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ORIGINAL RESEARCH

Risk Factors for Sarcopenia in Women with Type 2 Diabetes and the Effects of Metformin: A Cross-Sectional Study of 7,731 Patients from the UK Biobank

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Objective: To examine the sarcopenia risk factors and the association between metformin use and sarcopenia in female patients with Type 2 diabetes mellitus (T2DM) through a cross-sectional analysis of data from the UK Biobank.

Methods: In a cross-sectional analysis of 7,731 women with T2DM from the UK Biobank, participants were categorized into nonsarcopenia, probable sarcopenia, and sarcopenia groups based on the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) criteria. Logistic regression models were employed to investigate the association between metformin use and sarcopenia, adjusting for age, education, physical activity, and comorbidities.

Results: The prevalence of probable sarcopenia and sarcopenia was 16.2% and 3.4%, respectively, with rates increasing with age. Metformin use was significantly associated with a higher risk of sarcopenia (adjusted OR 1.13; 95% CI 1.01–1.26). This association remained consistent across various subgroups, including different age ranges and levels of physical activity.

Conclusion: Metformin use was cross-sectionally associated with higher odds of sarcopenia, particularly in older women with low physical activity and comorbidities. These findings highlight the need for further longitudinal and mechanistic studies to confirm the relationship and explore potential underlying mechanisms.

Keywords: sarcopenia, metformin, UK Biobank, type 2 diabetes mellitus

Introduction

Sarcopenia is a progressive and widespread skeletal muscle disease characterized by the accelerated loss of skeletal muscle mass and function, and is closely associated with a range of adverse health outcomes.[1] The concept of sarcopenia was first proposed by Irwin Rosenberg in 1989.[2] Research has shown that sarcopenia is closely associated with poor physical performance, functional impairment, and a significantly increased risk of falls, fractures, hospitalization, and even death.[3] As people age, muscle mass gradually decreases while fat tissue increases, leading to a rise in the incidence of sarcopenia. Sarcopenia is a significant contributing factor to many adverse events, significantly increasing the risk of various injuries, prolonged bed rest, disability, and even death, thereby having a major impact on the quality of life, especially for older patients.[4]

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease characterized primarily by high blood sugar, insulin resistance, and insufficient insulin secretion, resulting from the combined effects of genetic and environmental factors.[5] It was

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formerly known as non-insulin-dependent diabetes or adult-onset diabetes, accounting for over 90% of diabetes patients.[6,7] In 2017, the International Diabetes Federation (IDF) estimated that 425 million people worldwide had diabetes, and this number is expected to rise to 629 million by 2045.[7] Recent reports indicate that older individuals with diabetes have an increased risk of sarcopenia.[8] Sarcopenia is a risk factor for the development of T2DM, while T2DM is also a risk factor for the occurrence of sarcopenia.[9,10] Sarcopenia can impair the ability of older diabetics to perform daily activities and increase the risk of mortality, and diabetes is associated with reduced muscle strength and poor muscle quality.[8,11] Although the potential reasons for the coexistence of diabetes and sarcopenia are not yet fully understood, there is evidence that some mechanisms leading to sarcopenia are closely related to the pathophysiology of diabetes.[12]

Metformin is a first-line medication for the treatment of T2DM. It exerts its pharmacological effects by increasing liver's sensitivity to insulin, thereby inhibiting glucose output from the liver and lowering blood sugar levels. According to the latest guidelines, metformin is considered the preferred treatment option.[13] Reports have indicated that metformin has a positive effect on muscle mass and strength.[4,14,15] However, other studies suggest that it does not affect body composition or gait speed, showing no positive effects.[16,17] Additionally, some research indicates that metformin may have adverse effects on muscle.[15,18,19] It remains controversy whether metformin has a positive or negative impact on sarcopenia, particularly as studies in female T2DM patients are still relatively limited. Women exhibit differences from men in physiology, metabolism, and disease presentation, studies have found that women undergoing menopause and aging may experience deterioration in muscle quality and muscle strength, which may be related to estrogen deprivation,[20,21] and some studies have identified female gender as a risk factor for sarcopenia in T2DM.[14,22] Therefore, it is of great significance to investigate the mechanisms and clinical effects of metformin in female patients. Therefore, the present study aims to explore the impact of metformin on risk factors for sarcopenia through a cross-sectional study of 7,731 female T2DM patients from the UK Biobank, providing scientific evidence for clinical intervention.

