Article

Causality between Sarcopenia and Depression: A Bidirectional Mendelian Randomization Study

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Abstract

Background: Numerous observational studies have suggested a correlation between sarcopenia and depression, but the nature of this relationship requires further investigation.

Methods: This study employed bidirectional Mendelian randomization to explore this connection. Data from genome-wide association studies were used, encompassing measures of sarcopenia and mental factors, including depression and emotional states. The initial analysis concentrated on the impact of depression on sarcopenia, and then it examined the reverse relationship. The same methodology was applied to emotional data for validation.

Results: The results indicated a reciprocal causation between sarcopenia and depression, even when emotional state data were considered. Various emotions can impact sarcopenia, and in turn, sarcopenia can affect emotions, except subjective well-being. These findings highlight a cyclic deterioration between sarcopenia and depression, with a link to negative emotions and a partially ameliorative effect of subjective well-being on sarcopenia.

Conclusions: In summary, this study sheds light on the interplay between psychiatric factors and sarcopenia, offering insights into intervention and prevention strategies.

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Keywords

mendelian randomization analysis; genome-wide association study; sarcopenia; depression; mental health; negative emotion; causation

Introduction

Sarcopenia, a progressive musculoskeletal disorder that impacts all body systems, has been gaining increasing attention in the field [1]. The correlation between low muscle strength and adverse health outcomes, including falls, frailty, functional decline, fractures [2], cognitive decline [3], and cardiovascular disease [4], further underscores its significance. The impact of sarcopenia on public health is immeasurable. A meta-analysis revealed that the global prevalence of sarcopenia ranges from 10% to 27%, and the 18 to 60-year-old age group exhibits a higher prevalence rate, reaching 8% to 36% [5], challenging the common belief that it is exclusively an affliction of individuals aged 65 years and older.

Given the substantial potential harm of sarcopenia, implementing preventive measures has become an urgent priority. Although extensive research has been conducted on the pathogenic factors, mental health has not received as much attention as physical health. Depression, a pervasive and debilitating condition with widespread personal and societal health implications [6], has been linked to various diseases. Meta-analyses have indicated an association between sarcopenia and depression in older patients [7], and mediation analysis has demonstrated that depressive symptoms exert direct and indirect effects on muscle mass [8]. Contrary to the prevailing notion that the decline in muscle mass is solely due to reduced mobility caused by depression, traditional Chinese medicine posits that mental factors

directly impact the body [7]. Drawing from this hypothesis and the mediation analysis results, we contend that further research is necessary to delve deeper into the relationship between mental factors and sarcopenia.

In this study, we aim to explore this hypothesis using Mendelian randomization (MR) design, which employs single nucleotide polymorphisms (SNPs) associated with exposures (such as depression) as instrumental variables (IVs) to infer potential causal relationships between an exposure and an outcome (such as sarcopenia) [9]. The principle of random segregation and the combination of alleles theoretically ensures that the causal effect remains unaffected by confounding factors and reverse causality [10]. Our study aims to investigate the bidirectional causal relationship between depression and sarcopenia while incorporating variables such as mood changes to broaden the scope of our investigation and uncover the patterns of their interaction.

Materials and Methods

The data for this study were sourced from the open-access database Medical Research Council (MRC) Integrative Epidemiology Unit (IEU) OpenGWAS, a comprehensive collection of complete genome-wide association study (GWAS) summary datasets. This resource, developed at the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, serves as a repository for datasets that have already obtained ethical approvals during their initial research collection. Furthermore, datasets included in MRC IEU OpenGWAS are made available for download and use under their pre-existing permissions, as granted by the original studies. Additionally, we confirm that written informed consent was obtained from all subjects participating in this research or from their legal guardian(s) before their inclusion in the study in accordance with the Declaration of Helsinki.

Study Design Description

The present study used publicly available genome-wide association study (GWAS) summary statistics to implement a two-sample MR analysis. The original studies obtained ethical approval. A comprehensive summary of the data sources employed in this investigation can be found in **Supplementary Table 1**. Genetic instruments consisting of leading SNPs associated with sarcopenia and depression were extracted and used to conduct bidirectional two-sample MR (Fig. 1). It is an original one and produced by Microsoft Office PowerPoint 2010 (Washington, USA). To mitigate potential racial disparities, the current analyses were confined to individuals of European descent.

Selection of Instrumental Variables for MR Analyses

A series of quality control measures were performed to ensure the eligibility of the genetic instruments. Initially, SNPs strongly associated with the exposure factors (with $p < 5 \times 10^{-8}$) were included. Subsequently, clumping was conducted with an $R^2 < 0.001$ and a window size of 10,000 kb. A minor allele frequency (MAF) threshold of >0.01 was also applied to the outcome. Furthermore, each instrument was scrutinized in the PhenoScanner V2 GWAS database [11] to exclude SNPs associated with potential confounders (e.g., body mass index [12], diabetes [13,14], insomnia [15], systemic lupus erythematosus [16], and smoking [17]; **Supplementary Table 2**). Finally, efforts were made to harmonize the exposure and the outcome by eliminating palindromic SNPs and ensuring that the effect alleles corresponded to the same allele [18]. Furthermore, given that the use of fewer than 10 independent SNPs as instruments may result in decreased statistical efficiency in MR analysis [19], a relaxed threshold ($p < 1 \times 10^{-5}$) was employed to guarantee an adequate number of SNPs in cases where traits exhibited an insufficient SNP count (≤10) [20].

