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Associations of relative fat mass and BMI with all-cause mortality: Confounding effect of muscle mass

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Abstract

Objective: The study objective was to examine associations of relative fat mass (RFM) and BMI with all-cause mortality in the Dutch general population and to investigate whether additional adjustment for muscle mass strengthened these associations.

Methods: A total of 8433 community-dwelling adults from the PREVEND general population cohort (1997–1998) were included. Linear regression models were used to examine associations of RFM and BMI with 24-h urinary creatinine excretion, a marker of total muscle mass. Cox regression models were used to examine associations of RFM and BMI with all-cause mortality.

Results: The mean age of the cohort was 49.8 years (range: 28.8–75.7 years), and 49.9% ($n = 4209$) were women. In age- and sex-adjusted models, both RFM and BMI were associated with total muscle mass (24-h urinary creatinine excretion), and these associations were stronger with BMI (standardized beta $[S\beta]_{RFM}$: 0.29; 95% CI: 0.27–0.31 vs. $S\beta_{BMI}$: 0.38; 95% CI: 0.36–0.40; $p_{difference} < 0.001$). During a median follow-up period of 18.4 years, 1640 deaths (19.4%) occurred. In age- and sex-adjusted models, RFM was significantly associated with all-cause mortality (hazard ratio per 1-SD $[HR_{RFM}]$: 1.16; 95% CI: 1.09–1.24), whereas BMI was not (HR_{BMI}: 1.04; 95% CI: 0.99–1.10). After additional adjustment for muscle mass, associations of both RFM and BMI with all-cause mortality increased in magnitude (HR_{RFM}: 1.24; 95% CI: 1.16–1.32 and HR_{BMI}: 1.12; 95% CI: 1.06–1.19). Results were broadly similar in multivariable adjusted models.

Conclusions: In the general population, a higher RFM was significantly associated with mortality risk, whereas a higher BMI was not. Adjusting for total muscle mass increased the strength of associations of both RFM and BMI with all-cause mortality.

Navin Suthahar and Victor Zwartkruis contributed equally to this work.

INTRODUCTION

Worldwide obesity has tripled in the past 50 years, and obesity has now become a major global public health challenge [1–3]. Recent estimates have indicated that the burden of obesity will continue to increase, and by the year 2030, prevalence rates of obesity are expected to even exceed 50% in some parts of the world [4].

It is well recognized that obesity increases the risk of developing multiple diseases, such as type 2 diabetes, cardiopulmonary disease, chronic kidney disease, musculoskeletal disorders, and certain types of cancer [5, 6]. However, the relationship between obesity and mortality risk remains controversial: while a large body of evidence supports a "J-shaped" or a "U-shaped" association of body mass index (BMI) with all-cause mortality [7–9], a meta-analysis of 97 studies enrolling about 2.88 million adults from the United States with over 270,000 deaths during follow-up showed that overweight (BMI of 25 to 30 kg/m^2) was associated with an increased survival probability, that is, with lower all-cause mortality, and grade 1 obesity (BMI of 30 to 35 kg/m^2) was not associated with higher mortality [10]. A few more US-based general population studies also reported a lower mortality rate in individuals with overweight [11, 12], and a more recent study on Chinese adults showed that, in individuals without morbid obesity, higher BMI was associated with a progressively lower risk of mortality [13].

This discrepancy in association of BMI with mortality risk may arise, at least in part, due to the inability of BMI to differentiate between fat mass and lean body mass [14–16] in different population groups. Therefore, in the current study, we hypothesized that relative fat mass (RFM), a novel adiposity measure that strongly predicts whole-body fat percentage [17], would be more strongly associated with mortality risk than BMI. Furthermore, given that fat mass and muscle mass correlate with each other [18], and muscle mass showed an inverse association with mortality [19], we also hypothesized that additional adjustment for muscle mass will strengthen associations of both RFM and BMI with all-cause mortality.

Study Importance

What is already known?

- A large body of evidence supports a "J-shaped" or "U-shaped" association of BMI with all-cause mortality.
- However, several observational studies continue to report that individuals with mild to moderate obesity (based on BMI category) may have a survival benefit.

What does this study add?

- Relative fat mass (RFM) is a recently developed tool that better predicted whole body fat percentage than BMI. In the general population, we now show that RFM is a superior predictor of mortality risk compared with BMI.
- Adjustment for 24-h urinary creatine excretion (a surrogate of muscle mass) strengthened the associations of both RFM and BMI with all-cause mortality.

How might these results change the direction of research?

- Based on our results, we recommend the usage of RFM instead of BMI while examining associations of "obesity" with all-cause mortality and recommend additionally accounting for muscle mass for more accurate interpretation of results.

