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/m^2). Age- and sex-specific 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 ≥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.

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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 ∼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/m^2. 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 ÷ 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 (≥35.0). The following sex-specific clinical cutoffs were applied to create 3 groups of WC and %BF: WC: <94, 94–101.9, or ≥102 cm for men and <80, 80–87.9, or ≥88 cm for women (1); %BF ≤20%, 20.1–25%, or >25% for men and ≤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-it-yourself 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 age-specific 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. Log–log 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

TABLE 1
Participant characteristics[1]

	Men (n = 183,006)						Women (n = 220,193)					
		Grip strength						Grip strength				
Variable	All	Q1	Q2	Q3	Q4	Q5	All	Q1	Q2	Q3	Q4	Q5
Grip strength, kg	39.7 (8.8)	27.7 (4.9)	35.3 (26)	39.3 (2.7)	43.6 (2.9)	51.2 (4.9)	23.5 (6.2)	14.7 (3.6)	20.2 (2.1)	22.9 (2.1)	26.2 (2.1)	31.2 (3.5)
Age, y	56.2 (8.2)	56.4 (8.4)	55.8 (8.3)	56.5 (8.1)	56.5 (8.2)	55.6 (8.1)	56.0 (8.0)	56.7 (8.0)	55.8 (8.2)	56.5 (8.0)	55.7 (7.7)	55.4 (8.1)
Ethnicity												
White	94.4	89.6	93.7	95.5	96.3	96.6	94.4	90.9	94.0	95.1	95.9	95.6
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 therapy (W only)	N/A	N/A	N/A	N/A	N/A	N/A	7.5	7.4	7.2	7.2	7.7	7.9
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 consumption, d/wk	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)
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)	69.9 (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 cm (W)	25.4	23.7	24.5	25.4	25.7	27.2	21.9	21.3	21.8	21.9	22.1	22.3
≥102 cm (M); ≥88 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	69.6	74.4	69.8	69.7	67.8	67.1

(Continued)

TABLE 1 (*Continued*)

	Men (n = 183,006)						Women (n = 220,193)					
		Grip strength						Grip strength				
Variable	All	Q1	Q2	Q3	Q4	Q5	All	Q1	Q2	Q3	Q4	Q5
Fat-free mass, kg	63.8 (7.8)	61.0 (8.0)	62.3 (7.5)	63.3 (7.3)	64.5 (7.1)	67.3 (7.4)	44.5 (5.0)	43.4 (5.2)	43.7 (4.8)	44.0 (4.7)	44.8 (4.7)	46.3 (4.9)
Systolic blood pressure, mm Hg	140.9 (17.3)	139.2 (17.7)	139.8 (17.2)	141.1 (17.4)	142.0 (17.2)	142.3 (16.9)	135.0 (19.2)	134.3 (19.2)	133.8 (19.2)	135.2 (19.3)	135.1 (19.0)	136.1(19.1)
Diastolic blood pressure, mm Hg	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)
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 means (SDs) or %. Grip strength quintiles were sex- and age-specific. BMI (in kg/m^2) was used to categorize participants into normal weight (18 to <25), overweight (25 to <30), obesity class I (30 to <35) and obesity class II (≥35). Hypertension was defined as systolic or diastolic blood pressure ≥ 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 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

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 age-specific 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 all-cause 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 ∼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 all-cause 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

TABLE 2
Independent associations of grip strength with all-cause and CVD mortality[1]

Mortality outcome by sex and comparisons	Deaths, *n*	Person-years of follow-up	Mortality rate	HRs (95% CIs) for mortality			
				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)
Q5	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)
P-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							
Q1 (Ref.)	122	270,638	45.1	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	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)
Q3	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)
Q4	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)
Q5	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)
P-trend				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 ≥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/m^2). 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**).

