Independent and joint associations of grip strength and adiposity with all-cause and cardiovascular disease mortality in 403,199 adults: the UK Biobank study

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ABSTRACT

Background: Higher grip strength (GS) is associated with lower mortality risk. However, whether this association is independent of adiposity is uncertain.

Objective: The purpose of this study was to examine the associations between GS, adiposity, and mortality.

Design: The UK Biobank study is an ongoing prospective cohort of >0.5 million UK adults aged 40–69 y. Baseline data collection (2006–2010) included measurements of GS and adiposity indicators, including body mass index (BMI; in kg/m²). Age- and sexspecific GS quintiles were used. BMI was classified according to clinical cutoffs.

Results: Data from 403,199 participants were included in analyses. Over a median 7.0-y of follow-up, 8287 all-cause deaths occurred. The highest GS quintile had 32% (95% CI: 26%, 38%) and 25% (95% CI: 16%, 33%) lower all-cause mortality risks for men and women, respectively, compared with the lowest GS quintile, after adjustment for confounders and BMI. Obesity class II (BMI \geq 35) was associated with a greater all-cause mortality risk. The highest GS quintile and obesity class II category showed relatively higher all-cause mortality hazards (not statistically significant in men) than the highest GS quintile and the normal weight category; however, the increased risk was relatively lower than the risk for the lowest GS quintile and obesity class II category. All-cause mortality risks were generally lower for obese but stronger individuals than for nonobese but weaker individuals. Similar patterns of associations were observed for cardiovascular mortality.

Conclusions: Lower grip strength and excess adiposity are both independent predictors of higher mortality risk. The higher mortality risk associated with excess adiposity is attenuated, although not completely attenuated, by greater GS. Interventions and policies should focus on improving the muscular strength of the population regardless of their degree of adiposity. *Am J Clin Nutr* 2017;106:773–82.

Keywords: grip strength, adiposity, muscle strength, obesity, mortality, UK Biobank

INTRODUCTION

Obesity is a global public health concern (1). Excess adiposity is known to be associated with a greater risk of mortality and

cardiovascular disease (CVD), such as heart failure, hypertension, and coronary artery disease (2). However, substantial evidence (3) suggests that greater aerobic fitness can lower the risk of death and CVD associated with greater fatness.

Muscular fitness, a complementary aspect of overall fitness, has also been found to be a strong predictor of mortality (4). As such, grip strength (GS), a simple, inexpensive measure of overall muscular strength (5–7), has been recognized as a useful prognostic indicator of mortality (8, 9) as well as adverse health outcomes, such as sarcopenia and frailty (10). A few studies (11-14) have attempted to further explore the "fit-fat" paradigm in relation to mortality and muscle strength, suggesting that mortality risk may be reduced in individuals with greater muscle strength irrespective of weight status. However, the evidence on the associations of muscle strength and fatness with mortality has been predicated primarily on data from studies with a relatively small sample size (<8000) of men (11, 12) or older adults (13). Thus, the findings from these studies provide limited evidence on the RR of mortality for the combination of muscle strength and fatness for general adult populations. Furthermore, the majority of the studies have used BMI as a sole crude adiposity indicator (12-14). Abdominal adiposity defined by waist circumference (WC) predicts mortality independently of general adiposity [i.e., BMI and percentage of body fat (%BF)] (15). Hence, it is critical to discern the interactions of different adiposity

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Supplemental Figures 1–4, Supplemental Tables 1–5, and Supplemental References are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

Address correspondence to YK (e-mail: youngwon.kim@mrc-epid.cam.ac.uk). Abbreviations used: CVD, cardiovascular disease; GS, grip strength; MVPA, moderate-to-vigorous physical activity; WC, waist circumference; %BF, percentage of body fat.

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indicators and muscle strength with mortality in general populations of men and women. Therefore, the purpose of the present study is to examine the RR of all-cause and CVD mortality for GS, various clinical adiposity measures (BMI, WC, and %BF) and their interactions in middle-aged and older men and women.

METHODS

Study design and participants

UK Biobank is an ongoing UK national cohort of over half a million adults aged 40–69 y at recruitment. Individuals were contacted who were registered with the National Health Service and living <25 miles away from 1 of 22 assessment centers across the United Kingdom. Of those, >500,000 individuals had baseline data collected (2006–2010) that included a wide variety of physical measurements and biological samples, as well as questionnaires on sociodemographic factors, family history and early-life exposures, general health and disability, environmental and lifestyle factors, and psychological and cognitive states. The UK Biobank methodology is described in detail elsewhere (16). All participants provided written informed consent before participation, and the protocol of the UK Biobank project was approved by the North West Multicentre Research Ethics Committee.

Exposures

GS

GS was assessed once in each hand with the use of a Jamar J00105 hydraulic hand dynamometer, which can measure isometric grip force ≤ 90 kg (calibrated by staff at the start of each measurement day) with good reliability and reproducibility (17). The handle of the device was adjustable to 5 grip positions between 1-3/8 and 3-3/8 inches. Participants were allowed to choose a grip position that they felt most comfortable with. Each participant was asked to grasp the handle of the device in their right hand while sitting upright on a chair with their forearm on the armrest. They were required to maintain a 90° angle of their elbow adjacent to their side so that their thumb would face upwards while squeezing the handle as strongly as possible for \sim 3 s. The same protocol was undertaken with the left hand. For the current analysis, values from the 2 hands were averaged if available; otherwise, the value from a single hand was used in a small subsample (n = 1177).

Adiposity measures

BMI was calculated in kg/m². WC was measured with the use of a tape measure at the level of the umbilicus. Fat-free mass was assessed with the Tanita BC-418MA bioimpedance analyzer, from which %BF was calculated as 1 – fat-free mass \div body weight. BMI was categorized into normal weight (18.5– 24.9), overweight (25.0–29.9), obesity class I (30.0–34.9), and obesity class II (\geq 35.0). The following sex-specific clinical cutoffs were applied to create 3 groups of WC and %BF: WC: <94, 94–101.9, or \geq 102 cm for men and <80, 80–87.9, or \geq 88 cm for women (1); %BF \leq 20%, 20.1–25%, or >25% for men and \leq 30%, 30.1–33%, or >33% for women (18).

Outcomes

Participants were followed for mortality until 15 February 2016 through linkage with death records from the National Health Service Information Centre and the Scottish Morbidity Record. CVD mortality was defined with the use of International Classification of Diseases, 10th revision codes F01 and I00–I99. The median follow-up period was 7 y (IQR: 6.3–7.6 y).

Covariates

The following variables that could confound the associations between GS and mortality were included as covariates in the analyses: ethnicity (white, mixed, Asian or Asian British, black or black British, or other), smoking status (never, previous, or current), employment (unemployed or employed), Townsend deprivation index (a composite score of employment, car ownership, home ownership, and household overcrowding, with higher values indicating a given area's higher degree of deprivation), statin use (yes or no), hormone replacement therapy (yes or no; women only), alcohol consumption (never, previous, currently <3 times/wk, or currently ≥ 3 times/wk), processed or red meat consumption (days per week), resting pulse rate (beats per min), and moderate-to-vigorous physical activity (MVPA) (minutes per day). MVPA time was estimated based on self-reported walking, transportation activities, occupational activities and walking, strenuous and other exercise, and do-ityourself activities by calibrating them to heart rate and accelerometry data (19) from 12,435 UK adults participating in the Fenland project (20).

Statistical analyses

Cox regression models (with age as the underlying time scale) were used to estimate the associations of GS and adiposity with all-cause and CVD mortality. First, models were fit to estimate the associations between GS and mortality, with adjustment for potential confounders (model 1). Further adjustments for each of the 3 adiposity indicators (BMI, WC, and %BF) were made in 3 separate models (models 2a, 2b, and 2c). In parallel with the models that used GS as an exposure variable, models that used each adiposity measure as an exposure variable were also fitted with adjustment for the same covariates (model 1) and additional adjustments for GS (model 2). Models that used 5-kg increments in GS as an exposure were fitted by personal or lifestyle risk factor and disease status. The associations between GS and mortality were stratified by each adiposity variable. Sex- and agespecific quintiles of GS (1-Q) and different adiposity categories were combined to examine joint associations with mortality. All analyses were performed for men and women separately. Subgroup analyses and tests of interaction of GS with age, weight status, WC, %BF, MVPA, television viewing, smoking, alcohol consumption, hypertension, and diabetes were performed. Loglog plots provided support for the proportional hazards assumptions for all covariates. Sensitivity analyses were performed 1) with the use of the maximum GS from either hand, 2) with GS normalized for body weight or fat-free mass to account for variation by body size, 3) excluding the first 2-y mortality follow-up, and 4) excluding individuals who had chronic obstructive pulmonary disease or were current or previous smokers at baseline when examining adiposity as an exposure (the latter 2

	characteristics1	
TABLE 1	Participant	

Women (n = 220, 193)

Men (n = 183,006)