To assess the strength of the instrumental variables, the F-statistics of all genetic instruments were calculated using the genetic variant (R^2), sample size (N), and formula $F = R^2 \times (N - 2)/(1 - R^2)$. Genetic variants yielding F-statistics below 10 were deemed weak, as they may introduce bias into the results [21]. All the results of the IV selection are shown in **Supplementary Tables 3–18**.

Data Sources for Sarcopenia-Related Traits

According to the sarcopenia stepwise approach to diagnosis proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) [1], this study used grip strength (discovery), lean mass (diagnosed), and usual walking pace (severe) as the phenotypes of sarcopenia. Considering the distinct daily functions of the dominant hand and the non-dominant hand, this study included data on the grip strength of both hands and the "low grip strength that met the EWGSOP standard" so that they could corroborate each other. Two-handed grip strength data were obtained from the UK Biobank [22], and 461,089 (hand grip strength (right) HGS (R)) and 461,026 (hand grip strength (left) HGS (L)) participants were measured with a Jamar J00105 hydraulic hand dynamometer. The low grip strength data (HGS (LOW)) consisted of 48,596 cases (grip strength <30 kg male; <20 kg female) and 207,927 controls [23]. Given that appendicular lean mass (ALM) has a higher predictive ability for sarcopenia, this study used

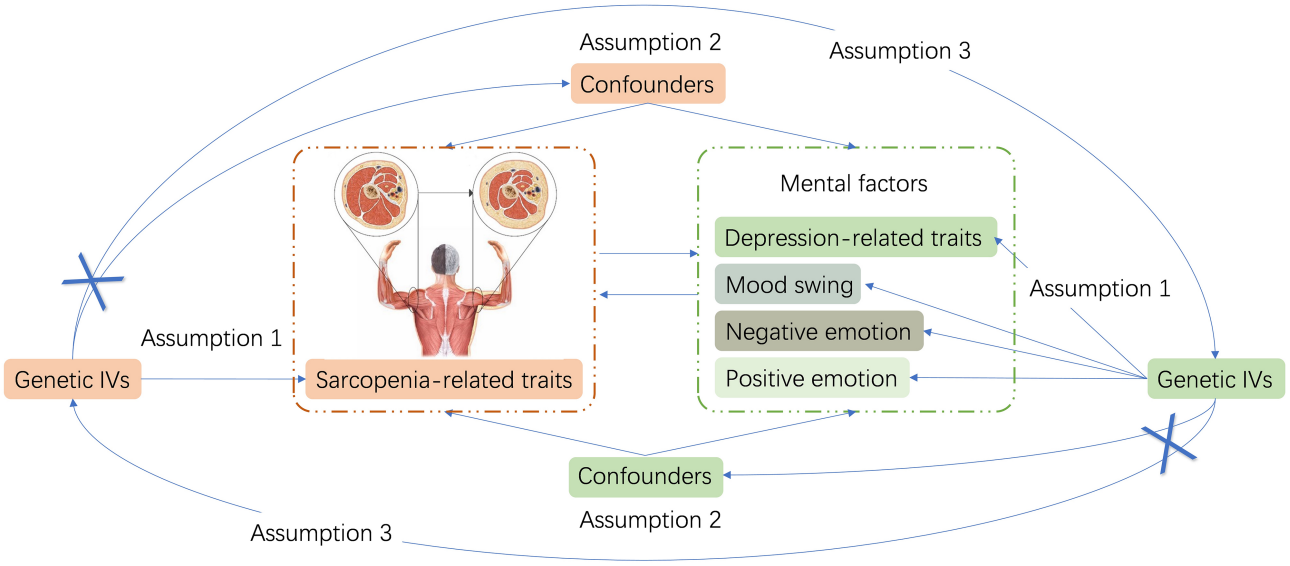

Fig. 1. An overview of study design and assumptions of the MR design: The right-to-left flow represented the forward MR analyses, with mental factors as the exposure and sarcopenia-related traits as the outcome. The left-to-right flow represented the reverse MR analyses, with sarcopenia-related traits as the exposure and mental factors as the outcome. Assumption 1: The instrumental variables are strongly associated with the factors they represent. Assumption 2: The instrumental variables are independent of any confounding factors. Assumption 3: The instrumental variables solely impact sarcopenia-related traits (in forward MR analysis) and mental factors (in reverse MR analysis) through the factors they represent, without any involvement of alternative pathways. IVs, instrumental variants; MR, Mendelian randomization.