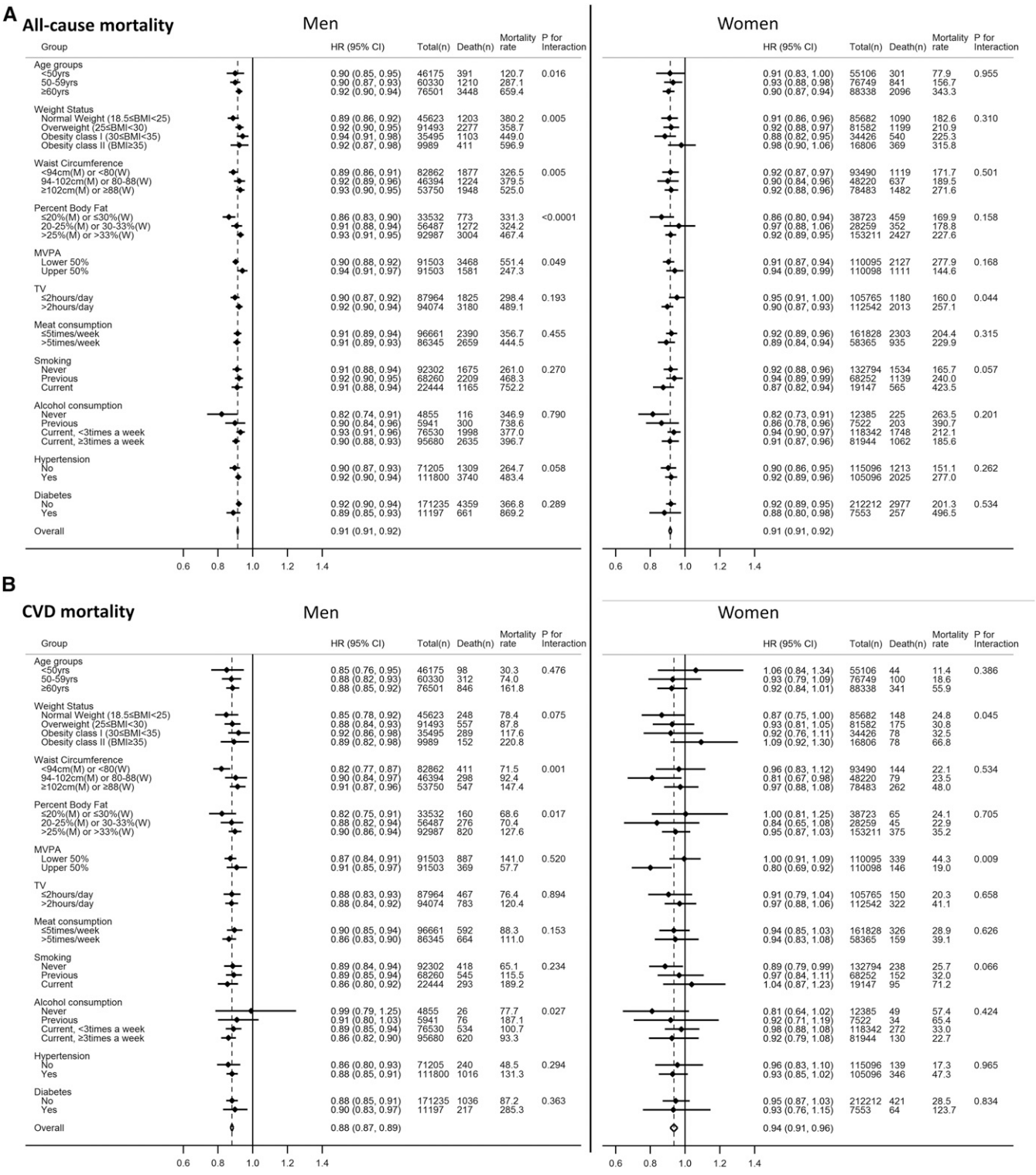

FIGURE 1 Associations of per-5-kg increment of grip strength with all-cause (A) and CVD (B) mortality for men and women. Models (with age as the underlying time variable) were adjusted for ethnicity (white, mixed, Asian or Asian British, black or black British, or other), smoking status (never, previous, 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/m^2) (except for models stratified by BMI, waist circumference, and percent body fat). Hypertension was defined as systolic or diastolic blood pressure ≥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 reported a physician diagnosis of diabetes or were undergoing glucose-lowering treatment. Mortality rate is the 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 BMI-stratified models. CVD, cardiovascular disease; M, men; MVPA, moderate-to-vigorous physical activity; TV, television; W, women.

