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ORIGINAL RESEARCH

Association Between Sarcopenia Susceptibility and Cesarean Section: A Study Based on National Health and Nutrition Examination Survey (NHANES) and Mendelian Randomization

Feng Tian[1,2,*], Huiying Pan[3,4,*], Qi Wu[2], Dapeng Jiang[2]

[1]Department of Pediatric Surgery, Suzhou Wujiang District Children's Hospital, Suzhou, Jiangsu Province, People's Republic of China; [2]Department of Oncology (Ward 2), Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China; [3]Department of Obstetrics and Gynecology, International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China; [4]Department of Obstetrics and Gynecology, Shanghai Key Laboratory of Embryo Original Diseases, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dapeng Jiang, Department of Oncology (Ward 2), Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China, Email jdp509@163.com

Objective: To investigate the relationship between sarcopenia susceptibility and cesarean section (CS) and to assess causality using Mendelian randomization (MR).

Methods: Data from 1,316 individuals aged from 20–59 in National Health and Nutrition Examination Survey (NHANES) 2013–2016 were included in the study. The association between sarcopenia and CS was investigated by adjusting for confounders using multivariable linear and logistic regression analysis. Two-sample bidirectional MR was employed to evaluate causal relationships. Genetic data associated with CS (n=462,933) and appendicular lean mass (ALM, n=450,243) were sourced from the largest genome-wide association studies (GWAS). The primary analytical method used was inverse variance-weighted (IVW).

Results: Based on the cross-sectional study, the number of CS was positively correlated with sarcopenia across all adjusted models, whereas no such association was observed with vaginal delivery (VD). Subgroup analyses indicated that these associations were primarily evident among premenopausal women. IVW-MR analysis revealed a significant association between sarcopenia and CS (OR=0.989, 95% CI: 0.984 to 0.994, P<0.001), but there was no statistically causal link in reverse (OR=2.100, 95% CI: 0.012 to 364.040, P=0.779).

Conclusion: A significant positive correlation and potential causal relationship between sarcopenia susceptibility and CS were identified, which highlighted the need for increased attention to sarcopenia in women with a history or high likelihood of CS, including but not limited to muscle health assessments during prepartum and postpartum periods, along with necessary muscle-strengthening interventions.

Keywords: sarcopenia, cesarean section, menopause, gestational diabetes mellitus (GDM), NHANES

Introduction

Sarcopenia, characterized by a decline in skeletal muscle mass, strength, and function, was initially considered age-related. However, updated definitions of the European Working Group on Sarcopenia in Older People in 2018 recognized its potential impact on younger individuals. Variations in diagnostic criteria have led to disparities in reported prevalence, ranging from 12.9% to 40.4%.[1,2] Sarcopenia not only adversely affects disease prognosis but is also associated with impaired growth and development, increased hospitalization frequency, dysregulated fat storage, and compromised immune function. These effects collectively contribute to diminished long-term quality of life, elevated risks of

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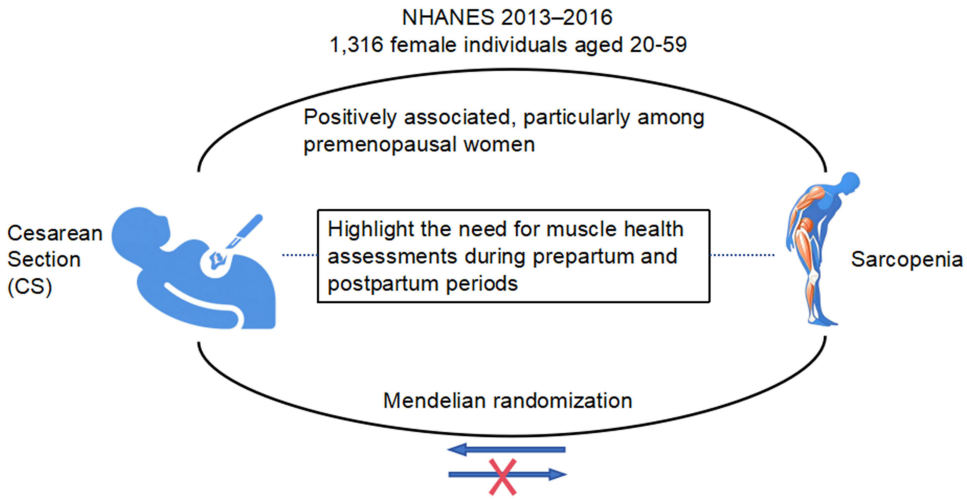
Graphical Abstract



complications, and higher mortality rates among affected patients.[3,4] Previous studies have demonstrated that sarcopenia in gynecologic cancer surgery patients is associated with increased postoperative complications, reduced overall survival, decreased surgical tolerance, and prolonged recovery time.[5,6] However, these studies have predominantly focused on elderly women, who are inherently more prone to comorbidities such as fatigue and cachexia, while limited attention has been given to younger or premenopausal women, particularly pregnant and parturient women.

Despite its broad implications, sarcopenia in younger populations—particularly pregnant women undergoing cesarean section (CS)—remains understudied. With the development and widespread adoption of CS techniques, the rates of CS have shown a generally high trend in many countries. For instance, the rates are 45.9% in Brazil, 25.9% in China, and 30.3% in the United States.[7] In contrast, the World Health Organization (WHO) recommends an ideal CS rate of 15%.[8] The factors influencing CS are multifaceted, encompassing not only medical indications like gestational diabetes mellitus (GDM) but also social circumstances and psychological states. Correspondingly, when compared to vaginal delivery (VD), CS presents distinct clinical characteristics including a prolonged recovery period and specific complications, which may exert long-term effects on maternal health beyond the female reproductive system.[9,10] Notably, current researches on CS have focused on perinatal exercise and rehabilitation,[11] and physical activity during pregnancy has been shown to reduce the incidence of CS, with a more pronounced effect observed in younger pregnant women.[12] However, there remains insufficient attention to the quality and function of overall skeletal muscle mass during the perinatal period, and the relationship between sarcopenia and CS remains unclear. Therefore, this study aimed to systematically explore the association between sarcopenia susceptibility and CS, with a focus on the potential long-term implications for maternal health.

