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Total and regional fat-to-muscle mass ratio and risks of incident all-cause dementia, Alzheimer's disease, and vascular dementia

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Abstract

Background The fat-to-muscle mass ratio (FMR), which integrates the antagonistic effects of fat and muscle mass, has been proposed as a useful indicator to assess disease risk independent of overall obesity. However, little is known about the association between FMR and dementia risk. We aimed to prospectively investigate the sex-specific associations between total and regional FMR and incident dementia.

Methods A total of 491 420 participants (223 581 men and 267 839 women; mean age 56.7 ± 8.2 and 56.3 ± 8.0 years old, respectively) free of dementia at baseline from the UK Biobank were included. Fat mass and muscle mass were measured using a bioelectrical impedance assessment device. Cox regression analyses were used to examine the associations of total and regional FMR with incident all-cause dementia, Alzheimer's disease (AD) and vascular dementia (VD). The shape of the associations of the continuous scale of FMR and incident dementia were examined using restricted cubic spline analysis.

Results During a median 8.65 years of follow-up, we documented 2 225 incident all-cause dementia cases, including 836 AD and 468 VD cases. There was an L-shaped association between whole body FMR and all-cause dementia risk in both sexes after adjusting body mass index (BMI) and other covariates (P for non-linear <0.001 in men and women), where all-cause dementia risk decreased steeply with increasing FMR and levelled off at around the medians (0.35 in men, 0.61 in women) with a hazard ratio (HR) of 0.78 (95% CI: 0.64, 0.96; $P = 0.019$) and 0.60 (0.47, 0.77; <0.001) per 1 standard deviation (SD) increase in men and women, respectively. Compared with other body parts, FMR of the leg showed the strongest inverse associations [HR (95% CI; P) per 1 SD below the medians: 0.60 (0.48, 0.75; <0.001); 0.61 (0.47, 0.79; <0.001) in men and women, respectively]. Specifically, the inverse associations of whole body FMR on all-cause dementia risk were significant only among participants over the age of 60 (P for trend <0.001). Multivariable adjusted Cox models showed inverse associations of whole body FMR with AD in men only (P for trend $= 0.003$), whereas no statistically significant decrease was detected in VD among men and women.

Conclusions Our analyses provide strong evidence for L-shaped associations of total and regional FMR with the development of dementia among participants aged 60 years or older independent of overall obesity.

Keywords Fat-to-muscle ratio; Dementia; Alzheimer's disease; Vascular dementia

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Introduction

Dementia, including Alzheimer's disease (AD) and vascular dementia (VD), is the fifth leading cause of death globally, affecting approximately 44 million people worldwide.[1] Due to the current lack of disease-modifying therapies, dementia prevention has become an urgent public health priority. Obesity, as measured by body mass index (BMI), has been reported to be associated with an increased risk of dementia in middle age and may reduce the risk of dementia in later life.[2–4] One hypothesis to explain the situation is a pattern of the so-called obesity paradox, in which excess weight, traditionally considered detrimental to health, may be beneficial in older adults to reduce the disease risk.[4] However, although BMI is widely accepted as an indicator of general adiposity in population-based studies, it cannot distinguish between fat and muscle mass, which is highly variable at the same BMI level.[5,6] Furthermore, body composition is more informative than BMI, because changes in BMI lag behind changes in body composition with dementia progression.[7]

Several studies have linked lean body mass, predominantly comprised of skeletal muscles, and subcutaneous fat mass with dementia risk[7–10]; however, inconsistent findings have been observed. An intriguing hypothesis is that components of body composition are intricately correlated; changes in one component usually lead to changes in other components.[11] Thus, not the absolute amount of body composition component but rather their interrelationship determined the dementia risk. An increasing number of studies emphasized the importance of the fat-to-muscle mass ratio (FMR) as a predictor of dementia.[7,8] However, it remains unclear whether FMR, which integrates the antagonistic effects of fat and muscle mass, is associated with dementia risk independent of overall obesity. In addition, identifying the associations of regional FMR could also help understand underlying site-focused clinical implications, which still need further investigation.

In the current study, we aimed to prospectively investigate the independent associations between FMR of the whole body, trunk, leg and arm measured by bioelectrical impedance analysis and the risk of dementia by sex among 491 420 participants from the UK Biobank (UKB).

