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Evaluating the effect of metformin on sarcopenia
A Mendelian randomization study

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Abstract

Sarcopenia is prevalent among elder patients with type 2 diabetes. As a first-line medication for managing type 2 diabetes, metformin has shown controversial effects on sarcopenia. This study aims to analyze the impact of metformin on sarcopenia using Mendelian randomization analysis. We selected 30 single nucleotide polymorphisms associated with metformin used as instrumental variables from genome-wide association studies. Mendelian randomization was conducted using inverse variance weighted (IVW), Mendelian randomization Egger, and weighted median methods. Additionally, we performed heterogeneity tests, Pleiotropy analyses, and sensitivity analyses to validate our findings. The IVW method indicated a *P*-value of .63 and an odds ratio (OR) of 0.93 (95% CI: 0.69–1.25) for the relationship between metformin use and walking pace. For appendicular lean mass, the IVW method showed a *P*-value of .42 and an OR of 0.69 (95% CI: 0.28–1.70). In contrast, the IVW analysis indicated a significant relationship between metformin use and right hand grip strength, with *P*-value of .01 and OR (95% CI) = 0.64 (0.45–0.91), as well as for left hand grip strength, with *P*-value of .01 and OR (95% CI) = 0.65 (0.45–0.92). Notably, a causal relationship was established between metformin use and lower hand grip strength, while no causal relationship was found between metformin use and walking pace or appendicular lean mass. This study suggests that caution is needed regarding long-term metformin use in the context of sarcopenia.

Abbreviations: GWAS = genome-wide association studies, IV = instrumental variable, IVW = inverse variance weighted, LD = linkage disequilibrium, MR-Egger = Mendelian randomization Egger, OR = odds ratio, SNP = single nucleotide polymorphism, T2DM = type 2 diabetes mellitus, WM = weighted median.

Keywords: diabetes, Mendelian randomization, metformin, sarcopenia

1. Introduction

Sarcopenia is a syndrome characterized by the progressive loss in muscle mass and strength associated with aging.[1–3] The prevalence is estimated to range from 10% to 27% among individuals aged 60 and older worldwide.[2] As the global population ages, the prevalence of sarcopenia is increasing, making it a critical public health concern. The multifaceted pathogenesis of sarcopenia includes mitochondrial dysfunction, inflammation, imbalances in muscle protein synthesis and degradation, and insulin resistance.[4–6] There is growing interest in sarcopenia among individuals with type 2 diabetes mellitus (T2DM), both in clinical practice and research. Selecting antidiabetic medications for this population with comorbid diabetes and sarcopenia requires special considerations.[7] It is essential to choose medications that not only achieve glycemic control but also help preserve muscle mass. Understanding these underlying mechanisms is vital for developing effective interventions and selecting appropriate treatments for elderly patients facing both sarcopenia and diabetes.

Metformin is a widely used antidiabetic medication primarily prescribed for the treatment of T2DM. In recent years, research has revealed that metformin may possess various potential anti-aging and muscle-protective effects beyond its glucose-lowering properties.[8] Some studies suggest that metformin may exert protective effects against sarcopenia by activating the AMP-activated protein kinase signaling pathway, improving mitochondrial function, and regulating inflammatory responses and autophagy.[5,8,9] However, the findings regarding the impact of metformin on sarcopenia are inconsistent. While some studies indicate that metformin can reduce the risk of sarcopenia and improve muscle quality and function,[8,10] others have reported conflicting results, even suggesting potential negative effects on muscle.[11,12] Additionally, the impact of metformin on sarcopenia is complicated by numerous confounding factors. Patients with T2DM often exhibit various comorbidities, such as cardiovascular disease,[13] and other metabolic disorders,[14] which can independently influence muscle health and function. Consequently, a clearer understanding of the

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The datasets generated during and/or analyzed during the current study are publicly available.

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relationship between metformin use and sarcopenia requires further investigation.