Methods

Study Design

This study comprises two components. First, data from the National Health and Nutrition Examination Survey (NHANES) was obtained to perform regression analyses to explore the relationship between CS and sarcopenia. Second, the causal effects of genetically predicted CS and sarcopenia were evaluated through Mendelian randomization (MR) analysis of summary statistics from the Genome-Wide Association Study (GWAS). This study was approved by the Ethics Committee of Suzhou Wujiang District Children's Hospital, Suzhou (No.2025009).

NHANES is a biennial, nationally representative survey conducted in the United States, encompassing household interviews, physical examinations, and laboratory tests. The study protocol for NHANES was approved by the National

Center for Health Statistics (NCHS), and informed consent was obtained from each participant. Publicly available NHANES data from two cycles (2013–2016) were utilized due to the availability of complete exposure and outcome variables relevant to the study. Among all participants (n=20,146), individuals were excluded based on the following criteria: (1) males and those aged under 18 years (n=13,844); (2) missing data on the number of CS and VD (n=3,874); (3) missing data on ALM and BMI (n=1,076); and (4) pregnancy, lactation at the time of the survey, and missing data on key covariates (n=36). Ultimately, 1,316 participants were included in the final analysis (Figure 1A).

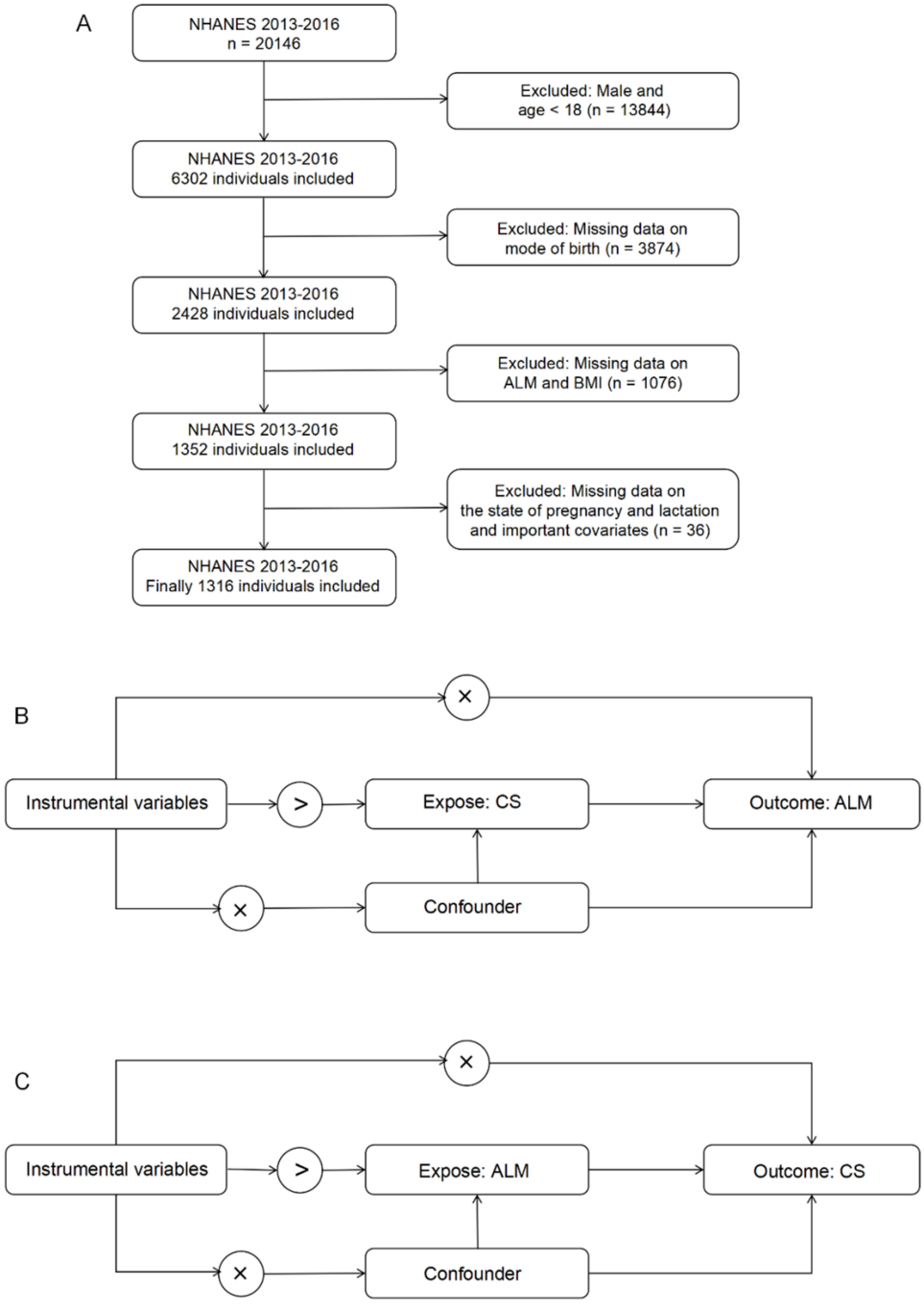


Figure 1 Study design overview: (**A**) Flowchart depicting the sample selection process from NHANES 2013–2016. (**B**) and (**C**) Explanation of the principles behind Mendelian randomization and the necessary assumptions to ensure unbiased estimation of causal effects.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; CS, cesarean section; ALM, appendicular lean mass.

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All the participants completed evaluations of their health and medical status through health assessments conducted in mobile units and structured home interviews. The ethical application of NHANES involving human subjects was approved by the NCHS Research Ethics Review Board, and informed consent was provided by each participant. The questions related to the mode and number of births were asked at the Mobile Examination Center (MEC) by trained interviewers. Both VD and CS were recorded according to the number of times, including stillbirths as well as live births. Pregnancy and lactation status were also reflected in the interviews.