Methods

Study population

The UKB is an ongoing prospective cohort study involving half a million participants aged 40–70 years who were recruited at 22 assessment centres throughout the United Kingdom between 2006 and 2010. Details of the UKB design, survey methods, and long-term follow-up have been described elsewhere previously.[12] At the baseline survey, participants completed a wide range of health-related information through touch-screen questionnaires and physical measurements. Blood samples were collected for genotyping and biochemical analysis. Ethics approval for the study was obtained from the National Information Governance Board for Health and Social Care in England and Wales, the Community Health Index Advisory Group in Scotland, and the North West Multicenter Research Ethics Committee. All participants provided written informed consent for the study.

In the current analysis, we excluded participants with dementia at baseline (n = 230) and those with missing information on body composition factors (fat and muscle mass in the whole body, arm, leg, and trunk) (n = 10 603) and BMI (n = 253), leaving a total of 491 420 participants for our analysis.

Exposure assessments

Following a standard protocol, participants had a range of physical measurements collected by the trained staff using well-calibrated instruments. Standing height was measured using a Seca 202 device. After the height measurements, weight and body composition were measured using a Tanita BC418MA body composition analyser. The analyser produces segmental readings of body composition for fat mass, fat-free mass, and predicted muscle mass in the trunk, right arm, left arm, right leg, and left leg based on the bioelectrical impedance analysis. The right and left arms/legs were combined as a whole. We calculated the FMR as fat mass divided by the predicted muscle mass of the corresponding part and was categorized into quintiles (Q1–Q5) from the lowest (Q1) to highest (Q5) values. BMI was calculated as weight in kilograms divided by height in meters squared.

Dementia diagnosis

The primary outcome in the present study was all-cause incident dementia, and the secondary outcomes were its two major component outcomes—AD and VD. Prevalent and incident dementia were ascertained through data linkage to hospital inpatient records from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales, using the International Classification of Diseases edition 9 and 10 (ICD-9, 10) codes (https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/alg_outcome_dementia.pdf) (detailed in Supporting Information, *Table* S1). Self-reported dementia cases at enrolment were additionally classified as prevalent dementia. Participants were considered at risk for dementia from the date of enrolment (2006–2010) and were followed up until the date of first diagnosis, date of death, date of loss to follow-up, or updating

date of linkages (31 March 2017, for England; 31 October 2016, for Scotland; and 29 February 2016, for Wales), whichever came first.

Covariates

We considered the following covariates for adjustment: age, self-reported ethnicity (white/others), educational level (university or college degree/others), Townsend Deprivation Index (an area-based deprivation measure for socio-economic status, TDI, quintiles 1, 2 to 4, and 5), family history of dementia (yes/no), current smoking (yes/no), alcohol frequency, healthy physical activity (defined as ≥150 min moderate activity per week or ≥75 min vigorous activity per week or equivalent combination or moderate physical activity at least 5 days a week, or vigorous activity once a week), vegetable, and fruit intake, fish and processed meat intake, baseline systolic blood pressure, prevalent diabetes (yes/no), baseline cholesterol, BP-lowering medication, cholesterol-lowering medication and BMI. Given the missing information (including participants who answered 'do not know', or 'prefer not to answer'), the median values for continuous covariates and a missing indicator for categorical covariates were imputed (all covariates <5% missing).

Statistical analyses

Baseline characteristics of the study participants were summarized for those with and without incident dementia as the mean (SD) for continuous variables or as the number of participants (percentage) for categorical variables; *t*-tests and χ^2 tests were used for continuous and categorical variables, respectively. Because it is known that men and women have markedly different body compositions, such as fat mass and predicted muscle mass, our analyses were stratified by sex.

Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between quintiles of FMR in the whole body and three other parts and incident dementia among men and women, respectively. Schoenfeld residuals were used to test the assumptions of proportional hazards, and no violation was found. The linear trend test was conducted by treating FMR as a continuous variable in the models. We also performed age-stratified analyses (<50, 50–60, and ≥60 years) and tested potential interactions by using the likelihood ratio test comparing models with and without a cross-product term.

The shape of the associations of the continuous scale of FMR and incident all-cause dementia were examined using restricted cubic spline analysis with knots at the 5th, 35th, 65th, and 95th percentiles. We also used a likelihood ratio test to evaluate the potential non-linear association by comparing a model with only a linear term and with linear and cubic spline terms. Because the FMR of the whole body and three parts were approximately log-linear above and below the median, we also entered FMR as a continuous variable and calculated the HR and 95% CI for per standard deviation (SD) increases above and below the median, respectively.