METHODS

The Prevention of REnal and Vascular ENd-Stage Disease (PREVEND) (1997–1998) is a Dutch cohort taken from the general population of Groningen, The Netherlands (https://umcgresearch.org/w/prevend). This observational study included 8592 participants (Figure S1) and was designed to prospectively evaluate whether increased urinary albumin excretion (UAE) in community-dwelling individuals was associated with cardiovascular and renal disease [20]. Participants underwent baseline examination in an outpatient clinic. Urine samples and fasting blood samples were collected, aliquoted, and stored at −80°C until analysis. From the baseline cohort ($N = 8592$), we excluded individuals with (i) missing RFM, BMI, and 24-h urinary creatinine excretion (UCE; $n = 149$) and (ii) values of RFM, BMI, and 24-h UCE below P25 − (1.5 × (P75 − P25)); ($n = 10$) [21], resulting in a final total of 8433 individuals (Figure S1). The PREVEND study conformed to the principles drafted in the Helsinki Declaration. The PREVEND study has been approved by the medical ethics committee of the University Medical Center Groningen (approval number: MEC96/01/022), and informed consent was provided by all participants.

Baseline measurements

Body weight, waist circumference (WC), and height were measured in a standing position during the baseline visit. WC was measured midway between the lowest rib and the iliac crest, at the end of expiration. RFM was calculated as follows: 64 − (20 × height / WC) + (12 × sex), with sex = 0 (men) and sex = 1 (women) [17]. BMI was calculated as the ratio of weight (in kilograms) to height (in meters) squared. Smoking was classified into four categories: nonsmokers, self-reported current smoking, smoking cessation within the previous year, and smoking cessation more than a year. Blood pressure (BP) was measured 10 times during 10 min using an automatic Dinamap XL Model 9300 series; BP was calculated as the mean of the last two measurements. Hypertension was defined as a systolic BP ≥140 mm Hg, a diastolic BP ≥90 mm Hg, or self-reported antihypertensive medication usage. Type 2 diabetes was defined as a fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), a

random plasma glucose ≥11.1 mmol/L (200 mg/dL), self-reporting of a physician diagnosis, or record of glucose-lowering medication use obtained from central pharmacy registry. History of cardiovascular disease (i.e., myocardial infarction, stroke, atrial fibrillation, or heart failure) was obtained from the registry of hospital discharge diagnoses or from self-report. History of cancer was based on participant questionnaire and was complemented by data from the Dutch nationwide network and registry of histopathology and cytopathology in The Netherlands (PALGA Foundation) [22]. Kidney dysfunction was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, and eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, based on creatinine and cystatin C levels in the majority of the population ($n = 7886$); in individuals with unavailable cystatin C measurements, eGFR was estimated using the CKD-EPI equation based on creatinine levels ($n = 513$) [23]. Total cholesterol measurement was done in plasma samples obtained during the baseline visit. Participants collected two 24-h urine collections during two consecutive days at baseline in the week prior to measurement. Urine samples were stored at 4°C for a maximum of 4 days before the visit, and 24-h UAE and 24-h UCE were measured in these samples. Participants were instructed orally and in writing to refrain from heavy exercise and to postpone urine collection in case of fever, urinary tract infection, or menstruation [19, 20]. Creatinine in urine was determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY), an automated enzymatic method [19]. Other assay-related details are provided elsewhere [23]. Data concerning mortality were collected through the municipal registry. Survival time was defined as the time from first visit to the date of death, until 1 January 2018. If a person moved to an unknown destination, the date on which that individual could no longer be tracked via the municipal registry was used as the censor date.

TABLE 1 PREVEND participant characteristics

	Men ($n = 4224$)	Women ($n = 4209$)
RFM, mean ± SD	25.3 ± 4.8	35.0 ± 6.2
BMI (kg/m^2), mean ± SD	26.3 ± 3.6	25.9 ± 4.7
Age (y), mean ± SD	51.0 ± 12.9	48.6 ± 12.3
Height (cm), mean ± SD	179.2 ± 7.4	166.8 ± 6.9
Smoking category, *n* (%)		
Nonsmokers	1048 (24.9)	1416 (33.8)
Current smokers	1464 (34.8)	1417 (33.8)
Stopped <1 y	143 (3.4)	176 (4.2)
Stopped >1 y	1533 (36.9)	1186 (28.3)
Diabetes, *n* (%)	181 (4.3)	133 (3.2)
Hypertension, *n* (%)	1677 (39.9)	1184 (28.2)
Dyslipidemia, *n* (%)	2551 (60.4)	2290 (54.4)
CVD, *n* (%)	424 (10.0)	218 (5.2)
Cancer, *n* (%)	153 (3.6)	118 (2.8)
Kidney dysfunction, *n* (%)	166 (3.9)	124 (3.0)
UAE (mg/24 h), median (P25, P75)	10.6 (6.9, 22.3)	8.5 (5.9, 14.4)
UAE category, *n* (%)		
<10 mg/24 h	1967 (46.6)	2505 (59.5)
10–30 mg/24 h	1445 (34.2)	1252 (29.7)
>30 mg/24 h	812 (19.2)	452 (10.7)
UCE (mg/24 h), mean ± SD	14.4 ± 3.3	10.1 ± 2.3

Note: Continuous variables are presented as mean ± SD or as median (P25, P75). Categorical variables are presented as count (percentage).
Abbreviations: CVD, cardiovascular disease; RFM, relative fat mass; UAE, 24-h urinary albumin excretion; UCE, 24-h urinary creatinine excretion.