				Grip strength						Grip strength		
Variable	IIV	Q1	Q2	Q3	Q4	Q5	All	QI	Q2	Q3	Q4	Q5
Grip strength, kg Age, y	39.7 (8.8) 56.2 (8.2)	27.7 (4.9) 56.4 (8.4)	35.3 (26) 55.8 (8.3)	39.3 (2.7) 56.5 (8.1)	43.6 (2.9) 56.5 (8.2)	51.2 (4.9) 55.6 (8.1)	23.5 (6.2) 56.0 (8.0)	14.7 (3.6) 56.7 (8.0)	20.2 (2.1) 55.8 (8.2)	22.9 (2.1) 56.5 (8.0)	26.2 (2.1) 55.7 (7.7)	31.2 (3.5) 55.4 (8.1)
Ethnicity White	94.4	89.6	93.7	95.5	96.3	9.66	94.4	6.06	94.0	95.1	95.9	92.6
Mixed	0.5	0.5	0.6	0.5	0.5	0.5	0.7	0.7	0.7	0.6	0.7	0.8
Asian/Asian British	2.6	6.3	3.2	2.0	1.2	0.7	2.1	5.0	2.5	1.7	1.2	0.6
Black/black British	1.6	2.0	1.5	1.4	1.4	1.7	1.8	1.8	1.6	1.7	1.5	2.4
Other	0.9	1.6	1.0	0.7	0.7	0.5	1.0	1.6	1.1	0.9	0.8	0.6
Smoking status												
Never	50.4	51.4	50.9	50.7	49.6	49.7	60.3	61.6	61.4	60.5	59.6	58.8
Previous	37.3	35.0	36.5	37.1	38.7	38.9	31.0	29.2	29.9	31.3	31.7	32.5
Current	12.3	13.6	12.6	12.1	11.7	11.4	8.7	9.2	8.7	8.2	8.7	8.7
Employment												
Unemployed	35.9	42.2	35.3	36.0	35.6	30.9	43.0	50.2	42.4	44.4	39.3	39.9
Townsend deprivation index	-1.33 (3.1)	-0.58(3.4)	-1.16 (3.1)	-1.44 (3.0)	-1.62 (2.9)	-1.79 (2.8)	-1.39(3.0)	-0.95 (3.2)	-1.28 (3.0)	-1.47 (3.0)	-1.57 (2.9) -	-1.59 (2.9)
Statin use	19.7	23.6	19.7	19.8	18.9	16.8	11.7	15.4	12.1	11.5	10.3	10.0
Hormone replacement	N/A	N/A	N/A	N/A	N/A	N/A	7.5	7.4	7.2	7.2	7.7	7.9
therapy (W only)												
Alcohol consumption												
Never	2.7	4.7	2.8	2.4	1.9	2.3	3.4	4.8	3.7	3.2	2.9	2.7
Current (<3 times/wk)	41.8	44.3	42.7	41.3	40.3	40.7	53.7	56.4	55.1	53.4	52.9	51.5
Current (≥3 times/wk)	52.3	45.9	51.0	53.5	55.1	55.3	37.2	29.8	35.2	38.2	39.7	41.7
Processed or red meat	1.04(0.60)	1.05(0.64)	1.04(0.61)	1.04(0.59)	1.03 (0.58)	1.05 (0.58)	0.78 (0.50)	0.79 (0.53)	0.78 (0.50)	0.78 (0.50)	0.78 (0.49)	0.78 (0.49)
consumption, d/wk												
Resting pulse rate, beats/min	68.3 (11.7)	69.5 (12.3)	68.4 (11.8)	68.0 (11.6)	67.9 (11.6)	67.9 (11.5)	70.1 (10.5)	70.8 (10.7)	70.1 (10.5)	(9.9 (10.4))	69.8 (10.4)	69.9 (10.6)
Self-reported MVPA time, min/d	82.3 (22.9)	78.4 (20.7)	81.8 (22.2)	82.4 (24.0)	83.1 (23.0)	85.3 (23.6)	51.6 (19.5)	49.2 (16.1)	51.0 (18.8)	51.3 (18.8)	52.5 (19.5)	53.5 (22.9)
BMI, kg/m ²	27.7 (4.2)	27.7 (4.6)	27.6 (4.3)	27.6 (4.1)	27.7 (3.9)	28.2 (3.9)	27.0 (5.1)	27.6 (5.5)	26.9 (5.1)	26.8 (5.0)	26.8 (4.9)	27.0 (5.0)
Normal weight	25.0	28.0	27.8	25.9	24.3	19.6	39.2	35.0	39.9	40.6	41.0	39.1
Overweight	50.1	46.2	48.6	50.6	51.7	52.9	37.3	37.0	37.0	37.3	37.5	37.7
Obesity class I	19.4	19.1	18.0	18.5	19.3	22.0	15.8	17.9	15.7	15.2	14.8	15.5
Obesity class II	5.5	6.7	5.6	5.0	4.7	5.5	7.7	10.1	7.4	6.9	6.7	7.6
WC, cm	96.6 (11.1)	97.0 (12.0)	96.2 (11.4)	96.2 (11.0)	96.4 (10.7)	97.3 (10.5)	84.5 (12.4)	86.0 (13.1)	84.2 (12.3)	83.9 (12.1)	83.8 (12.1)	84.6 (12.2)
<94 cm (M); <80 cm (W)	45.3	44.8	47.5	46.6	46.0	41.8	42.5	37.9	43.2	44.1	44.4	42.1
94-101.9 cm (M); 80-87.9	25.4	23.7	24.5	25.4	25.7	27.2	21.9	21.3	21.8	21.9	22.1	22.3
cm (W)												
$\geq 102 \text{ cm (M)}; \geq 88 \text{ cm (W)}$	29.4	31.5	28.1	28.0	28.3	30.9	35.6	40.8	34.9	34.0	33.5	35.6
%BF	25.1 (5.8)	25.8 (6.1)	25.2 (5.9)	25.0 (5.7)	24.8 (5.6)	24.7 (5.5)	36.4(6.9)	37.5 (7.0)	36.5 (6.9)	36.4 (6.8)	36.1 (6.8)	36.0 (6.9)
≤20% (M); ≤30% (W)	18.3	16.5	18.2	18.8	19.1	18.9	17.6	14.4	17.2	17.5	18.7	19.5
20.1–25% (M); 30.1–33% (W)	30.9	27.5	30.3	31.0	32.1	33.1	12.8	11.2	13.0	12.8	13.5	13.4
>25% (M); >33% (W)	50.8	56.0	51.5	50.2	48.8	47.9	69.69	74.4	69.8	69.7	67.8	67.1

GRIP STRENGTH, ADIPOSITY, AND MORTALITY

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			Men $(n =$: 183,006)					women (n	i = 220, 193		
				Grip strength					-	Grip strength		
Variable	IIV	QI	Q2	Q3	Q4	Q5	All	Q1	Q2	Q3	Q4	Q5
Fat-free mass, kg Systolic blood pressure, mm	63.8 (7.8) 140.9 (17.3)	61.0 (8.0) 139.2 (17.7)	62.3 (7.5) 139.8 (17.2)	63.3 (7.3) 141.1 (17.4)	64.5 (7.1) 142.0 (17.2)	67.3 (7.4) 142.3 (16.9)	44.5 (5.0) 135.0 (19.2)	43.4 (5.2) 134.3 (19.2)	43.7 (4.8) 133.8 (19.2)	44.0 (4.7) 135.2 (19.3)	44.8 (4.7) 135.1 (19.0)	46.3 (4.9) 136.1(19.1)
нg Diastolic blood pressure, mm ис	84.3 (9.9)	83.2 (10.1)	83.8 (10.0)	84.3 (9.9)	84.8 (9.9)	85.4 (9.8)	80.7 (10.0)	80.2 (10.0)	80.1 (10.0)	80.5 (9.9)	80.8 (9.9)	81.5 (9.9)
нg Hypertension	61.1	60.3	58.7	60.9	62.4	62.8	47.7	49.3	46.0	47.9	46.8	48.6
Diabetes	6.1	9.7	6.5	5.8	4.9	4.1	3.4	5.4	3.6	3.1	2.8	2.6
¹ Data are presented as m obesity class I (30 to <35) and	ans (SDs) or 9	%. Grip strengt I (≥35). Hyper	h quintiles wer tension was de	re sex- and age fined as systoli	-specific. BMI c or diastolic b	(in kg/m ²) was lood pressure $\frac{1}{2}$	s used to catego ≥140/90 mm H	orize participan g, reported phy	ts into normal 'sician diagnosi	weight (18 to 4 is of hypertensi	<25), overwei£ ion, or reported	ht (25 to <30), medication use

to regulate blood pressure. Participants were considered to have diabetes if they reported a physician diagnosis of diabetes, or were taking a glucose-lowering treatment. M, men; MVPA, moderate-to-vigorous physical activity; N/A, not applicable; Q, quintile; W, women; WC, waist circumference; %BF, percentage of body fat to minimize the risk of reverse causality). All analyses were performed in Stata/SE, version 14 (StataCorp LLC).

RESULTS

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Of an initial sample of 502,639 participants who underwent baseline data collection, individuals were excluded if they had a history of heart attack, stroke, or cancer at baseline (n = 55,401) to minimize the risk of reverse causality (8, 21), their censoring date was before the date of baseline data collection (n = 3), or they had missing values on any of the variables (n = 44,036), leaving 403,199 participants in the final analytic sample (**Supplemental Figure 1**).

Table 1 shows the participants' characteristics across quintiles of GS. The specific cutoffs to create the sex- and agespecific quintiles of GS are shown in **Supplemental Table 1**. A total of 8081 all-cause deaths occurred during 1,268,314 person-years of follow-up for men and 1,533,538 person-years for women. Differences in BMI, WC, and %BF across quintiles of GS and the correlations between these variables (**Supplemental Table 2**) were minimal.

