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Total and regional fat-to-muscle mass ratio measured by bioelectrical impedance and risk of incident type 2 diabetes

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Abstract

Background The fat-to-muscle mass ratio (FMR) might be an indicator to assess type 2 diabetes risk independent of general obesity. However, no longitudinal studies have explored the extent to which total and regional FMRs may confer risks. We aimed to measure the sex-specific associations between FMRs of the arm, leg, trunk and whole body and incident type 2 diabetes.

Methods A total of 464 817 participants (207 286 men and 257 531 women, mean age 56.5 ± 8.2 and 56.2 ± 8.0 years old, respectively) free of diabetes at baseline were included in this prospective cohort study with UK Biobank data. Fat mass and muscle mass were estimated using a bioelectrical impedance assessment device (Tanita BC 418MA). FMR was calculated as fat mass divided by muscle mass in corresponding body parts (total body, arm, leg and trunk). Cox proportional hazard models were used to estimate the aforementioned associations among men and women. Interaction analyses were performed between FMRs and body mass index (BMI) categories (BMI < 25 kg/m^2 and BMI ≥ 25 kg/m^2).

Results Over the median 11.0 years (5 057 534 person-years) of follow-up, we documented 11 618 cases of type 2 diabetes. There was a significantly positive association between total and regional FMR and incident type 2 diabetes, even after adjusting for BMI and other covariates. Compared with other body parts, FMRs of the whole body and leg showed the strongest relationship among men and women, respectively (hazard ratio per 1 SD, 95% confidence interval: 1.67, 1.55–1.80; 1.45, 1.39–1.53). A significant interaction (P for interaction < 0.001) between BMI category and FMRs of different body parts was observed. In the stratified analysis by BMI category and tertiles of FMRs, overweight/obese individuals with a high FMR tertile tended to have the highest hazard ratio, ranging from 5.91 to 7.94 in whole body and regional areas.

Conclusions In this large prospective study, higher total and regional FMRs were associated with a higher risk of developing type 2 diabetes, independent of BMI. This association was markedly strengthened in participants with BMI ≥ 25 kg/m^2.

Keywords Bioelectrical impedance; Fat-muscle mass ratio; General adiposity; Type 2 diabetes

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Introduction

Type 2 diabetes poses a great burden on the social and healthcare systems. The global diabetes prevalence in 2019 was estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030, contributing to one in nine deaths among adults.[1,2] Therefore, prevention of type 2 diabetes is essential. In the American Diabetes Association guidelines, a screening test is recommended in adults with overweight or obesity who have one or more diabetes-associated risk factors, and furthermore, achieving and maintaining a 7% loss of initial body weight is highly recommended to prevent diabetes.[3,4] These evidence-based recommendations indicate that adiposity could be key among various risk factors for type 2 diabetes prevention.

Bioelectric impedance assessment (BIA) represents a simple, inexpensive, and non-invasive means of assessing body composition and can be performed across a wide range of subjects with regard to age, sex, and body shape.[5] A number of validation studies have led to the conclusion that compared with dual-energy X-ray absorptiometry (DEXA), segmental BIA is an adequate method to assess body composition.[6,7]

It is reasonable that adiposity could be defined based on body composition, such as high fat mass and low muscle mass, rather than indirect indices, such as body mass index (BMI), which is commonly used as an estimate of general adiposity in both clinical work and population studies.[8] There is a close link among higher fat mass, lower muscle mass, and incident diabetes.[9,10] An interesting hypothesis is that fat mass represents the metabolic load, muscle mass represents metabolic capacity, and they interact to determine metabolic risk.[8] Thus, the fat-to-muscle mass ratio (FMR) could be a potential body composition indicator for type 2 diabetes. Previous studies found that the FMR was associated with metabolic syndrome and hypertension in both sexes in a cross-sectional setting.[11–13] However, no longitudinal studies have explored associations between total and regional FMR and incident type 2 diabetes. Because muscle gain/exercise could be site focused, this association in different body parts, including the arm, leg, and trunk, has potential clinical implications and should be further measured. Moreover, considering that BMI has been associated with fat mass, muscle mass, and incident diabetes, a hypothesis was formed that BMI might modify the association between the FMR and incident type 2 diabetes.

