No genetically predicted association between sarcopenia and COVID-19

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Abstract

Objectives: Previous observational studies have revealed a connection between sarcopenia and COVID-19. To evaluate their causal relationship, we utilized a bidirectional two-sample Mendelian randomization (MR) analysis to study the link of cause and effect between sarcopenia and COVID-19. **Methods:** Inverse variance weighting (IVW), MR-Egger, weighted, and weighted median were used in this research. Then we used the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and MR-Egger regression methods to estimate the pleiotropy of instrumental variables (IVs), while the outliers were excluded by MR-PRESSO. Moreover, we used Cochran's Q statistic to evaluate the heterogeneity among the IVs. And we used leave-one-out sensitivity analysis to identify the SNPs that significantly affect the outcomes. Finally, the Bonferroni correction was used to correct each result. **Results:** The IVW results suggested that faster WP decreased the risk of all types of COVID-19 (COVID-19 infection: OR = 0.469, 95% CI: 0.326,0.676, P = 4.82E-05; COVID-19 hospitalization: OR = 0.247, 95% CI: 0.122,0.502, P = 1.11E-04; severe COVID-19: OR = 0.120, 95% CI: 0.046,0.314, P = 1.53E-05). However, there was no causal relationship between ASM, LH or RH and COVID-19, and WP adjusted for BMI had no significant connection with all types of COVID-19. Furthermore, no causal association of COVID-19 on sarcopenia was observed in the results of reverse MR analysis. **Conclusion:** Our bidirectional two-sample MR study suggests the causal relationship between WP and COVID-19 but it may be caused by the mediating role of BMI, thus there is no causal association between sarcopenia and COVID-19.

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Abstract:

Objectives: Previous observational studies have revealed a connection between sarcopenia and COVID-19. To evaluate their causal relationship, we utilized a bidirectional two-sample Mendelian randomization (MR) analysis to study the link of cause and effect between sarcopenia and COVID-19.

Methods: Inverse variance weighting (IVW), MR-Egger, weighted, and weighted median were used in this research. Then we used the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and MR-Egger regression methods to estimate the pleiotropy of instrumental variables (IVs), while the outliers were excluded by MR-PRESSO. Moreover, we used Cochran's Q statistic to evaluate the heterogeneity among the IVs. And we used leave-one-out sensitivity analysis to identify the SNPs that significantly affect the outcomes. Finally, the Bonferroni correction was used to correct each result.

Results: The IVW results suggested that faster WP decreased the risk of all types of COVID-19 (COVID-19 infection: OR = 0.469, 95% CI: 0.326,0.676, P = 4.82E-05; COVID-19 hospitalization: OR = 0.247, 95% CI: 0.122,0.502, P = 1.11E-04; severe COVID-19: OR = 0.120, 95% CI: 0.046,0.314, P = 1.53E-05). However, there was no causal relationship between ASM, LH or RH and COVID-19, and WP adjusted for BMI had no significant connection with all types of COVID-19. Furthermore, no causal association of COVID-19 on sarcopenia was observed in the results of reverse MR analysis.

Conclusion: Our bidirectional two-sample MR study suggests the causal relationship between WP and COVID-19 but it may be caused by the mediating role of BMI, thus there is no causal association between sarcopenia and COVID-19.

Keywords: COVID-19; Sarcopenia; Appendicular lean mass; Hand grip strength; Usual walking pace; Mendelian randomization.

1 Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly and became a severe global public problem[1]. Currently, the pandemic of COVID-19 is relatively under control but still caused high morbidity and mortality to the whole society. As of May 3, 2023, COVID-19 had been reported 765, 222, 932 cases globally and had accounted for 6921614 deaths[2]. The clinical manifestations of COVID-19 patients are various, ranging from mild and asymptomatic cases to severe cases, including cough, fever, myalgias and headache[3]. Moreover, various comorbidities, which included interstitial pneumonia, cytopenia, myocarditis, arthralgia, and sarcopenia, frequently occur in COVID-19 patients[4-11]. While, sarcopenia, the manifestation of skeletal muscles caused by COVID-19, is attracting extensive attention.