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among individuals. They arise from alterations in a single nucleotide within the DNA sequence, leading to differences in genetic information. SNPs can influence various traits and diseases by affecting gene function or expression. Mendelian randomization (MR) is a statistical method that uses SNPs as instrumental variables (IVs) to assess the causal effects of exposure factors on outcomes. Compared to traditional observational studies, MR better controls for confounding factors and reverse causation, providing more reliable causal inferences.[15,16] To date, no studies have utilized Mendelian randomization to explore the relationship between metformin and sarcopenia. Therefore, conducting this research may provide more robust evidence for the application of metformin in the prevention and treatment of sarcopenia, ultimately contributing to improved health outcomes for elderly patients facing these challenges. This study aims to fill this gap by investigating the potential causal effects of metformin on traits related to sarcopenia, which could inform clinical decision-making and therapeutic strategies.

2. Method

2.1. Study design

A 2-sample MR method was used to explore the causal association between metformin use and traits related to sarcopenia. In our research, the exposure factor is defined as metformin. The outcome variables encompass traits related to sarcopenia, including walking pace, appendicular lean mass, and hand grip strength. The ethical approval was not required, because data for this study were obtained from the publicly available database.

2.2. Data source

Information about SNPs involved in this study was obtained from an open-access genome-wide association studies (GWAS) database (https://gwas.mrcieu.ac.uk/). Genetic IVs were generated from a meta-analysis of a large-scale GWAS on metformin treatment, which included data from 462,933 European individuals published in 2018, comprising 11,552 cases and 451,381 controls. The data for these outcome variables were also sourced from European populations: the walking pace analysis included 459,915 samples, the appendicular lean mass analysis comprised 450,243 samples, and the right and left hand grip strength analyses involved 461,089 and 461,026 samples, respectively. Sample information are provided below in Table 1.

2.3. Instrumental variables selection

In MR, the selection of IVs must adhere to 3 key assumptions: (1) the IVs had a significant relationship with the exposure. (2) The IVs had no pleiotropic correlations with any known confounding factors, and (3) the IVs had no association with the outcome, with the possible exception of how the link was mediated by their association with the exposure.[16,17] Specifically, we selected SNPs associated with metformin at a genome-wide significance level ($P < 5 \times 10^{-8}$) to ensure a strong relevance to the exposure. To minimize linkage disequilibrium (LD) and ensure the independence of instruments, we applied an LD threshold of $r^2 < 0.001$ and a physical distance of 10,000 kb. We utilized the LDtrait tool (https://ldlink.nih.gov/?tab=ldtrait) to exclude SNPs associated with traits related to sarcopenia, thereby reducing potential pleiotropic effects. Furthermore, we calculated the F-statistic for each SNP and retained only those with $F > 10$ to avoid weak instrument bias. For SNPs not present in the outcome dataset, we sought suitable proxies or excluded them if none were available.

2.4. Data analysis

We employed 3 analytical methods to assess the causal effect of metformin on sarcopenia traits: inverse variance weighted (IVW), Mendelian randomization Egger (MR-Egger), and weighted median (WM). Typically, the IVW method serves as the primary analytical approach in MR, offering the most accurate estimates of causal linkage in the absence of pleiotropy. We utilized a random-effects IVW model when heterogeneity among the IVs was present; otherwise, a fixed-effects IVW model was applied.[17] As complementary methods, MR-Egger and weighted median analyses are equally important.[18,19] To evaluate heterogeneity, we conducted several tests, including the Cochrane Q test, leave-one-out analysis, and the MR-Egger intercept test. The MR-Egger intercept test and the Mendelian randomization pleiotropy residual sum and outlier test were utilized to detect pleiotropy and correct horizontal pleiotropy by removing outliers. All data analyses were conducted in R software (version 4.3.2) with the R packages "TwosampleMR" and "MRPRESSO." The difference was considered statistically significant only if the P-value < .05.

3. Result

3.1. SNPs selection

After the selection process, there were 30 SNPs as IVs satisfying the 3 main hypotheses of MR. All F-values were > 10, indicating that the IVs selected were strong IVs.

