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Age-specific and sex-specific associations of visceral adipose tissue mass and fat-to-muscle mass ratio with risk of mortality

Bowei Yu[1], Ying Sun[1], Xinyue Du[2,3], Haojie Zhang[1], Chi Chen[1], Xiao Tan[4,5], Zhongyi Yang[2,3]*, Yingli Lu[1]* & Ningjian Wang[1]*

[1]*Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China;* [2]*Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai, China;* [3]*Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China;* [4]*Department of Medical Sciences, Uppsala University, Uppsala, Sweden;* [5]*School of Public Health, Zhejiang University, Hangzhou, China*

Abstract

Background Limited studies have explored the association between visceral adipose tissue (VAT) mass and fat-to-muscle mass ratio (FMR) and mortality. We aimed to evaluate the sex-specific association of VAT and FMR with all-cause and cause-specific mortality by age.

Methods A total of 438 896 participants (49.8% men, mean age ± standard deviation: 57 ± 8 years for men; 56 ± 8 years for women) were included from the UK Biobank cohort. The nature of VAT was predictive, as obtained by sex-stratified, non-linear prediction models. Fat and muscle mass were estimated using a bioelectrical impedance assessment device. FMR was calculated as the fat mass divided by the muscle mass in the whole body. VAT and FMRs were divided into quintiles in ascending order, and the 3rd quintile was used as the reference. Cox regression analyses were used to estimate the associations between VAT, FMR and mortality.

Results During a median of 12.4 years of follow-up, we documented 29 903 deaths. After adjusting for various covariates, the individuals in the highest quintiles of VAT and FMR had the highest hazard ratios (HRs) of all-cause mortality [1.24 (95% confidence interval: 1.17–1.33) for VAT and 1.24 (1.17–1.31) for FMR in men; and 1.11 (1.03–1.21) for VAT in women], except that the 1st quintile of FMR in women had the greatest HR [1.18 (1.09–1.27)]. Significant interactions were observed in both sexes according to age category (P for interaction < 0.05). Among men <50 years, participants in the 1st and 5th quintiles of VAT and FMR had significantly higher risks of mortality [1.30 (1.02–1.66) and 1.67 (1.27–2.19) in VAT; 1.25 (0.99–1.56) and 1.41 (1.11–1.79) in FMR, respectively]; in women, this phenomenon was observed in the ≥60 age group [1.16 (1.06–1.27) and 1.19 (1.08–1.31) in VAT; 1.18 (1.08–1.29) and 1.11 (1.01–1.22) in FMR, respectively]. VAT showed a linear positive association with mortality in women <60 years and a J-shaped association from respiratory disease in both sexes ≥60 years. FMR showed a linear positive association with mortality from cancer in men <60 years and a J-shaped association with mortality from cause-specific mortality in both sexes ≥60 years, except for mortality from cardiovascular disease in men.

Conclusions Most associations of VAT and FMR with all-cause mortality were J-shaped and were significantly modified by age status (<50, 50–59 and ≥60 years). The clinical implication is that regarding body composition and VAT mass, different health strategies may be adopted for people of different sexes and ages.

Keywords Visceral adipose tissue; Fat-to-muscle mass ratio; All-cause mortality; UK Biobank

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**Correspondence to: Ningjian Wang, MD, PhD, and Yingli Lu, MD, PhD, Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200011, China. Email: wnj486@126.com and luyingli2008@126.com;*
Zhongyi Yang, MD, PhD, Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai 200011 China. Email: yangzhongyi21@163.com
Bowei Yu, Ying Sun and Xinyue Du contributed equally to this manuscript.

Introduction

Obesity is associated with an increased risk of cardiovascular[1] and metabolic[2] diseases and even death.[3] Anthropometric measures of obesity, such as body mass index (BMI),[4] waist circumference and waist-to-hip ratio,[5,6] have been used in many studies. However, fat distribution and body composition are highly variable even among individuals even with the same BMI. These anthropometric measures may be too general to recognize fat distribution[7,8] and body composition.[9]

Visceral adipose tissue (VAT) is an important part of fat distribution and an independent predictor of health outcomes.[10,11] Notably, direct measurements of VAT are not usually feasible in large epidemiological studies because sophisticated devices are needed, such as dual-energy X-ray absorptiometry (DEXA). Some studies (three using devices and two using a prediction model) have measured the associations between VAT mass and mortality,[12–16] and the studies that used devices to measure VAT showed inconsistent results.[13–15] Moreover, these studies had some shortcomings, including a relatively short time of follow-up time, relatively small sample size, specific populations (e.g. very old people), lack of an age-specific association analysis and/or unadjusted common confounding factors. Considering age-related changes in body composition and VAT and their effects on health outcomes,[17] the age-dependent and sex-dependent associations between VAT and mortality remain largely unclear.

To improve the feasibility of VAT-associated studies, investigators have recently developed equations to predict VAT, including various anthropometric dimensions that are more easily measured than VAT itself, using sex-stratified and non-linear prediction models.[18] One study used DEXA to measure the VAT data of 4198 participants and then modelled and predicted the VAT data of 325 153 participants in the UK Biobank (UKB) database. In-sample validation of the models was performed by calculating the coefficients of determination [R^2 = 0.76; 95% confidence interval (CI): 0.74–0.78]. To the best of our knowledge, this is the largest study to date validating the algorithm for estimating VAT against VAT derived from gold-standard body composition measurements. No study has ever used this predicted VAT to explore its association with mortality.

An interesting hypothesis is that metabolic capacity and metabolic load interact to determine metabolic risk.[19] Developed by Jonathan CK Wells, 'metabolic capacity' is represented by lean tissue development that occurs in early life, promoting glucose homoeostasis, whereas 'metabolic load' is represented by fat mass imposed by subsequent growth, thus challenging glucose homoeostasis.[20] We previously found that a higher fat-to-muscle mass ratio (FMR) was associated with a higher risk of developing type 2 diabetes.[21] However, although a number of studies have linked body composition to mortality,[22] few studies have considered the ratio of fat and muscle mass in the general population.

Therefore, in this prospective cohort of the UKB, we tested the hypothesis that VAT predicted using anthropometric regression equations and FMR were associated with all-cause and cause-specific [cardiovascular disease (CVD), cancer and respiratory disease] mortality. We explored age-specific (<50, 50–59 and ≥60 years) and sex-specific associations.

Materials and methods

Study design and participants

The UKB is a prospective cohort study that included more than 500 000 community-dwelling adults aged 38–73 years between 2006 and 2010 (https://www.ukbiobank.ac.uk/). Detailed information about the UKB has been provided in a previous study.[23] We declare that all data are publicly available in the UKB repository.[23] The North West Multi-centre Research Ethics Committee approved the UKB study, and all participants provided written informed consent. A total of 502 461 participants were recruited. We excluded participants with missing values on the parameters required to predict VAT (n = 53 414) or missing data on fat mass and muscle mass (n = 1196), as well as those without follow-up time related to death (n = 1). Additionally, to avoid the effect of extreme values of predicted VAT, we excluded individuals whose VAT mass was under the 1st percentile or over the 99th percentile (n = 8954) among all participants. The final sample was 438 896 (218 425 men and 220 471 women).

