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Original Study

Preserved Lower Limb Muscle Mass Prevents Insulin Resistance Development in Nondiabetic Older Adults

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A B S T R A C T

Objective: To investigate roles of sarcopenia indexes in prediction of development of insulin resistance in nondiabetic older adults.
Design: A 2-year follow-up cohort.
Setting and participants: The Tanno-Sobetsu study, a prospective observational cohort, included 194 community-dwelling nondiabetic older adults during 2017-2019.
Methods: Lower limb, upper limb, appendicular, and trunk muscle masses by a bioelectrical impedance analysis, grip strength, knee extension torque, and walking speed were measured in study participants aged ≥65 years (79 men and 115 women) at baseline. Muscle mass and strength were divided by the weight, and then multiplied by 100 to calculate the weight ratio (%). Insulin resistance was assessed by homeostasis model (HOMA-IR) at baseline, and the study participants whose HOMA-IR was less than 1.73 at baseline were followed for a maximum of 2 years. The study endpoint was development of insulin resistance defined as HOMA-IR ≥1.73. The adjusted hazard ratio (HR) of each sarcopenia component for development of insulin resistance was calculated.
Results: Lower limb muscle mass (HR 0.88, 95% CI 0.79-0.98) and appendicular muscle mass (HR 0.89, 95% CI 0.81-0.99), but not other sarcopenia components, were associated with the development of insulin resistance, independently of sex and age, HOMA-IR, and waist circumference at baseline.
Conclusions and Implications: The loss of lower limb muscle mass is a significant risk factor for development of insulin resistance independently of obesity in nondiabetic older adults. The lower limb muscle mass may be a novel target of interventions for the prevention of diabetes in older adults.

The population of Japan is rapidly aging, with the percentage of the population aged ≥65 years at 28.8% in 2021, and is estimated to reach 33.3% by 2036.[1] One of the most common diseases that increases with ageing is type 2 diabetes.[2,3] Because type 2 diabetes in older adults is a strong risk factor for atherosclerotic cardiovascular events and death,[4,5] the numbers of diabetes and diabetes-related deaths are predicted to further increase in the next decades. Insulin resistance is a major pathophysiology underlying prediabetic glucose intolerance and type 2 diabetes. It has long been known that the accumulation of visceral fat is closely related to the development of insulin resistance.[6] However, it has been reported that older adults often have increased insulin resistance without obesity, unlike the middle aged.[7] In fact, 75% of patients with type 2 diabetes aged ≥65 years are nonobese in Japan.[8] Therefore, interventions other than those to reduce visceral fat mass might be important for prevention of diabetes in older adults.

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Sarcopenia is an age-related decline in skeletal muscle mass, strength and function, which is associated with increased disability in older adults.[9,10] Because skeletal muscle is a major target organ for insulin, sarcopenia is thought to influence risk of development of insulin resistance. In fact, several cross-sectional studies have shown an association between sarcopenia and increased insulin resistance.[11,12] In our recent cross-sectional study, among the components of sarcopenia, loss of lower limb muscle mass was found to be strongly associated with insulin resistance in nondiabetic older adults.[13] However, there are few longitudinal studies on the relationship between sarcopenia and insulin sensitivity, and results of a recent study suggests that sarcopenia, which was defined by low muscle mass, low muscle strength and/or walking speed has little impact on risk of insulin resistance.[14] To our knowledge, no study has examined relationships between multiple indices of sarcopenia and temporal change in insulin sensitivity in older adults. This issue was examined in the present study by use of data from a cohort that has been prospectively followed for decades.