In this prospective cohort of 464 817 participants from the UK Biobank (UKB), we aimed to measure the sex-specific associations between FMR of the arm, leg, trunk, and whole body and incident type 2 diabetes. We further examined the effect modification by general overweight or obesity status defined by BMI in these associations.[14]

Materials and methods

Study design and sample

The UKB is a prospective cohort study that included more than 500 000 community-dwelling adults aged 40–69 years across the United Kingdom between 2006 and 2010 (https://www.ukbiobank.ac.uk/). Detailed information about the UKB has been provided in a previous study.[15] We declare that all data are publicly available in the UKB repository.[15] The North West Multi-Center Research Ethics Committee Study approved the UKB study, and all participants provided written informed consent.

A total of 502 505 participants were recruited. We excluded those with missing values on body composition parameters (fat mass and muscle mass in arm, leg, trunk, and whole body) (n = 11 443) and those with diabetes at baseline (n = 27 397). The final sample was 464 817 (207 286 men and 257 531 women).

Exposure and outcome

At baseline, data on body size and composition were collected by trained healthcare technicians or nurses certified to conduct assessments of participants using a standard protocol. Height (cm) was measured using a Seca 240 cm height measure (SECA, Hamburg, Germany). Weight (kg), BMI (weight in kg divided by square of height in meters), and body composition data (fat percentage; fat mass; fat free mass; and muscle mass for right arm, right leg, left arm, left leg, and trunk) were estimated using an eight-contact electrode Tanita BC418MA segmental body composition analyser (Tanita, Japan). This device estimates body composition by bioimpedance analysis. When a participant was wheelchair-bound, an amputee, unable to grip the handles of the Tanita analyser, unable to stand, unwilling to remove their shoes, wearing a plaster cast, pregnant, or using a pacemaker, bioelectrical impedance was impossible. FMR was calculated as fat mass divided by muscle mass in corresponding body parts. The right and left arms were combined into one part [fat mass (right arm + left arm)/muscle mass (right arm + left arm)], which was also applied to the legs. Therefore, FMRs in the whole body and three body parts (arm, leg, and trunk) were the exposures to be explored.

The outcome, type 2 diabetes, was extracted from 'first occurrence of health outcomes defined by a 3-character International Statistical Classification of Diseases and Related Health Problems 10th Revision code' (category ID in UKB 1712). The diagnosis of incident type 2 diabetes was obtained by using linkage with death register, primary care, and hospital inpatient records. Detailed information regarding the linkage procedure is available online (https://biobank.ctsu.ox.ac.uk/crystal/exinfo.cgi?src=diag_xtabs_HES).

Covariates

The following potential confounders were included in the analysis: participants' age, ethnicity (White/others), education (university or college degree/others), the Townsend index reflecting socio-economic status (continuous); current smoking (yes, no), drinking status (drinks per week, continuous variable), physical activity at goal or not (≥150 min/week of moderate intensity, or ≥75 min/week of vigorous intensity, or an equivalent combination), and dietary score ≥4 [vegetable intake ≥4 tablespoons each day (median); fresh fruit intake ≥2 pieces each day (median); oily and non-oily fish intake at least twice each week (median); urinary sodium <68.45 mmol/L (median); and processed meat intake no more than twice each week (median)]. Each favourable diet factor received one point, with a total score ranging from 0 to 5, which has been used in previous studies[16]): systolic blood pressure, total cholesterol, use of blood pressure--lowering medications (yes/no), and cholesterol-lowering medications (yes/no). If the covariate information was missing, we imputed median values for continuous variables or used a missing-indicator approach for categorical variables.

Statistical analyses

Data analyses were performed using IBM SPSS Statistics, Version 25 (IBM Corporation, Armonk, NY, USA) and SAS 9.2 (SAS Institute, Cary, NC). A P value < 0.05 indicated statistical significance (two-sided). Because body composition such as fat and muscle mass is markedly differently distributed between men and women, analyses were intended to be separately conducted for men and women.

