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ORIGINAL RESEARCH

Sex Differences in the Association of Body Composition and Cardiovascular Mortality

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BACKGROUND: To determine whether differences in body composition contribute to sex differences in cardiovascular disease (CVD) mortality, we investigated the relationship between components of body composition and CVD mortality in healthy men and women.

METHODS AND RESULTS: Dual energy x-ray absorptiometry body composition data from the National Health and Nutrition Examination Survey 1999–2004 and CVD mortality data from the National Health and Nutrition Examination Survey 1999–2014 were evaluated in 11 463 individuals 20 years of age and older. Individuals were divided into 4 body composition groups (low muscle mass–low fat mass—the referent; low muscle–high fat; high muscle–low fat, and high muscle–high fat), and adjusted competing risks analyses were performed for CVD versus non-CVD mortality. In women, high muscle/high fat mass was associated with a significantly lower adjusted CVD mortality rate (hazard ratio [HR], 0.58; 95% CI, 0.39–0.86; P=0.01), but high muscle/low fat mass was not. In men, both high muscle–high fat (HR, 0.74; 95% CI, 0.53–1.04; P=0.08) and high muscle–low fat mass (HR, 0.40; 95% CI, 0.21–0.77; P=0.01) were associated with lower CVD. Further, in adjusted competing risks analyses stratified by sex, the CVD rate in women tends to significantly decrease as normalized total fat increase (total fat fourth quartile: HR, 0.56; 95% CI, 0.34–0.94; P<0.03), whereas this is not noted in men.

CONCLUSIONS: Higher muscle mass is associated with lower CVD and mortality in men and women. However, in women, high fat, regardless of muscle mass level, appears to be associated with lower CVD mortality risk. This finding highlights the importance of muscle mass in healthy men and women for CVD risk prevention, while suggesting sexual dimorphism with respect to the CVD risk associated with fat mass.

Key Words: adipose tissue ■ cardiovascular events ■ muscle ■ women

According to the American Heart Association, in 2013 there were 5 million myocardial infarctions (MIs) in men and 3 million MIs in women.[1] Unfortunately, despite suffering fewer MIs, women suffered an equivalent number of cardiovascular deaths, and similarly, the reduction in cardiovascular disease (CVD) mortality that has occurred in both sexes over the past 50 years is occurring at a slower rate in women as compared with men. Even more worrying is the fact that the MI rate appears to be increasing in women between the ages of 35 and 54.[2–4] A recent study found that women, compared with men, have significantly higher levels of cardiometabolic biomarkers associated with adiposity and adverse cardiovascular risk.[5] There are many physiologic differences between men and women, and it is possible that sex differences in body composition also play a significant role in the sexual dimorphism of CVD mortality.

We have previously noted that in a group of patients with CVD, the subgroup of individuals with high muscle and low fat mass had the lowest mortality risk compared with other body composition subtypes.[6] Because of known sex differences in CVD risk[3,5] and body composition,[7] we hypothesized that the relative

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CLINICAL PERSPECTIVE

What Is New?

- Cardiovascular disease risk is decreased by high muscle mass in men and women, but in women cardiovascular disease risk is also decreased by high fat regardless of the muscle mass level.

What Are the Clinical Implications?

- This unique finding emphasizes the importance of public health messages to increase activity and to improve muscle mass rather than focus on weight loss.

Nonstandard Abbreviations and Acronyms

BAT	brown adipose tissue
FMI	total body fat mass index
MMI	total body muscle mass index
NHANES	National Health and Nutrition Examination Survey

CVD mortality import of fat and muscle mass may be different in women compared with men in a population of healthy individuals. To investigate this hypothesis, we used body composition data derived from dual energy x-ray absorptiometry (DXA), performed as a part of the National Health and Nutrition Examination Survey (NHANES). Understanding sex differences in the components of body composition, and their CVD mortality implications, is of vital importance in developing sex-appropriate guidelines with respect to exercise and nutrition as preventative strategies against the development of CVD.

METHODS

All data and materials pertaining to our study are publicly available from the Centers for Disease Control and Prevention/National Center for Health Statistics and can be accessed at https://wwwn.cdc.gov/nchs/nhanes/ Since 2003, the National Center for Health Statistics Research Ethics Review Board approval and documented consent was obtained from all participants.

Cohort

We used DXA data from the NHANES 1999–2004, linked to mortality data from 1999 to 2014. NHANES uses a stratified, multistage, probability cluster design[8] to evaluate the general, noninstitutionalized population of the United States. DXA body composition data from 3 NHANES survey cycles (1999–2000, 2001–2002, and 2003–2004) were used for this analysis.

Our analysis includes 11 463 individuals >20 years of age with complete DXA body composition data.

Measurements of Body Composition

Whole-Body DXA Data

Whole-body DXA exams were obtained from a QDR 4500A fan beam densitometer following procedures recommended by the manufacturer (Hologic, Inc., Bedford, MA). A detailed description of the raw DXA body composition data are provided on the NHANES website.[9] Regional and full-body DXA results were set to missing if the exams contained artifacts that could affect the accuracy of the DXA results, such as prosthetic devices, implants, or other extraneous objects. The precision of the DXA instrument used in the NHANES study has been reported previously.[10–12]

The NHANES data sets contained whole-body DXA measurements of fat mass (grams) and muscle mass (grams) for each subject. The main index of adiposity used for this study was total body fat mass index (FMI; total body fat mass/height^2), and the main index of muscle mass used for this study was total body muscle mass index (MMI; total body muscle mass/height^2). Four body composition phenotypes, representing possible combinations of muscle and fat mass (using the sex-specific medians of FMI and MMI) were created:

Low muscle–low fat mass: MMI < median and FMI < median.
Low muscle–high fat mass: MMI < median and FMI ≥ median.
High muscle–low fat mass: MMI ≥ median and FMI < median.
High muscle–high fat mass: MMI ≥ median and FMI ≥ median.

