International Journal of Women's Health

Dovepress
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ORIGINAL RESEARCH

Causal Associations Between Sarcopenia and Gestational Diabetes Mellitus

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Introduction: Sarcopenia may affect the onset of gestational diabetes mellitus (GDM). However, the causal relationship between sarcopenia and GDM remains unclear. In this study, we used a bi-directional Mendelian randomization (MR) approach to explore this intricate relationship.

Methods: This study utilized data from FinnGen datasets and genome-wide association studies. A bi-directional MR study was conducted. First, a forward MR analysis evaluated the causality of sarcopenia on GDM risk, with sarcopenia-related traits as exposures and GDM as the outcome. Second, in the reverse MR analysis, we assessed whether GDM influenced sarcopenia-related traits. Finally, sensitivity analysis was conducted to assess the robustness of the MR analysis.

Results: Forward MR analysis revealed that appendicular lean mass (odds ratio [OR] = 1.2182, 95% confidence interval [CI]: 1.1397–1.3021, P < 0.0001), right-hand grip strength (OR= 1.4194, 95% CI: 1.0773–1.8701, P= 0.0128), left-hand grip strength (OR= 1.6064, 95% CI: 1.2829–2.0115, P < 0.0001), and usual walking pace (OR= 3.3676, 95% CI: 1.8769–6.0423, P < 0.0001) were associated with an increased risk of GDM. However, according to the reverse MR results, GDM had no causal effect on sarcopenia. No pleiotropy was observed.

Conclusion: In summary, sarcopenia had a significant causal influence on GDM, while GDM did not causally affect sarcopenia.

Keywords: gestational diabetes mellitus, Mendelian randomization, sarcopenia, appendicular lean mass, hand grip strength, usual walking pace

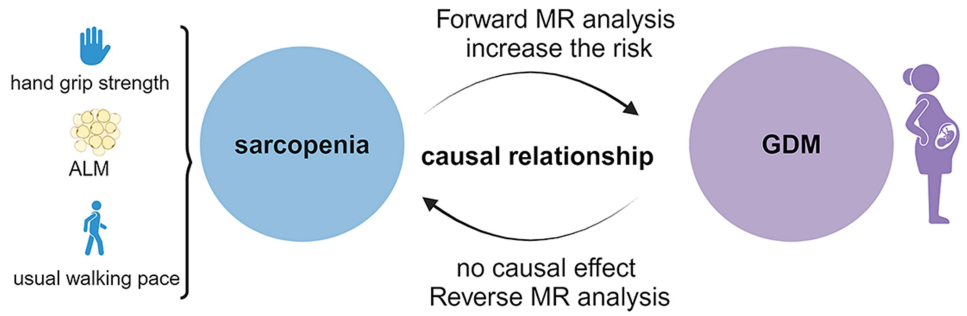
Introduction

Gestational diabetes mellitus (GDM) is a common metabolic disorder that occurs during pregnancy and its incidence is increasing. It is associated with a range of complications affecting both the mother and fetus during pregnancy and childbirth, leading to extensive health and economic burden.[1] Hence, there is increasing importance in recognizing women at risk of GDM. Sarcopenia, a condition characterized by the loss of muscle mass and function, has traditionally been linked to the aging process in the elderly,[2] but it is now acknowledged that the onset of sarcopenia can occur at an earlier stage in life.[3] Sarcopenia is driven by biological changes in muscle structure, hormonal imbalances, and inadequate energy intake.[4]

Muscles play a crucial role in the overall metabolic health, including energy expenditure, insulin sensitivity, and blood glucose stability. Consequently, sarcopenia can have adverse effects on metabolic health, leading to insulin resistance and abnormalities in glucose metabolism. Multiple studies have indicated that sarcopenia is associated with higher fasting blood glucose,[5] insulin resistance,[6] hyperlipidemia[7] and type 2 diabetes mellitus.[8] Type 2 diabetes mellitus is characterized by insulin resistance and abnormal lipid metabolism and may promote the development of sarcopenia. A Mendelian randomization (MR) study explored the causal relationship between sarcopenia and type 2 diabetes mellitus, revealing a bi-directional causal relationship between handgrip strength and type 2 diabetes mellitus as well

Received: 9 October 2024
Accepted: 24 January 2025
Published: 1 February 2025

Graphical Abstract



as between walking pace and type 2 diabetes mellitus. Sarcopenia and type 2 diabetes mellitus may reciprocally exert a substantial causal influence on each other.[9] Another meta-analysis showed an elevated prevalence of sarcopenia in individuals with diabetes. The development of sarcopenia is increased by risk factors such as glycated hemoglobin, diabetic nephropathy, visceral fat area, duration of diabetes, and C-reactive protein.[10]

GDM and sarcopenia have common risk factors. However, the potential causal relationship between sarcopenia and GDM remains unknown. Observational studies have the limitations such as difficulty in establishing causation, selection bias, less control over variables and retrospective data collection challenges.[11] In recent years, MR has emerged as a powerful tool for assessing causal relationships in observational studies.[12] MR leverages genetic variations found in the natural population as instrumental variables to mimic the conditions of a randomized experiment, providing valuable insights into causality.

Therefore, this study sought to employ MR methodology to investigate the causal relationship between genetic variants associated with sarcopenia and GDM. Through this approach, we aimed to enhance our understanding of how sarcopenia may influence the risk of GDM, thereby providing valuable insights into the development of strategies to improve maternal health and pregnancy outcomes through early prevention and intervention.

