Title: Joint impact of muscle mass and waist circumference on Type 2 Diabetes in Japanese middle-aged adults: the Circulatory Risk in Communities Study (CIRCS)

Running Title: muscle, abdominal obesity and type 2 diabetes

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Abstract

Background: Although evidence about skeletal muscle mass loss and type 2 diabetes risk has accumulated, little information is available on the combined effect of skeletal muscle mass and abdominal obesity on type 2 diabetes. We examined whether skeletal muscle mass and abdominal obesity were synergistically associated with the prevalence of type 2 diabetes.

Methods: Skeletal muscle mass and waist circumference (WC) were measured in 1,515

Japanese aged 40–69 years. Relative muscle mass was calculated as percentage of total skeletal muscle mass in body weight (SMM%). Type 2 diabetes was identified as fasting serum glucose ≥ 7.0 mmol/L (126 mg/dL), non-fasting serum glucose ≥ 11.1 mmol/L (200 mg/dL), hemoglobin A1c ≥ 6.5%, and/or diabetes medication use.

Results: The multivariable-adjusted odds ratio (OR) of prevalent diabetes from the lowest to third quartiles of SMM% compared to the highest quartile was gradually higher in both sexes. The association between a high WC and prevalent diabetes was similar. The multivariable-adjusted OR (95% confidence intervals) for the prevalence of type 2 diabetes in the low skeletal muscle mass/high WC group was 3.19 (1.78–5.71) for men and 4.46 (2.09–9.51) for women compared with the high skeletal muscle mass/low WC group. The relative excess risk due to interaction was 2.2 (0.5–3.9) in men and 2.8 (0.2–5.3) in women for an excess burden of type 2 diabetes for low skeletal muscle mass and high WC.

Conclusions: Low skeletal muscle mass and abdominal obesity were synergistically associated with presence of type 2 diabetes.

Highlights

This cross-sectional study of middle-aged men and women showed that low skeletal

muscle mass and abdominal obesity were associated with a higher prevalence of type 2 diabetes in both sexes. In addition, low skeletal muscle mass and abdominal obesity were synergistically associated with presence of type 2 diabetes in Japanese middle-aged adults. In clinical practice, the assessment of skeletal muscle mass and abdominal obesity may be useful for preventing and controlling type 2 diabetes.

Keyword: skeletal muscles mass, waist circumference, type 2 diabetes mellitus

Introduction

The prevalence of diabetes is increasing[1] and this increase is projected to continue until 2030 worldwide.[2] Physical activity and diet are primary components of diabetes prevention.[3, 4] Exercise training increases skeletal muscle mass and improves hyperglycemia in type 2 diabetes.[5] The muscle is the largest organ involved in glucose metabolism. Low skeletal muscle mass may increase one's risk of diabetes[6] through hyperglycemia,[7] decreasing beta-cell function,[8] and increasing insulin resistance.[9] Visceral adiposity impairs glucose tolerance[10] and increases insulin resistance, [11, 12] leading to type 2 diabetes. Waist circumference (WC), a useful index for measuring abdominal adipose tissue,[13, 14] is associated with the incidence of diabetes mellitus.[15]

Among patients with type 2 diabetes, a low skeletal muscle mass and high fat mass are reportedly synergistically associated with high hemoglobin A1c (HbA1c) levels.[16] In contrast, among Japanese Americans without diabetes, such a synergistic association of visceral fat gain and thigh muscle loss was not found in relation to the risk of incident type 2 diabetes.[17] A low muscle mass and a high visceral adiposity synergistically may worsen insulin resistance and glucose metabolism, but robust evidence in this regard is limited and there is little evidence of this in the general population.

This study aimed to examine whether the combination of low skeletal muscle mass and high WC, a surrogate marker of abdominal adipose tissue,[13, 14] is synergistically associated with the prevalence of type 2 diabetes among a community-based Japanese population, which is relatively lean with a lower prevalence of type 2 diabetes than in Western populations.