Table 2 summarizes the associations between GS and allcause mortality. The highest quintiles of GS had considerably lower risks of all-cause mortality in both men and women (except for quintile 2) than the lowest quintiles of GS after adjusting for confounders (model 1) plus additional adjustments for each adiposity measure (model 2): P-trend <0.0001. Specifically, hazards of all-cause mortality were $\sim 32\%$ lower (95% CI: 26%, 38%) and 25% (95% CI: 16%, 33%) for men and women, respectively, in quintile 5 of GS than for men and women in quintile 1 of GS after adjusting for confounders and BMI (model 2a). The HR per 5-kg increase in GS was 0.92 for both men (95% CI: 0.90, 0.93) and women (95% CI: 0.89, 0.95) after adjusting for all confounders and BMI (model 2a). Sensitivity analyses found similar associations with the maximal GS from either hand, and GS unnormalized or normalized for body weight or fat-free mass (Supplemental Figure 2). Another sensitivity analysis removing the first 2 y of follow-up yielded similar results (Supplemental Table 3). The associations of GS with CVD mortality were similar to the associations with allcause mortality for men (Table 2). Although the HRs were not statistically significant in women, the *P*-trends were all <0.05. The associations of per 5-kg increase in GS with all-cause and CVD mortality were significant (P values < 0.05) for almost all subgroups examined in both men and women (Figure 1) with some exceptions, particularly for women.

The associations of adiposity measures with all-cause and CVD mortality after adjusting for confounders (model 1) and GS (model 2) are shown in **Supplemental Table 4**. There were "J-shaped" associations between BMI and mortality risk (i.e., there was substantially lower hazard of all-cause mortality only in overweight men compared with normal weight men), which persisted even after excluding individuals who had chronic obstructive pulmonary disease or were current or previous smokers at baseline (**Supplemental Table 5**). The highest categories of BMI (i.e., obesity class II) and WC (i.e., abdominal obesity in men) were associated with increased hazards of all-cause and CVD mortality.

Figure 2 shows joint associations of GS quintiles and adiposity categories with all-cause mortality. More obese men with

Independent associations of grip strength with all-cause and CVD mortality¹

					HRs (95% CIs) for mortality						
Mortality outcome by sex and comparisons	Deaths, n	Person-years of follow-up	Mortality rate	Model 1	Model 2a	Model 2b	Model 2c				
All-cause											
Men	5049	1,268,314	398.1								
Grip strength											
Q1 (Ref.)	1389	241,358	575.5	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)				
Q2	933	232,139	401.9	0.80 (0.73, 0.87)	0.81 (0.75, 0.88)	0.80 (0.73, 0.87)	0.80 (0.73, 0.87)				
Q3	920	253,118	363.5	0.71 (0.65, 0.77)	0.72 (0.66, 0.78)	0.70 (0.65, 0.77)	0.71 (0.65, 0.77)				
Q4	972	268,240	362.4	0.72 (0.66, 0.78)	0.73 (0.67, 0.79)	0.72 (0.66, 0.78)	0.72 (0.66, 0.78)				
Q5	835	273,460	305.3	0.67 (0.62, 0.73)	0.68 (0.62, 0.74)	0.67 (0.61, 0.73)	0.67 (0.62, 0.74)				
P-trend				< 0.0001	< 0.0001	< 0.0001	< 0.0001				
Per 5-kg increment				0.91 (0.90, 0.93)	0.92 (0.90, 0.93)	0.91 (0.90, 0.93)	0.91 (0.90, 0.93)				
Women	3238	1,533,538	211.1								
Grip strength											
Q1	746	270,638	275.6	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)				
Q2	652	274,981	237.1	0.96 (0.86, 1.06)	0.97 (0.87, 1.08)	0.97 (0.87, 1.07)	0.96 (0.86, 1.06)				
Q3	656	316,838	207.0	0.81 (0.73, 0.90)	0.82 (0.74, 0.91)	0.82 (0.74, 0.91)	0.81 (0.73, 0.90)				
Q4	592	323,506	182.0	0.79 (0.71, 0.88)	0.80 (0.72, 0.89)	0.80 (0.71, 0.89)	0.79 (0.71, 0.88)				
Q5	592	347,576	170.3	0.74 (0.67, 0.83)	0.75 (0.67, 0.84)	0.74 (0.67, 0.83)	0.74 (0.67, 0.83)				
P-trend				< 0.0001	< 0.0001	< 0.0001	< 0.0001				
Per 5-kg increment				0.91 (0.89, 0.94)	0.92 (0.89, 0.95)	0.91 (0.89, 0.94)	0.91 (0.89, 0.94)				
CVD											
Men	1256	1,268,314	99.0								
Grip strength											
Q1 (Ref.)	373	241,358	154.5	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)				
Q2	246	232,139	106.0	0.81 (0.69, 0.96)	0.82 (0.70, 0.97)	0.81 (0.69, 0.95)	0.81 (0.69, 0.96)				
Q3	222	253,118	87.7	0.66 (0.56, 0.78)	0.67 (0.56, 0.79)	0.67 (0.56, 0.79)	0.67 (0.57, 0.79)				
Q4	235	268,240	87.6	0.68 (0.58, 0.81)	0.69 (0.58, 0.81)	0.68 (0.58, 0.81)	0.69 (0.58, 0.82)				
05	180	273,460	65.8	0.58 (0.48, 0.69)	0.57 (0.47, 0.68)	0.57 (0.47, 0.68)	0.58 (0.48, 0.70)				
<i>P</i> -trend				< 0.0001	< 0.0001	< 0.0001	< 0.0001				
Per 5-kg increment				0.88 (0.84, 0.91)	0.88 (0.85, 0.91)	0.88 (0.85, 0.91)	0.88 (0.86, 0.92)				
Women	485	1,533,538	31.6								
Grip strength		,									
O1 (Ref.)	122	270.638	45.1	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)				
02	98	274,981	35.6	0.93 (0.72, 1.22)	0.93 (0.71, 1.21)	0.95 (0.73, 1.24)	0.94 (0.72, 1.23)				
03	89	316.838	28.1	0.73 (0.56, 0.97)	0.72 (0.55, 0.95)	0.75 (0.57, 0.99)	0.74 (0.56, 0.97)				
04	92	323,506	28.4	0.85 (0.65, 1.12)	0.83 (0.63, 1.10)	0.86 (0.65, 1.13)	0.85 (0.65, 1.12)				
05	84	347.576	24.2	0.74 (0.56, 0.98)	0.73 (0.55, 0.97)	0.74 (0.56, 0.98)	0.74 (0.56, 0.98)				
<i>P</i> -trend	~ .	, 0		0.028	0.021	0.021	0.027				
Per 5-kg increment				0.93 (0.87, 0.99)	0.93 (0.86, 1.01)	0.94 (0.87, 1.01)	0.94 (0.87, 1.01)				

¹ All Cox regression models used age as the underlying time variable. The quintiles of grip strength were sex- and age-specific. The mortality rate is the crude mortality rate/100,000 person-years. Model 1: adjusted for ethnicity (white, mixed, Asian/Asian British, black/black British, or other), smoking status (never, previous, or current), employment (unemployed or employed), Townsend deprivation index, statin use (yes or no), hormone replacement therapy (yes or no; women only), alcohol consumption (never, previous, currently <3 times/wk, currently \geq 3 times/wk), processed or red meat consumption (days per week), resting pulse rate (beats per minute), and moderate-to-vigorous physical activity time (minutes per day). Model 2a: adjusted for all confounders included in Model 1 plus BMI (in kg/m²). Cases with BMI <18.5 (*n* = 369 for men; *n* = 1525 for women) were excluded. Model 2b: adjusted for all confounders included in model 1 plus waist circumference. Model 2c: adjusted for all confounders included in model 1 plus percent body fat. CVD, cardiovascular disease; Q, quintile; Ref., reference.

lower GS had higher risks of all-cause mortality than normal weight men with the highest category of GS. For example, men with the highest BMIs (i.e., obesity class II) and lowest category of GS had an 89% higher risk of all-cause mortality (HR: 1.89; 95% CI: 1.50, 2.39) compared with the normal weight men with the highest GS. A notable observation was the relatively higher mortality risks for normal weight men with lower GS in comparison with more obese men with higher GS. Similar trends were observed for WC and %BF as adiposity indicators.

Similarly, more obese women with lower GS had generally higher all-cause mortality risks than normal weight women with higher GS. The HR for women with the highest BMIs (i.e., obesity class II) and lowest GS was 1.69 (95% CI: 1.32, 2.16) compared with normal weight women with the highest GS. The higher GS quintiles in the obesity class II category were associated with significantly higher risks of all-cause mortality compared with the reference group. Joint analyses with WC and %BF as adiposity indicators found more obese women with higher GS to have lower all-cause mortality risks than nonobese women with lower GS. These associations were, in general, similar to the associations observed for CVD mortality (**Figure 3**).

