Prediabetes is an independent risk factor for sarcopenia in older men, but not in older women: the Bunkyo Health Study

Hideyoshi Kaga1, Yoshifumi Tamura1,2,3*, Yuki Someya2, Hitoshi Naito4, Hiroki Tabata2, Saori Kakehi2,3, Nozomu Yamasaki1, Motonori Sato1, Satoshi Kadowaki1, Ruriko Suzuki1, Daisuke Sugimoto1, Ryuzo Kawamori1,2,3 & Hirotaka Watada1,2

1Department of Metabolism and Endocrinology, Graduate School of Medicine, Juntendo University, Tokyo, Japan; 2Sportology Center, Graduate School of Medicine, Juntendo University, Tokyo, Japan; 3Sports Medicine and Sportology, Graduate School of Medicine, Juntendo University, Tokyo, Japan

Abstract

Background Sarcopenia is a major cause of disability in the elderly. Although type 2 diabetes is a risk factor for increased sarcopenia, the relationship between prediabetes and sarcopenia has not been elucidated. We aimed to examine the relationship between sarcopenia and prediabetes.

Methods The design of this study is a cross-sectional study. We evaluated glucose metabolism using the 75-g oral glucose tolerance test and glycated haemoglobin, appendicular skeletal muscle mass, and hand grip strength in 1629 older adults living in an urban area of Tokyo, Japan. We investigated the frequency of sarcopenia in participants with normal glucose tolerance (NGT), prediabetes and diabetes. A multivariable logistic regression model was used to analyse the association between glucose tolerance and the prevalence of sarcopenia.

Results The mean age of participants was 73.1 ± 5.4 years. In men, 44.3% had NGT, 26.6% had prediabetes, and 29.1% had diabetes. In women, the distribution was 56.1%, 28.8% and 15.2%. The prevalence of sarcopenia was 12.7% in men and 11.9% in women. Logistic regression revealed that prediabetes and diabetes are independent risk factors for sarcopenia in men (prediabetes, odds ratio [OR] = 2.081 [95% confidence interval {CI}: 1.031–4.199]; diabetes, OR = 2.614 [95% CI: 1.362–5.018]) and diabetes, but not prediabetes, is an independent risk factor for sarcopenia in women (prediabetes, OR = 1.036 [95% CI: 0.611–1.757]; diabetes, OR = 2.099 [95% CI: 1.146–3.844]). In both sexes, higher age (men, OR = 1.086 [95% CI: 1.028–1.146]; women, OR = 1.195 [95% CI: 1.142–1.251]), higher body fat percentage (men, OR = 1.346 [95% CI: 1.240–1.461]; women, OR = 1.218 [95% CI: 1.138–1.303]) and lower body mass index (men, OR = 0.371 [95% CI: 0.299–0.461]; women, OR = 0.498 [95% CI: 0.419–0.593]) were independent risk factors for sarcopenia.

Conclusions Although we confirmed that diabetes mellitus is associated with sarcopenia in both sexes, prediabetes is associated with sarcopenia in men, but not in women.

Keywords sarcopenia; muscle strength; prediabetes; type 2 diabetes

Received: 7 September 2021; Revised: 16 March 2022; Accepted: 18 August 2022

*Correspondence to: Yoshifumi Tamura, Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Email: y-s-tamura@juntendo.ac.jp

© 2022 The Authors. Journal of Cachexia, Sarcopenia and Muscle published by John Wiley & Sons Ltd on behalf of Society on Sarcopenia, Cachexia and Wasting Disorders. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
Introduction

The number of elderly people has increased worldwide. The ageing rate in Japan is the highest in the world. A serious social problem in an aged society is the increase in the number of elderly people who need long-term care. Sarcopenia, defined as a decrease in skeletal muscle mass, strength and function, is recognized to be a common condition in elderly people who need long-term care. Patients with diabetes mellitus have lower muscle strength than people without diabetes mellitus, and type 2 diabetes is associated with accelerated loss of leg muscle strength in elderly individuals. In fact, type 2 diabetes has been identified as a risk factor for sarcopenia. Because body mass index (BMI) of patients with diabetes mellitus in Asian countries is much lower than in other countries and low BMI is a strong predictor of sarcopenia, sarcopenia easily develops in elderly Asians with diabetes.