3.2. Causal effects of metformin use on traits related to sarcopenia

The MR analysis results are shown in Table 2. In the MR analysis of metformin use and walking pace, none of the three MR methods showed statistically significant results, with p-values ranging from 0.56 to 0.75. Similar to walking pace, no significant associations were found across all methods (P-values:

Table 1

Summary of the genome-wide association study data.

	Consortium	GWAS ID	Variable type	Sample size	Population	Sex	Year
Metformin	MRC-IEU	ukb-b-14609	Binary	462,933	European	M/F	2018
Walking pace	MRC-IEU	ukb-b-4711	Categorical Ordered	459,915	European	M/F	2018
Appendicular lean mass	UKB	ebi-a-GCST90000025	Continuous	450,243	European	NA	2020
Hand grip strength (right)	MRC-IEU	ukb-b-10215	Continuous	461,089	European	M/F	2018
Hand grip strength (left)	MRC-IEU	ukb-b-7478	Continuous	461,026	European	M/F	2018

GWAS = genome-wide association studies.

Table 2

Mendelian randomization analysis of the main results.

Outcome	SNPs, n	Method	OR (95% CI)	*P* effect
Walking pace	30	IVW	0.93 (0.69–1.25)	.63
	30	MR-Egger	1.24 (0.61–2.49)	.56
	30	WM	1.04 (0.80–1.37)	.75
Appendicular lean mass	30	IVW	0.69 (0.28–1.70)	.42
	30	MR-Egger	1.43 (0.17–12.04)	.75
	30	WM	1.16 (0.76–1.77)	.49
Hand grip strength (right)	30	IVW	0.64 (0.45–0.91)	.01
	30	MR-Egger	0.48 (0.21–1.12)	.10
	30	WM	0.55 (0.41–0.76)	<.001
Hand grip strength (left)	30	IVW	0.65 (0.45–0.92)	.01
	30	MR-Egger	0.59 (0.25–1.36)	.22
	30	WM	0.65 (0.47–0.90)	.01

Exposure is treatment/medication code: metformin.

IVW = inverse variance weighted, MR = Mendelian randomization, OR = odds ratio, SNP = single nucleotide polymorphism, WM = weighted median.