Baseline characteristics of the study population are reported as the means or percentages according to participants with gender-specific tertiles of FMR in the whole body. Cumulative cases of type 2 diabetes were calculated during follow-up visits. Follow-up time was determined from the baseline date (date of attending assessment centre) to the diagnosis of type 2 diabetes, death, or censoring date (31 August 2019), whichever came first.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals for the associations between FMR of whole and three body parts and the risk of incident type 2 diabetes among men and women. All FMRs were log-transformed and then standardized. Model 1 was adjusted for age, ethnicity (White/others), education (university or college degree/others), the Townsend index, current smoking (yes, no), drinking status (drinks, continuous variable), and dietary score ≥4. Model 2 was further adjusted for physical activity at goal (yes, no), systolic blood pressure, total cholesterol, use of blood pressure-lowering medications (yes/no), and cholesterol-lowering medications (yes/no). Model 3 was adjusted for the terms in Model 2 and BMI.

The interaction analysis between FMRs and BMI categories (BMI < 25 kg/m^2 and BMI ≥ 25 kg/m^2) was performed by using the likelihood ratio test comparing models with and without a cross-product term. Moreover, stratified analyses were performed a priori according to BMI category. Similar Cox regression models were used separately for normal weight (BMI < 25 kg/m^2) and overweight/obese (BMI ≥ 25 kg/m^2) participants. We also depicted the joint association of sex-specific tertiles of FMRs and BMI category (BMI < 25 kg/m^2 and BMI ≥ 25 kg/m^2). Using participants with the lowest FMR tertile and BMI < 25 kg/m^2 as a reference, multivariate HRs of type 2 diabetes were obtained in the remaining joint categories.

We further performed subgroup analyses to examine the relationship between FMR and type 2 diabetes stratified by age (≥60 or <60 years), physical activity at goal (yes or no), hypertension (yes or no), and dyslipidaemia (yes or no).

We conducted sensitivity analyses restricted to subjects with incident type 2 diabetes ≥ 1 year from baseline to minimize the possible influence of reverse causality. Fasting time was further adjusted.

Results

Table 1 shows the baseline characteristics of the participants according to the tertiles of FMR for the whole body. For both men and women, the participants with a higher FMR of the whole body were more likely to be older and have higher Townsend deprivation index scores. In addition, they were less likely to have a healthy diet and physical activity volume at goal and had higher systolic blood pressure and total cholesterol. Furthermore, greater BMI was clearly observed among participants with higher levels of FMR. Similar characteristics for FMR of the arm, leg, and trunk were also observed in Supporting Information, *Tables* S1–S3.

Over the median 11.0 years (5 057 534 person-years) of follow-up, we documented 11 618 cases of type 2 diabetes. The associations between FMRs of different body parts and incident type 2 diabetes in multivariate-adjusted models among men and women are presented in *Table* 2. The associations were significant in all models. Adjusting for demographic variables, lifestyle, metabolic factors, and medications did not materially change the significance. Even in the final model, adjusting for BMI clearly attenuated the associations, but they remained evident in both sexes. Adjusting for waist circumference instead of BMI had similar results (*Table* S4). Remarkably, a sex difference seemed to exist in this relationship. Among the body parts, the FMR of the leg showed the strongest association with diabetes among women (HR per 1 SD, 95% confidence interval: 1.67, 1.55–1.80), while in men, the total FMR showed the strongest association with diabetes (HR per 1 SD: 1.45, 1.39–1.53).

Table 1 Baseline characteristics for men and women by tertiles of FMR for whole body