Similar to diabetes, the prevalence of prediabetes, defined as elevated fasting plasma glucose, postprandial hyperglycaemia or both, is increased with ageing. Prediabetes is often diagnosed by health check-ups and outpatient clinic in Japan, because annual blood glucose or HbA1c check are obligated to Japanese people over 40 years old. Because prediabetes is established as a risk factor for cardiovascular disease, intensive prevention for cardiovascular disease is now recommended not only for diabetes but also for prediabetes in clinical guideline. In terms of sarcopenia, previous studies have revealed that hand grip strength adjusted by BMI or body weight is associated with prediabetes in East Asians. Therefore, prediabetes may be a risk for sarcopenia, and healthcare providers may need to pay attention to the development of sarcopenia in prediabetes as well as diabetes. However, the association between prediabetes and sarcopenia has not been clarified yet.

In this context, the purpose of the present study was to clarify the association between prediabetes and prevalence of sarcopenia in community-dwelling elderly Japanese individuals.

Research design and methods

Study design and participants

The study subjects were all participants in the Bunkyo Health Study. The Bunkyo Health Study is a prospective cohort study designed to clarify whether muscle function (muscle mass, muscle strength and insulin sensitivity) is associated with multiple diseases that necessitate long-term care, and we performed cross-sectional analysis using the baseline data of the study. Briefly, in this study, we recruited elderly subjects aged 65–84 years living in Bunkyo-ku, an urban area in Tokyo, Japan. Exclusion criteria consisted of pacemaker or defibrillator placement and diabetes requiring insulin therapy. Subjects underwent measurements over 2 days. On the first day, we evaluated cognitive function using questionnaires. We also evaluated muscle strength and physical performance. On the second day, after an overnight fast, we evaluated brain lesions with magnetic resonance imaging (MRI), bone mineral density with dual-energy X-ray absorptiometry, arteriosclerosis with the cardio-ankle vascular index, abdominal fat distribution with MRI, and glucose tolerance with a 75-g oral glucose tolerance test (75-g OGTT). The study protocol was approved by the ethics committee of Juntendo University in November 2015 (Nos. 2015078, 2016138, 2016131, 2017121 and 2019085). This study was carried out in accordance with the principles outlined in the Declaration of Helsinki. All participants gave written informed consent and were informed that they had the right to withdraw from the trial at any time.

Definition of glucose tolerance

We administered the 75-g OGTT to all participants and measured haemoglobin A1c on the same day. According to the diagnostic criteria by the Japan Diabetes Society, diabetes was defined as fasting plasma glucose ≥126 mg/dL, 2-h glucose level after 75-g OGTT ≥200 mg/dL, haemoglobin A1c ≥6.5% or use of oral hypoglycaemic agents. Normal glucose tolerance (NGT) was defined as fasting plasma glucose <110 mg/dL, 2-h glucose level after the 75-g OGTT <140 mg/dL, and haemoglobin A1c <6.5%. The remaining participants were defined as prediabetes.

Muscle strength measurement

Grip strength was measured twice on each side using a hand grip dynamometer (T.K.K.5401, Takei Scientific Instruments Co., Ltd., Niigata, Japan). We used the average of the maximum values for each side for handgrip strength. We evaluated isokinetic muscle strength of knee extensors and flexors using a dynamometer (BIODEX system 3 or 4, Biodex Medical Systems, Upton, NY, USA). Isokinetic peak torque of knee extensors and flexors was measured at an angular velocity of 60°/s. During the test, participants were encouraged to exert maximal muscle force.

Physical function tests

We administered other physical function tests, including a one-leg standing test (balance test), which measured the duration that subjects could stand on one leg with their eyes open; maximum gait speed (10-m walking test); and a Timed Up and Go test (TUG), which measures the time that it took
for a participant to stand up from a seated position, walk 3 m, turn, walk back and sit down again.