Methods

Participants

This longitudinal study used data from the Tanno-Sobetsu study, a prospective community-based cohort study aimed at elucidation of cardiovascular risk factors.[15]

Of the 605 residents who underwent a medical examination in Sobetsu Town in 2017, a total of 342 individuals aged ≥65 years also underwent sarcopenia-related testing. The inclusion criterion of the age for sarcopenia-related tests was ≥65 years according to the definition of an older adult because sarcopenia is more frequent and a larger social issue in older adults than in younger ones.[9] As we previously reported,[16,17] insulin resistance was defined as the homeostasis model assessment of insulin resistance (HOMA-IR) ≥1.73. The sensitivity and specificity of HOMA-IR ≥1.73 were 64.3% and 78.9%, respectively, when insulin resistance determined by euglycemic hyperinsulinemic glucose clamp technique was used as a gold standard.[16,17] From the 342 residents, 130 individuals who already had insulin resistance (HOMA-IR ≥ 1.73) or type 2 diabetes [fasting glucose ≥ 126 mg/dL, hemoglobin A_{1c} (HbA_{1c}) ≥ 6.5% or with treatment for diabetes] at baseline and 18 individuals who could not be followed up or had missing data were excluded. The remaining 194 individuals contributed to analyses in the present study (Supplementary Figure 1).

This study conformed to the principles outlined in the Declaration of Helsinki and was performed with the approval of the institutional ethical committee of Sapporo Medical University (approval number: 24-2-21). Written informed consent was received from all of the participants.

Anthropometrics and Sociodemographic Data

Participants received a medical examination in the early morning after overnight fasting. Height and weight were measured using a digital scale (TANITA Co, Ltd); body mass index was calculated as weight (kg) / height (m) squared. Waist circumference was measured around the height of the navel when viewed from the front after exhaling. Information regarding regular medication for type 2 diabetes and smoking habit (current/former/never) was collected by public health nurses in an interview form.

Muscle Mass Measurements

Muscle mass (kg) was measured using a bioelectrical impedance analysis (BIA; In Body 470; In Body Japan Co), and lower limb, upper limb, and trunk muscle masses were also determined at baseline. In addition, appendicular muscle mass was calculated as a sum of the lower and upper limb muscle masses. Each muscle mass was divided by the weight and multiplied by 100 to calculate the weight ratio (%).[18] This system applies electricity at frequencies of 5, 50, 250, and 500 kHz through the body. It has been shown that the coefficients of determination (R^2) between the muscle mass measured by the BIA and the muscle mass measured by the dual-energy X-ray absorptiometry method, which is the most reliable method for determination of body composition, are high (ie, R^2 = 0.88 in men and 0.83 in women).[19]

Muscle Strength and Muscle Function Measurements

As indexes of muscle strength, grip strength, and isometric knee extension torque were measured at baseline. The grip strength (kg) of both hands was measured twice using a Smedley-type grip strength meter (Grip D; Takei Scientific Instruments Co, Ltd) when the participants were standing with full elbow extension.[20] The knee extension torque (Nm) of both sides was measured twice using a handheld dynamometer (mobie MT-100; SAKAI Med Co, Ltd). The participants sat on a chair with 90° knee flexion, and the force sensor was fixed to the distal side of the leg by a belt.[21] The knee extension torque was calculated by multiplying the maximal isometric knee extension force by the lower leg length. The handgrip strength and the knee extension torque were adopted as the average value on both sides, divided by weight, and multiplied by 100 to calculate the weight ratio (%). Muscle function was assessed by comfortable walking speed at baseline. The comfortable walking speed was measured by 4-m walking test, which was set at an acceleration road and a deceleration road of 1 m as in a previous report.[22]

Serum Measurements

The serum biochemical parameters measured were fasting glucose, fasting insulin, HbA_{1c}, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, highly sensitive C-reacting protein, and albumin. HOMA-IR was calculated using the formula: fasting glucose (mg/dL) × fasting insulin (μU/mL) / 405.

Follow-up and Study Endpoint

The endpoint of this study was development of insulin resistance (ie, HOMA-IR ≥ 1.73). The study participants were followed until the annual examination in 2019. Individuals who did not receive health examinations in 2018 or 2019 were defined as censored cases at the time of the last health checkup. The mean of the follow-up was 1.8 years, median 2 years, range 1-2 years.

Statistical Analysis

All numerical values are expressed as mean ± SD or medians and range. The Student *t* test, Mann-Whitney *U* test, and chi-square method were used to compare baseline characteristics between groups, if appropriate. The participants were divided into 2 groups by HOMA-IR at the end of the follow-up: participants with HOMA-IR ≥1.73 and those with HOMA-IR <1.73 at the end of the follow-up were grouped into an insulin resistance group and a non–insulin resistance group, respectively.