In trying to understand the effect of total fat on cardiovascular risk, we assessed the effect of 2 important adipose tissue depots. Trunk fat includes both subcutaneous and visceral fat in the abdomen, which has been associated with both metabolic syndrome and cardiovascular risk. However, it has been shown that trunk fat estimated by DXA has greater correlation with total abdominal fat than visceral fat.[13,14] On the other hand, gluteofemoral fat is associated with a protective lipid and glucose profile and decrease in cardiovascular and metabolic risk.[15–17] To understand sex differences in the relative effects of trunk and leg fat on cardiovascular risk, we performed analyses stratified by sex and examined the cardiovascular risk associated with a primary predictor of quartiles of either total fat, leg fat, or trunk fat quartiles.

Outcomes

NHANES 1999–2004 participants were assessed for cardiovascular mortality from the National Health Interview Survey through December 31, 2014, by the National Center for Health Statistics Research Data Center. The National Center for Health Statistics has linked the NHANES 1999–2014 with death certificate records from the National Death Index. Because of confidentiality protections, the public-use files (which we used) include only a limited set of mortality variables. Synthetic data were substituted for the actual date and underlying cause-of-death data for selected decedent records. The file was also limited to include only the top 9 leading underlying causes of death based on "Deaths: Leading Causes for 2015," in which the top 2 causes, diseases of heart (heart disease) and malignant neoplasms (cancer), accounted for 45.3% of all deaths in 2015. Heart disease included acute/chronic rheumatic fever and heart diseases; hypertensive heart disease; ischemic heart disease; acute/subacute endocarditis; diseases of the pericardium and acute myocarditis; heart failure; atherosclerosis; aortic aneurysm and dissection; and diseases of arteries, arterioles, and capillaries. We evaluated the relation between body composition and the CVD mortality rate and risk using a competing risk model since there was substantial non-CVD mortality. We used a survey-weighted version of the model by Fine and Gray.[18]

Covariates

A full description of covariates is available on the NHANES website.[9] Age, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, and other [includes individuals not identifying as Hispanic, Black or White, such as Asian or mixed race individuals]), sex and smoking status (current, past, never) were determined from questionnaires. Diabetes mellitus was defined by the presence of ≥1 of the following 3 conditions: (1) glycosylated hemoglobin ≥6.5%,[19] (2) fasting glucose ≥7 mmol/L (126 mg/dL), or (3) self-report. Menopause was defined as cessation of menses for ≥12 months (the question used was, "Have you had at least 1 menstrual period in the past 12 months excluding vaginal blood loss caused by medical conditions, hormone therapy, or surgeries?"). The question used to determine use of hormone replacement therapy was, "Have you ever used female hormones such as estrogen and progesterone? Please include any forms of female hormones, such as pills, cream, patch, and injectable, but do not include birth control methods or use for infertility." Thus, the covariate menopause was constructed as a 3-level variable with response to either no menopause, menopause without hormone replacement therapy, or menopause with hormone replacement therapy. Cancer status was ascertained from a question regarding diagnosis of cancer of any organ other than squamous cell skin cancer (history of nonsquamous cancer diagnosis [yes/no]).

Statistical Analysis

Descriptive statistics (mean, SD, and percentage) were computed for the 4 body composition phenotypes for the N=5627 female and for the N=5836 male participants >20 years of age (Table 1). Missing DXA data, attributable to no scan or an invalid scan, were not missing completely at random but were more frequently missing with greater age, body mass index, weight, and height. Therefore, carrying out analyses excluding those with missing values could lead to biased estimates. For this reason, missing DXA data were imputed by the National Center for Health Statistics using multiple-imputation methodology.[9] Multiple imputation was done before data were made publicly available for analysis. However, it was estimated that of the 21 230 eligible DXA participants ≥8 years of age who participated in the Mobile Exam Center examinations in 1999 to 2004, scans with 100% nonmissing data were obtained from 16 973 (80.0%) participants. Five versions of imputed values were generated randomly and independently, resulting in 5 complete data sets of measured and imputed values. We carried out analyses involving DXA data in each of the 5 data sets separately and combined the results according to Rubin's rules.[20] Thus, standard errors and *P* values reflect both within–data set and between–data set variations.

Unadjusted plots of CVD mortality incidence versus follow-up time by body composition group were computed in women and men separately using the methods of Gray for competing risk outcomes (CVD mortality versus non-CVD mortality) and accounting for sampling weights.[18]

The relation between the CVD mortality rate versus body composition group, both unadjusted and adjusted for covariates, was assessed using the Fine–Gray competing risk model, accounting for survey weights.[18] The hazard ratios (HRs) and their corresponding 95% CIs and *P* values are reported. Three different models were fit in women and in men: Model 1 adjusts for age, ethnicity, smoking history (yes/no), and history of nonsquamous cancer diagnosis (yes/no). Model 2, in women only, additionally included menopause (no menopause, menopause without hormone replacement therapy, menopause with hormone replacement therapy). Model 3 additionally included serum high-density lipoprotein (mg/dL), serum total cholesterol (mg/dL), hypertension (yes/no) diagnosis of diabetes mellitus (yes/no/