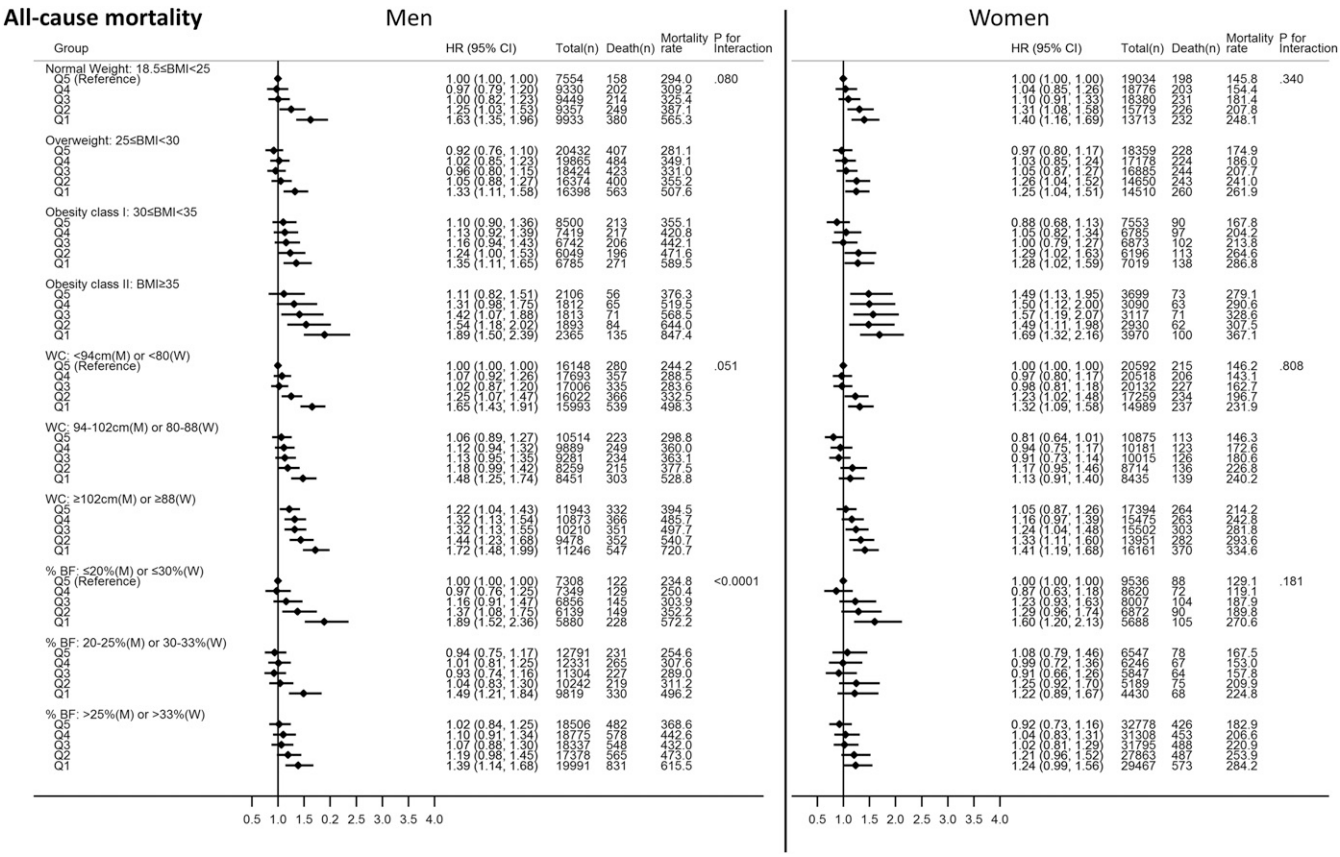

FIGURE 2 Joint associations of grip strength and BMI (in kg/m^2), waist circumference, or %BF with all-cause mortality for men and women. All Cox regression models (with age as the underlying time variable) were adjusted for ethnicity (white, mixed, Asian or Asian British, black or black British, or 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 ≥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 men; 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 ∼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 sex- and 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