Sarcopenia is a generalized and progressive skeletal muscle disease with loss of muscle mass acceleratively, which causes a series of other negative consequences, such as frailty, diminished quality of life and mortality[12-14]. Sarcopenia is largely attributable to aging, which typically occurs in older-aged people[15]. The European Working Group on Sarcopenia in Older People 2 (EWGSOP 2) showed that the prevalence of sarcopenia in men is 1.3% and in women is 0.4%[16]. Furthermore, it has been discovered that the systemic disease that may invoke inflammatory processes can lead to sarcopenia, such as organ failure, malignancy or COVID-19[17].

Recently, the relationship between sarcopenia and COVID-19 has generated an abundance of discussions. Sarcopenia was reported to be in connection with the increasing severity and morality of COVID-19[18]. A few studies suggested that patients infected with COVID-19 had a higher incidence of sarcopenia, which varies among patients infected with different types of COVID-19[19, 20]. Patients in ICU who had COVID-19 were inclined to be diagnosed with sarcopenia, compared to other patients hospitalized for COVID-

19[20, 21]. Moreover, the risk of sarcopenia was higher among the patients after severe or moderate COVID-19 infection with prolonged length of hospital stay and invasive mechanical ventilation[22]. However, some studies indicated that sarcopenia was unrelated to mortality of COVID-19[23, 24]. The conclusion about the relationship between sarcopenia and COVID-19 is inconsistent and the causal effect of sarcopenia on COVID-19 remains ambiguous.

Moreover, the majority of the above conclusions between sarcopenia and COVID-19 were from observational studies. Owing to the inherent defects of traditional designs, these observational studies cannot completely exclude the possibility of confounding factors, which may lead to biased associations and conclusions[25]. In addition, the randomized controlled trial (RCT) is immoral and impractical to perform due to the severe negative consequences of COVID-19 and the requirement of abundant human resources and time-consuming follow-up[26]. Estimating whether there is a link of cause and effect between sarcopenia and COVID-19 is urgently necessary. If the link of causation between sarcopenia and COVID-19 can be clarified, maybe more novel measures can be conducted to prevent the development of sarcopenia in COVID-19 patients; meanwhile, the patients with sarcopenia infected with COVID-19 can also get more beneficial care and treatment.

Under this circumstance, Mendelian randomization (MR) is an advanced study to assess the causal connection between sarcopenia and COVID-19. MR analysis uses genetic variants as instrumental variables (IVs) of exposures to evaluate the causality of exposure factors and outcomes[27]. Compared to observational studies, MR analysis can efficiently eliminate confounding factors and identify influencing factors of a certain outcome[28]; for the reason that genetic variations are assigned at random at conception, the confounding factors may not affect the connection between genetic variants and outcomes [27]. Furthermore, compared to RCT, the majority of the open-access data utilized in MR analysis comes from extensive genome-wide association studies (GWAS)[28], which avoids medical ethical issues and has no use for extensive human resources but expands its scope and power in statistics.

In the current study, we utilized a bidirectional two-sample MR study to evaluate the causal relationships of sarcopenia and COVID-19, which may benefit the formulation of strategies to promote the care and treatment of patients with sarcopenia during the COVID-19 pandemic.

2 Materials and methods

2.1 Study design

In the present study, we utilized two-sample MR studies to evaluate the causal relationship between sarcopenia and COVID-19. We chose four measures of sarcopenia, which included appendicular lean mass (ASM), left-hand grip strength (LH), right-hand grip strength (RH) and usual walking pace (WP). For COVID-19, we selected COVID-19 infection, COVID-19 hospitalization, severe COVID-19 as measures. Additionally, that body mass index (BMI) as a confounding factor, IVs of WP adjusted for BMI were used for further study of the causal connection between COVID-19 and WP.

2.2 Data Sources and single-nucleotide polymorphism (SNP) Selection

2.2.1 GWAS of sarcopenia

Genetic association of four measures of sarcopenia, including ASM, LH, RH and WP, were retrieved from the IEU[29], which included 450, 243, 461, 026, 461, 089 and 459, 915 participants, respectively (Supplement **Table S1**). The independent genetic variants of WP adjusted for BMI were retrained from the BMI-adjusted GWAS, including 450, 967 individuals of European ancestry from the UK Biobank[30]. The corresponding genetic information of SNPs about 3 different types of COVID-19 infection was reviewed and collected in the sarcopenia consortium, respectively.