Statistical analyses

Normally distributed data are presented as mean (SD) and non-normally distributed data as median, Q1–Q3 (50th percentile, 25th–75th percentile). Categorical variables are represented as count (percentage).

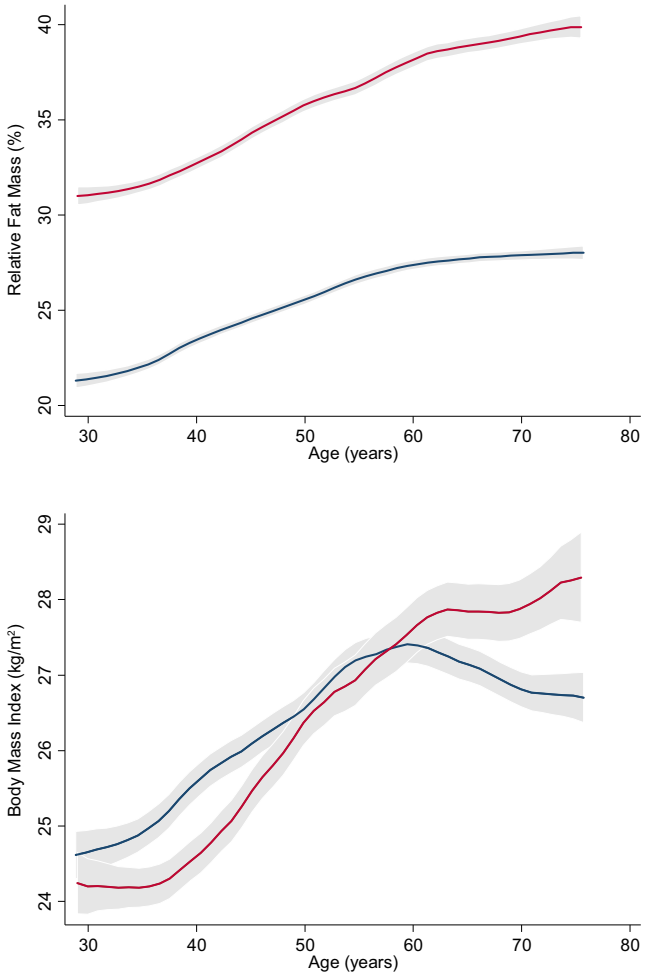

FIGURE 1 Sex-specific associations of relative fat mass and BMI with age using kernel-weighted local polynomial smoothing graphic modeling. Blue lines represent men, and red lines represent women; gray bands represent prediction intervals. [Color figure can be viewed at wileyonlinelibrary.com]

Cross-sectional analyses

Univariable associations of adiposity measures (RFM and BMI) and muscle mass (24-h UCE) [19] with age were graphically modeled using kernel-weighted local polynomial smoothing technique [24]. Age (and sex) adjusted associations of RFM and BMI with 24-h UCE were examined using linear regression models, and direct comparisons were made by bootstrapping the 95% confidence interval (CI) of the difference of the β coefficients. Age-adjusted associations of RFM and BMI with 24-h UCE in women and in men were also graphically modeled by means of regression analysis using a restricted cubic spline function to check for possible deviations from linearity [24].

Longitudinal analyses

In primary analyses, we examined associations of RFM and BMI with all-cause mortality using Cox regression models adjusting for age and sex, and thereafter additionally adjusting for 24-h UCE. To assess the best fitting functional form for adiposity measures and their associations with all-cause mortality, we also performed fractional polynomial regression analysis [23]. Additionally, we examined associations of RFM and BMI with all-cause mortality across tertiles of 24-h UCE. In secondary analyses, we examined associations of RFM and BMI with all-cause mortality using Cox regression models adjusting for age, sex, smoking status, prevalent diabetes, hypertension, cardiovascular disease, cancer, kidney dysfunction, and UAE, and thereafter additionally adjusting for 24-h UCE. In sensitivity analyses, we performed similar analyses after excluding individuals with chronic disease (i.e., history of heart failure, cancer, or kidney dysfunction; $n = 559$).

RFM, BMI, and UCE were standardized sex-specifically when used as continuous variables in linear and Cox regression models. Results were expressed as standardized beta (Sβ) or as hazard ratio (HR) with 95% CI based on robust standard error estimates. Statistical analyses were performed using STATA version 14 and R version 4.0.5.

RESULTS

Our study included 8433 community-dwelling adults from the PREVEND cohort. The mean age of the cohort was 49.8 ± 12.7 years, and 4209 (49.9%) were women. Participant characteristics are provided in Table 1. Mean RFM was 35.0% in women and 25.3% in men. Mean BMI was slightly lower in women than in men (25.9 kg/m^2 vs. 26.3 kg/m^2), and mean 24-h UCE, reflecting total muscle mass, was also lower in women than in men (10.1 mg/24 h vs. 14.4 mg/24 h).