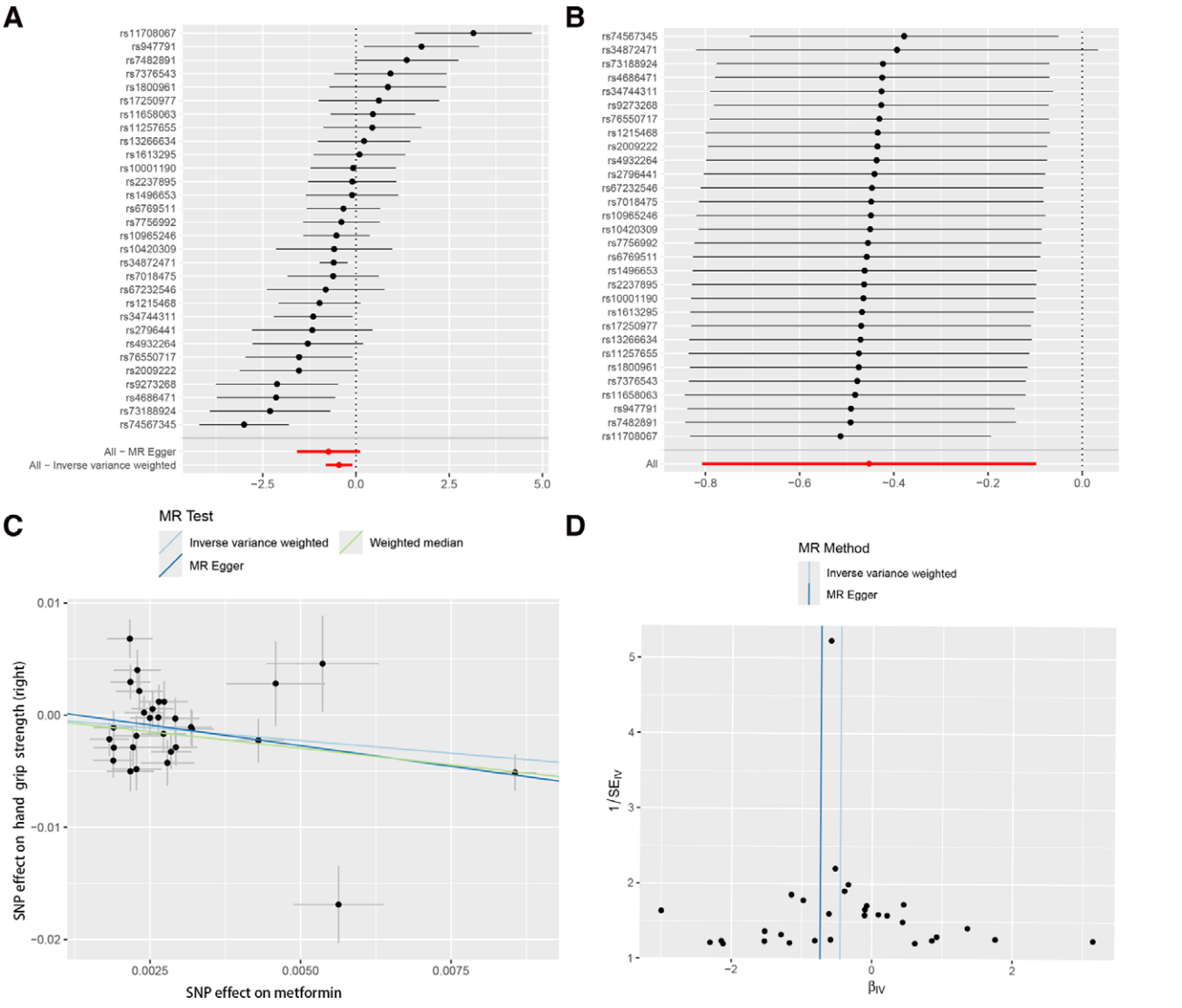

Figure 1. Visualization of Mendelian randomization analysis using metformin and right hand grip strength. (A) Random IVW analysis of the causal association of metformin with right hand grip strength. The black dots and bars indicate the causal estimate and 95% CI using each SNP. The red dot and bar indicate the overall estimate and 95% CI meta-analyzed by the random-effect IVW and MR-Egger method. (B) Leave-one-out analysis plots for metformin use on right hand grip strength. (C) Scatter plot of the effects of genetic variants on the metformin use and right hand grip strength. The slopes of the solid lines denote the magnitudes of the associations estimated from the MR analyses. (D) A funnel plot of the causal effect of metformin use on right hand grip strength. IVW = inverse-variance weighted, MR = Mendelian randomization, SNP = single nucleotide polymorphism.