The hazard ratio (HR) and 95% CI of each muscle mass, muscle strength, and walking speed at baseline for development of insulin resistance were calculated using the Cox proportional hazards model. Age and sex were selected as confounding factors in model 1. In model 2, the baseline HOMA-IR was added to the confounding factors used in

model 1, and the baseline waist circumference together with the confounding factors in model 2 was incorporated in model 3. Finally, model 4 added baseline triglycerides and HDL-C to the confounding factors used in model 3. Similar Cox proportional hazard model analyses were conducted for males and females separately. IBM SPSS Statistics version 22 (IBM Inc) was used for statistical analysis. The significance level in all analyses was set at $P < .05$.

Results

The characteristics of the study participants at baseline are shown in Table 1. Mean height, weight, lower limb muscle mass, upper limb muscle mass, appendicular muscle mass, trunk muscle mass, handgrip strength, knee extension torque, fasting glucose, and percentages of participants with smoking were significantly higher in men than in women. Total cholesterol, HDL-C, and LDL-C were significantly higher in women than in men. There was no significant difference in age, body mass index, waist circumference, comfortable walking speed, fasting insulin, HOMA-IR, HbA_{1c}, triglycerides, highly sensitive C-reacting protein, or serum albumin between men and women.

Differences in baseline characteristics between the non−insulin resistance group and insulin resistance group are presented in Table 2. Mean weight, body mass index, waist circumference, fasting glucose, fasting insulin, HOMA-IR, and triglycerides were significantly higher in the insulin resistance group than in the non−insulin resistance group. On the other hand, lower limb muscle mass, upper limb muscle mass, appendicular muscle mass, trunk muscle mass, handgrip strength, and knee extension torque were significantly higher in the non−insulin resistance group than in the insulin resistance group. There was no significant difference in mean age, percentage of men, height, walking speed, HbA_{1c}, total cholesterol, HDL-C, LDL-C, highly sensitive C-reacting protein, albumin, or percentages of smokers between the 2 groups.

Results of Cox proportional hazards model analyses for development of insulin resistance are shown in Table 3. HRs of lower limb muscle mass, upper limb muscle mass, appendicular mass, trunk muscle mass, grip strength, and knee extension torque for development of insulin resistance were significantly low when adjusted for sex and age (model 1): 0.81, 0.50, 0.83, 0.86, 0.90, and 0.49, respectively. HRs of lower limb muscle mass and appendicular muscle mass for development of insulin resistance were significantly low after additional adjustment with baseline HOMA-IR (model 2), with baseline HOMA-IR plus baseline waist circumference (model 3) or with baseline HOMA-IR and waist circumference plus baseline triglycerides and HDL-C (model 4).

Table 4 shows the HR and 95% CI of each sarcopenia-related index for development of insulin resistance in women and men groups of participants. In women, age-adjusted HR (model 1) of lower limb muscle mass, upper limb muscle mass, appendicular mass, trunk muscle mass, and grip strength for development of insulin resistance were significantly low: 0.75, 0.41, 0.79, 0.84, and 0.02, respectively. When additionally adjusted for baseline HOMA-IR (model 2), the statistical significance of lower limb muscle mass, appendicular muscle mass, and trunk muscle mass remained, and the association of lower limb muscle mass and appendicular muscle mass with change in HRs remained significant when baseline waist circumference was added to the adjustment (model 3) or when triglycerides and HDL-C were added to the adjustment (model 4). In contrast to those in women, association between development of insulin resistance and indices of muscle mass, muscle strength, or walking speed was not detected by HRs and 95% CI in men. The point estimates of HRs of the muscle mass indices in men were not much different from those in women, but 95% CIs of the HRs were larger in men.