Associations of RFM and BMI with age in women and in men are shown in Figure 1. In women, the shape of association of RFM with higher age was linear, and in men the shape was linear until around 60 years. The shape of association of BMI with higher age was also approximately linear in women, but BMI had an inverted-U relationship with age in men, with the peak of the curve around 60 years. Associations of 24-h UCE with age in men and in women are shown in Figure 2. In women, a steady inverse relationship between total muscle mass and increasing age was observed. In men, the inverse

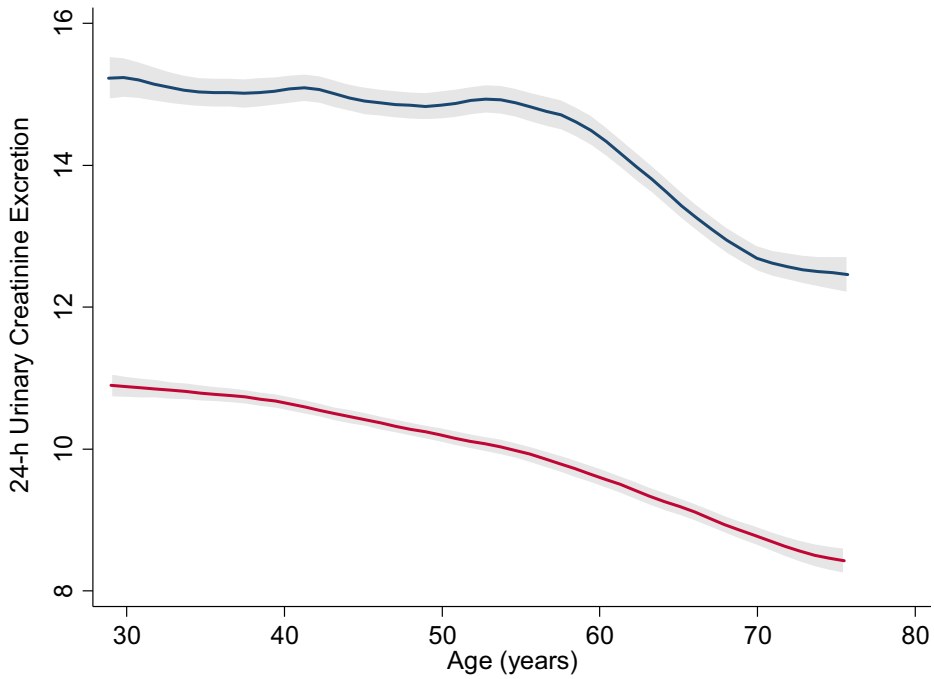

FIGURE 2 Sex-specific associations of 24-h urinary creatinine excretion, a marker of total muscle mass, with age using kernel-weighted local polynomial smoothing graphic modeling. Blue lines represent men, and red lines represent women; gray bands represent 95% prediction intervals. [Color figure can be viewed at wileyonlinelibrary.com]

relationship between age and muscle mass became apparent at around 60 years.

Associations of RFM and BMI with 24-h UCE in the total population after adjusting for age and sex are shown in Table 2 and Figure 3. Generally, associations of BMI with 24-h UCE were stronger than those of RFM with 24-h UCE (Sβ: 0.38 [0.36–0.40] vs. 0.29 [0.27–0.31]; $p_{difference} < 0.001$). Among sexes, both RFM and BMI were more strongly associated with 24-h UCE in men than in women (Table 2).

TABLE 2 Associations of RFM and BMI with 24-h urinary creatinine excretion

	RFM	BMI
	Sβ (95% CI)	Sβ (95% CI)
Total	0.29 (0.27–0.31)	0.38 (0.36–0.40)
Men	033 (0.29–0.36)	0.43 (0.40–0.45)
Women	0.26 (0.23–0.29)	0.34 (0.31–0.36)

Note: In linear regression models, RFM, BMI, and 24-h urinary creatinine excretion were standardized sex-specifically. While examining associations in the total population, models were adjusted for age and sex; in sex-specific analysis, models were adjusted only for age.
Abbreviations: RFM, relative fat mass; Sβ, standardized beta.

All-cause mortality

During a median follow-up of 18.4 years, 1640 individuals died (589 women and 1051 men). This corresponded to an incidence rate of 12.4 events per 1000 person-years in the total population (8.7 and 16.4 events per 1000 person-years in women and men, respectively). Participant characteristics according to mortality status during follow-up are provided in Table 3. In a multivariable model including all baseline characteristics (except RFM, BMI, and 24-h UCE), the following variables were significantly associated with all-cause mortality: age, male sex, smoking status, and presence of diabetes mellitus, hypertension, cardiovascular disease, cancer, kidney dysfunction, and albuminuria ($p_{all} < 0.001$) (Table S1). In both sexes 24-h UCE was inversely associated with all-cause mortality (Table S2).

