ORIGINAL ARTICLE

Physical Activity and Mortality Across Levels of Adiposity: A Prospective Cohort Study From the UK Biobank

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Abstract

Objective: To examine the combined and stratified associations of physical activity and adiposity measures, modelled as body mass index (BMI), abdominal adiposity (waist circumference), and body fat percentage (BF) with all-cause mortality.

Patients and Methods: Using the UK Biobank cohort, we extracted quintiles of self-reported weekly physical activity. Categories of measured BMI, waist circumference, and BF were generated. Joint associations between physical activity-adiposity categories and mortality were examined using Cox proportional hazards models adjusted for demographic, behavioral, and clinical covariates. Physical activity-mortality associations were also examined within adiposity strata. Participants were followed from baseline (2006 to 2010) through January 31, 2018.

Results: A total of 295,917 participants (median follow-up, 8.9 years, during which 6684 deaths occurred) were included. High physical activity was associated with lower risk of premature mortality in all strata of adiposity except for those with BMI $\geq$35 kg/m^2. Highest risk (HR, 1.54; 95% CI; 1.33 to 1.79) was observed in individuals with low physical activity and high BF as compared with the high physical activity—low BF referent. High physical activity attenuated the risk of high adiposity when using BF (HR, 1.24; 95% CI; 1.04 to 1.49), but the association was weaker with BMI (HR, 1.45; 95% CI; 1.21 to 1.73). Physical activity also attenuated the association between mortality and high waist circumference.

Conclusion: Low physical activity and adiposity were both associated with a higher risk of premature mortality, but high physical activity attenuated the increased risk with adiposity irrespective of adiposity metric, except in those with a BMI $\geq$35 kg/m^2.

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Physical inactivity has been considered as one of the biggest public health problems of the 21st Century because of its high prevalence and large disease burden.[1] Strong evidence shows an inverse dose-response relationship between physical activity and all-cause mortality[2,3] and the Scientific Advisory Committee for the 2018 US Physical Activity Guidelines concluded that this relationship is observed in all strata of weight status as determined by body mass index (BMI).[4] Although a high level of physical activity may be helpful in maintaining a healthy body weight,[5] it is also plausible that physical activity exerts benefits on health and longevity independent of maintaining healthy bodyweight. These effects may include a favorable glycemic control[6] and lower blood pressure[7] which are considered key mediators of adiposity related morbidity and mortality.[8] It is therefore possible that the risk of mortality may be a function of the combined effect of physical activity and BMI. Current evidence suggests that the increased risk of premature death in individuals with a high adiposity is attenuated but not eliminated by physical activity.[9-13]

However, the existing evidence is limited by using BMI as a proxy for adiposity. Although BMI is the most widely used

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measure for adiposity, it is a poor indicator of adiposity because it does not distinguish between body fat mass and lean mass.[14] This is important because while fat mass is considered the main cause of obesity-related health risks,[15] muscle mass has been inversely associated with the risk of death.[16] Therefore, using BMI may result in misclassification of individuals with high lean mass as overweight or obese. Further, previous studies have mostly relied on self-reported height and weight[10-12,17] which are subject to cognitive biases.[18,19] Body fat percentage (BF) is a direct measurement of adiposity and is associated with increased risk of premature mortality.[20-27] However, it is unclear if physical activity modulates the association between BF and all-cause mortality.

We aimed to examine the combined and stratified associations of physical activity and adiposity measures, modelled as BMI, abdominal adiposity (waist circumference) and BF, with all-cause mortality.