Discussion

The results of this longitudinal study indicate that lower limb muscle mass, but not muscle strength (grip strength, knee extensor torque), or walking speed, was associated with significant increase in risk for development of insulin resistance independently of obesity in older Japanese. The findings suggest that loss of skeletal muscle mass,

Table 1
Baseline Characteristics in Men and Women

	Total (N = 194)	Men (n = 79)	Women (n = 115)	*P*
Age, y	75.1 (6.6)	75.6 (6.2)	74.7 (6.8)	.39
Height, cm	154.9 (8.9)	162.7 (6.0)	149.5 (6.0)	< .001
Weight, kg	53.5 (9.7)	58.9 (9.4)	49.8 (8.1)	< .001
BMI	22.2 (3.1)	22.2 (3.1)	22.2 (3.0)	.96
Waist circumference, cm	82.6 (9.6)	81.8 (9.4)	83.2 (9.8)	.33
Skeletal muscle mass, kg weight ratio (%)				
Lower limb muscle mass	25.8 (3.2)	27.9 (2.6)	24.3 (2.7)	< .001
Upper limb muscle mass	6.99 (1.10)	8.09 (0.72)	6.24 (0.54)	< .001
Appendicular muscle mass	32.8 (4.1)	36.0 (3.1)	30.6 (3.2)	< .001
Trunk muscle mass	37.7 (4.5)	40.4 (3.7)	35.8 (3.9)	< .001
Muscle strength				
Hand grip strength, kg weight ratio (%)	54.2 (13.2)	61.6 (13.4)	49.2 (10.3)	< .001
Knee extension torque, Nm weight ratio (%)	127.5 (42.1)	137.0 (44.7)	121.7 (39.6)	.020
Walking speed: comfortable speed, m/s	1.18 (0.23)	1.14 (0.23)	1.20 (0.23)	.11
Biochemical				
Fasting glucose, mg/dL	94.5 (9.6)	96.4 (9.7)	93.2 (9.4)	.020
Fasting insulin, μU/mL	4.13 (1.50)	3.89 (1.34)	4.30 (1.58)	.05
HOMA-IR	0.97 (0.36)	0.93 (0.34)	0.99 (0.38)	.27
HbA_{1c}, %	5.58 (0.30)	5.54 (0.28)	5.60 (0.32)	.19
Total cholesterol, mg/dL	209.7 (36.1)	195.3 (32.1)	219.6 (35.5)	< .001
HDL-C, mg/dL	68.4 (20.1)	61.6 (13.9)	73.0 (22.3)	< .001
LDL-C, mg/dL	121.9 (27.8)	114.1 (27.0)	127.2 (27.1)	.001
Triglycerides, mg/dL	84.5 (67.0-109.0)	82.0 (67.0-112.0)	88.0 (67.0-108.0)	.67
Highly sensitive C-reacting protein, mg/dL	0.04 (0.02-0.09)	0.04 (0.02-0.10)	0.04 (0.02-0.08)	.21
Albumin, g/dL	4.44 (0.22)	4.41 (0.24)	4.46 (0.21)	.14
Smoking: current/never/former, n (%)	13 (7) / 137(71) / 44 (23)	11 (14) / 27 (34) / 41 (52)	2 (2) / 110 (96) / 3 (3)	< .001

BMI, body mass index.
Data are presented as means (SDs), medians (interquartile ranges) or percentages.

Table 2
Baseline Characteristics of the Participants With or Without Insulin Resistance