2.2.2 GWAS of COVID-19

We got the data on COVID-19 from the COVID-19 host genetics initiative GWAS (Release 5)[31]. All of the participants in the data that we chose were from the European population. We evaluated the causal

connection between 3 different types of COVID-9 and sarcopenia, including COVID-19 infection (total participants = 1, 683, 768), COVID-19 hospitalization (total participants = 1, 887, 658) and severe COVID-19 (total participants = 1, 388, 342) (Supplement**Table S1**).

2.2.3 SNP Selection

We screened SNPs that had a strong connection with exposure factors ($P < 5\times10^{-8}$) from the GWAS data of exposure. We eliminated linkage disequilibrium (LD) between SNPs using a clustering process ($R^2 < 0.001$ and clumping distance = 10, 000 kb) and SNPs having a minor frequency of alleles were removed (MAF < 0.01) to ensure the results were practicable and undisturbed. The SNPs we selected in exposure GWAS were matched with the GWAS data of outcomes. If SNPs cannot be found in the GWAS data of outcomes, the proxy SNPs with significant LD ($r^2 > 0.8$) were employed. Finally, once the palindrome SNPs were excluded, the rest of the SNPs were chosen as IVs.

2.3 Statistical analyses

In the current research, we estimated the causal association between sarcopenia (including ASM, LH, RH, WP and WP adjusted for BMI) and COVID-19 (including COVID-19 infection, COVID-19 hospitalization and severe COVID-19) using four complementary methods, which included inverse variance weighting (IVW), MR-Egger, weighted and weighted median. Meanwhile, we evaluated the potential level pleiotropy of IVs using MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and MR-Egger regression[32, 33]. Additionally, the MR-PRESSO analysis was also used to find abnormal values in IVs[33]. If MR-PRESSO detected a significant horizontal pleiotropy, it should be removed and then repeat MR-PRESSO and MR-Egger tests to eliminate the horizontal pleiotropic SNP. After that we detected and quantified the heterogeneity among IVs utilizing Cochran's Q statistic[34]. To ensure the accuracy of causal association estimation, SNPs that significantly affect the outcomes were identified and removed using leave-one-out sensitivity analysis. There are five measures of sarcopenia (ASM, LH, RH, WP and WP adjusted for BMI) and three measures of COVID-19 (COVID-19 infection, COVID-19 hospitalization and severe COVID-19) in this study, therefore the Bonferroni correction was performed to adjust the results and$P$ -value less than 0.0042 (0.05/4*3) was considered statistically significantly[35, 36]. All statistical analyses were performed using the package "TwoSampleMR" and "MRPRESSO" in R version 4.1.1.

3 RESULTS

3.1 Instrumental Variables (IVs) selection

3.1.1 IVs of sarcopenia

Following the clumping procedure, 690 SNPs, 157 SNPs, 176 SNPs, and 57 SNPs were shown to be closely related ($P < 5\times10^{-8}$) to ASM, LH, RH, and WP, respectively, and no LD was screened out. The MAF of the SNPs aforementioned was at least 0.01.

There were 16 IVs of ASM which were identified as palindromic SNPs in all COVID-19 outcomes and removed. There were 71 SNPs of ASM which were not present in COVID-19 infection GWAS data, but only 18 of them were substituted by their proxy SNPs. 96 SNPs of ASM were absent in COVID-19 hospitalization GWAS data while 29 of them were supplanted by their proxy SNPs. In severe COVID-19 GWAS data, 67 SNPs of ASM cannot be found, and 13 SNPs were replaced by proxy SNPs. No proxy SNPs for the rest of the SNPs can be found in the outcome GWAS data. Ultimately 621 IVs of ASM on COVID-19 infection, 607 IVs of ASM on COVID-19 hospitalization and 620 IVs of ASM on severe COVID-19 were included in the MR analysis (Supplementary **Table S2**).

As palindromic SNPs were identified, 3 IVs of LH (rs72977282, rs3959716, rs35054365) were removed in all COVID-19 outcomes. 8 SNPs of LH were not detected in COVID-19 infection GWAS data and 9 SNPs of LH were not found in both COVID-19 hospitalization and severe COVID-19 GWAS data. While only 5 SNPs (rs112485536, rs13356200, rs113315602, rs56060323, rs8101782) were replaced by their proxy SNPs (rs67833811, rs10940168, rs60080738, rs10507644, rs7258994), and no proxy SNPs for other SNPs can be

found. Ultimately 151 IVs of LH on COVID-19 infection and 150 IVs of LH on both COVID-19 hospitalization and severe COVID-19 were included in the MR analysis (Supplementary **Table S3**).