Table 1. Complete Study Population Demographics

Variable	High Muscle–High Fat (N=3927)	High Muscle–Low Fat (N=1691)	Low Muscle–High Fat (N=1741)	Low Muscle–Low Fat (N=4104)	*P* Value
Age, y, n (%)					<0.001
<50	1993 (50.8)	1222 (72.3)	371 (21.3)	2003 (48.8)	
50–59	626 (15.9)	186 (11)	245 (14.1)	512 (12.5)	
60–64	430 (10.9)	106 (6.3)	225 (12.9)	308 (7.5)	
≥65	878 (22.4)	177 (10.5)	900 (51.7)	1281 (31.2)	
Sex, n (%)					<0.001
Female	2065 (52.6)	704 (41.6)	733 (42.1)	2125 (51.8)	
Male	1862 (47.4)	987 (58.4)	1008 (57.9)	1979 (48.2)	
Race/ethnicity, n (%)					<0.001
White	1849 (47.1)	708 (41.9)	994 (57.1)	2335 (56.9)	
Black	967 (24.6)	597 (35.3)	101 (5.8)	482 (11.7)	
Hispanic	1015 (25.8)	325 (19.2)	602 (34.6)	1095 (26.7)	
Other*	96 (2.4)	61 (3.6)	44 (2.5)	192 (4.7)	
Diabetes mellitus, n (%)					<0.001
No	3333 (84.9)	1571 (92.9)	1448 (83.2)	3781 (92.2)	
Borderline	79 (2)	18 (1.1)	35 (2)	39 (1)	
Yes	514 (13.1)	102 (6)	258 (14.8)	282 (6.9)	
Cancer, n (%)					<0.001
No	3697 (94.1)	1627 (96.2)	1563 (89.8)	3803 (92.7)	
Yes	230 (5.9)	64 (3.8)	178 (10.2)	301 (7.3)	
Smoking status, n (%)					<0.001
No	2028 (51.6)	907 (53.6)	802 (46.1)	1970 (48)	
Unknown	3 (0.1)	4 (0.2)	3 (0.2)	4 (0.1)	
Yes	1896 (48.3)	780 (46.1)	936 (53.8)	2130 (51.9)	
Trunk fat–leg fat ratio	1.6 (1.3–1.9)	1.3 (1.1–1.7)	1.7 (1.4–2.1)	1.3 (1.1–1.7)	<0.001
Systolic blood pressure	125 (115–138)	118 (110–130)	131 (118–147)	121 (109–136)	<0.001
High-density lipoprotein	45 (38–55)	51 (42–61)	47 (40–58)	55 (45–67)	<0.001
Total cholesterol	203 (178–231)	193 (168–222)	206 (182–234)	198 (174–225)	<0.001
C-reactive protein	0.3 (0.2–0.7)	0.1 (0–0.3)	0.3 (0.1–0.6)	0.1 (0.1–0.3)	<0.001
Serum creatinine	131 (80–188)	138 (79–203)	104 (62–153)	102 (55–161)	<0.001
CVD mortality, n (%)	187 (4.8)	40 (2.4)	169 (9.7)	274 (6.7)	
Non-CVD mortality, n (%)	532 (13.5)	136 (8.0)	506 (29.1)	780 (19.0)	<0.001
Assumed alive, n (%)	3208 (81.7)	1515 (89.6)	1066 (61.2)	3050 (74.3)	
Body mass index, %					
<25	0	27.2	3.6	76.7	<0.001
25–30	20.6	70.2	75.0	23.3	
>30	79.4	2.5	21.4	0	

Number ranges in parentheses indicate upper and lower 95 percentile levels. CVD indicates cardiovascular disease.
*Other includes individuals not identifying as Hispanic, Black or White, such as Asian or mixed race individuals.

borderline), and (log scale) C-reactive protein. Further, to determine whether the association between CVD mortality and body composition is different in older versus younger age groups, we assessed the significance of an age by body composition interaction term in model 3.

To understand the effect of different fat depots on cardiovascular mortality, competing risk models were also used to assess the association between the CVD mortality rate versus quartiles of either total, leg, or trunk standardized fat mass, stratified by sex and adjusted by the covariates in model 3 above.

The survey weights were computed using the weights and clustering provided by the NHANES survey. These weights are accounted for in all models and CVD mortality incidence estimates to make the results representative of the US population.

Results were computed using SAS 9.4 (SAS Inc., Cary, NC) and R 3.5.2 (R Project for Statistical Computing, www.r-project.org).

RESULTS

The total study cohort included 11 463 individuals >20 years of age (N=5627 women and N=5836 men). Table 1 shows the baseline characteristics. Significant differences were seen between demographic features in the 4 body composition phenotypes by age. Individuals <50 years of age were more likely to be in one of the high-muscle-mass groups, whereas individuals >65 years of age were more likely to be in the low-muscle–high-fat group. Differences were also seen by race/ethnicity, with a predominance of non-Hispanic Black individuals in the high-muscle groups. Regarding diabetes mellitus diagnosis, >10% of individuals with high fat mass—regardless of muscle mass level—had a diagnosis of diabetes mellitus. Current smokers were equally distributed in all body composition groups; a higher amount of trunk fat relative to thigh fat is present in individuals in the high-fat groups; systolic blood pressure, cholesterol levels, and C-reactive protein were highest in individuals with high fat mass. Median follow-up time in men was 157 months, and median follow-up time in women was 160 months.

Unadjusted plots of CVD mortality incidence over time by body composition group differ by sex. In women >20 years of age, those in the higher-muscle-mass groups had lower mortality compared with those in the low-muscle-mass groups, independent of fat mass (Figure [A]). In men, the lowest cardiovascular mortality was in the higher-muscle-mass–low-fat group. The higher-muscle-mass–higher-fat and lower-muscle-mass–low-fat groups both had similar intermediate cardiovascular mortality, and the lower-muscle-mass–high-fat group had the highest cardiovascular mortality (Figure [B]).