In age- and sex-adjusted models, RFM was significantly associated with all-cause mortality in the total population (HR: 1.16; 95% CI: 1.09–1.24), whereas BMI was not (HR: 1.04; 95% CI: 0.99–1.10).

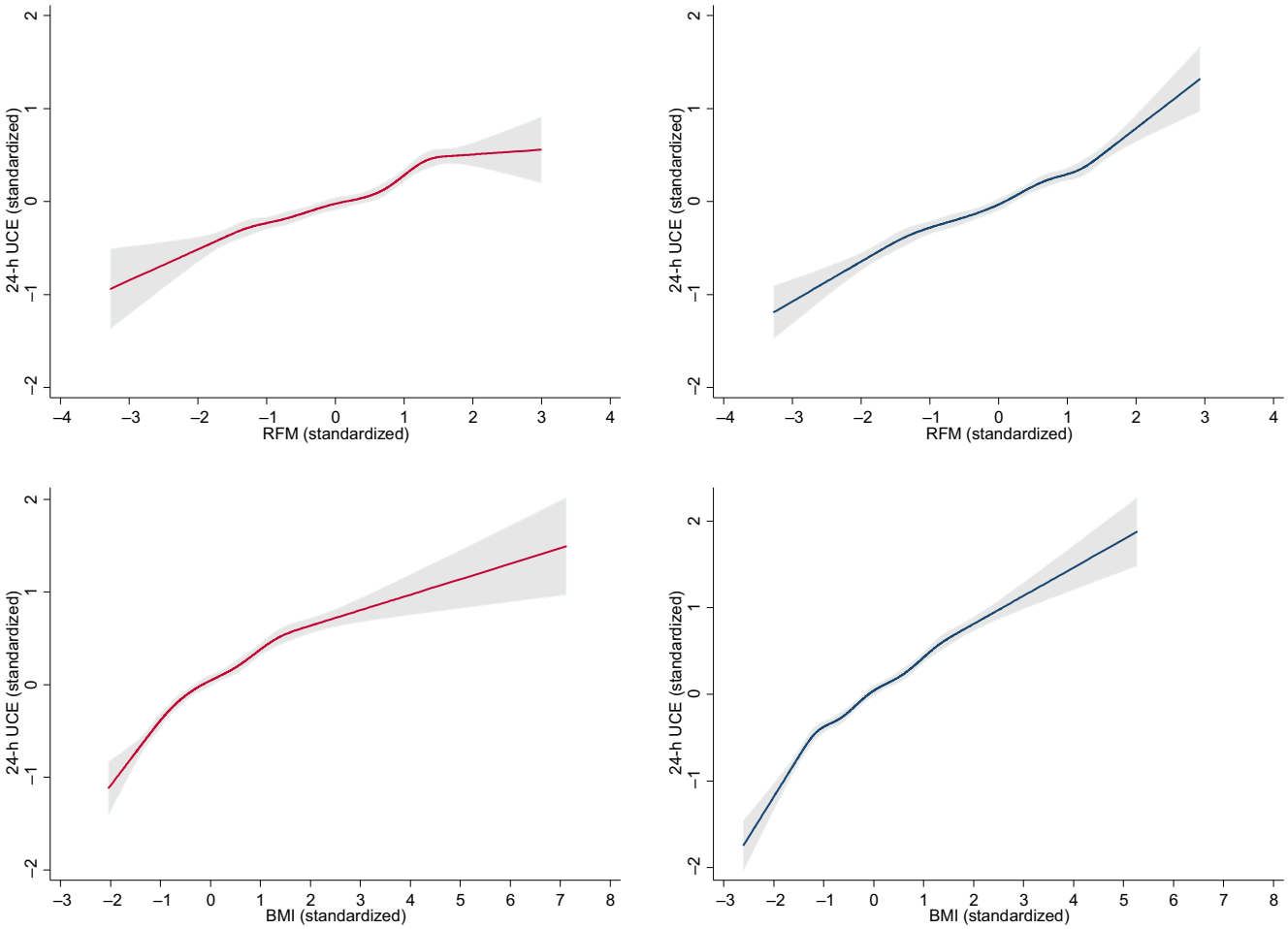

FIGURE 3 Age-adjusted associations of RFM and BMI with 24-h UCE, a marker of total muscle mass. Blue lines represent men, and red lines represent women; gray bands represent 95% prediction intervals. RFM, relative fat mass; UCE, urinary creatinine excretion. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Participant characteristics according to all-cause mortality status