Participants aged 20 to 59 years were eligible for the NHANES 2013 to 2016 dual-energy x-ray absorptiometry (DXA), the primary method for measuring body composition. From the DXA measurement, appendicular lean mass (ALM) was the sum of lean mass for all 4 extremities (arms and legs), and the sarcopenia index (SI) = ALM (in kg)/ body mass index (BMI (kg/m²)) which was used to assess the degree of muscle loss (ML), and sarcopenia was defined using the Foundation for the National Institutes of Health definition: SI <0.512 in women (men, <0.789).[13]

To reduce potential influence of confounding factors, multivariable adjustment models were employed. The study accounted for various covariates, which included age, race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other/multiracial), education attainment (less than 9th grade, 9–11th grade, high school graduate/ GED or equivalent, some college or AA degree, college graduate or above), poverty index ratio (PIR), health hypertension (yes or no), diabetes (yes or no), GDM (yes or no), the concentration of testosterone, estradiol, sex hormone binding globulin (SHBG), 25(OH)D3 in serum, drinking behavior (yes/no, based on at least 12 alcohol drinks in the last year), smoking behavior (Never smoker, Former smoker and Current smoker based on at least 100 cigarettes in life and smoking cessation at the time of the survey) and physical activities. Participants reported their leisure-time physical activity using the Global Physical Activity Questionnaire (GPAQ) and the frequency of moderate recreational activities (MRA) and vigorous recreational activities (VRA) per week was obtained. Both VRA and MRA were defined as activities sustained for at least 10 minutes. The variance inflation factor (VIF) was utilized to assess multicollinearity among the variables.

For the MR analysis, we employed a bidirectional two-sample MR analysis design and utilized publicly accessible summary statistics derived from extensive GWAS datasets. For CS, genetic data deposited in the UK Biobank was obtained, which including 462,933 European participants (dataset: ukb-b-6863). As for sarcopenia, genetic data for ALM was gathered using 450,243 European participants in the UK Biobank Study (dataset: ebi-a-GCST90000025).[14,15] The assumptions of the MR models were illustrated in Figure 1B and C.

Statistical Analysis

Multiple linear regression and binary logistic regression were used to analyze the associations between VD/CS with SI/ sarcopenia, which were evaluated in three progressively adjusted models. The results were reported as regression coefficients (β) and odds ratios (OR) with their corresponding 95% confidence intervals (CI). Given the strong association between age and sarcopenia, the potential interaction between age and the number of CS on sarcopenia was analyzed. Subsequently, considering the potential influence of age, subgroups were stratified by age, and regression analyses were performed again within each subgroup.

As for two-sample MR analysis, genetic instruments were selected using "TwoSampleMR" R package and the primary analytical method employed was inverse variance weighted (IVW). Recognizing that ALM exhibited substantially more candidate single nucleotide polymorphisms (SNPs) than CS, we implemented stringent selection criteria to minimize instrumental variable redundancy while ensuring high SNP specificity and minimizing weak instrument bias. The genome-wide significance threshold was set at $P < 5\times10^{-9}$, the linkage disequilibrium (r^2) threshold was set at 0.0001, and a genetic distance of 1×10^6 KB was used to screen for instrumental variables without linkage effects. F statistics ($F=\beta^2/se^2$) were calculated to assess the strength of each instrument and ensure that each SNP is strongly associated with exposure ($F > 10$). Sensitivity analyses confirmed that a lenient threshold introduced >200 ALM-associated SNPs, whereas further stringency did not significantly alter SNP counts. Additionally, the Cochrane Q test was conducted to examine possible heterogeneity and directional pleiotropy separately to confirm the robustness of the MR analysis findings. Where heterogeneity was detected, a random-effects IVW approach was further employed for the analysis. The pleiotropy assessment was conducted by MR-Egger regression.

R software (version 4.2) was used for data analysis and complex sampling weights was applied to ensure the representativeness of the study population. A significance level of $P < 0.05$ was considered statistically significant.

Results

1,316 female individuals aged 20–59 were included finally. Table 1 presents the baseline characteristics of the entire population and participants categorized by sarcopenia and CS, while the Pearson's Chi-square test revealed a significant association between sarcopenia and CS (P = 0.001). When stratified by sarcopenia, a large number of variables showed

Table 1 Baseline Characteristics Stratified by Sacropenia and CS

	N[a]	Overall	By Sacropenia			By CS		
			Non-Sacropenia	Sacropenia	P Value[c]	Non-CS	CS	P Value[c]
		N = 1316 (100%)[b]	N = 1173 (91%)[b]	N = 143 (9.1%)[b]		N = 674 (53%)[b]	N = 642 (47%)[b]	
Age (years)	1316	43.0 (35.0, 51.0)	43.0 (35.0, 51.0)	45.0 (37.0, 54.0)	0.13	43.0 (35.0, 51.0)	44.0 (35.0, 51.0)	0.8
Race	1316				**<0.001**			**0.022**
Non-Hispanic White		447 (60%)	403 (60%)	44 (54%)		241 (61%)	206 (58%)	
Non-Hispanic Black		318 (15%)	311 (16%)	7 (3.4%)		171 (15%)	147 (14%)	
Mexican American		220 (10%)	161 (8.5%)	59 (28%)		86 (8.0%)	134 (13%)	
Other/multiracial		173 (8.4%)	166 (8.9%)	7 (3.1%)		98 (9.4%)	75 (7.1%)	
Other Hispanic		158 (6.9%)	132 (6.4%)	26 (12%)		78 (6.4%)	80 (7.5%)	
Education.attainment	1316				**0.005**			0.5
Less Than 9th Grade		78 (3.7%)	56 (3.1%)	22 (10%)		37 (2.9%)	41 (4.7%)	
9–11th Grade		152 (8.9%)	126 (8.3%)	26 (14%)		70 (8.6%)	82 (9.2%)	
High School Grade/GED		278 (20%)	246 (20%)	32 (23%)		154 (21%)	124 (18%)	
Some College or AA degree		494 (37%)	448 (37%)	46 (39%)		254 (37%)	240 (37%)	
College Graduate or above		314 (31%)	297 (32%)	17 (13%)		159 (30%)	155 (31%)	0.5
Poverty index	1226	2.55 (1.27, 4.90)	2.75 (1.33, 4.95)	1.79 (1.02, 3.79)	**0.001**	2.59 (1.27, 5.00)	2.50 (1.29, 4.61)	0.5
Testosterone (ng/dL)	1275	20 (14, 28)	21 (14, 28)	18 (15, 24)	**0.044**	20 (15, 28)	20 (14, 27)	0.6
Estradiol (pg/mL)	1259	49 (12, 110)	50 (12, 112)	34 (9, 78)	0.2	54 (13, 110)	44 (10, 110)	0.4
SHBG (nmol/L)	1163	60 (39, 88)	62 (41, 91)	44 (34, 69)	**<0.001**	61 (40, 92)	59 (39, 88)	0.5
25(OH)D3 (nmol/L)	1290	61 (43, 79)	62 (43, 80)	57 (38, 69)	0.022	63 (44, 80)	59 (43, 78)	0.2
Days of vigorous recreational activities per week	1316				0.057			0.14
0		1021 (74%)	896 (72%)	125 (87%)		522 (73%)	499 (75%)	
1		29 (2.6%)	28 (2.8%)	1 (0.4%)		16 (2.7%)	13 (2.4%)	
2		50 (3.7%)	48 (4.0%)	2 (0.8%)		25 (4.5%)	25 (2.7%)	
3		104 (9.3%)	95 (9.5%)	9 (6.6%)		54 (8.7%)	50 (9.9%)	
4		55 (5.8%)	53 (6.3%)	2 (1.1%)		22 (4.6%)	33 (7.1%)	
5		34 (2.9%)	30 (2.8%)	4 (3.8%)		21 (3.6%)	13 (2.1%)	
6		16 (1.3%)	16 (1.4%)	0 (0%)		10 (1.6%)	6 (0.8%)	
7		7 (0.8%)	7 (0.9%)	0 (0%)		4 (1.3%)	3 (0.2%)	