Four multivariate models were constructed for the outcome of cardiovascular mortality (for women (Table 2, Figure S1) and for men (Table 3). In all models, individuals with low muscle–low fat mass were the referent group. In women, model 1 demonstrated only nonsignificant trends toward lower cardiovascular mortality rate in groups having high fat and either high muscle (HR, 0.76; 95% CI, 0.53–1.08; *P*=0.13) or low muscle (HR, 0.69; 95% CI, 0.44–1.08; *P*=0.11). In men, model 1 demonstrated that having high muscle mass and low fat mass (HR, 0.42; 95% CI, 0.22–0.80; *P*=0.01) was associated with lower mortality. Further adjustments for menopausal status and use of hormone replacement therapy were made, for women, in model 2. After this adjustment in women, there was still only nonsignificant trends toward lower cardiovascular mortality rate in groups having high fat and either high muscle (HR, 0.72; 95% CI, 0.50–1.03; *P*=0.07) or low muscle (HR, 0.66; 95% CI, 0.42–1.05; *P*=0.08). Following further adjustment for other cardiovascular risk factors (high-density lipoprotein, total cholesterol, hypertension, and diabetes mellitus) in model 3, the high-fat-mass phenotypes were significantly associated with reduced cardiovascular mortality in women with high muscle mass (HR, 0.58; 95% CI, 0.39–0.86; *P*=0.01) and low muscle mass (HR, 0.59; 95% CI, 0.37–0.94; *P*=0.03). In men, the high-muscle–low-fat-mass phenotype (HR, 0.40; 95% CI, 0.21–0.77; *P*=0.01) was significantly associated with lower cardiovascular mortality, while the high-muscle–high-fat-mass phenotype (HR, 0.74; 95% CI, 0.53–1.04; *P*=0.08) showed a nonsignificant trend to association with lower cardiovascular mortality. In model 3, we assessed the significance of an age by body composition interaction in those <60 years of age versus ≥60 years of age. In men, the HR is not significantly different in those <60 years of age versus ≥60 years of age, with an overall *P* value of 0.376. In women, there was no significant age with body composition interaction for group 1 (*P*=0.181) or group 2 (*P*=0.377), but there was a significant interaction for group 3 (*P*=0.005).We previously reported an HR=0.580 in group 3, and we noted that this appeared to be the “average” of HR=0.690 in younger subjects (<60 years of age) with HR=0.476 in older subjects (≥60 years of age). Thus, in women, high muscle–high fat is more protective in older subjects than in younger subjects.

Following stratification by sex, cardiovascular mortality in quartiles of total, trunk, and leg fat was assessed, with adjustment for all covariates of model 3 (Table 4.). Women, but not men, had significant negative association between increasing quartiles of total fat and cardiovascular mortality (HR, 0.55; 95% CI, 0.34–0.87; *P*=0.01; and HR, 0.56; 95% CI, 0.34–0.94; *P*=0.03 in the third and fourth quartiles, respectively) and by comparison in men (HR, 0.91; 95% CI, 0.59–1.40; *P*=0.67; and HR, 0.80; 95% CI, 0.51–1.33; *P*=0.30 in the third and fourth quartiles, respectively.) In women, similar significant negative associations were noted between cardiovascular risk and increasing quartiles of leg fat (HR, 0.42; 95% CI, 0.27–0.66; *P*=0.0002 in the third quartile; and HR, 0.64; 95% CI, 0.41–0.98; *P*=0.04 in the fourth quartile) and trunk fat (HR, 0.59; 95 CI, 0.36–0.97; *P*=0.04 in the third quartile; and HR, 0.53; 95% CI, 0.32–0.90; *P*=0.02 in the fourth quartile). In men, the cardiovascular death rate did not significantly decrease with increasing quartiles of total, leg, and trunk fat.

DISCUSSION

We determined, in this study, that while the association between a higher muscle mass and a lower cardiovascular risk rate is seen in healthy men and women, sex differences exist with respect to the association between fat mass and cardiovascular risk. These findings