	Total (N = 194)	Non–Insulin Resistance Group (HOMA-IR < 1.73) (n = 132)	Insulin Resistance Group (HOMA-IR ≥ 1.73) (n = 62)	*P*
Age, y	75.1 (6.6)	75.0 (6.6)	75.3 (6.6)	.78
Men, n (%)		56 (42)	23 (37)	.48
Height, cm	154.9 (8.9)	154.7 (8.7)	155.0 (9.2)	.88
Weight, kg	53.5 (9.7)	51.9 (9.3)	57.0 (9.6)	.001
BMI	22.2 (3.1)	21.5 (2.9)	23.6 (2.9)	< .001
Waist circumference, cm	82.6 (9.6)	80.8 (9.5)	86.5 (8.8)	< .001
Skeletal muscle mass, kg weight ratio (%)				
Lower limb muscle mass	25.8 (3.2)	26.4 (3.1)	24.5 (3.1)	< .001
Upper limb muscle mass	6.99 (1.10)	7.12 (1.13)	6.71 (1.00)	.015
Appendicular muscle mass	32.8 (4.1)	33.5 (4.0)	31.2 (3.9)	< .001
Trunk muscle mass	37.7 (4.5)	38.6 (4.3)	35.8 (4.2)	< .001
Muscle strength				
Hand grip strength, kg weight ratio (%)	54.2 (13.2)	55.8 (13.5)	50.9 (11.9)	.015
Knee extension torque, Nm weight ratio (%)	127.5 (42.1)	132.9 (39.5)	117.2 (45.4)	.021
Walking speed: Comfortable speed, m/s	1.18 (0.23)	1.20 (0.22)	1.13 (0.24)	.07
Biochemical				
Fasting glucose, mg/dL	94.5 (9.6)	93.5 (9.6)	96.8 (9.4)	.020
Fasting insulin, μU/mL	4.13 (1.50)	3.66 (1.19)	5.12 (1.58)	< .001
HOMA-IR	0.97 (0.36)	0.84 (0.28)	1.23 (0.38)	< .001
HbA_{1c}, %	5.58 (0.30)	5.56 (0.31)	5.61 (0.30)	.33
Total cholesterol, mg/dL	209.7 (36.1)	211.2 (34.0)	206.5 (40.3)	.39
HDL-C, mg/dL	68.4 (20.1)	69.6 (17.6)	65.7 (24.4)	.20
LDL-C, mg/dL	121.9 (27.8)	123.2 (25.8)	119.2 (31.6)	.36
Triglycerides, mg/dL	84.5 (67.0-109.0)	80.5 (64.0-103.5)	97.5 (74.7-133.2)	.001
Highly sensitive C-reacting protein, mg/dL	0.04 (0.02-0.09)	0.04 (0.02-0.09)	0.04 (0.02-0.08)	.46
Albumin, g/dL	4.44 (0.22)	4.43 (0.20)	4.46 (0.25)	.42
Smoking: current/never/former, n (%)	13 (7)/ 137 (71)/ 44 (23)	10 (7)/ 91 (69)/ 31 (23)	3 (5)/ 46 (74)/ 13 (21)	.68

BMI, body mass index.
Data are presented as means (SDs), medians (interquartile ranges), or percentages.

rather than decrease in muscle strength and muscle function, predisposes older adults to subsequent reduction of insulin sensitivity.

Skeletal muscle is the target tissue of insulin and responsible for about 70% of glucose clearance.[23] Therefore, the loss of muscle mass is expected to result in a reduction in glucose disposal, leading to increase in HOMA-IR. However, metabolic alterations associated with skeletal muscle changes appears to contribute to insulin resistance.[24–26] Age-related progressive loss of muscle mass is associated with increase in intermuscular fat and intracellular lipids.[27–29] Although triglyceride is the main storage form of lipid, the derivatives such as ceramide and diacylglycerol are thought to contribute to insulin resistance by impairing insulin receptor-mediated signaling in skeletal muscle.[27] The impaired insulin signaling not only suppresses glucose uptake and its intracellular metabolism but also induces negative protein balance by reduced protein synthesis and increased proteolysis.[24–26] The impairment of insulin signaling is unlikely to be the only mechanism of insulin resistance in skeletal muscle. Involvement of mitochondrial dysfunction, inflammation, and upregulated myostatin in development of both insulin resistance and sarcopenia has also been proposed.[24,25] Epidemiologic studies also support a causal role of insulin resistance in progression of sarcopenia.[30–32] An earlier longitudinal study that enrolled ambulatory men aged ≥65 years has shown that greater lean mass loss occurred during 4.6-year follow-up in nondiabetic insulin-resistant men than in insulin-sensitive men.[30] Type 2 diabetes in older adults (aged 70-79 years) has been reported to be associated with accelerated loss of leg muscle mass and strength during 3-6 years of follow-up.[31,32] Taken together, the findings in basic and population studies suggest that mechanisms of sarcopenia and insulin resistance can form a vicious cycle, leading to simultaneous progression of sarcopenia and glucose intolerance.