Methods

Design and Participants

The UK Biobank is a large-scale prospective study aimed at exploring the impact of genetics, lifestyle, and environmental factors on the health and diseases of middle-aged and older adults.[23] The baseline assessment of the study was completed between 2006 and 2010 at 22 centers in England, Wales, and Scotland, recruiting a total of 502,140 adults aged 37 to 73. Participants underwent a comprehensive assessment that included self-reported questionnaires (demographics, lifestyle, health status), physical measurements (grip strength, height, BMI, etc)., and the collection of blood and urine samples, with data accuracy verified through nurse interviews (such as medical history and medication use).[23] The Townsend Deprivation Index (TDI) is a continuous variable of socio-economic status provided by UK Biobank, where higher values are associated with lower economic status.[24] Comorbidities were identified using diagnoses recorded with the International Classification of Diseases 10th revision (ICD-10), which can be directly retrieved from the UK Biobank database. Some questionnaires and measurement methods used in the UK Biobank differed from those commonly used in current standards and definitions of sarcopenia.[23] Therefore, the standards and definitions used in this study were adjusted based on the available data from UK Biobank participants. For more detailed information about the UK Biobank project, please visit https://www.ukbiobank.ac.uk/. All participants provided written informed consent, and ethical approval was granted by the NHS National Research Ethics Service (Reference: 21/NW/0157). Data for this work was obtained from UK Biobank under the approved application No. 117320.

Diabetes status was self-reported in the baseline questionnaire. Among the diabetic participants, the type of diabetes was clarified during the interviews. This study only included data from white female participants with T2DM. Participants who reported having type 1 diabetes or gestational diabetes during the interviews were excluded from the study. Additionally, participants were excluded if they had any of the following conditions: (i) myopathy, myasthenia gravis, stroke, paralysis, muscular dystrophy, (ii) non-white, or (iii) if they lacked complete data, resulting in a total of 7,731 cases of women with T2DM included in the analysis.[25,26] (Figure 1)