1059 loci identified by ALM at the genome-wide significance level as specific indicators of lean mass [24]. Finally, the usual walking pace (UWP), which is a measure of muscle function performance, was also included in this study. The UK Biobank included data of 459,915 participants.

Data Sources for Mental Factors

Depression was examined as the principal mental factor in this study. We briefly summarized the developmental trajectory of depression across six dimensions, encompassing "Depressed affect" [25], "Frequency of depressed mood in last 2 weeks", "Depression (broad)" [26], "Feelings of tiredness during worst episode of depression", "Major depressive disorder (probable)", and "Major depressive disorder (ICD-10 coded)" by amalgamating data sourced from the UK Biobank and a meta-analysis of genome-wide association studies, we aimed to provide a more comprehensive elucidation of depression.

After obtaining the preliminary findings regarding depression and sarcopenia, we subsequently incorporated "Mood swing", "Negative emotion", and "Positive emotion" for further examination to determine whether the emotional fluctuations preceding depression possess sufficient potential to correlate with sarcopenia. The segment encompassing "Mood swing" involved item-level analyses [27] and corroborated with UK Biobank data to mutually validate the findings. In the section addressing "Negative emotion", we specifically identified the most prevalent occurrences of "Feeling nervous" and "Feeling miserable" among clinical patients. For the division concerning "Positive emotion", we elected "Subjective well-being" [28] as the focal point of analysis.

Statistical Analyses

All analyses were conducted using TwoSampleMR v0.5.7 (Release date: 2023-05-29) [29]. The principal MR methodology in this study was inverse-variance weighted (IVW) regression. Furthermore, we embraced complementary techniques, including MR-Egger regression, weighted median, and simple mode, to estimate the causal impact of exposure on outcomes and ensure consistent results [30,31]. Subsequently, sensitivity analyses were undertaken to assess the robustness and pleiotropy of the causal estimates (**Supplementary Tables 19–21**). In cases where Cochran's Q statistic suggested heterogeneity among distinct genetic variants, a random-effect model IVW MR analysis was employed [32]. We also conducted an MR-Egger intercept test for pleiotropy [33].

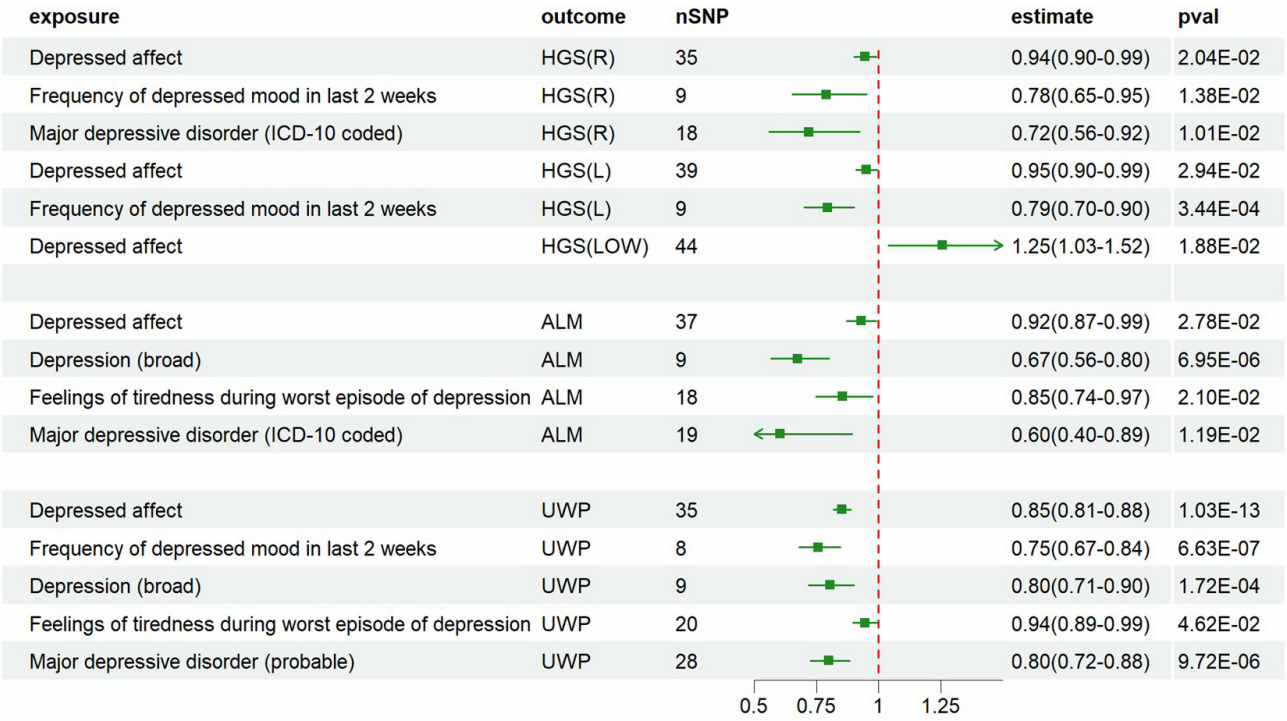

Fig. 2. Forward MR estimates between depression and sarcopenia with outliers removed. HGS (R), hand grip strength (right); HGS (L), hand grip strength (left); HGS (LOW), low grip strength data (60 years and older) (European Working Group on Sarcopenia in Older People (EWGSOP)); ALM, appendicular lean mass; UWP, usual walking pace; nSNPs, number of single nucleotide polymorphisms.