To examine the robustness of our results, we also performed several sensitivity analyses: (i) examined the independent associations between whole body fat and muscle mass and all-cause dementia risk; (ii) excluded participants diagnosed with dementia during the first 2 years of follow-up (n = 109) to minimize the possibility of reverse causation; (iii) excluded participants with a cancer diagnosis at baseline (n = 53 355) because their body composition may have changed as a result of the diagnosis of their condition; and (iv) conducted the Fine-Grey subdistribution hazard model to account for death as a competing risk. All analyses were performed using Stata version 15.0 (StataCorp). The statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Baseline characteristics

The participants of 491 420 individuals comprised 223 581 men (mean age 56.7 ± 8.2 years old) and 267 839 women (mean age 56.3 ± 8.0 years old). During a median of 8.65 years (interquartile range (IQR): 8.12–9.34 years, 4.3 million person-years) of follow-up, we documented 2 225 incident all-cause dementia, of which 836 were AD and 468 were VD. Baseline characteristics according to dementia status are presented in *Table* 1. Overall, participants with incident dementia were more likely to be older; be higher deprived; be less physically active; have a family history of dementia; and have hypertension, diabetes, and taking antihypertensive and lipid-lowering medications among men and women.

Fat-to-muscle ratio and dementia risk

The association between the FMRs of the whole body and regional parts and the risk of all-cause dementia is shown in *Table* 2. After adjusting for demographic covariates, lifestyle factors, vascular risk factors, and medication, we observed significant inverse associations between the FMR of the whole body, trunk, arm, and leg and dementia risk among men and women. Further adjusting for BMI, the association between FMR in the arm and dementia risk attenuated to be non-significant among men and women, whereas FMR of the whole body, trunk, and leg remained similar. Compared with those in the lowest quintile (Q1), the highest quintile

Table 1 Baseline characteristics of participants (N = 491 420), stratified by dementia status at the end of follow-up

Characteristics	Men			Women		
	Dementia	No dementia	*P*-value	Dementia	No dementia	*P*-value
N (%)	1220 (0.54)	222 361 (99.45)	-	1005 (0.38)	266 834 (99.62)	-
Age, years	64.14 (5.02)	56.67 (8.19)	<0.001	63.97 (5.28)	56.31 (7.99)	<0.001
White	1153 (94.51)	209 338 (94.14)	0.453	956 (95.12)	251 623 (94.30)	0.258
University or college degree	249 (20.41)	74 902 (33.68)	<0.001	166 (16.52)	82 773 (31.02)	<0.001
Current smoker	162 (13.28)	27 632 (12.43)	0.324	107 (10.65)	23 713 (8.89)	0.042
Daily drinker	303 (24.84)	56 426 (25.38)	0.692	117 (11.64)	43 009 (16.12)	<0.001
Family history of dementia	228 (18.69)	24 269 (10.91)	<0.001	226 (22.49)	32 511 (12.18)	<0.001
Townsend deprivation index	−0.84 (3.35)	−1.27 (3.14)	<0.001	−0.71 (3.39)	−1.35 (3.03)	<0.001
Healthy physical activity	784 (64.26)	160 060 (71.98)	<0.001	604 (60.10)	179 956 (67.44)	0.002
Vegetable intake, tablespoons/day	5.23 (4.37)	4.67 (3.41)	<0.001	5.35 (3.56)	5.09 (3.22)	0.009
Fruit intake, pieces/day	3.30 (3.52)	2.76 (2.56)	<0.001	4.03 (3.55)	3.34 (2.55)	<0.001
Fish intake >2 times/week	687 (56.31)	110 916 (49.88)	<0.001	594 (59.10)	142 193 (53.29)	<0.001
Processed meat intake <2 times/week	657 (53.99)	125 477 (56.49)	0.122	719 (71.61)	211 217 (79.24)	<0.001
Cholesterol, mmol/L	5.20 (1.19)	5.50 (1.09)	<0.001	5.85 (1.23)	5.86 (1.09)	0.792
SBP, mmHg	143.18 (19.44)	140.80 (17.16)	<0.001	143.28 (20.28)	135.34 (18.86)	<0.001
BMI, kg/m^2	27.89 (4.62)	27.83 (4.23)	0.642	27.41 (5.41)	27.09 (5.17)	0.044
Diabetes mellitus	219 (17.95)	15 362 (6.91)	<0.001	108 (10.75)	9789 (3.67)	<0.001
Anti-hypertensive medication	199 (16.31)	21 807 (9.81)	<0.001	147 (14.63)	27 133 (10.17)	<0.001
Lipid-lowering medication	476 (39.02)	49 893 (22.44)	<0.001	321 (31.94)	33 264 (12.47)	<0.001

Mean (SD) for continuous variables and number (percentage) for categorical variables. BMI, body mass index; SBP, systolic blood pressure.