Methods

Study Subjects

We included 1,525 individuals aged 40–69 years from a northeastern rural community of Japan, Ikawa town, and a western suburban community (n = 760), Minami-takayasu district of Yao city (n = 755), both of which were sub-cohorts of the Circulatory Risk in

Communities Study(CIRCS).[18] In 2017–2019, we measured skeletal muscle mass, WC, and cardiovascular risk variables of the study participants. Because the data were collected as a part of the municipal government health check activities, we did not obtain an informed consent for each study subject, but we provided opt out opportunities. Then, we used anonymous data for the present analyses. This study was approved by the Ethics Committee of Osaka Center for Cancer and Cardiovascular Disease Prevention and Osaka University.

We excluded participants for whom data were missing for skeletal muscle mass, WC, smoking habit, or usual alcohol intake (n = 7). Participants with histories of infantile paralysis (n = 2) and lymphedema (n = 1) were also excluded due to possibility of measurement error of muscle mass. A total of 1,515 men and women were finally included in the current analysis.

Assessment of skeletal muscle mass, WC, and other covariates

Skeletal muscle mass was measured with a bioelectrical impedance analyzer (InBody 770; InBody Co., Seoul, Korea) because of its feasibility in community-based surveys and measurement reliability.[19] The muscle mass measured with this method is highly correlated with that measured by using the dual-energy X-ray absorptiometry (DXA) method, the gold standard measure of muscle mass.[20, 21] Since a higher fat mass

overestimates skeletal muscle mass,[22] we used the relative skeletal muscle mass (SMM%) as total skeletal muscle mass [kg]/body weight [kg] × 100.[23]

WC was measured at the umbilicus level using a tape measure with the participant in a standing position and breathing normally. Height and weight were measured with the participant wearing light clothing. We asked participants about their medical history, smoking habits, frequency and amount of alcohol intake, physical activity and family history of diabetes mellitus. Current smoker was defined as smoking ≥ 1 cigarette a day. The usual alcohol intake was converted to grams of ethanol per day based on the Japanese traditional unit “go” including 23 g ethanol in a unit. Physical activity was asked as “Are you exercising or walking for at least 15 minutes at a time for more than three months? (yes or no)”.

Definition of type 2 diabetes

Venous blood was drawn into a plain plastic tube for serum and whole blood processing. Serum was separated within 30 min after the blood draw. These samples were transported to the Osaka Center for Cancer and Cardiovascular Disease Prevention on dry ice for extraction of the serum samples and with ice cooling for the whole blood samples from Ikawa town and with ice cooling for both samples from Minami-takayasu

district. Serum glucose was measured by hexokinase and glucose-6-phosphate dehydrogenase methods with an automatic analyzer (TBA-2000FR; Toshiba, Tochigi, Japan), while HbA1c was measured by high performance liquid chromatography with an HLC-723 G8 (Tosoh, Tokyo, Japan). Type 2 diabetes was defined as fasting serum glucose ≥ 7.00 mmol/L, non-fasting serum glucose ≥ 11.1 mmol/L, HbA1c ≥ 6.5% and/or initiation of treatment with glucose-lowering medication or insulin injection.

Statistical analysis

SMM% and WC were categorized into sex-specific quartiles. We calculated age-adjusted mean values for participants' characteristics by using analysis of covariance and calculated age-adjusted proportions using logistic regression according to SMM% or WC quartiles.

The odds ratios (ORs) and 95% confidence intervals (CIs) of prevalent diabetes and were calculated for each group using a logistic regression model of quartiles of SMM% and WC. The linear trend of the association was tested by modeling the continuous variable of SMM% or WC which was assigned the median value of SMM% or WC in each group. The multivariable adjustment included age (continuous), smoking habit (never, former, or current), alcohol intake (never, former, or current), physical

activity (yes or no), family history of diabetes mellitus (yes or no), and WC or SMM% (continuous).

To assess the joint impact of skeletal muscle mass and visceral adiposity, we divided the SMM% and WC into high and low groups using the sex-specific median value, and create the 2 × 2 combination of SMM% and WC since the number of participants may not be enough for 4 × 4 combination. We calculated the relative excess risk due to interaction (RERI) as the OR (low skeletal muscle mass + high WC) - OR (low skeletal muscle mass) - OR (high WC) + 1 where the ORs were adjusted for the above confounding variables.[24] We also calculated the 95% CI for RERI and tested RERI using the z test.