Furthermore, we employed a leave-one-out IVW regression analysis to assess the resilience of the results and produce visual representations. We also used a Mendelian Randomization-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis to identify outlier SNPs reflecting potential pleiotropy and corrected for horizontal pleiotropy by removing such outliers [34]. Concurrently, we created funnel, forest, and scatter plots to present the outcomes. Associations with p values below 0.004 (0.05/11) were deemed statistically significant evidence of a causal association, while p values between 0.004 and 0.05 were regarded as evidence of potential causal association [20].

Results

Sarcopenia and Depression

Forward MR Analyses

Fig. 2 shows a summary of positive findings ($p < 0.05$), and the complete results can be found in **Supplementary Table 22**. After the removal of outliers, the IVW analysis unveiled a notable association between depression and sarcopenia. The various stages of depression exerted an influence on the sarcopenia phenotype. Noteworthy associations included the correlation between "Frequency of depressed mood in the last 2 weeks" and HGS (L) (odds ratio (OR) = 0.79, 95% confidence interval (CI) 0.70–0.90; $p = 3.44 \times 10^{-4}$), "Depression (broad)" and ALM (OR = 0.67, 95% CI 0.56–0.80; $p = 6.95 \times 10^{-6}$), "Depression effect" and UWP (OR = 0.85, 95% CI 0.81–0.88; $p = 1.03 \times 10^{-13}$), "Frequency of depressed mood in the last 2 weeks" and UWP (OR = 0.75, 95% CI 0.67–0.84; $p = 6.63 \times 10^{-7}$), "Depression (broad)" and UWP (OR = 0.80, 95% CI 0.71–0.90; $p = 1.72 \times 10^{-4}$), and "Major depressive disorder (probable)" versus UWP (OR = 0.80, 95% CI 0.72–0.88; $p = 9.72 \times 10^{-6}$). These findings indicate that depression significantly impacts every aspect of the disease, spanning from sarcopenia discovery to diagnosis and severity. Furthermore, all MR-Egger intercept tests yielded no evidence of horizontal pleiotropy, while the stability of the results was confirmed through leave-one-out analyses.

Reverse MR Analyses

Fig. 3 shows a summary of positive findings ($p < 0.05$), and the complete results can be found in **Supplementary Table 23**. After the elimination of outliers, the IVW results revealed a significant association between sarcopenia

