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RECEIVED 10 February 2023

ACCEPTED 27 April 2023

PUBLISHED 10 May 2023

CITATION

Liu C, Liu N, Zeng Y, Xiao B, Wang P,
Zhou C, Xia Y, Zhao Z, Xiao T and Li H
(2023) COVID-19 and sarcopenia-related
traits: a bidirectional Mendelian
randomization study.
Front. Endocrinol. 14:1162936.
doi: 10.3389/fendo.2023.1162936

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COVID-19 and sarcopenia-related traits: a bidirectional Mendelian randomization study

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Background: Emerging evidence suggested that coronavirus disease 2019 (COVID-19) patients were more prone to acute skeletal muscle loss and suffer sequelae, including weakness, arthromyalgia, depression and anxiety. Meanwhile, it was observed that sarcopenia (SP) was associated with susceptibility, hospitalization and severity of COVID-19. However, it is not known whether there is causal relationship between COVID-19 and SP-related traits. Mendelian randomization (MR) was a valid method for inferring causality.

Methods: Data was extracted from the COVID-19 Host Genetic Initiative and the UK Biobank without sample overlapping. The MR analysis was performed with inverse variance weighted, weighted median, MR-Egger, RAPS and CAUSE, MR-APSS. Sensitivity analysis was conducted with MR-Egger intercept test, Cochran's Q test, MR-PRESSO to eliminate pleiotropy.

Results: There was insufficient result in the MR-APSS method to support a direct causal relationship after the Bonferroni correction. Most other MR results were also nominally consistent with the MR-APSS result.

Conclusions: Our study first explored the causal relationship between COVID-19 and SP-related traits, but the result indicated that they may indirectly interact with each other. We highlighted that older people had better absorb enough nutrition and strengthen exercise to directly cope with SP during the COVID-19 pandemic.

KEYWORDS

COVID-19, sarcopenia, mendelian randomization, long COVID-19, aging

Introduction

The coronavirus disease 2019 (COVID-19) has evolved into an ongoing global pandemic affecting more than 600 million people, resulting in nearly 7 million deaths (1). Age, concurrent frailty and comorbidities were associated with higher risk of being positive for COVID-19, hospitalized and mortality (2). Meanwhile, accumulating evidence

suggests that COVID-19 survivors could experience various sequelae, mainly including weakness, arthromyalgia, depression, anxiety and memory loss (3). Due to the complicated pathogenesis of COVID-19, the extremely challenging pandemic has forced people to live with COVID-19, which means it is important to evaluate the relevance between COVID-19 and other comorbidities.

Sarcopenia (SP) is the loss of skeletal muscle mass associated with aging which causes an involution of muscle strength, and/or low physical performance (4). Skeletal muscle-related traits have been widely reported in both acute COVID-19 and post-acute sequelae of COVID-19 (5). Recent findings have shown that higher grip strength was associated with a lower risk of COVID-19 hospitalization and a better prognosis (6, 7). Another study reported that there was no significant difference in grip strength among COVID-19 patients with different severity after 12 weeks (8). A retrospective study showed that an acute skeletal muscle loss was evident in consecutive hospitalized patients with COVID-19 compared with those without COVID-19 and contributed to poor clinical outcomes (9). COVID-19 patients with SP had a higher number of persistent symptoms than patients without SP, but that was not statistically significant (10). These observational studies show that there appears to be a correlation between COVID-19 and SP, but it is inconsistent. These results also made it elusive to assess the causal relationship between COVID-19 and SP-related traits.

Mendelian randomization (MR) is a valid approach to infer possible causality between exposure and outcome, reducing bias from confounding factors and reverse causality in epidemiological studies (11). In the present study, we performed a two-sample MR to assess the potential causal effect between COVID-19 and SP-related traits using instrumental variables (IVs) from the summary genome-wide association study (GWAS) datasets. Overall, Results obtained in this study may help for identify the role of SP in the pandemic to reduce infection and attenuate clinical symptoms. It can also provide new insight into dealing with the post-acute sequelae of COVID-19 to treat or prevent the persistence of these long-lasting symptoms.