Exposure

At baseline, data on body size and composition were collected by trained healthcare technicians or nurses 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 the square of the height in meters) and body composition data (fat mass and muscle mass) were estimated using an eight-contact electrode Tanita BC418MA segmental body composition analyser (Tanita, Japan). This device estimates body composition by bioimpedance analysis (BIA). 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. Segmental BIA is an appropriate way to assess body composition in people of different sexes, ages and body shapes.[24,25]

We used sex-stratified and non-linear prediction models for VAT mass based on the UKB cohort.[18] In-sample validation of the models was performed by calculating the R^2

among the white-British population (2010 and 2188 women and men, respectively). None of the models showed a predicted R^2 that was significantly lower than its corresponding R^2 [predicted R^2: 0.75 (0.73–0.77) in women and 0.76 (0.74–0.77) in men; corresponding R^2: 0.76 (0.74–0.78) in women and 0.77 (0.75–0.78) in men], which referred to a mean bias of 0.00004 kg in women and 0.00054 kg in men between estimated and DEXA-determined VATs. Thus, the models we used in the present study for estimating VAT were not overfitted.

The specific formulas of VAT are shown below:

Male:-17.02*age+8.335*wst + 10.34*hip-50.71*hgt + 71.21*wgt + 106.4*lrm-35.20*rrm + 160.5*llg-50.25*rlg-85.24*wlb + 0.3914*age*wgt + 0.3042*wst*wgt-0.5459*-hip*wgt-0.7007*lrm*hgt + 0.2020*rrm*hgt-1.006*llg*hgt + 0.2949*rlg*hgt + 0.5900*wlb*hgt + 2,286;

Female:-5.531*age+34.84*hmp-24.67*wst + 26.24*hip-13.83*hgt + 26.30*wgt + 83.11*lrm-1.599*rrm + 89.01*llg + 24.24*rlg-89.59*wlb + 0.2111*age*wgt + 0.7424*wst*wgt-0.6694*hip*wgt-0.5454*lrm*hgt + 0.005128*rrm*hgt-0.5817*llg*hgt-0.1415*rlg*hgt + 0.5903*wlb*hgt-281.6

(hmp, menopausal status; wst, waist circumference; hip, hip circumference; hgt, height; wgt, weight; lrm, impedance of the left arm; rrm, impedance of the right arm; llg, impedance of the left leg; rlg, impedance of the right leg; wlb, impedance of the whole body).

FMR was calculated as fat mass divided by muscle mass in the whole body.

All-cause mortality and cause-specific mortality

The primary outcome in the present study was all-cause related death obtained through linkage to death certificates held within the NHS Central Register through 30 July 2021. Detailed codes were according to the International Classification of Diseases, 10th revision (ICD10). We further identified three specific causes of mortality (both primary and contributory causes of death), including CVD with codes I20–25 and I60–69; cancer with codes C00–99, D37–39 and D40–48; and respiratory disease with codes J00-J99, for the secondary analysis.

Covariates

The following potential confounders were included in the analysis: age, sex, ethnicity (white/others), education (university or college degree/others), 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, ≥75 min/week of vigorous intensity or an equivalent combination), BMI (continuous), systolic blood pressure (continuous), total cholesterol (continuous), diabetes (yes/no), cholesterol-lowering medication (yes/no), blood pressure medication (yes/no), insulin (yes/no) 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; this method has been used in previous studies.[26] If the covariate information was missing, we imputed median values for continuous variables or used a missing-indicator approach for categorical variables.

Statistical analysis

IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA) and R software, version 4.0.2 (R Project for Statistical Computing), were used to perform the data analyses. The P value was two-sided, and $P < 0.05$ was considered significant in all-cause mortality. We also used Bonferroni correction for the P value in the cause-specific mortality and $P < 0.017$ (0.05/3) was considered significant. The analyses were intended to be performed by sex and age (<50, 50–59 and ≥60 years) categories in all-cause mortality. However, in cause-specific analyses, the outcome sample was too small in the <50 age group, which would lead to fluctuating results; thus, <60 and ≥60 years categorization was used. Baseline characteristics were reported as the means ± standard deviations or percentages by quintiles of VAT and FMR.

The follow-up time was calculated from the baseline date (date of attending the assessment centre) to the date of death or censoring (30 July 2021). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for the associations between quintiles (ascending order) of VAT and FMR and the risk of all-cause mortality and cause-specific mortality, which included death from cardiovascular disease, cancer and respiratory disease, using mid-quintile as the reference. The multivariable model was adjusted for age, ethnicity, education, Townsend index, smoking status, drinking, physical activity at goal, healthy diet score ≥4, BMI, total cholesterol, systolic blood pressure, diabetes, cholesterol-lowering medication, blood pressure medication and insulin. The interaction analysis between VAT, FMR and age categories was performed using the likelihood ratio test comparing models with and without a cross-product term. We also used restricted cubic splines with five knots at the 5th, 27.5th, 50th, 72.5th and 95th percentiles to reveal the non-linear associations of VAT and FMR with all-cause mortality.

Results

A total of 438 896 participants (49.8% men, mean age ± standard deviation: 57 ± 8 years for men; 56 ± 8 years for women) were included. *Tables* 1 and 2 show the baseline characteristics of the participants according to the quintiles of VAT and FMR, respectively. Both men and women with greater VAT mass and FMR were more likely to be older, have a higher socio-economic level, have a higher prevalence of diabetes and hypertension and have a greater BMI. Moreover, they tended to have an unhealthy diet and lower physical activity levels.

During a median of 12.4 years of follow-up, we identified 10 976 and 18 927 deaths in men and women, respectively. *Table* 3 shows the associations of VAT and FMR with all-cause mortality in multivariable-adjusted models in different age groups. Men and women in the highest quintile of VAT had the greatest risk of death [HR 1.24 (95% CI 1.17–1.33) and 1.11 (1.03–1.21) vs. 3rd quintile, respectively]. For FMR, HRs in the 5th and 1st quintiles were significantly greater than those in the 3rd quintile in men [1.24 (1.17–1.31) and 1.07 (1.01–1.14), respectively]; however, only the HR in the 1st quintile was significantly greater than that in the 3rd quintile in women [1.18 (1.09–1.27)].

In the stratified analysis according to age category, significant interactions were observed in both sexes (P for interaction < 0.05). In the <50 age group among men, VAT in both the 5th and 1st quintiles was significantly associated with a high risk of mortality [1.67 (1.27–2.19) and 1.30 (1.02–1.66), respectively]; in the older groups, however, the associations were linearly positive [HR in the 5th quintile: 1.32 (1.14–1.53) among the 50–59 age group and 1.22 (1.13–1.32) among the ≥60 age group]. In women, the condition was rather different. In the younger groups, the associations were more prone to be linearly positive; however, in the ≥60 age group, VAT in both the 5th and 1st quintiles had a significantly higher risk [1.19 (1.09–1.31) and 1.16 (1.06–1.27), respectively]. Regarding the FMR, the trends were rather similar to those for VAT in both men and women. In the <50 age group among men, both very low (quintile 1) and very high (quintile 5) FMRs increased the risk of mortality compared with the FMR in quintile 3, whereas this phenomenon was observed in the ≥60 age group in women.