METHODS

Data Source and Study Population

We used data from the UK Biobank Resource (Application Number 29717). The UK Biobank is a population-based cohort examining the interrelations between environment, lifestyle, and genes, designed to improve the prevention, diagnosis, and treatment of chronic diseases.[28] Between 2006 and 2010, a total of 502,682 participants (approximately 5.5% of 9.2 million invited) aged 37 to 82 years were recruited via 22 assessment centers across England, Wales, and Scotland. Upon visiting the assessment centers, participants gave written informed consent before data collection, which included a touch-screen questionnaire, a wide variety of physical measurements, biological sampling, and linkage with electronic registries. Ethical approval was obtained by the North-West Research Ethics Committee. The full details of the protocol are available elsewhere.[29]

Measurements

Physical activity was assessed using an adapted version of the International Physical Activity Short Form questionnaire (IPAQ-SF). The participants reported the number of days engaging in bouts of walking, and moderate and vigorous intensity physical activity lasting for more than 10 minutes in a typical week. Total weekly physical activity was defined as metabolic equivalents (METs) in minutes per week (MET-min/week) calculated as the sum of walking (3.3 METs) and moderate (4.0 METs) and vigorous activities (8.0 METs). Following the IPAQ-SF guidelines for data processing and analysis,[30] all cases with incomplete responses or missing information for number of days or duration were excluded (n=92,411). All individuals reporting greater than 960 minutes of physical activity (ie, walking and moderate-to-vigorous physical activity [MVPA] combined) per day were also excluded. Time spent walking and doing moderate-or-vigorous activity was truncated at 180 min/day. We also excluded participants if they reported greater than 24 h/day of the combination of walking, MVPA, sleep time (missing values replaced with 8 h/day) and total screen time (sum of leisure time television and computer use). Thereafter, participants were categorized into age- (using 10-year age strata) and sex-specific quintiles of total weekly physical activity.[31]

Height and weight were measured during the initial visit to the assessment center. Calculated as weight(kg)/height(m)^2, BMI was categorized following the World Health Organization's criteria[32] into underweight ($<$18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), obese class 1 ($\geq$30.0 kg/m^2) and obese class 2 ($\geq$35kg/m^2). Cutoff points for obesity in waist circumference (WC) were set at greater than or equal to 88 cm for women and greater than or equal to 102 cm for men.[33] Using the Tanita BC-418MA body composition analyzer (Tanita Corporation, Tokyo, Japan), BF was measured by bio-impedance following standardized protocols. In the absence of population-based cutoff points for BF, we created four groups of BF maintaining the sex-specific distribution in the normal-weight, overweight, obese class 1, and obese class 2 BMI categories as: low, medium-low, medium-high, and high BF. By doing so, the sample-distribution of BF categories is identical to the distribution in BMI categories (ie, 42% [n=64,673] women with normal weight BMI would yield 42% with low BF, although not necessarily contain the same individuals). All anthropometric measurements were performed by trained clinical staff following standardized protocols.[29]

Covariates

Age was calculated as the difference between date of birth and date of baseline assessment. Self-reported sociodemographic covariates include: ethnicity (categorized as White, Asian, Black, others, and mixed background), education (categorized as no qualifications, not college or university degree, and college or university degree), marital status (recoded as living with partner or not living with partner), and employment status (recoded as employed or not employed) were self-reported. The Townsend score was used as a marker of area-based socioeconomic status, derived from postcode of residence and census data on housing, employment, social class, and car availability[34] and analyzed as a continuous variable.

Lifestyle covariates were also measured by self-report. We created a dietary pattern covariate based on meeting at least two of three healthy eating targets related to food types: 1) less than or equal to 3 weekly servings of red meat and less than or equal to 1 servings/week of processed meat; 2) greater than or equal to 2 servings per week of fish including at least one with oily fish; 3) greater than or equal to 5 servings per day of fruits and vegetables.[35] Frequency of adding salt after cooking was included as four categories (never, sometimes, usually, and always). Frequency of alcohol intake was considered as four categories (never, previous, current and <3 times/week, and current and ≥3 times/week). Smoking was considered as three categories (never, previous, and current smoker). Leisure-time screen use was created by summing the reported time spent watching television and using a computer outside of work and thereafter categorized as less than 2, 2 to 3, 3 to 4, 4 to 5, and greater than 5 h/day.[36]

Baseline health status (asthma, history of depression, women taking hormone replacement therapy, diabetes, hypertension, and statins medication) were extracted from a combination of self-report, verbal interview with a trained nurse, and hospital records.[29] In combination with the hospital records, we used clinical measurements of blood pressure (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) and hemoglobin A_{1c} (≥48 mmol/L) to identify potentially undiagnosed hypertensive and diabetic patients, respectively.