(*Continued*)

Table 1 (Continued).

	N[a]	Overall	By Sacropenia			By CS		
			Non-Sacropenia	Sacropenia	P Value[c]	Non-CS	CS	P Value[c]
		N = 1316 (100%)[b]	N = 1173 (91%)[b]	N = 143 (9.1%)[b]		N = 674 (53%)[b]	N = 642 (47%)[b]	
Days of moderate recreational activities per week	1316				0.3			0.8
0		741 (51%)	647 (50%)	94 (63%)		380 (50%)	361 (52%)	
1		72 (5.5%)	69 (5.9%)	3 (1.7%)		37 (5.7%)	35 (5.3%)	
2		121 (11%)	110 (11%)	11 (7.1%)		64 (11%)	57 (11%)	
3		152 (14%)	138 (14%)	14 (8.5%)		80 (15%)	72 (13%)	
4		81 (7.3%)	74 (7.2%)	7 (8.4%)		34 (6.3%)	47 (8.5%)	
5		94 (7.6%)	86 (7.6%)	8 (6.9%)		52 (8.1%)	42 (7.0%)	
6		15 (0.7%)	12 (0.6%)	3 (1.5%)		6 (0.5%)	9 (0.9%)	
7		40 (3.4%)	37 (3.4%)	3 (3.4%)		21 (3.6%)	19 (3.2%)	
Smoking behavior	1315				0.9			**0.024**
Current smoker		305 (24%)	270 (24%)	35 (24%)		162 (24%)	143 (25%)	
Former smoker		196 (18%)	180 (18%)	16 (15%)		117 (21%)	79 (13%)	
Never smoker		814 (58%)	722 (58%)	92 (61%)		394 (55%)	420 (62%)	
Alcohol consumption	1316				**<0.001**			0.08
Drinker		875 (74%)	799 (75%)	76 (59%)		468 (76%)	407 (71%)	
Non-drinker		441 (26%)	374 (25%)	67 (41%)		206 (24%)	235 (29%)	
Hypertension	1316				**0.012**			>0.9
High blood pressure		386 (25%)	335 (24%)	51 (39%)		195 (25%)	191 (25%)	
Non-high blood pressure		930 (75%)	838 (76%)	92 (61%)		479 (75%)	451 (75%)	
Diabetes	1316				**0.039**			0.1
Diabetes		104 (5.7%)	85 (5.2%)	19 (11%)		41 (4.6%)	63 (6.9%)	
Non-diabetes		1212 (94%)	1088 (95%)	124 (89%)		633 (95%)	579 (93%)	
GDM	1316				0.7			**0.01**
GDM		188 (13%)	165 (13%)	23 (12%)		70 (10.0%)	118 (16%)	
Non-GDM		1128 (87%)	1008 (87%)	120 (88%)		604 (90%)	524 (84%)	

Notes: [a]N not Missing (unweighted). [b]Median (IQR) for continuous; n (%) for categorical. [c]Design-based Kruskal–Wallis test; Pearson's Chi-square test: Rao & Scott adjustment. Bold values indicate statistically significant differences ($P < 0.05$).

Abbreviations: CS, cesarean section; VD, vaginal delivery; SHGB, sex hormone binding globulin; GDM, gestational diabetes mellitus.

significant group differences, including common covariates such as race and poverty index, as well as testosterone and SHBG. In contrast, factors with significant differences between the CS groups included race, smoking, and GDM.

The number of CSs and VDs were each used as independent variables. SI served as the dependent variable in multiple linear regression analyses, whereas the presence or absence of sarcopenia was the dependent variable in binary logistic regression analyses. Three regression models were constructed separately to minimize the influence of confounding variables. Model 1 included only the counts of VD and CS for each. Model 2 was further adjusted for age, education level, race, and poverty index. Model 3 additionally incorporated hypertension, diabetes, smoking, alcohol consumption, sex steroid hormones, and 25(OH)D3. To ensure that the VIF for each variable in the effective model was <10 and the

Table 2 Associations Among CS/VD and SI/Sarcopenia Using Multiple Linear Regression and Binary Logistic Regression

	Multiple Linear Regression			Binary Logistic Regression		
		CS	VD		CS	VD
Model 1 (unadjusted)	β (95% CI)	−0.012 (−0.021, −0.005)	−0.002 (−0.007, 0.003)	OR (95% CI)	1.359 (1.159, 1.593)	0.992 (0.831, 1.184)
	P value	0.004	0.43	P value	<0.001	>0.9
	VIF	/	/	VIF	/	/
Model 2 (partial adjusted)	β (95% CI)	−0.009 (−0.015, −0.003)	0.005 (0.001, 0.009)	OR (95% CI)	1.254 (1.079, 1.460)	0.890 (0.729, 1.086)
	P value	0.007	0.031	P value	0.008	0.265
	VIF	1.488	4.777	VIF	1.832	1.746
Model 3 (fully adjusted)	β (95% CI)	−0.008 (−0.015, −0.001)	0.006 (0.001, 0.011)	OR (95% CI)	1.372 (1.167, 1.613)	0.861 (0.670, 1.107)
	P value	0.047	0.053	P value	0.002	0.265
	VIF	3.436	9.334	VIF	3.048	4.012

Abbreviations: CS, cesarean section; VD, vaginal delivery; SI, sarcopenia index; VIF, variance inflation factor.