In *Figure* 1, we used restricted cubic splines to further present the non-linear associations of VAT and FMR with all-cause mortality. For men, the relationships between VAT and FMR and all-cause mortality were J-shaped (P for non-linear < 0.001) in the three age groups. The trends in women were different from those in men. In the <50 and 50–59 age groups, VAT showed a linear positive association, whereas there was a J-shaped association in the ≥60 age group. The non-linear relationship between FMR and all-cause mortality was non-significant in the <50 and 50–59 age groups. However, in the ≥60 age group, there was a U-shaped association.

We further examined the association between VAT and FMR and cause-specific mortality (*Table* 4). Among the <60 age group in men and women, we found a J-shaped association between VAT and mortality from cancer and respiratory disease in men and a positive linear association in women from three specific causes. Compared with participants in the 3rd quintile of VAT, those within the highest quintile had the highest risk of mortality from CVD [1.31 (1.02–1.67) for men; 1.32 (0.86–2.03) for women], cancer [1.35 (1.13–1.60) for men; 1.34 (1.12–1.62) for women] and respiratory disease [1.78 (1.35–2.35) for men; 1.78 (1.23–2.57) for women]. The FMR quintiles showed a linear positive association with mortality from cancer, whereas there was a J-shaped association with mortality from respiratory disease in men aged <60 years. Participants in the 5th quintile of FMR had the greatest HRs of risk mortality from CVD [1.30 (1.04–1.63)] and respiratory disease [1.63 (1.28–2.07)] for men and cancer [1.17 (1.00–1.35) for men; 1.16 (0.96–1.41) for women]. The results were quite different in the ≥60 age group. VAT quintiles were not significantly associated with CVD-associated death but were positively associated with cancer and respiratory diseases ($P < 0.017$) in men; meanwhile, in women, VAT showed a J-shaped association with respiratory disease. Except for CVD in women who had the highest HR in the 1st quintile [1.31 (1.04–1.64)], the other groups all had the highest HR in the 5th quintile. We found a J-shaped association between FMR and mortality from all three diseases in both sexes among the ≥60 age group, except for mortality from CVD in men. Participants within the highest FMR quintile had the highest risk of mortality from CVD [1.29 (1.14–1.45) for men], cancer [1.16 (1.06–1.27) for men; 1.17 (1.04–1.33) for women] and respiratory disease [1.57 (1.37–1.77) for men; 1.28 (1.05–1.56) for women], whereas the 1st quintile of FMR in women had the highest HR in mortality from CVD [1.27 (1.03–1.58)].

Discussion

In this large-scale prospective cohort study with an approximately 12-year follow-up time, the linear and non-linear association of VAT mass and FMR with all-cause and cause-specific mortality in the general population was explored. Among all men and women, VAT and FMR had J-shaped associations with all-cause mortality, except that FMR showed an anti-J-shaped association with all-cause mortality in women. The age category (<50, 50–59 and ≥60 years) significantly modified the associations of VAT mass and FMR with all-cause mortality. We also found different trends in VAT and FMR in different age groups with respect to cause-specific mortality in men and women.

Table 1 Baseline characteristics for men and women by quintiles of visceral adipose tissue

	Visceral adipose tissue				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Men (n = 218 425, 49.8%)					
Visceral adipose tissue (g)	693.91 ± 241.53	1246.44 ± 120.96	1647.38 ± 115.99	2101.94 ± 153.31	2981.94 ± 484.67
Visceral adipose tissue bounds (g)	<1027.88	1027.88–1450.28	1450.29–1853.81	1853.82–2392.14	>2392.14
Fat-to-muscle mass ratio	0.24 ± 0.05	0.31 ± 0.05	0.36 ± 0.05	0.41 ± 0.05	0.50 ± 0.08
Age (years)	54.45 ± 8.52	55.85 ± 8.34	56.97 ± 8.11	57.85 ± 7.84	58.57 ± 7.47
University or college degree (%)	44.2	37.5	33.4	28.6	24.3
Townsend deprivation index	−1.25 ± 3.18	−1.45 ± 3.07	−1.45 ± 3.06	−1.34 ± 3.10	−0.96 ± 3.22
White (%)	94	93.8	94.2	95.1	96.3
Diabetes (%)	2.4	3.4	4.9	7.5	14.9
Hypertension (%)	14.0	20.5	25.6	32.2	41.3
Drinks per week (glasses)	9.60 ± 11.12	10.72 ± 11.06	11.28 ± 11.59	11.73 ± 12.25	11.54 ± 13.29
Current smoking (%)	14.4	12.4	11.9	11.5	11.3
Physical activity at goal (%)	61.5	57.1	53.3	49.3	42.8
Body mass index (kg/m^2)	23.42 ± 1.68	25.68 ± 1.46	27.34 ± 1.54	29.27 ± 1.74	33.20 ± 3.10
Total cholesterol (mmol/L)	5.45 ± 1.02	5.60 ± 1.09	5.61 ± 1.14	5.53 ± 1.16	5.30 ± 1.19
Systolic blood pressure (mmHg)	137.11 ± 18.04	141.30 ± 18.00	143.75 ± 18.33	145.43 ± 18.05	146.63 ± 18.31
Healthy diet (%)	40.4	39.2	37.7	35.6	33.8
Cholesterol-lowering medication (%)	10.4	16.5	21.7	27.8	36.0
Anti-hypertensive medication (%)	10.5	16.6	22.2	29.4	41.6
Fat mass (kg)	13.31 ± 2.86	17.96 ± 2.28	21.34 ± 2.39	25.18 ± 2.77	33.07 ± 5.64
Muscle mass (kg)	56.33 ± 6.04	58.23 ± 5.92	59.94 ± 5.97	62.18 ± 6.12	66.83 ± 6.85
Women (n = 220 471, 50.2%)					
Visceral adipose tissue (g)	195.28 ± 101.72	460.21 ± 65.244	693.52 ± 71.56	985.89 ± 102.68	1588.51 ± 333.64
Visceral adipose tissue bounds (g)	<344.73	344.73–573.15	573.16–821.72	821.73–1181.32	>1181.32
Fat-to-muscle mass ratio	0.42 ± 0.09	0.53 ± 0.0	0.61 ± 0.09	0.70 ± 0.10	0.85 ± 0.13
Age (years)	52.03 ± 8.01	55.64 ± 7.96	57.38 ± 7.71	58.35 ± 7.54	58.58 ± 7.40
University or college degree (%)	44.2	35.5	30.4	26.5	23.3
Townsend deprivation index	−1.53 ± 2.93	−1.63 ± 2.89	−1.55 ± 2.93	−1.33 ± 3.02	−0.84 ± 3.24
White (%)	95.4	95.3	94.8	94.2	93.6
Diabetes (%)	1.1	1.2	1.9	3.4	9.1
Hypertension (%)	9.2	14.5	20.2	27.1	38.5
Drinks per week (glasses)	5.90 ± 6.76	6.02 ± 7.05	5.95 ± 7.32	5.77 ± 7.65	4.97 ± 7.73
Current smoking (%)	9.1	8.4	8.6	8.5	8.7
Physical activity at goal (%)	57.4	53.5	50.5	46.8	39.8
Body mass index (kg/m^2)	21.98 ± 1.94	24.16 ± 1.97	26.05 ± 2.20	28.52 ± 2.68	33.42 ± 4.25
Total cholesterol (mmol/L)	5.57 ± 1.00	5.88 ± 1.06	6.02 ± 1.11	6.06 ± 1.17	5.88 ± 1.20
Systolic blood pressure (mmHg)	129.26 ± 18.78	134.34 ± 20.02	138.10 ± 20.04	141.33 ± 19.78	143.54 ± 19.18
Healthy diet (%)	57.9	58.3	57.8	56.4	53.2
Cholesterol-lowering medication (%)	3.3	6.5	10.5	15.6	23.6
Anti-hypertensive medication (%)	5.1	9.4	14.3	20.8	32.6
Fat mass (kg)	16.69 ± 4.05	21.29 ± 3.96	25.10 ± 4.23	29.87 ± 4.97	39.26 ± 7.82
Muscle mass (kg)	40.05 ± 3.58	40.29 ± 3.60	41.10 ± 3.69	42.56 ± 3.82	46.29 ± 4.69

Mean ± SD for continuous variables and percentage for categorical variables.