We used SAS (version 9.4; SAS Institute, Cary, NC, USA) for the statistical analyses. All p values for the statistical tests were two-tailed, and values of $p < 0.05$ were considered statistically significant.

Results

Participants of both sexes with lower skeletal muscle mass were older and had age-adjusted mean values of higher body mass index (BMI), WC, HbA1c, and fasting glucose (Table 1). The age-adjusted proportion of diabetes mellitus was 14.8% for Q1

(lowest), 16.2% for Q2, 9.7% for Q3, and 10.2% for Q4 of SMM% in men; the corresponding proportions were 4.3%, 4.8%, 4.8% and 1.3% in women. Individuals of both sexes with higher WC showed similar trends as those with lower skeletal muscle mass in terms of BMI, HbA1c, and fasting glucose, except for age in men (Table 2). The association between WC and age was not similar to that with skeletal muscle mass in men. The trend of age between Q1 to Q4 of WC was not significant.

Table 3 shows sex-specific age-adjusted and multivariable-adjusted ORs (95% CI) of prevalent type 2 diabetes according to quartiles of SMM% levels. Lower skeletal muscle mass was associated with the higher prevalence of type 2 diabetes in both men and women. These inverse associations were similar even after the adjustment for smoking status, alcohol intake, and family history. The multivariable-adjusted ORs (95% CI) for the lowest versus highest quartiles of SMM% levels were 3.75 (1.81–7.80), P for trend < 0.001 in men and 9.57 (2.83–32.32), P for trend < 0.001 in women. However, further adjustment for WC largely attenuated the associations towards non-significance: 1.73 (0.67–4.47) P for trend = 0.15 in men and 3.21 (0.86–12.06), P for trend = 0.14 in women.

As shown in Table 4, individuals of both sexes with higher WC had the higher prevalence of type 2 diabetes, the same as individuals with low skeletal muscle mass.

The multivariable-adjusted ORs for the highest versus lowest quartiles of WC was 4.31 (2.06–9.03), P for trend < 0.001 in men and 10.82 (3.22–36.34), P for trend < 0.001 in women. Further adjusting for SMM%, the association with WC and prevalence of type 2 diabetes was attenuated and no longer statistically significant in men but was significant in women. OR further adjusted for SMM% was 2.17 (0.84–5.60), P for trend = 0.09 in men and 5.99 (1.63–21.97), P for trend = 0.002 in women.

Table 5 indicates the results of the prevalence of type 2 diabetes according to the combination of SMM% and WC. Participants with low skeletal muscle mass and high WC were more likely to have type 2 diabetes than those with high skeletal muscle mass and low WC. The association did not extensively change after further adjustment for the confounding variables; the multivariable-adjusted OR of prevalent diabetes for low skeletal muscle mass and high WC was 3.19 (1.78–5.71) in men and 4.46 (2.09–9.51) in women. The RERI was 2.2 (0.5–3.9) in men (p=0.03) and 2.8 (0.2–5.3) in women (p=0.01).

Discussion

In the current cross-sectional study of 1,515 middle-aged men and women, low skeletal muscle mass and high WC were synergistically rather than additively associated with

the higher prevalence of type 2 diabetes independently of age, smoking and drinking habits, and family history of diabetes.

Abdominal obesity assessed by WC is a well-established risk factor of type 2 diabetes.[25, 26] Cross-sectional and longitudinal studies have shown that skeletal muscle mass as absolute amount[26-30] or relative to body weight[6, 9, 31, 32] was inversely associated with the prevalence or incidence of type 2 diabetes. A cross-sectional study of 249 type 2 diabetes patients aged 39–70 years indicated that high fat and low muscle were synergistically associated with HbA1c levels.[16] The mean values of HbA1c were 7.6% for the low fat and high muscle group, 7.5% for the low fat and low muscle group, 7.7% for the high fat and high muscle group, and 8.1% for the high fat and low muscle group. However, statistical testing of the synergistic effect was not performed. Conversely, a study of 440 Japanese American men and women aged 34–75 years showed that a 5-year increase in thigh muscle (TM) and visceral fat (VF) was associated with the risk of 5-year incident diabetes adjusted for baseline visceral fat and thigh muscle area.[17] In that study, ORs (95% CI) of incident diabetes at the 5-year follow-up with reference to the TM gain and VF loss group was 3.42 (0.79–14.7) for the TM loss and VF loss group, 7.17(1.97–26.13) for the TM gain and VF gain group, and 3.07 (0.74–12.76) for the TM loss and VF gain group. The excess risk of type 2 diabetes associated with low