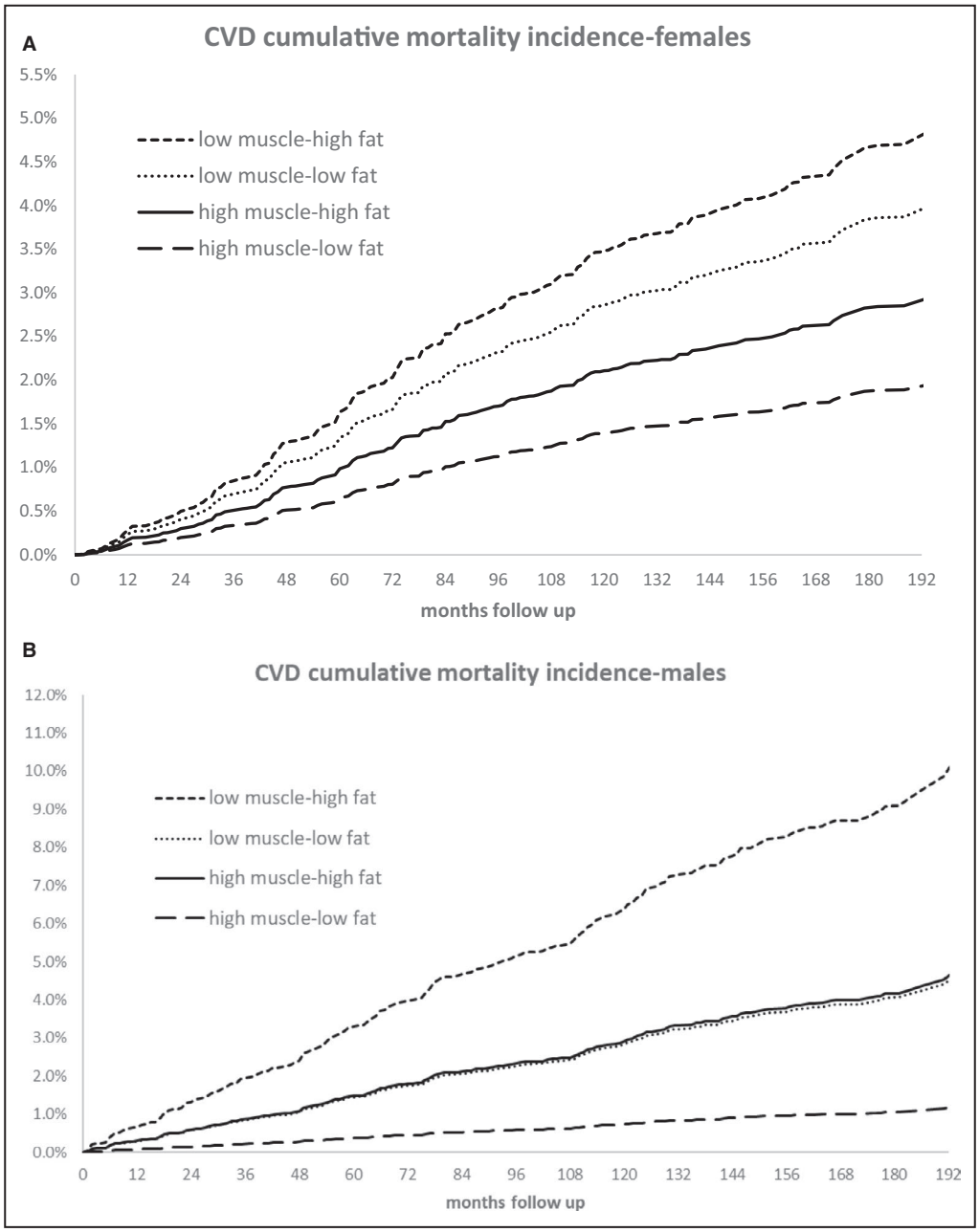

Figure. Unadjusted plots of CVD mortality incidence over time by body composition group in women and men.

A, Unadjusted plot of CVD cumulative mortality incidence in women with low muscle–high fat, low muscle–low fat, high muscle–high fat, or high muscle–low fat. Overall $P<0.001$. **B**, Unadjusted plot of CVD cumulative mortality incidence in men with low muscle–high fat, low muscle–low fat, high muscle–high fat, or high muscle–low fat. Overall $P=0.009$. CVD indicates cardiovascular disease.

will help elucidate the role of body composition as a potential causative factor in the sex differences in cardiovascular mortality.[2] Modifiable cardiovascular risk factors and their differential effects in women versus men must be better understood; thus, our study is of significance because it is the first to evaluate the effect on cardiovascular mortality of specific components of body composition in healthy individuals using data from DXA scanning, given that DXA scans are considered to be the "gold standard" for assessment of body composition.[21]

Sex differences in CVD have been well documented, and in fact it has been noted that compared with men, women have higher rates of mortality from MI, and are more likely to be younger and present with risk factors that are not as well controlled.[22–24] It is possible

Table 2. Adjusted Competing Risks Model for CVD Mortality Outcome With Women >20 Years of Age From the NHANES Population

Variable	Model 1–4 Covariates				Model 2 With Menopause-5 Covariates				Model 3–10 Covariates			
	HR	Lower	Upper	*P* Value	HR	Lower	Upper	*P* Value	HR	Lower	Upper	*P* Value
Body composition												
Low muscle–low fat	1.00*				1.00*				1.00*			
Low muscle–high fat	0.688	0.437	1.084	0.107	0.664	0.422	1.046	0.078	0.589	0.370	0.938	0.026
High muscle–low fat	0.870	0.473	1.601	0.655	0.874	0.471	1.621	0.669	0.834	0.445	1.562	0.571
High muscle–high fat	0.755	0.527	1.083	0.127	0.718	0.501	1.028	0.071	0.580	0.392	0.859	0.007
Age ≥60 y	18.06	11.70	27.89	0.000	14.46	8.23	25.44	0.000	11.05	6.19	19.73	0.000
Smoking history (yes vs no)	0.950	0.699	1.289	0.740	0.957	0.704	1.300	0.777	0.950	0.695	1.299	0.749
Race/ethnicity												
White	1.00*				1.00*				1.00*			
Hispanic	1.032	0.588	1.811	0.913	0.891	0.508	1.565	0.689	0.839	0.485	1.451	0.530
Black	1.683	1.052	2.693	0.030	1.453	0.899	2.348	0.127	1.128	0.678	1.875	0.643
Other‡	0.518	0.171	1.574	0.246	0.462	0.153	1.394	0.170	0.367	0.120	1.124	0.079
Cancer history (nonsquamous cell)	1.597	1.080	2.363	0.019	1.534	1.029	2.287	0.036	1.446	0.965	2.165	0.074
Menopause with HRT					1.130	0.462	2.766	0.788	1.004	0.409	2.462	0.993
Menopause without HRT					2.269	0.972	5.292	0.058	1.970	0.839	4.626	0.120
Menopause status unknown					1.127	0.313	4.060	0.855	1.005	0.275	3.671	0.995
HDL-per unit									1.001	0.993	1.009	0.852
Total cholesterol-per unit									1.003	0.999	1.007	0.177
Log 10 CRP									See curve-not constant†			0.012
Log 10 CRP squared									See curve-not constant†			0.008
Hypertension (yes vs no)									1.745	1.215	2.506	0.003
Diabetes mellitus—borderline (vs none)									1.301	0.459	3.691	0.621
Diabetes mellitus (vs none)									2.098	1.448	3.041	0.000

n=5621 of 5627, 271 CVD deaths, 867 non-CVD deaths. Lower=lower 95% CI; upper=upper 95% CI. CRP indicates C-reactive protein; CVD, cardiovascular disease; HR, hazard ratio, and NHANES, National Health and Nutrition Examination Survey.