	Men		Women	
	No ACM ($n = 3173$)	ACM ($n = 1051$)	No ACM ($n = 3620$)	ACM ($n = 589$)
RFM, mean ± SD	24.5 ± 4.7	27.6 ± 4.1	34.4 ± 6.1	38.7 ± 5.9
BMI, kg/m^2, mean ± SD	26.1 ± 3.6	27.0 ± 3.7	25.7 ± 4.6	27.6 ± 5.0
Age, y, mean ± SD	46.7 ± 11.0	63.9 ± 9.2	46.5 ± 11.1	61.8 ± 10.7
Height, cm, mean ± SD	180.1 ± 7.3	176.8 ± 7.1	167.2 ± 6.8	164.1 ± 6.7
Smoking category, *n* (%)				
Nonsmoker	922 (29.2)	126 (12.0)	1250 (34.6)	166 (28.4)
Current smoker	1067 (33.8)	397 (37.9)	1177 (32.6)	240 (41.0)
Stopped <1 y	115 (3.6)	28 (2.7)	160 (4.4)	16 (2.7)
Stopped >1 y	1056 (33.4)	497 (47.4)	1023 (28.3)	163 (27.9)
Diabetes, *n* (%)	69 (2.2)	112 (10.8)	74 (2.1)	59 (10.1)
Hypertension, *n* (%)	971 (30.8)	706 (67.6)	831 (23.0)	353 (59.9)
CVD, *n* (%)	167 (5.3)	257 (24.5)	141 (3.9)	77 (13.1)
Cancer, *n* (%)	54 (1.7)	99 (9.4)	87 (2.4)	31 (5.3)
Kidney dysfunction, *n* (%)	28 (0.9)	138 (13.2)	61 (1.7)	63 (10.8)
UAE (mg/24 h), median (P25, P75)	9.4 (6.6, 17.1)	18.9 (9.9, 49.2)	8.2 (5.8, 13.4)	11.3 (6.8, 26.4)
UAE category, *n* (%)				
<10 mg/24 h	1701 (53.6)	266 (25.3)	2241 (61.9)	264 (44.8)
10–30 mg/24 h	1048 (33.0)	397 (37.8)	1068 (29.5)	184 (31.2)
>30 mg/24 h	424 (13.4)	388 (36.9)	311 (8.6)	141 (23.9)
UCE (mg/24 h), mean ± SD	14.8 ± 3.2	13.3 ± 3.2	10.3 ± 2.2	9.1 ± 2.3

Note: Continuous variables are presented as mean ± SD or as median (P25, P75). Categorical variables are presented as count (percentage).
Abbreviation: ACM, all-cause mortality; CVD, cardiovascular disease; RFM, relative fat mass; UAE, 24-h urinary albumin excretion; UCE, 24-h urinary creatinine excretion.

When models were additionally adjusted for 24-h UCE, this resulted in stronger associations of both RFM and BMI with all-cause mortality (Tables 4 and 5). Sex did not significantly modify associations of both RFM and BMI with all-cause mortality ($p_{int} > 0.1$ for all). Potential non-linear associations of RFM and BMI with mortality risk were assessed using fractional polynomial regression analyses (Figure 4).

In multivariable-adjusted models, RFM was significantly associated with all-cause mortality in the total population (HR: 1.08; 95% CI: 1.01–1.15), whereas BMI was not (HR: 1.01; 95% CI: 0.95–1.06). When models were additionally adjusted for 24-h UCE, this resulted in stronger associations of both RFM and BMI with all-cause mortality (Table 5). Sex did not significantly modify associations of both RFM and BMI with all-cause mortality in the total population, and in sex-specific analyses, the effect size of RFM was larger than that of BMI, particularly in women (HR: 1.24, 95% CI: 1.12–1.38 vs. HR: 1.12, 95% CI: 1.03–1.23) (Table 5).

Sensitivity analysis

Results were broadly similar when we performed the analyses after excluding individuals with chronic disease (Table S3).

As exploratory analyses, we examined participant characteristics as well as associations of RFM and BMI with all-cause mortality across sex-pooled tertiles of 24-h UCE (Tables S4 and S5).

DISCUSSION

The key findings of our study are as follows: (i) RFM was less strongly associated with total muscle mass than BMI; (ii) a higher RFM was significantly associated with mortality risk whereas a higher BMI was not; and (iii) adjusting for total muscle mass strengthened associations of both RFM and BMI with all-cause mortality.

RFM is a newly developed marker of adiposity that better predicted whole-body fat percentage measured by dual-energy X-ray absorptiometry than BMI [17]. It is a composite parameter derived from height and WC, and it is designed to roughly reflect sex-specific differences in body fat percentages. For instance, mean RFM values are around 35% in women and 25% in men in the PREVEND cohort, and around 40% in women and 28% in men in the National Health and Nutrition Examination Survey (NHANES) cohort [25]. This is indeed more reflective of physiology as women generally have a higher percentage of body fat than men.