Table 2 Baseline characteristics for men and women by quintiles of fat-to-muscle mass ratio

	Fat-to-muscle mass ratio				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Men (n = 218 425, 49.8%)					
Fat-to-muscle mass ratio	0.22 ± 0.04	0.30 ± 0.02	0.36 ± 0.01	0.41 ± 0.02	0.52 ± 0.06
Fat-to-muscle mass ratio bounds	<0.27	0.27–0.32	0.33–0.37	0.38–0.45	>0.45
Visceral adipose tissue (g)	798.95 ± 366.10	1309.86 ± 362.31	1667.50 ± 391.35	2075.68 ± 446.93	2820.52 ± 624.96
Age (years)	54.52 ± 8.37	55.79 ± 8.31	56.82 ± 8.11	57.66 ± 7.93	58.90 ± 7.53
University or college degree (%)	43.6	37.8	33.5	29.3	23.7
Townsend deprivation index	−1.34 ± 3.12	−1.48 ± 3.05	−1.45 ± 3.05	−1.30 ± 3.12	−0.90 ± 3.27
White (%)	95.2	94.7	94.4	94.4	94.8
Diabetes (%)	2.8	3.8	5.3	7.7	13.7
Hypertension (%)	15.5	21.1	26.1	31.3	39.6
Drinks per week (glasses)	9.80 ± 11.44	10.77 ± 11.08	11.23 ± 11.69	11.54 ± 12.15	11.53 ± 13.09
Current smoking (%)	14.5	12.3	11.8	11.7	11.3
Physical activity at goal (%)	63.1	57.1	53.2	48.9	41.8
Body mass index (kg/m^2)	23.98 ± 2.07	25.96 ± 2.12	27.37 ± 2.27	29.06 ± 2.51	32.53 ± 3.60
Total cholesterol (mmol/L)	5.42 ± 1.01	5.58 ± 1.08	5.58 ± 1.13	5.54 ± 1.18	5.36 ± 1.20
Systolic blood pressure (mmHg)	137.60 ± 17.85	141.36 ± 18.12	143.48 ± 18.14	145.21 ± 18.22	146.63 ± 18.58
Healthy diet (%)	40.9	39.0	37.7	35.6	33.6
Cholesterol-lowering medication (%)	10.9	16.7	21.6	27.3	35.9
Anti-hypertensive medication (%)	11.7	17.0	22.4	28.8	40.4
Fat mass (kg)	13.22 ± 2.73	18.14 ± 2.29	21.50 ± 2.64	25.30 ± 3.23	32.71 ± 5.95
Muscle mass (kg)	58.99 ± 6.54	59.67 ± 6.68	60.27 ± 6.91	61.24 ± 7.16	63.35 ± 7.69
Women (n = 220 471, 50.2%)					
Fat-to-muscle mass ratio	0.39 ± 0.06	0.52 ± 0.03	0.61 ± 0.03	0.71 ± 0.03	0.88 ± 0.10
Fat-to-muscle mass ratio bounds	<0.47	0.47–0.55	0.56–0.64	0.65–0.77	>0.77
Visceral adipose tissue (g)	252.59 ± 167.93	499.73 ± 200.84	717.90 ± 245.81	989.09 ± 310.77	1464.12 ± 437.60
Age (years)	54.07 ± 8.25	55.80 ± 8.16	56.97 ± 7.96	57.58 ± 7.82	57.57 ± 7.74
University or college degree (%)	42.3	35.4	30.9	27.3	23.9
Townsend deprivation index	−1.50 ± 2.95	−1.61 ± 2.90	−1.53 ± 2.92	−1.32 ± 3.04	−0.90 ± 3.21
White (%)	95.4	95.4	95.1	94.3	93.2
Diabetes (%)	1.4	1.8	2.5	3.9	7.0
Hypertension (%)	11.6	15.8	20.9	26.1	35.2
Drinks per week (glasses)	6.05 ± 6.96	6.11 ± 7.29	5.89 ± 7.26	5.63 ± 7.47	4.94 ± 7.54
Current smoking (%)	10.2	8.6	8.5	8.3	7.6
Physical activity at goal (%)	58.8	53.9	50.7	46.2	38.4
Body mass index (kg/m^2)	21.93 ± 1.87	24.17 ± 1.88	26.08 ± 2.14	28.49 ± 2.59	33.46 ± 4.30
Total cholesterol (mmol/L)	5.66 ± 1.03	5.87 ± 1.09	5.98 ± 1.12	6.00 ± 1.15	5.89 ± 1.17
Systolic blood pressure (mmHg)	130.60 ± 19.81	134.71 ± 20.20	137.88 ± 20.22	140.14 ± 19.83	142.31 ± 19.29
Healthy diet (%)	59.2	58.4	57.7	55.8	52.5
Cholesterol-lowering medication (%)	5.2	8.0	11.3	15.0	20.0
Anti-hypertensive medication (%)	7.4	10.7	15.1	20.2	28.8
Fat mass (kg)	15.64 ± 2.87	21.06 ± 2.27	25.19 ± 2.66	30.16 ± 3.44	40.17 ± 7.34
Muscle mass (kg)	40.40 ± 3.69	40.74 ± 3.70	41.46 ± 3.88	42.69 ± 4.23	45.31 ± 5.01

Mean ± SD for continuous variables and percentage for categorical variables.