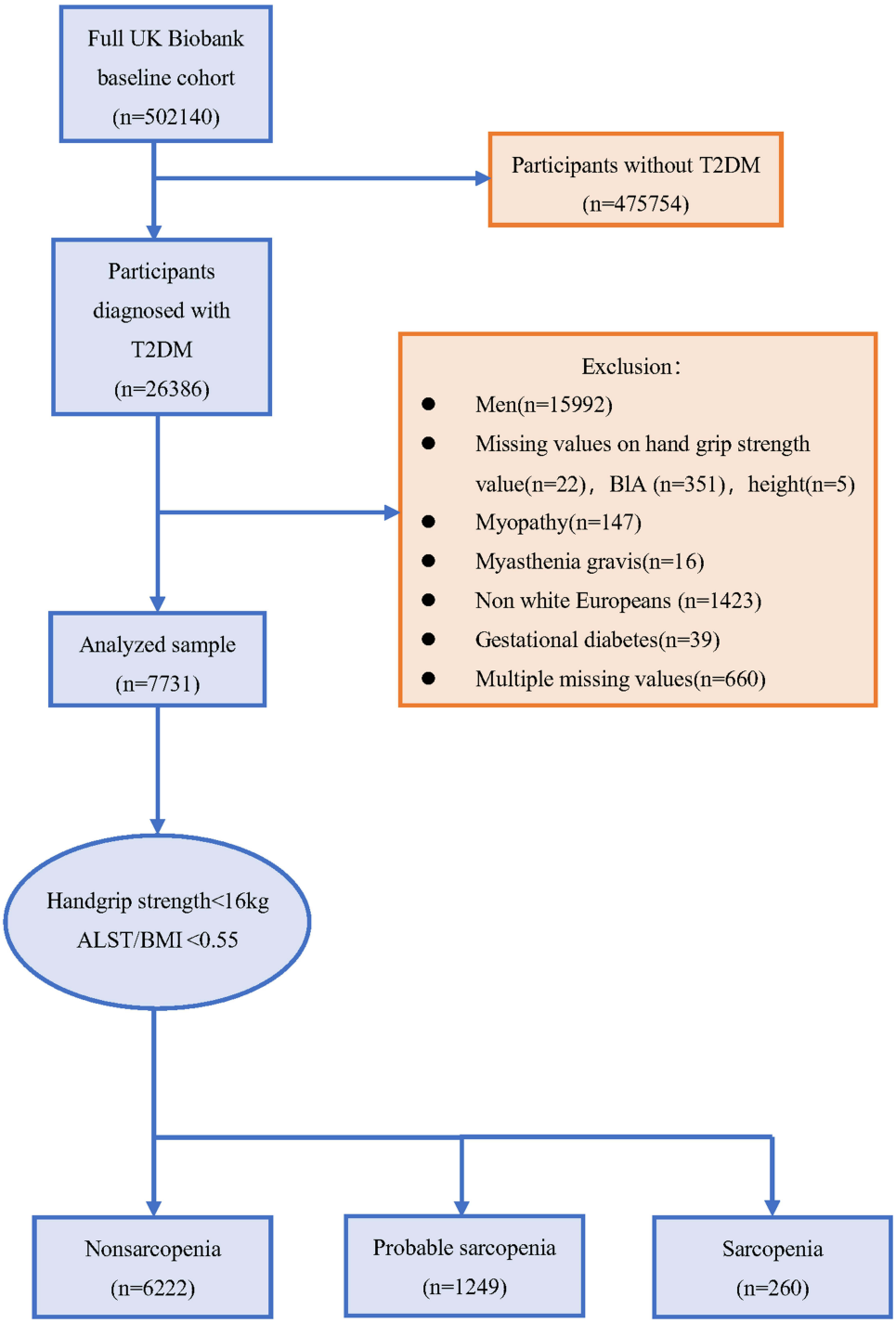

Figure 1 Study flowchart of inclusion and exclusion of participants.
Abbreviations: ALST, appendicular lean soft tissue; BMI, body mass index; T2DM, type 2 diabetes mellitus; BIA, bio-impedance analysis.

Assessment of Metformin

In the baseline interview, the research nurse recorded participants' medical history and information on regular prescription medications through verbal interviews. For participants reporting diabetes, further confirmation was made regarding whether they regularly took prescription medications, and specific drug names were inquired about. Based on the patients' reported use of metformin, the study divided the T2DM patients into a metformin group and a non-metformin group.

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Assessment of Probable and Confirmed Sarcopenia

In this study, we conducted an assessment of sarcopenia strictly according to the guidelines established by the European Working Group on Sarcopenia in Older People (EWGSOP2), covering three dimensions: muscle strength, muscle mass, and physical performance.[3]

The measurement of muscle strength was conducted by trained research nurses using the Jamar J00105 hydraulic hand dynamometer during the baseline measurements of the UK Biobank. The specific procedure involved having participants sit comfortably with their forearms resting on armrests, followed by measuring grip strength in both hands separately. We then took the average of these two measurements to determine the participant's personal grip strength representative value. According to the EWGSOP2 standards, a grip strength of <16kg for women is classified as low grip strength.[3,26] Bioimpedance analysis to determine appendicular lean mass was performed using the Tanita BC-418MA body composition analyzer, and subsequent assessments included dual-energy X-ray absorptiometry to evaluate Fat-free mass (FFM).[27] Muscle mass was then assessed using the ratio of appendicular lean soft tissue (ALST) to the body mass index (BMI) (weight/height^2). The calculation of ALST was completed using an equation developed by Dodds et al, which utilized data from UK Biobank participants.[25] The equation is as follows: ALST (kg) = (0.958 × [Appendicular FFM (kg)]) - (0.166 × S) - 0.308 (where S is the gender parameter, with a value of 0 for females and 1 for males). Additionally, standing height was measured using the Seca 202 height measuring device, and weight measurement was conducted simultaneously with the bioimpedance measurement. We expressed BMI as a continuous variable. Women with an ALST/BMI value of less than 0.55 were considered to have low muscle mass.[26]

In this study, we classified participants with low grip strength but normal muscle mass were categorized as probable sarcopenia, while those with both low grip strength and low muscle mass were diagnosed as having sarcopenia.

Assessment of Covariates

This study collected demographic characteristics (age and BMI) and socioeconomic factors (education level), dividing the population into two groups based on whether they obtained a college degree or above. Lifestyle factors (alcohol consumption, physical activity) were assessed, with participants categorized as current drinkers, non-drinkers, or former drinkers based on their drinking status. The intensity and frequency of physical activity were evaluated using the self-reported short International Physical Activity Questionnaire (IPAQ).[28] Comorbidities (fractures, hyperlipidemia, tumors, and hemiplegia) were diagnosed according to the ICD-10, with hyperlipidemia defined as the use of cholesterol-lowering medication or low-density lipoprotein levels exceeding 4.0 mmol/L. All of the above were included as covariate information.

Statistical Analysis

To describe the baseline characteristics, the normality test was first conducted on the data. Continuous variables that conform to a normal distribution are represented by the mean (and standard deviation [SD]), while continuous variables that do not conform to a normal distribution are represented by the median (and interquartile range [IQR]). Categorical variables are represented by the number of cases (and percentage). To calculate the statistical significance of differences between groups, categorical variables are compared using the chi-square test, and continuous variables that do not conform to a normal distribution are compared using the Mann–Whitney *U*-test or the Kruskal–Wallis *H*-test. We employed ordinal multivariable logistic regression to analyze the relationship between sarcopenia status (nonsarcopenia, possible sarcopenia, sarcopenia) and metformin use. This model did not utilize a reference category but instead estimated cumulative odds ratios for progression to higher levels of sarcopenia. Binary multivariable logistic regression was used to examine the association between grip strength and muscle mass with metformin use, with low grip strength and low muscle mass serving as reference categories, respectively. In all adjusted statistical analyses, metformin was retained as a covariate. Other variables were included only if they were associated with the outcome of interest in univariate models ($p<0.05$) and had complete data. Data are reported as odds ratios (OR) and 95% confidence intervals CIs). The models were ultimately adjusted age, alcohol consumption, education level, IPAQ category, and comorbidities (yes or no). To