In the current study, we found that RFM was approximately linearly associated with increasing age in both sexes, suggesting that body fat increases with increasing age in both women and men. Interestingly, we observed that, while BMI was positively associated with increasing age in women, it had an "inverted U-shaped" relationship with increasing age in men. This could potentially be because associations of BMI with muscle mass are stronger than those of RFM with muscle mass,

TABLE 4 Age and sex-adjusted associations of RFM and BMI with all-cause mortality

	Age + sex		Age + sex + 24-h UCE	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Total population				
RFM	1.16 (1.09–1.24)	<0.001	1.24 (1.16–1.32)	<0.001
BMI	1.04 (0.99–1.10)	0.111	1.12 (1.06–1.19)	<0.001
Men				
RFM	1.15 (1.06–1.24)	<0.001	1.23 (1.13–1.33)	<0.001
BMI	1.05 (0.99–1.12)	0.130	1.14 (1.07–1.23)	<0.001
Women				
RFM	1.20 (1.09–1.33)	<0.001	1.28 (1.15–1.42)	<0.001
BMI	1.04 (0.96–1.14)	0.336	1.11 (1.02–1.21)	0.021

Note: RFM and BMI were standardized sex-specifically.
Abbreviations: HR, hazard ratio per unit change in standardized RFM and BMI; RFM, relative fat mass; UCE, urinary creatinine excretion.

TABLE 5 Multivariable-adjusted associations of RFM and BMI with all-cause mortality

	Multivariable model		Multivariable model + 24-h UCE	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Total population				
RFM	1.08 (1.01–1.15)	0.018	1.14 (1.07–1.22)	<0.001
BMI	1.01 (0.95–1.06)	0.770	1.08 (1.02–1.15)	0.010
Men				
RFM	1.04 (0.96–1.14)	0.281	1.10 (1.01–1.19)	0.036
BMI	1.00 (0.93–1.07)	0.975	1.07 (0.99–1.15)	0.107
Women				
RFM	1.15 (1.04–1.28)	0.007	1.24 (1.12–1.38)	<0.001
BMI	1.04 (0.95–1.13)	0.388	1.12 (1.02–1.23)	0.014

Note: Multivariable models were adjusted for age, sex, smoking, diabetes mellitus, hypertension, history of cardiovascular disease, cancer, kidney dysfunction, and albumin categories. RFM and BMI were standardized sex-specifically.
Abbreviations: HR, hazard ratio per unit change in standardized RFM and BMI; RFM, relative fat mass; UCE, urinary creatinine excretion.

and with increasing age, men tend to lose muscle at a more rapid rate than they gain fat. This assertion is further strengthened by the observation that BMI was indeed more strongly associated with 24-h UCE (i.e., muscle mass) than RFM (Table 2) and that muscle mass declined more rapidly after age 60 years in men (Figure 2).

Previous studies examining associations of obesity (using BMI) with all-cause mortality have reported on the "obesity survival paradox," that is, individuals with moderate obesity are not at an increased risk of dying compared to their counterparts without obesity, and individuals with mild obesity or those with overweight may even have a survival benefit [10, 13]. Such a phenomenon does not seem to be limited to the general population but has also been observed among heart failure [26], cancer [27], and other patient populations [28, 29].

In the current study, we show that the associations between excessive fat mass and all-cause mortality were present when RFM was used as a marker of adiposity, but it was absent when BMI was used as a marker of adiposity. This reinforces the view that the obesity survival paradox may, indeed, arise to a certain extent due to the usage of BMI as a marker of adiposity [30]. Indeed, a recent study conducted on patients with heart failure illustrated that anthropometric indices that did not incorporate "body weight" in the equation showed less evidence for the obesity survival paradox [31]. The most likely explanation for the paradoxical associations of BMI with all-cause mortality, after also taking into consideration the results from our study, would be that BMI not only relates less strongly with fat mass but also relates more strongly with muscle mass.

Another key finding from the current study was that, after accounting for muscle mass, the magnitude of associations of both BMI and RFM with all-cause mortality increased. Similar observations were reported in a study conducted by Abramowitz et al. on 11,687 US adults, in which muscle mass was assessed using the dual-energy X-ray absorptiometry technique [32]. Together, these data suggest that, while using anthropometric indices of adiposity to examine associations of fat mass with all-cause mortality, it may be essential to additionally adjust for muscle mass before interpreting the results.

This study had some limitations. First, although RFM predicts fat mass more accurately than BMI, it does not distinguish visceral fat from subcutaneous fat. More accurate quantification of fat compartments is possible using imaging methods such as computerized tomography (CT) or magnetic resonance imaging [33]; however, their applicability in large population-based cohorts is generally limited. Second, 24-h UCE is known to be a strong predictor of muscle mass, not only in healthy individuals but also in individuals with kidney disease [34]. Studies have suggested that there is a good correlation between 24-h UCE and CT-measured skeletal muscle mass [35], and in some cases 24-h UCE may even be a better predictor of muscle mass than imaging-based estimation. This is because 24-h UCE reflects metabolically active muscle mass and is not confounded by intramuscular fat accumulation or water content [36, 37]. However, we acknowledge that meat consumption could affect the creatinine-muscle mass equivalence [38]; because dietary data were not available for the current study, this should be considered a limitation. Third, the PREVEND study, by design, enrolled a higher proportion of individuals with mildly elevated UAE [20]. For interpretation of results, this may not be consequential because previous studies have shown that results from the PREVEND study are comparable to the results from general population cohorts such as LifeLines [39] and the Framingham Heart Study [40]. Fourth, our study was conducted on a predominantly White population from the northern Netherlands, limiting generalizability to other population groups and ethnicities. Finally, this is an observational study, and it cannot be established that the associations identified represent cause-and-effect relationships.