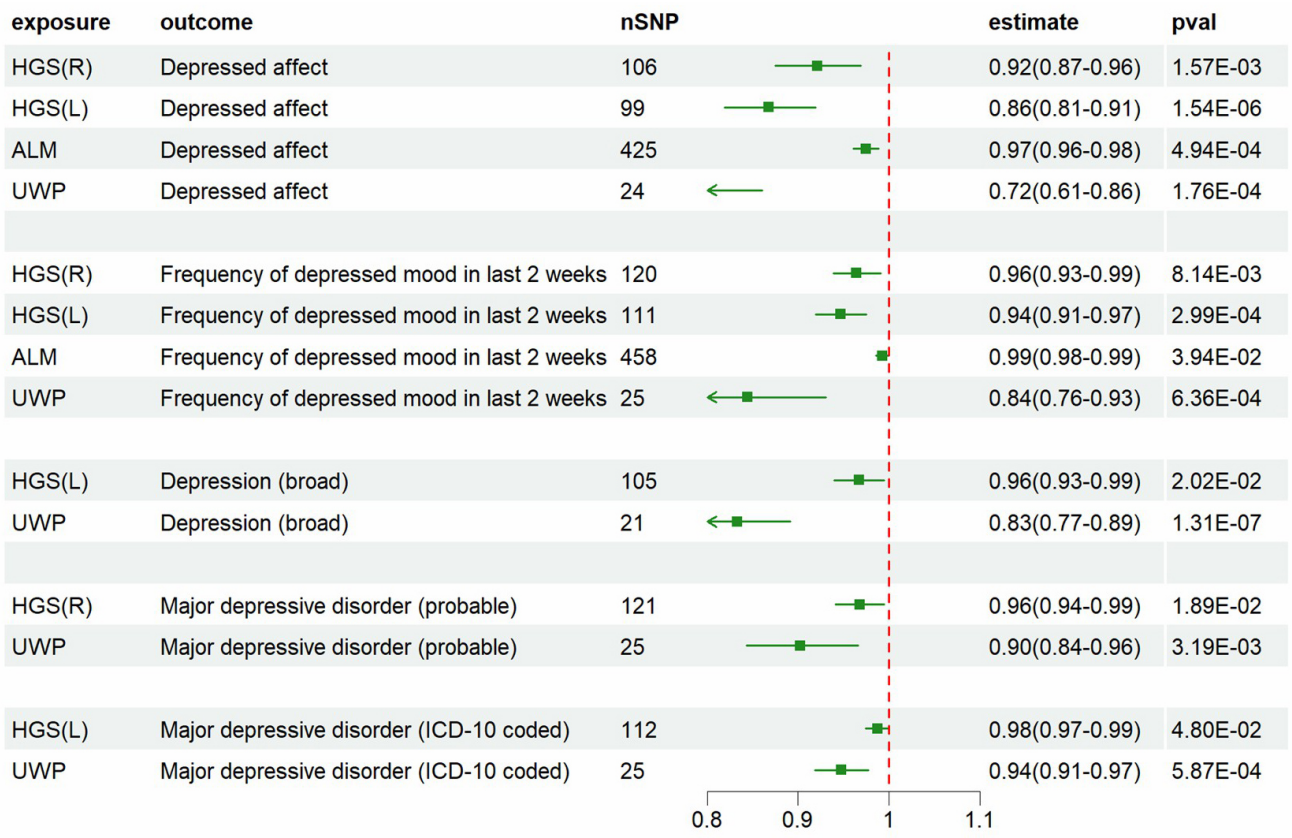

Fig. 3. Reverse MR estimates between depression and sarcopenia with outliers removed. HGS (R), hand grip strength (right); HGS (L), hand grip strength (left); ALM, appendicular lean mass; UWP, usual walking pace; nSNPs, number of single nucleotide polymorphisms.

and depression. All three stages of sarcopenia exerted an influence on depression. With the exception of ALM on "Frequency of depressed mood in the last 2 weeks" (OR = 0.99, 95% CI 0.98–0.99; $p = 3.94 \times 10^{-2}$), HGS (L) on "Depression (broad)" (OR = 0.96, 95% CI 0.93–0.99; $p = 2.02 \times 10^{-2}$), HGS (R) on "Major depressive disorder (probable)" (OR = 0.96, 95% CI 0.94–0.99; $p = 1.89 \times 10^{-2}$), and HGS (L) on "Major depressive disorder (ICD-10 coded)" (OR = 0.98, 95% CI 0.97–0.99; $p = 4.80 \times 10^{-2}$), all other combinations exhibited statistically significant correlations. Additionally, all MR-Egger intercept tests demonstrated the absence of horizontal pleiotropy, further affirming the robustness of the findings, as confirmed by the leave-one-out analyses.

Sarcopenia and Mood Swings

Fig. 4 shows a summary of the positive findings ($p < 0.05$), and the complete results can be found in **Supplementary Tables 22,23**. With mood swings as the parameter of investigation and outliers excluded, the MR analysis revealed deleterious impacts of mood swings on the three sarcopenia phenotypes, and these correlations were statistically significant. Subsequent reverse MR analysis showed that, except for HGS (LOW), the three sarcopenia phenotypes exhibited a considerable protective influence on mood swings. In other words, as the performance of these phenotypes improved, the occurrence of mood swings decreased. All MR-Egger intercept tests yielded no evidence of horizontal pleiotropy, and the results were further fortified by the stability demonstrated in the leave-one-out analyses.

Sarcopenia and Negative/Positive Emotion

Fig. 5 shows a summary of positive findings ($p < 0.05$), and the complete results can be found in **Supplementary Tables 22,23**. By taking negative/positive emotion as the parameter of investigation and eliminating outliers, the MR analysis revealed that positive emotion ("Subjective well-being") exhibits a suggestive protective influence on the ALM phenotype used in diagnosing sarcopenia (OR = 1.06, 95% CI 1.00–1.12; $p = 3.74 \times 10^{-2}$). Conversely,