or loss of muscle and high or gain of fat was consistently observed in Japanese American and our Japanese samples. However, Japanese Americans also showed the excess risk of type 2 diabetes associated with muscle gain and fat gain, while our Japanese participants did not. The discrepancy between the two studies may be due in part to the lack of statistical power (the number of participants with type 2 diabetes was 23 in the Japanese American cohort versus 12 in the Japanese cohort). Another explanation is that, in Japanese Americans, the muscle gain and fat gain group had a larger mean fat change than the muscle loss and fat gain group, leading to the excess risk of type 2 diabetes.[17]

Possible biological mechanisms underlying the effect of low skeletal muscle mass and high abdominal fat mass are as follows. Skeletal muscle is the largest organ consuming glucose, generating and storing glycogen in response to insulin. Low muscle mass has capacity limits for such functions, resulting in reduced insulin sensitivity.[9] Conversely, a high WC reflects a high abdominal fat mass, which serves as dense energy storage as well as the largest endocrine organ secreting adipocytokines such as tumor necrosis factor-α, free fatty acid, interleukin-6, and adiponectin.[33, 34] These factors worsen insulin resistance by reducing both insulin signaling and the expression of key proteins for glucose uptake for metabolism. When skeletal muscle mass loss and

increased WC coexist, glucose metabolism may become worse in nature, in the other words, a high skeletal muscle mass or a low WC may contribute to normalize glucose metabolism. However, the mechanism by which glucose metabolism synergistically worsens is unclear.

The strength of our study is its large population of men and women with standardized measurement for skeletal muscle mass, WC, and other cardiovascular risk factors.

However, our study has several limitations. First, this was a cross-sectional study, and thus, causality was not necessarily indicated. Second, the measurement error of muscle mass cannot be eliminated. The absolute muscle mass amount measured by the bioelectrical impedance analysis method tends to be overestimated compared to that measured by the DXA method. However, the overestimation was not changed depending on the presence or absence of diabetes.[20] The current findings are comparable to the results using the DXA method because of the strong correlation between muscle mass assessments with the two methods.[21] Third, residual or unmeasured confounding factors may exist.

In conclusion, the combination of low skeletal muscle mass and high WC was associated with the higher prevalence of diabetes in middle-aged men and women. The

assessments of abdominal obesity and skeletal muscle mass may be important to preventing and controlling type 2 diabetes. In addition, low skeletal muscle mass and high WC were synergistically associated with the higher frequency of prevalent type 2 diabetes. In clinical practice, the assessment of skeletal muscle mass and abdominal obesity may be useful for preventing and controlling type 2 diabetes. Longitudinal research is needed to confirm the joint impact on incident type 2 diabetes.

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References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since

1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; 387:1513-1530.

2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047-1053.

3. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P*, et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344:1343-1350.

4. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ*, et al.* Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2011; 305:1790-1799.

5. Yalamanchi SV, Stewart KJ, Ji N, Golden SH, Dobs A, Becker DM*, et al.* The relationship of fasting hyperglycemia to changes in fat and muscle mass after exercise training in type 2 diabetes. *Diabetes Res Clin Pract* 2016; 122:154-161.

6. Hong S, Chang Y, Jung HS, Yun KE, Shin H, Ryu S. Relative muscle mass and the risk of incident type 2 diabetes: A cohort study. *PLoS One* 2017; 12:e0188650.

7. Kalyani RR, Tra Y, Egan JM, Ferrucci L, Brancati F. Hyperglycemia is associated

with relatively lower lean body mass in older adults. *J Nutr Health Aging* 2014; 18:737-743.