*Referent group.

†Log CRP/Log CRP ^2 is not constant as the effect of CRP on CVD mortality is *not* linear on either the original or log scale plot. The plot of CRP vs CVD mortality is included in Figure S1.

‡Other includes individuals not identifying as Hispanic, Black or White, such as Asian or mixed race individuals.

that sex differences in levels of lean body mass and fat mass also play a significant role in the sexual dimorphism of CVD mortality.

The protective effect of increased lean body mass (measured with imaging and functional methodologies) on CVD risk has been noted in several studies. Low muscle mass noted on imaging studies, using DXA, has been associated with increased cardiovascular mortality.[25,26] Measures of muscle function, such as hand grip strength, have also been noted to have a protective effect on CVD risk in large population studies.[27,28]

Specifically, the high-muscle/low-fat-mass phenotype has been shown to be associated with lower cardiovascular mortality in our previous study of patients with preexisting CVD.[6] The current study shows that a high muscle mass is associated with lower cardiovascular mortality in women and men, and in both sexes, higher fat levels were associated with a higher CVD mortality with either high muscle or low muscle mass. However, in adjusted competing risks models, in women, high fat mass regardless of muscle mass level was associated with a significantly lower cardiovascular mortality rate compared with women with low muscle–low fat mass. We noted that adjustment for both hormone replacement therapy (in women) and traditional cardiovascular risk factors (including cholesterol, blood pressure, and dysglycemia [including prediabetes and diabetes mellitus]) was required to note the association between high fat mass, in both high-muscle–high-fat and low-muscle–high-fat groups, and lower CVD mortality. Similarly in men, adjustment for traditional cardiovascular risk factors (including cholesterol, blood pressure, and dysglycemia [including prediabetes and diabetes mellitus]) was required to note the association between high muscle mass, in either the high-muscle–high-fat or high-muscle–low-fat groups, and lower cardiovascular mortality. The

Table 3. Adjusted Competing Risks Model for CVD Mortality Outcome With Men >20 Years of Age From the NHANES Population

Variable	Model 1–4 Covariates				Model 3–9 Covariates			
	HR	Lower	Upper	*P* Value	HR	Lower	Upper	*P* Value
Low muscle–low fat	1.00				1.00			
Low muscle–high fat	1.32	0.95	1.85	0.100	1.069	0.753	1.519	0.708
High muscle–low fat	0.42	0.22	0.80	0.008	0.403	0.211	0.769	0.006
High muscle–high fat	1.03	0.75	1.41	0.859	0.738	0.525	1.039	0.082
Age ≥60 y	10.19	7.42	14.00	0.000	7.082	4.983	10.066	0.000
Smoking history (yes vs no)	1.24	0.94	1.63	0.136	1.171	0.880	1.559	0.280
White	1.00				1.00			
Hispanic	1.00	0.63	1.58	0.998	0.953	0.595	1.526	0.842
Black	1.46	0.95	2.27	0.088	1.192	0.761	1.867	0.444
Other*	0.85	0.40	1.80	0.672	0.767	0.364	1.616	0.485
Cancer history (nonsquamous cell skin)	0.93	0.61	1.41	0.733	0.840	0.547	1.291	0.427
High-density lipoprotein per unit					0.992	0.983	1.002	0.121
Total cholesterol—per unit					0.999	0.995	1.003	0.566
log 10 CRP—per log unit					1.390	1.053	1.836	0.020
Hypertension (yes vs no)					1.947	1.443	2.628	0.000
Diabetes mellitus—borderline (vs none)					2.072	0.979	4.386	0.057
Diabetes mellitus (vs none)					2.291	1.659	3.164	0.000

n=5827 of 5836, 399 CVD deaths, 1087 non CVD deaths. Lower=lower 95% CI; upper=upper 95% CI. CRP indicates C-reactive protein; CVD, cardiovascular disease; HR, hazard ratio, and NHANES, National Health and Nutrition Examination Survey.

*Other includes individuals not identifying as Hispanic, Black or White, such as Asian or mixed race individuals.

negative association between total fat and cardiovascular mortality in women was consistently noted when sequential quartiles of total fat were evaluated. Further, the negative association noted with sequential quartiles of leg fat in women, given the cardiometabolic protective effect of gluteofemoral fat,[15] was biologically plausible.

The differential quantitative effect on cardiovascular mortality of body fat mass in women versus men has been previously noted by others, including Lavie et al.[29] In a study of 570 patients with coronary heart disease, individuals were divided into 4 groups of low or high muscle mass combined with low or high fat mass (comparable to the 4 body composition phenotype groups in our study) using measurement of body fat by skin-fold thickness assessment (and muscle mass as a derivative of 1-body fat×body mass index). In the overall study population, it was noted that mortality was lowest in the high-muscle-mass–high-body-fat mass group, and in women of higher fat mass, when this term was entered into a model simultaneously with higher muscle mass, higher fat mass was independently associated with lower cardiovascular mortality. Further, in women >75 years of age[30] and in frail elderly women, a similar protective effect of higher levels of total body fat (measured by DXA) on total mortality has been noted.

The most widely used definition of frailty includes measures of muscle strength (hand grip strength, walking speed), in addition to significant weight loss.[31] It has been noted that dynapenia and slow gait speed are significantly associated with[32] and appear to be important in driving the increased risk of CVD and increased all-cause mortality noted to be associated with frailty. However, the significance of weight loss as a contributor to frailty, and the importance of higher adiposity in surviving critical illness,[27,32,34–37] indicates that mortality/cardiovascular protection requires higher levels of adiposity.

