Sarcopenia-related Traits, Body Mass Index and Ovarian Cancer Risk: Investigation of Causal Relationships Through Multivariable Mendelian Randomization Analyses

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Abstract

Objective: This study was aimed at exploring the causal relationships of four sarcopenia-related traits (appendicular lean mass, usual walking pace, right hand grip strength, and levels of moderate to vigorous physical activity) with body mass index (BMI) and ovarian cancer risk, by using univariable and multivariable Mendelian randomization (MR) methods.

Materials and Methods: Univariable and multivariable MR was performed to estimate causal relationships among sarcopenia-related traits, BMI, and ovarian cancer risk, in aggregated genome-wide association study (GWAS) data from the UK Biobank. Genetic variants associated with each variable ($P < 5 \times 10^{-8}$) were identified as instrumental variables. Three methods—inverse variance weighted (IVW) analysis, weighted median analysis, and MR-Egger regression—were used.

Results: Univariable MR analyses revealed positive causal effects of high appendicular lean mass ($P = 0.02$) and high BMI ($P = 0.001$) on ovarian cancer occurrence. In contrast, a genetically predicted faster usual walking pace was associated with lower risk of ovarian cancer ($P = 0.03$). No evidence was found supporting roles of right hand grip strength and levels of moderate to vigorous physical activity in ovarian cancer development ($P = 0.56$ and $P = 0.22$, respectively). In multivariable MR analyses, the association between a genetically predicted faster usual walking pace and lower ovarian cancer risk remained significant ($P = 0.047$).

Conclusions: Our study highlights a role of slower usual walking pace in the development of ovarian cancer. Further studies are required to validate our findings and understand the underlying mechanisms.

Keywords

Body mass index, Mendelian randomization, ovarian cancer, sarcopenia.

Statement of significance

The causal relationship between sarcopenia and ovarian carcinogenesis remains unclear. Our findings support a role of slower usual walking pace in the development of ovarian cancer.

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Introduction

Ovarian cancer ranked among the most prevalent gynecological malignancies in 2018, with 294,414 incident cases and 184,799 deaths globally [1, 2]. Because ovarian cancer frequently has subtle signs and symptoms, most diagnoses occur in advanced disease stages [3]. The prognosis is poor, with an estimated 5-year survival rate of 17% to 29% [4].

Sarcopenia [5], characterized by progressive loss of skeletal muscle mass, strength, and function, is associated with unfavorable outcomes in patients with cancer [6]. Further evidence suggests that sarcopenia may predict unfavorable surgical outcomes and higher risk of mortality in patients with ovarian cancer [7–10]. A recent propensity score-matched cohort study conducted in an Asian population has demonstrated that sarcopenia may be a risk factor for ovarian cancer, and has reported an adjusted incidence rate ratio of 1.43 [11]. Nevertheless, limited evidence is available regarding the link between sarcopenia and ovarian cancer risk. The association between sarcopenia and ovarian cancer risk needs to be thoroughly investigated.

Mendelian randomization (MR) is a widely accepted analytical method used to establish causality in observational studies, particularly in the presence of potential confounding and reverse causation [12, 13]. The MR approach, using instrumental genetic variables, can be applied to elucidate the relationship between sarcopenia and ovarian cancer risk [14]. To our knowledge, no investigation to date has examined the potential causal links between sarcopenia and ovarian cancer risk.

Therefore, in this study, we sought to conduct both univariable and multivariable MR analyses to investigate the potential causal relationship between traits associated with sarcopenia and ovarian cancer risk, after adjustment for body mass index (BMI). We used data from two independent population-scale genetic databases for this analysis.

Methods

Ethical considerations

This study was approved by the local institutional review boards at the Third Affiliated Hospital of Sun Yat-sen University (approval number [2022]02-220-01). Because the data used for this analysis were in the public domain (UK Biobank data), informed written consent was not required.

Study design and data sources

The instrumental variables used in our analysis were required to satisfy three critical assumptions for MR analyses (**Figure 1**): (i) genetic variants exhibiting strong associations with traits associated with sarcopenia; (ii) genetic variants independent of potential confounding factors; and (iii) genetic variants influencing ovarian cancer risk solely through the risk factor, without involvement in alternative pathways (exclusion restriction assumption) [15, 16].