**Other measurements**

Appendicular skeletal muscle mass (ASM) was evaluated with bioelectrical impedance analysis (InBody770, InBody Japan Inc., Tokyo, Japan). Physical activity was evaluated using the International Physical Activity Questionnaire, which assesses different types of physical activity, such as walking and both moderate- and high-intensity activities. Nutritional status was evaluated using a brief self-administered diet history questionnaire that contained 58 items about fixed portions and food types. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medications. Dyslipidaemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol < 40 mg/dl, triglycerides ≥ 150 mg/dl, or current use of lipid-lowering agents.

**Definition of sarcopenia**

Sarcopenia was defined as weak hand grip (<28 kg for men and <18 kg for women) and low ASM (<7.0 kg/m² for men and <5.7 kg/m² for women) based on the definition of the Asian Working Group for Sarcopenia (AWGS) 2019.14

**Statistical analysis**

Participants were divided into three groups (NGT, prediabetes and diabetes) for each sex. We used IBM SPSS Statistics for Windows, version 25.0. (IBM Corp., Armonk, NY, USA) for statistical analysis. Data are presented as means ± SD or number (%). There were considerable differences in body composition, muscle strength, physical function and glucose tolerance by sex. Therefore, all analyses were stratified by sex. Differences in means and proportions were tested using ANOVA and the χ² test. ASM, muscle strength and physical function differences were tested using ANCOVA with adjustment for age, BMI, % body fat, daily physical activity level, energy intake and cerebrovascular disease. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between glucose tolerance and the prevalence of sarcopenia, with adjustments for potential confounders. In this study, three models were generated in regression analysis. Model 1 was adjusted for age. Model 2 was adjusted for variables in Model 1 plus BMI, % body fat, physical activity level and energy intake. Model 3 was adjusted for variables in Model 2 plus cerebrovascular disease. We determined the potential confounders based on prior knowledge, which is the most used method in epidemiology. Previous reports suggested that BMI, % body fat, daily physical activity level, energy intake and cerebrovascular disease are associated with muscle mass or muscle strength,15–18 and several intervention studies have suggested causal relationships between the several factors raised and muscle mass or strength or physical function.19 All statistical tests were two-sided with a 5% significant level.

**Results**

**Characteristics by glucose tolerance status**

The characteristics of the study participants are shown in Table 1. The mean age of subjects was 73.1 ± 5.4 years. Of 1629 participants, 156 participants (9.6%) were diagnosed with diabetes because they were taking oral hypoglycaemic agents. In the remaining 1473 participants, 2 participants had missing data on 2-h glucose level after the 75-g OGTT. One was diagnosed with diabetes, and the other was diagnosed with NGT based on fasting plasma glucose and haemoglobin A1c levels. In the Bunkyo Health Study, 187 (11.5%) were newly diagnosed with diabetes mellitus. In men, 44.3% of participants had NGT, 26.6% had prediabetes, and 29.1% had diabetes mellitus. In women, the distribution was 56.1%, 28.8% and 15.2%. Participants with prediabetes and diabetes were significantly older than those with NGT in each sex. Men in the Diabetes group had significantly lower energy intake than men in the prediabetes group. Women in the diabetes group had significantly shorter education duration than women in the NGT and prediabetes groups. Women in the diabetes group had significantly lower physical activity level than women in the NGT group. The NGT group had significantly lower BMI and % body fat than the prediabetes and diabetes groups in both sexes. The prediabetes group had higher subcutaneous fat area than the NGT group in both sexes. Visceral fat area increased as glucose tolerance worsened in both sexes.

Table 2 shows blood test data in each glucose tolerance status group. Fasting plasma glucose, haemoglobin A1c and alanine aminotransferase levels increased as glucose tolerance worsened. Gamma glutamyl transpeptidase levels were significantly higher in the diabetes group compared with the NGT group in both sexes. Aspartate aminotransferase levels were significantly higher in the diabetes group compared with the NGT group in both sexes. The prevalence of sarcopenia and mean values of ASM, muscle strength and physical function parameters in each glucose tolerance status group. In this cohort, the prevalence of sarcopenia was 12.7% in men and 11.9% in women. ASM was comparable across groups in both men.
and women. After adjustment, in men, hand grip strength was lower in the diabetes group than in the NGT group, while hand grip strength was lower in the diabetes group than in the NGT and prediabetes groups in women. On the other hand, after adjustment, muscle strength in knee extensors and flexors, balance, maximum gait speed, and TUG scores were comparable across glucose tolerance status groups in both sexes.