	N	Tertile 1	Tertile 2	Tertile 3
Men (*n* = 207 286, 4.6%)				
Age (years)	207 286	54.8 ± 8.4	56.5 ± 8.2	58.1 ± 7.8
White (%)	207 286	95.3	94.9	95.2
Body mass index (kg/m^2)	207 286	24.5 ± 2.3	27.2 ± 2.3	31.2 ± 3.9
Townsend deprivation index	207 127	−1.4 ± 3.1	−1.5 ± 3.0	−1.1 ± 3.2
University or college degree (%)	203 364	43	34.9	26.9
Drinks per week	207 286	10.1 ± 11.3	11.3 ± 11.6	11.8 ± 12.7
Current smoking (%)	207 092	13.9	11.9	11.5
Healthy diet (%)	201 772	40.9	38.5	35
Physical activity at goal (%)	199 617	63.2	55.8	47.4
Systolic blood pressure (mmHg)	193 592	139 ± 18	143 ± 18	146 ± 18
Total cholesterol (mmol/L)	195 094	5.5 ± 1.0	5.7 ± 1.1	5.6 ± 1.1
Anti-hypertensive medication (%)	205 216	12.1	20	32.2
Cholesterol-lowering medication (%)	205 216	10.9	18.5	27.1
Women (*n* = 257 351, 55.6%)				
Age (years)	257 531	54.5 ± 8.2	56.8 ± 7.9	57.4 ± 7.7
White (%)	257 531	95.5	95.4	94.2
Townsend deprivation index	257 531	−1.5 ± 2.9	−1.5 ± 2.9	−1.1 ± 3.2
Body mass index (kg/m^2)	257 471	22.6 ± 2.1	26.1 ± 2.3	31.9 ± 4.6
University or college degree (%)	252 818	40.1	30.7	24.9
Drinks per week	257 531	6.1 ± 7.1	5.9 ± 7.3	5.2 ± 7.6
Current smoking (%)	257 285	10	8.7	8.1
Healthy diet (%)	252 730	59.5	58.6	54.6
Physical activity at goal (%)	244 915	58.7	52.4	43.5
Systolic blood pressure (mmHg)	240 164	132 ± 19	138 ± 20	141 ± 19
Total cholesterol (mmol/L)	240 486	5.8 ± 1.0	6.0 ± 1.1	6.0 ± 1.1
Anti-hypertensive medication (%)	256 213	8.2	14.8	24.7
Cholesterol-lowering medication (%)	256 213	5.4	10.3	15.4

FMR, fat-to-muscle mass ratio.
Mean ± SD for continuous variables and percentage for categorical variables.

We conducted a stratified analysis according to BMI status to evaluate whether normal weight (BMI $<$ 25 kg/m^2) or overweight/obese (BMI $\geq$ 25 kg/m^2) modified the association between FMR and the risk of type 2 diabetes (*Table* 3). We observed a significant interaction between total and regional FMRs and BMI category on the risk of type 2 diabetes in both sexes (all *P* for interaction $<$ 0.001). The overweight/obese individuals tended to have higher HRs than the normal weight participants. Considering that even within the normal weight and overweight/obese groups, BMI may also vary and contribute to the risk of diabetes, we further adjusted for BMI. A significant interaction existed only in the total FMR in men and leg FMR in women (*P* for interaction 0.032 and $<$0.001, respectively).

Participants were further divided into joint categories of sex-specific tertiles of FMR and BMI category to measure the joint associations. The low tertile of FMR with BMI $<$ 25 kg/m^2 was set as the reference. As shown in *Figure* 1, we documented a consistent and graded increasing risk of type 2 diabetes with increasing categories of FMR and BMI. The participants in the high tertile of total and regional FMR with BMI $\geq$ 25 kg/m^2 had the highest risk of developing diabetes. Similarly, the overweight/obese plus high FMR tertile in the whole body and leg showed the strongest associations with diabetes among men (HR per 1 SD 6.75, 5.98–7.63) and women (HR per 1 SD 7.94, 6.97–9.05), respectively.

Subgroup analyses were further examined to assess the relationships between FMR and type 2 diabetes (*Table* S5). The associations per 1 SD increment of total and regional FMR were broadly similar among subgroups that were classified by age, physical activity at goal, hypertension, and dyslipidaemia. In sensitivity analyses, the results remained similar when restricting the analysis to the subjects with incident type 2 diabetes $\geq$ 1 year from baseline or further adjusting for fasting time (*Tables* S6–S7).

Discussion

In this large-scale prospective cohort study with an approximately 11 year follow-up time, FMRs of the whole body, arm, leg, and trunk were significantly associated with incident diabetes, independent of BMI, or waist circumference. FMRs of the whole body and leg showed the strongest associations in men and women, respectively. Moreover, these associations were strongly modified by BMI category for both sexes. The positive association between FMR and incident diabetes was markedly strengthened among overweight/obese participants. Further intervention studies are warranted to explore whether amelioration of FMR could reduce diabetes risk.