Materials and Methods

Study Design

In this study, we utilized a bi-directional MR study design, employing two-sample MR methodologies and various genome-wide association study (GWAS) summary level datasets to elucidate the causal relationship between sarcopenia-related traits and GDM risk. Sarcopenia was measured using appendicular lean mass (ALM), right-hand grip strength, left-hand grip strength, and usual walking pace.[2,13]

This study was conducted in two stages to explore the causal association between sarcopenia and GDM. In the first stage, exposure was related to sarcopenia-related traits, with GDM considered as the outcome. In the second stage, GDM was investigated as an exposure, while sarcopenia-related traits were the outcome. A detailed illustration of the study design is shown (Figure 1).

Data Sources for GDM and Sarcopenia

The open GWAS database established by the MRC Integrated Epidemiology Unit and UK Biobank are expansive biomedical databases and research resources.[14,15] The summary-level GWAS data correlated with GDM were obtained from the FinnGen datasets, and the GWAS ID of GDM was finngen_R10_GEST_DIABETES. This dataset included 14,718 GDM patients and 215,592 controls. The GWAS summary data for ALM were derived from a GWAS with 244,730 UK Biobank participants (dataset ID: ebi-a-GCST90000027), with no difference in genetic effects between sexes or among different age strata.[16] We also collected GWAS summary data from the UK Biobank for hand grip strength (right) in 461,089 people

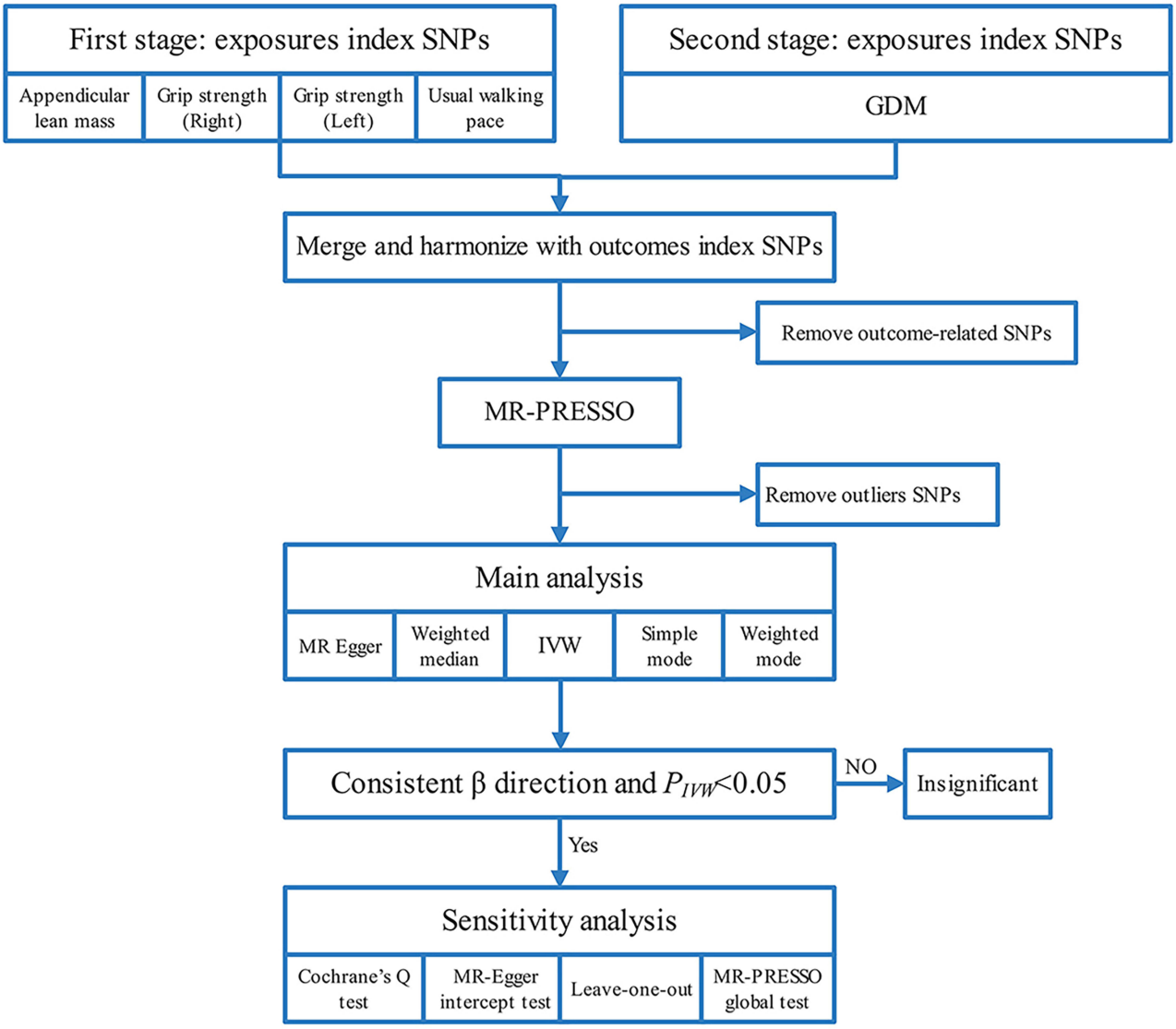


Figure 1 Overall design of the MR analysis in the present study.
Abbreviations: GDM, gestational diabetes mellitus; IVW, inverse-variance weighted; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

(dataset ID: ukb-b-10215), hand grip strength (left) in 461,026 people (dataset ID: ukb-b-7478), and usual walking pace in 459,915 people (dataset ID: ukb-b-4711) (Table 1). The participants of this study were exclusively of European origin.