Materials and methods

Study design

The MR analysis was performed to explore the causality between COVID-19 and SP-related traits. In the forward MR analysis, COVID-19 was considered as the exposure and SP-related traits were considered as the outcome, whereas the reverse MR analysis investigated SP-related traits as the exposure and COVID-19 as the outcome. The following 3 main assumptions were satisfied (1): the IV is tightly associated to exposure; (2) the IV is not related to any confounder of the exposure-outcome connection; (3) the IV can only affect the outcome *via* the exposure (11).

Data source

In this MR study, GWAS summary statistics for COVID-19 phenotypes were extracted from the COVID-19 Host Genetic

Initiative (HGI) (Round 5) (12). COVID-19 phenotypes included severity (4,792-1,054,664), hospitalization (8,316-1,549,095), susceptibility (3,2494-1,316,207). The COVID-19 cases were diagnosed by laboratory confirmation or by electrical health records (using physician notes or ICD), or self-reported COVID-19 infections from the patients. Severe COVID-19 cases were defined as patients who died or required respiratory support (including bilevel positive airway pressure, continuous positive airway pressure, intubation, or high-flow nasal cannula). The controls were defined as the individuals enrolled in the cohorts and not included as cases. The COVID-19 related data was retrieved from the European population except the UK Biobank participants. The data and more information can be found online.

All the GWAS summary statistics for SP-related traits were extracted from the UK Biobank. UK Biobank is a large-scale biomedical database and research resource, globally accessible to approved researchers undertaking vital research into the most common and life-threatening diseases, containing in-depth genetic and health information from 500 000 UK participants (13). Appendicular lean mass (ALM) has been proposed as a validated and reliable indicator of muscle mass in older adults (14). ALM was quantified by appendicular fat-free mass using the bioelectrical impedance analysis with 450,243 UK Biobank individuals and adjusted by appendicular fat mass and other covariates (15). Grip strength has been widely recognized as a significant indicator of SP (16). The hand grip strength was measured with a calibrated device in a simple and non-invasive way and adjusted for hand size (17). The UK Biobank grip strength data was adjusted for age, age², sex, sex × age, and sex × age² (13), including 461,089 individuals of European descent for right hand grip strength and 461,026 individuals for left hand grip strength (18). The summary-level statistics of walking pace were also obtained from the UK Biobank, including 459,915 individuals of European ancestry (18).

The genetic IVs of COVID-19 and SP-related traits were retrieved from publicly available database without sample overlapping. Ethical permission was not applicable to this study. More details for phenotype and previously ethical approval can be found in the original publications or GWAS (12, 15, 18).

MR analysis

Independent single nucleotide polymorphisms (SNPs) at the genome-wide significance level ($p < 5 \times 10^{-8}$) were selected as IVs for exposure (clumping $r^2 = 0.001$ and kb = 10,000) (19). Related data of IVs were also extracted from the outcome datasets without proxies. After harmonizing each pair of the exposure and outcome datasets, the inverse variance weighted (IVW) model were conducted to assess the causality. The IVW method can provide the most accurate and stable estimation of causal effects when all IVs were valid without directional pleiotropy (20). MR-Egger intercept test was employed to evaluate horizontal pleiotropy (21). MR pleiotropy residual sum and outlier (MR-PRESSO) was conducted to identify and obtain corrected results by removing pleiotropic IVs (22). After that, The IVW method was reperformed

to assess the robustness. Several sensitivity analyses were also performed, including weighted median estimation, MR-Egger regression, MR Robust Adjusted Profile Score (RAPS). The weighted median method could control the Type 1 error rates and provide consistent causal estimates when more than 50% IVs were valid and enrolled (23). MR-Egger regression could test IVs with considerable pleiotropy and heterogeneity, whereas this approach had poor statistical power and required larger sample size (21). RAPS could tackle the idiosyncratic pleiotropy even for up to hundreds of weak IVs (24). Heterogeneity across these selected IVs was assessed by Cochran's Q statistic. F statistic was calculated to test the strength of genetic IVs and genetic IV with F statistics > 10 was statistically considered as a strong instrument to minimize bias. The proportion of variance explained was also measured.