Tables 4 and 5 show the ORs of each glucose tolerance group for sarcopenia in men and women, respectively. In men, after full adjustment, prediabetes and diabetes were each independently associated with a higher OR for sarcopenia when compared with NGT (prediabetes, 2.081 [95% CI: 1.031–4.199]; diabetes, 2.614 [95% CI: 1.362–5.018]). On the other hand, only diabetes was independently associated with increased ORs for sarcopenia in women (prediabetes, 1.036 [95% CI: 0.611–1.757]; diabetes, 2.099 [95% CI: 1.146–3.844]). In addition, age and % body fat were positively correlated, and BMI was negatively correlated with the prevalence of sarcopenia in both sexes.

Discussion

Sarcopenia and reduced muscle strength are associated with diabetes; however, these associations are not fully understood in prediabetes. The present study revealed that prediabetes and diabetes are independently associated with a higher OR for sarcopenia in men, but only diabetes is associated with increased ORs in women. These findings highlight the importance of early intervention in prediabetes to prevent the progression to sarcopenia in both sexes.
## Table 3: Comparison of arm and leg strength and physical function by glucose tolerance status and sex

|                      | Men                                |          | Women                                |          |
|----------------------|------------------------------------|----------|--------------------------------------|----------|
|                      | NGT                                | Prediabetes | Diabetes                            |          |
| Sarcopenia (%)       | 8.6%                               | 13.7%     | 18.0%                                | 0.007<sup>a</sup> |
| ASM (kg/m²)          | 7.35 ± 0.62                        | 7.33 ± 0.65 | 7.33 ± 0.68                          | 0.967<sup>c</sup> |
| Low ASM (%)          | 31.6%                              | 28.4%     | 31.5%                                | 0.734<sup>a</sup> |
| Hand grip strength (kg) | 33.1 ± 5.4                        | 32.1 ± 6.1 | 31.1 ± 5.6<sup>*</sup>               | 0.048<sup>b</sup> |
| Low hand grip strength (%) | 17.1%                            | 21.9%     | 30.5%                                | 0.002<sup>a</sup> |
| Muscle strength in knee extensors (Nm/kg) | 1.53 ± 0.39                      | 1.49 ± 0.39 | 1.41 ± 0.38                          | 0.313<sup>c</sup> |
| Muscle strength in knee flexors (Nm/kg) | 0.75 ± 0.25                      | 0.73 ± 0.25 | 0.68 ± 0.23                          | 0.369<sup>c</sup> |
| Balance (s)          | 57.2 ± 44.0                        | 48.1 ± 44.0 | 38.5 ± 40.2                          | 0.095<sup>b</sup> |
| Maximum gait speed (m/s) | 2.01 ± 0.37                      | 1.93 ± 0.39 | 1.90 ± 0.38                          | 0.220<sup>b</sup> |
| Timed Up and Go test score (s) | 6.3 ± 1.2                        | 6.6 ± 1.6  | 6.8 ± 2.1                            | 0.506<sup>b</sup> |

Note: Data are means ± SD.
ASM, appendicular skeletal muscle mass; BMI, body mass index; NGT, normal glucose tolerance; Nm, Newton meters.
<sup>a</sup>P value for χ² test.
<sup>b</sup>P value for ANCOVA with adjustment for age, BMI, % body fat, daily physical activity level, energy intake and cerebrovascular disease.
<sup>c</sup>P value for ANCOVA with adjustment for age, % body fat, daily physical activity level, energy intake and cerebrovascular disease.
<sup>*</sup><p><i>p</i> < 0.05 vs. NGT with Bonferroni correction.
<sup>†</sup><p><i>p</i> < 0.05 vs. prediabetes with Bonferroni correction.