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All-cause mortality	Men					Wo	men				
Group	HR (95% CI)	Total(n) Deat	Mortalit n(n) rate	y P for Interaction			HR (95% CI)	Total(n)	Death(n)	Mortality rate	P for Interaction
Age groups <50/yrs ≥60yrs ≥60yrs	0.90 (0.85, 0.95) 0.90 (0.87, 0.93) 0.92 (0.90, 0.94)	46175 391 60330 1210 76501 3448	120.7 287.1 659.4	0.016		-	0.91 (0.83, 1.00) 0.93 (0.88, 0.98) 0.90 (0.87, 0.94)	55106 76749 88338	301 841 2096	77.9 156.7 343.3	0.955
Weight Status I Normal Weight (18.5≤BMI<25)	0.89 (0.86, 0.92) 0.92 (0.90, 0.95) 0.94 (0.91, 0.98) 0.92 (0.87, 0.98)	45623 1203 91493 2277 35495 1103 9989 411	380.2 358.7 449.0 596.9	0.005	-++	•	0.91 (0.86, 0.96) 0.92 (0.88, 0.97) 0.88 (0.82, 0.95) 0.98 (0.90, 1.06)	85682 81582 34426 16806	1090 1199 540 369	182.6 210.9 225.3 315.8	0.310
Waist Circumference I <94cm(M) or <80(W)	0.89 (0.86, 0.91) 0.92 (0.89, 0.96) 0.93 (0.90, 0.95)	82862 1877 46394 1224 53750 1948	326.5 379.5 525.0	0.005			0.92 (0.87, 0.97) 0.90 (0.84, 0.96) 0.92 (0.88, 0.96)	93490 48220 78483	1119 637 1482	171.7 189.5 271.6	0.501
Percent Body Fat ≤20%(M) or ≤30%(W) 20-25%(M) or 3-33%(W) ⇒25%(M) or >33%(W) ↓	0.86 (0.83, 0.90) 0.91 (0.88, 0.94) 0.93 (0.91, 0.95)	33532 773 56487 1272 92987 3004	331.3 324.2 467.4	<0.0001		+	0.86 (0.80, 0.94) 0.97 (0.88, 1.06) 0.92 (0.89, 0.95)	38723 28259 153211	459 352 2427	169.9 178.8 227.6	0.158
MVPA Lower 50% Upper 50%	0.90 (0.88, 0.92) 0.94 (0.91, 0.97)	91503 3468 91503 1581	551.4 247.3	0.049		_	0.91 (0.87, 0.94) 0.94 (0.89, 0.99)	110095 110098	2127 1111	277.9 144.6	0.168
TV I ≤2hours/day ↓ >2hours/day	0.90 (0.87, 0.92) 0.92 (0.90, 0.94)	87964 1825 94074 3180	298.4 489.1	0.193	4	-	0.95 (0.91, 1.00) 0.90 (0.87, 0.93)	105765 112542	1180 2013	160.0 257.1	0.044
Meat consumption ≤5times/week >5times/week	0.91 (0.89, 0.94) 0.91 (0.89, 0.93)	96661 2390 86345 2659	356.7 444.5	0.455			0.92 (0.89, 0.96) 0.89 (0.84, 0.94)	161828 58365	2303 935	204.4 229.9	0.315
Smoking Never Previous Current	0.91 (0.88, 0.94) 0.92 (0.90, 0.95) 0.91 (0.88, 0.94)	92302 1675 68260 2209 22444 1165	261.0 468.3 752.2	0.270	- -+ -+-	-	0.92 (0.88, 0.96) 0.94 (0.89, 0.99) 0.87 (0.82, 0.94)	132794 68252 19147	1534 1139 565	165.7 240.0 423.5	0.057
Alcohol consumption	$\begin{array}{c} 0.82 \ (0.74, \ 0.91) \\ 0.90 \ (0.84, \ 0.96) \\ 0.93 \ (0.91, \ 0.96) \\ 0.90 \ (0.88, \ 0.93) \end{array}$	4855 116 5941 300 76530 1998 95680 2635	346.9 738.6 377.0 396.7	0.790		<u>.</u>	0.82 (0.73, 0.91) 0.86 (0.78, 0.96) 0.94 (0.90, 0.97) 0.91 (0.87, 0.96)	12385 7522 118342 81944	225 203 1748 1062	263.5 390.7 212.1 185.6	0.201
Hypertension No Yes	0.90 (0.87, 0.93) 0.92 (0.90, 0.94)	71205 1309 111800 3740	264.7 483.4	0.058	4		0.90 (0.86, 0.95) 0.92 (0.89, 0.96)	115096 105096	1213 2025	151.1 277.0	0.262
	0.92 (0.90, 0.94) 0.89 (0.85, 0.93)	171235 4359 11197 661	366.8 869.2	0.289			0.92 (0.89, 0.95) 0.88 (0.80, 0.98)	212212 7553	2977 257	201.3 496.5	0.534
Diabetes I No Yes I						-					
Diabetes No Yes Overall I 0.6 0.8 1.0	0.91 (0.91, 0.92) I I 1.2 1.4				0 .6 0.8	1.0 1.2	0.91 (0.91, 0.92) I 1.4				
Diabetes No Yes Overall I CVD mortality	0.91 (0.91, 0.92)	Total(n) Deat	Mortalit	y P for	0.6 0.8	Wo	0.91 (0.91, 0.92) 1 1.4 MEN HR (95% CI)	Total(n)	Death(n)	Mortality	P for
Diabetes No Yes Overall CVD mortality Group Age groups SD-59trps	0.91 (0.91, 0.92) I I 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.85 (0.76, 0.93)	Total(n) Deatt	Mortalit n(n) rate 30.3 74.0	y P for Interaction 0.476	0.6 0.8	Wo	0.91 (0.91, 0.92) 1 1.4 MR (95% CI) 106 (0.84, 1.34) 0.93 (0.79, 1.09)	Total(n)	Death(n)	Mortality rate	P for Interaction 0.386
Diabetes No Yes Overall 0.6 0.8 1.0 CVD mortality Group Age groups 550yrs 550yrs 560yrs 500yr	0.91 (0.91, 0.92) I I 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.85, 0.92) 0.85 (0.78, 0.92) 0.85 (0.78, 0.92)	Total(n) Deatl 46175 98 60330 312 76501 846 45623 248	Mortalit (n) rate 30.3 74.0 161.8 78.4	y P for Interaction 0.476 0.075		Wo	0.91 (0.91, 0.92) 1 1.4 MR (95% Cl) 1 06 (0 84, 1.34) 0.93 (0.79, 1.09) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.92 (0.75, 1.90)	Total(n) 55106 76749 88338 85662	Death(n) 44 100 341 148	Mortality rate 11.4 18.6 55.9 24.8	P for Interactio 0.386 0.045
Diabetes No Yes Overall CVD mortality Group Age groups 50/59yrs 50/50/50/50/50/50/50/50/50/50/50/50/50/5	0.91 (0.91, 0.92) I I I 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.86 (0.85, 0.32) 0.86 (0.85, 0.32) 0.86 (0.84, 0.33) 0.89 (0.84, 0.33) 0.89 (0.82, 0.38) 0.89 (0.82, 0.38)	Total(n) Deatl 46175 98 60330 312 76501 84 91493 557 9989 152	Mortalit 30.3 74.0 161.8 78.4 87.8 117.6 220.8	y P for Interaction 0.476 0.075		Wo	0.91 (0.91, 0.92) I I.4 HR (95% Cl) 1.6 (0.84, 1.34) 0.93 (0.79, 1.09) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.93 (0.81, 1.01) 0.93 (0.75, 1.00) 0.92 (0.75, 1.10) 1.09 (0.92, 1.30)	Total(n) 55106 76749 88368 85682 81582 34426 16806	Death(n) 44 100 341 148 175 78 78 78	Mortality rate 11.4 18.6 55.9 24.8 30.8 32.5 66.8	P for Interactio 0.386 0.045
Diabetes No Yes Overall I I I 0.6 0.8 1.0 CVD mortality Group Age groups 50-59yrs 50-50yrs	0.91 (0.91, 0.92) 1.2 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.85, 0.92) 0.88 (0.85, 0.92) 0.88 (0.85, 0.92) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.89 (0.84, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98) 0.99 (0.98, 0.98)	Total(n) Deatl 46175 98 60330 312 76501 846 91493 557 35495 289 9989 152 82862 411 46394 298 53760 547	Mortalit 30.3 74.0 161.8 78.4 87.8 117.6 220.8 71.5 92.4 147.4	y P for Interaction 0.476 0.075 0.001		Wo	0.91 (0.91, 0.92) I I.4 HR (95% Cl) 106 (0 84, 1 34) 0.93 (0 79, 1 09) 0.92 (0 84, 1 01) 0.92 (0 84, 1 01) 0.96 (0 83, 1 12) 0.97 (0 88, 1 08) 0.97	Total(n) 55106 76749 88368 85682 81582 81582 81582 81582 81582 93490 48220 78483	Death(n) 44 100 341 148 175 78 78 144 79 262	Mortality rate 11.4 18.6 55.9 24.8 30.8 32.5 66.8 22.1 23.5 48.0	P for Interactio 0.386 0.045 0.534
Diabetes No Yes Overall CVD mortality Group Age groups -50yrs 50-59yrs -50yrs 50-59yrs -50yrs	0.91 (0.91, 0.92) 1.2 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.85, 0.92) 0.85 (0.78, 0.92) 0.85 (0.78, 0.92) 0.85 (0.78, 0.92) 0.85 (0.84, 0.93) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.99 (0.82, 0.98) 0.99 (0.82, 0.98) 0.89 (0.82, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.84, 0.94) 0.99 (0.94, 0.94) 0.99 (0.94, 0.94) 0.99 (0.94, 0.94) 0.99 (0.94, 0.94) 0.99 (0.94, 0.94) 0	Total(n) Deatl 46175 98 60330 312 76501 846 91493 557 35495 289 9989 152 82862 411 46594 298 53760 547 33532 160 56487 276	(n) Mortalit 30.3 74.0 161.8 77.8 117.6 220.8 71.5 92.4 147.4 68.6 70.4 127.6	y P for Interaction 0.476 0.075 0.001 0.017		Wo	0.91 (0.91, 0.92) 1 1.4 HR (95% Cl) 106 (0.84, 1.34) 0.93 (0.79, 1.09) 0.92 (0.84, 1.01) 0.93 (0.84, 1.01) 0.93 (0.84, 1.01) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.92 (0.84, 1.01) 0.96 (0.83, 1.12) 0.86 (0.63, 1.12) 0.86 (0.63, 1.12) 0.86 (0.65, 1.08) 1.00 (0.81, 1.25) 0.84 (0.65, 1.08) 1.00 (0.81, 1.25) 0.84 (0.65, 1.08)	Total(n) 55106 76749 885682 84582 34426 16806 93490 48220 78483 38723 28529 153211	Death(n) 44 100 341 175 78 78 144 79 262 65 45 375	Mortality rate 11.4 18.6 55.9 24.8 30.8 32.5 66.8 22.1 23.5 48.0 24.1 22.9 35.2	P for Interactio 0.386 0.045 0.534 0.705
Diabetes No Yes Overall CVD mortality Group Age groups 50-59yrs 50-59yrs 50-59yrs 50-59yrs 50-59yrs 50-59yrs 1.0 CVD mortality Weight Status Normal Weight (18.55BMI<25) Overweight (255BMI<20) Obestly Class II (30MM/53) Obestly Class	0.91 (0.91, 0.92) 1.2 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.85 (0.76, 0.95) 0.88 (0.84, 0.93) 0.88 (0.84, 0.93) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.89 (0.82, 0.98) 0.82 (0.77, 0.87) 0.91 (0.87, 0.96) 0.82 (0.77, 0.97) 0.96 (0.82, 0.94) 0.97 (0.85, 0.97)	Total(n) Death 46175 98 60330 312 76501 846 45623 248 93493 557 35455 289 53750 547 33532 160 56487 276 92987 820 91503 887	n(n) Mortalit 30.3 74.0 161.8 78.4 87.8 117.6 220.8 71.5 92.4 147.6 92.4 147.6 127.6 141.0 57.7	 Y P for Interaction 0.476 0.075 0.001 0.017 0.520 		Wo	0.91 (0.91, 0.92) 1 1.4 men HR (95% Cl) 106 (0.84, 1.34) 0.93 (0.79, 1.09) 0.92 (0.84, 1.01) 0.93 (0.84, 1.05) 0.92 (0.84, 1.05) 0.92 (0.84, 1.05) 0.92 (0.84, 1.05) 0.92 (0.84, 1.05) 0.92 (0.84, 1.05) 0.92 (0.84, 1.05) 0.92 (0.84, 1.05) 0.93 (0.81, 1.05) 0.93 (0.81, 1.05) 0.95 (0.88, 1.08) 1.00 (0.91, 1.25) 0.84 (0.65, 1.08) 0.95 (0.87, 1.03) 1.00 (0.91, 1.19) 0.80 (0.693, 0.92)	Total(n) 55106 76749 88338 85682 81582 93492 185821 78483 38723 28259 153211 153211 153211 153211	Death(n) 44 100 341 148 175 78 78 144 79 262 65 45 375 375 339 146	Mortality rate 11.4 18.6 55.9 24.8 30.8 32.5 66.8 22.1 23.5 48.0 24.1 22.5 48.0 24.1 23.5 48.0 24.1 23.5 48.0 24.1 23.5 19.0	P for Interactio 0.386 0.045 0.534 0.705 0.009