Actually, a small subset of SNPs were included as IVs for causal inference due to the strict inclusion and exclusion criteria, especially for COVID-19. MR Causal Analysis Using Summary Effect Estimates (CAUSE) and MR Accounting for Pleiotropy and Sample Structure simultaneously (MR-APSS) were employed to improve statistical power in the analysis, mainly by relaxing the threshold to utilize more IVs instead of only IVs at the genome-wide significance level (25, 26). Compared with other methods, the CAUSE method could avoid more false positives and calculate the shared (non-causal) effect, accounting for correlated pleiotropy induced by confounders or unmeasured shared factors. The q value was also calculated as an estimate of the proportion of pleiotropic variants (25). Default parameters were used in the CAUSE procedures ($p < 5 \times 10^{-3}$) (https://jean997.github.io/cause/ldl_cad.html). MR-APSS was a recently proposed method in 2022, accounting for sample structure as a major confounding factor including cryptic relatedness, population stratification, and sample overlap (26). We employed the same parameters as used in an originally example recommended by the authors ($p < 5 \times 10^{-5}$) (https://github.com/YangLabHKUST/MR-APSS/blob/master/MRAPSS_Rpackage_Tutorial.pdf).

Concerning multiple testing of COVID-19 and SP-related traits, we conservatively adjusted the p-values after the Bonferroni correction ($p = 0.05/12 = 4.17E-03$). The MR analyses were conducted with the R packages "MungeSumstats", "TwosampleMR", "CAUSE", "MRAPSS" in the R statistical software (Version 4.1.3).

Results

Stage 1: a bi-directional two-sample MR analysis

In the forward MR analysis, we analyzed the causal effect of COVID-19 on SP-related traits. The IVW results suggested that susceptibility, hospitalization and severity of COVID-19 had no causal effect on ALM, right hand grip strength, left hand grip strength and walking pace after the Bonferroni correction (Table 1; Figure 1). Consistently, the weighted median, the RAPS, the MR-Egger, the CAUSE, the MR-APSS methods further strengthened the hypothesis that COVID-19 was not a causal risk factor for SP-

related traits (Table 2). Notably, several results indicated the nominal causality of COVID-19 on SP-related traits using the IVW and the RAPS methods, contradicting the results with the CAUSE, the MR-APSS methods. The median shared effect ranged from -0.04 to 0.03 in the CAUSE methods, suggesting rarely bias induced by horizontal pleiotropy. The low q indicated poor correlation between genetic effects of COVID-19 on SP-related traits.

In the reverse MR analysis, similar results were identified in the five MR tests, reflecting that SP-related traits had no causal effect on COVID-19 after the Bonferroni correction (Tables 3, 4). The median shared effect ranged from -3.02 to 0.36, meaning bias induced by pleiotropic variants.

Stage 2: sensitivity analysis

To evaluate the robustness of the above results, extensive sensitivity analyses were performed, including Cochran's Q test, MR-Egger intercept test, MR-PRESSO global test, and F statistics (Table 5). The Cochran's Q test identified 2 pair of the exposure and outcome datasets so that a random-effects model was applied for them. After removing outliers detected by MR-PRESSO (Supplementary Table 1), we only observed significantly horizontal pleiotropy of walking pace on hospitalization in MR-Egger intercept test. All the F statistics of selected IVs were above than 10, indicating that they were valid enough to minimize potential bias. The proportion of variance explained grew with the increasing IVs, especially in the MR-APSS, the CAUSE methods (Supplementary Table 2). Details of IVs were provided in Additional Tables.

Discussion

Based on the MR results in our analysis, we conservatively summarized that there was insufficient evidence to determine a causal link between COVID-19 and SP-related traits after the Bonferroni correction. Most MR results were also nominally consistent with the conclusion. We performed the first bi-directional two-sample MR analysis to evaluate causal relationship between COVID-19 and SP-related traits, using the MR-APSS method.