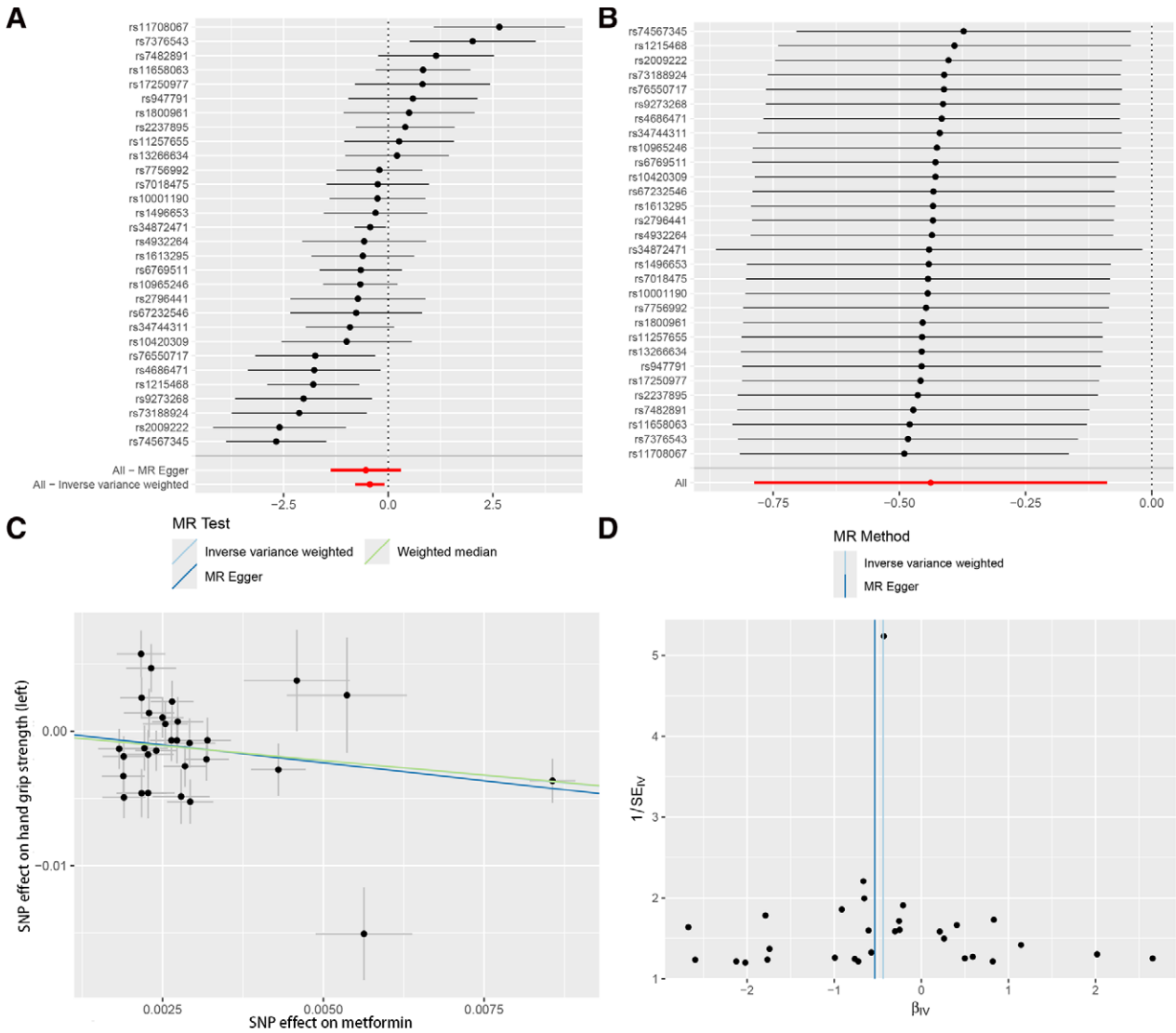

Figure 2. Visualization of Mendelian randomization analysis using metformin and left hand grip strength. (A) Random IVW analysis of the causal association of metformin with left hand grip strength. The black dots and bars indicate the causal estimate and 95% CI using each SNP. The red dot and bar indicate the overall estimate and 95% CI meta-analyzed by the random-effect IVW and MR-Egger method. (B) Leave-one-out analysis plots for metformin use on left hand grip strength. (C) Scatter plot of the effects of genetic variants on the metformin use and lefthand grip strength. The slopes of the solid lines denote the magnitudes of the associations estimated from the MR analyses. (D) A funnel plot of the causal effect of metformin use on left hand grip strength. CI = confidence interval, IVW = inverse-variance weighted, MR = Mendelian randomization, SNP = single nucleotide polymorphism.

Table 3

Testing for pleiotropy and heterogeneity.