VIF for the number of VDs and CSs were <5, education level was excluded from Model 3 of the logistic regression and VRA, MRA and GDM were also not included in the model due to their high collinearity. The results indicated that, across all three models, an increase in the number of CS was associated with a decrease in SI and an increase in sarcopenia, whereas no such association was observed for VD. The effect of age did not show statistical significance in the two groups of models. Details are presented in Table 2.

To further explore the potential impact of age, the interaction between the number of CS and age was assessed. No significant interaction was observed in the linear regression model (β=−0.023, 95% CI: −0.054 to 0.009, P=0.171) while a reverse interaction was detected in the logistic regression model (OR=3.783, 95% CI: 1.860 to 7.657, P=0.001), which resulted in inconsistent findings and may reflect age-related non-linear relationship in sarcopenia development. Based on these findings, plots showing the relationship between age and the proportion of sarcopenia were generated for individuals with and without a history of CSs (Figure 2). The inflection point of the CS group was located at coordinates

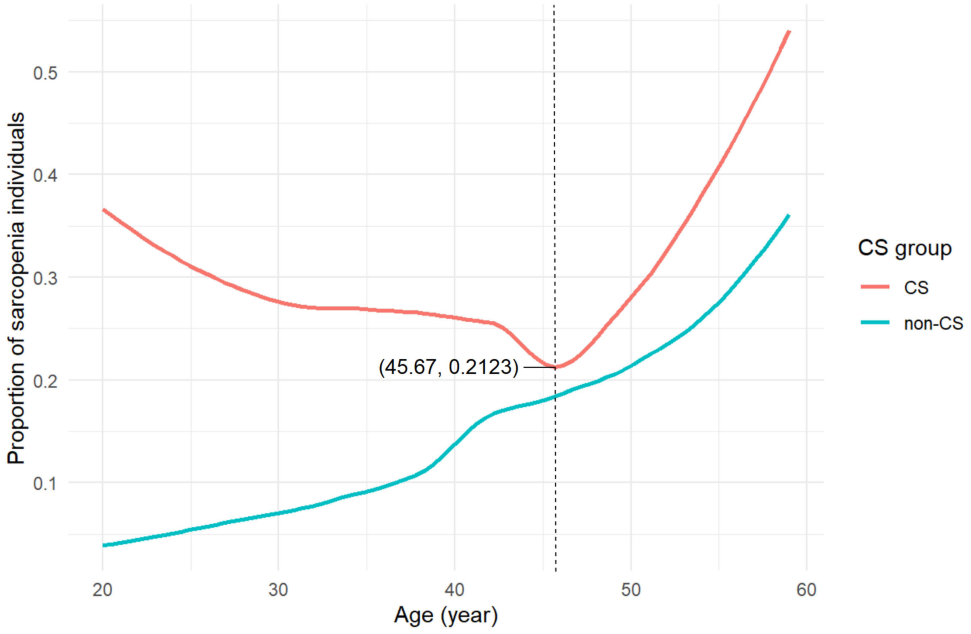

Figure 2 Relationship between age and sarcopenia percentage in groups with and without CS history.
Abbreviation: CS, cesarean section.

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(45.67, 0.2123) and it revealed a distinct difference between the two groups before approximately 45 years of age, which diminished and converged after the age of 45. The inflection point at 45.67 years aligned with the average perimenopausal transition, suggesting that hormonal changes of menopause may attenuate CS-associated sarcopenia risk postmenopause. To further investigate these findings, the entire sample was divided into two subgroups based on age: those aged 45 years and younger, and those older than 45 years. Regression analyses, consistent with the three models presented in Table 2, were performed for CS frequency within each subgroup. The subgroup aged 45 years and younger included 786 individuals, with the remaining 530 individuals allocated to the subgroup aged over 45 years. The subgroup analysis indicated that individuals aged 45 years and younger maintained trends consistent with the overall sample, while the subgroup of those aged over 45 years demonstrated no statistical significance. Detailed results are presented in Table 3.

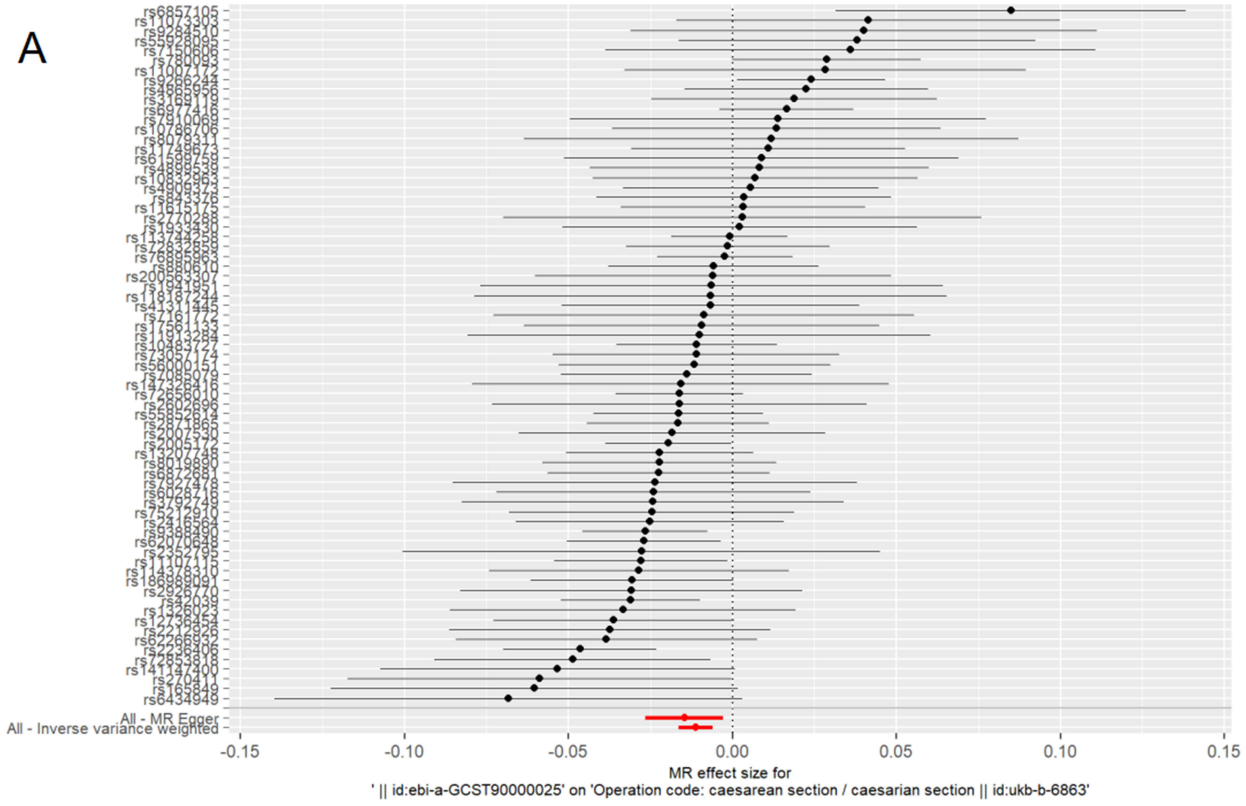
Secondary analyses of covariates found that SHBG demonstrated significant associations in Model 3 of the multiple linear regression model ($\beta = 1.620 \times 10^{-4}$, 95% CI = 4.062×10^{-5} to 2.834×10^{-4}, P = 0.026) among all the individuals. Additionally, in the subgroup of aged > 45 years, SHBG showed a significant correlation in Model 3 of the multiple linear regression analysis ($\beta = 3.710 \times 10^{-4}$, 95% CI: 9.013×10^{-5} to 6.519×10^{-4}, P = 0.027). However, this correlation was not statistically significant in the subgroup of aged ≤ 45 years, and the prediction of sarcopenia showed no statistical significance in the binary logistic model.

