitive performance. SNP, single nucleotide polymorphism.

3.3 Heterogeneity and sensitivity test

To evaluate the heterogeneity of our results, we conducted the Cochran's Q test. The Q-test revealed a statistically insignificant level of heterogeneity, as shown in table 1, indicating no heterogeneity. This indicates that the use of different genetic variants in different populations may have little effect on the results.

To evaluate the impact of individual genetic variants on our results, we performed leave-one-out sensitivity analysis (Fig 3). The results showed that None of the genetic variants had a definitive effect on the overall result, but the maximum effect of a single variant ranged from -0.065 to -0.005, indicating that our primary finding was robust.

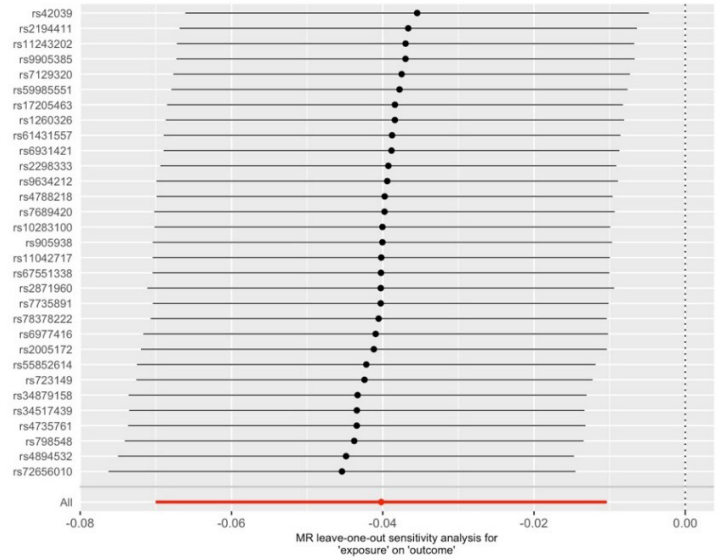

Figure 3: "Leave-one-out" analysis to investigate whether the causal association was driven by a unique single nucleotide polymorphism. MR, Mendelian randomization.

In conclusion, our results suggest that there are some limitations to the interpretability of our findings, due to heterogeneity and multiple effects. However, the leave-one-out sensitivity analysis provided reassurance that our primary finding was robust, and further investigation is warranted to explore the

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sources of heterogeneity and multiple effects.

4. Discussions

Aging is characterized by a gradual decline in both physical and cognitive functions [18]. Among these, sarcopenia, age-related loss of muscle mass and function, and cognitive impairment are critical aspects that affect the quality of life in the elderly [19]. This research aimed to elucidate the relationship between sarcopenia and cognitive performance, drawing upon recent studies that explore these complex interactions.

The global increase in the elderly population has increased the prevalence of age-related conditions such as sarcopenia and cognitive impairment. While traditionally studied in isolation, emerging research suggests that these conditions may be interrelated, potentially influencing each other's progression. Recent studies have suggested a bidirectional relationship between sarcopenia and cognitive performance, where the decline in muscle mass and function may contribute to cognitive impairment, while cognitive decline could exacerbate the progression of sarcopenia [20]. This intricate interplay underscores the need for further investigations to elucidate the underlying mechanisms and causal relationships between these two age-related conditions.

The weak correlation between sarcopenia and cognitive performance observed in this study can be attributed to several interrelated factors, as elucidated by recent academic research. First, systemic inflammation, known to intertwine with both sarcopenia and cognitive impairment, may obscure direct relationships by simultaneously affecting muscle and brain function [23]. Second, the heterogeneity in the study designs and the measures used to assess both sarcopenia and cognitive function might have contributed to the inconsistent findings in research [24]. Lastly, overlapping yet distinct pathophysiological pathways, such as abnormalities in insulin and protein metabolism and mitochondrial dysfunction, signify that while muscle health and cognitive function may deteriorate concurrently, they do not always do so in lockstep [23].

Mendelian randomization (MR) offers a powerful approach for exploring the causal relationships between exposures and outcomes by leveraging genetic variants as instrumental variables [17]. When applied to the study of sarcopenia and cognitive performance, MR can provide valuable insights into whether there is a causal relationship between muscle health and cognitive function [21]. One of the key advantages of MR is its ability to mitigate confounding and reverse causation biases, which commonly plague observational studies. Using genetic variants as proxies for the exposure of interest (such as sarcopenia-related factors) and assessing their impact on the outcome (cognitive performance), MR can help establish a more robust and unbiased estimate of causality [18].

However, the application of MR in studying the relationship between sarcopenia and cognitive performance is limited. One significant challenge is the availability of suitable genetic instruments that are robustly associated with sarcopenia but not with potential confounders of the relationship, such as lifestyle factors or comorbidities. Moreover, the assumptions of MR, including the absence of horizontal pleiotropy (where genetic variants influence the outcome through pathways other than the exposure of interest), need to be carefully evaluated to ensure the validity of causal inference [22].

In conclusion, the investigation of the relationship between sarcopenia and cognitive performance using Mendelian randomization holds great promise for advancing our understanding of these interconnected age-related conditions. By addressing methodological challenges, leveraging genetic instruments effectively, and exploring new avenues of research, future studies may uncover novel insights into the causal pathways linking muscle health and cognitive decline, ultimately informing targeted interventions and strategies for preserving physical and cognitive well-being in aging populations. Research should aim to unravel the nuances of this relationship and explore effective combined strategies for prevention and management. In this study, preliminary evidence from inverse variance weighted MR suggests that sarcopenia may causally influence cognitive performance, and limitations were identified. Further large-scale studies are needed to validate the genetic instruments and establish the nature of any causal relationship between these important aging phenotypes.

5. Conclusion

The Mendelian randomization analysis results show a weak causal relationship between sarcopenia and cognitive performance

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