	Pleiotropy test				Heterogeneity test					
	MR_Egger			PRESSO	MR_Egger			IVW		
	Intercept	SE	*P*	*P*	Q	df	*P*	Q	df	*P*
Walking pace	<0.001	-0.002	>.99	>.99	<0.001	28	>.99	<0.001	29	>.99
Appendicular lean mass	-0.002	0.003	.47	.97	327.95	28	<.001	334.43	29	<.001
Hand grip strength (right)	<0.001	0.001	.48	.91	87.78	28	<.001	89.43	29	<.001
Hand grip strength (left)	<0.001	0.001	.80	.77	86.91	28	<.001	87.11	29	<.001

.42–.75). However, the IVW method showed a strong significant negative association between metformin use and right hand grip strength (odds ratio [OR]: 0.64, 95% CI: 0.45–0.91, $P = .01$) (Fig. 1A and C), The WM method also indicated a significant negative association (OR: 0.55, 95% CI: 0.41–0.76, $P < .001$). The IVW method revealed a significant negative association between metformin use and left hand grip strength (OR: 0.65, 95% CI: 0.45–0.92, $P = .01$) (Fig. 2A, C), while the WM method also showed a significant negative association (OR: 0.65, 95% CI: 0.47–0.90, $P = .01$).

3.3. Sensitivity analysis

Pleiotropy and heterogeneity tests were conducted to assess the validity of our MR analyses (Table 3). The MR-Egger intercept test for pleiotropy showed no significant evidence of directional pleiotropy for any of the outcomes (all $P > .05$). The Mendelian randomization pleiotropy residual sum and outlier global test also indicated no significant pleiotropy (all $P > .77$). Heterogeneity tests revealed significant heterogeneity for appendicular lean mass, right hand grip strength, and left hand grip strength in both MR-Egger and IVW analyses (all $P < .001$) according to Cochran Q test. However, the funnel plot appeared relatively symmetrical (Figs. 1D and 2D). The Q statistics for these outcomes were notably high, particularly for appendicular lean mass ($Q = 327.95$ for MR-Egger and $Q = 334.43$ for IVW). In contrast, walking pace showed no significant heterogeneity ($P = 1$ for both MR-Egger and IVW). Finally, the leave-one-out sensitivity test demonstrated that the causal effect of metformin use on hand grip strength was not significantly affected by leaving out any single SNP (Figs. 1B and 2B).

4. Discussion

The potential link between metformin and sarcopenia has been a topic of interest for some time; however, much of the evidence remains in the preliminary phase, characterized by various confounding factors that complicate the interpretation of this association. In this study, we utilized a two-sample MR approach to examine the causal relationship between metformin use and sarcopenia traits. Our findings indicate that metformin use may be causally associated with an increased risk of sarcopenia, particularly affecting hand grip strength. This suggests a causal relationship between metformin and a decline in muscle function.

While numerous studies explore the effects of metformin on muscle strength and atrophy, large-scale clinical trials or meta-analyses are limited. Much of the existing evidence comes from smaller studies, animal models, or in vitro experiments, which may not fully translate to human populations. Therefore, more comprehensive and larger clinical trials are needed to clarify the effects of long-term metformin use on muscle function. Some studies suggest that metformin may negatively impact muscle strength. For instance, metformin treatment has been linked to decreased muscle fiber cross-sectional area in mice, suggesting a detrimental effect on muscle size and potentially strength.[12] Although normal-density thigh muscle area increased following progressive resistance exercise training, metformin attenuated this gain, suggesting a potential risk of muscle atrophy.[20] Conversely, other research indicates that metformin may have beneficial effects on muscle function. For example, metformin has been shown to reduce inflammation and improve insulin sensitivity in skeletal muscle, which could enhance muscle strength and function.[21] Furthermore, metformin use during bed rest may reduce muscle fibrosis during the re-ambulation period. Individuals treated with metformin exhibited less atrophy of type I myofibers during periods of disuse, along with reduced pro-inflammatory transcriptional profiles and lower muscle collagen deposition during recovery.[22]