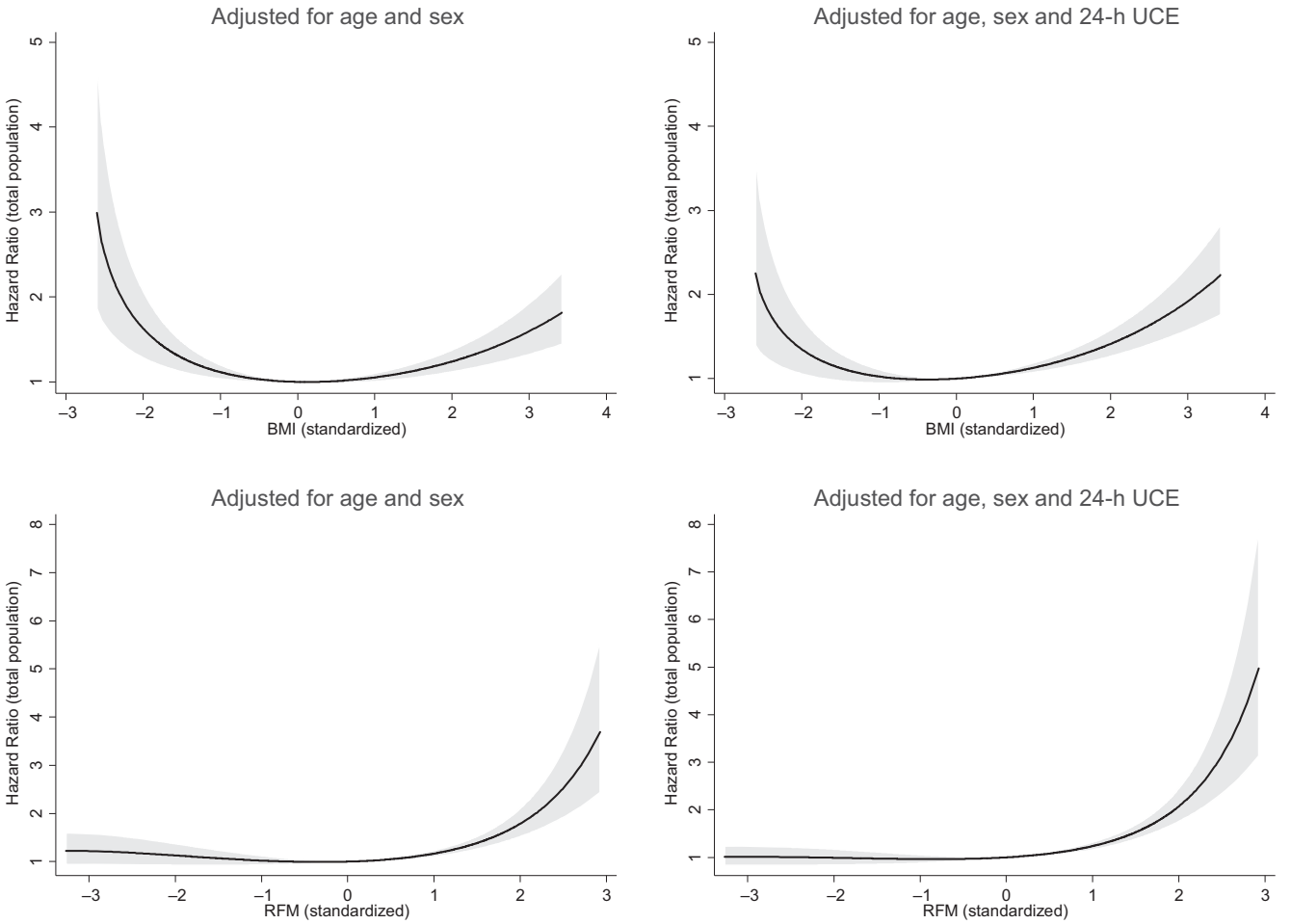

FIGURE 4 Fractional polynomial modeling of associations of RFM and BMI with all-cause mortality in the total population. Black lines represent hazard ratios; gray bands represent 95% prediction intervals. RMF, relative fat mass; UCE, urinary creatinine excretion.

CONCLUSION

In the general population, a higher RFM was associated with mortality risk, whereas a higher BMI was not. Additional adjustment for muscle mass strengthened associations of both RFM and BMI with all-cause mortality. These results highlight the superiority of RFM and the inadequacy of BMI in estimation of mortality risk in the general population, and they suggest that, while using anthropometric indices to examine associations of fat mass with mortality risk, it may be essential to account for muscle mass before interpreting the results.O

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

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

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