8. Sakai S, Tanimoto K, Imbe A, Inaba Y, Shishikura K, Tanimoto Y*, et al.* Decreased β-Cell Function Is Associated with Reduced Skeletal Muscle Mass in Japanese Subjects without Diabetes. *PLoS One* 2016; 11:e0162603.

9. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *J Clin Endocrinol Metab* 2011; 96:2898-2903.

10. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE*, et al.* Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. *Diabetes Care* 2003; 26:650-655.

11. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab* 2001; 86:5366-5371.

12. Katsuki A, Sumida Y, Urakawa H, Gabazza EC, Murashima S, Maruyama N*, et al.* Increased visceral fat and serum levels of triglyceride are associated with insulin resistance in Japanese metabolically obese, normal weight subjects with normal glucose tolerance. *Diabetes Care* 2003; 26:2341-2344.

13. Kuk JL, Lee S, Heymsfield SB, Ross R. Waist circumference and abdominal adipose tissue distribution: influence of age and sex. *Am J Clin Nutr* 2005; 81:1330-1334.

14. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S*, et al.* Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes Res Clin Pract* 2009; 83:100-105.

15. Xue H, Wang C, Li Y, Chen J, Yu L, Liu X*, et al.* Incidence of type 2 diabetes and number of events attributable to abdominal obesity in China: A cohort study. *J Diabetes* 2016; 8:190-198.

16. Terada T, Boulé NG, Forhan M, Prado CM, Kenny GP, Prud'homme D*, et al.* Cardiometabolic risk factors in type 2 diabetes with high fat and low muscle mass: At baseline and in response to exercise. *Obesity (Silver Spring)* 2017; 25:881-891.

17. Han SJ, Kim SK, Fujimoto WY, Kahn SE, Leonetti DL, Boyko EJ. Effects of combination of change in visceral fat and thigh muscle mass on the development of type 2 diabetes. *Diabetes Res Clin Pract* 2017; 134:131-138.

18. Yamagishi K, Muraki I, Kubota Y, Hayama-Terada M, Imano H, Cui R*, et al.* The Circulatory Risk in Communities Study (CIRCS): A Long-Term Epidemiological Study for Lifestyle-Related Disease Among Japanese Men and Women Living in

Communities. *J Epidemiol* 2019; 29:83-91.

19. Gibson AL, Holmes JC, Desautels RL, Edmonds LB, Nuudi L. Ability of new octapolar bioimpedance spectroscopy analyzers to predict 4-component-model percentage body fat in Hispanic, black, and white adults. *Am J Clin Nutr* 2008; 87:332-338.

20. Lee SY, Ahn S, Kim YJ, Ji MJ, Kim KM, Choi SH*, et al.* Comparison between Dual-Energy X-ray Absorptiometry and Bioelectrical Impedance Analyses for Accuracy in Measuring Whole Body Muscle Mass and Appendicular Skeletal Muscle Mass. *Nutrients* 2018; 10.

21. Kyle UG, Genton L, Hans D, Pichard C. Validation of a bioelectrical impedance analysis equation to predict appendicular skeletal muscle mass (ASMM). *Clin Nutr* 2003; 22:537-543.

22. Marcell TJ. Sarcopenia: causes, consequences, and preventions. *J Gerontol A Biol Sci Med Sci* 2003; 58:M911-916.

23. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002; 50:889-896.

24. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect

modification and interaction. *Int J Epidemiol* 2012; 41:514-520.

25. Kodama S, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, Yachi Y*, et al.* Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: a meta-analysis. *Am J Epidemiol* 2012; 176:959-969.

26. Marott SC, Nordestgaard BG, Tybjærg-Hansen A, Benn M. Components of the Metabolic Syndrome and Risk of Type 2 Diabetes. *J Clin Endocrinol Metab* 2016; 101:3212-3221.

27. Han SJ, Boyko EJ, Kim SK, Fujimoto WY, Kahn SE, Leonetti DL. Association of Thigh Muscle Mass with Insulin Resistance and Incident Type 2 Diabetes Mellitus in Japanese Americans. *Diabetes Metab J* 2018; 42:488-495.