Table 3 Hazard ratios of all-cause mortality according to visceral adipose tissue and fat-to-muscle mass ratio quintiles by age

	All	<50 years	50–59 years	≥60 years	*P* for interaction
Men					
N	218 425	50 742	69 793	97 890	
Quintile of VAT					
1 (lowest)	1.02(0.95–1.08)	1.30(1.02–1.66)	0.93(0.82–1.06)	1.01(0.95–1.09)	<0.001
2	0.94(0.89–0.99)	1.02(0.81–1.28)	0.81(0.72–0.90)	0.96(0.90–1.02)	
3 (reference)	1	1	1	1	
4	1.00(0.95–1.06)	1.22(0.98–1.53)	0.94(0.84–1.05)	1.04(0.97–1.10)	
5 (highest)	1.24(1.17–1.33)	1.67(1.27–2.19)	1.32(1.14–1.52)	1.22(1.13–1.32)	
P for trend	0.001	0.38	0.006	0.005	
Quintile of FMR					
1 (lowest)	1.07(1.01–1.14)	1.25(0.99–1.56)	1.02(0.91–1.16)	1.05(0.99–1.12)	0.004
2	0.97(0.92–1.02)	1.00(0.80–1.25)	0.97(0.86–1.09)	0.95(0.90–1.01)	
3 (reference)	1	1	1	1	
4	1.03(0.98–1.08)	1.12(0.90–1.39)	1.06(0.95–1.18)	1.04(0.98–1.10)	
5 (highest)	1.24(1.17–1.31)	1.41(1.11–1.79)	1.35(1.19–1.53)	1.23(1.16–1.32)	
P for trend	<0.001	0.48	0.002	<0.001	
Women					
N	220 471	52 983	73 037	94 451	
Quintile of VAT					
1 (lowest)	1.06(0.98–1.15)	0.98(0.73–1.32)	0.96(0.82–1.13)	1.16(1.06–1.27)	<0.001
2	1.03(0.96–1.11)	1.21(0.92–1.58)	0.97(0.84–1.12)	1.05(0.96–1.14)	
3 (reference)	1	1	1	1	
4	0.98(0.92–1.05)	1.12(0.86–1.47)	1.12(0.97–1.29)	1.01(0.93–1.09)	
5 (highest)	1.11(1.03–1.21)	1.24(0.90–1.72)	1.32(1.11–1.57)	1.19(1.08–1.31)	
P for trend	0.913	0.50	0.009	0.51	
Quintile of FMR					
1 (lowest)	1.18(1.09–1.27)	0.99(0.75–1.32)	1.15(0.98–1.34)	1.18(1.08–1.29)	0.001
2	1.07(1.00–1.15)	1.01(0.78–1.32)	1.12(0.97–1.29)	1.02(0.94–1.11)	
3 (reference)	1	1	1	1	
4	1.01(0.95–1.08)	0.94(0.73–1.23)	1.08(0.94–1.25)	1.02(0.94–1.11)	
5 (highest)	1.07(0.99–1.16)	1.11(0.80–1.53)	1.16(0.97–1.38)	1.11(1.01–1.22)	
P for trend	0.016	0.94	0.68	0.17	

FMR, fat-to-muscle mass ratio; VAT, visceral adipose tissue.
Data are hazard ratios (95% confidence intervals). The model was adjusted for age, ethnicity (white/others), education (university or college degree/others), Townsend index (continuous), smoking status (current, ever, or never), drinking (continuous), physical activity at goal (yes/no), healthy diet score> = 4 (yes/no), BMI (continuous), total cholesterol (continuous), systolic blood pressure (continuous), diabetes (yes/no), cholesterol-lowering medication (yes/no), blood pressure medication (yes/no) and insulin (yes/no).

Most previous studies found that higher VAT is associated with increased all-cause mortality.[12,27,28] However, one study did not find an association between VAT and all-cause mortality,[14] which might be due to differences in adjusted covariates. In our study, multiple covariates were adjusted, and stratified analyses based on age category were performed. In addition to the fact that large VAT mass was associated with greater mortality risk, we found that men with very small amounts of VAT also had a higher risk of all-cause mortality, especially in the <50 age group; in women, this association was observed in the ≥60 age group. Differences in age groups were also shown in the results of a study by Jared et al. There was a J-shaped trend between waist circumference and all-cause mortality among men aged 30–64 years, with those in the lowest waist circumference quintile having a higher risk of mortality than those in the third quintile, as well as a negative association in those aged ≥65 years.[29] A 6-year Korean cohort study examining the association between visceral fat area and all-cause mortality found that the association was U-shaped in older women.[30] Another study involving women aged 30–55 found that low levels of increased waist circumference were not significantly associated with all-cause mortality, and a significant and positive association was observed only in the highest quintile of waist circumference.[31] Furthermore, compared with subcutaneous adipose tissue, VAT in most obese patients has more macrophages expressing cytokines/chemokines,[32] leading to a more complex and intense inflammatory response. Interleukin-6 is one of the markers, and its expression is significantly reduced in subcutaneous adipose tissue.[33] Subcutaneous adipose tissue is also less associated with markers of systemic inflammation than VAT.[34] Excess VAT can affect health through abnormal haemodynamics and activation of cholesterol crystals.[35] However, we consider an appropriate amount of VAT to be necessary to support, stabilize and protect the viscera and play an important role in metabolic processes, such as insulin resistance, lipolysis, and glucose uptake.[36]

The fat-to-muscle mass ratio has been used in past studies to discuss the relationship with metabolic diseases[21,37] and has become a new indicator for cardiometabolic risk.[38] However, few studies have considered FMR as a risk factor for all-cause and cause-specific mortality. Only one study found that the fat-to-lean mass ratio was an independent predictor of cardiac events and all-cause mortality in 131 patients un-