Both univariable and multivariable MR analyses were conducted. We created genetic instruments for traits associated with sarcopenia and ovarian cancer by identifying genome-wide significant single-nucleotide polymorphisms (SNPs) within the UK Biobank data from participants of European ancestry [17, 18] (https://www.ukbiobank.ac.uk/). The sarcopenia-related traits considered in our analysis were

appendicular lean mass, usual walking pace, right hand grip strength, and levels of moderate to vigorous physical activity. The usual walking pace was self-reported as slow, steady/average, or brisk. We selected the lead SNPs that were associated with these traits and displayed conditionally genome-wide significant associations as the genetic instruments for investigating the causal links between sarcopenia-related traits and ovarian cancer.

Mendelian randomization analyses

Initially, to assess the individual effects of sarcopenia-related traits on ovarian cancer risk, we conducted univariable MR analyses with the inverse-variance weighted (IVW) method. Subsequently, we implemented sensitivity analyses designed to address pleiotropy concerns; these analyses included the weighted median estimator, MR-pleiotropy residual sum, and outlier analysis. To further explore the robustness of our findings and account for potential confounding factors, we performed multivariable MR analyses. We considered all instrumental variables associated with appendicular lean mass, usual walking pace, right hand grip strength, and moderate to vigorous physical activity levels, to determine their independent effects ovarian cancer risk. Additionally, we conducted multivariable MR analyses adjusting for BMI, to avoid potential confounding due to obesity.

Statistical analysis

In both the univariable and multivariable MR analyses, all genetic variants associated with the exposure traits exhibited highly significant associations with ovarian cancer, with a significance threshold of $P < 5 \times 10^{-8}$. A summary of the data sources is presented in **Table 1**.

We used three distinct approaches to assess the causal effects: the weighted median method, IVW method, and MR-Egger method. Notably, the IVW approach was considered the most reliable for MR analyses in this study. Furthermore, we conducted a variety of sensitivity analyses to validate the accuracy of our MR estimates. First, we applied Cochran's Q test to evaluate the heterogeneity among the genetic instruments, with a significance threshold of $P < 0.05$. Second, we used both the MR-Egger regression intercept and MR pleiotropy residual sum and outlier
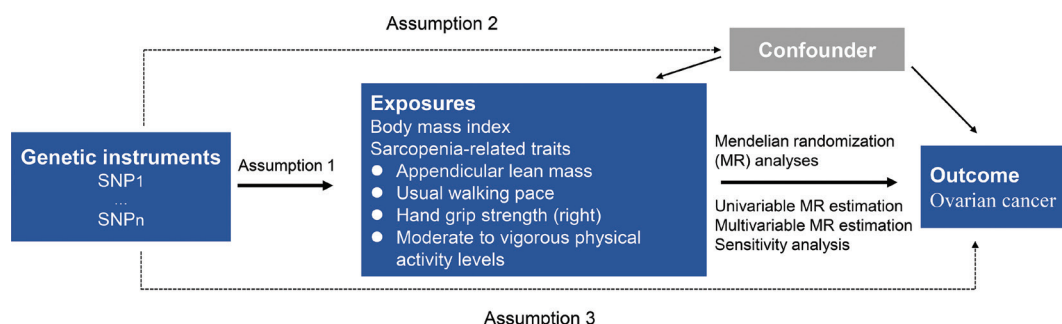

Figure 1 Study design overview. Abbreviations: SNP: single-nucleotide polymorphism; MR: Mendelian randomization.