Table 2 Multivariable-adjusted HRs (95% CIs) for type 2 diabetes by total and regional FMR

	Incident diabetes HRs (95% CI)	
	Men	Women
Whole body		
Unadjusted	2.58 (2.51–2.66)	2.68 (2.59–2.77)
Model 1	2.41 (2.34–2.48)	2.46 (2.38–2.54)
Model 2	2.20 (2.13–2.27)	2.20 (2.13–2.28)
Model 3	1.45 (1.39–1.53)	1.23 (1.16–1.30)
Arm		
Unadjusted	1.96 (1.93–2.00)	2.70 (2.62–2.78)
Model 1	1.89 (1.85–1.93)	2.56 (2.48–2.64)
Model 2	1.77 (1.73–1.81)	2.29 (2.22–2.37)
Model 3	1.14 (1.09–1.19)	1.37 (1.26–1.49)
Leg		
Unadjusted	2.19 (2.14–2.24)	2.90 (2.81–2.99)
Model 1	2.06 (2.02–2.11)	2.67 (2.55–2.80)
Model 2	1.91 (1.87–1.96)	2.38 (2.30–2.46)
Model 3	1.34 (1.30–1.39)	1.67 (1.55–1.80)
Trunk		
Unadjusted	2.40 (2.34–2.45)	2.16 (2.10–2.22)
Model 1	2.30 (2.24–2.36)	2.02 (1.96–2.08)
Model 2	2.14 (2.08–2.21)	1.87 (1.81–1.93)
Model 3	1.38 (1.32–1.45)	1.11 (1.11–1.12)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; FMR, fat-to-muscle mass ratio.
Data are hazards ratios (95% confidence interval). All FMRs were log-transformed and then standardized. Model 1 was adjusted for age, ethnicity (White/others), education (university or college degree/others), Townsend index (continuous), current smoking (yes, no), drinking status (drinks, continuous variable), and dietary score ≥4. Model 2 was further adjusted for physical activity at goal (yes, no), systolic blood pressure, total cholesterol, use of blood pressure-lowering medications (yes/no), and cholesterol-lowering medications (yes/no). Model 3 was adjusted for terms in Model 2 and BMI (continuous).

To our knowledge, this is the first study to explore the association between total and regional FMR and the risk of incident type 2 diabetes. Because it is not feasible to use expensive technologies such as DEXA to measure body composition in large epidemiological studies, previous studies mainly used anthropometric methods to examine the relationship between obesity and the risk of type 2 diabetes. Although there were many anthropometric indices indicating adiposity, until now, BMI has remained the most commonly used measurement reflecting general adiposity. Undoubtedly, greater BMI increases the risk of type 2 diabetes.[17] However, this measure does not discriminate fat mass and muscle mass, and it does not provide segmental body information. Studies have shown that it is critical to understand the independent roles of total and regional fat mass and lean mass in mortality and cardiovascular disease.[18,19] Our findings indicate that BMI or waist circumference does not fully capture the association between body composition and diabetes risk, and FMR considering both fat mass and muscle mass may fill the gap, at least partly.

Excessive fat deposition is metabolically harmful, whereas muscle mass may play a beneficial role in diabetes risk. Findings from two large prospective cohorts indicated that fat mass had a consistently stronger association with type 2 diabetes risk than BMI.[20] Son *et al*. found that a low appendicular skeletal muscle mass index increased diabetes risk independent of general obesity in middle-aged adults[10]; however, in another study that included older participants (mean age, 73 years), no significant association was found.[21] Our subgroup analysis also indicated that such an association in participants over 60 was diminished, although still significant. However, a limited number of studies have considered a combination of fat mass and muscle mass measures as a single parameter to prospectively assess diabetes risk. It seems that only cross-sectional studies measured these associations. One study including 875 individuals found that total FMR was strongly associated with diabetes, impaired fasting glucose, and impaired glucose tolerance.[13] These results support our findings, indicating that the balance of fat mass and muscle mass could be a considerable factor when assessing diabetes risk in the general population.