## Table 4: Associations between sarcopenia and glucose tolerance in men

|                      | Model 1                      | Model 2                      | Model 3                      |
|----------------------|------------------------------|------------------------------|------------------------------|
| Glucose tolerance    |                              |                              |                              |
| Prediabetes          | 1.491 (0.823–2.698)          | 1.890 (0.946–3.775)          | 2.081 (1.031–4.199)          |
| Diabetes             | 2.028 (1.168–3.523)          | 2.602 (1.326–4.971)          | 2.614 (1.362–5.018)          |
| Age (per 1 year)     | 1.112 (1.064–1.163)          | 1.087 (1.030–1.147)          | 1.086 (1.028–1.146)          |
| BMI (per 1 kg/m²)    |                              |                              |                              |
| % Body fat (per 1.0%)|                              |                              |                              |
| Daily physical activity (per 1 MET/hour/week) | 0.993 (0.985–1.000)      | 0.993 (0.985–1.000)      | 0.993 (0.985–1.000)      |
| Energy intake (per 100 kcal) | 0.991 (0.945–1.040)       | 0.990 (0.943–1.040)       | 0.990 (0.943–1.040)       |
| CVD                  |                              |                              | 3.470 (1.104–10.906)        |

Note: Model 1 was adjusted for age. Model 2 was adjusted for variables in Model 1 plus body mass index, % body fat, physical activity and energy intake. Model 3 was adjusted for variables in Model 2 plus CVD.
Abbreviations: BMI, body mass index; MET, metabolic equivalent; CVD, cerebrovascular disease.

## Table 5: Associations between sarcopenia and glucose tolerance for women

|                      | Model 1                      | Model 2                      | Model 3                      |
|----------------------|------------------------------|------------------------------|------------------------------|
| Glucose tolerance    |                              |                              |                              |
| Prediabetes          | 0.886 (0.546–1.440)          | 1.052 (0.623–1.775)          | 1.036 (0.611–1.757)          |
| Diabetes             | 1.403 (0.825–2.287)          | 2.091 (1.142–3.829)          | 2.099 (1.146–3.844)          |
| Age (per 1 year)     | 1.159 (1.114–1.207)          | 1.196 (1.142–1.252)          | 1.195 (1.142–1.251)          |
| BMI (per 1 kg/m²)    |                              |                              |                              |
| % Body fat (per 1.0%)|                              |                              |                              |
| Daily physical activity (per 1 MET/hour/week) | 0.998 (0.992–1.004)      | 0.998 (0.992–1.004)      | 0.998 (0.992–1.004)      |
| Energy intake (per 100 kcal) | 0.979 (0.937–1.022)       | 0.979 (0.938–1.022)       | 0.979 (0.938–1.022)       |
| CVD                  |                              |                              | 1.346 (0.400–4.529)         |

Note: Model 1 was adjusted for age. Model 2 was adjusted for variables in Model 1 plus body mass index, % body fat, physical activity and energy intake. Model 3 was adjusted for variables in Model 2 plus CVD.
Abbreviations: BMI, body mass index; MET, metabolic equivalent; CVD, cerebrovascular disease.
abetes is an independent risk factor for sarcopenia in men, but not in women.

The present study was the first to show that prediabetes is associated with sarcopenia in men. A previous study of a community-dwelling cohort in the United Kingdom involving participants with NGT and prediabetes also showed an association between an increase in 2-h glucose levels during 75-g OGTT and a decrease in hand grip strength. In addition, ORs for poor physical function in men with diabetes mellitus or impaired glucose tolerance were 2.73 and 1.62 compared with NGT, respectively. Interestingly, these relationships were weaker and statistically non-significant in women. The English Longitudinal Study of Ageing, which included 3404 older adults, also showed that diabetes predicted sarcopenia in men (OR: 2.43 [95% CI: 1.5–3.95]), but not in women (OR: 1.49 [95% CI: 0.83–2.68]). These data suggested that reduced glucose tolerance is associated with reduced muscle strength and poor physical function in men with and without diabetes mellitus. In terms of muscle mass, lower lean body mass with ageing was associated with incident diabetes in men, but not in women. These sex differences might be associated with different rates in muscle decline with ageing in males and females; declines in muscle mass and strength with ageing are greater in men than in women. However, in the present study, muscle strengths in lower limb were not reduced in both sexes. Our preliminary analysis revealed that the hand grip strength and muscle strength in knee extensor was only moderately correlated (men, r = 0.408, P < 0.001; women, r = 0.374, P < 0.001), suggesting these muscle strengths are differently regulated. In fact, the lower limb muscle is a weight-bearing muscle and the hand grip muscle is a non-weight-bearing muscle; thus, these differences may modify the effects of prediabetes on muscle volume and strength.