More detailed information about variable extraction and recoding is given in Supplementary Table 1 (available online at http://www.mayoclinicproceedings.org).

Outcome

Date of death was obtained from death certificates held by the National Health Service Information Centre for participants (England and Wales) and the National Health Service Central Register Scotland (Scotland). Person-years were calculated from the date attending the assessment center to the date of death, emigration, loss to follow-up, or January 31, 2018, for England and Wales and November 30, 2016, for Scotland, whichever came first.

Statistical Analyses

First, we examined the combined associations of adiposity and physical activity with all-cause mortality by creating 12 mutually exclusive categories where physical activity quintiles were further collapsed into three groups by combining quintiles 2 and 3 (medium activity) and quintiles 4 and 5 (most active). This analysis allows for direct comparison across participants with different

TABLE 1. Characteristics of Included Participants by Sex and Quintiles of Total Physical Activity in MET-min/week[a]

	Women (n=152,563)					Men (n=143,354)				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
PA quintile n	30,394	30,556	30,539	30,537	30,537	28, 628	28,625	28,708	28,719	28,674
Median	384	1010	1779	2994	5799	347	1032	1866	3192	6524
Age, years, mean ± SD	55.8 ± 7.9	55.8 ± 8.0	55.8 ± 8.0	55.8 ± 8.1	55.9 ± 8.0	56.2 ± 8.1	56.2 ± 8.1	56.3 ± 8.2	56.32 ± 8.2	56.3 ± 8.2
Adiposity-related variables										
BMI, kg/m^2, mean ± SD	28.1 ± 5.6	26.9 ± 4.9	26.5 ± 4.7	26.2 ± 4.5	26.05 ± 4.4	28.5 ± 4.5	27.7 ± 4.0	27.4 ± 3.8	27.3 ± 3.8	27.3 ± 3.8
BMI categories, kg/m^2										
18.5-24.9	33	41	44	46	48	21	26	28	29	28
25-29.9	37	37	37	37	36	48	51	52	51	52
30-34.9	19	15	13	12	12	23	18	17	17	17
≥35	11	7	6	5	4	8	5	4	4	4
WC, cm, mean ± SD	86.9 ± 13.1	84.2 ± 11.9	83.1 ± 11.5	82.3 ± 11.2	81.8 ± 11.2	99.4 ± 11.8	96.8 ± 10.8	95.5 ± 10.3	94.8 ± 10.3	94.5 ± 10.3
WC categories										
<88 cm W, <102 cm M	57	66	69	72	73	62	71	75	77	78
≥88 cm W, ≥102 cm M	43	34	31	28	27	38	29	25	23	22
BF	38.1 ± 6.7	36.5 ± 6.6	35.8 ± 6.5	35.2 ± 6.6	34.8 ± 6.7	26.4 ± 5.7	25.2 ± 5.5	24.5 ± 5.5	24.1 ± 5.6	23.9 ± 5.6
BF categories[b]										
Low	31.39	39.98	44.12	47.43	50.00	18.43	24.32	28.12	31.03	32.30
Medium-low	38.22	38.03	37.35	36.30	34.83	49.13	51.37	51.28	49.99	49.72
Medium-high	18.96	1524	12.82	11.66	10.98	23.77	19.03	16.73	15.32	14.92
High	11.44	6.76	5.71	4.61	4.19	8.67	5.28	3.87	3.66	3.06
Sociodemographic variables										
Ethnicity										
White	95	95	96	96	95	95	96	96	96	96
Asian	2	2	2	2	2	3	2	2	2	2
Black	2	2	1	1	1	1	1	1	1	1
Others / Mixed background	1	1	1	1	2	1	1	1	1	1
Townsend deprivation index, mean ± SD	-1.6 ± 2.9	-1.6 ± 2.9	-1.6 ± 2.9	-1.6 ± 2.9	-1.5 ± 2.9	-1.6 ± 3.0	-1.7 ± 3.0	-1.7 ± 2.9	-1.6 ± 2.9	-1.3 ± 3.0
Education										
No qualifications	12	10	11	12	15	10	9	9	12	19
Not college/university degree	52	50	50	51	55	48	45	46	49	56
University degree	36	40	39	37	30	42	46	45	39	25
Marital status, living with partner	71	71	72	71	71	80	80	80	80	80
Currently employed	65	63	61	58	58	71	68	66	64	67
Lifestyle covariates[c]										
Diet pattern, meeting 2 targets	70	76	79	81	81	52	60	63	66	64
Salt intake										
Never/rarely	56	58	59	60	59	54	56	57	56	55