validate the reliability of the results, we assessed multicollinearity for all covariates across models: as shown in Table S1, all variance inflation factors were below 2, indicating no significant multicollinearity.

Statistical analysis was conducted using R (version 4.4.2), RStudio (version 2024.12.0 + 467), and SPSS (version 27.0.1.0). A p-value < 0.05 was considered statistically significant. All tests were two-tailed.

Results

Baseline Characteristics

Inclusion and exclusion criteria are shown in Figure 1, and a total of 7731 white women participated in this study. Table 1 shows the baseline characteristics of the participants.

Table 1 Univariate Analysis of Baseline Characteristics Among Nonsarcopenia, Probable Sarcopenia, and Sarcopenia Subjects

Parameter	Total (N=7731)	Nonsarcopenia (N=6222)	Probable Sarcopenia (N=1249)	Sarcopenia (N=260)	*P* value
Age					<0.001
<65	5487(71)	4526(82.5)	798(14.5)	163(3.0)	
≥65	2244(29)	1696(75.6)	451(20.1)	97(4.3)	
BMI					<0.001
24<	741(9.6)	621(83.8)	120(16.2)	0(0.0)	
24~28	1508(19.5)	1258(83.4)	242(16.0)	8(0.5)	
≥28	5482(70.9)	4343(79.2)	887(16.2)	252(4.6)	
Education					<0.001
Middle school and below	6068(78.5)	4802(79.1)	1032(17.0)	234(3.9)	
College and above	1663(21.5)	1420(85.4)	217(13.0)	26(1.6)	
Smoking					0.891
Former	2888(37.4)	2331(80.7)	457(15.8)	100(3.5)	
Current	722(9.3)	586(81.2)	111(15.4)	25(3.5)	
Never	4121(53.3)	3305(80.2)	681(16.5)	135(3.3)	
Alcohol					<0.001
Former	628(8.1)	442(70.4)	149(23.7)	37(5.9)	
Current	6380(82.5)	5246(82.2)	945(14.8)	189(3.0)	
Never	723(9.4)	534(73.9)	155(21.4)	34(4.7)	
Physical activity					<0.001
Low	1406(18.2)	1074(76.4)	266(18.9)	66(4.7)	
Moderate	4620(59.8)	3695(80.0)	768(16.6)	157(3.4)	
High	1705(22.1)	1453(85.2)	215(12.6)	37(2.2)	
TDI					<0.001
<-1.60	3761(48.6)	3133(83.3)	538(14.3)	90(2.4)	
≥1.60	3970(51.4)	3089(77.8)	711(17.9)	170(4.3)	
Metformin					0.001
Yes	3717(48.1)	2938(79.0)	630(16.9)	149(4.0)	
No	4014(51.9)	3284(81.8)	619(15.4)	111(2.8)	
Fractured broken bones					<0.001
Yes	950(12.3)	691(72.7)	216(22.7)	43(4.5)	
No	6781(87.7)	5531(81.6)	1033(15.2)	217(3.2)	
Stroke					0.001
Yes	190(2.5)	118(62.1)	66(34.7)	6(3.2)	
No	7541(97.5)	6104(80.9)	1183(15.7)	254(3.4)	
Hypertension					<0.001
Yes	5175(66.9)	4005(77.4)	963(18.6)	207(4.0)	
No	2556(33.1)	2217(86.7)	286(11.2)	53(2.1)	

(*Continued*)

Table 1 (Continued).