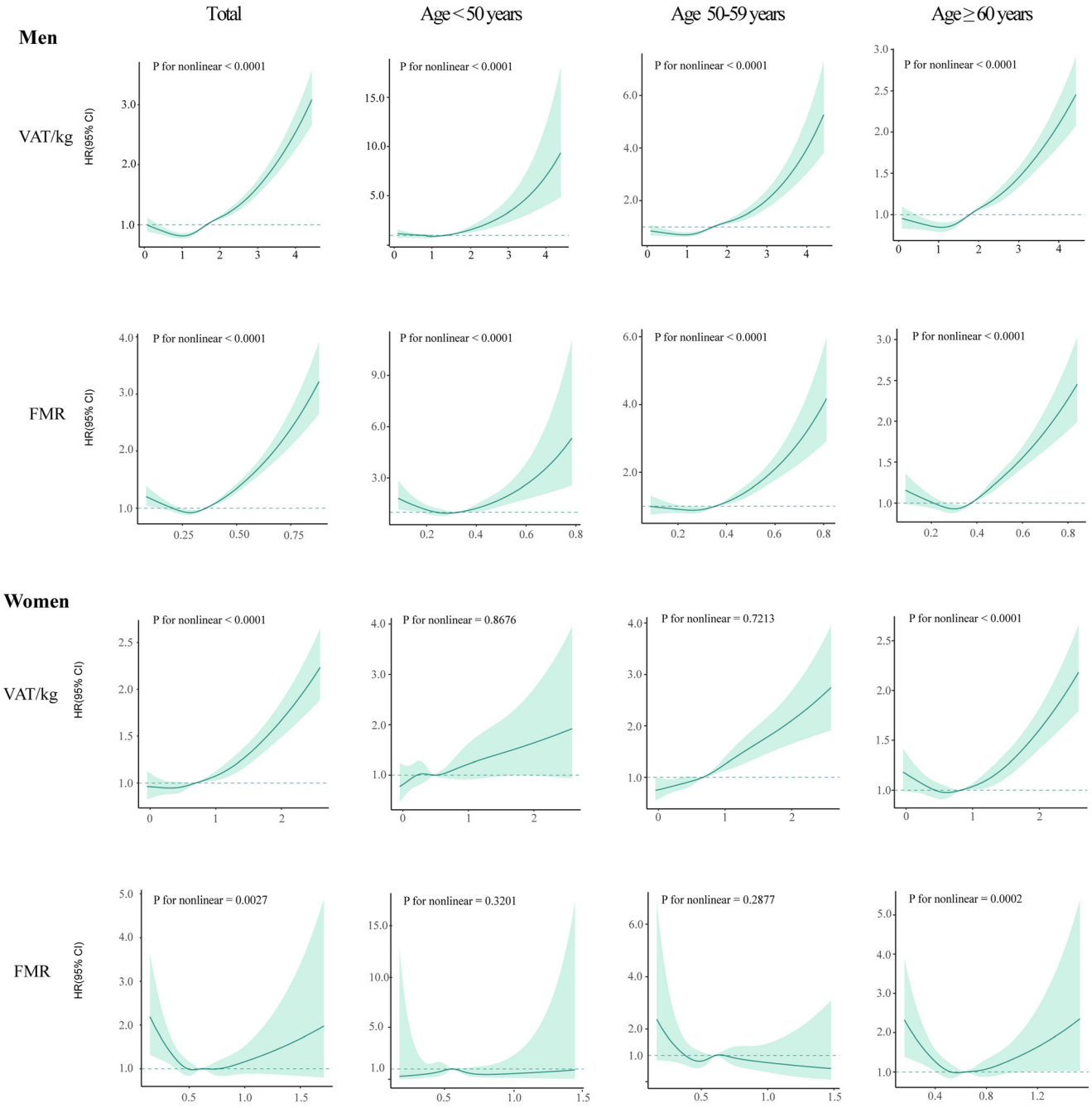

Figure 1 Association of visceral adipose tissue and fat-to-muscle mass ratio with all-cause mortality in men and women. Hazard ratios are indicated by solid lines, and 95% confidence intervals are indicated by shaded areas. The reference points for VAT and FMR are the lowest values for each, with knots placed at the 5th, 27.5th, 50th, 72.5th and 95th percentiles of each distribution. The model was adjusted for age, ethnicity (white/others), education (university or college degree/others), Townsend index (continuous), smoking status (current, ever, or never), drinking (continuous), physical activity at goal (yes/no), healthy diet score> = 4 (yes/no), BMI (continuous), total cholesterol (continuous), systolic blood pressure (continuous), diabetes (yes/no), cholesterol-lowering medication (yes/no), blood pressure medication (yes/no) and insulin (yes/no). FMR, fat-to-muscle mass ratio; VAT, visceral adipose tissue.

dergoing haemodialysis.[39] In our study, the FMR results were similar to those of VAT. The highest quintile of FMR increased the risk of mortality in both men and women of all ages. Interestingly, the risk of mortality was also significantly increased in the lowest quintile of FMR in the <50 age group of men and the ≥60 age group of women. Janne et al. found that body fat showed a J-shaped association and that fat-free mass showed an anti-J-shaped association with mortality in people aged 50–64 years in both sexes,[S1(Data S1)] which means that the relationship between FMR and mortality depends on

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Table 4 Hazard ratio (95% CI) of cause-specific mortality according to visceral adipose tissue quintiles and fat-to-muscle ratio

	VAT		FMR	
	<60 years	≥60 years	<60 years	≥60 years
Cardiovascular disease death				
Men				
No. of deaths (%)	1.10	3.90	1.10	3.90
1 (lowest)	1.08(0.85–1.38)	1.02(0.89–1.16)	1.23(0.97–1.55)	1.04(0.91–1.18)
2	1.01(0.81–1.26)	0.94(0.84–1.06)	1.02(0.82–1.28)	1.03(0.92–1.16)
3 (reference)	1	1	1	1
4	0.98(0.80–1.21)	0.94(0.84–1.05)	1.17(0.95–1.43)	1.04(0.93–1.17)
5 (highest)	1.31(1.02–1.67)	1.09(0.94–1.25)	1.30(1.04–1.63)	1.29(1.14–1.45)
P for linear/nonlinear trend	0.58/0.03	0.78/0.61	0.38/0.04	0.02/0.08
Women				
No. of deaths (%)	0.30	1.40	0.30	1.40
1 (lowest)	0.64(0.38–1.06)	1.31(1.04–1.64)	0.83(0.53–1.29)	1.27(1.03–1.58)
2	0.76(0.49–1.16)	1.06(0.86–1.31)	0.93(0.63–1.36)	0.96(0.78–1.18)
3 (reference)	1	1	1	1
4	1.15(0.81–1.63)	1.07(0.88–1.31)	0.84(0.59–1.19)	0.98(0.81–1.20)
5 (highest)	1.32(0.86–2.03)	1.21(0.96–1.54)	0.76(0.49–1.17)	1.11(0.89–1.39)
P for linear/nonlinear trend	0.01/0.46	0.57/0.02	0.70/0.44	0.35/<0.001
Cancer death				
Men				
No. of deaths (%)	2.10	7.20	2.10	7.20
1 (lowest)	0.90(0.76–1.05)	0.89(0.81–0.98)	0.92(0.79–1.07)	0.98(0.90–1.08)
2	0.81(0.70–0.94)	0.97(0.89–1.06)	0.94(0.81–1.08)	0.92(0.85–1.00)
3 (reference)	1	1	1	1
4	1.02(0.89–1.17)	1.11(1.02–1.21)	1.05(0.92–1.20)	1.05(0.97–1.14)
5 (highest)	1.35(1.13–1.60)	1.29(1.16–1.44)	1.17(1.00–1.35)	1.16(1.06–1.27)
P for linear/nonlinear trend	0.001/<0.001	<0.001/0.03	0.01/0.02	0.001/0.01
Women				
No. of deaths (%)	1.80	4.80	1.80	4.80
1 (lowest)	0.93(0.78–1.11)	1.01(0.89–1.13)	1.10(0.93–1.31)	1.06(0.95–1.19)
2	0.98(0.84–1.14)	1.03(0.92–1.14)	1.12(0.96–1.30)	1.00(0.90–1.11)
3(reference)	1	1	1	1
4	1.15(0.99–1.33)	1.01(0.91–1.13)	1.16(1.00–1.35)	1.08(0.97–1.20)
5 (highest)	1.34(1.12–1.62)	1.21(1.07–1.38)	1.16(0.96–1.41)	1.17(1.04–1.33)
P for linear/nonlinear trend	0.004/0.38	0.22/0.05	0.69/0.21	0.22/0.01
Respiratory death				
Men				
No. of deaths (%)	0.90	4.10	0.90	4.10
1 (lowest)	1.05(0.81–1.35)	1.00(0.88–1.14)	0.93(0.73–1.18)	0.99(0.88–1.12)
2	0.93(0.74–1.18)	0.95(0.85–1.07)	0.94(0.74–1.18)	0.92(0.82–1.03)
3 (reference)	1	1	1	1
4	1.08(0.85–1.36)	1.06(0.95–1.19)	1.07(0.86–1.34)	1.08(0.97–1.21)
5 (highest)	1.78(1.35–2.35)	1.36(1.18–1.56)	1.63(1.28–2.07)	1.57(1.39–1.77)
P for linear/nonlinear trend	0.05/<0.001	0.01/<0.001	0.001/<0.001	<0.001/<0.001
Women				
No. of deaths (%)	0.40	1.90	0.40	1.90
1 (lowest)	0.95(0.64–1.41)	1.16(0.96–1.40)	1.13(0.79–1.62)	1.19(0.99–1.43)
2	0.92(0.64–1.32)	0.94(0.79–1.13)	1.04(0.74–1.45)	1.06(0.89–1.26)
3 (reference)	1	1	1	1
4	1.30(0.95–1.78)	0.92(0.78–1.10)	1.12(0.82–1.52)	1.04(0.88–1.24)
5 (highest)	1.78(1.23–2.57)	1.27(1.03–1.55)	1.10(0.76–1.61)	1.28(1.05–1.56)
P for linear/nonlinear trend	0.01/0.86	0.97/<0.001	0.96/0.04	0.99/<0.001