Diabetes No Yes Overall 0.6 0.8 1.0 CVD mortality Group Age groups 50.59yrs 5	0.91 (0.91, 0.92) I I I 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.85, 0.92) 0.88 (0.85, 0.92) 0.88 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.94) 0.99 (0.84, 0.91) 0.91 (0.85, 0.97) 0.98 (0.84, 0.92) 0.88 (0.84, 0.91) 0.98 (0.84, 0.92) 0.88 (0.84,	Total(n) Deatt 46175 98 60330 312 76501 846 45623 248 91493 557 35495 289 53750 547 33532 160 95485 286 53750 547 33532 160 91503 887 91503 369 87964 467 94074 783	n(n) rate 30.3 74.0 161.8 78.4 87.8 117.6 220.4 147.4 68.6 70.4 127.6 141.0 57.7 76.4 120.4	 y P for Interaction 0.476 0.075 0.001 0.017 0.520 0.894 		Wo	0.91 (0.91, 0.92) I.4 HR (95% Cl) 1.6 HR (95% Cl) 1.6 (0.84, 1.34) 0.93 (0.75, 1.00) 0.93 (0.84, 1.01) 0.87 (0.75, 1.00) 0.93 (0.84, 1.01) 0.97 (0.75, 1.00) 0.92 (0.75, 1.11) 1.09 (0.92, 1.30) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.96 (0.83, 1.12) 0.91 (0.79, 1.04) 0.97 (0.78, 1.06) 0.91 (0.79, 1.04) 0.97 (0.78, 1.06)	Total(n) 55106 76749 88338 85682 81582 34426 16806 93490 78483 38723 78483 38723 153211 110095 1105765 1105765	Death(n) 44 100 341 148 175 78 78 78 78 78 78 78 78 78 78 78 78 78	Mortality rate 11.4 18.6 55.9 24.8 30.8 30.25 66.8 22.1 23.5 48.0 24.1 22.9 35.2 44.3 19.0 20.3 41.1	P for Interactio 0.386 0.045 0.534 0.705 0.009 0.658
Diabetes No Yes Overall Group Age groups Age groups 4 50/59yrs 50-59yrs 50	0.91 (0.91, 0.92) 1.2 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.85, 0.92) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.75, 0.91) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.93 (0.84, 0.91) 0.91 (0.85, 0.92) 0.88 (0.84, 0.92) 0.98 (0.84, 0.92) 0.98 (0.84, 0.92) 0.98 (0.84, 0.92) 0.98 (0.84, 0.92) 0.99 (0.85, 0.94) 0.86 (0.83, 0.94) 0.99 (0.85, 0.	Total(n) Deatl 46175 98 60330 312 76501 84 91493 527 9389 152 82862 411 46334 298 9289 152 82862 411 46334 298 53750 547 33532 160 52987 820 91503 369 87964 467 94074 783 98645 592 98345 664	n(n) Mortalit 30.3 74.0 161.8 78.4 87.8 122.8 71.5 92.4 147.4 68.6 70.4 127.6 141.0 57.7 76.4 120.4 12	 Y P for Interaction 0.476 0.075 0.001 0.017 0.520 0.894 0.153 		Wo	0.91 (0.91, 0.92) I I.4 HR (95% Cl) I 06 (0.84, 1.34) 0.93 (0.75, 1.09) 0.92 (0.84, 1.01) 0.93 (0.84, 1.01) 0.93 (0.84, 1.01) 0.94 (0.85, 1.02) 0.94 (0.85, 1.03) 1.00 (0.94, 1.02) 0.94 (0.85, 1.03) 1.00 (0.94, 1.02) 0.95 (0.87, 1.03) 1.00 (0.94, 1.02) 0.95 (0.87, 1.03) 1.00 (0.94, 1.02) 0.95 (0.87, 1.03) 1.00 (0.94, 1.02) 0.95 (0.87, 1.03) 1.00 (0.94, 1.02) 0.94 (0.85, 1.03) 0.94 (0.85, 1.03) 0.94 (0.85, 1.03) 0.94 (0.85, 1.03)	Total(n) 55106 76749 81582 81582 93490 93490 93490 93490 93490 93490 16808 93490 16808 16808 93490 16828 11098 11008 11008 11008 11008 11008 11008 11008 11008 11008 11008 11008 11008 110	Death(n) 44 100 341 148 175 78 144 79 262 65 375 339 146 150 322 326 159	Mortality rate 11.4 18.6 55.9 24.8 32.5 66.8 22.1 23.5 48.0 24.1 22.9 35.2 44.3 19.0 20.3 41.1 28.9 39.1	P for Interactio 0.386 0.045 0.534 0.705 0.009 0.658 0.626
Diabetes No Yes Overall 0.6 0.8 1.0 CVD mortality Group Age groups 4.50yrs 50-59yrs 50	0.91 (0.91, 0.92) 1.2 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.85, 0.92) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.78, 0.22) 0.85 (0.75, 0.91) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.91 (0.85, 0.94) 0.93 (0.84, 0.91) 0.91 (0.85, 0.94) 0.88 (0.84, 0.92) 0.99 (0.85, 0.94) 0.86 (0.83, 0.90) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.84, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.84, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.84, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.84, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.85, 0.94) 0.86 (0.84, 0.94) 0.86 (0.85, 0.94) 0.85 (0.94) 0.	Total(n) Deati 46175 98 60330 312 76501 84 91493 527 9389 152 82862 411 45332 160 56485 276 52957 820 91503 887 91503 369 87964 467 94074 783 96661 592 66245 545 92302 418 66265 545 92302 418 66260 545	n(n) Mortalit 30.3 74.0 161.8 78.4 87.8 220.8 71.5 92.4 147.4 68.6 724 147.4 68.6 72.6 141.0 57.7 76.4 127.6 141.0 57.7 76.4 129.6 111.0 65.1 111.5 199.2	 Y P for Interaction 0.476 0.075 0.001 0.017 0.520 0.894 0.153 0.234 		Wo	0.91 (0.91, 0.92) 1.4 HR (95% Cl) 1.6 (0.84, 1.34) (0.93 (0.75, 1.09) (0.92 (0.84, 1.01) 0.87 (0.75, 1.00) (0.92 (0.84, 1.01) 0.87 (0.75, 1.00) (0.92 (0.84, 1.01) 0.96 (0.83, 1.05) (0.97 (0.88, 1.08) 1.00 (0.81, 1.25) (0.86 (0.68, 0.92) (0.91 (0.79, 1.04) (0.97 (0.88, 1.06) (0.94 (0.85, 1.03) (0.94 (0.85, 1.0	Total(n) 55106 76748 81582 81582 93490 93490 93490 93490 93490 93490 160765 28259 153211 110095 110598 53365 132794 68252 132794	Death(n) 44 100 341 148 175 78 78 144 79 262 65 375 339 146 150 322 326 159 236 159 232 326 159 238 159	Mortality rate 11.4 18.6 55.9 24.8 30.2 66.8 22.1 23.5 48.0 24.1 22.9 35.2 44.3 19.0 20.3 41.1 28.9 39.1 25.7 32.0 77.2	P for Interactio 0.386 0.045 0.534 0.705 0.009 0.658 0.626 0.066
Diabetes No Yes	0.91 (0.91, 0.92) 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.82, 0.33) 0.88 (0.84, 0.93) 0.89 (0.82, 0.94) 0.99 (0.84, 0.91) 0.91 (0.87, 0.92) 0.85 (0.84, 0.93) 0.92 (0.84, 0.93) 0.92 (0.84, 0.93) 0.92 (0.84, 0.93) 0.93 (0.84, 0.93) 0.91 (0.87, 0.96) 0.91 (0.87, 0.96) 0.92 (0.75, 0.91) 0.88 (0.84, 0.91) 0.97 (0.84, 0.91) 0.97 (0.84, 0.91) 0.87 (0.84, 0.91) 0.87 (0.84, 0.91) 0.88 (0.83, 0.93) 0.88 (0.83, 0.93) 0.88 (0.84, 0.92) 0.99 (0.85, 0.94) 0.99 (0.85, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.99 (0.85, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.93) 0.89 (0.84, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.83, 0.94) 0.86 (0.85, 0.94) 0.88 (0.85, 0.94	Total(n) Deat 46175 98 60330 312 76501 846 45623 248 93493 557 325495 282862 93593 152 82862 411 46343 298 53750 547 33532 160 56467 276 92987 820 91503 369 87964 467 94074 783 996661 592 82302 418 92302 418 92302 418 92302 418 92503 544 293 76 92302 418 92503 544 95680 644 95680 642 95680 642 95680 642	n(n) Mortalit 30.3 74.0 161.8 78.4 87.8 117.6 220.8 71.5 92.4 147.4 127.4 147.0 124.4 127.6 141.0 57.7 76.4 120.4 88.3 111.0 65.1 115.5 199.2 77.7 187.1 100.7 93.3	 P for Interaction 0.476 0.075 0.001 0.017 0.520 0.894 0.153 0.234 0.027 		Wo	0.91 (0.91, 0.92) I I.4 HR (95% Cl) I 06 (0 84, 1.34) 0.93 (0 75, 1.09) 0.92 (0.84, 1.01) 0.93 (0 75, 1.01) 0.93 (0 84, 1.01) 0.93 (0 84, 1.01) 0.93 (0 84, 1.01) 0.93 (0 84, 1.01) 0.93 (0 84, 1.05) 0.93 (0 84, 1.05) 0.93 (0 84, 1.05) 0.94 (0 83, 1.08) 0.97 (0 88, 1.08) 0.95 (0 87, 1.03) 0.96 (0 83, 1.12) 0.91 (0 79, 1.04) 0.97 (0 88, 1.06) 0.94 (0 85, 1.03) 0.94 (0 85, 1.04) 0.97 (0 88, 1.06) 0.95 (0 67, 1.23) 0.94 (0 85, 1.03) 0.94 (0 85, 0.03) 0.94 (0 85	Total(n) 55106 85502 81582 81582 81582 81582 81582 81582 81582 81582 81582 81582 81582 81582 81582 8259 153211 110098 105765 112542 161828 58365 132794 110098 132794 110098 132794 110098 132794 110098 132794 110098	Death(n) 44 100 341 148 778 78 144 175 78 262 65 45 339 146 150 322 326 152 95 238 152 95 49 34 24 24 24 24 25 25 25 25 25 25 25 25 25 25	Mortality rate 11.4 18.6 55.9 24.8 30.8 32.5 48.0 22.9 35.2 44.3 19.0 20.3 41.1 28.9 39.1 22.0 77.2 57.4 65.4 33.0 72.2,7	P for Interactio 0.386 0.045 0.534 0.705 0.009 0.658 0.626 0.066 0.424
Diabetes No Yes Image: Constraint of the second of the second of the seco	0.91 (0.91, 0.92) 1.2 1.2 1.4 Men HR (95% Cl) 0.85 (0.76, 0.95) 0.88 (0.82, 0.93) 0.88 (0.82, 0.93) 0.88 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.93) 0.89 (0.82, 0.94) 0.99 (0.84, 0.97) 0.91 (0.87, 0.96) 0.82 (0.75, 0.91) 0.88 (0.84, 0.93) 0.89 (0.82, 0.94) 0.87 (0.84, 0.91) 0.88 (0.84, 0.92) 0.99 (0.85, 0.94) 0.89 (0.82, 0.94) 0.89 (0.85, 0.94) 0.86 (0.82, 0.90) 0.86 (0.82, 0.90) 0.86 (0.82, 0.91)	Total(n) Deat 46175 98 60330 312 776501 84 94523 248 91493 557 35495 258 82862 411 46394 298 53750 547 33532 160 56487 276 91503 869 91503 869 94074 783 96661 592 94054 664 922042 16 622444 293 46551 26 59533 544 59633 534 95650 520 91503 547 93074 783 94074 783 96661 592 48551 26 59850 520 71205 240 71205 240	n(n) Mortalit 30.3 74.0 161.8 78.4 87.8 1220.8 71.5 92.4 147.4 68.6 70.4 127.6 141.0 57.7 76.4 122.6 141.0 57.7 76.4 120	 Y P for Interaction 0.476 0.075 0.001 0.017 0.520 0.894 0.153 0.234 0.027 0.294 		Wo	0.91 (0.91, 0.92) 1.4 HR (95% Cl) 1.6 HR (95% Cl) 1.6 (0.84, 1.34) 0.93 (0.75, 1.09) 0.92 (0.84, 1.01) 0.87 (0.75, 1.00) 0.92 (0.84, 1.01) 0.87 (0.75, 1.00) 0.92 (0.84, 1.01) 0.87 (0.75, 1.00) 0.92 (0.75, 1.11) 1.09 (0.92, 1.30) 0.96 (0.83, 1.12) 0.84 (0.65, 1.08) 0.95 (0.87, 1.03) 1.00 (0.91, 1.09) 0.80 (0.69, 0.92) 0.91 (0.79, 1.04) 0.94 (0.85, 1.03) 0.94 (0.85, 1.03) 0.92 (0.74, 1.91) 1.04 (0.87, 1.23) 0.81 (0.64, 1.02) 0.92 (0.74, 1.91) 0.92 (0.74, 1.91	Total(n) 55106 86338 85682 81582 81582 93490 93490 93490 93490 93490 100565 100565 82259 110058 100565 82552 1112542 161828 58365 112542	Death(n) 44 100 341 148 175 78 78 78 78 78 282 65 339 144 150 322 326 159 238 152 95 49 34 139 346	Mortality rate 11.4 55.9 24.8 30.8 30.5 66.8 22.5 66.8 22.5 48.0 22.9 35.2 44.3 19.0 20.3 44.1 122.9 35.2 44.3 19.0 20.3 41.1 28.9 39.1 71.2 57.4 65.4 47.3	P for Interactio 0.386 0.045 0.534 0.705 0.009 0.658 0.626 0.066 0.424 0.965