There were 8 IVs of RH which were identified as palindromic SNPs in all COVID-19 outcomes and removed. 5 SNPs of RH failed to appear in COVID-19 infection GWAS data, and 6 SNPs of RH in both COVID-19 hospitalization and severe COVID-19 GWAS data, respectively. But 2 SNPs of RH (rs13356200, rs113315602) in all three types of COVID-19 GWAS data were displaced by their proxy SNPs (rs7711053, rs60080738) and no proxy SNPs for other SNPs can be identified. Ultimately 163 IVs of RH on COVID-19 infection, 161 IVs of RH on COVID-19 hospitalization and 165 IVs of RH on severe COVID-19 were included in the MR analysis (Supplementary**Table S4**).

As palindromic SNPs were identified in all COVID-19 outcomes, the IV of WP, rs11881338, was removed. Ultimately 56 IVs of WP were included in the MR analysis (Supplementary **Table S5**).

3.1.2 IVs of WP adjusted for BMI

Following the clumping procedure, 14 SNPs were shown to be highly related ($P < 5\times10^{-8}$) with WP adjusted for BMI and no LD were screened out. The MAF of the SNPs aforementioned was at least 0.01. All SNPs were found in COVID-19 infection, COVID-19 hospitalization, and severe COVID-19 GWAS data, and no palindromic SNP was found (Supplementary **Table S6**).

3.1.3 IVs of COVID-19

Following the clumping procedure, 7 SNPs, 5 SNPs and 8 SNPs were shown to be highly related ($P < 5\times10^{-8}$) with COVID-19 infection, COVID-19 hospitalization, and severe COVID-19 respectively, and no LD was screened out. As palindromic SNPs identified, rs757405, rs12482060 of COVID-19 infection, rs35081325 of COVID-19 hospitalization and rs35081325 of severe COVID-19 were removed. Ultimately 5 IVs of COVID-19 infection, 2 IVs of COVID-19 hospitalization and 4 IVs of severe COVID-19 were included in the MR analysis (Supplementary **Table S7-S9**).

3.2 Causal relationship between sarcopenia and COVID-19

3.2.1 ASM on COVID-19

From the IVW results, higher ASM increased the risk to infect COVID-19 (OR = 1.044, 95% CI: 1.001,1.089, $P = 0.044$). However, the impact of COVID-19 infection vanished after applying the Bonferroni correction. No discernible impacts of ASM on COVID-19 hospitalization (OR = 0.970, 95% CI: 0.888,1.060, $P = 0.506$) and severe COVID-19 (OR = 0.988, 95% CI: 0.859,1.137, $P = 0.867$) were observed in the current research (**Figure 1** and Supplementary **Table S10**).

3.2.2 LH on COVID-19

The IVW results suggested that higher LH was strongly linked to a higher probability of developing severe COVID-19 (OR = 1.733, 95% CI: 1.072,2.802, $P = 0.025$), but the causal relationship disappeared after applying the Bonferroni correction. Furthermore, no connections between LH and COVID-19 infection (OR = 1.147, 95% CI: 0.963,1.365, $P = 0.123$), as well as COVID-19 hospitalization (OR = 1.147, 95% CI: 0.837,1.573, P = 0.393), were causative (**Figure 1** and Supplementary**Table S11**).

3.2.3 RH on COVID-19

The results revealed that higher RH can increase the probability of severe COVID-19 (OR = 1.620, 95% CI: 1.009,2.603, $P = 0.046$), but the impacts faded away after applying Bonferroni correction. Meanwhile, no discernible impacts of RH on COVID-19 infection (OR = 1.154, 95% CI: 0.985, 1.351, $P = 0.076$) and COVID-19 hospitalization were observed in the current research (OR = 1.271, 95% CI: 0.943,1.714, $P = 0.115$) (**Figure 1** and Supplementary**Table S12**).

3.2.4 WP on COVID-19

The IVW results indicated that faster WP decreased the risk of all types of COVID-19 (COVID-19 infection: OR = 0.469, 95% CI: 0.326,0.676,P = 4.82E-05; COVID-19 hospitalization: OR = 0.247, 95% CI: 0.122,0.502, P = 1.11E-04; severe COVID-19: OR = 0.120, 95% CI: 0.046,0.314, P = 1.53E-05), which persisted after Bonferroni correction (**Figure 1** and Supplementary **Table S13**).