28. Yeung CHC, Au Yeung SL, Fong SSM, Schooling CM. Lean mass, grip strength and risk of type 2 diabetes: a bi-directional Mendelian randomisation study. *Diabetologia* 2019; 62:789-799.

29. Larsen BA, Allison MA, Laughlin GA, Araneta MR, Barrett-Connor E, Wooten WJ*, et al.* The association between abdominal muscle and type II diabetes across weight categories in diverse post-menopausal women. *J Clin Endocrinol Metab* 2015; 100:E105-109.

30. Eastwood SV, Tillin T, Wright A, Mayet J, Godsland I, Forouhi NG*, et al.* Thigh fat and muscle each contribute to excess cardiometabolic risk in South Asians, independent of visceral adipose tissue. *Obesity (Silver Spring)* 2014; 22:2071-2079.

31. Son JW, Lee SS, Kim SR, Yoo SJ, Cha BY, Son HY*, et al.* Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. *Diabetologia* 2017; 60:865-872.

32. Han TS, Al-Gindan YY, Govan L, Hankey CR, Lean MEJ. Associations of BMI, waist circumference, body fat, and skeletal muscle with type 2 diabetes in adults. *Acta Diabetol* 2019.

33. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004; 89:2548-2556.

34. Andersson CX, Gustafson B, Hammarstedt A, Hedjazifar S, Smith U. Inflamed adipose tissue, insulin resistance and vascular injury. *Diabetes Metab Res Rev* 2008; 24:595-603.

Table 1. Sex-specific age-adjusted characteristics of participants according to quartiles of SMM%

	Men					Women				
Quartiles of SMM% level	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
SMM% median (range)	28.9 (23.4-30.2)	31.2 (30.3-32.1)	33.2 (32.1-34.0)	35.5 (34.1-41.3)	P for trend	23.9 (18.7-25.0)	26.0 (25.0-27.0)	28.0 (27.0-29.2)	30.6 (29.2-37.6)	P for trend
No. of participants	131	131	131	131		247	248	248	248	
Age (years)	60.3 (0.8)	59.6 (0.8)	57.8 (0.8)	56.3 (0.8)	<0.001	60.7 (0.5)	59.6 (0.5)	55.5 (0.5)	53.7 (0.5)	<0.001
Height (cm)	165.5 (0.5)	167.7 (0.5)	168.6 (0.5)	169.8 (0.5)	<0.001	151.9 (0.3)	154.1 (0.3)	156.8 (0.3)	158.5 (0.3)	<0.001
Weight (kg)	76.2 (0.8)	70.8 (0.8)	66.1 (0.8)	60.8 (0.8)	<0.001	61.4 (0.5)	56.0 (0.5)	53.2 (0.5)	48.9 (0.5)	<0.001
BMI (kg/m²)	27.7 (0.2)	25.1 (0.2)	23.2 (0.2)	21.0 (0.2)	<0.001	26.5 (0.2)	23.5 (0.2)	21.6 (0.2)	19.4 (0.2)	<0.001
Waist circumference (cm)	94.4 (0.6)	87.6 (0.6)	82.3 (0.6)	76.9 (0.6)	<0.001	88.5 (0.5)	82.0 (0.5)	78.0 (0.5)	72.3 (0.5)	<0.001
Diabetes mellitus (%)	14.8	16.2	9.7	10.2	<0.001	4.3	4.8	4.8	1.3	<0.001
HbA1c (%)	6.1 (0.1)	5.9 (0.1)	5.8 (0.1)	5.8 (0.1)	<0.001	6.0 (0.0)	5.8 (0.0)	5.7 (0.0)	5.7 (0.0)	<0.001
HbA1c (mmol/mol)	42.7 (0.6)	39.8 (0.6)	39.3 (0.6)	38.9 (0.6)	<0.001	41.0 (0.3)	39.2 (0.3)	38.7 (0.3)	39.5 (0.3)	<0.001
Fasting glucose (mmol/l)	6.1(0.1)	5.8(0.1)	5.8(0.1)	5.4(0.1)	<0.001	5.4(0.1)	5.3(0.1)	5.3(0.1)	5.1(0.1)	0.001
Current drinker (%)	73.2	70.7	74.6	71.5	0.75	26.2	26.4	27.6	29.3	0.04
Current smoker (%)	30.0	33.4	28.9	36.9	0.01	4.9	4.1	7.0	4.0	0.80
Physical activity (%)	44.0	41.6	41.6	50.6	0.10	48.6	45.2	49.7	55.9	0.007
Family history (%)	18.1	20.0	21.2	14.2	0.27	25.9	24.1	26.2	24.0	0.51

SMM%, percentage of total skeletal muscle mass in body weight

Values are shown as median (range) for muscle mass, age-adjusted mean (standard error) for continuous variables, and proportion for categorical variables.