Table 1 Characteristics of the GWAS Summary Data

Exposures/Outcomes	Ethnicity	Consortium	Total Population	PMID	Number of SNPs	Year
Body mass index	European	NA	461,460	NA	9,851,867	2018
Appendicular lean mass	European	NA	450,243	33097823	18,071,518	2020
Usual walking pace	European	MRC-IEU	459,915	NA	9,851,867	2018
Right hand grip strength	European	MRC-IEU	461,089	NA	9,851,867	2018
Moderate to vigorous physical activity levels	European	NA	377,234	29899525	11,808,007	2018
Ovarian cancer	European	UK Biobank	199,741	NA	9,822,229	2021

(MR-PRESSO) global test to assess horizontal pleiotropy [19]. MR-PRESSO was applied to validate the results obtained from the IVW model, and identify potential outliers and correct for horizontal pleiotropy through their removal. Finally, to estimate and quantify the effects of mediators, and to account for the influence of BMI on our MR estimates, we conducted multivariable MR analyses. We used a linkage disequilibrium threshold of $r^2 = 0.001$ within a distance of 10,000 kb for appendicular lean mass, and a linkage disequilibrium threshold of $r^2 = 0.01$ within a distance of 5,000 kb for three other sarcopenia-related traits in this analysis.

All statistical analyses were performed in R, version 4.1.3 (R Foundation for Statistical Computing). A P value < 0.05 was considered to indicate significant associations.

Results

Univariable Mendelian randomization analyses of sarcopenia-related traits associated with ovarian cancer risk

We conducted a standard IVW analysis alongside MR-Egger analysis, accounting for potential horizontal pleiotropy, to investigate the associations between the effects of SNPs on the four sarcopenia-related traits and the effects of SNPs on ovarian cancer risk. The findings are presented in **Figures 2–4**, **Table 2**, and **Supplementary Tables 1–5**.

Table 2 shows the results of univariable MR analyses examining the relationships among sarcopenia-related traits, BMI, and ovarian cancer. In the univariable analyses with the IVW method, significant causal estimates indicated that higher appendicular lean mass and higher BMI were associated with greater risk of ovarian cancer (odds ratio, 1.001; 95% confidence interval, 1.000–1.002; $P = 0.02$; odds ratio, 1.002; 95% confidence interval, 1.001–1.004; $P = 0.001$) (**Table 2**). In contrast, genetically predicted usual walking pace was inversely associated with ovarian cancer risk (odds ratio, 0.990; 95% confidence interval, 0.981–0.999; $P = 0.03$) (**Table 2**). For the associated SNPs and the related SNPs, no significant associations were detected between right hand grip strength, or moderate to vigorous physical activity levels, and ovarian cancer risk.

Cochran's Q test did not reveal any significant heterogeneity among the genetic instruments (all P values > 0.05; **Table 2**). MR-Egger regression analysis yielded non-significant results, thus indicating the absence of horizontal pleiotropy

(MR-Egger intercept P values > 0.05; **Table 2**). Furthermore, no pleiotropic outliers were identified through MR-PRESSO analyses. The MR-PRESSO global test indicated no evidence of directional pleiotropy.

Figure 2 shows a traditional scatter plot of summary data estimates for the associations between four sarcopenia-related traits (appendicular lean mass, usual walking pace, hand grip strength (right), and levels of moderate to vigorous physical activity), BMI and ovarian cancer risk using different MR methods. The scatter plot shows the outcomes of the MR statistical approach and the causal effects derived from the individual instrumental variables, which were transformed to a log scale for subsequent model fitting. Vertical and horizontal lines centered at each data point show 95% confidence intervals for the associations. The slopes of the lines in the scatter plot represent the log-odds ratio of ovarian cancer risk based on different MR estimators. Additionally, we conducted funnel plot analysis (**Figure 3**) to show the location of directional horizontal pleiotropy for the casual associations between sarcopenia-related traits, BMI and ovarian cancer risk. The inverse variance weighted MR estimate of each SNP indicated no evidence of publication bias (**Figure 3**).

Multivariable Mendelian randomization analyses

When considering mutual adjustments for sarcopenia-related traits and BMI in the multivariable MR analyses, we observed that the genetically predicted usual walking pace showed an inverse association with ovarian cancer risk (odds ratio, 0.989; 95% confidence interval, 0.979–1.000; $P = 0.047$) (**Figure 4**). No evidence from multivariable MR analyses supported roles of appendicular lean mass, right hand grip strength, levels of moderate to vigorous physical activity, and BMI in ovarian cancer development (**Figure 4**).