The results of the present study suggest that the lower limb muscle mass exerts more influence on the development of insulin resistance

Table 3
Hazard Ratio for Development of Insulin Resistance, by Baseline Muscle Mass, Muscle Strength, and Walking Speed

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Muscle mass, weight ratio								
Lower limb muscle mass	0.81 (0.73-0.90)	< .001	0.88 (0.79-0.97)	.017	0.88 (0.79-0.98)	.031	0.89 (0.79-0.98)	.044
Upper limb muscle mass	0.50 (0.32-0.78)	.003	0.66 (0.42-1.05)	.07	0.70 (0.42-1.16)	.16	0.68 (0.41-1.14)	.14
Appendicular muscle mass	0.83 (0.76-0.91)	< .001	0.89 (0.81-0.97)	.016	0.89 (0.81-0.99)	.030	0.90 (0.81-0.99)	.039
Trunk muscle mass	0.86 (0.81-0.93)	< .001	0.89 (0.85-1.01)	.06	0.91 (0.81-1.03)	.14	0.90 (0.79-1.02)	.11
Muscle strength, weight ratio								
Hand grip strength	0.90 (0.10-0.81)	.030	0.55 (0.04-7.27)	.65	1.06 (0.06-18.2)	.96	0.92 (0.05-16.0)	.95
Knee extension torque	0.49 (0.24-0.97)	.040	0.76 (0.36-1.57)	.45	0.83 (0.39-1.75)	.63	0.71 (0.33-1.52)	.38
Walking speed: comfortable speed, m/s	0.34 (0.10-1.09)	.07	0.39 (0.12-1.27)	.12	0.43 (0.31-1.38)	.15	0.33 (0.10-1.11)	.07

Model 1: adjusted for sex and age at baseline; model 2: model 1 + HOMA-IR at baseline; model 3: model 2 + waist circumference at baseline; model 4: model 3 + triglycerides and HDL-C at baseline.

Table 4
Hazard Ratio for Development of Insulin Resistance, by Baseline Muscle Mass, Muscle Strength, and Walking Speed, by Gender

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Muscle mass (weight ratio)								
Lower limb muscle mass								
Women	0.75 (0.65-0.87)	< .001	0.82 (0.71-0.96)	.014	0.80 (0.66-0.97)	.025	0.80 (0.66-0.97)	.025
Men	0.86 (0.73-1.03)	.11	0.93 (0.78-1.10)	.33	0.93 (0.78-1.10)	.41	0.96 (0.79-1.15)	.68
Upper limb muscle mass								
Women	0.41 (0.21-0.81)	.010	0.57 (0.28-1.16)	.12	0.61 (0.28-1.34)	.22	0.59 (0.27-1.33)	.20
Men	0.56 (0.31-1.02)	.06	0.74 (0.41-1.36)	.34	0.77 (0.38-1.56)	.48	0.79 (0.38-1.62)	.52
Appendicular muscle mass								
Women	0.79 (0.69-0.89)	< .001	0.85 (0.74-0.97)	.017	0.83 (0.70-0.98)	.020	0.83 (0.70-0.98)	.029
Men	0.87 (0.75-1.01)	.07	0.93 (0.80-1.07)	.33	0.93 (0.80-1.08)	.38	0.96 (0.81-1.12)	.61
Trunk muscle mass								
Women	0.84 (0.77-0.92)	< .001	0.90 (0.81-0.99)	.039	0.87 (0.75-1.01)	.06	0.86 (0.74-1.01)	.06
Men	0.90 (0.80-1.01)	.07	0.97 (0.85-1.10)	.70	1.05 (0.82-1.34)	.69	1.00 (0.78-1.29)	.96
Muscle strength, weight ratio								
Hand grip strength								
Women	0.02 (0.01-0.56)	.022	0.17 (0.01-9.12)	.39	0.38 (0.01-33.4)	.67	0.41 (0.01-36.9)	.69
Men	0.29 (0.01-6.55)	.43	1.45 (0.04-47.2)	.83	2.78 (0.05-129.9)	.60	1.71 (0.03-85.3)	.78
Knee extension torque								
Women	0.98 (0.97-1.01)	.21	0.99 (0.97-1.01)	.43	0.99 (0.97-1.01)	.41	0.46 (0.15-1.37)	.16
Men	1.01 (0.98-1.01)	.52	1.01 (0.98-1.02)	.66	1.01 (0.98-1.02)	.69	1.08 (0.38-3.06)	.87
Walking speed: Comfortable speed, m/s								
Women	0.36 (0.11-1.18)	.09	0.42 (0.13-1.38)	.15	0.48 (0.14-1.59)	.23	0.39 (0.11-1.37)	.14
Men	1.03 (0.13-7.71)	.97	1.55 (0.19-12.7)	.67	1.52 (0.18-12.6)	.69	1.35 (0.14-12.7)	.79