Continued on next page

TABLE 1. Continued

	Women (n=152,563)					Men (n=143,354)				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
PA quintile n	30,394	30,556	30,539	30,537	30,537	28, 628	28,625	28,708	28,719	28,674
Median	384	1010	1779	2994	5799	347	1032	1866	3192	6524
Lifestyle covariates[c], continued										
Sometimes	28	28	27	27	27	28	28	28	28	28
Usually	11	10	10	10	10	13	12	12	12	13
Always	5	4	4	3	4	5	4	3	4	4
Alcohol intake										
Never	5	5	4	4	5	3	2	2	2	2
Previous	3	2	3	3	3	3	2	2	2	3
Current, <3 times/week	55	52	51	52	54	42	39	38	40	44
Current, ≥3 times/week	37	41	42	41	38	52	57	58	56	51
Smoking status										
Never	61	62	61	61	61	52	54	54	53	49
Previous	30	31	32	32	31	36	36	36	37	38
Current	9	7	7	7	8	12	10	10	10	13
Screen time, h/day										
<2	12	14	15	15	15	8	10	11	10	10
2-3	19	21	21	22	22	15	17	18	17	18
3-4	22	23	24	23	24	20	22	22	23	24
4-5	19	18	18	18	18	19	19	19	20	21
>5	28	23	22	22	21	38	32	30	30	27
Health-related covariates										
Diagnosed asthma	13	11	12	11	11	12	10	11	10	10
History of depression	8	6	6	5	6	5	4	3	3	3
Taking HRT, women	8	7	7	7	8	NA	NA	NA	NA	NA
Diabetes	4	3	3	3	3	9	6	5	5	5
Hypertension	48	45	44	44	44	61	59	58	59	60
Taking statins medication	10	8	8	8	7	18	16	15	14	12

[a]BF, total body fat percentage; BMI, body mass index; HRT, hormone replacement therapy; M, men; MET, metabolic equivalent; NA, not applicable; PA, physical activity; W, women; WC, waist circumference.

[b]The four BF groups were created maintaining the sex-specific distribution in the normal-weight to obese type 2 BMI categories as: low, medium-low, medium-high, and high BF.

[c]Dietary pattern is based on meeting at least two of three healthy eating targets related to food types: 1) ≤3 weekly servings of red meat and ≤1 servings/week of processed meat; 2) ≥2 servings per week of fish including at least one with oily fish; and 3) ≥5 servings per day of fruits and vegetables.

Values are percentages unless stated otherwise.

combinations of physical activity and adiposity with the most active and with lowest adiposity as the reference. Second, we analyzed the associations between physical activity (using quintiles) and all-cause mortality in different strata of adiposity (BMI, WC, and BF), using the least active quintile as the reference. Both analyses were performed using Cox proportional hazard regression models with age as the underlying time scale and with various levels of adjustment. Model 1 (crude model) was adjusted for age and sex. Model 2 was additionally adjusted for the Townsend deprivation index, ethnicity, education, marital status, salt intake, dietary pattern, alcohol intake, smoking status, employment, screen time, asthma, depression, and hormone replacement therapy (women only). Finally, model 3 was further adjusted for prevalent diabetes, hypertension, and use of statins medication. We verified the proportional hazards assumption of the models by visual inspection of log-log plots. In addition, we examined interactions between physical activity (PA) and adiposity variables using a likelihood-ratio test.