In the bidirectional two-sample MR analysis, 73 SNPs were selected as instrumental variables for ALM, and 2 SNPs were selected as instrumental variables for CS. Each SNP had an F-value greater than 10. Given the presence of heterogeneity in the results, a random-effects IVW approach was employed. The IVW analysis revealed a causal link between sarcopenia and CS (OR=0.989, 95% CI: 0.984 to 0.994, P<0.001). However, there was no statistically causal link in reverse (OR=2.100, 95% CI: 0.012 to 364.040, P=0.779). Although MR indicated that the impact of ALM on the risk of CS was relatively minor, the CS rate among sarcopenic patients, after weighted calculation, was 65.2%, which was 45.4% higher than that in the non - sarcopenic group, which suggested that the actual clinical impact of muscle loss may be more significant. Detailed results are shown in Figure 3. The pleiotropy analysis of the model with 73 SNPs showed no evidence of pleiotropy (P = 0.525).

Table 3 Subgroup Analysis: Associations Among CS and SI/Sarcopenia Using Multiple Linear Regression and Binary Logistic Regression (Subgrouping by Age, ≤45 Vs >45 Years)

		Multiple Linear Regression			Binary logistic regression	
		Age ≤ 45	**Age > 45**		**Age ≤ 45**	**Age > 45**
Model 1 (unadjusted)	β (95% CI)	−0.015 (−0.023, −0.007)	−0.010 (−0.023, 0.003)	OR (95% CI)	1.589 (1.329, 1.899)	1.091 (0.816, 1.461)
	P value	<0.001	0.158	P value	<0.001	0.560
	VIF	/	/	VIF	/	/
Model 2 (partial adjusted)	β (95% CI)	−0.009 (−0.017, −0.002)	−0.001 (−0.021, 8.4×10-5)	OR (95% CI)	1.427 (1.127, 1.807)	1.054 (0.849, 1.308)
	P value	0.023	0.093	P value	0.008	0.642
	VIF	1.814	2.401	VIF	3.120	1.362
Model 3 (fully adjusted)	β (95% CI)	−0.009 (−0.017, −0.001)	0.005 (−0.017, 0.007)	OR (95% CI)	1.576 (1.242, 1.997)	1.194 (0.928, 1.535)
	P value	0.046	0.441	P value	0.002	0.187
	VIF	1.842	5.930	VIF	4.255	2.303

Abbreviations: CS, cesarean section; VD, vaginal delivery; SI, sarcopenia index; VIF, variance inflation factor.