Table 2 All-cause dementia risk (HR (95% CI)) according to quintile of FMR, stratified by sex

Quintile of FMR	Men [HR (95% CI)]			Women [HR (95% CI)]		
	Range	Model 1	Model 2	Range	Model 1	Model 2
Whole body						
Q1 (lowest)	0.03-0.27	1 (ref)	1 (ref)	0.05-0.47	1 (ref)	1 (ref)
Q2	0.27-0.33	0.69 (0.57, 0.84)	0.70 (0.57, 0.85)	0.47-0.57	0.77 (0.63, 0.95)	0.78 (0.63, 0.96)
Q3	0.33-0.38	0.73 (0.60, 0.87)	0.74 (0.61, 0.90)	0.57-0.66	0.68 (0.55, 0.83)	0.69 (0.55, 0.86)
Q4	0.38-0.45	0.62 (0.52, 0.75)	0.64 (0.51, 0.78)	0.66-0.78	0.62 (0.51, 0.76)	0.64 (0.50, 0.81)
Q5 (highest)	0.45-1.27	0.63 (0.52, 0.75)	0.65 (0.51, 0.84)	0.78-2.46	0.53 (0.43, 0.65)	0.55 (0.40, 0.76)
P for trend	-	<0.001	0.001	-	<0.001	<0.001
Trunk						
Q1 (lowest)	0.03-0.30	1 (ref)	1 (ref)	0.03-0.40	1 (ref)	1 (ref)
Q2	0.30-0.37	0.81 (0.67, 0.98)	0.82 (0.68, 1.00)	0.40-0.50	0.68 (0.56, 0.84)	0.71 (0.57, 0.87)
Q3	0.37-0.44	0.74 (0.61, 0.89)	0.76 (0.62, 0.93)	0.50-0.60	0.64 (0.53, 0.79)	0.68 (0.55, 0.84)
Q4	0.44-0.52	0.69 (0.58, 0.83)	0.72 (0.59, 0.89)	0.60-0.72	0.67 (0.55, 0.82)	0.73 (0.58, 0.92)
Q5 (highest)	0.52-6.40	0.67 (0.56, 0.81)	0.73 (0.57, 0.93)	0.72-12.75	0.53 (0.43, 0.65)	0.60 (0.46, 0.79)
P for trend	-	<0.001	0.007	-	<0.001	0.005
Arm						
Q1 (lowest)	0.04-0.24	1 (ref)	1 (ref)	0.04-0.44	1 (ref)	1 (ref)
Q2	0.24-0.28	0.79 (0.66, 0.96)	0.84 (0.69, 1.01)	0.44-0.55	0.85 (0.69, 1.04)	0.90 (0.72, 1.11)
Q3	0.28-0.32	0.73 (0.61, 0.88)	0.80 (0.65, 0.98)	0.55-0.66	0.78 (0.63, 0.96)	0.86 (0.68, 1.09)
Q4	0.32-0.38	0.69 (0.57, 0.83)	0.78 (0.63, 0.98)	0.67-0.83	0.69 (0.56, 0.85)	0.81 (0.62, 1.06)
Q5 (highest)	0.38-2.79	0.75 (0.63, 0.90)	0.94 (0.72, 1.22)	0.83-3.04	0.63 (0.51, 0.77)	0.84 (0.57, 1.24)
P for trend	-	0.003	0.445	-	<0.001	0.190
Leg						
Q1 (lowest)	0.01-0.23	1 (ref)	1 (ref)	0.07-0.59	1 (ref)	1 (ref)
Q2	0.23-0.27	0.74 (0.62, 0.89)	0.73 (0.60, 0.88)	0.59-0.68	0.78 (0.63, 0.96)	0.78 (0.63, 0.98)
Q3	0.27-0.31	0.66 (0.55, 0.80)	0.64 (0.53, 0.78)	0.68-0.76	0.73 (0.59, 0.90)	0.74 (0.59, 0.92)
Q4	0.31-0.37	0.56 (0.47, 0.68)	0.54 (0.44, 0.66)	0.76-0.87	0.57 (0.46, 0.70)	0.58 (0.45, 0.75)
Q5 (highest)	0.37-1.60	0.56 (0.47, 0.68)	0.52 (0.41, 0.66)	0.87-2.19	0.54 (0.44, 0.67)	0.56 (0.40, 0.79)
P for trend	-	<0.001	<0.001	-	<0.001	<0.001

Model 1 was adjusted for age, self-reported ethnicity (White/others), educational level (university or college degree/others), socio-economic status (categories derived from Townsend deprivation index quintiles 1, 2 to 4, and 5), family history of dementia (yes/no), current smoking (yes/no), alcohol frequency, healthy physical activity, vegetable, and fruit intake, fish and processed meat intake, systolic blood pressure, prevalent diabetes, cholesterol, BP-lowering medication, and cholesterol-lowering medication. Model 2 was further adjusted for BMI. BMI, body mass index; CI, confidence interval; FMR, fat-to-muscle mass ratio; HR, hazard ratio; ref, reference.