Discussion

To our knowledge, this study provides the first MR analyses investigating potential causal relationships between genetically determined sarcopenia-related traits and ovarian cancer risk. Our multivariable MR analyses revealed a significant association between genetically predicted slower usual walking pace and ovarian cancer risk, after accounting for BMI. In contrast, we found no sufficient evidence of causal links between other sarcopenia-related traits—i.e.,
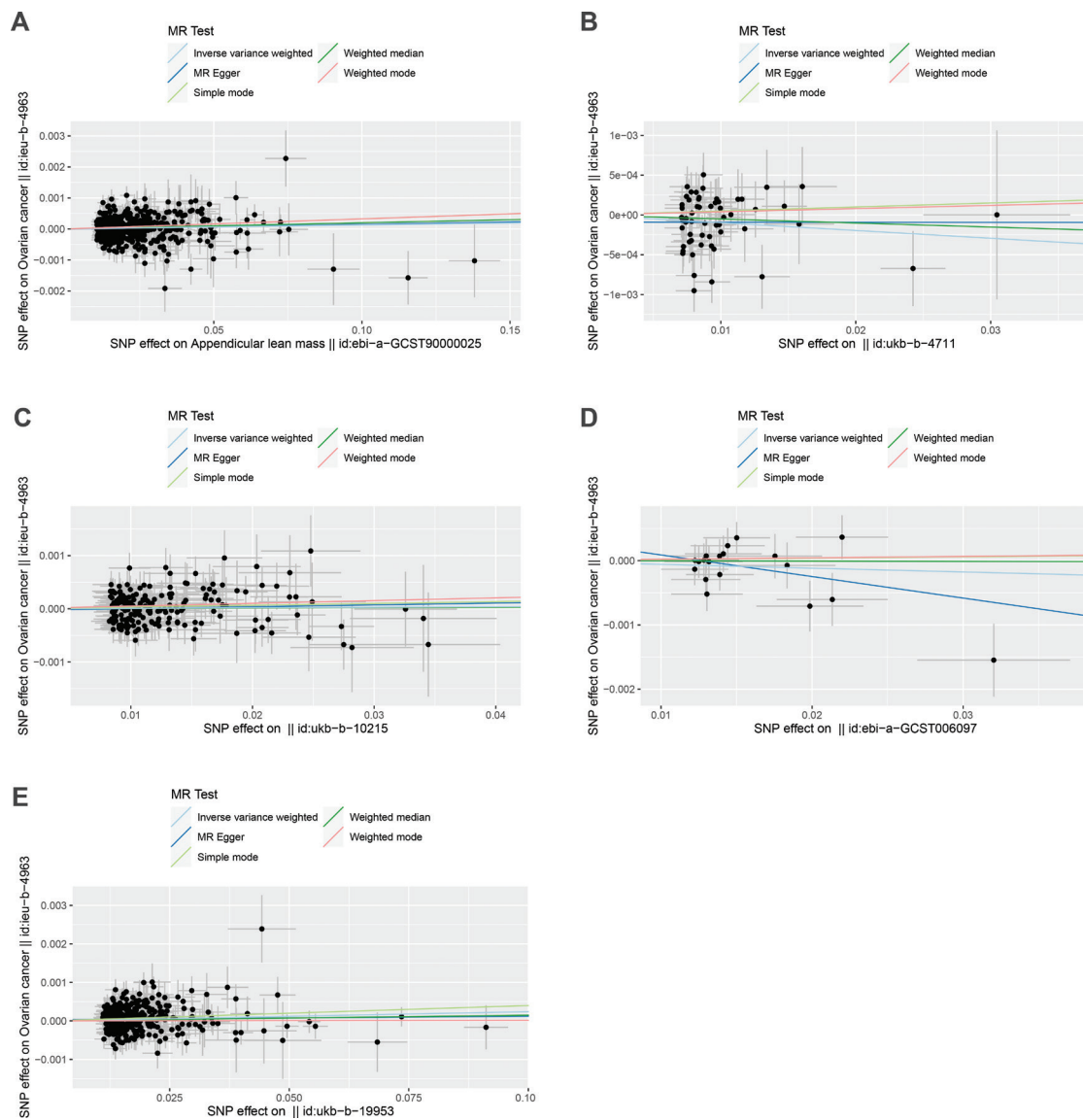
Figure 2 Scatter plot of Mendelian randomization effect size for causal associations between sarcopenia-related traits and ovarian cancer. (A) Appendicular lean mass, (B) usual walking pace, (C) right hand grip strength, (D) moderate to vigorous physical activity levels, and (E) body mass index.

appendicular lean mass, right-hand grip strength, and moderate-to-vigorous physical activity levels—and ovarian cancer.