Parameter	Total (N=7731)	Nonsarcopenia (N=6222)	Probable Sarcopenia (N=1249)	Sarcopenia (N=260)	*P* value
Hyperlipidemia					<0.001
Yes	596(7.7)	421(70.6)	143(24.0)	32(5.4)	
No	7135(92.3)	5801(81.3)	1106(15.5)	228(3.2)	
Neoplasm					<0.001
Yes	2364(30.6)	1840(77.8)	435(18.4)	89(3.8)	
No	5367(69.4)	4382(81.6)	814(15.2)	171(3.2)	
Heart failure					<0.001
Yes	557(7.2)	384(68.9)	145(26.0)	28(5.0)	
No	7174(92.8)	5838(81.4)	1104(15.4)	232(3.2)	
CVD					<0.001
Yes	905(11.7)	678(74.9)	184(20.3)	43(4.8)	
No	6826(88.3)	5544(81.2)	1065(15.6)	217(3.2)	
COPD					<0.001
Yes	701(9.1)	480(68.5)	171(24.4)	50(7.1)	
No	7030(90.9)	5742(81.7)	1078(15.3)	210(3.0)	
PVD					0.01
Yes	267(3.5)	196(73.4)	57(21.3)	14(5.2)	
No	7464(96.5)	6026(80.7)	1192(16.0)	246(3.3)	
Cerebrovascular disease					<0.001
Yes	419(5.4)	295(70.4)	101(24.1)	23(5.5)	
No	7312(94.6)	5927(81.1)	1148(15.7)	237(3.2)	
Dementia					<0.001
Yes	373(4.8)	270(72.4)	83(22.3)	20(5.4)	
No	7358(95.2)	5952(80.9)	1166(15.8)	240(3.3)	
Liver disease					0.044
Yes	183(2.4)	133(72.7)	41(22.4)	9(4.9)	
No	7548(97.6)	6089(80.7)	1208(16.0)	251(3.3)	
Hemiplegia					<0.001
Yes	153(2.0)	89(58.2)	52(34.0)	12(7.8)	
No	7578(98.0)	6133(80.9)	1197(15.8)	248(3.3)	

Notes: Variables are presented as median (IQR) or n (%).
Abbreviations: BMI, body mass index; TDI, Townsend deprivation index; CVD, Atherosclerotic heart disease; COPD, chronic obstructive pulmonary disease; PVD, Peripheral vascular disease.

A total of 6,222 participants (80.48%) were classified as nonsarcopenia, 1,249 participants (16.16%) as probable sarcopenia, and 260 participants (3.36%) as diagnosed with sarcopenia. Compared to participants without sarcopenia, those with probable or diagnosed sarcopenia were older, had a higher BMI, lower education levels, less personal physical activity, higher Townsend deprivation scores, and were currently not drinking alcohol. Smoking status had no significant impact on the incidence of sarcopenia. Regarding the use of metformin, the prevalence of sarcopenia and probable sarcopenia in the metformin group was 4.0% and 16.9%, respectively ($P < 0.001$). In contrast, the prevalence in the non-metformin group was 2.8% and 15.4%. In terms of comorbidities, patients with sarcopenia and probable sarcopenia had more comorbidities, with higher incidences of fractures, strokes, hypertension, hyperlipidemia, neoplasms, heart failure, atherosclerotic heart disease, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, cerebrovascular disease, dementia, liver disease, and hemiplegia compared to the normal group. (Table 1)

Association Between Sarcopenia and Metformin

Table 2 shows the results of multivariable logistic regression models examining the relationship between the use of metformin and the state of sarcopenia and its components. Using the non-metformin group as a reference, the use of metformin was

Table 2 Association of Metformin Use with the State of Sarcopenia and Its Components in Multivariate Logistic Regression Models

Metformin			
Dependent Variables		**OR (95% CI)**	***P***
Sarcopenia			
	Model 1 (Unadjusted)	1.20 (1.08 ~ 1.35)	0.001
	Model 2 (Adjusted [a])	1.13 (1.01 ~ 1.26)	0.042
Handgrip strength			
	Model 1 (Unadjusted)	1.19 (1.07 ~ 1.33)	0.002
	Model 2 (Adjusted [a])	1.12 (1.00 ~ 1.26)	0.056
ALST/BMI			
	Model 1 (Unadjusted)	1.36 (1.18 ~ 1.56)	<0.001
	Model 2 (Adjusted [a])	1.29 (1.11 ~ 1.49)	<0.001

Notes: [a]The state of sarcopenia (nonsarcopenia=0, possible sarcopenia=1, sarcopenia=2) is an ordinal multivariate logistic regression model (proportional odds model). Grip strength and muscle mass are binary logistic regression models, with the reference category being: normal grip strength (≥16 kg) and normal muscle mass (ALST/BMI≥0.55). All ORs were adjusted for age, alcohol consumption, physical activity, educational level, fractured broken bones, hyperlipidemia, neoplasm, and hemiplegia.
Abbreviations: ALST, appendicular lean soft tissue; BMI, body mass index.

positively correlated with the prevalence of sarcopenia in Model 1. After further adjustments for age, alcohol consumption, physical activity, education level, fractured broken bones, hyperlipidemia, neoplasm, and hemiplegia, the results indicated that subjects using metformin had a higher risk of developing sarcopenia, with an odds ratio (OR) of 1.13 in Model 2. The ordinal multivariate logistic regression model results for metformin and sarcopenia are detailed in Table 3, where metformin, age,