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(Q5) of FMR in the whole body had a 35% (HR: 0.65; 95% CI: 0.51, 0.84; $P = 0.001$) and 45% (HR: 0.55; 95% CI: 0.40, 0.76; $P < 0.001$) lower dementia risk among men and women, respectively. Multivariable adjusted Cox models showed inverse associations of whole body FMR with AD in men only (P for trend = 0.003 in men, 0.185 in women), whereas the association with VD was not statistically significant although the HR point estimates were decreased among men and women (*Table* 3).

In the restricted cubic spline analysis, *Figure* 1 visualized the associations between FMRs and all-cause dementia risk. There was an L-shaped association between whole body FMR and all-cause incident dementia (P for non-linear <0.001 in men and women), showing a substantial decrease until around the medians (0.35 in men and 0.61 in women), and then was relatively flat afterwards. Below the medians, the HRs per 1 SD higher of FMR of the whole body were 0.78 (95% CI: 0.64, 0.96; $P = 0.019$) in men and 0.60 (95% CI: 0.47, 0.77; $P < 0.001$) in women. Among the regional body parts, FMR of the leg showed the strongest association, with a 40% (HR: 0.60; 95% CI: 0.48, 0.75; $P < 0.001$) and 39% (HR: 0.61; 95% CI: 0.47, 0.79; $P < 0.001$) risk reduction per 1 SD higher among men and women, respectively.

Subgroup analyses and sensitivity analyses

We additionally examined the independent associations of whole body fat and muscle mass and all-cause dementia risk. Compared with the lowest quintiles, the highest quintiles of fat mass were associated with reduced HRs for dementia, while the highest quintiles of muscle mass were associated with a statistically significant reduced dementia risk among men but not women (Supporting Information, *Table* S2).

The patterns of association between FMR and all-cause dementia risk differed when stratified by age. Specifically, the inverse effects of FMR on the risk of dementia were significant only among participants over the age of 60 (Supporting Information, *Table* S3). Among participants aged 50 to 60 years, the associations between total and regional FMR and dementia risk were non-significant, while the effects among participants aged below 50 years seemed to be less precision due to a reduced number of dementia cases.

Excluding participants diagnosed with dementia within 2 years of follow-up generated similar results, providing evidence against reverse causation (Supporting Information, *Table* S4). Excluding participants with a baseline cancer history and using the Fine-Grey subdistribution hazard

Table 3 Alzheimer's disease and vascular dementia risk [HR (95% CI)] according to quintile of FMR, stratified by sex

Quintile of FMR	Alzheimer's disease		Vascular dementia	
	Men	Women	Men	Women
Whole body				
Q1 (lowest)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0.61 (0.45, 0.83)	0.74 (0.53, 1.05)	0.82 (0.54, 1.26)	0.82 (0.48, 1.41)
Q3	0.62 (0.45, 0.85)	0.75 (0.53, 1.07)	0.74 (0.48, 1.13)	0.58 (0.32, 1.03)
Q4	0.54 (0.38, 0.76)	0.70 (0.47, 1.03)	0.56 (0.36, 0.89)	0.63 (0.34, 1.15)
Q5 (highest)	0.51 (0.33, 0.79)	0.72 (0.43, 1.20)	0.83 (0.50, 1.07)	0.50 (0.23, 1.09)
P for trend	0.003	0.185	0.232	0.070
Trunk				
Q1 (lowest)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0.72 (0.54, 0.98)	0.65 (0.46, 0.92)	0.89 (0.58, 1.36)	0.55 (0.32, 0.95)
Q3	0.68 (0.50, 0.93)	0.86 (0.62, 1.20)	0.76 (0.49, 1.17)	0.56 (0.33, 0.96)
Q4	0.58 (0.41, 0.81)	0.80 (0.55, 1.14)	0.69 (0.45, 1.08)	0.73 (0.42, 1.24)
Q5 (highest)	0.58 (0.38, 0.88)	0.78 (0.51, 1.21)	0.79 (0.48, 1.29)	0.49 (0.25, 0.94)
P for trend	0.005	0.628	0.217	0.201
Arm				
Q1 (lowest)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0.83 (0.61, 1.12)	0.94 (0.67, 1.33)	0.57 (0.36, 0.90)	1.10 (0.63, 1.91)
Q3	0.75 (0.54, 1.05)	1.01 (0.70, 1.47)	0.81 (0.53, 1.23)	0.95 (0.52, 1.74)
Q4	0.70 (0.49, 1.02)	0.88 (0.57, 1.36)	0.66 (0.42, 1.04)	0.87 (0.44, 1.71)
Q5 (highest)	0.90 (0.58, 1.41)	0.91 (0.48, 1.70)	0.92 (0.55, 1.54)	1.22 (0.49, 3.04)
P for trend	0.333	0.674	0.940	0.802
Leg				
Q1 (lowest)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0.65 (0.48, 0.88)	0.76 (0.54, 1.07)	0.81 (0.54, 1.20)	0.79 (0.45, 1.40)
Q3	0.64 (0.47, 0.88)	0.66 (0.46, 0.95)	0.50 (0.32, 0.76)	0.70 (0.39, 1.24)
Q4	0.41 (0.28, 0.58)	0.60 (0.40, 0.90)	0.54 (0.35, 0.83)	0.54 (0.29, 1.02)
Q5 (highest)	0.49 (0.32, 0.74)	0.51 (0.30, 0.88)	0.55 (0.35, 0.89)	0.53 (0.24, 1.19)
P for trend	<0.001	0.011	0.008	0.068