It has been noted that peripheral fat (especially leg fat) protects against cardiovascular risks,[15,16] offsetting the metabolic effect of abdominal fat. In fact, in the INTERHEART (a global study of risk factors in acute myocardial infarction) study, in 27 000 participants, a significant association was noted between a larger hip circumference and a lower risk for MI.[38] When severely obese, premenopausal women (body mass index >40 kg/m^2) were evaluated with DXA,[16] a significant negative correlation between cardiovascular risk factors (blood pressure, plasma lipids, glucose) and leg fat mass was noted, such that assessed metabolic parameters were not significantly different from those of subjects with body mass index <40 kg/m^2. Further, sexual dimorphism exists with respect to the metabolic activity of the leg fat depot, with contributory factors including the relative activity of lipoprotein lipase (an enzyme that allows a change from the

Table 4. Adjusted Competing Risks Model, Stratified by Sex, for CVD Mortality Outcome and Quartiles of Total Fat, Leg Fat, and Trunk Fat

	Females					Males				
	Quartile	Leg Fat Per BMI Squared				Quartile	Leg Fat Per BMI Squared			
Quartile	Midpoint	HR	Lower	Upper	*P* Value	Midpoint	HR	Lower	Upper	*P* Value
1st	2.75	1.00	Ref			1.59	1.00	Ref		
2nd	3.66	0.562	0.367	0.862	0.008	2.13	0.792	0.535	1.174	0.246
3rd	4.53	0.419	0.267	0.657	0.000	2.61	0.733	0.485	1.107	0.139
4th	6.14	0.635	0.412	0.981	0.041	3.43	0.920	0.631	1.342	0.667
	Quartile	Trunk Fat Per BMI Squared				Quartile	Trunk Fat Per BMI Squared			
Quartile	Midpoint	HR	Lower	Upper	*P* Value	Midpoint	HR	Lower	Upper	*P* Value
1st	2.95	1.00	Ref			2.23	1.00	Ref		
2nd	4.80	0.725	0.457	1.150	0.172	3.57	1.003	0.636	1.581	0.990
3rd	6.26	0.594	0.362	0.973	0.038	4.59	0.840	0.520	1.356	0.476
4th	8.53	0.534	0.315	0.904	0.020	6.29	0.890	0.560	1.415	0.623
	Quartile	Total Fat Per BMI Squared				Quartile	Total Fat Per BMI Squared			
Quartile	Midpoint	HR	Lower	Upper	*P* Value	Midpoint	HR	Lower	Upper	*P* Value
1st	7.17	1.00	Ref			4.90	1.00	Ref		
2nd	10.12	0.832	0.534	1.298	0.418	6.99	0.724	0.455	1.153	0.173
3rd	12.74	0.546	0.341	0.874	0.012	8.56	0.911	0.592	1.402	0.672
4th	17.10	0.562	0.336	0.939	0.028	11.33	0.795	0.513	1.232	0.304

Lower=lower 95% CI; upper=upper 95% CI. BMI indicates body mass index; CVD, cardiovascular disease; and HR, hazard ratio.

long-term storage form of fat/energy as triglycerides, into nonesterified fatty acids that allow the organism to be resupplied with energy). In women, lipoprotein lipase activity is higher in leg adipocytes compared with other fat depots,[39] while in men testosterone suppresses lipoprotein lipase activity in leg adipocytes.[40] Adipose tissue blood flow is also an important determinant of fat metabolism in various fat depots, and it has been noted that in women, postprandially, there is an increase in adipose tissue blood flow in abdominal and femoral areas, whereas in men an increase in adipose tissue blood flow occurs only in the abdominal depot.[41] Lower-body fat depots are also associated with a beneficial adipokine production profile. Leptin is a hormone important in regulation of appetite and energy intake, and it is noted that there are sexual differences in the concentrations of circulating leptin.[42,43] Leptin levels correlate with leg fat mass,[44] and thus higher-amplitude leptin secretions have been noted in lower-body obesity in women compared with men.[45]

However the potential protective effect of adiposity against cardiovascular mortality is conceptually at odds with the obesity paradox, according to which the association between mortality and body mass index is actually determined by the relative abundance of the 2 elements of body composition (lean body mass and fat mass)[46,47] such that mortality risk is at the lowest with higher lean mass, and risk increases as fat mass increases. However, the level of adiposity that confers protection over risk does appear to vary by sex,[48] and further lack of association of overweight or obesity with an increased risk of CVD might be influenced by confounding, including undiagnosed disease leading to weight loss and premature death.[46–48]

Premenopausal women have a favorable distribution of adipose tissue, which tends to accumulate 50% in the abdomen and the remainder in the periphery (subcutaneous deposits in the gluteal and femoral area where the metabolic effect is positive[49]) whereas in men 98% of adipose tissue is in the visceral region of the upper body, which has adverse metabolic consequences.[50,51] However, adipose tissue redistribution (with accumulation of greater abdominal fat) occurs in females during and after menopause, and it has been noted that central adipose tissue distribution is positively associated with increased risk of secondary cardiovascular events in women.[3] While it was noted that a significant negative association existed between trunk fat and cardiovascular mortality (in women; Table 4) in this study, previous studies have noted that DXA trunk fat measurements are associated with total abdominal adipose tissue rather than visceral adipose tissue, when compared with the gold standard of magnetic resonance imaging and computed tomography measures of visceral adiposity.[13,14] A greater total adipocyte burden may not carry negative metabolic implications