Sarcopenia has been proposed as a factor significantly contributing to poorer prognosis among individuals with ovarian cancer [20]. As demonstrated in a meta-analysis, a low skeletal muscle index and skeletal muscle radiation attenuation are both significantly associated with diminished overall survival in patients with ovarian cancer (hazard ratio: 1.11, 95% confidence interval: 1.03–1.20, $P = 0.007$; hazard ratio: 1.14, 95% confidence interval: 1.08–1.20, $P < 0.001$) [9]. Additionally, a correlation has been suggested between sarcopenia and the risk of several chronic diseases, such as cardiovascular diseases, and metabolic syndrome [21, 22]. Although substantial evidence supports the role of sarcopenia in poorer outcomes among patients with ovarian cancer, much less is known regarding the influence of sarcopenia on cancer pathogenesis. Kim et al. have reported that sarcopenia and sarcopenic obesity may be associated with

gastric carcinogenesis, thereby potentially serving as novel risk factors for gastric cancer development [23]. Several studies have also reported that sarcopenia might serve as a risk factor for colorectal neoplasia [24–26], in agreement with our findings suggesting that sarcopenia might be a potential ovarian cancer risk factor. However, recent MR analyses investigating the effects of sarcopenia on colorectal cancer by using large-scale GWAS summary data have revealed that greater appendicular lean mass is associated with a higher risk of colorectal cancer—a finding contradicting the conclusion of Kim et al. [27]. The differences in findings across studies might be partly explained by the different study populations; consequently, whether sarcopenia is potential risk factor for cancer pathogenesis remains unclear.

Among the four investigated sarcopenia-related traits, genetically predicted slower usual walking pace was significantly associated with an increased risk of ovarian cancer. This finding may have several explanations. Slower usual walking pace is frequently observed in patients with
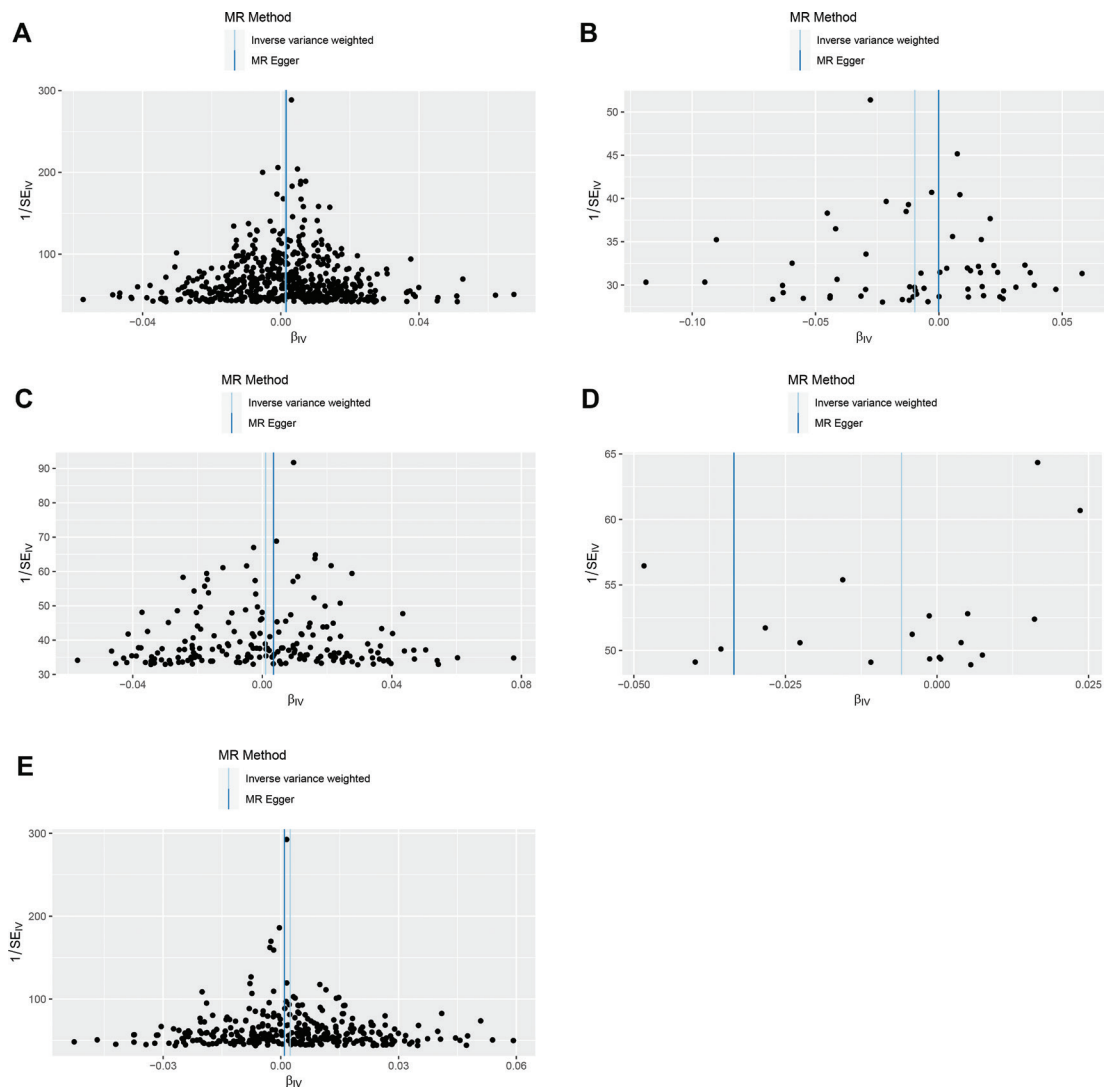
Figure 3 Funnel plot of causal associations between sarcopenia-related traits and ovarian cancer. (A) Appendicular lean mass, (B) usual walking pace, (C) right hand grip strength, (D) moderate to vigorous physical activity levels, and (E) body mass index.