Actually, several studies with related themes were reported. Three MR studies indicated that genetic evidence did not support a significant causal effect between COVID-19 and telomere length (27–29), although the cohort study in UK Biobank showed that shorter telomere length was associated with higher risk of adverse COVID-19 outcomes (29). A MR study including 261,000 older participants estimated that telomere length would not affect grip strength, sarcopenia, or falls (30). Telomere length did not occupy a unique position in the causal relationship between COVID-19 and SP-related traits. Another three MR studies suggested that physical activity had no causal effect on COVID-19 outcomes after the Bonferroni correction, but the results nominally contradicted each other (31–33). Meanwhile, the observational study also reported a

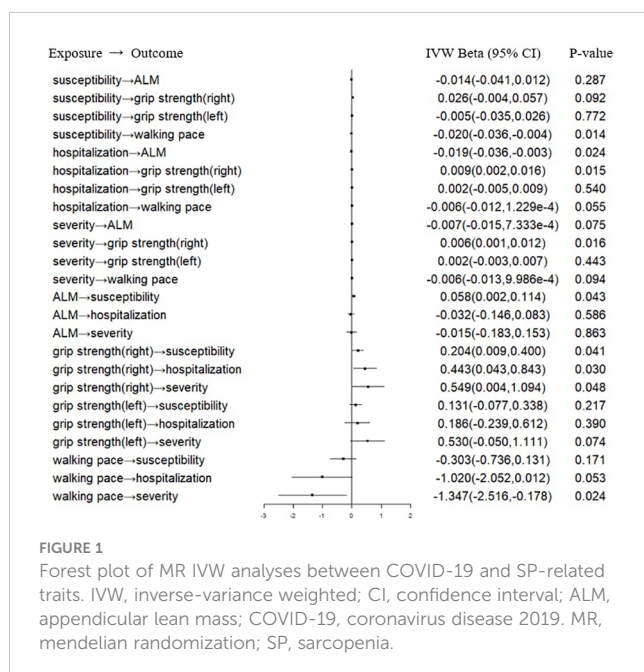
TABLE 1 Primary mendelian randomization estimates of COVID-19 on sarcopenia-related traits.

Exposures	Outcomes	IVW		Weighted median		MR-Egger		RAPS	
		Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
susceptibility	ALM	-0.014(-0.041, 0.012)	0.287	-0.013(-0.043, 0.017)	0.381	-0.010(-0.079, 0.059)	0.821	-0.014(-0.043, 0.014)	0.314
susceptibility	grip strength (right)	0.026(-0.004, 0.057)	0.092	NA	NA	NA	NA	0.026(-0.007, 0.060)	0.123
susceptibility	grip strength (left)	-0.005(-0.035, 0.026)	0.772	NA	NA	NA	NA	-0.005(-0.037, 0.028)	0.787
susceptibility	walking pace	-0.020(-0.036, -0.004)	0.014	-0.010(-0.030, 0.010)	0.311	0.006(-0.064, 0.077)	0.877	-0.016(-0.036, 0.004)	0.110
hospitalization	ALM	-0.019(-0.036, -0.003)	0.024	NA	NA	NA	NA	-0.020(-0.038, -0.002)	0.032
hospitalization	grip strength (right)	0.009(0.002, 0.016)	0.015	0.008(-3.972e-4, 0.016)	0.062	0.003(-0.013, 0.019)	0.711	0.009(0.001, 0.016)	0.021
hospitalization	grip strength (left)	0.002(-0.005, 0.009)	0.540	4.071e-4(-0.008, 0.009)	0.925	-0.001(-0.018, 0.015)	0.888	0.002(-0.005, 0.009)	0.620
hospitalization	walking pace	-0.006(-0.012, 1.229e-4)	0.055	-0.003(-0.010, 0.004)	0.400	-2.331e-4(-0.014, 0.014)	0.976	-0.006(-0.012, 8.030e-4)	0.087
severity	ALM	-0.007(-0.015, 7.333e-4)	0.075	-0.005(-0.014, 0.005)	0.350	-0.002(-0.032, 0.028)	0.919	-0.007(-0.019, 0.005)	0.269
severity	grip strength (right)	0.006(0.001, 0.012)	0.016	0.007(6.797e-4, 0.013)	0.030	9.228e-4(-0.013, 0.015)	0.899	0.007(0.001, 0.012)	0.019
severity	grip strength (left)	0.002(-0.003, 0.007)	0.443	2.161e-4(-0.006, 0.007)	0.948	-0.002(-0.015, 0.012)	0.806	0.002(-0.004, 0.007)	0.515
severity	walking pace	-0.006(-0.013, 9.986e-4)	0.094	-0.003(-0.008, 0.003)	0.373	0.005(-0.012, 0.023)	0.594	-0.004(-0.011, 0.002)	0.151

NA occurred because only two valid instruments were included in the analysis.

Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.

COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; IVW, inverse variance weighted; MR-RAPS, Mendelian Randomization Robust Adjusted Profile Score. NA, not applicable.



protective effect of objectively measured physical activity on COVID-19 outcomes (33). A meta-analysis of 7 randomized controlled trials showed that exercise could improve muscle mass, muscle strength, and walking speed in 3 months (34). A recent study including 435,504 UK Biobank participants observed a paradoxical result that lean mass index was not associated with COVID-19 phenotypes in a prospective cohort study while lean mass had a significant positive causal effect on COVID-19 outcomes in related MR analysis, which might require more robust MR Methods and better lean mass related data sources (35). Combined, due to ethical and practical constraints, cross-sectional designs and most low-quality randomized controlled trials could only provide correlation rather than causality. Meanwhile, although MR study could evaluate causality, it was also affected by quality of data sources and MR methods. Our MR results so far did not conflict with most findings of related MR studies or RCTs.

Undoubtedly, there were many clinical studies with high quality observed that COVID-19 was associated with acute SP in hospital and SP in long COVID-19 syndrome (9, 10). It was also observed that the presence of SP in the general population was positively correlated with the infection rate of COVID-19 (36), which contributed to poor clinical outcomes. Obviously, they appeared

TABLE 2 Mendelian randomization estimates of COVID-19 on sarcopenia-related traits using the CAUSE and MR-APSS methods.

Exposures	Outcomes	CAUSE			MR-APSS	
		Median causal effect (95% CI)	Median q (CI)	P causal vs sharing	Beta (95% CI)	p
susceptibility	ALM	0.03 (-0.53,0.48)	0.03 (0,0.22)	1	0.081 (-0.397,0.559)	0.740
susceptibility	grip strength (right)	0.01 (-0.16,0.18)	0.04 (0,0.24)	0.94	-0.295 (-0.993,0.404)	0.408
susceptibility	grip strength (left)	0.01 (-0.16,0.18)	0.04 (0,0.24)	0.99	-0.429 (-1.005,0.147)	0.144
susceptibility	walking pace	-0.01 (-0.16,0.13)	0.04 (0,0.23)	0.98	-0.124 (-0.702,0.455)	0.675
hospitalization	ALM	-0.04 (-0.2,0.09)	0.06 (0,0.24)	0.93	-0.069 (-0.735,0.598)	0.840
hospitalization	grip strength (right)	0 (-0.10,0.09)	0.03 (0,0.23)	0.55	-0.098 (-0.455,0.260)	0.593
hospitalization	grip strength (left)	0 (-0.10,0.10)	0.03 (0,0.22)	1.00	-0.257 (-0.592,0.077)	0.132
hospitalization	walking pace	0 (-0.06,0.05)	0.05 (0,0.25)	0.80	-0.045 (-0.306,0.216)	0.735
severity	ALM	0.02 (-0.15,0.07)	0.07 (0,0.26)	0.21	-0.011 (-0.465,0.443)	0.962
severity	grip strength (right)	-0.02 (-0.04,0.02)	0.08 (0.01,0.25)	0.37	-0.023 (-0.274,0.228)	0.858
severity	grip strength (left)	-0.02 (-0.05,0.03)	0.07 (0.01,0.25)	0.98	-0.150 (-0.386,0.097)	0.215
severity	walking pace	-0.01 (-0.04,0.04)	0.05 (0,0.25)	0.47	-0.118 (-0.269,0.034)	0.127

Sharing model better fit for the data in the CAUSE method.

Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.

COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; CAUSE, Causal Analysis Using Summary Effect Estimates; MR-APSS, MR Accounting for Pleiotropy and Sample Structure simultaneously.

TABLE 3 Primary mendelian randomization estimates of sarcopenia-related traits on COVID-19.

Exposures	Outcomes	IVW		Weighted median		MR-Egger		RAPS	
		Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
ALM	susceptibility	0.058 (0.002, 0.114)	0.043	0.082 (-0.012, 0.176)	0.086	0.053 (-0.079, 0.186)	0.430	0.070 (0.009, 0.131)	0.024
ALM	hospitalization	-0.032 (-0.146, 0.083)	0.586	-0.080 (-0.268, 0.107)	0.402	-0.262 (-0.540, 0.016)	0.065	-0.017 (-0.146, 0.112)	0.800
ALM	severity	-0.015 (-0.183, 0.153)	0.863	-0.009 (-0.255, 0.238)	0.945	-0.299 (-0.692, 0.095)	0.138	-0.022 (-0.200, 0.157)	0.814
grip strength (right)	susceptibility	0.204 (0.009, 0.400)	0.041	0.124 (-0.172, 0.420)	0.411	0.342 (-0.406, 1.091)	0.372	0.142 (-0.070, 0.354)	0.191
grip strength (right)	hospitalization	0.443 (0.043, 0.843)	0.030	0.538 (-0.047, 1.123)	0.072	0.276 (-1.272, 1.824)	0.728	0.261 (-0.180, 0.701)	0.246
grip strength (right)	severity	0.549 (0.004, 1.094)	0.048	0.594 (-0.212, 1.400)	0.148	1.347 (-0.678, 3.373)	0.195	0.604 (0.035, 1.173)	0.038
grip strength (left)	susceptibility	0.131 (-0.077, 0.338)	0.217	0.024 (-0.286, 0.334)	0.880	0.288 (-0.586, 1.162)	0.520	0.060 (-0.187, 0.308)	0.632
grip strength (left)	hospitalization	0.186 (-0.239, 0.612)	0.390	0.378 (-0.284, 1.040)	0.263	0.067 (-1.768, 1.903)	0.943	0.186 (-0.282, 0.654)	0.436
grip strength (left)	severity	0.530 (-0.050, 1.111)	0.074	0.570 (-0.291, 1.432)	0.194	1.232 (-1.025, 3.489)	0.287	0.525 (-0.082, 1.133)	0.090
walking pace	susceptibility	-0.303 (-0.736, 0.131)	0.171	-0.238 (-0.881, 0.405)	0.469	1.441 (-0.751, 3.634)	0.205	-0.239 (-0.733, 0.256)	0.344
walking pace	hospitalization	-1.020 (-2.052, 0.012)	0.053	-1.022 (-2.273, 0.229)	0.109	4.373 (-0.413, 9.160)	0.081	-0.988 (-2.003, 0.026)	0.056
walking pace	severity	-1.347 (-2.516, -0.178)	0.024	-1.222 (-2.967, 0.524)	0.170	1.114 (-4.976, 7.204)	0.722	-1.405 (-2.690, -0.119)	0.032

Bonferroni corrected significance level (0.05/12 = 0.004) was used to correct for multiple comparisons. p<0.004.

COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; IVW, inverse variance weighted; MR-RAPS, Mendelian Randomization Robust Adjusted Profile Score.

TABLE 4 Mendelian randomization estimates of sarcopenia-related traits on COVID-19 using the CAUSE and MR-APSS methods.