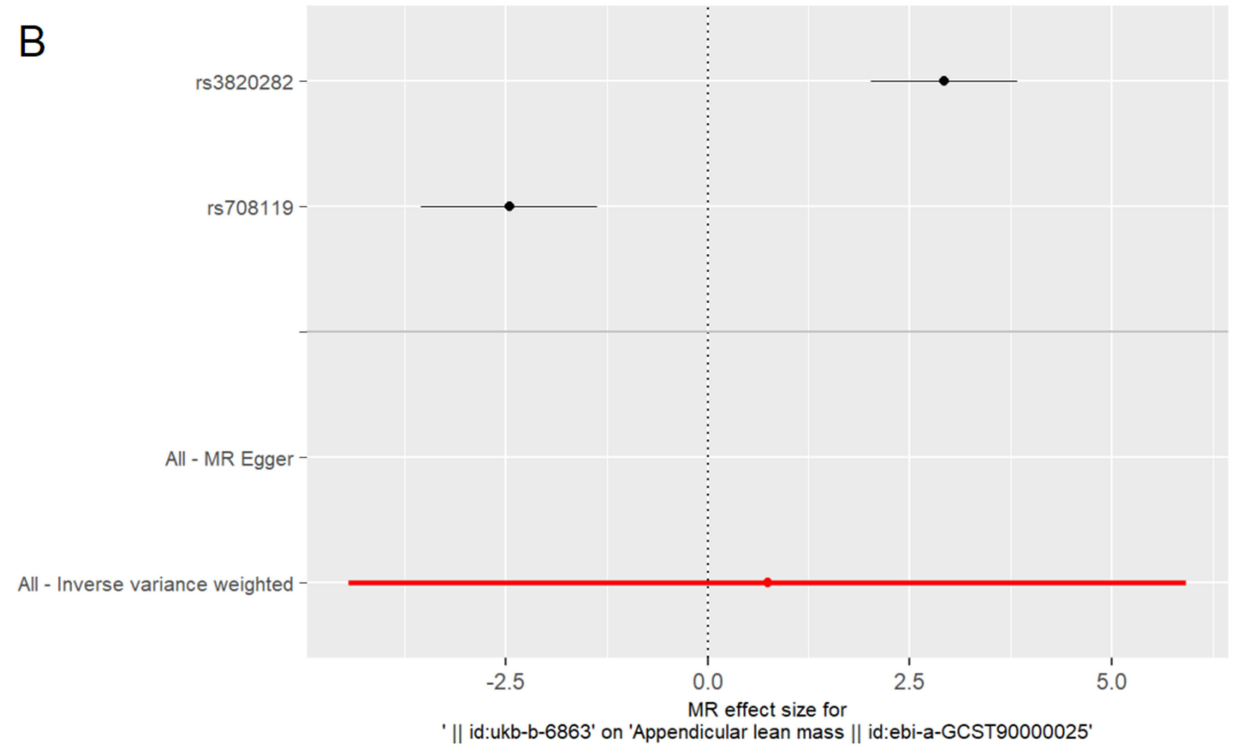


Figure 3 Forest plot demonstrates summary estimates of bidirectional causal relationships between ALM and CS. (**A**) Causality between ALM and CS; (**B**) Reverse causality between CS and ALM.

Abbreviations: ALM, appendicular lean mass; CS, cesarean section.

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Discussion

Sarcopenia is a skeletal muscle disorder characterized by the accelerated loss of muscle mass and function, associated with numerous adverse outcomes, emphasizing the comprehensive assessment of muscle strength, quality, and function.[16] The pathophysiological mechanisms of sarcopenia are complex, involving the interplay of multiple factors and pathways including skeletal muscle protein metabolism, different muscle fiber types, neuromuscular control, vascular dysfunction, extracellular matrix, inflammation and oxidative stress, hormonal changes.[16,17] Recent studies have also gradually revealed that sarcopenia, as a systemic disease, is associated with diseases of various systems to varying degrees, including but not limited to the cardiovascular, diabetic, and gynecological disorders.[6,18,19] Compared with VD, women who had a CS experience were more likely to report extreme tiredness and back pain at 6 months postpartum and at 12 months postpartum.[10] These symptoms, closely linked to sarcopenia, not only reflect its clinical manifestations but also impact treatment adherence and rehabilitation.[20,21] Furthermore, CS is associated with significant alterations in maternal glucose, lipid, and amino acid metabolism, as well as changes in inflammatory responses and hormonal levels. These metabolic and physiological changes may indirectly affect muscle mass and function, potentially leading to long-term systemic impacts on maternal health.[22] However, investigating is particularly challenging due to the complexity of longitudinal follow-up, heterogeneity in postpartum recovery, and the multifactorial nature of conditions such as sarcopenia. Thus, utilizing data from the NHANES and GWAS databases while accounting for methodological considerations, this study not only identified an increased prevalence of sarcopenia among women with a history of CS, but also revealed a potential causal link between genetically influenced sarcopenia susceptibility and CS. These findings not only highlight the need for long-term sarcopenia monitoring and intervention in women with CS history, but also emphasize the crucial role of pre-pregnancy muscular health management to preserve delivery options, which collectively underscore the necessity for comprehensive strategies to protect muscular health throughout women's reproductive lifespan and beyond.

In recent years, sarcopenia has gained increasing attention in younger individuals including children. The histological changes in muscle fibers, neuromuscular regulation, and endocrine-metabolic pathways differ between age-related sarcopenia in the elderly and sarcopenia in younger populations, which highlight that age is not the sole determinant of sarcopenia, suggesting the involvement of other complex factors in its pathogenesis.[23] Despite the relatively low prevalence of sarcopenia in young individuals, its longer duration may lead to more severe long-term health issues.[24] In this study, age distribution suggested that the association between sarcopenia and CS may be primarily concentrated in women before early menopause. Furthermore, the results indicated that among premenopausal women, those who underwent CS had a higher prevalence of sarcopenia, with the risk of sarcopenia showing a positive correlation with the number of CS procedures. As individuals entered the postmenopausal period and gradually transition into old age, these associations became no longer significant. Incorporating the causal relationship assessment from MR analysis, it was found that premenopausal women with sarcopenia susceptibility may have a higher likelihood and proportion of CS. This difference may be primarily attributed to the fact that, after the age of 45, the impact of age and post - menopausal hormonal changes on sarcopenia far exceeds that of the mode of delivery. Additionally, some patients with severe sarcopenia may not survive to the age of 45, which also contributes to it. Furthermore, sarcopenia is associated with congenital factors or childhood conditions, such as congenital heart disease, metabolic disorders, chronic diseases, and physical inactivity during childhood and adolescence.[4,25–27] All these findings stressed the feasibility of early preventive and therapeutic strategies for ML or sarcopenia in younger individuals, where timely detection and management could provide long-term benefits.

An MR study recently demonstrated a significant causal effect of sarcopenia on GDM, whereas no causal influence of GDM on sarcopenia was identified reversely. The study hypothesized that reduced muscle mass may exert its effects through multiple pathways, including inflammatory factors, energy metabolism, and hormonal regulation.[28] In the MECs of NHANES, sarcopenia was assessed based on the status at the time of the survey, while GDM was evaluated retrospectively. Given that age and other factors may have already influenced sarcopenia, this could explain the lack of significant differences observed between sarcopenia and GDM. Common medical factors influencing the decision for CS include fetal factors (such as fetal distress, abnormal fetal presentation, and multiple gestations) and maternal factors (such as gestational hypertension, GDM, contracted pelvis, and uterine scar).[7,29] Combining the trends in Figure 2, where

the prevalence of sarcopenia before menopause increases with age among women without a CS history but decreases with age among those with a CS history, it can be hypothesized that, the decline in muscle mass and function may compromise the physical strength required during childbirth. Additionally, sarcopenia susceptibility may increase the likelihood of CS through pathways such as GDM, with this effect gradually diminishing with age but persisting until menopause.