A strong interaction between BMI category and FMRs on type 2 diabetes was found. We suppose one of the main reasons is that within the different BMI categories, the magnitude of the relationships between BMI, fat mass, and muscle mass were quite different. In our study, in participants with BMI < 25 kg/m^2 and ≥ 25 kg/m^2, the correlation coefficients between total FMR and BMI in men were 0.475 and 0.695, respectively, which shows a tighter relationship between total FMR and BMI for those in the BMI ≥ 25 kg/m^2 category (*Figure* S1). This phenomenon has been observed in previous studies.[9,10] One study found that the inverse association between thigh muscle area and diabetes was markedly weakened at higher BMI levels,[9] probably because in participants with higher BMI, excessive fat mass in the whole body may counteract the protective effect of muscle mass. Thus, considering muscle and fat mass together may avoid such problems.

The association between FMR and type 2 diabetes is biologically plausible. Insulin resistance, followed by subsequent compensatory β cell dysfunction, plays a key role in the pathogenesis of type 2 diabetes.[22] The main insulin-sensitive tissues, including the adipose tissue and skeletal muscle assessed here, are profoundly affected by altered body composition.[23] Adipose tissue secretes a number of adipokines and cytokines. For example, adiponectin is positively associated with insulin sensitivity, but TNF-α and IL-6 can activate inflammatory responses.[24,25] Adiposity induces low adiponectin levels and high proinflammatory cytokines that may exacerbate insulin resistance.[26] Skeletal muscle accounts for ∼57% of insulin-stimulated glucose utilization among women and ∼77% in men.[27] Increased intramyocellular lipid content secondary to elevated plasma fatty free acid levels and/or excessive lipid intake will both decrease the capacity of fatty acid oxidation and develop insulin resistance.[28] More importantly, myokines secreted by muscle could crosstalk with adipokines to maintain a balanced body metabolic state. For example, administration of

Table 3 Multivariable-adjusted HRs (95% CIs) for type 2 diabetes among normal weight and overweight/obese participants by FMRs

	Normal weight HR (95% CI)	Overweight/obese HR (95% CI)	*P* for interaction
Men			
Whole body			
Model 1	1.35 (1.21–1.51)	2.34 (2.26–2.42)	<0.001
Model 2	1.26 (1.12–1.41)	2.15 (2.07–2.22)	<0.001
Model 3	1.26 (1.11–1.43)	1.44 (1.36–1.52)	0.032
Arm			
Model 1	1.52 (1.35–1.72)	1.87 (1.82–1.91)	<0.001
Model 2	1.24 (1.09–1.41)	1.68 (1.64–1.72)	<0.001
Model 3	1.23 (1.06–1.43)	1.10 (1.06–1.15)	0.295
Leg			
Model 1	1.34 (1.18–1.51)	1.95 (1.90–2.00)	<0.001
Model 2	1.24 (1.09–1.40)	1.83 (1.78–1.88)	<0.001
Model 3	1.24 (1.07–1.44)	1.32 (1.27–1.37)	0.148
Trunk			
Model 1	1.31 (1.18–1.45)	2.24 (2.17–2.31)	<0.001
Model 2	1.23 (1.11–1.36)	2.09 (2.02–2.16)	<0.001
Model 3	1.22 (1.09–1.36)	1.36 (1.29–1.44)	0.079
Women			
Whole body			
Model 1	1.30 (1.14–1.47)	2.23 (2.14–2.33)	<0.001
Model 2	1.20 (1.06–1.36)	2.03 (1.94–2.12)	<0.001
Model 3	1.04 (0.88–1.22)	1.08 (1.01–1.16)	0.396
Arm			
Model 1	1.31 (1.14–1.50)	2.43 (2.34–2.53)	<0.001
Model 2	1.20 (1.04–1.37)	2.20 (2.11–2.29)	<0.001
Model 3	0.98 (0.80–1.18)	1.11 (0.98–1.24)	0.989
Leg			
Model 1	1.45 (1.26–1.67)	2.52 (2.42–2.62)	<0.001
Model 2	1.31 (1.13–1.51)	2.28 (2.19–2.38)	<0.001
Model 3	1.17 (0.97–1.41)	1.57 (1.43–1.72)	<0.001
Trunk			
Model 1	1.18 (1.06–1.31)	1.73 (1.66–1.80)	<0.001
Model 2	1.12 (1.00–1.25)	1.62 (1.55–1.69)	<0.001
Model 3	0.99 (0.87–1.13)	1.01 (0.96–1.06)	0.437