Exposures	Outcomes	CAUSE			MR-APSS	
		Median causal effect (95% CI)	Median q (CI)	P causal vs sharing	Beta (95% CI)	p
ALM	susceptibility	0.26 (-0.25,0.94)	0.08 (0,0.28)	0.28	0.008 (0.002,0.015)	0.008
grip strength (right)	susceptibility	-0.7 (-6.8,1.99)	0.01 (0,0.18)	1	0.001 (-0.007,0.008)	0.836
grip strength (left)	susceptibility	-1.08 (-6.53,3.57)	0.01 (0,0.16)	0.97	-0.004 (-0.015,0.008)	0.506
walking pace	susceptibility	0.36 (-1.77,2.63)	0.04 (0,0.24)	0.57	0.019 (-0.005,0.043)	0.120
ALM	hospitalization	-0.42 (-7.28,4.85)	0.03 (0,0.2)	1	0.013 (-0.015,0.041)	0.348
grip strength (right)	hospitalization	-0.62 (-10.87,7.35)	0.02 (0,0.2)	1	0.016 (-0.021,0.052)	0.394
grip strength (left)	hospitalization	0.16 (-2.28,2.46)	0.03 (0,0.22)	0.90	0.019 (-0.008,0.046)	0.176
walking pace	hospitalization	-1.25 (-7.62,3.68)	0.03 (0,0.22)	0.75	-0.002 (-0.031,0.026)	0.887
ALM	severity	-1.18 (-11.66,6.27)	0.02 (0,0.2)	1	0.016 (-0.023,0.056)	0.416
grip strength (right)	severity	-0.4 (-4.38,3.2)	0.03 (0,0.22)	0.81	-0.037 (-0.089,0.016)	0.173
grip strength (left)	severity	-2.32 (-8.05,2.36)	0.08 (0,0.32)	0.25	-0.033 (-0.102,0.035)	0.343
walking pace	severity	-3.02 (-11.97,2.81)	0.09 (0,0.33)	0.18	-0.055 (-0.161,0.051)	0.307

Sharing model better fit for the data in the CAUSE method.

Bonferroni corrected significance level ($0.05/12 = 0.004$) was used to correct for multiple comparisons. $p < 0.004$.

COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; CAUSE, Causal Analysis Using Summary Effect Estimates; MR-APSS, MR Accounting for Pleiotropy and Sample Structure simultaneously.

to form a dangerous vicious cycle. However, our MR results did not provide sufficient evidence to support a direct interaction between COVID-19 and SP, so that other factors may participate in this cycle to assist its formation. Malnutrition, reduced activity, distress and anxiety were likely to play indispensable roles in the cycle. Compared to discharged patients, patients with COVID-19 who died had higher nutritional and SP risk, lower albumin and total protein (37, 38). The muscle would atrophy significantly within two days after fixation and progress over the next 5 days (39). Patients with COVID-19 usually stay in hospital for more than 10 days (40, 41). During the acute period of COVID-19, common symptoms included depression mood (32.6%), anxiety (35.7%), insomnia (41.9%) (42). During the lockdown period, malnutrition, reduced activity, distress and anxiety were also prevalent (43–45), which was also positively correlated with susceptibility, hospitalization and severity of COVID-19 (46). These factors might act as competitive confounders in an observational study or mediating factors in a MR study. Cognitive impairment, frailty and other aging-associated diseases had the potential to serve as candidate factors (47, 48). On the basis of these observations and our MR results, we highlighted that older people should pay more attention to prevention, diagnosis, and treatment of SP instead of specific interactions between COVID-19 and SP, which would make it easier to break the dangerous vicious cycle and improve quality of life. In addition, targeting other mediating factors might also play a role. Nutritional supplementation and muscle training could provide significant improvement in muscle function and strength for COVID-19 survivors (49, 50).

In the COVID-19 pandemic, it has been reported that patients with more severe COVID-19 infection had a higher elevated serum creatine kinase level and more prone to rhabdomyolysis (51, 52),

indicating that COVID-19 could cause damage to skeletal muscle. The mechanisms of individual organ damage might involve a systemic inflammatory response (53). In autopsy analysis, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus particles were detected in organs including the heart, liver and kidney (54–56), while SARS-CoV virus particle could not be detected in skeletal muscle in SARS patients (57). Combined our MR results, we prefer that skeletal muscle injury is attributed to systemic inflammation instead of direct virus invasion. Nowadays, most countries and regions stopped requiring SARS-CoV-2 testing in public places, and mandatory quarantine (58). After vaccination, older people can adopt healthy lifestyles by increasing physical activity, improving glycemic control and body weight to reverse the situation in preparation for the next COVID-wave. Obviously, future studies across RCT or basic research from a variety of ethnic backgrounds are required to completely disentangle pathogenic mechanisms and develop effective interventions for attenuate clinical symptoms.