FIGURE 1 Associations of per-5-kg increment of grip strength with all-cause (A) and CVD (B) mortality for men and women. Models (with age as the underlying time variable) were adjusted for ethnicity (white, mixed, Asian or Asian British, black or black British, or other), smoking status (never, previous, or current; except for models stratified by smoking status), employment (unemployed or employed), Townsend deprivation index, statin use (yes or no), hormone replacement therapy (yes or no; women only), alcohol consumption (never, previous, currently <3 times/wk, or currently ≥ 3 times/wk; except for models stratified by alcohol consumption), processed or red meat consumption (days per week; except for models stratified by processed or red meat consumption), resting pulse rate (beats per minute), MVPA time (minutes per day; except for models stratified by MVPA), and BMI (in kg/m²) (except for models stratified by BMI, waist circumference, and percent body fat). Hypertension was defined as systolic or diastolic blood pressure $\ge 140/90$ mm Hg, reported physician diagnosis of hypertension, or reported medication use to regulate blood pressure. Participants were considered to have diabetes if they. Cases with BMI <18.5 (n = 369 for men; n = 1525 for women) were excluded in the BMI-stratified models. CVD, cardiovascular disease; M, men; MVPA, moderate-to-vigorous physical activity; TV, television; W, women.



FIGURE 2 Joint associations of grip strength and BMI (in kg/m²), waist circumference, or %BF with all-cause mortality for men and women. All Cox regression models (with age as the underlying time variable) were adjusted for ethnicity (white, mixed, Asian or Asian British, black or black British, or other), smoking status (never, previous, or current), employment (unemployed or employed), Townsend deprivation index, statin use (yes or no), hormone replacement therapy (yes or no; women only), alcohol consumption (never, previous, currently <3 times/wk, or currently \geq 3 times/wk), processed or red meat consumption (days per week), resting pulse rate (beats per minute), and moderate-to-vigorous physical activity time (minute per day). The quintiles of grip strength were sex and age specific. Mortality rate is crude mortality rate per 100,000 person-years. Cases with BMI <18.5 (*n* = 369 for mer, *n* = 1525 for women) were excluded in the models with BMI. M, Men; Q, quintile; W, women; WC, waist circumference; %BF, percentage of body fat.