Sarcopenia, a prevalent condition characterized by the loss of skeletal muscle mass and strength, is particularly pronounced among individuals with diabetes mellitus.[6,7] The molecular mechanisms underlying sarcopenia are complex and involve multiple interconnected signaling pathways. These intricate mechanisms encompass inflammation, hormonal changes, and mitochondrial dysfunction, all of which significantly contribute to the progressive loss of muscle mass and strength.[2,3] Risk factors for sarcopenia include, but are not limited to, aging, chronic diseases, metabolic alterations, and poor nutrition.[23] Given the detrimental effects of sarcopenia, such as an increased risk of falls, fractures, and decreased quality of life,[24] it is essential to implement effective intervention strategies. Therefore, investing in effective treatment options for sarcopenia is of paramount importance. The main treatment options for sarcopenia include anabolic steroids,[25] growth hormone therapies,[26] anti-inflammatory drugs,[27] and nutritional supplements.[28,29] Additionally, some antidiabetic medications have been shown to have protective effects on muscle. For instance, a prospective study was conducted on overweight and obese patients with T2DM to evaluate the effects of liraglutide treatment on sarcopenia. The results indicated that liraglutide may act as a potential anabolic agent for skeletal muscle, leading to improvements in the skeletal muscle index.[30] Hence, the choice of antidiabetic therapy should consider not only glycemic control but also the potential impact on muscle health for patients with sarcopenia and diabetes.

In our MR analysis, Cochran Q test showed significant heterogeneity, and the funnel plot also appeared to exhibit some degree of heterogeneity. This situation requires a rational and objective interpretation. First, the significant heterogeneity indicated by Cochran Q test suggests that there may be genuine differences in effect sizes across the studies included in our analysis.[31] Additionally, the sensitivity of Cochran Q test to detect heterogeneity can sometimes lead to significant results even with minor variations, particularly in studies with small sample sizes. Meanwhile, it is important to note that the funnel plot can sometimes mask subtle biases or variations, especially if the sample sizes of the studies are large and contribute to a misleading sense of symmetry.[32] Based on our observation of substantial heterogeneity, we employed a random-effects IVW model in MR analysis instead of fixed-effects model, enabling a more reliable estimation of the causal relationship.[33] However, we need to acknowledge that a negative pleiotropy test result alongside significant heterogeneity was observed in our MR analysis. While pleiotropic effects may not be influencing our IVs, the variability among study results requires careful consideration.

The current study presents several significant strengths. Firstly, it utilized large-scale GWAS summary statistics in conjunction with MR analysis, which minimizes the risk of confounding factors. Secondly, the strong estimated effects of each instrumental variable (with all F-statistics exceeding 10) help mitigate the risk of weak instrumental bias. Additionally, multiple sensitivity analyses were conducted to ensure that the association between metformin treatment and sarcopenia is both reliable and stable. However, there are notable limitations to consider. Firstly, all participants in this study were from Europe, which may restrict the applicability of our findings to other ethnic groups. Secondly, we were unable to assess how variations in metformin dosage and treatment duration impact the risk of sarcopenia. Thirdly, we could not determine whether the causal relationship is influenced by gender, comorbidities, or other medical conditions. Moreover, our selection criteria for SNPs may not encompass all relevant genetic variants influencing metformin use, potentially leading to residual confounding. While we employed LDtrait to exclude SNPs with known associations to sarcopenia-related traits, undetected or unmeasured pleiotropic effects cannot be entirely ruled out. Overall, these factors could significantly influence the drug's effect on muscle health, and their absence may limit the applicability of our findings to real-world clinical scenarios.

5. Conclusion

Our MR analysis indicates that metformin use may be associated with an increased risk of sarcopenia, particularly affecting hand grip strength. This finding challenges the prevailing notion of metformin as solely beneficial, suggesting that its effects on muscle health may be more complex. Given the widespread use of metformin among older adults, it is crucial

for clinicians to exercise caution when prescribing this medication to elderly patients, especially those already at risk for muscle loss. Further rigorous basic experiments and well-designed clinical trials are necessary to elucidate the mechanisms underlying metformin's impact on sarcopenia and to identify specific populations that may be more vulnerable to its adverse effects on muscle health.

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