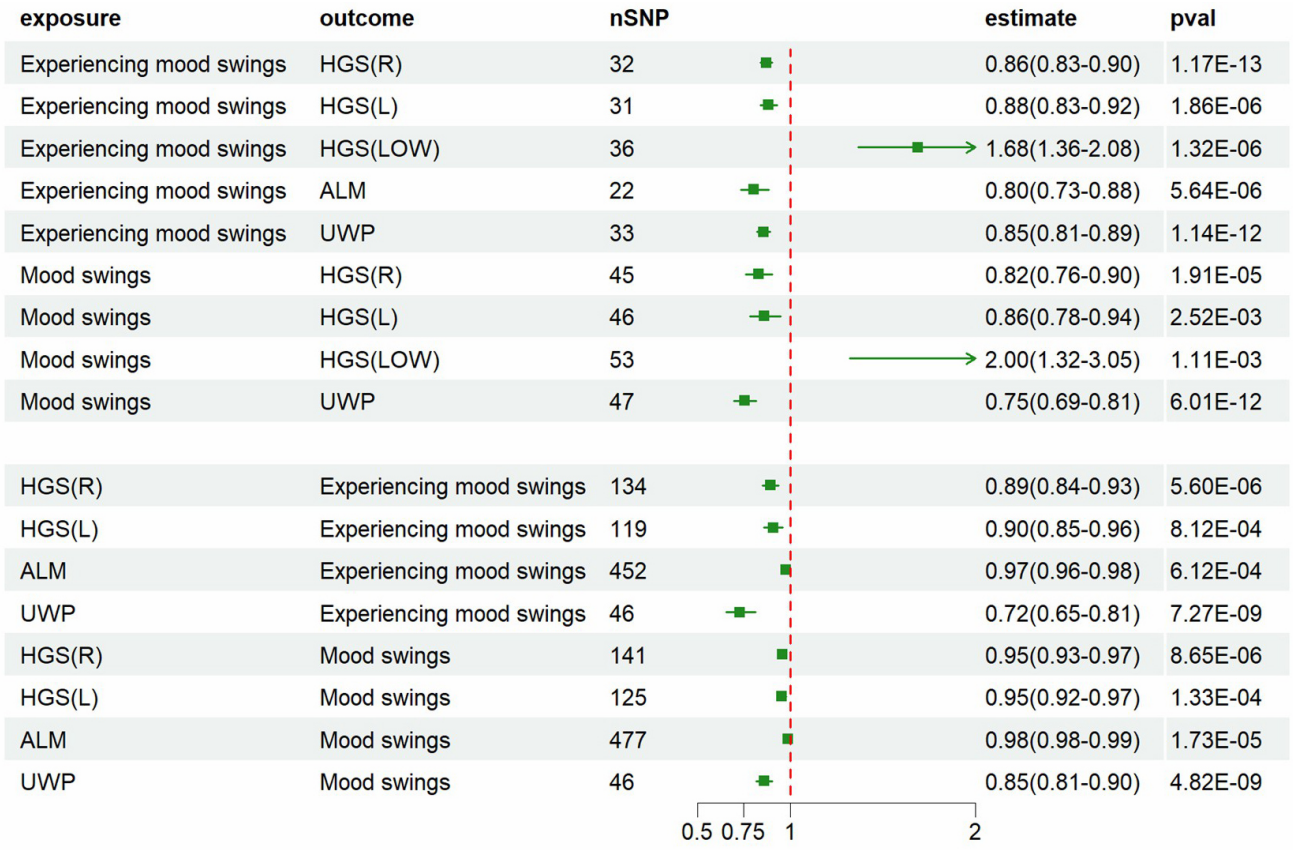

Fig. 4. Bidirectional MR estimates between mood swings and sarcopenia with outliers removed. HGS (R), hand grip strength (right); HGS (L), hand grip strength (left); HGS (LOW), low grip strength data (60 years and older) (EWGSOP); ALM, appendicular lean mass; UWP, usual walking pace; nSNPs, number of single nucleotide polymorphisms.

negative emotion ("Feeling nervous" and "Feeling miserable") significantly impairs sarcopenia detection (hand grip strength) and diagnosis (ALM).

After performing reverse MR analysis, it was revealed that, except for HGS (LOW), all three sarcopenia phenotypes displayed a noteworthy protective effect on negative emotion, indicating that as the phenotypic performance improved, the occurrence of negative emotion decreased accordingly. However, no statistical significance was observed regarding positive emotion. All MR-Egger intercept tests confirmed the absence of horizontal pleiotropy, further solidifying the validity of the results as supported by leave-one-out analyses, which demonstrate their steadfastness.

Discussion

In this MR study, a significant potential causal relationship between mental factors, such as depression, and sarcopenia was identified. We observed that both depression and negative emotions contribute to the exacerbation of the sarcopenia phenotype, whereas positive emotions have a beneficial impact on alleviating sarcopenia. Reverse MR also revealed a strong negative influence of sarcopenia phenotype deterioration on depression and negative emotions. Our findings were demonstrated to be robust through a series of sensitivity analyses and pleiotropic evaluations.

A previous study did not demonstrate such a correlation in South Korea [35]. However, in a cross-sectional study conducted in Japan, although depressed mood was not associated with muscle mass loss, there was an association with muscle strength and physical performance [36]. Further research has confirmed the relationship between depression and sarcopenia through clinical observations of patients with liver cancer [37], lung cancer [38], and kidney disease [39]. It is important to note that while many studies conducted in various locations have shown an association between depression and sarcopenia or its clinical phenotypes, most of these studies focused on elderly patients with depression. Thus, it remains inconclusive whether age, as a confounding factor, mediates the interaction between depression and sarcopenia. Nonetheless, the MR analysis ef-