Table 3 The Results of Ordinal Multivariate Logistic Regression Model of Influencing Factors of Sarcopenia in Subjects

Variables	**Reference**	**OR**	**95% CI**	***P***
Metformin				
Yes	No	1.13	1.01 ~ 1.26	0.042
Age				
≥65	<65	1.39	1.23 ~ 1.57	<0.001
Alcohol				
Current	Previous	0.55	0.46 ~ 0.66	<0.001
Never	Previous	0.80	0.63 ~ 1.02	0.075
IPAQ				
Moderate	Low	0.80	0.69 ~ 0.93	0.003
High	Low	0.58	0.48 ~ 0.70	<0.001
Educational background				
College or University degree	Others	0.72	0.62 ~ 0.84	<0.001
Hyperlipidemia				
Yes	No	1.55	1.29 ~ 1.88	<0.001
Fractured broken bones				
Yes	No	1.15	1.02 ~ 1.30	<0.001
Neoplasm				
Yes	No	1.28	1.09 ~ 1.50	0.020
Hemiplegia				
Yes	No	2.54	1.83 ~ 3.51	<0.001

Notes: This is an ordinal three-category logistic regression model. Dependent variable: nonsarcopenia=0, possible sarcopenia=1, sarcopenia=2. Independent variables: Primary predictor: metformin. Covariates: age, alcohol, IPAQ, educational background, hyperlipidemia, fracture broken bones, neoplasm, hemiplegia.
Abbreviation: IPAQ: International Physical Activity Questionnaire.

Variables	n (%)	Not using metformin No. of events/ No. of total	Using metformin No. of events/ No. of total	OR (95%CI)	*P*	P for interaction
All patients	7731 (100.00)	730/4014	779/3717	1.19 (1.07 ~ 1.33)	0.002	
Educational background						0.920
Others	6068 (78.49)	600/3064	666/3004	1.17 (1.03 ~ 1.32)	0.013	
College or University degree	1663 (21.51)	130/950	113/713	1.19 (0.90 ~ 1.56)	0.217	
Alcohol						0.490
Previous	628 (8.12)	76/283	110/345	1.27 (0.90 ~ 1.80)	0.170	
Current	6380 (82.52)	578/3400	556/2980	1.12 (0.98 ~ 1.27)	0.084	
Never	723 (9.35)	76/331	113/392	1.36 (0.97 ~ 1.90)	0.074	
IPAQ						0.507
Low	1406 (18.19)	148/647	184/759	1.08 (0.84 ~ 1.38)	0.547	
Moderate	4620 (59.76)	446/2422	479/2198	1.23 (1.07 ~ 1.43)	0.004	
High	1705 (22.05)	136/945	116/760	1.07 (0.82 ~ 1.40)	0.614	
Fractured broken bones						0.863
No	6781 (87.71)	589/3468	661/3313	1.22 (1.08 ~ 1.38)	0.002	
Yes	950 (12.29)	141/546	118/404	1.19 (0.89 ~ 1.58)	0.247	
Hyperlipidaemia						0.567
No	7135 (92.29)	653/3745	681/3390	1.19 (1.06 ~ 1.34)	0.004	
Yes	596 (7.71)	77/269	98/327	1.07 (0.75 ~ 1.52)	0.720	
Neoplasm						0.612
No	5367 (69.42)	490/2834	495/2533	1.16 (1.01 ~ 1.33)	0.033	
Yes	2364 (30.58)	240/1180	284/1184	1.24 (1.02 ~ 1.50)	0.033	
Hemiplegia						0.283
No	7578 (98.02)	701/3933	744/3645	1.18 (1.05 ~ 1.33)	0.004	
Yes	153 (1.98)	29/81	35/72	1.70 (0.89 ~ 3.24)	0.110	
Age						0.686
< 65	5487 (70.97)	487/2939	474/2548	1.15 (1.00 ~ 1.32)	0.048	
⩾65	2244 (29.03)	243/1075	305/1169	1.21 (1.00 ~ 1.47)	0.055	

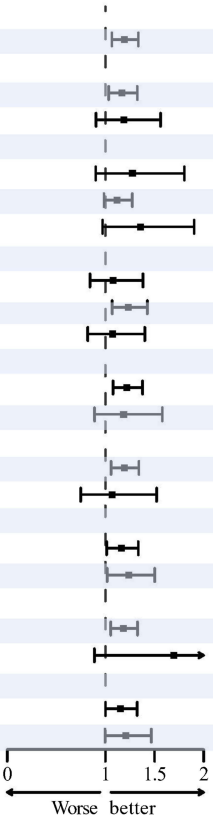

Figure 2 The results of subgroup analysis and interaction.
Abbreviation: IPAQ, International Physical Activity Questionnaire.

fractured broken bones, hyperlipidemia, neoplasm, and hemiplegia were identified as significant risk factors for sarcopenia, while education level, physical activity, and current alcohol consumption were protective factors. As shown in Table S2, for ALST/BMI, patients using metformin were 29% more likely to have low muscle mass than those not using metformin (adjusted OR 1.29; 95% CI 1.11~1.49); Table S3 shows similar results for handgrip strength (adjusted OR 1.12; 95% CI 1.00 ~ 1.26), although this was not statistically significant.