Table 2. Sex-specific age-adjusted characteristics of participants according to quartiles of WC

	Men					Women				
Quartiles of WC levels	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
WC median (range)	75.0 (58.0-79.0)	82.0 (80.0-84.0)	87.0 (85.0-90.0)	96.0 (91.0-122.0)	P for trend	69.0 (58.0-73.0)	77.0 (74.0-79.0)	82.0 (80.0-85.0)	90.0 (86.0-117.0)	P for trend
No. of participants	139	120	128	137		251	246	234	260	
Age (years)	58.0 (0.8)	59.8 (0.8)	57.8 (0.8)	58.4 (0.8)	0.51	55.0 (0.6)	56.5 (0.6)	58.6 (0.6)	59.5 (0.5)	<0.001
Height (cm)	166.4 (0.5)	167.9 (0.5)	168.4 (0.5)	168.9 (0.5)	<0.001	154.9 (0.3)	155.2 (0.3)	155.7 (0.3)	155.5 (0.3)	0.17
Weight (kg)	57.9 (0.5)	65.2 (0.6)	70.2 (0.5)	80.5 (0.5)	<0.001	46.1 (0.4)	51.3 (0.4)	56.2 (0.4)	65.4 (0.4)	<0.001
BMI (kg/m²)	20.9 (0.2)	23.1 (0.2)	24.8 (0.2)	28.2 (0.2)	<0.001	19.3 (0.1)	21.3 (0.1)	23.2 (0.2)	27.1 (0.1)	<0.001
SMM%	34.7 (0.2)	32.8 (0.2)	31.6 (0.2)	29.6 (0.2)	<0.001	29.5 (0.1)	27.7 (0.1)	26.6 (0.1)	25.0 (0.1)	<0.001
Diabetes mellitus (%)	14.7	12.4	17.3	25.8	<0.001	4.0	3.4	6.7	10.2	<0.001
HbA1c (%)	5.7 (0.1)	5.8 (0.1)	5.9 (0.1)	6.2 (0.1)	<0.001	5.7 (0.0)	5.8 (0.0)	5.9 (0.0)	5.9 (0.0)	<0.001
HbA1c (mmol/mol)	38.5 (0.6)	38.9 (0.7)	40.4 (0.6)	42.8 (0.6)	<0.001	38.1 (0.3)	38.8 (0.3)	39.9 (0.3)	40.6 (0.3)	<0.001
Fasting glucose (mmol/l)	5.5(0.1)	5.7(0.1)	5.8(0.1)	6.1(0.1)	0.009	5.1(0.1)	5.2(0.1)	5.5(0.1)	5.3(0.1)	<0.001
Current drinker (%)	73.1	63.5	77.1	74.0	0.63	26.2	31.6	23.0	24.0	0.12
Current smoker (%)	30.1	28.1	31.9	26.5	0.19	4.8	3.5	6.8	6.1	0.08
Physical activity (%)	44.0	42.1	43.3	40.7	0.08	48.8	54.3	47.3	42.6	0.01
Family history (%)	18.2	17.6	21.8	19.0	0.09	25.9	28.8	26.4	26.4	0.32

WC, waist circumference; BMI, body mass index; SMM%, percentage of total skeletal muscle mass in body weight

Values are shown as median (range) for muscle mass, age-adjusted mean (standard error) for continuous variables, and proportion for categorical variables.