Women (n = 115); men (n = 79).
Model 1, adjusted for age at baseline; model 2, model 1 + HOMA-IR at baseline; model 3, model 2 + waist circumference at baseline; model 4, model 3 + triglycerides and HDL-C at baseline.

than the upper limb muscle mass and trunk muscle mass. The difference in the contribution in muscle mass regions might be attributable to absolute size of skeletal muscle mass. The lower limb muscle mass was approximately 26% of total muscle mass, and the upper limb muscle mass was approximately 7%. The trunk muscle was approximately 38%, but it included smooth muscles of internal organs since bioelectrical impedance analysis was used for determination of muscle mass. It is notable that the loss of lower limb muscle mass is associated with age-related decreased physical activity and is more remarkable than the loss of upper limb muscle mass.[33,34] Therefore, lower limb skeletal muscle mass is likely to be an important predictor of insulin resistance and also a target for preventive strategies in older adults.

Although results of the analysis of total participant data showed statistical significance in the decreased HR of lower limb muscle mass for development of insulin resistance (Table 3), significant decrease in the HR was observed in women but not in men in subgroup analyses (Table 4). Women, regardless of age, are known to have less muscle mass than men,[34,35] and in this study, women had less muscle mass than men, corrected for body weight to account for physique at baseline. Thus, the loss of muscle mass in women may sensitively reflect the development of insulin resistance. However, it is difficult to conclude that there is a sex difference in a role of lower limb muscle mass as a risk factor of insulin resistance. Point estimates of HR for lower limb muscle mass in men showed a similar trend to women, and the sample size of male participants was relatively small, leaving a possibility of type 2 error in the statistical analysis of HR. This issue needs to be addressed in the future by enrollment of a large number of cases.

Scott et al[14] reported that sarcopenic obesity and sarcopenic nonobesity did not appear to confer greater risk for incident metabolic syndrome or insulin resistance than obesity alone during a 5-year follow-up in community-dwelling older men. They argue that avoiding age-related increases in body fat is more important than preventing the sarcopenia in order to reduce the incidence of metabolic syndrome and insulin resistance in older adults. The findings by Scott et al are apparently contradictory to the results of the present study. However, it is difficult to sort out reasons for the apparent difference because there were major differences in study methods. Scott et al determined HOMA-IR only at 5 years of follow-up, and its change during the follow-up was unclear. They defined sarcopenia as low appendicular muscle mass, which is combined with low hand grip strength and/or low gait speed according to the European Working Group on Sarcopenia (EWGSOP) criteria. Although the participants in both of the studies were community-dwelling older adults, the inclusion criteria of age (≥70 years), sex (only men), and ethnicity of the study participants (Caucasians), and exclusion criteria (only living in a residential aged care facility) in a study by Scott et al were different from those in the present study. In addition, a proportion of participants with obesity (42.6%) was different between the 2 studies. Nevertheless, roles of muscle mass loss in each body region, functional capacity of the skeletal muscle, increase in adipose tissue, and preexisting change in insulin sensitivity in development of insulin resistance and diabetes need to be further investigated by use of standardized indexes of muscle mass and functions.