Selection of Genetic Instruments

To ascertain the causal connection between sarcopenia and GDM, we employed four distinct sets of genetic instruments representing traits of sarcopenia when sarcopenia was present: a) index single-nucleotide polymorphisms (SNPs)

Table 1 Phenotype Source and Description

Phenotype	Consortium	Sample Size	Population	No. of SNPs	GWAS ID
GDM	FinnGen	14,718 cases and 215,592 controls	European	21,298,922	finngen_R10_GEST_DIABETES
Appendicular lean mass	NA	244,730	European	18,164,071	ebi-a-GCST90000027
Grip strength (Right)	MRC-IEU	461,089	European	9,851,867	ukb-b-10215
Grip strength (Left)	MRC-IEU	461,026	European	9,851,867	ukb-b-7478
Usual walking pace	MRC-IEU	459,915	European	9,851,867	ukb-b-4711

Abbreviations: GDM, gestational diabetes mellitus; GWAS, genome-wide association study; SNPs, single-nucleotide polymorphisms.

https://doi.org/10.2147/IJWH.S494910

representing ALM, b) index SNPs representing right-hand grip strength, c) index SNPs representing left-hand grip strength, and d) index SNPs representing usual walking pace. We also explored the genetic instruments representing GDM when GDM was studied as exposure in the second stage of MR analysis.

Genetic instruments were selected according to the following criteria: a) GWAS-correlated P-value $\geq 5\times10^{8}$ as the threshold for SNPs, b) linkage disequilibrium $r^2 < 0.001$, and c) clumping distance < 10 MB as the cut-off value to assess the independent SNPs in linkage equilibrium. Furthermore, we also computed the F value and considered an F value greater than 10 to be sufficiently robust to address any potential issues related to weak instrument bias, ensuring the reliability of the selected SNPs.

In accordance with these recommendations, we initially selected a set of independent SNPs that were strongly associated with each exposure variable before matching in the outcome database. Outcome-related SNPs were removed during harmonization. We utilized the harmonized data function provided by TwoSampleMR (version 0.5.6) to ensure that the effect allele of each SNP was aligned with the corresponding allele of the exposure.[17] Subsequently, using the procedure of MR-PRESSO (version 1.0, 1000 repeated settings), any outlier SNPs were excluded, enabling us to proceed with the MR analysis.

Mendelian Randomization Analysis

We used five distinct MR methods, including random-effect inverse-variance weighted (IVW), MR Egger, weighted median, simple mode, and weighted mode, to account for variant heterogeneity and investigate the potential impact of pleiotropy.

The primary outcome was assessed using the IVW method, whereas the other four methods were used to improve the IVW estimates as they could provide more robust estimates in a broader set of scenarios, despite being less efficient.[18] MR Egger permits all genetic variants to exhibit pleiotropic effects, but it necessitates that these pleiotropic effects are unrelated to the association between the variant and the exposure.[19] The weighted median approach permits the inclusion of potentially flawed instruments, assuming that a minimum of half of the instruments utilized in the MR analysis are reliable.[20] If the direction of β-value in the other four MR methods was inconsistent with the IVW method, the MR results were considered insignificant.

Analysis of Horizontal Pleiotropy and Heterogeneity

To further ensure the reliability of MR causal impact estimates, we performed pleiotropy and heterogeneity analyses. The pleiotropy test function in the two-sample MR package was used to determine whether the SNPs were suitable instrumental variables. Horizontal pleiotropy was evaluated using the MR-Egger intercept test and MR-PRESSO global test.[21] If pleiotropy was not significant ($P > 0.05$), instrumental variables were used. A funnel plot was used to evaluate potential directional pleiotropy. Cochran's Q test was used to assess heterogeneity among the selected instrumental variables.

Statistics

Statistical analyses were conducted using the R software (version 4.3.0), and statistical significance was determined using a two-tailed P-value < 0.05.

Results

Forward MR Analysis

In the first stage of MR analysis, following the removal of outlier SNPs through MR-PRESSO, 358 index SNPs were selected to genetically predict ALM, 146 index SNPs were used to genetically predict right-hand grip strength, 128 index SNPs were used to genetically predict left-hand grip strength, and 50 SNPs were used to predict usual walking pace (Table S1 - S4).

We conducted a comprehensive MR study to investigate genetic predictors of sarcopenia in relation to GDM. The IVW results of ALM (OR= 1.2182, 95% CI: 1.1397–1.3021, P<0.0001), right-hand grip strength (OR= 1.4194, 95% CI: 1.0773–1.8701, P= 0.0128), left-hand grip strength (OR= 1.6064, 95% CI: 1.2829–2.0115, P<0.0001) and usual walking

pace (OR= 3.3676, 95% CI: 1.8769–6.0423, P<0.0001) were found to increase the risk of GDM. The other four MR methods yielded consistent results (Figures 2 and 3A - D). Sarcopenia had a causal effect on GDM.

To evaluate the robustness and reliability of the MR results, Cochran's Q test, leave-one-out analysis, the MR-PRESSO global test, and the MR-Egger intercept test were employed for statistically significant estimates (Table 2 and Figure S1A - D). The results of the MR-PRESSO global test indicated the presence of horizontal pleiotropy in ALM, right-hand grip strength, and usual walking pace. However, it is important to note that all MR-Egger intercept test P-values were > 0.05, suggesting the absence of horizontal pleiotropy. The primary method for evaluating horizontal pleiotropy was the MR-Egger intercept. No outliers were detected in the leave-one-out plot (Figure S2A - D). Heterogeneity was observed in ALM, right-hand grip strength, and usual walking pace, as indicated by Cochran's Q test (P < 0.05), except for left-hand grip strength. Because we employed random-effects IVW as our primary result, the presence of heterogeneity was considered acceptable.