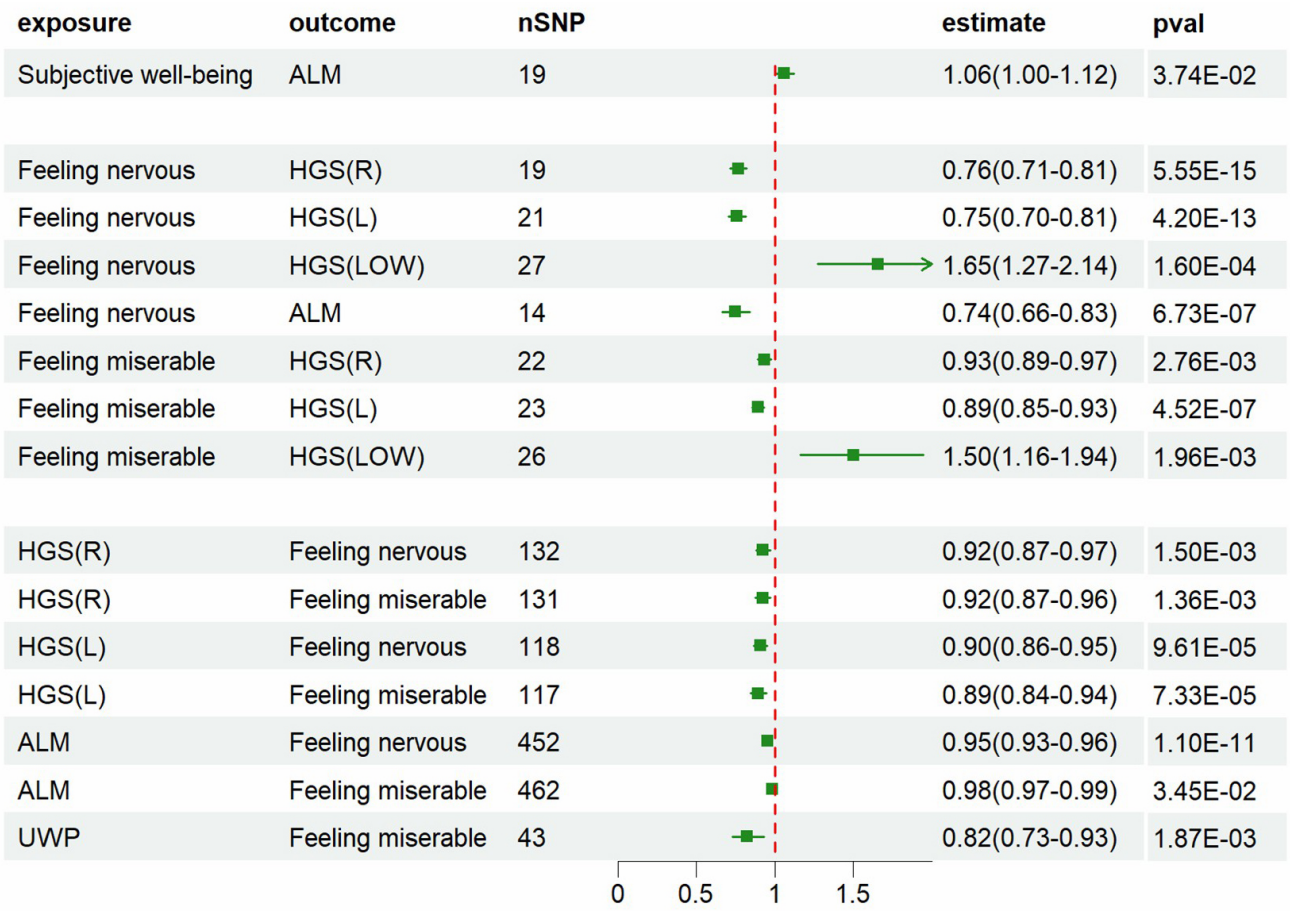

Fig. 5. Bidirectional MR estimates between negative/positive emotion and sarcopenia with outliers removed. HGS (R), hand grip strength (right); HGS (L), hand grip strength (left); HGS (LOW), low grip strength data (60 years and older) (EWGSOP); ALM, appendicular lean mass; UWP, usual walking pace; nSNPs, number of single nucleotide polymorphisms.

fectively mitigates such confounding variables. Therefore, despite the unknown underlying mechanism, there are reasonable grounds to infer that depression exerts a detrimental effect on sarcopenia.

Although it is not difficult to understand that decreased physical activity leads to reduced daily activities and consequently depressed mood [40], contrary to our expectations, the reverse MR analysis demonstrated that decreased physical function is directly reflected in mental level. As hypothesized by Pasco *et al*. [41], a shared pathophysiological pathway between sarcopenia and depression establishes a connection between skeletal muscle and cerebral function. Furthermore, the neurotrophic factor, brain-derived neurotrophic factor (BDNF), is secreted during muscle contraction and influences anxiety and emotional states in the brain [42]. It also is considered a biomarker for assessing depression treatment response [43,44]. Increased BDNF levels may indicate the effectiveness of antidepressant medication. However, due to its large size, BDNF's therapeutic effects are hindered by the blood-brain barrier and other biological membranes [45]. One study in animals with traumatic brain injuries has shown that disrupted blood-brain barriers lead to BDNF efflux, which is associated with the onset of depression [42].