This study is the first bi-directional MR study to evaluate causal relationship between COVID-19 and SP-related traits, using the MR-APSS method. All parameters were set according to recommendations and thresholds were not relaxed. The COVID-19 related data was retrieved from the European population except the UK Biobank participants and the sarcopenia related data was extracted from the UK Biobank, which avoided sample overlapping and reduced bias. Extremely strict parameters and F statistic were used to ensure the validity of IV. CAUSE and MR-APSS were performed to include more IVs to improve statistical power, and consistent results were obtained. Nevertheless, there were several potential limitations in our MR analysis. First, all the data came from the European population therefore our result might only apply

TABLE 5 Sensitivity analysis of the primary causal association between COVID-19 and sarcopenia-related traits .

Exposures	Outcomes	Cochran's Q (P)	MR-Egger (P)	MR-PRESSO (P)	F
susceptibility	ALM	0.975	0.916	0.025	58.413
susceptibility	grip strength (right)	0.780	NA	<0.001	33.786
susceptibility	grip strength (left)	0.683	NA	0.019	33.786
susceptibility	walking pace	0.073	0.511	0.181	51.485
hospitalization	ALM	0.185	NA	<0.001	54.200
hospitalization	grip strength (right)	0.933	0.523	<0.001	88.914
hospitalization	grip strength (left)	0.480	0.680	<0.001	88.914
hospitalization	walking pace	0.476	0.444	0.022	87.276
severity	ALM	0.052	0.705	<0.001	68.426
severity	grip strength (right)	0.858	0.431	0.025	67.269
severity	grip strength (left)	0.697	0.576	0.040	67.269
severity	walking pace	0.028	0.247	0.007	69.587
ALM	susceptibility	0.123	0.945	0.095	101.024
ALM	hospitalization	0.064	0.073	0.022	101.717
ALM	severity	0.006	0.119	0.002	99.158
grip strength (right)	susceptibility	0.141	0.707	<0.001	47.652
grip strength (right)	hospitalization	0.141	0.826	0.019	47.716
grip strength (right)	severity	0.318	0.423	0.256	47.600
grip strength (left)	susceptibility	0.061	0.715	0.041	48.385
grip strength (left)	hospitalization	0.054	0.896	0.073	48.466
grip strength (left)	severity	0.752	0.530	0.764	48.466
walking pace	susceptibility	0.178	0.118	0.195	40.294
walking pace	hospitalization	0.038	0.030	0.039	40.294
walking pace	severity	0.289	0.423	0.321	40.294

NA occurred because only two valid instruments were included in the analysis.

COVID-19, The coronavirus disease 2019; ALM, appendicular lean mass; MR, mendelian randomization; CI, confidence interval; IVW, inverse variance weighted; MR-RAPS, Mendelian Randomization Robust Adjusted Profile Score. NA, not applicable.

to Europeans. Second, it was difficult to completely remove mediation and pleiotropy so that we cannot rule out the possibility that mediating factors mediating the causality between COVID-19 and SP-related traits. Third, though the GWAS data was constantly being updated, better data sources were still required, especially for COVID-19.

Conclusion

The mechanisms between COVID-19 and SP have not yet been fully elucidated. Our MR results did not support a direct causal relationship after the Bonferroni correction, indicating that they may indirectly interact with each other through systemic inflammatory response and other diseases. Our new insights might inform better practices to recognize, evaluate and both prevent and treat SP in the COVID-19 pandemic. We highlighted

that older people should absorb adequate nutrition and strengthen exercise to cope with SP and break the dangerous vicious cycle.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding authors.

Author contributions

CL had the idea and drafted the final manuscript, NL performed data analysis, YZ and BX created the tables. Other authors gave constructive suggestions during the process. TX and HL drafted the final manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Research Project of Human Health Commission (grant number 202204073071).

Acknowledgments

All data used in this study were obtained from openly available databases and consortiums. The authors thank all investigators for providing the data publicly.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2023.1162936/full#supplementary-material>

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