There are limitations in this study. First, the sample size of the present study was relatively small (ie, 194), because this cohort included those who voluntarily underwent a specific health checkup in Sobetsu Town. Nevertheless, we were still able to detect significant and relevant differences between groups (ie, non–insulin resistance or insulin resistance groups). In the future, this issue should be addressed by enrolling more participants to allow for improved statistical power, additional analysis of more confounding factors, and calculation of cutoff values for lower limb muscle mass. Second, because the follow-up period for the target was as short as 2 years, it possibly led to underestimation of the impact of sarcopenia on the development of insulin resistance. Third, multivariate analysis of model 4 adjusted for the inclusion of HDL-C may partially explain the confounding factor physical activity,[36] but does not reflect actual measurements of physical activity. Fourth, we used HOMA-IR, an index that has been used in numerous epidemiologic studies. HOMA-IR is reasonably correlated with insulin sensitivity determined with hyperinsulinemic euglycemic glucose clamp ($r = 0.51$-0.65),[37] but we

cannot exclude the possibility of some underestimation of insulin resistance of the skeletal muscle.[38] Finally, because this study enrolled only subjects who voluntarily received health checkups, we cannot exclude self-selection bias. Although there are these limitations, the research findings would contribute to the prevention of diabetes mellitus and arteriosclerotic disease in older adults, promoting the identification of risk for individuals on the development of insulin resistance and enhancing the development of efficient preventive exercise programs.

Conclusions and Implications

The results of the present longitudinal study suggest that loss of lower limb muscle mass is a risk factor for development of insulin resistance independent of obesity in nondiabetic older Japanese adults although such a role of risk factor is not shared by upper limb muscle mass, trunk muscle mass, muscle strength, or muscle function. Whether strategies to preserve lower limb muscle mass can prevent diabetes in older adults remains to be further investigated. This association needs to be confirmed in further large-scale longitudinal studies.

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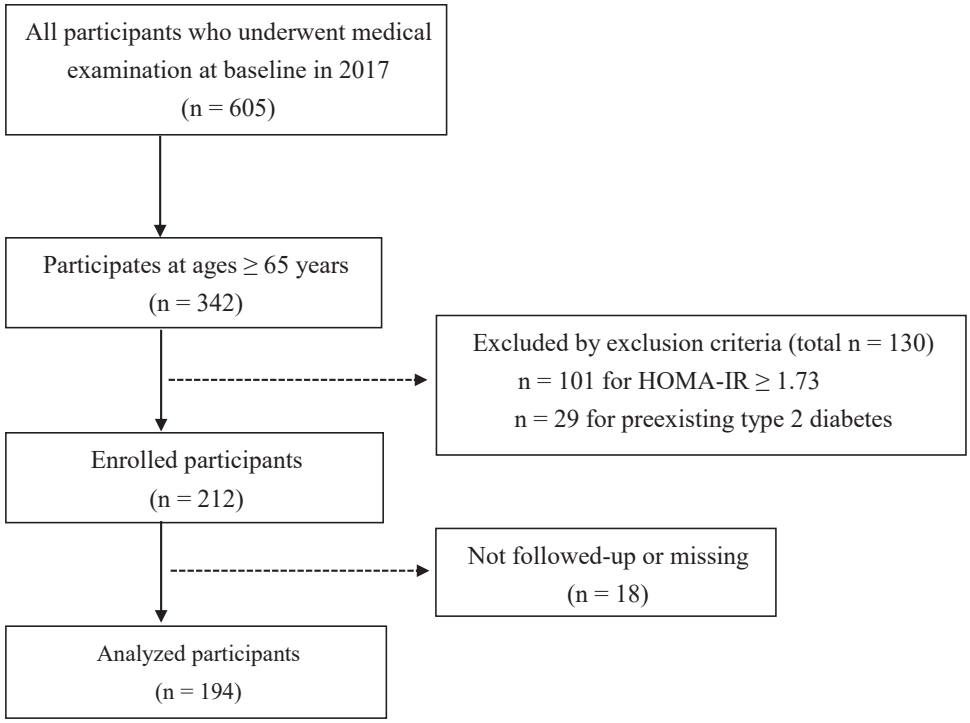

Supplementary Fig. 1. A flowchart of participants in the study cohort.