Subgroup Analysis and Interaction Tests

Although subgroup analysis indicated that metformin use may be associated with sarcopenia in certain subgroups (such as those under 65 years of age, with lower educational levels, engaging in moderate physical activity, without comorbidities, or with neoplasms) ($p<0.05$). However, formal interaction analysis revealed no statistically significant interactions across any subgroups. Thus, the effect of metformin was consistent across different subgroups, with its use consistently associated with the occurrence of sarcopenia. (Figure 2)

Discussion

In this study, we conducted a cross-sectional analysis using the UK Biobank database to explore the relationship between metformin and sarcopenia. We found that, after multivariable adjustment, in female patients with T2DM who may have or have been confirmed to have sarcopenia, the use of metformin, older age (≥65 years), and comorbidities were associated with higher odds of sarcopenia, while higher education and more physical activity were associated with lower odds. Interaction analysis showed that each factor acted independently. According to the definition of sarcopenia, when examining which components contributed to these associations, we found that low muscle mass was associated with the use of metformin, low physical activity, and low education level, but not with comorbidities. Individuals using metformin

had a higher risk of low grip strength, but this association was not significant after adjusting for confounding factors. This result suggests that metformin may primarily increase the risk of sarcopenia by reducing muscle mass rather than directly impairing muscle function, which is consistent with the finding in some studies.[17,29]

Sarcopenia is also associated with the individual's sex, with postmenopausal women experiencing a decline in estrogen levels, which can affect muscle and bone health.[30] This risk is further increased by diabetes.[31] Conversely, the relatively elevated ketone levels observed in men appear to promote muscle protein synthesis, thereby offering a degree of protection to muscles against diabetes-related pathophysiological processes.[32] Furthermore, lifestyle factors have been demonstrated to exert an influence on the subject. Some women may exhibit poor dietary habits, such as picky eating and dieting, which can result in insufficient nutrient intake, thereby affecting muscle synthesis and repair.[33] Furthermore, the time and intensity of physical labor and activity in women are typically lower than in men, which may further exacerbate the decrease in muscle mass and strength.[34] Nonetheless, there is limited evidence regarding the relationship between metformin and the incidence of sarcopenia and its components in patients with T2DM, especially among female patients, and the conclusions of various studies are inconsistent. Previous studies consistent with our findings have shown that using GWAS data and Mendelian randomization confirmed that three drugs that can induce sarcopenia include metformin (PRR=7.41, x^2=58).[18] Another mechanistic study indicated that metformin treatment regulates myostatin in skeletal muscle cells through the AMPK-FoxO3a-HDAC6 axis, thereby impairing muscle function. The muscle atrophy effect of metformin is more pronounced in wild-type (WT) mice than in db/db mice, suggesting that metformin-mediated muscle dysfunction may involve more complex mechanisms.[29] Our findings contradict a previous observational study that recruited 1,732 older T2DM patients for a cross-sectional study, which found that metformin had a protective effect against sarcopenia in these patients (Chen et al, 2020).[14] A recent study also explored the protective effect of metformin against sarcopenia using the NHANES database combined with GWAS data, and identified GDF15 as a potential therapeutic target for sarcopenia through molecular docking.[35] This discrepancy may stem from differences in sample characteristics, as our study population was limited to white women, and metabolic variations across racial and gender groups could further complicate the comparability of results. Additionally, differences in study design and unmeasured confounding factors within the research equally influence the findings. Prospective studies are needed to validate this inconsistency.