We defined sarcopenia as the combination of both weak hand grip strength and low ASM in the present study. ASM and the prevalence of low ASM were very similar among the groups, whereas hand grip strength was significantly lower in subjects with diabetes than NGT. These data suggested that old adults with diabetes have low hand grip strength, even if they have something similar muscle mass. A previous study suggested that muscle quality, defined as muscle strength divided by corresponding muscle mass, is lower in patients with diabetes compared with individuals without diabetes. On the other hand, in men, post hoc analysis did not show significant difference in hand grip strength between NGT and prediabetes, and the prevalence of low hand grip strength was also comparable between NGT and prediabetes. However, prediabetes was independently associated with a higher OR for sarcopenia when compared with NGT in men. These results suggest that low ASM and low hand grip strength are more likely to be combined in prediabetes, which may account for the increased risk of sarcopenia in prediabetes. However, the mechanisms leading to sarcopenia in prediabetes and diabetes have not been elucidated yet. Hyperglycaemia reduces contractile function and force generation of muscle in mice. Insulin resistance is also associated with reduced muscle strength. Diabetic neuropathy occurs in patients with diabetes or prediabetes and is associated with impaired muscle strength in patients with diabetes. These factors might contribute to lower hand grip strength and higher prevalence of sarcopenia in prediabetes and diabetes. On the other hand, it could be also possible that sarcopenia cause prediabetes, because skeletal muscle is one of the major organs of insulin-stimulated glucose uptake during postprandial state, and in fact, several studies showed that decreased muscle mass is associated with elevated glucose level during OGTT. Thus, the causal relationship between prediabetes and sarcopenia may be bidirectional; however, in the present study, the deterioration of glucose metabolism was not accompanied by a decrease in muscle mass.

Non-Asian patients with diabetes have much higher BMI than Asian patients with diabetes. ASM is positively associated with BMI. Thus, the prevalence of sarcopenia could be lower in non-Asian patients with diabetes compared with Asian patients with diabetes. In the present study, the prevalence of sarcopenia, defined as low hand grip strength and low ASM (AWGS 2019) was 12.7% and 11.9% in men and women, respectively. If we applied the cutoff values for grip strength and ASM from the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), the prevalence of sarcopenia would be 10.5% and 6.8% in men and women, respectively (data not shown). Similarly, in a community-dwelling Korean cohort, the prevalence of sarcopenia defined by hand grip strength and ASM was 14.4% in men and 6.4% in women with AWGS2019 cutoff values and 11.9% in men and 6.7% in women with EWGSOP2 cutoff values. In contrast, using the same hand grip strength and ASM cutoff values in the EWGSOP2 criteria, the prevalence of sarcopenia in a community-dwelling elderly European cohort was 0.6–3.1% in men and 0–2.4% in women. Thus, the prevalence of sarcopenia in Asians could be much higher than in Europeans. It remains unclear whether prediabetes is associated with sarcopenia in non-Asians.

Our data suggest a few clinical implications. As the present study suggested that sarcopenia develops even before diabetes develops, healthcare providers in hospital and community should recognize that prediabetes is a risk factor for sarcopenia and screen high-risk old prediabetes for sarcopenia. In addition, healthcare providers should encourage high-risk old prediabetes to prevent the development of sarcopenia by exercise and consumption of adequate amounts of protein. Of course, for efficient prevention of sarcopenia, the establishment of efficient intervention is required in the near future.