in women, as the mechanism by which a reservoir of adipocytes is expanded (either adipocyte hypertrophy leading to cellular enlargement or adipocyte hyperplasia leading to a greater number of adipocytes) will determine the nature of the metabolic response. Hypertrophy leads to cellular hypoxia and endoplasmic reticular stress and thus triggers an inflammatory response attributable to the inability of the enlarged cell to compensate for increased functional demands. On the other hand, adipose cell hyperplasia does not elicit such a negative metabolic response, as the increased cell number (rather than size) does not compromise cell function. It has been noted that at the same age and weight, men expand fat by the process of adipocyte hypertrophy. However, in women, in adipocyte reservoirs, the process of adipocyte hyperplasia predominates.[52] Hence, despite an increase in adipose tissue deposits in women, such as pericardial, subcutaneous abdominal, mesenteric abdominal, and perimuscular, the process of hyperplasia of adipocytes may protect against adipocyte intracellular hypoxia and subsequent inflammation. Further, with respect to pericardial adiposity, noninflamed adipose tissue could give rise to healthy extracellular matrix-associated mesenchymal cells, which after an acute cardiovascular event may display cardiovascular autoreparative potential upon migrating to the injured myocardial site.[53,54] Finally, brown adipose tissue (BAT) is known to have the physiologic ability for enhanced energy expenditure and other positive metabolic effects such as insulin sensitivity.[55] However, BAT was not recognized to functionally exist in adults until the 1990s.[56] It has been noted that BAT deposits in females are more prominent,[57] which is consistent with the greater sensitivity to cold exposure by women.[58] Further, while BAT mass is known to decline with aging, the decline is more rapid in men.[59] Thus, in women, a greater BAT mass may contribute to the cardiovascular protection offered by an expanded fat mass.

Our study has limitations that should be acknowledged. First, a cause-and-effect relationship between level of total MMI or total FMI and CVD mortality cannot be established by a prospective cohort study. However, we were able to evaluate the value of the combination of total MMI and total FMI, as predictors of cardiovascular mortality in a large sample of women and men with national representativeness. Further, DXA estimates total muscle mass from 2-dimensional projected images without regard for muscle composition. Lipid infiltration of muscle in those who lead sedentary lifestyles and in aging populations[60] may lead to an overestimation of effective muscle mass by DXA. Use of methodologies that physiologically take into account muscle mass, such as bioelectrical impedance or computed tomography/magnetic resonance imaging, may be useful in verifying our findings.

In conclusion, this study demonstrates that in women, as in men, higher muscle mass has a protective effect with respect to cardiovascular mortality. However, in women, a phenotype consisting of high total fat mass and high muscle mass offered significant protection against cardiovascular mortality beyond hormonal, cardiovascular, and metabolic risk factors. This finding represents an important extension of our previous work on muscle mass and mortality. It highlights the importance of recognizing that sexual dimorphism exists with respect to the most favorable body composition to potentially decrease cardiovascular mortality in women. Specifically, it demonstrates the potential importance of advice to maximize muscle mass in women. This diverges from the current emphasis on weight loss in CVD prevention, and thus methods to practically achieve such body composition alteration need to be further evaluated.

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Disclosures

None.

Supplementary Material

Figure S1

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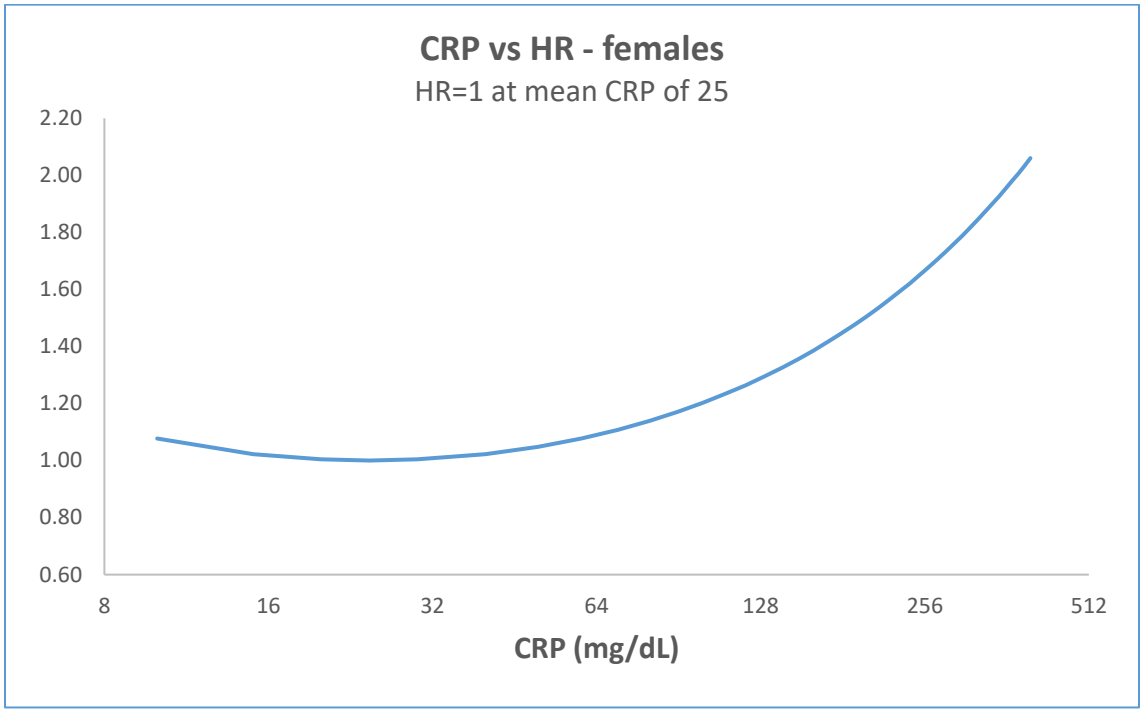
SUPPLEMENTAL MATERIAL

Figure S1. C reactive protein (CRP) versus CVD mortality Hazard Ratio (HR), model 3 in females.



The effect of CRP (mg/dL) on CVD mortality. This plot is included as in Table 2, in model 3 it is noted that log CRP /Log CRP ^2 is not constant and the effect of CRP on CVD mortality is not linear on either the original or log scale plot.