Reverse MR Analysis

In the second stage, we explored the effect of GDM on sarcopenia after removing outlier SNPs using MR-PRESSO. We identified nine index SNPs of GDM on genetic prediction of ALM, eight index SNPs of GDM on genetic prediction of right-hand grip strength, nine index SNPs of GDM on genetic prediction of left-hand grip strength, and ten index SNPs of GDM on genetic prediction of usual walking pace (Tables S5 - S8). The IVW analysis showed that GDM had no causal effect on ALM (β= −0.0057, 95% CI: −0.0395–0.0282, P= 0.7424), right-hand grip strength (β= 0.0098, 95% CI: −0.0036–0.0231, P= 0.1509), left-hand grip strength (β= 0.0125, 95% CI: 0.0018–0.0232, P= 0.0225), and usual walking pace (β= −0.0158, 95% CI: −0.0282 - −0.0035, P= 0.0119) (Table 3).

The Cochran's Q test, MR-Egger intercept test, MR-PRESSO global test and leave-one-out analysis were performed to verify the reliability of the reverse MR analysis results (Table 4). The MR-PRESSO global test and MR-Egger intercept test results had P-values of > 0.05, indicating that no horizontal pleiotropy was detected. According to the leave-one-out analysis, eliminating one SNP did not change the directionality of the results, except for the GDM estimates in ALM (Figure S3A - D). All Cochran's Q tests had P-values > 0.05, except for ALM and left-hand grip strength, which had P-values < 0.05.

Discussion

Our study provides compelling evidence to support a causal relationship between sarcopenia and GDM development. The MR analysis revealed a robust association between genetic variants linked to sarcopenia and increased risk of GDM, shedding light on the potential significance of muscle health during pregnancy. Our study investigated the previously

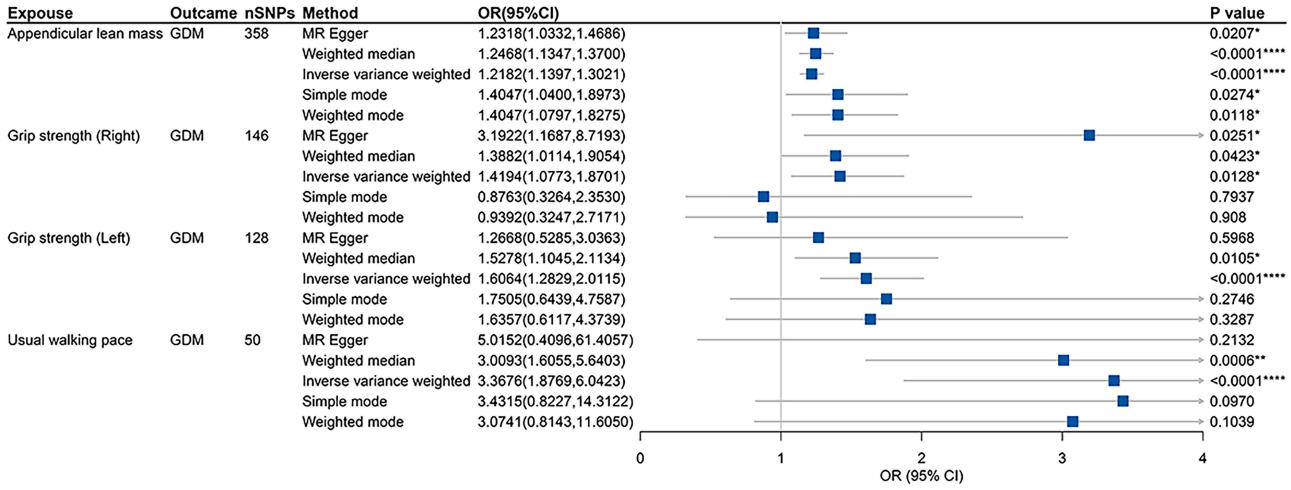


Figure 2 Multivariate MR analyses of sarcopenia and GDM. P<0.05:*, P<0.01:**, P<0.001:***, P<0.0001:****.
Abbreviations: GDM, gestational diabetes mellitus; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

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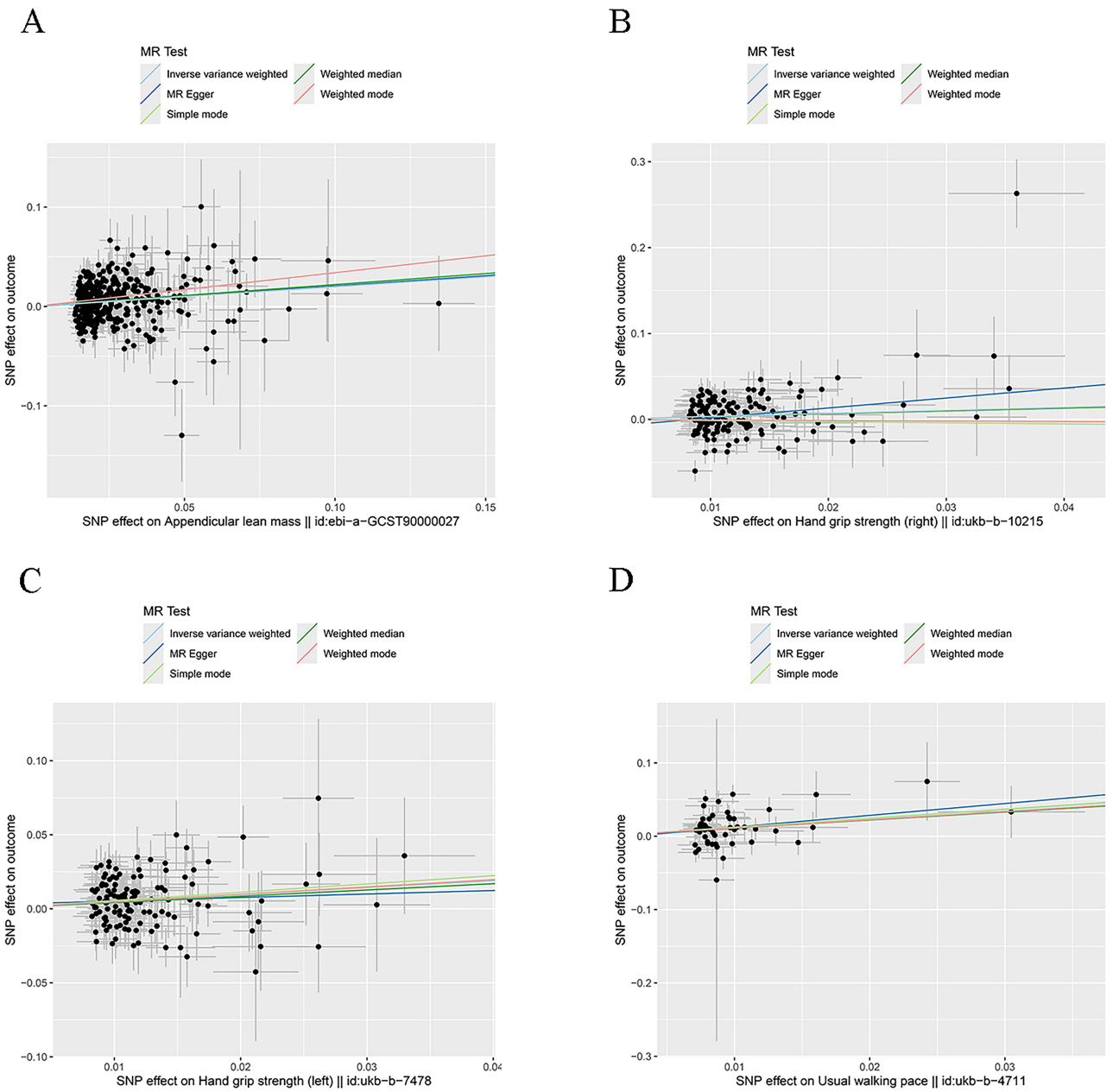