Interestingly, congenital blood-brain barrier dysfunction in mice does not result in BDNF leakage, which can lead to the onset of depressive symptoms [46]. Antidepressants can elevate BDNF levels, suggesting that exogenous BDNF continues to impact endogenous BDNF despite the integrity of the blood-brain barrier. There is a possibility that BDNF functions through a mechanism similar to that of thyroid hormone. It has been confirmed that exogenous BDNF can penetrate the blood-brain barrier via a "Trojan horse" mechanism [45,47]. This finding proposes a new approach for depression treatment by enhancing physical function to increase peripheral BDNF levels and using drugs to strengthen the carrier. BDNF's influence on muscle satellite cells has also been investigated [42,48]. It is

hypothesized that BDNF is linked to the co-occurrence of sarcopenia and depression. Additionally, there is a potential to improve sarcopenia through emotional interventions, thus expanding the strategies for intervening and treating sarcopenia.

Although this study represents an inaugural endeavor to examine a plausible bidirectional causal association between sarcopenia and depression utilizing an MR approach, it is imperative to acknowledge that certain limitations are inherent in our investigation. Firstly, despite carefully selecting highly correlated SNPs, it is essential to recognize that they cannot be considered exact surrogates for the exposures being studied [49]. Furthermore, a significant portion of our research on depression and psychological factors relies on self-reported data, which inherently cannot eliminate the potential influence of cognitive biases and affective states. While this does not undermine the utility of self-report measures, future studies should contemplate the inclusion of objective benchmarks to demarcate individual emotional states and establish more precise boundaries within the realm of mental and emotional phenomena. Thirdly, it is important to recognize that the UK Biobank dataset used in this study includes only populations of European ancestry, thus warranting further verification to ascertain the generalizability of the findings to other ethnic groups. Fourthly, to procure an adequate number of SNPs and ensure the accuracy of the outcomes, it was occasionally necessary to relax the threshold. Complete elimination of potential pleiotropic effects is challenging due to the limited understanding of confounding factors and the unavailability of individual-level data [50]. Fifthly, the possibility of sample overlap between exposure and outcome may introduce a weakened instrumental bias.

Despite our robust inference of causal effects using powerful instrumental variables, supported by F-statistics exceeding 10 and various statistical metrics to address outliers, we strongly advocate for additional research to validate and corroborate our findings. Lastly, while our Mendelian randomization analysis suggests an association between depression and sarcopenia, it cannot directly establish causality. Intervention studies, such as randomized controlled trials, are needed to further elucidate the causal nature of this relationship.

Conclusions

Our study has revealed the potential existence of reciprocal causation between sarcopenia and depression. This bidirectional causal relationship between sarcopenia and depression may indicate the presence of a pernicious cycle, significantly increasing the risk of sarcopenia onset and the exacerbation of depression in afflicted individuals. Nevertheless, it is worth noting that subjective well-being has the potential to ameliorate sarcopenia, thereby offering a preliminary theoretical basis for the prevention and intervention of sarcopenia and depression.

Abbreviations

MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; GWAS, genome-wide association study; MAF, minor allele frequency; EWGSOP, European Working Group on Sarcopenia in Older People; HGS (R), hand grip strength (right); HGS (L), hand grip strength (left); HGS (LOW), low grip strength data; ALM, appendicular lean mass; UWP, usual walking pace; MR-PRESSO, Mendelian Randomization-Pleiotropy RESidual Sum and Outlier; BDNF, brain-derived neurotrophic factor; MRC, Medical Research Council; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

Conceptualization, YZL and XJS; methodology, YZL; software, LJH; validation, LJH, JLL, RS and MT; formal analysis, YZL; investigation, XJS; resources, LJH; data curation, JLL; writing-original draft preparation, YZL; writing—review and editing, RS, MT and XJS; visualization, RS; supervision, YZL; project administration, YZL; funding acquisition, YZL. All authors contributed to important editorial changes in the manuscript. All authors have read and agreed to the published version of the manuscript and all authors agreed to be 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.

Ethics Approval and Consent to Participate

All methods described in this study were conducted in strict accordance with the relevant guidelines and regulations of our local regulatory agencies. Additionally, we confirm that written informed consent was obtained from

all subjects participating in this research or from their legal guardian(s) before their inclusion in the study in accordance with the Declaration of Helsinki.

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We would like to extend our sincere gratitude to the developers and maintainers of the public database, as well as Professor Lixue Yang, for their invaluable contributions to our research. The availability of the public database provided us with a rich and reliable source of data, which served as a fundamental resource for our study. The diligent efforts and expertise of the database team are greatly appreciated, as their work enabled us to explore our research questions in depth. We would also like to express our deep appreciation to Professor Lixue Yang for his rigorous review and constructive feedback. His expertise and guidance have significantly improved the reliability and accuracy of our research, and we are grateful for his invaluable insights.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.v52i4.1679.

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