There are several limitations in this study. First, we did not evaluate peripheral neuropathy and duration of diabetes in subjects with previously diagnosed diabetes. A previous study
showed that muscle quality is associated with duration of diabetes, and diabetes starting in midlife and longer duration of diabetes are significant risk factors for incident sarcopenia. Second, we defined sarcopenia based on hand grip strength and ASM. Thus, it remains unclear whether definite sarcopenia including physical performance is also associated with prediabetes. Third, the association between prediabetes and sarcopenia became significant with Model 3, while not significant in Model 1 and Model 2, suggesting that prediabetes may be a less clear and weaker risk factor for sarcopenia than diabetes. However, there were several confounding factors that weakened the association between prediabetes and sarcopenia without adjustment (downward bias). Finally, the present study is cross-sectional and thus cannot establish causality.

In conclusion, the present study revealed that prediabetes is an independent risk factor for sarcopenia in men, but not in women, while diabetes is an independent risk factor for reduced hand grip strength and sarcopenia in both sexes. These associations were still significant after adjustment for many confounders, suggesting that elevated glucose level might be an important contributor to decreased muscle strength. Thus, our study suggested that prediabetic men and diabetic men and women are a high-risk population of sarcopenia. Further studies are required to determine whether a combination of exercise and nutrition therapy can prevent sarcopenia in these high-risk population.

Funding information

This study was supported by Strategic Research Foundation at Private Universities (S1411006) and KAKENHI (18H03184) grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Mizuno Sports Promotion Foundation; and the Mitsui Life Social Welfare Foundation.

Acknowledgements

The authors would like to thank Liu L., Aoki T., Nakagata T., Hui H. and all staff for their contributions to data collection at the Sportology Center. The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021.

Conflict of Interest

The authors have nothing to disclose.

References

1. Park SW, Goodpaster BH, Strotmeyer ES, de Rekeneire N, Harris TB, Schwartz AV, et al. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes 2006;55:1813–1818.

2. Park SW, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C, et al. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes Care 2007;30:1507–1512.

3. Nakamura K, Yoshida D, Honda T, Hata J, Shibata M, Hirakawa Y, et al. Midlife and late-life diabetes and sarcopenia in a general older Japanese population: the Hisayama Study. J Diabetes Invest. 2021;12:1899–1907.

4. Maskarinec G, Grandinetti A, Matsuura G, Sharma S, Mau M, Henderson BE, et al. Diabetes prevalence and body mass index differ by ethnicity: the Multiethnic Cohort. Ethn Dis 2009;19:49–55.

5. Iannuzzi-Such M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci 2002;57:M772–M777.

6. Feng L, Gao Q, Hu K, Wu M, Wang Z, Chen F, et al. Prevalence and risk factors of sarcopenia in patients with diabetes: a meta-analysis. J Clin Endocrinol Metab 2021;107:1470–1483.

7. Munshi MN, Pandya N, Umpierrez GE, DiGenio A, Zhou R, Riddle MC. Contributions of basal and prandial hyperglycemia to total hyperglycemia in older and younger adults with type 2 diabetes mellitus. J Am Geriatr Soc 2013;61:535–541.

8. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255–232.

9. Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ 2020;370:m2297.

10. Jang BN, Nari F, Kim S, Park EC. Association between relative handgrip strength and prediabetes among South Korean adults. PLoS One 2020;15:e0240027.

11. Hu S, Gu Y, Lu Z, Zhang Q, Liu L, Meng G, et al. Relationship between grip strength and prediabetes in a large-scale adult population. Am J Prev Med 2019;56:844–851.

12. Someya Y, Tamura Y, Kaga H, Nojiri S, Shimada K, Daida H, et al. Skeletal muscle function and need for long-term care of urban elderly people in Japan (the Bunkyo Health Study): a prospective cohort study. BMJ Open 2019:e031584.

13. Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, et al. Japanese clinical practice guideline for diabetes 2019. J Diabetes Invest 2020;11:1020–1076.

14. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc 2020;21:300–307.e2.