All models were adjusted for age, self-reported ethnicity (White/others), educational level (university or college degree/others), socio-economic status (categories derived from Townsend deprivation index quintiles 1, 2 to 4, and 5), family history of dementia (yes/no), current smoking (yes/no), alcohol frequency, healthy physical activity, vegetable, and fruit intake, fish and processed meat intake, systolic blood pressure, prevalent diabetes, cholesterol, BP-lowering medication, cholesterol-lowering medication and BMI. BMI, body mass index; CI, confidence interval; FMR, fat-to-muscle mass ratio; HR, hazard ratio; ref, reference.

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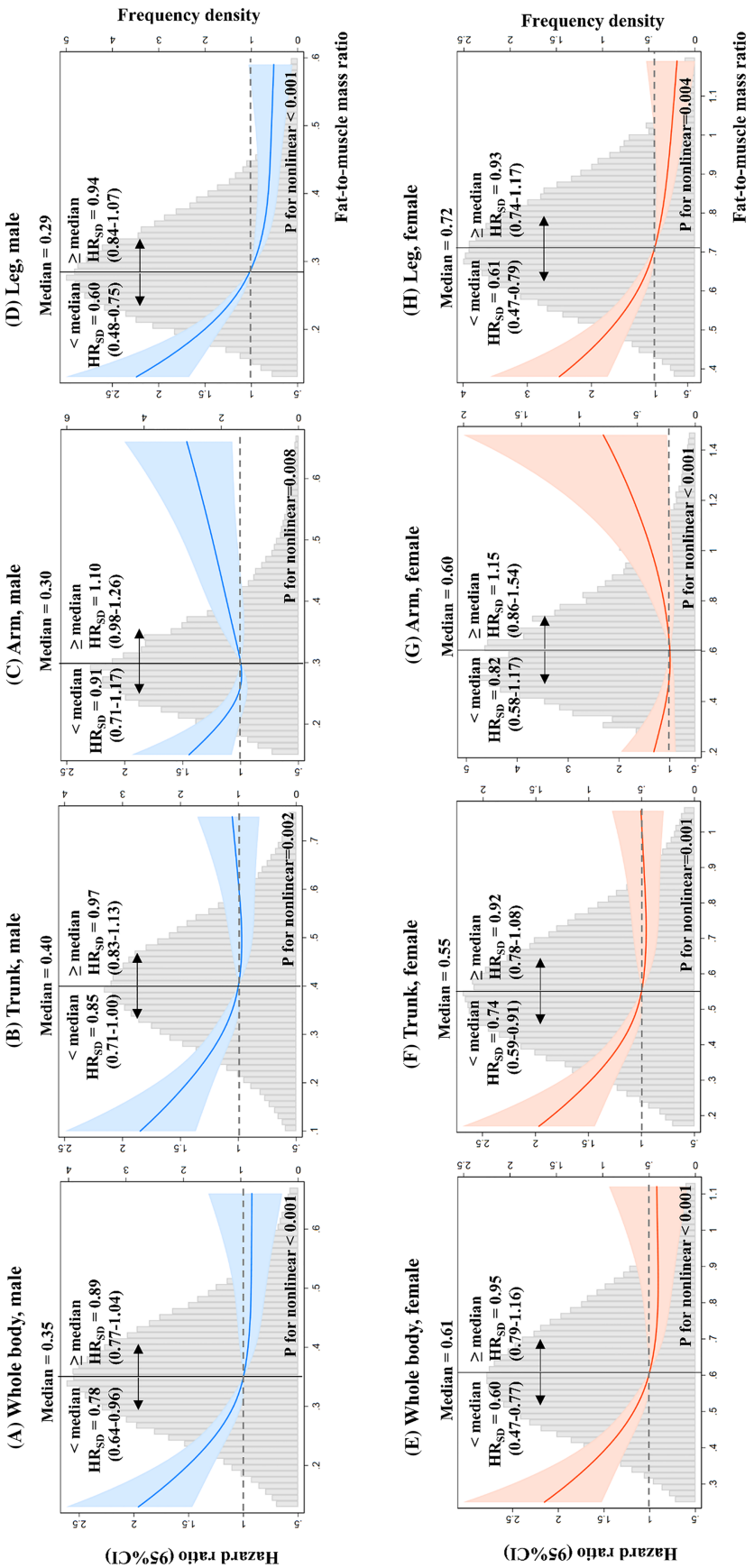