Sarcopenia−related traits	p value		OR (95% CI)
Appendicular lean mass	0.080	■	1.002 (1.000 to 1.004)
Usual walking pace	0.047	⊢■⊣	0.989 (0.979 to 1.000)
Hand grip strength (right)	0.850	⊢■⊣	1.001 (0.994 to 1.008)
Moderate to vigorous physical activity levels	0.260	⊢■⊣	0.996 (0.990 to 1.003)
Body mass index	0.590	■	0.999 (0.996 to 1.002)
		0.95 1 1.05	

Figure 4 Associations of sarcopenia-related traits and body mass index with ovarian cancer in multivariable Mendelian randomization analyses.

greater amounts of body fat, thereby increasing the extragonadal production of estrogen, a factor contributing to the development of ovarian cancer [28]. Moreover, elevated adiposity has been proposed to contribute to elevated insulin-like growth factor 1 (IGF-1) levels, thereby promoting cellular proliferation and regulating the synthesis and availability of sex steroid hormones, which play crucial roles in the development of ovarian cancer [28]. Current evidence regarding the link between ovarian cancer and sarcopenia remains insufficient, and the underlying mechanism warrants further investigation.

The association between appendicular lean mass and ovarian cancer risk observed herein was opposite from our hypothesis. The univariable MR analyses revealed significant

Table 2 Associations of Sarcopenia-related Traits with Ovarian Cancer in Univariable Mendelian Randomization Analysis