Figure 3 Scatter plot of the causality of sarcopenia on GDM. (**A**) The causality of appendicular lean mass on GDM. (**B**) The causality of grip strength (right) on GDM. (**C**) The causality of grip strength (left) on GDM. (**D**) The causality of usual walking pace on GDM.
Abbreviations: GDM, gestational diabetes mellitus; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

unexplored causal relationship between sarcopenia and GDM. This novel approach stems from the growing recognition of the role of sarcopenia in metabolic health, and its relevance to pregnancy outcomes.

The observed causal link between sarcopenia and GDM prompted further exploration of the underlying mechanisms (Figure 4). The skeletal muscle, constituting the largest organ in terms of mass, serves as the primary regulator of glucose homeostasis, accounting for 80% of the uptake of postprandial blood glucose, playing a critical role in maintaining normal insulin sensitivity.[22] Reduced muscle mass has been associated with decreased glucose uptake and utilization, potentially contributing to hyperglycemia. Insulin resistance is caused by reduced sensitivity of muscles to the insulin released by the pancreas, resulting in impaired glucose uptake and elevated blood glucose levels.[23] Park et al[24] carried out a cross-sectional study involving 372,399 Korean individuals to explored the relationship between skeletal muscle

Table 2 Heterogeneity and Pleiotropy Testing of Sarcopenia on Genetic Prediction of GDM

Exposure	Outcome	Cochrane's Q Test				MR-Egger Intercept Test		MR-PRESSO Global Test
		MR Egger_Q	MR Egger_P	IVW_Q	IVW_P	Egger_ intercept	P value	P value
Appendicular lean mass	GDM	455.5132	0.0003	455.5361	0.0003	−0.0003	0.8935	<0.001
Grip strength (Right)	GDM	271.8968	<0.001	276.9953	<0.001	−0.0099	0.1025	<0.001
Grip strength (Left)	GDM	140.1567	0.1835	140.4947	0.1949	0.0029	0.5825	0.0840
Usual walking pace	GDM	89.0740	0.0003	89.2648	0.0004	−0.0037	0.7499	0.0020

Abbreviations: GDM, gestational diabetes mellitus; IVW, inverse-variance weighted; MR, Mendelian randomization.

Table 3 MR Results From GDM on Genetic Prediction of Appendicular Lean Mass, Grip Strength (Right and Left) and Usual Walking Pace

Exposure	Outcome	nSNPs	Method	P value	β (95% CI)
GDM	Appendicular lean mass	9	MR Egger	0.8886	0.0080(−0.0999–0.1159)
			Weighted median	0.1507	−0.0210(−0.0495–0.0076)
			Inverse variance weighted	0.7424	−0.0057(−0.0395–0.0282)
			Simple mode	0.1973	0.0537(−0.0212–0.1286)
			Weighted mode	0.1836	−0.0239(−0.0561–0.0083)
GDM	Grip strength (Right)	8	MR Egger	0.1125	0.0411(−0.0023–0.0845)
			Weighted median	0.0301	0.0186(0.0018–0.0355)
			Inverse variance weighted	0.1509	0.0098(−0.0036–0.0231)
			Simple mode	0.1646	0.0184(−0.0048–0.0417)
			Weighted mode	0.0885	0.0184(0.0002–0.0367)
GDM	Grip strength (Left)	9	MR Egger	0.0710	0.0364(0.0029–0.0699)
			Weighted median	0.0151	0.0175(0.0034–0.0316)
			Inverse variance weighted	0.0225	0.0125(0.0018–0.0232)
			Simple mode	0.2189	0.0152(−0.0071–0.0376)
			Weighted mode	0.0280	0.0193(0.0052–0.0335)
GDM	Usual walking pace	10	MR Egger	0.4374	0.0141(−0.0197–0.0478)
			Weighted median	0.2130	−0.0081(−0.0207–0.0046)
			Inverse variance weighted	0.0119	−0.0158(−0.0282 - −0.0035)
			Simple mode	0.6138	−0.0058(−0.0274–0.0158)
			Weighted mode	0.2237	−0.0091(−0.0226–0.0045)