Figure 1 Associations of fat-to-muscle mass ratio (fmr) with all-cause dementia, stratified by sex. the hazard ratios derived from multivariate cox models are shown on the *y*-axis, and the distributions of FMR are shown on the secondary *y*-axis. (A–D) FMR of the whole body, trunk, arm and leg in men; (E–H) FMR of the whole body, trunk, arm and leg in women. Hazard ratios are indicated by solid lines and 95% CIs by shaded areas. The reference point is the 50th percentile for each FMR, using four knots at the 5th, 35th, 65th, and 95th percentiles. Individuals below the 1st or above the 99th percentiles were excluded. All models were adjusted for age, self-reported ethnicity (White/others), educational level (university or college degree/others), socio-economic status (categories derived from Townsend deprivation index quintiles 1, 2 to 4, and 5), family history of dementia (yes/no), current smoking (yes/no), alcohol frequency, healthy physical activity (yes/no), vegetable, and fruit intake, fish and processed meat intake, systolic blood pressure, prevalent diabetes, cholesterol, BP-lowering and cholesterol-lowering medication and body mass index. Standard deviations: 0.10, 0.12, 0.09, and 0.09 for FMR of the whole body, trunk, arm and leg in men, 0.17, 0.18, 0.24, and 0.16 for FMR of the whole body, trunk, arm and leg in women.

model, the results remained similar (Supporting Information, *Table* S4).

Discussion

This is the first prospective study exploring the associations of FMR with dementia risk. The present study showed an essential indicator—FMR in cognitive health, with individuals at higher ratios having decreased risks for all-cause dementia independent of overall obesity, especially among participants aged 60 years or older. These results suggested that a higher FMR—given that the dementia risk decreased until around the medians (0.35 in men, 0.61 in women), a higher FMR usually implied an FMR above the median—might be a target in reducing dementia risk in later life.

Several epidemiological studies have examined the associations of fat mass and muscle mass individually with the risk of developing dementia; however, these findings were not always consistent. A longitudinal study of 344 older adults (mean age, 78 years; 62.2% women), with a median follow-up period of 6 years, found evidence that a low lean mass, especially appendicular lean mass, was associated with increased dementia risk,[7] while in another cross-sectional study including 3 025 women aged 75 years and older, no significant difference was evidenced, which is in line with our results in women.[9] When fat mass was considered, the Age Gene/Environment Susceptibility Study involving 5 169 participants (mean age, 76 years; 57.1% women) reported that higher amounts of abdominal and thigh subcutaneous fat mass were associated with a decreased dementia risk among women.[8] Likewise, a study based on the UKB including 400 000 participants aged 37–73 years old, with a median follow-up of 8.1 years, revealed a monotonic inverse association of fat mass and dementia risk in both sexes.[13] However, the protective evidence is not broadly consistent, with some studies reporting a positive association between fat mass and dementia risk[14] and others reporting no association,[7,10] but these studies were restricted to an older population with comparatively smaller sample size. The reasons for the apparent differences in these associations are not clear, but a large prospective study (≈ 500 000 participants) might be necessary to observe an increased dementia risk, and it is critical to consider fat mass and muscle mass together to avoid such problems.