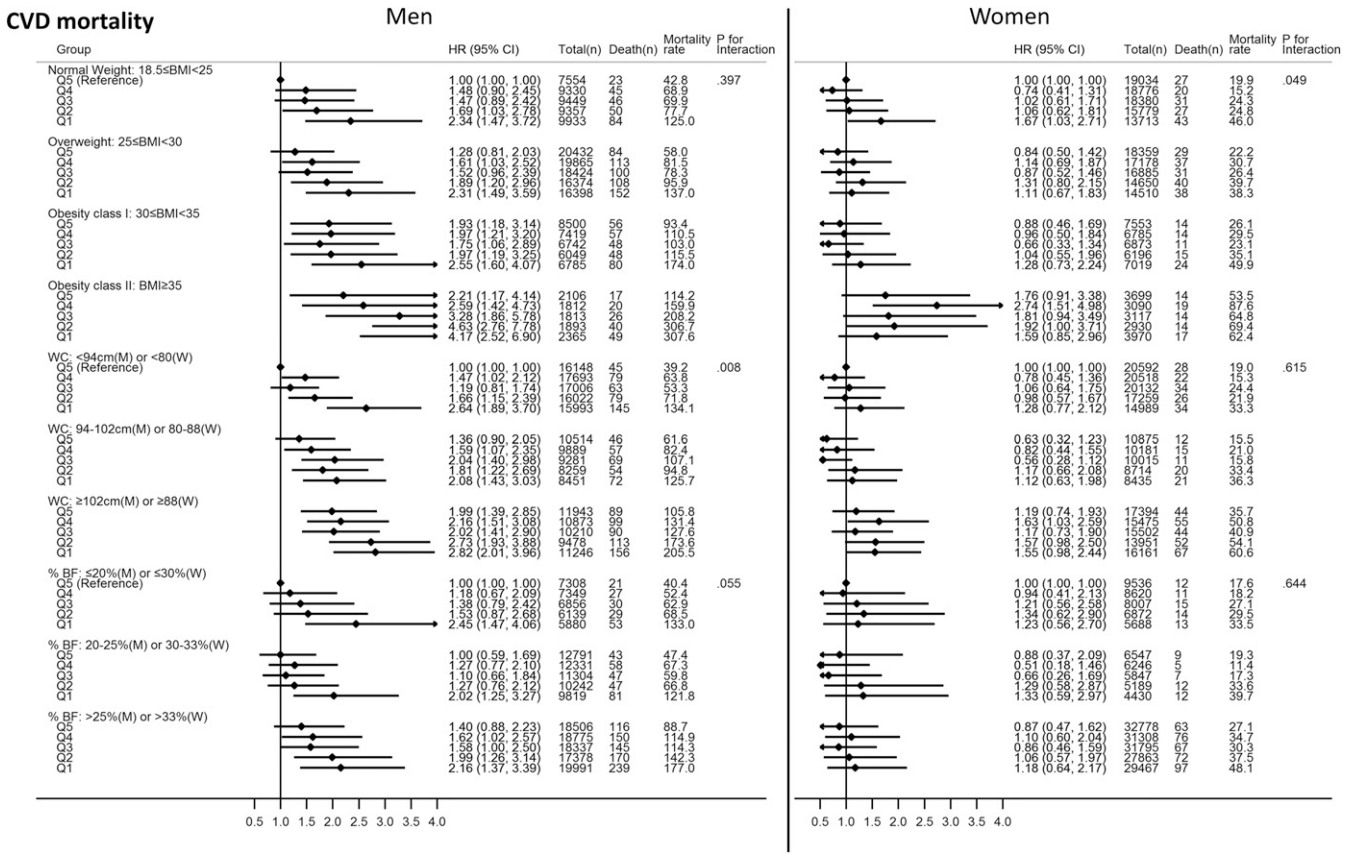

FIGURE 3 Joint associations of grip strength and BMI (in kg/m^2), waist circumference, or %BF with CVD mortality for men and women. All Cox regression models (with age as the underlying time variable) were adjusted for ethnicity (white, mixed, Asian or Asian British, black or black British, or other), 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 whole-body 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.

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