3.2.5 WP adjusted for BMI on COVID-19

The IVW results displayed that there were no causal effects of WP adjusted for BMI on COVID-19 infection (OR = 0.717, 95% CI: 0.380, 1.351, P = 0.303), COVID-19 hospitalization (OR = 0.367, 95% CI: 0.115, 1.171, P = 0.090) and severe COVID-19 (OR = 0.220, 95% CI: 0.030, 1.627, P= 0.138) (**Figure 1** and Supplementary **Table S14**).

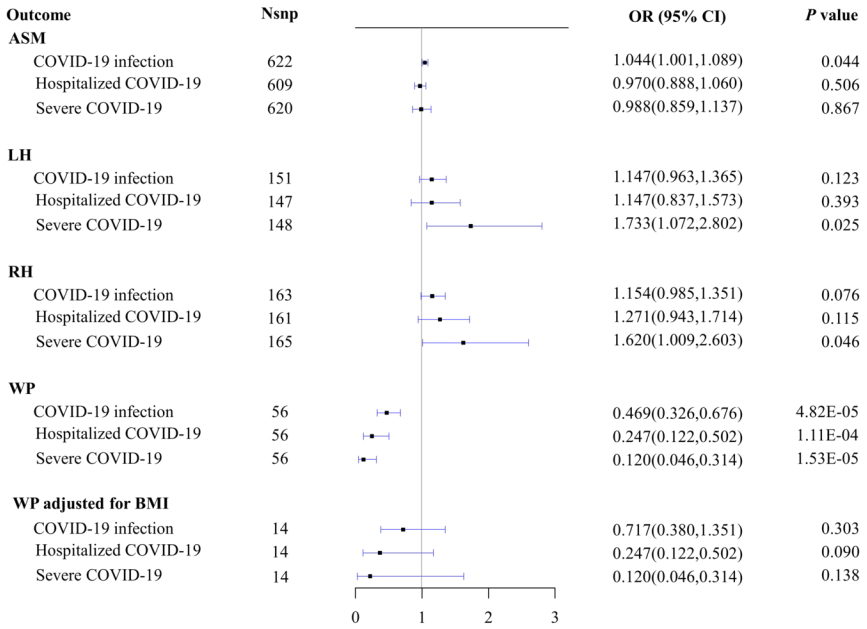

Figure 1: Mendelian randomization (MR) estimate results of sarcopenia on COVID-19.

Abbreviations: ASM: appendicular lean mass; LH: left-hand grip strength; RH: right-hand grip strength; WP: usual walking pace.

3.2.6 COVID-19 infection on sarcopenia

From the IVW results, COVID-19 infection may decline the occurrence of ASM (OR = 0.970, 95% CI: 0.947,0.993, P = 0.011), but the effect disappeared after applying Bonferroni correction. Moreover, no connections were present between COVID-19 infection and LH (OR = 1.013, 95% CI: 0.988,1.039, P = 0.311), RH (OR = 1.018, 95% CI: 0.998,1.039, P = 0.073) and WP (OR = 0.987, 95% CI: 0.968,1.006,P = 0.184) (**Figure 2** and Supplementary **Table S15**).

3.2.7 COVID-19 hospitalization on sarcopenia

The IVW results suggested that COVID-19 hospitalization was strongly correlated with the enhancive RH (OR = 1.009, 95% CI: 1.000,1.018,P = 0.039), but the effect vanished after applying Bonferroni correction. And no discernible impacts of COVID-19 hospitalization on ASM (OR = 0.988, 95% CI: 0.972,1.003, P = 0.124), LH (OR = 0.996, 95% CI: 0.984,1.009, P = 0.589) and WP (OR = 0.990, 95% CI: 0.977,1.002, P = 0.114) were observed (**Figure 2** and Supplementary **Table S16**).

3.2.8 Severe COVID-19 on sarcopenia

According to the IVW results, ASM (OR = 0.990, 95% CI: 0.977,1.003,P = 0.114), LH (OR = 0.998, 95% CI: 0.991,1.005, P = 0.601), RH (OR = 1.005, 95% CI: 0.999,1.011, P = 0.135) and WP (OR = 0.994, 95% CI: 0.987,1.001, P = 0.086) did not appear to cause the severe COVID-19 (all $P > 0.05$) (**Figure 2** and Supplementary **Table S17**).