This study contributes to the substantially larger than previous studies and the first literature comprehensively estimating the fat and muscle mass on dementia. In our study, we found that higher FMR was associated with a decreased likelihood of all-cause dementia in older adults. Several biological hypotheses have been proposed to explain the observed associations. Most importantly, the endocrine aspects of adipose tissue, mediated by adipokines, may hold clues to understand the association with dementia.[15] For example, leptin, a protein hormone secreted primarily by adipose tissue, could enter the central nervous system and cerebrospinal fluid and affect learning and memory processes controlled by the hippocampus,[16] and has been reported to be associated with a reduced incidence of dementia in later life.[17] However, a study of middle-aged women with up to 32 years of follow-up did not find a protective effect of leptin against dementia in midlife, possibly because leptin is a short-term marker of body composition rather than a long-term indicator,[18] which aligns closely with so-called 'obesity paradox'. Second, there is evidence that people with relatively high fat mass might have increased intake of vitamin E and vitamin D, which may affect cognition by attenuating the toxic effects of beta-amyloid[19] or regulating neurotrophic expression.[20] Third, a specific protective role of leg subcutaneous fat has been reported to be associated with long-chain fatty acid storage, thus protecting from the adverse effects associated with ectopic fat deposition.[21] Further research is needed to understand the underlying mechanisms and develop effective preventative strategies.

Regarding dementia subtypes, we observed that the inverse FMR-AD association was significant only in men. Although there is some evidence for a sex-specific effect on the obesity-related AD risk, the nature of this association is not fully understood. Sex hormone and inflammation seemed to be involved. For example, among people genetically susceptible to AD, a stronger risk of AD was observed in men with lower BMI compared with women, possibly due to the identification of testosterone as a risk factor for AD in the preclinical phase and its association with adipogenesis inhibition in men.[22] In addition, findings point to that obesity in women leads to a greater increase in inflammatory responses than in men, and there is a greater association between inflammation and AD risk in women.[23] Therefore, our findings underlined the importance of sex-specific analysis in future studies of FMR and dementia risk. When VD was considered as the outcome, we found no statistically significant association between FMR and VD among men and women. Due to the relatively lower case numbers for VD in our study, and the HR point estimates actually decreased among men and women, the non-significant finding for this outcome might not be interpreted simply as the absence of an association.

Our findings have implication for future research because our study offers new insights concerning current methodologic challenges of identifying independent roles of fat and muscle mass on dementia risk—given fat and muscle mass are intricately correlated. Furthermore, our prospective results highlighted the public health implication of stratifying strategies for dementia prevention, for example, monitoring the configuration of body composition, particularly of the legs, in reducing the incidence rate of dementia and progressive disability among older adults with a possibly poor cognitive condition. However, because higher FMR is associated with an increased risk of type 2 diabetes and metabolic syndrome,[24,25] we need to maximize the public health bene-

fits while maintaining a balance among those diseases. It will, therefore, be essential to develop strategies to meet the challenges of establishing a relatively beneficial threshold.

The present study has several strengths, including the large sample size and relatively long-term follow-up, the prospective design, the use of standardized protocols of data collection, and the multiple covariates allowed for rigorous adjustments. More importantly, we considered a combination of fat and muscle mass to assess the association between FMR, which integrates the effects of fat and muscle mass, and dementia outcomes. However, the study also had several potential limitations. First, although UKB represents a large population-based resource, the sample was limited to mainly Europeans and participants tended to be healthier, which may affect the generalizability of the results to the UK population as well as other broader populations. Second, weight loss and body composition redistribution may be markers of preclinical dementia,[26] which might result in reverse causation, although our results remained unchanged when we excluded participants diagnosed with dementia during the first 2 years of follow-up. Third, the present study used a single measurement of body composition at baseline, which did not take into account changes in body composition before and after assessment. Future research is needed to investigate the time-dependent dynamic analyses of FMR on dementia outcomes. Finally, although we adjusted the analyses for a range of potential confounders, residual confounding may still exist; and due to the observational nature of our study, the causality of the observed associations cannot be confirmed.

Conclusions

Our analyses provided strong evidence that higher total and regional FMR, especially in later life, are independently associated with a lower risk of all-cause dementia. Regarding dementia subtypes, a higher FMR was statistically associated with lower AD risk in men, but not with VD risk in both men and women. Our study highlighted the importance of early monitoring FMR with the aim of alleviating the negative cognitive consequences.

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Ethics statement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[27] The UK Biobank study was approved by the National Information Governance Board for Health and Social Care in England and Wales, the Community Health Index Advisory Group in Scotland and the North West Multicenter Research Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave written informed consent.

Online supplementary material

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

Conflict of interest

Wenxiu Wang, Yongchun Luo, Zhenhuang Zhuang, Zimin Song, Ninghao Huang, Yueying Li, Xue Dong, Wendi Xiao, Yimin Zhao, and Tao Huang declare that they have no conflict of interest.

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