Table 3. Sex-specific age-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals of prevalent type 2 diabetes according to quartiles of SMM%

	Quartiles of SMM% levels				
	Q1 (low)	Q2	Q3	Q4 (high)	P for trend
Men					
No. at risk	131	131	131	131	
No. of cases	40	23	13	13	
Age-adjusted OR	3.43 (1.72-6.87)	1.70 (0.82-3.56)	0.95 (0.42-2.14)	reference	<0.001
Multivariable-adjusted OR†	3.75(1.81-7.80)	1.66(0.77-3.56)	0.90(0.39-2.09)	reference	<0.001
Further adjustment for WC	1.73(0.67-4.47)	1.05(0.45-2.45)	0.73(0.31-1.73)	reference	0.16
Women					
No. at risk	247	248	248	248	
No. of cases	38	17	13	3	
Age-adjusted OR	9.25 (2.77-30.90)	3.87 (1.10-13.61)	3.87 (1.08-13.86)	reference	<0.001
Multivariable-adjusted OR†	9.57(2.83-32.32)	4.22(1.19-15.02)	4.14(1.14-15.03)	reference	<0.001
Further adjustment for WC	3.21(0.86-12.06)	2.25(0.61-8.33)	2.85(0.77-10.54)	reference	0.14

SMM%, percentage of total skeletal muscle mass in body weight; OR, odds ratio

†Adjusted for age, smoking, alcohol, physical activity and family history of diabetes

Table 4. Sex-specific age-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals of prevalent type 2 diabetes according to quartiles of WC quartile

	Quartiles of WC levels				
	Q1 (low)	Q2	Q3	Q4 (high)	P for trend
Men					
No. at risk	139	120	128	137	
No. of cases	12	17	23	37	
Age-adjusted OR	reference	1.64 (0.74-3.61)	2.42 (1.14-5.13)	4.02 (1.98-8.20)	<0.001
Multivariable-adjusted OR†	reference	1.61(0.71-3.65)	2.34(1.08-5.10)	4.31(2.06-9.03)	<0.001
Further adjustment for SMM%	reference	1.29(0.56-2.99)	1.53(0.65-3.62)	2.17(0.84-5.60)	0.09
Women					
No. at risk	251	246	234	260	
No. of cases	3	10	21	37	
Age-adjusted OR	reference	3.15 (0.85-11.66)	6.49 (1.90-22.22)	10.35 (3.12-34.30)	<0.001
Multivariable-adjusted OR†	reference	3.02(0.80-11.31)	6.16(1.78-21.35)	10.82(3.22-36.34)	<0.001
Further adjustment for SMM%	reference	2.43(0.64-9.22)	4.20(1.17-15.12)	5.99(1.63-21.97)	0.002

WC, waist circumference; OR, odds ratio

†Adjusted for age, smoking, alcohol, physical activity and family history of diabetes

Table 5. Sex-specific age-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals of prevalent type 2 diabetes according to the combination of SMM% and WC

	Combination of SMM% and WC					
	Low/High	Low/Low	High/High	High/Low	RERI (95% CI)	P-value for RERI
Men						
No. at risk	201	61	64	198		
No. of cases	55	8	5	21		
Age-adjusted OR	3.04 (1.75-5.30)	1.05 (0.43-2.53)	0.85 (0.30-2.38)	reference	2.1 (0.6-3.7)	0.02
Multivariable-adjusted OR†	3.19(1.78-5.71)	1.13(0.45-2.84)	0.89(0.31-2.57)	reference	2.2 (0.5-3.9)	0.03
Women						
No. at risk	363	132	131	365		
No. of cases	51	4	7	9		
Age-adjusted OR	4.30 (2.05-9.03)	0.81 (0.24-2.70)	2.04 (0.74-5.65)	reference	2.5 (0.02-4.9)	0.03
Multivariable-adjusted OR†	4.46(2.09-9.51)	0.78(0.23-2.65)	1.93(0.68-5.44)	reference	2.8(0.2-5.3)	0.01

SMM%, percentage of total skeletal muscle mass in body weight; WC, waist circumference; OR, odds ratio

Low SMM% was defined as <32.1% for men and <27.0% for women. High WC was > 85.0 cm for men and 80.0 cm for women.

†Adjusted for smoking, alcohol, physical activity and family history of diabetes

RERI=relative excess risk due to interaction