BMI, body mass index; CI, confidence interval; FMR, fat-to-muscle mass ratio; HR, hazard ratio.
Data are hazards ratios (95% confidence interval). All FMRs were log-transformed and then standardized. Model 1 was adjusted for age, ethnicity (White/others), education (university or college degree/others), Townsend index (continuous), current smoking (yes, no), drinking status (drinks, continuous variable), and dietary score ≥4. Model 2 was further adjusted for physical activity at goal (yes, no), systolic blood pressure, total cholesterol, use of blood pressure-lowering medications (yes/no), and cholesterol-lowering medications (yes/no). Model 3 was adjusted for terms in Model 2 and BMI (continuous).

leptin promotes irisin-induced myogenesis,[29] and overexpression of myostatin increases circulating adiponectin levels.[30]

The strengths of our study included a large sample size and relatively long follow-up duration, which enabled adequate power to study the associations and interactions in detail. We collected various covariates, including demographic information, lifestyle factors, metabolic factors, and medications, which allowed for relatively rigorous adjustments. Our study also has some limitations. First, this is an observational study, and the association between FMR and the risk of type 2 diabetes cannot be interpreted as a causal relationship. Intervention trials are further needed. Second, body composition was not measured with high precision by imaging techniques such as DEXA and magnetic resonance. In such a large cohort, bioimpedance may be a feasible measurement, and studies have concluded that the single-frequency bioimpedance that was used in our study is an adequate method to assess body composition in large epidemiological studies, although they agree that most single-frequency bioimpedance equations underestimate fat mass compared to DEXA.[31] The eight-electrode bioimpedance system improves the association with DEXA % fat estimates over those provided by conventional foot–foot bioimpedance and may offer acceptable estimates of total and appendicular body composition.[6,7] However, we recognize this limitation and suggest future studies using imaging techniques to confirm our findings. Third, some factors affecting bioimpedance results, such as hydration, room temperature, or prior exercise, were not intentionally controlled. Because it normally required more than 1 h to complete the assessments before the bioimpedance measurement in the UKB assessment centre with stable temperature, most of the participants were likely to be in a steady state when reaching the bioimpedance room. Additionally, we noticed that before the bioimpedance measurement, the participants had to be in a calm state for blood pressure testing. We have no evidence that hydration was controlled. However, a study showed that BIA results are most affected by whether subjects were in a fasting or a fed state,[32] so we further adjusted for fasting time in the sensitivity analysis. The results were