Exposures	MR Analysis					Heterogeneity			Pleiotropy	
	MR Method	nSNP	Beta	OR (95% CI)	P Value	Method	Cochran's Q	P Value	Egger-intercept	P value
Appendicular lean mass	MR-IVW	572	0.002	1.001 (1.000–1.002)	0.02	IVW	558.40	0.64	−6.40e-6	0.82
	Weighted median	572	0.001	1.002 (1.000–1.004)	0.03					
	MR-Egger	572	0.002	1.002 (0.999–1.004)	0.24					
Usual walking pace	MR-IVW	59	−0.010	0.990 (0.981–0.999)	0.03	IVW	75.19	0.06	−8.99e-5	0.61
	Weighted median	59	−0.005	0.995 (0.984–1.006)	0.38					
	MR-Egger	59	0.000	1.000 (0.963–1.038)	1.00					
Right hand grip strength	MR-IVW	193	0.002	1.001 (0.998–1.004)	0.56	IVW	165.46	0.92	−3.02e-5	0.68
	Weighted median	193	0.003	1.001 (0.996–1.006)	0.78					
	MR-Egger	193	0.006	1.003 (0.992–1.016)	0.57					
Moderate to vigorous physical activity levels	MR-IVW	19	−0.006	0.994 (0.985–1.004)	0.22	IVW	21.45	0.26	0.000	0.20
	Weighted median	19	0.000	1.000 (0.988–1.012)	0.95					
	MR-Egger	19	−0.034	0.967 (0.927–1.008)	0.14					
Body mass index	MR-IVW	310	0.002	1.002 (1.001–1.004)	0.001	IVW	344.86	0.08	3.06e-5	0.49
	Weighted median	310	0.001	1.001 (0.998–1.005)	0.002					
	MR-Egger	310	0.001	1.001 (0.996–1.005)	0.002					

Abbreviations: SNP: single-nucleotide polymorphism; MR: Mendelian randomization; OR: odds ratio; CI: confidence interval; IVW: inverse-variance weighted.

causal estimates linking greater appendicular lean mass to an elevated risk of ovarian cancer—an effect opposite from that observed between usual walking pace and ovarian cancer, possibly because in our MR analyses, appendicular lean mass was not adjusted for BMI, which has been associated with elevated ovarian cancer risk [29, 30]. After the potential confounding role of obesity was accounted for in multivariable MR analyses, the association between genetically predicted appendicular lean mass and ovarian cancer risk was not significant, thus suggesting no sufficient evidence supporting a role of appendicular lean mass in ovarian cancer development.

Our study has several strengths. We used a recently developed multivariable Mendelian model enabling direct effects of multiple exposures to be assessed simultaneously by incorporating genetic variants from each risk factor into the same model. The multivariable Mendelian model allowed us to account for potential confounding due to sarcopenia-related traits, and to estimate the direct genetic liability for ovarian cancer, thus providing confidence in the robustness of the results and strengthening causal inference. Another study strength was the use of UK Biobank data, with large sample sizes supporting measurement precision. To our knowledge, this study provides the first MR evaluation of the potential causal relationships between genetically determined sarcopenia-related traits and ovarian cancer risk to date.

This study also has several limitations. First, addressing pleiotropy in gene-based MR studies remains challenging, particularly given the considerable variation in the numbers of SNPs associated with various sarcopenia-related traits. To address the potential for unbalanced pleiotropy, we conducted multiple sensitivity analyses, including MR-Egger regression and the MR-PRESSO global test. MR-Egger consistently produced stable results, and the MR-PRESSO analyses detected no pleiotropic outliers, thereby suggesting no evidence of directional pleiotropy. These findings enhance the reliability of the study's conclusions. Second, we did not investigate the direct biological mechanisms mediating the causal relationship between sarcopenia-related traits and ovarian cancer. Third, because of data availability constraints, the generalizability of the study's findings is limited to individuals of European ancestry. Finally, the association between genetically predicted usual walking pace and ovarian cancer risk did not show high significance in multivariable Mendelian model ($P = 0.047$), possibly because of the unbalanced distribution of sarcopenia-related traits. Further validation in larger populations is required to confirm our study's conclusions.

Conclusions

In conclusion, this MR study provides genetic evidence supporting causal inverse associations between sarcopenia and ovarian cancer. These findings emphasize the critical need for early identification of modifiable risk factors for ovarian cancer in early prevention and intervention strategies to mitigate the risk of adverse outcomes. However, further work is required to confirm our findings and elucidate the biological mechanisms underlying this association.

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

Abbreviations

MR, Mendelian randomization
SNP, single-nucleotide polymorphism
IVW, inverse-variance weighted
MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier
BMI, body mass index

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