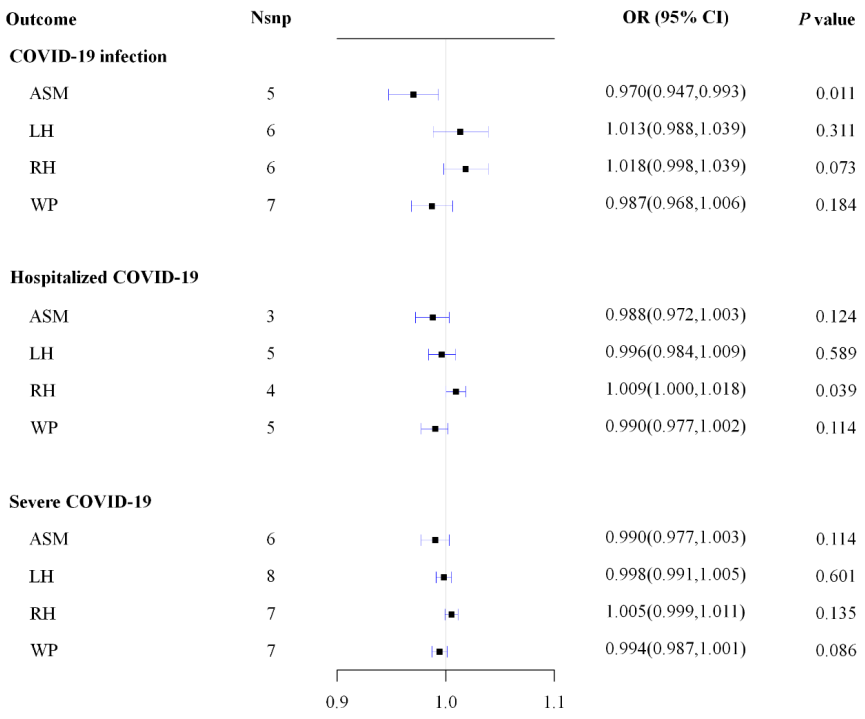

Figure 2: Mendelian randomization (MR) estimate results of COVID-19 on sarcopenia.

Abbreviations: ASM: appendicular lean mass; LH: left-hand grip strength; RH: right-hand grip strength; WP: usual walking pace.

3.3 Pleiotropy and Sensitivity Analysis

Heterogeneity was observed among the IVs of ASM on severe COVID-19 (Q = 709.239, P = 0.005), IVs of LH on COVID-19 infection (Q = 186.904, P = 0.019), IVs of COVID-19 infection on WP (Q = 13.297, P = 0.039), IVs of COVID-19 hospitalization on LH (Q = 10.107, P = 0.039), IVs of COVID-19 hospitalization on WP (Q = 13.953, P = 0.007), IVs of severe COVID-19 on ASM (Q = 14.177, P = 0.015), and IVs of severe COVID-19 on WP (Q = 13.665,P = 0.034). SNPs with horizontal pleiotropy were defined as outliers with the MR-PRESSO global test, of which Supplementary**Tables S2-S9** were displayed. Then, after outliers were removed, the MR-Egger regression and MR-PRESSO global test revealed that the horizontal pleiotropy between IVs of sarcopenia and COVID-19 were eliminated. And leave-one-out analysis indicated that the outcomes were not caused by any SNPs. The results of the pleiotropic and sensitivity analysis were shown in Supplementary **Tables S10-S17** .

4 Discussion

In this study, we conducted a bidirectional two-sample MR study to explore the causal association between sarcopenia (ASM, LH, RH, WP) and COVID-19. After Bonferroni correction, except for WP, there were no

significant associations observed between ASM, LH or RH and COVID-19. Nevertheless, the causal effect of WP on COVID-19 disappeared after adjusting for BMI.

According to the IVW results, slow WP was significantly associated with an increased risk of COVID-19 infection. Consistent with our study, a prospective study indicated that the illness of patients with COVID-19 infection tended to get aggravated more frequently among patients with fatigue and slow WP[37]. The role of WP in the development of COVID-19 may attribute to the decline in immune function caused by low physical activity and longtime of bed rest during the COVID-19 pandemic[38]. Research indicated that SARS-CoV-2 can survive in host cells by evading the host immune mechanism to cause COVID-19 infection[39]. If the immune function of patients with sarcopenia was declined, not only the symptoms of patients may be aggravated, but also the risk of COVID-19 infection may get increased. Studies found that WP can be influenced by age and BMI[40, 41]. Considering that the GWAS data stratified by age were not available, and BMI can reflect physical conditions including age directly or indirectly, we re-analyzed the causal effect of WP on COVID after adjusting for BMI.