The lower GS quintiles had relatively higher all-cause (**Supplemental Figure 3**) and CVD mortality (**Supplemental Figure 4**) risks compared with the highest GS quintile within each adiposity stratum in both men and women.

DISCUSSION

This study investigated the complex interplay of GS and various clinical adiposity measures with mortality from all causes and CVD in middle-aged and older men and women. Overall, greater GS was strongly associated with lower all-cause mortality risks, independent of adiposity measures. Moreover, every 5-kg increment in GS was associated with an $\sim 8\%$ lower hazard of mortality across nearly all subgroups defined by demographic and lifestyle risk factors or disease status. In contrast, adiposity measures had nonsignificant or inconsistent associations with mortality, although obesity class II and abdominal obesity were strong predictors of mortality, independent of GS. The mortality risk was highest for men and women with the lowest GS and the highest adiposity in the combined analyses. More importantly, obese individuals with greater GS had lower or similar mortality risks compared with nonobese individuals with lower GS. The associations between GS and CVD mortality were comparable to the findings for all-cause mortality. Overall, our findings

provide compelling rationales for developing interventions and policies to improve muscular strength and reduce excess adiposity to minimize mortality risk.

The findings of this study are consistent with previous research by Leong et al. (9), which also demonstrated the high prognostic value of GS for various mortality and adverse health outcomes in 139,691 adults from 17 countries of different economic status. The HR of all-cause mortality for every 5-kg reduction was 1.16 in the Leong et al. (9) study but 1.08 (i.e., 1/0.92) in the present study. Some potential reasons for the difference are the use of sexand age-specific quintiles of GS to account for the inherent variation of GS by sex and age, because GS is higher in men and younger individuals, and the exclusion of baseline medical conditions to minimize potential bias due to underlying subclinical conditions on GS and mortality in the present study. Furthermore, the use of a substantially larger sample allowed for comprehensive subgroup analyses of a number of lifestyle risk factors as well as disease status.

The present study is generally consistent with the previous studies (11-14) in terms of the independent and joint associations of GS and adiposity with mortality outcomes. For instance, greater muscle strength predicted mortality independent of adiposity (11-14). In addition, the highest mortality risk was observed in individuals with the lowest category of muscle strength

CVD mortality	Men					1		V	Nomen				
Group		HR (95% CI)	Total(n)	Death(n)	Mortality rate	P for Interaction			HR (95% CI)	Total(n)	Death(n)	Mortality rate	P for Interaction
Normal Weight: 18.5≤BMI<25 Q5 (Reference) Q4 Q3 Q2 Q1		1.00 (1.00, 1.00) 1.48 (0.90, 2.45) 1.47 (0.89, 2.42) 1.69 (1.03, 2.78) 2.34 (1.47, 3.72)	7554 9330 9449 9357 9933	23 45 46 50 84	42.8 68.9 69.9 77.7 125.0	.397	÷		1.00 (1.00, 1.00) 0.74 (0.41, 1.31) 1.02 (0.61, 1.71) 1.06 (0.62, 1.81) 1.67 (1.03, 2.71)	19034 18776 18380 15779 13713	27 20 31 27 43	19.9 15.2 24.3 24.8 46.0	.049
Overweight: 25≤BMI<30 Q5 Q4 Q3 Q2 Q1		1.28 (0.81, 2.03) 1.61 (1.03, 2.52) 1.52 (0.96, 2.39) 1.89 (1.20, 2.96) 2.31 (1.49, 3.59)	20432 19865 18424 16374 16398	84 113 100 108 152	58.0 81.5 78.3 95.9 137.0				0.84 (0.50, 1.42) 1.14 (0.69, 1.87) 0.87 (0.52, 1.46) 1.31 (0.80, 2.15) 1.11 (0.67, 1.83)	18359 17178 16885 14650 14510	29 37 31 40 38	22.2 30.7 26.4 39.7 38.3	
Obesity class I: 30≤BMI<35 Q5 Q4 Q3 Q2 Q1		1.93 (1.18, 3.14) 1.97 (1.21, 3.20) 1.75 (1.06, 2.89) 1.97 (1.19, 3.25) 2.55 (1.60, 4.07)	8500 7419 6742 6049 6785	56 57 48 48 80	93.4 110.5 103.0 115.5 174.0			<u> </u>	0.88 (0.46, 1.69) 0.96 (0.50, 1.84) 0.66 (0.33, 1.34) 1.04 (0.55, 1.96) 1.28 (0.73, 2.24)	7553 6785 6873 6196 7019	14 14 11 15 24	26.1 29.5 23.1 35.1 49.9	
Obesity class II: BMI≥35 Q5 Q4 Q3 Q2 Q1		2.21 (1.17, 4.14) 2.59 (1.42, 4.73) 3.28 (1.86, 5.78) 4.63 (2.76, 7.78) 4.17 (2.52, 6.90)	2106 1812 1813 1893 2365	17 20 26 40 49	114.2 159.9 208.2 306.7 307.6				1.76 (0.91, 3.38) 2.74 (1.51, 4.98) 1.81 (0.94, 3.49) 1.92 (1.00, 3.71) 1.59 (0.85, 2.96)	3699 3090 3117 2930 3970	14 19 14 17	53.5 87.6 64.8 69.4 62.4	
WC: <94cm(M) or <80(W) Q5 (Reference) Q4 Q3 Q2 Q1		1.00 (1.00, 1.00) 1.47 (1.02, 2.12) 1.19 (0.81, 1.74) 1.66 (1.15, 2.39) 2.64 (1.89, 3.70)	16148 17693 17006 16022 15993	45 79 63 79 145	39.2 63.8 53.3 71.8 134.1	.008			1.00 (1.00, 1.00) 0.78 (0.45, 1.36) 1.06 (0.64, 1.75) 0.98 (0.57, 1.67) 1.28 (0.77, 2.12)	20592 20518 20132 17259 14989	28 22 34 26 34	19.0 15.3 24.4 21.9 33.3	.615
WC: 94-102cm(M) or 80-88(W) Q5 Q4 Q3 Q2 Q1		1.36 (0.90, 2.05) 1.59 (1.07, 2.35) 2.04 (1.40, 2.98) 1.81 (1.22, 2.69) 2.08 (1.43, 3.03)	10514 9889 9281 8259 8451	46 57 69 54 72	61.6 82.4 107.1 94.8 125.7		•!!		0.63 (0.32, 1.23) 0.82 (0.44, 1.55) 0.56 (0.28, 1.12) 1.17 (0.66, 2.08) 1.12 (0.63, 1.98)	10875 10181 10015 8714 8435	12 15 11 20 21	15.5 21.0 15.8 33.4 36.3	
WC: ≥102cm(M) or ≥88(W) Q5 Q4 Q3 Q2 Q1		1.99 (1.39, 2.85) 2.16 (1.51, 3.08) 2.02 (1.41, 2.90) 2.73 (1.93, 3.88) 2.82 (2.01, 3.96)	11943 10873 10210 9478 11246	89 99 90 113 156	105.8 131.4 127.6 173.6 205.5				1.19 (0.74, 1.93) 1.63 (1.03, 2.59) 1.17 (0.73, 1.90) 1.57 (0.98, 2.50) 1.55 (0.98, 2.44)	17394 15475 15502 13951 16161	44 55 44 52 67	35.7 50.8 40.9 54.1 60.6	
% BF: ≤20%(M) or ≤30%(W) Q5 (Reference) Q4 Q3 Q2 Q1		1.00 (1.00, 1.00) 1.18 (0.67, 2.09) 1.38 (0.79, 2.42) 1.53 (0.87, 2.68) 2.45 (1.47, 4.06)	7308 7349 6856 6139 5880	21 27 30 29 53	40.4 52.4 62.9 68.5 133.0	.055		• <u>·</u>	1.00 (1.00, 1.00) 0.94 (0.41, 2.13) 1.21 (0.56, 2.58) 1.34 (0.62, 2.90) 1.23 (0.56, 2.70)	9536 8620 8007 6872 5688	12 11 15 14	17.6 18.2 27.1 29.5 33.5	.644
% BF: 20-25%(M) or 30-33%(W) Q5 Q4 Q3 Q2 Q1		1.00 (0.59, 1.69) 1.27 (0.77, 2.10) 1.10 (0.66, 1.84) 1.27 (0.76, 2.12) 2.02 (1.25, 3.27)	12791 12331 11304 10242 9819	43 58 47 47 81	47.4 67.3 59.8 66.8 121.8		t t	<u> </u>	0.88 (0.37, 2.09) 0.51 (0.18, 1.46) 0.66 (0.26, 1.69) 1.29 (0.58, 2.87) 1.33 (0.59, 2.97)	6547 6246 5847 5189 4430	957 122	19.3 11.4 17.3 33.6 39.7	
% BF: >25%(M) or >33%(W) Q5 Q4 Q3 Q2 Q1		1.40 (0.88, 2.23) 1.62 (1.02, 2.57) 1.58 (1.00, 2.50) 1.99 (1.26, 3.14) 2.16 (1.37, 3.39)	18506 18775 18337 17378 19991	116 150 145 170 239	88.7 114.9 114.3 142.3 177.0		titi		0.87 (0.47, 1.62) 1.10 (0.60, 2.04) 0.86 (0.46, 1.59) 1.06 (0.57, 1.97) 1.18 (0.64, 2.17)	32778 31308 31795 27863 29467	63 76 67 72 97	27.1 34.7 30.3 37.5 48.1	
	0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0	0					0.5 1.	0 1.5 2.0 2.5 3.0 3.	5 4.0				