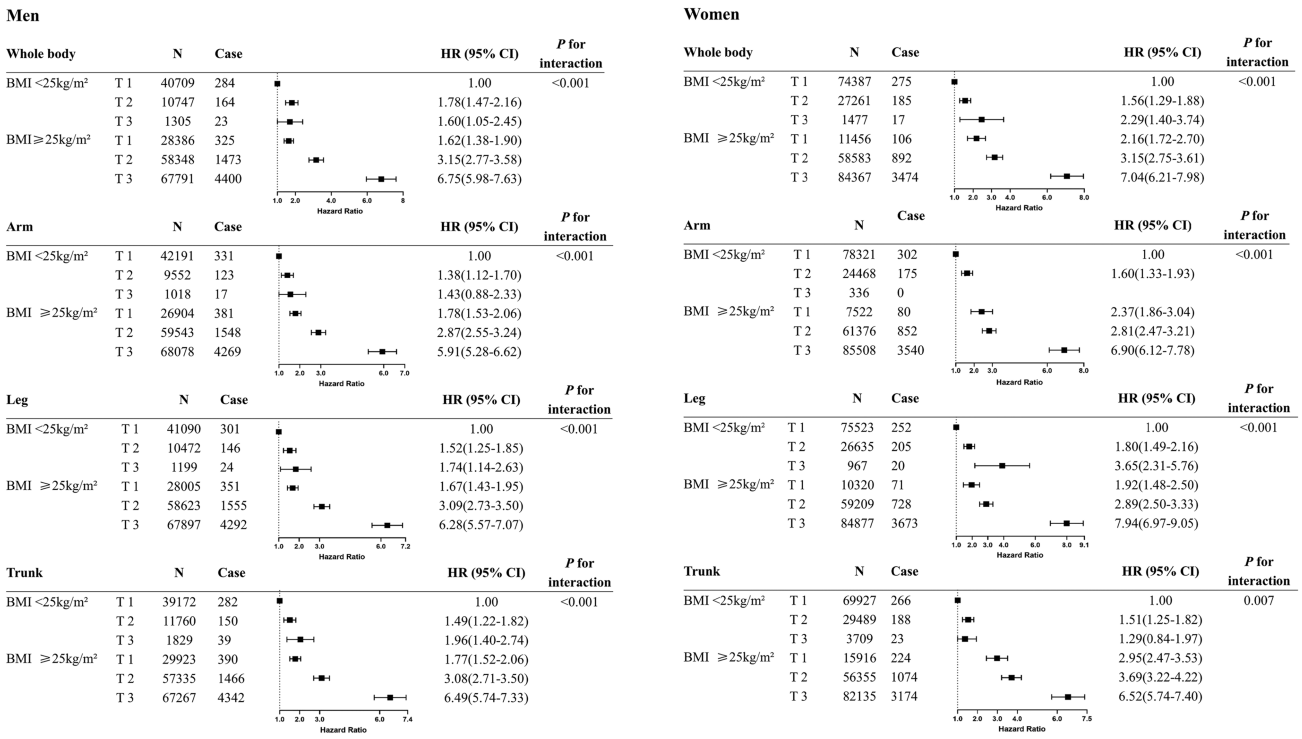

Figure 1 Multivariate hazard ratios of type 2 diabetes according to joint categories of BMI category and tertiles of fat-to-muscle mass ratios. Model was adjusted for age, ethnicity (White/others), education (university or college degree/others) and the Townsend index (continuous), current smoking (yes, no), drinking status (drinks, continuous variable), physical activity at goal (yes, no), dietary score ≥4, systolic blood pressure, total cholesterol, use of blood pressure-lowering medications (yes/no), and cholesterol-lowering medications (yes/no). BMI, body mass index; CI, confidence interval; HR, hazard ratio.

not significantly changed. Fourth, the proportion of underweight participants (BMI $\leq$ 18.5 kg/m^2) was just 0.5% (n = 2353); thus, evaluations could not be performed in this subgroup. Finally, this cohort included people of European descent aged 40–69 years, mostly White British individuals, which limits the generalizability to other ethnicities, such as Asians and Blacks. The UKB aimed to be representative of the general population but was unrepresentative in terms of lifestyle because of a 'healthy volunteer' selection bias.[33] Therefore, generalizing summary statistics to the general population should be done with caution.

Conclusion

In the present prospective cohort study, total and regional FMRs were independently associated with the risk of type 2 diabetes. FMRs of the whole body and leg showed the strongest associations with incident diabetes in men and women, respectively. These associations were obviously strengthened among participants with BMI over 25 kg/m^2. The clinical implications might be to stratify strategies for diabetes prevention, for example, targeting lowering fat mass and increasing muscle mass, especially among people with BMI over 25 kg/m^2.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics for men and women by tertiles of FMR for arm
Table S2. Baseline characteristics for men and women by tertiles of FMR for leg
Table S3. Baseline characteristics for men and women by tertiles of FMR for trunk
Table S4. Multivariable-adjusted HRs (95%CIs) for type 2 diabetes when adjusting waist circumference instead of BMI
Table S5. Multivariable-adjusted HRs (95%CIs) for type 2 diabetes by age, physical activity at goal, hypertension and dyslipidemia
Table S6. Multivariable-adjusted HRs (95%CIs) for type 2 diabetes ≥ 1 year from the baseline
Table S7. Multivariable-adjusted HRs (95%CIs) for type 2 diabetes when further adjusting for fasting time
Figure S1. The scatter plot of whole body FMR and BMI (BMI $<$ 25 kg/m^2 and BMI $\geq$ 25 kg/m^2) among men and women

Conflict of interest

No potential conflicts of interest relevant to this article were reported for any author.

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