Abbreviations: GDM, gestational diabetes mellitus; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

Table 4 Heterogeneity and Pleiotropy Testing of GDM on Genetic Prediction of Sarcopenia

Exposure	Outcome	Cochrane's Q Test				MR-Egger Intercept Test		MR-PRESSO Global Test
		MR Egger_Q	MR Egger_P	IVW_Q	IVW_P	Egger_ intercept	P value	P value
GDM	Appendicular lean mass	22.1910	0.0024	22.4112	0.0042	−0.0015	0.7997	0.0650
GDM	Grip strength (Right)	5.3435	0.5006	7.5431	0.3746	−0.0034	0.1886	0.2790
GDM	Grip strength (Left)	4.3863	0.7344	6.5565	0.5851	−0.0029	0.1842	0.1540
GDM	Usual walking pace	13.1586	0.1065	18.7215	0.0277	−0.0037	0.1032	0.1360

Abbreviations: GDM, gestational diabetes mellitus; IVW, inverse-variance weighted; MR, Mendelian randomization.

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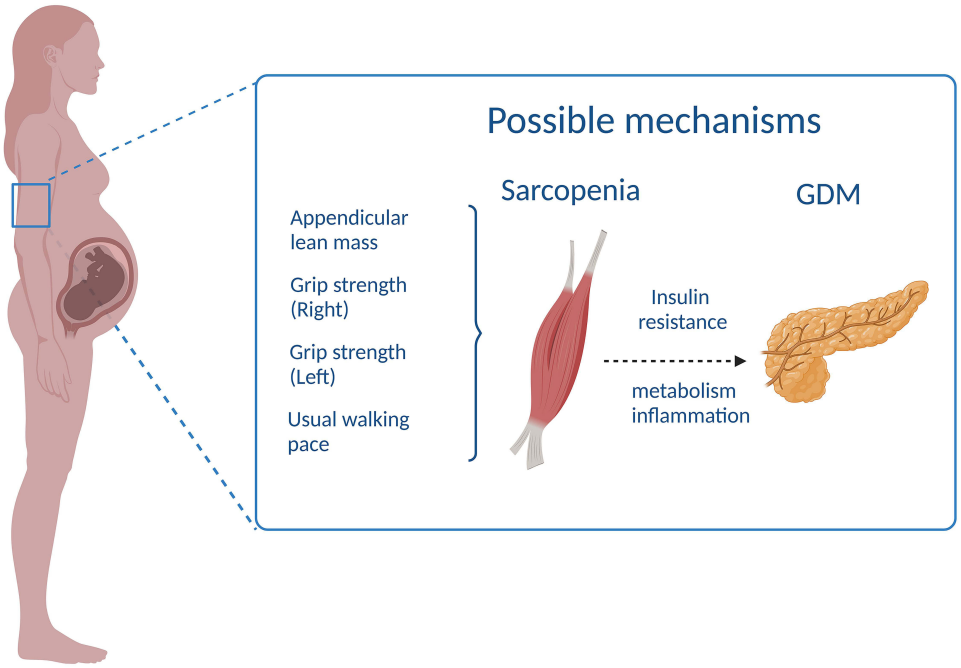

Figure 4 The two-sample MR framework showed that sarcopenia potentially causes GDM.
Notes: Figure 4 was created in BioRender. žÄ, OE. (2025) http://BioRender.com/i60o427.).
Abbreviations: GDM, gestational diabetes mellitus; MR, Mendelian randomization.

mass and diabetes incidence, insulin resistance, glycated hemoglobin. Their findings indicated that skeletal muscle mass was negatively associated with the incidence of diabetes, insulin resistance, and glycated hemoglobin. A prospective cohort study aimed to investigate the association between insulin resistance from early adulthood to middle age and ALM in individuals without diabetes found that a trajectory of high insulin resistance was associated with a reduction in ALM/BMI among middle-aged individuals (β= −0.043, 95% CI: −0.063 – −0.023).[25] Insulin resistance throughout early and middle adulthood has a long-lasting impact on the health of skeletal muscles, which may initiate a pathway of harm to muscular health by potentially disrupting the normal physiological environment. This disruption could involve damage to capillary ultrastructure, inflammation, and, over time, muscle atrophy.[26] Additionally, the depletion of muscle mass plays a role in the development of glucose intolerance and the promotion of gluconeogenesis, subsequently exacerbating insulin resistance. Consistent with prior research on sarcopenia and diabetes, our study confirmed that sarcopenia plays a role in the development of GDM. Sarcopenia can disrupt glucose metabolism and lead to insulin resistance,[27] elevating the risk of GDM.[28]

Muscle tissue contributes to the regulation of inflammation and metabolism in the body.[29,30] In a typical physiological state, pro-inflammatory cytokines play a role in regulating the balance between skeletal muscle synthesis and metabolic breakdown. However, in instances of muscle atrophy, there is an upregulation in the expression of proinflammatory cytokines, resulting in increased skeletal muscle breakdown metabolism. Moreover, these cytokines can hinder protein synthesis within the skeletal muscle cells, ultimately compromising muscle function. Anti-inflammatory cytokines can enhance glucose metabolism in muscles, serve as recruiting factors for skeletal muscle cells during the muscle growth process, and promote muscle growth and regeneration. In a cohort of Chinese participants, elevated levels of the inflammatory cytokines TWEAK and TNF-α were linked to a higher likelihood of developing sarcopenia, whereas increased concentrations of the metabolic hormone insulin-like growth factor 1, insulin, and adiponectin were linked to a reduced risk of sarcopenia.[31] A meta-analysis including 3072 participants with sarcopenia and 8177 controls found that sarcopenia was significantly associated with high levels of C-reactive protein, while serum IL6 and TNF-α levels were not significantly different compared with the control.[32] Sarcopenia can lead to an increased release of inflammatory cytokines, which can disrupt normal insulin signaling, further exacerbating insulin resistance and high blood glucose.[33]