FIGURE 3 Joint associations of grip strength and BMI (in kg/m²), waist circumference, or %BF with CVD mortality for men and women. All Cox regression models (with age as the underlying time variable) were adjusted for ethnicity (white, mixed, Asian or Asian British, black or black British, or other), smoking status (never, previous, or current), employment (unemployed or employed), Townsend deprivation index, statin use (yes or no), hormone replacement therapy (yes or no; women only), alcohol consumption (never, previous, currently ≤ 3 times/wk, or currently ≥ 3 times/wk), processed or red meat consumption (days per week), resting pulse rate (beats per minute), and moderate-to-vigorous physical activity time (minutes per day). The quintiles of grip strength were sex and age specific. Mortality rate is crude mortality rate per 100,000 person-years. Cases with BMI <18.5 (*n* = 369 for men; *n* = 1525 for women) were excluded in the models with BMI. CVD, cardiovascular disease; M, men; Q, quintile; W, women; WC, waist circumference; %BF, percentage of body fat.

and the highest category of adiposity, implying the interactive impacts of muscle strength and adiposity on mortality (11, 12, 14). However, a novel observation of the present study is that strong obese individuals had relatively lower mortality risks than weak nonobese individuals. This suggests that improving muscle strength may be a more important public health priority than reducing adiposity in decreasing mortality risks, although excessive adiposity itself is a strong risk factor of mortality (15). Another novel aspect of this study compared with the previous studies (11–14) is the use of a large cohort data set, which enabled the creation of multiple subgroups of GS and various clinical adiposity indicators in examining the joint associations with mortality in men and women separately.

The present study found that men had more consistent associations between GS and mortality (independent of adiposity) than women, which is in line with previous research (13). There is also evidence on the weaker associations of GS with all-cause mortality for women (22). In this regard, convincing evidence suggests that the age-related decline in muscle strength in women (particularly after menopause) can be prevented through estrogen hormone replacement therapy (23). However, none of the previous studies (13, 22) included estrogen hormone replacement therapy as a potential confounder in the models for women, whereas the present study did. Our study clearly demonstrated lower mortality rates for both men and women with greater GS. Moreover, given that current public health guidelines (24) recommend that both men and women do muscle-strengthening activities ≥ 2 times/wk, interventions and policies should be designed and implemented in a way to encourage both sexes to engage in regular muscle-strengthening activities, regardless of their degree of adiposity.

Compelling evidence suggests that resistance exercise can result in improvements in muscle strength (including GS) and neuromotor functions in healthy and clinical adult populations (25). It appears that muscle strength gained through resistance exercise can diminish rapidly after the termination of training. but its effects on neuromotor functions can be sustained for a relatively long period of time even with a weekly session of moderate-to-vigorous intensity resistance exercise (25). We observed weak relations between GS and adiposity measures, suggesting that greater GS is determined based on better neuromotor functions rather than higher adiposity itself. Nonetheless, it is important to point out that the effects of resistance training are typically site specific (26), so training to improve GS alone may not necessarily yield favorable effects on other parts of the body. Thus, efforts should be placed on improving wholebody muscle strength as well as neuromuscular functions.

The effects of resistance training on reducing metabolic risk are also well documented. Specifically, glucose metabolisms and insulin sensitivity can be enhanced in response to resistance exercise (27). In the present study, the prevalence of diabetes was lower in both men and women across incremental GS quintiles. It may be that participation in resistance training was higher in those with greater GS because people use their hands in most upper-body resistance training. This finding suggests that individuals with greater muscle strength may sustain metabolically healthier lives. Furthermore, a meta-analysis of randomized controlled trials concluded that resistance training programs reduced concentrations of lipids and lipoproteins circulating in the bloodstream (28). However, high-intensity resistance training may increase arterial stiffness (29), which may then increase the risk of mortality and CVD (30). More evidence is needed to determine the specific dose-response relation between resistance training and health outcomes.

This study is not without limitations. First, the use of data from an observational prospective study cannot fully determine causal relations between GS and mortality. However, we excluded individuals with critical medical conditions at baseline in the primary analysis and further excluded individuals who died in the first 2 y of follow-up and individuals who had respiratory disease or were current or previous smokers at baseline in the sensitivity analysis to minimize the risk of reverse causality. Second, due to the lack of sampling strategies for recruiting samples in UK Biobank, our results may only be generalizable to those with similar characteristics to the sample analyzed in this study. Another limitation is the measurement method for aerobic fitness, a strong mortality predictor (31). Ideally, this is measured as oxygen consumption during maximal exercise tests. We adjusted for resting pulse rate instead, which is strongly associated with maximal oxygen consumption (32). The relatively low number of death cases in the analysis of CVD mortality is another limitation. Finally, the use of self-reported data for some of the covariates may have increased the risk of residual confounding.

In conclusion, men and women with greater GS had lower risks of all-cause and CVD mortality, independent of adiposity. Although excess adiposity per se presents substantial risk of mortality, the risk associated with excess adiposity was reduced, although not completely eliminated, through greater GS. Public health efforts should aim to improve the muscle strength of the population across all degrees of adiposity.

The authors' responsibilities were as follows—YK: designed the study, performed the statistical analysis, and drafted an initial version of the manuscript; KW, D-CL, SJS, NW, and SB: contributed to conceptualizing the study idea and developing the analytical plans and provided assistance with the statistical analysis; and all authors: critically reviewed and approved the final version of the manuscript and agreed to be responsible for all facets of this work. None of the authors reported a conflict of interest related to the study.

REFERENCES

- WHO Consultation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:1–253.
- Poirier P, Giles TD, Bray GA, Hong YL, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss - an update of the 1997 American Heart Association Scientific Statement on obesity and heart disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898–918.

- Barry VW, Baruth M, Beets MW, Durstine JL, Liu JH, Blair SN. Fitness vs. fatness on all-cause mortality: a meta-analysis. Prog Cardiovasc Dis 2014;56:382–90.
- Ruiz JR, Sui X, Lobelo F, Morrow JR., Jackson AW, Sjöström M, Blair SN. Association between muscular strength and mortality in men: prospective cohort study. BMJ 2008;337:a439.
- Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM, Ferrucci L. Ageassociated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol 2003;95:1851– 60.
- Bohannon RW. Hand-grip dynamometry provides a valid indication of upper extremity strength impairment in home care patients. J Hand Ther 1998; 11: 258–60.
- Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing 1994;23: 132–7.
- Cooper R, Kuh D, Hardy R; Mortality Review Group, FALCon and HALCyon Study Teams. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 2010; 341:c4467.
- Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr., Orlandini A, Seron P, Ahmed SH, Rosengren A, Kelishadi R, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet 2015;386:266–73.
- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–23.
- Ruiz JR, Sui X, Lobelo F, Lee DC, Morrow JR., Jackson AW, Hebert JR, Matthews CE, Sjostrom M, Blair SN. Muscular strength and adiposity as predictors of adulthood cancer mortality in men. Cancer Epidemiol Biomarkers Prev 2009;18:1468–76.
- Rantanen T, Harris T, Leveille SG, Visser M, Foley D, Masaki K, Guralnik JM. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. J Gerontol A Biol Sci Med Sci 2000;55:M168–73.
- Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. Int J Epidemiol 2007;36:228–35.
- Stenholm S, Mehta NK, Elo IT, Heliovaara M, Koskinen S, Aromaa A. Obesity and muscle strength as long-term determinants of all-cause mortality-a 33-year follow-up of the Mini-Finland Health Examination Survey. Int J Obes (Lond) 2014;38:1126–32.
- Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, et al. Aortic pulse wave velocity improves cardiovascular event prediction an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014;63:636–46.
- UK Biobank Coordinating Centre. UK Biobank: protocol for a largescale prospective epidemiological resource. Design 2007;06:1–112.
- Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, Sayer AA. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing 2011;40:423–9.
- 18. Bray GA. Fat distribution and body weight. Obes Res 1993;1:203-5.
- Brage S, Westgate K, Franks PW, Stegle O, Wright A, Ekelund U, Wareham NJ. Estimation of free-living energy expenditure by heart rate and movement sensing: a Doubly-Labelled Water Study. PLoS One 2015;10:e0137206.
- O'Connor L, Brage S, Griffin SJ, Wareham NJ, Forouhi NG. The crosssectional association between snacking behaviour and measures of adiposity: the Fenland Study, UK. Br J Nutr 2015;114:1286–93.
- Andersen K, Rasmussen F, Held C, Neovius M, Tynelius P, Sundstrom J. Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study. BMJ 2015;351:h4543.
- Katzmarzyk PT, Craig CL. Musculoskeletal fitness and risk of mortality. Med Sci Sports Exerc 2002;34:740–4.
- Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci 1993;84:95–8.
- WHO. Global recommendations on physical activity for health. Geneva (Switzerland): WHO; 2010.

- 25. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59.
- Layne JE, Nelson ME. The effects of progressive resistance training on bone density: a review. Med Sci Sports Exerc 1999;31:25–30.
- 27. Strasser B, Pesta D. Resistance training for diabetes prevention and therapy: experimental findings and molecular mechanisms. BioMed Res Int 2013;2013:805217.
- Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Prev Med 2009;48:9–19.

- Miyachi M. Effects of resistance training on arterial stiffness: a metaanalysis. Br J Sports Med 2013;47:393–6.
- Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness a systematic review and meta-analysis. J Am Coll Cardiol 2010;55: 1318–27.
- Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women a meta-analysis. JAMA 2009;301:2024–35.
- Blair SN, Wei M, Lee CD. Cardiorespiratory fitness determined by exercise heart rate as a predictor of mortality in the Aerobics Center Longitudinal Study. J Sports Sci 1998;16:S47–55.