In secondary analyses, SHBG showed a certain potential to assess muscle mass decline, especially in women older than 45 years old. SHBG is produced and secreted by the liver into the bloodstream. Its concentration is regulated through multiple pathways, including TNF-α, IL-1β, adiponectin, and HNF-4α. SHBG which not only functions in the bloodstream but also accumulates in various tissues like brain, uterus, and testes, binds to sex steroid hormones like androgens and estrogens and modulates their bioavailability, as well as influences the actions of sex hormones.[30,31] A recent study has shown that SHBG levels in women are negatively correlated with low muscle mass, and the role of SHBG appears to be more pronounced in women. This may be attributed to the fact that SHBG influences muscle mass by modulating the bioavailability of estrogens and testosterone, and the impact of estrogens on muscle mass is more direct in women.[32] In addition, the homeostasis of female sex hormones keeps SHBG levels relatively stable before menopause. In the early post-menopausal stage, SHBG levels drop transiently due to estrogen fluctuations. Subsequently, SHBG levels gradually rise under the influence of other hormones and liver metabolism.[33] Given the significant decline in estrogen levels post-menopause, which predisposes women to metabolic disturbances such as insulin resistance and dyslipidemia, and considering that lower levels of SHBG have been associated with an increased risk of various metabolic issues,[34] which are closely linked to the development of sarcopenia.[17] It is speculated that the reduction in SHBG levels in postmenopausal women may reflect an increased risk of metabolic disturbances, which in turn could be associated with a decline in muscle mass. The results of this study indicated that SHBG may better reflect continuous muscle mass decline rather than dichotomous sarcopenia diagnosis. Despite the relatively small effect sizes of SHBG, it holds potential as a supplementary tool for the detection of ML in female populations, especially among postmenopausal women. However, the underlying mechanism still requires more research to be explored.

Postpartum recovery is a multidimensional process that encompasses physical, psychosocial, and emotional health, though standardized assessment guidelines remain lacking.[35] Exercise has a positive impact on the physical and mental health of postpartum women, including cardiovascular health, weight management, pelvic floor function, postpartum depression, overall body image, and self-confidence.[36,37] Compared with VD, CS is associated with delayed recovery, slower return to exercise initiation and intensity, unresolved pain and functional limitations, which may have a greater potential impact on both physiological and psychological aspects.[38,39] Moreover, lifestyle interventions, particularly exercise with a focus on resistance training is recommended as the primary approaches for prevention and improvement on sarcopenia, which has been demonstrated to be safe and effective in older adults and individuals with chronic diseases,[40,41] its role in postpartum CS recovery requires further investigation. MR analysis identified an association between genetically predicted muscle mass (ALM) and lower CS risk, while a bidirectional causality or coexistence relationship between CS and sarcopenia cannot be robustly assessed, leading to a potential feedback loop. In the GWAS database, instrumental variables for ALM far outnumber those for CS, necessitating extremely strict criteria to reduce the number of SNPs, ultimately leaving only two SNPs representing CS. Although pleiotropy was absent (P=0.525), the limited CS SNPs precluded robust reverse-direction MR analysis. Besides, post-CS pain and psychological distress may have a side effect on muscle health via fear of movement, which could further limit physical activity and worsen ML. Although rigorous MR analyses did not find evidence that CS causes changes in muscle mass, NHANES-based research showed that even after adjusting for covariates such as age and race, the number of CS deliveries in premenopausal young women is correlated with both SI and sarcopenia, which suggests that prioritizing the assessment of muscle status in women before childbirth and after CS to mitigate the impact of sarcopenia holds clear potential benefits. These nuanced findings strongly warrant rigorous, long-term prospective investigations to further characterize the temporal relationship between CS and muscle mass dynamics, particularly through detailed tracking of pre- and post-delivery muscle status.

This study has several limitations. First, while NHANES data collection is highly standardized, the retrospective questionnaire of the cross-sectional study could not ascertain the clinical indications for CS, nor the longitudinal muscle

mass changes from pre-pregnancy to postpartum periods, which preclude causal inference about CS's role in sarcopenia development, particularly those without clear medical indications. Second, restricted geographic representation (US/Europe populations) and unmeasured confounders like ethnic-specific factors may limit generalizability. Third, the MR analysis had limited power to detect bidirectional effects due to insufficient instrumental variables for CS (only 2 SNPs). While the primary analysis (ALM→CS) showed significance, the process of proving reverse causality (CS→ALM) may be less than perfect statistically.

Despite these limitations, the study has notable strengths. It represented the first pioneering investigation into the association between CS and sarcopenia, broadening the understanding of CS's long-term impact on maternal health by revealing that sarcopenia may exist both before and after CS, emphasizing the need for early screening and intervention on maternal health. Prenatal muscle assessment or intervention may benefit women during childbirth, premenopausal women with multiple CS deliveries may benefit from routine sarcopenia screening to mitigate long-term musculoskeletal morbidity. It is particularly urgent in high-CS-rate regions where preventive strategies could reduce healthcare burdens. Furthermore, the integration of large-scale observational data with MR analysis not only strengthens the reliability of the cross-sectional findings but also provides robust evidence for a potential causal relationship between sarcopenia susceptibility and CS. This innovative approach sets a foundation for future research to explore the mechanisms underlying this association and to develop targeted interventions for at-risk populations.

Conclusion

A significant positive correlation and potential causal relationship between sarcopenia susceptibility and CS were identified through nationally representative data from the NHANES database and MR analysis, extending from the pre-pregnancy period through menopause. These findings highlight the need for increased attention to sarcopenia in women with a history or high likelihood of CS, including but not limited to muscle health assessments during prepartum and postpartum periods, along with necessary muscle-strengthening interventions, as well as efforts to reduce the incidence of non-medically indicated CS. Further research is warranted to explore the underlying mechanisms and deeper relationships between these two conditions.

Ethical Statement

The data used in this study were obtained from publicly available, free-access sources. The studies were conducted in accordance with the local legislation and institutional requirements. All participants provided informed consent, and the publicly available data have been de-identified. This study was approved by the Ethics Committee of Children's Hospital of Wujiang District, Suzhou (No.2025009). Also, the relevant accession numbers have been included in the manuscript, and further details regarding ethical exemption can be found on the official websites of the respective databases: https://www.cdc.gov/nchs/nhanes/about/erb.html?CDC_AAref_Val=https://www.cdc.gov/nchs/nhanes/irba98.htm, and https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics.

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Disclosure

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