The potential mechanisms for sarcopenia in female patients with T2DM are complex and influenced by multiple factors. The prevalence of sarcopenia increases with age, and our study reflects this characteristic, which is consistent with several other studies.[14,22] In our study, the prevalence of sarcopenia and probable sarcopenia in the population under 65 years old is 17.5%, while in those over 65 years old, it is 24.4%. Additionally, regarding the relationship between education level and sarcopenia, we found that a higher level of education is associated with a lower prevalence of sarcopenia. This is consistent with previous research findings.[36] However, some other studies disagree with this conclusion, possibly due to differences in the composition of study subjects or inconsistent criteria for assessment.[37,38] Furthermore, individuals with higher education levels tend to have a stronger health awareness and pay more attention to nutritional intake and regular exercise, which can help maintain skeletal muscle quality. Additionally, those with higher education may have better access to health knowledge and adopt more scientific disease management approaches, thereby reducing their risk of developing the condition. In our study, physical activity was associated with lower odds of sarcopenia, with a strong correlation remaining even after adjusting for confounding factors, regardless of whether it was moderate or high physical activity, which aligns with the conclusions of several previous studies.[39,40] We observed that current alcohol intake was associated with a lower odds of sarcopenia, which differs from the findings of a previous systematic review on the association between alcohol consumption and the risk of sarcopenia.[41] This observation may reflect the influence of unmeasured confounding rather than a true protective effect.

Subgroup analysis and interaction tests showed no significant effect modification by metformin on the development of sarcopenia across different subgroups. Epidemiologically, sarcopenia is more common in older adults, and its incidence increases with age.[1] However, our data showed that although the P-value for the age group ≥ 65 years was close to but did not reach significance, both age groups exhibited a trend of increased risk of sarcopenia associated with metformin use. In patients with an educational background categorized as "other" (non-college or above), the OR for metformin use was 1.17 (95% CI: 1.03–1.32, P=0.013), indicating a significant association, suggesting that we should provide more protective measures for this population. We

did not observe any influence of alcohol on the effect of metformin on sarcopenia. Physical activity promotes muscle hypertrophy by activating AMPK4 and inhibiting DRP-1.[42] In a randomized controlled trial in Brazil, 44 older patients with T2DM showed increased lower limb strength and muscle mass after 12 weeks of moderate physical activity.[43] In our results, the OR for participants using metformin was 1.23 (95% CI: 1.07–1.43, P=0.004), showing a significant association; however, in patients with low and high levels of physical activity, the results did not reach significance (P-values were 0.547 and 0.614, respectively). This suggests that the level of physical activity may be an important moderating factor in the relationship between metformin and sarcopenia. In patients with and without neoplasms, the relationship between metformin use and sarcopenia reached significance (P-values were both 0.033). This indicates that neoplasms may not be a major moderating factor in the relationship between metformin and sarcopenia, but the neoplasms themselves and their treatment may have an independent effect on muscle health.[44] Additionally, we found that the effect of metformin on sarcopenia was not significant in the presence of comorbidities such as fractures, hyperlipidemia, and hemiplegia. We believe this may be due to the low statistical power resulting from the small number of participants in these subgroups, and this difference is not sufficient to alter the main conclusions of this study.

Compared to previous studies, our research has several advantages. First, it utilizes data from the UK Biobank to explore the relationship between female T2DM patients and sarcopenia, with a large sample size, thus ensuring substantial statistical power. Additionally, by adjusting for other risk factors through multifactorial logistic regression analysis, we minimized the impact of other factors on the primary research outcomes.

Limitations

This study has certain limitations. First, it employed a cross-sectional design, making it impossible to determine causal relationships and resulting in a limited level of evidence. Further randomized controlled trials (RCTs) are needed to verify the associations and establish causality. Second, the observational data used in this study are influenced by confounding factors, although we adjusted for as many covariates as possible. Third, the number of patients with sarcopenia was relatively small, preventing further analysis of patients with severe sarcopenia. Fourth, this study included only white female participants, thus precluding a comprehensive assessment of sex-specific and racial differences in the association between metformin and sarcopenia. Finally, the lack of metformin dosage data in the UK Biobank database hinders direct analysis of the dose-response relationship. Future research needs more detailed clinical data, including specific metformin dosage information and timing of medication, to further explore and validate these findings.

Conclusions

In summary, we found that older age (≥65 years), low levels of physical activity, low education, and comorbidities are risk factors for sarcopenia in female patients with T2DM. Metformin use was cross-sectionally associated with higher odds of sarcopenia. However, further longitudinal studies and clinical trials are needed to confirm our findings.

Data Sharing Statement

Data for this work was obtained from UK Biobank under the approved application No. 117320 in www.ukbiobank.ac.uk/enable-your-research/register.

Ethics Approval and Consent to Participate

The ethical approval for UK Biobank studies from the NHS National Research Ethics Service on June 29, 2021 (Ref: 21/NW/0157) is applicable for this study. All participants provided written informed consent prior to study entry. The authors confirm adherence to the ethical guidelines for authorship and publication outlined by International Journal of Women's Health. This study was exempt from approval by the institutional review board of the Sun Yat-sen Memorial Hospital, Sun Yat-sen University because it used publicly available data (registration number: SYSEC2-2025-BA-915).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is 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.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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