Previous studies revealed that serum inflammatory cytokines in women with GDM increased during gestation,[34] and the high levels of proinflammatory cytokines were associated with insulin resistance. Therefore, we can infer that pregnant women diagnosed with sarcopenia experience enhanced expression and secretion of pro-inflammatory cytokines. This leads to an imbalance between proinflammatory and anti-inflammatory cytokines, ultimately impairing glucose homeostasis and promoting the occurrence and development of GDM.

The skeletal muscle is one of the primary energy-consuming organs. Reduced muscle mass may result in decreased basal metabolic rate and reduced energy expenditure. This can lead to energy accumulation within the body, exacerbating metabolic disturbances. Mitochondria within muscle cells are crucial for energy production. A decrease in muscle mass may be accompanied by mitochondrial dysfunction, including ATP synthesis and oxidative phosphorylation, leading to the disruption of energy metabolism. This can exacerbate insulin resistance and contribute to diabetes development. Crane et al[35] discovered that individuals with sarcopenia show increased lipid accumulation and a reduced number of mitochondria in muscle cells, resulting in reduced mitochondrial function and lipid metabolism. Lipid signaling pathways were impaired in adipocytes of sarcopenic muscle. The muscle tissue also plays a crucial role in hormonal regulation, including insulin, estrogen, and other hormones involved in pregnancy. Sarcopenia may disrupt the normal regulation of these hormones, contributing to metabolic disturbances.[36] Shao et al[37] through a biopsy of rectus abdominis muscle, observed that the level of membrane protein plasma cell membrane glycoprotein-1 increased by approximately 63% in the GDM group. Their findings indicate that heightened phosphorylation of serine/threonine residues in muscle insulin receptors results in reduced insulin receptor tyrosine kinase activity. These post-receptor defects in the insulin signaling pathway may play a role in the pathophysiology of GDM. Understanding these mechanistic pathways is essential to elucidate the precise physiological connections between sarcopenia and GDM.

The prevalence of sarcopenia was found 2–3 times higher in people with type 2 diabetes mellitus than in control.[38] Type 2 diabetes mellitus is associated with poorer skeletal muscle strength and quality and a greater loss of muscle mass. Diabetes and sarcopenia have a causal relationship. However, GDM was not identified as a risk factor for sarcopenia in our study. Our findings have several clinical implications. Recognizing sarcopenia as a potential risk factor for GDM can inform prenatal care and management strategies. Implementing interventions aimed at preserving or enhancing muscle mass and function during pregnancy may help mitigate the risk of GDM. Such interventions may include tailored exercise and nutritional support programs.

It is crucial to acknowledge the strengths and limitations of the study. MR analysis allowed us to establish a causal link between sarcopenia-related genetic variants and GDM risk, providing a robust foundation for our findings. However, selection bias may have been present because of the binary exposures used in MR analysis. Additionally, the homogeneity of the study population, which primarily consisted of individuals of European descent, limits the generalizability of our findings to diverse ethnic and racial groups. Future research should explore in greater detail the specific mechanisms linking sarcopenia and GDM. Longitudinal studies that track muscle health throughout pregnancy and its impact on glucose metabolism are warranted. We are currently conducting a prospective study to investigate whether pregnant women with sarcopenia are more likely to develop GDM than those without sarcopenia. Furthermore, investigating potential interventions to prevent or mitigate GDM risk in individuals at risk of sarcopenia could advance personalized prenatal care.

Conclusion

In conclusion, our study adds to the growing body of evidence suggesting that sarcopenia plays a causal role in the development of GDM, whereas GDM does not causally affect sarcopenia. This newfound understanding opens avenues for targeted interventions and personalized care to reduce the burden of GDM among pregnant individuals. Further research is needed to refine our understanding of the intricate physiological pathways involved, and to develop effective strategies for prevention and management.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Statement

This study is exempt from ethics approval based on item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China. The details are as follows:

- Item 1 of Article 32: using legally obtained public data or conducting research through observation without interfering with public behavior.
- Item 2 of Article 32: using anonymized information data to conduct research.

Acknowledgments

We sincerely thank the UK Biobank and FinnGen datasets for providing GWAS data.