As the results showed, after adjusting by BMI, there was no significant relationship between WP and COVID-19, suggesting that BMI is involved in the effect of WP on COVID-19. As we all know, WP and COVID-19 were both associated with BMI [42, 43], and the causal association between them may be due to the mediating role of BMI. An MR study pointed out that genetically predicted higher BMI is significantly linked with an elevated probability of COVID-19 infection and hospitalization[44]. Another prospective community-based cohort study found a linear increase in the risk of hospitalization and death caused by severe COVID-19 at a BMI above 23 kg/m^2[45]. Furthermore, some studies found that patients with BMI outside the normal range are more susceptible to COVID-19[46, 47]. Moreover, it was also revealed that too high or low BMI usually led to slow WP in patients with COVID-19[42]. It may attribute to the association of adipose tissue with complement system hyperactivation, chronic inflammation and the presence of other complications[48], which damage skeletal muscle. Therefore, we speculate that the effect of WP on COVID-19 may be caused by the role of BMI.

In this study, we failed to figure out the causal effect of ASM, LH or RH on COVID-19. However, a previous observational study indicated that increased hand grip strength was related to shorter severe COVID-19 inpatient stays[49]. In another retrospective observational study, higher hand grip strength was associated with lower COVID-19 severity, which acted as the protective factor for severe COVID-19[50]. Additionally, due to the reduction of muscle mass of the patients with low ASM, the adipose tissue gradually replaced the muscle fibers[13]. The replacement consumes the adipose tissue, which was suggested to be a probable risk factor for COVID-19 infection[43], and it may be helpful to decrease the prevalence of COVID-19. Due to the studies above almost observational studies, the conclusions cannot completely exclude the possibility of confounding factors, which led to the inconsistency.

Furthermore, the reverse MR study showed that there was no connection between COVID-19 and sarcopenia, which differs from the results of others. In a cross-sectional study, it has been proposed that patients with COVID-19 had lower mean hand grip strength values[51]. It may attribute to the strong injurious stimulation of acute severe inflammation caused by COVID-19 infection[38]. Among the various harmful effects of inflammation, the increased concentration of c-reactive protein (CRP), TNF-alpha and IL-6 have been the strongest connection with the reduction of skeletal muscle fibers[52]; and the high level of inflammatory factors may impact the acute changes of the amount, structure and function of skeletal muscles[53], which causes sarcopenia. The results in this study differed from previous studies possibly because these studies were cross-sectional studies, which only found the short-term, reversible and non-pathogenic effects resulting from fatigue caused by COVID-19, rather than the direct causal relationship.

5 Strengths and limitations

There are some strengths in this study. First of all, we selected four measures of sarcopenia, including ASM, LH, RH and WP, to explore the association of sarcopenia and COVID-19 in this study. Additionally, to eliminate the impact of BMI on the association of WP and COVID-19, we used WP adjusted for BMI

to analyze the relationship between WP and COVID-19. However, the GWAS data used in this study all originated from European ancestry, thus it exists a racial heterogeneity and cannot be extrapolated to other races. Furthermore, because the GWAS data was not available, we only adjusted for WP by BMI, but not by other factors, such as age, resulting in limited interpretation of the results.

6 Conclusions

In conclusion, the present study points out the causal relationship between WP and COVID-19 but it may be caused by the mediating role of BMI, thus there is no causal association between sarcopenia and COVID-19.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The publicly available datasets used in the present study are included in the article/Supplementary material.

Conflict of interest statement

All authors affirm that there are no potential conflicts of interest including any financial or commercial ties.

Author contribution statement

Hai-Feng Pan developed the idea and proofread the manuscript. Sha-Sha Tao performed the statistical analysis and completed the manuscript writing. Yi-Qing Xu participated in the literature search and data collection. Xiao-Fan Dai, Yan Zhao, Ling-Qiong Jiang, Yang Fang and Ruo-Di Zhang participated in the creation of the charts and language editing. The submitted version has been viewed by all writers and is now ready for publishing.

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