15. Su Y, Yuki M, Otsuki M. Prevalence of stroke-related sarcopenia: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2020;29:105092.

16. Steff M, Bohannon RW, Sontakova L, Tufano JJ, Shills K, Holmerova I. Relationship between sarcopenia and physical activity in older people: a systematic review and meta-analysis. Clin Interv Aging 2017;12:835–845.

17. Graf CE, Pichard C, Herrmann FR, Sieber CC, Zekry D, Genton L. Prevalence of low muscle mass according to body mass index in older adults. Nutrition 2017;34:124–129.

18. Robinson S, Cooper C, Aihie SA. Nutrition and sarcopenia: a review of the evidence.
and implications for preventive strategies. *J Aging Res* 2012;2012:510801.

19. Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Med Dir Assoc* 2017;18:e1–e16.

20. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? *Diabetes Care* 2005;28:2541–2542.

21. Yang L, Smith L, Hamer M. Gender-specific risk factors for incident sarcopenia: 8-year follow-up of the English longitudinal study of ageing. *J Epidemiol Community Health* 2019;73:86–88.

22. Kalyani RR, Metter EJ, Xue QL, Egan JM, Chia CW, Saudek CD, Ferrucci L. Glucose and insulin measurements from the oral glucose tolerance test and relationship to muscle mass. *J Gerontol A Biol Sci Med Sci* 2012;67:74–81.

23. Helander I, Westerblad H, Katz A. Effects of glucose on contractile function, [Ca2+]i, and glycogen in isolated mouse skeletal muscle. *Am J Physiol Cell Physiol* 2002;282:C1306–C1312.

24. Abbatecola AM, Ferrucci L, Ceda G, Russo CR, Lauretani F, Bandinelli S, et al. Insulin resistance and muscle strength in older persons. *J Gerontol A Biol Sci Med Sci* 2005;60:1278–1282.

25. Barzilay JI, Cotsonis GA, Walston J, Schwartz AV, Satterfield S, Mijlickovic I, et al. Insulin resistance is associated with decreased quadriceps muscle strength in nondiabetic adults aged ≥70 years. *Diabetes Care* 2009;32:736–738.

26. Singleton JR, Smith AG, Marcus RL. Exercise as therapy for diabetic and prediabetic neuropathy. *Curr Diab Rep* 2015;15:120.

27. Andersen H, Nielsen S, Mogensen CE, Jakobsen J. Muscle strength in type 2 diabetes. *Diabetes* 2004;53:1543–1548.

28. Almurdhi MM, Reeves ND, Bowling FL, Boulton AJ, Jeziorska M, Malik RA. Reduced lower-limb muscle strength and volume in patients with type 2 diabetes in relation to neuropathy, intramuscular fat, and vitamin D levels. *Diabetes Care* 2016;39:441–447.

29. Kalyani RR, Metter EJ, Ramachandran R, Chia CW, Saudek CD, Ferrucci L. Gender and insulin measurements from the oral glucose tolerance test and relationship to muscle mass. *J Gerontol A Biol Sci Med Sci* 2012;67:74–81.

30. Rattarasarn C, Leelawattana R, Soonthornpun S. Contribution of skeletal muscle mass on sex differences in 2-hour plasma glucose levels after oral glucose load in Thai subjects with normal glucose tolerance. *Metabolism* 2010;59:172–176.

31. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48:16–31.

32. Kim M, Won CW. Sarcopenia in Korean community-dwelling adults aged 70 years and older: application of screening and diagnostic tools from the Asian Working Group for Sarcopenia 2019 update. *J Am Med Dir Assoc* 2020;21:752–758.

33. Van Ancum JM, Alcazar J, Mekers CGM, Nielsen BR, Suetta C, Maier AB. Impact of using the updated EWGSOP2 definition in diagnosing sarcopenia: a clinical perspective. *Arch Gerontol Geriatr* 2020;90:104125.

34. von Haehling S, Morley JE, Coats AJ, Anker SD. Ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*: update 2021. *J Cachexia Sarcopenia Muscle* 2021;12:2259–2261.