FMR, fat-to-muscle mass ratio; VAT, visceral adipose tissue.
Data are hazard ratios (95% confidence intervals). Bonferroni correction was used and $P < 0.017$ (0.05/3) was considered statistically significant. Linear trend was quantified with Wald test for linear trend by assigning median value to each category and modelling this variable as continuous variable. Potential non-linear relation was tested using restricted cubic spline model. The model was adjusted for age, ethnicity (white/others), education (university or college degree/others), Townsend index (continuous), smoking status (current, ever, or never), drinking (continuous), physical activity at goal (yes/no), healthy diet score> = 4 (yes/no), BMI (continuous), total cholesterol (continuous), systolic blood pressure (continuous), diabetes (yes/no), cholesterol-lowering medication (yes/no), blood pressure medication (yes/no), and insulin (yes/no).

which one was more influential. The results of a study by Dong Hoon Lee on people aged 40–75 years emphasized a greater role of lean body mass in the observed J-shaped association between BMI and mortality.[S2] However, Matteo et al. suggested that calf skeletal muscle and fat mass were not important risk factors for mortality in elderly individuals.[S3] We think that the difference is due to age and sex differences in body composition, high-density lipoprotein cholesterol, tri-

glycerides, insulin resistance, adiponectin concentrations and inflammatory cytokines.[S4, S5]

When further exploring the associations of VAT and FMR with death from specific causes, we found that the associations with CVD in our study were only significant for VAT in women <60 years old and FMR in women ≥60 years old. Aki[S6] and Eun[S7] suggested that VAT and FMR were associated with CVD, respectively. However, in research by Marcel, greater VAT was only significantly associated with stroke or myocardial infarction in men, and lower muscle density did not show a relationship with CVD.[13] According to an integrative review, visceral obesity and CVD risk are controversial. Despite the risk of visceral obesity being consistently associated with CVD in adults, this association disappears in sex-specific analyses and analyses of older adults.[S8] VAT synthesizes and secretes a number of bioactive mediators known as adipokines. On the one hand, adiponectin and omentin prevent atherosclerosis. On the other hand, leptin and resistin induce inflammation and endothelial dysfunction, increasing the risk of atherosclerotic plaque vulnerability and rupture.[S9] In addition, there were sex differences in the associations between FMR and CVD. We consider women to a higher FMR and men to a higher VAT, and this difference may be related to sex-related body fat distribution and sex hormone differences. Chen also found sex differences in FMR as an indicator of cardiometabolic risk.[38]

There are contradictions between obesity and cancer. Some studies suggest that weight gain increases the risk of endometrial, kidney and pancreatic cancer,[S10] but others have found that weight gain reduces the risk of premenopausal breast cancer, non-small cell lung cancer and head and neck cancers.[S11] These studies suggest that FMR may also be associated with cancer. Only a 2009 case–control study directly discussed FMR and cancer, and it found that women with a higher FMR had an increased risk of breast cancer.[S12] Our study showed that individuals with lower VAT and FMR had lower HRs of mortality from cancer, although the 1st and 2nd quintiles of FMR in men had a non-significantly higher risk of mortality from cancer than the 3rd quintile. The explanation for the obesity paradox in cancer remains unclear.[S13] Potential explanations of the obesity paradox in cancer patients may include methodological issues and clinical aspects.[S14, S15] BMI as a measure of obesity cannot fully represent the level of individual obesity. Confounding factors and reverse causality can also affect conclusions. In addition, some studies posit that excess fat tissue can provide a nutrient reserve in the face of surgical intervention and anticancer treatments. The paradox may also be explained in part by the fact that patients with less aggressive tumours and obese patients tend to receive more medical check-ups.

In the analysis of respiratory diseases, we found that most sex-specific and age-specific associations of VAT and FMR were J-shaped. The influence of body composition on respiratory diseases may exist and deserves further investigation. Recent research found a link between VAT and the severity of COVID-19.[S16] Another study reported that chest CT images of chronic obstructive pulmonary disease with severely restricted airflow showed more VAT and fat mass accumulation and less muscle mass.[S17] In addition, sarcopenia showed a positive association with respiratory morbidity and mortality, but overweight and obesity reduced the risk of respiratory disease mortality; however, no association was found between sarcopenia obesity and respiratory mortality.[S18] It was possible that fat mass reduced lung function, but muscle mass had a larger impact on respiratory mortality. Therefore, as an indicator that considers both fat and muscle factors, FMR has a suggestive significance for us to maintain the balance of muscle and fat.

The main strengths of our research are the prospective design, large sample size with more than 400 000 participants and relatively long follow-up duration (median: 12.4 years), which increase the credibility of our research. In addition, various covariates were adjusted. There are also several limitations of our study. First, as this was an observational study, the association of VAT and FMR with mortality cannot be interpreted as a causal relationship. Second, the VAT prediction models were proven to be feasible in previous large population studies, but they were not as accurate as the imaging results. There remains a lack of accuracy and validity on the estimated VAT mass used in the study. Fat and muscle mass were also not measured by imaging techniques such as DEXA and magnetic resonance. However, bioimpedance may be a feasible measurement and an adequate method to assess body composition in large epidemiological studies. Third, although the mortality of specific causes was discussed, due to limited data, the subjects of discussion were relatively general and were not further subdivided. As mentioned above, the associations between cancer and obesity vary by anatomical site.[S11] Furthermore, those with diseases and co-morbidities existing before the UKB measurement day were not included in the study analysis. Fourth, we cannot entirely rule out the possibility of unmeasured or unknown confounding factors that may account for the associations observed in this study. Last, the population we studied was primarily of European descent, aged 40–69 years, and comprised mostly white British individuals, without considering the influence of different races, such as Asians and African Americans. The UKB is also unrepresentative in terms of lifestyle because of a 'healthy volunteer' selection bias. Therefore, generalizing the findings to the wider population should be done with caution.

In conclusion, most associations of VAT mass and FMR with all-cause mortality were J-shaped in the overall cohorts of men and women. Age significantly modified the associations. The clinical implications might involve different health strategies for people of different sexes and ages. Moderate levels of VAT and FMR are recommended for younger men, and very low levels of VAT and FMR are not recommended

for older women. Whether these measures benefit health needs further interventional study.