Author Contributions

Zilian Wang and Dongyu Wang are considered co-corresponding authors. All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Funding was provided by the National Key Research and Development Program of China (No: 2021YFC2700700).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2022;377:e067946. doi:10.1136/bmj-2021-067946
2. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16–31. doi:10.1093/ageing/afy169
3. Sayer AA, Syddall H, Martin H, Patel H, Baylis D, Cooper C. The developmental origins of sarcopenia. *J Nutr Health Aging*. 2008;12(7):427–432. doi:10.1007/BF02982703
4. Li CW, Yu K, Shyh-Chang N, et al. Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. *J Cachexia, Sarcopenia Muscle*. 2022;13(2):781–794. doi:10.1002/jcsm.12901
5. Chen R, Zhang L, Zhang M, et al. The triglyceride-glucose index as a novel marker associated with sarcopenia in non-diabetic patients on maintenance hemodialysis. *Ren Fail*. 2022;44(1):1615–1621. doi:10.1080/0886022X.2022.2128373
6. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic syndrome and sarcopenia. *Nutrients*. 2021;13(10):3519. doi:10.3390/nu13103519
7. Lin MH, Chiu SY, Chang PH, Lai YL, Chen PC, Ho WC. Hyperlipidemia and statins use for the risk of new diagnosed sarcopenia in patients with chronic kidney: a population-based study. *Int J Environ Res Public Health*. 2020;17(5):1494.
8. Izzo A, Massimino E, Riccardi G, Della Pepa G. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. *Nutrients*. 2021;13(1):183. doi:10.3390/nu13010183
9. Chen S, Yan S, Aiheti N, et al. A bi-directional Mendelian randomization study of sarcopenia-related traits and type 2 diabetes mellitus. *Front Endocrinol*. 2023;14:1109800. doi:10.3389/fendo.2023.1109800
10. Feng L, Gao Q, Hu K, et al. Prevalence and risk factors of sarcopenia in patients with diabetes: a meta-analysis. *J Clin Endocrinol Metab*. 2022;107(5):1470–1483. doi:10.1210/clinem/dgab884
11. Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plast Reconstr Surg*. 2010;126(6):2234–2242. doi:10.1097/PRS.0b013e3181f44abc
12. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. *JAMA*. 2017;318(19):1925–1926. doi:10.1001/jama.2017.17219
13. Chen LK, Woo J, Assantachai P, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc*. 2020;21(3):300–307.e302. doi:10.1016/j.jamda.2019.12.012
14. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife*. 2018;7. doi:10.7554/eLife.34408
15. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203–209. doi:10.1038/s41586-018-0579-z
16. Pei YF, Liu YZ, Yang XL, et al. The genetic architecture of appendicular lean mass characterized by association analysis in the UK Biobank study. *Commun Biol*. 2020;3(1):608. doi:10.1038/s42003-020-01334-0

17. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol*. 2017;46(6):1734–1739. doi:10.1093/ije/dyx034
18. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. 2017;36(11):1783–1802. doi:10.1002/sim.7221
19. Slob EAW, Groenen PJF, Thurik AR, Rietveld CA. A note on the use of Egger regression in Mendelian randomization studies. *Int J Epidemiol*. 2017;46(6):2094–2097. doi:10.1093/ije/dyx191
20. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
21. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. doi:10.1038/s41588-018-0099-7
22. Merz KE, Thurmond DC. Role of skeletal muscle in insulin resistance and glucose uptake. *Compr Physiol*. 2020;10(3):785–809.
23. Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. *Diabetes Metab J*. 2022;46(1):15–37. doi:10.4093/dmj.2021.0280
24. Park JH, Lee MY, Shin HK, Yoon KJ, Lee J, Park JH. Lower skeletal muscle mass is associated with diabetes and insulin resistance: a cross-sectional study. *Diabetes Metab Res Rev*. 2023;39(7):e3681. doi:10.1002/dmrr.3681
25. Zhong VW, Bancks MP, Schreiner PJ, et al. Insulin resistance since early adulthood and appendicular lean mass in middle-aged adults without diabetes: 20 years of the CARDIA study. *J Diabetes Complications*. 2019;33(1):84–90. doi:10.1016/j.jdiacomp.2018.09.011
26. Bazzano LA, Tingting D. Long-term effects of insulin resistance on appendicular lean muscle. *J Diabetes Complications*. 2019;33(1):13–14. doi:10.1016/j.jdiacomp.2018.10.019
27. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. *J Endocrinol*. 2016;229(2):R67–81. doi:10.1530/JOE-15-0533
28. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. *Int J mol Sci*. 2018;19(11):3342. doi:10.3390/ijms19113342
29. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. *Nat Metab*. 2020;2(9):817–828. doi:10.1038/s42255-020-0251-4
30. Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. *J Clin Invest*. 2017;127(1):43–54. doi:10.1172/JCI88880
31. Li CW, Yu K, Shyh-Chang N, et al. Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention. *J Cachexia, Sarcopenia Muscle*. 2019;10(3):586–600. doi:10.1002/jcsm.12417
32. Bano G, Trevisan C, Carraro S, et al. Inflammation and sarcopenia: a systematic review and meta-analysis. *Maturitas*. 2017;96:10–15. doi:10.1016/j.maturitas.2016.11.006
33. Wiedmer P, Jung T, Castro JP, et al. Sarcopenia - Molecular mechanisms and open questions. *Ageing Res Rev*. 2021;65:101200. doi:10.1016/j.arr.2020.101200
34. Pinto Y, Frishman S, Turjeman S, et al. Gestational diabetes is driven by microbiota-induced inflammation months before diagnosis. *Gut*. 2023;72(5):918–928. doi:10.1136/gutjnl-2022-328406
35. Crane JD, Devries MC, Safdar A, Hamadeh MJ, Tarnopolsky MA. The effect of aging on human skeletal muscle mitochondrial and intramyocellular lipid ultrastructure. *J Gerontol a Biol Sci Med Sci*. 2010;65(2):119–128. doi:10.1093/gerona/glp179
36. Morley JE. Hormones and Sarcopenia. *Curr Pharm Des*. 2017;23(30):4484–4492. doi:10.2174/1381612823666161123150032
37. Shao J, Catalano PM, Yamashita H, et al. Decreased insulin receptor tyrosine kinase activity and plasma cell membrane glycoprotein-1 overexpression in skeletal muscle from obese women with gestational diabetes mellitus (GDM): evidence for increased serine/threonine phosphorylation in pregnancy and GDM. *Diabetes*. 2000;49(4):603–610. doi:10.2337/diabetes.49.4.603
38. Trierweiler H, Kisielewicz G, Hoffmann Jonasson T, Rasmussen Petterle R, Aguiar Moreira C, Zeghbi Cochenski Borba V. Sarcopenia: a chronic complication of type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2018;10(1):25. doi:10.1186/s13098-018-0326-5