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Conflict of interest

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

Online supplementary material

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

References

1. Csige I, Ujvárosy D, Szabó Z, L$Calibri(TrueType)$"182ff89e}őrincz I, Paragh G, Harangi M, et al. The impact of obesity on the cardiovascular system. *J Diabetes Res* 2018;**2018**:3407306.
2. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res* 2020;**126**:1477–1500.
3. Jura M, Kozak LP. Obesity and related consequences to ageing. *Age (Dordr)* 2016;**38**:23.
4. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. *Lancet Diabetes Endocrinol* 2018;**6**:944–953.
5. Welborn TA, Dhaliwal SS. Preferred clinical measures of central obesity for predicting mortality. *Eur J Clin Nutr* 2007;**61**:1373–1379.
6. Jayedi A, Soltani S, Zargar MS, Khan TA, Shab-Bidar S. Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies. *BMJ* 2020;**370**:m3324.
7. Nevill AM, Stewart AD, Olds T, Holder R. Relationship between adiposity and body size reveals limitations of BMI. *Am J Phys Anthropol* 2006;**129**:151–156.
8. Goyal A, Nimmakayala KR, Zonszein J. Is there a paradox in obesity? *Cardiol Rev* 2014;**22**:163–170.
9. Kok P, Seidell JC, Meinders AE. The value and limitations of the body mass index (BMI) in the assessment of the health risks of overweight and obesity. *Ned Tijdschr Geneeskd* 2004;**148**:2379–2382.
10. Lee SW, Son JY, Kim JM, Hwang SS, Han JS, Heo NJ. Body fat distribution is more predictive of all-cause mortality than overall adiposity. *Diabetes Obes Metab* 2018;**20**:141–147.
11. Dong B, Peng Y, Wang Z, Adegbija O, Hu J, Ma J, et al. Joint association between body fat and its distribution with all-cause mortality: a data linkage cohort study based on NHANES (1988-2011). *PLoS ONE* 2018;**13**:e0193368.
12. Brown JC, Harhay MO, Harhay MN. Anthropometrically-predicted visceral adipose tissue and mortality among men and women in the third national health and nutrition examination survey (NHANES III). *Am J Hum Biol* 2017;**29**:e22898.
13. Ballin M, Nordström P, Niklasson J, Nordström A. Associations of visceral adipose tissue and skeletal muscle density with incident stroke, myocardial infarction, and all-cause mortality in community-dwelling 70-year-old individuals: a prospective cohort study. *J Am Heart Assoc* 2021;**10**:e020065.
14. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol* 2013;**62**:921–925.
15. Katzmarzyk PT, Mire E, Bouchard C. Abdominal obesity and mortality: the Pennington Center longitudinal study. *Nutr Diabetes* 2012;**2**:e42.
16. He Q, Liu S, Feng Z, Li T, Chu J, Hu W, et al. Association between the visceral adiposity index and risks of all-cause and cause-specific mortalities in a large cohort: findings from the UK biobank. *Nutr Metab Cardiovasc Dis* 2022;**32**:2204–2215.
17. Swainson MG, Batterham AM, Hind K. Age- and sex-specific reference intervals for visceral fat mass in adults. *Int J Obes (Lond)* 2020;**44**:289–296.
18. Karlsson T, Rask-Andersen M, Pan G, Höglund J, Wadelius C, Ek WE, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med* 2019;**25**:1390–1395.
19. Bosy-Westphal A, Braun W, Geisler C, Norman K, Müller MJ. Body composition and cardiometabolic health: the need for novel concepts. *Eur J Clin Nutr* 2018;**72**:638–644.
20. Wells JCK. Body composition and susceptibility to type 2 diabetes: an evolutionary perspective. *Eur J Clin Nutr* 2017;**71**:881–889.
21. Wang N, Sun Y, Zhang H, Chen C, Wang Y, Zhang J, et al. Total and regional fat-to-muscle mass ratio measured by bioelectrical impedance and risk of incident type 2 diabetes. *J Cachexia Sarcopenia Muscle* 2021;**12**:2154–2162.
22. Lee DH, Giovannucci EL. Body composition and mortality in the general population: a review of epidemiologic studies. *Exp Biol Med (Maywood)* 2018;**243**:1275–1285.
23. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;**12**:e1001779.
24. Malavolti M, Mussi C, Poli M, Fantuzzi AL, Salvioli G, Battistini N, et al. Cross-calibration of eight-polar bioelectrical impedance analysis versus dual-energy X-ray absorptiometry for the assessment of total and appendicular body composition in healthy subjects aged 21-82 years. *Ann Hum Biol* 2003;**30**:380–391.
25. Pietrobelli A, Rubiano F, St-Onge MP, Heymsfield SB. New bioimpedance analysis system: improved phenotyping with whole-body analysis. *Eur J Clin Nutr* 2004;**58**:1479–1484.
26. Pazoki R, Dehghan A, Evangelou E, Warren H, Gao H, Caulfield M, et al. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation* 2018;**137**:653–661.

27. Saad RK, Ghezzawi M, Horanieh R, Khamis AM, Saunders KH, Batsis JA, et al. Abdominal visceral adipose tissue and all-cause mortality: a systematic review. *Front Endocrinol (Lausanne)* 2022;**13**:922931.
28. Brown JC, Harhay MO, Harhay MN. Visceral adipose tissue dysfunction and mortality among a population-based sample of males and females. *Diabetes Metab* 2016; **42**:382–385.
29. Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL. Comparison of overall obesity and body fat distribution in predicting risk of mortality. *Obesity (Silver Spring)* 2009;**17**:1232–1239.
30. Shil Hong E, Khang AR, Roh E, Jeong Ku E, An Kim Y, Min Kim K, et al. Counterintuitive relationship between visceral fat and all-cause mortality in an elderly Asian population. *Obesity (Silver Spring)* 2015;**23**: 220–227.
31. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation* 2008;**117**:1658–1667.
32. Harman-Boehm I, Blüher M, Redel H, Sion-Vardy N, Ovadia S, Avinoach E, et al. Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the comorbidities of obesity. *J Clin Endocrinol Metab* 2007;**92**:2240–2247.
33. le Jemtel TH, Samson R, Milligan G, Jaiswal A, Oparil S. Visceral adipose tissue accumulation and residual cardiovascular risk. *Curr Hypertens Rep* 2018;**20**:77.
34. Neeland IJ, Ayers CR, Rohatgi AK, Turer AT, Berry JD, Das SR, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. *Obesity (Silver Spring)* 2013;**21**:E439–E447.
35. Suzuki K. Chronic inflammation as an immunological abnormality and effectiveness of exercise. *Biomolecules* 2019;**9**:223.
36. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev* 2010;**11**:11–18.
37. Liu D, Zhong J, Ruan Y, Zhang Z, Sun J, Chen H. The association between fat-to-muscle ratio and metabolic disorders in type 2 diabetes. *Diabetol Metab Syndr* 2021;**13**:129.
38. Chen YY, Fang WH, Wang CC, Kao TW, Yang HF, Wu CJ, et al. Fat-to-muscle ratio is a useful index for cardiometabolic risks: a population-based observational study. *PLoS ONE* 2019;**14**:e0214994.
39. Lee HS, Kim SG, Kim JK, Lee YK, Noh JW, Oh J, et al. Fat-to-lean mass ratio can predict cardiac events and all-cause mortality in patients undergoing hemodialysis. *Ann Nutr Metab* 2018;**73**:241–249.
40. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021. *J Cachexia Sarcopenia Muscle* 2021;**12**:2259–2261.