To minimize potential influence of reverse causality (ie, undiagnosed, subclinical disease(s) potentially affecting physical activity and mortality), follow-up was commenced 2 years after the baseline examination (excluding 1204 participants) and we excluded all participants reporting any prevalent chronic neurologic degenerative problems, chronic widespread pain, chronic respiratory diseases (including chronic obstructive pulmonary disease), liver failure or cirrhosis, psychological or psychiatric problems, substance abuse or dependency and eating disorders, as well as those with a BMI less than 18.5 kg/m^2 (to avoid including individuals with illness-related weight loss) and pregnant women at baseline (n=35,094). Additionally, participants with prevalent cancer (excluding nonmelanoma skin cancer) or cardiovascular disease (CVD) identified from self-report or flagged in hospital records were excluded before analysis (n=63,193). We also excluded participants with missing covariates from the analysis (n=14,687). Details of exclusions are presented in the Supplementary Figure (available online at http://www.mayoclinicproceedings.org).

We repeated the analysis with restriction to never smokers (n=168,654) to accommodate potential residual confounding from smoking. For this purpose, obesity classes I and II were combined due to the low number of cases in each of these categories. Similarly, the two highest categories of BF were combined.

Finally, we analyzed the joint associations between PA and cause-specific mortality (CVD and cancer), across strata of adiposity accounting for competing risks using the subdistribution method of Fine and Gray.[37] For CVD mortality, we treated all other causes of death as competing events with all noncancer deaths treated as competing events when cancer-related mortality was the outcome.

All analyses were performed using statistical software Stata 16 (StataCorp LP, College Station, TX). *P* values less than or equal to 0.05 were considered statistically significant.

RESULTS

A total of 295,917 participants (mean age ± SD, 56.0 ± 8.1 years; range, 38.9 to 73.7 years; 51.6% women) were included in the analysis (Table 1). Median follow-up time was 8.9 years, during which 6,684 deaths occurred.

The bivariate Pearson's correlations between BMI and BF were 0.85 (women) and 0.79 (men) with similar correlations of 0.87 and 0.81 (women) and 0.87 and 0.79 (men) observed between BMI and WC and between BF and WC, respectively. A summary of the median and range of weekly physical activity levels per quintile, sex, and age strata, is presented in Supplementary Table 2 (available online at http://www.mayoclinicproceedings.org). The PA level in the lowest and highest quintiles of PA (368 and 6132 MET-min/week) corresponds to approximately 16 and 265 minutes of daily walking, respectively. The hazard ratios (HRs) of all-cause

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TABLE 2. Hazard Ratios of All-Cause Mortality for Physical Activity and Adiposity Measures in the Included Sample[a]

	Hazard ratios (95% CI)		
	Model 1[b]	Model 1a[c]	Model 3a[d]
PA quintiles			
Q1 (less active)	1 (reference)	1 (reference)	1 (reference)
Q2	0.82 (0.77 to 0.89)	0.85 (0.79 to 0.92)	0.89 (0.82 to 0.95)
Q3	0.80 (0.74 to 0.86)	0.84 (0.78 to 0.91)	0.88 (0.81 to 0.95)
Q4	0.83 (0.77 to 0.89)	0.87 (0.81 to 0.94)	0.89 (0.83 to 0.96)
Q5 (most active)	0.80 (0.75 to 0.86)	0.85 (0.79 to 0.92)	0.84 (0.78 to 0.91)
BMI, kg/m^2			
18.5-24.9	1 (reference)	1 (reference)	1 (reference)
25-29.9	1.01 (0.96 to 1.08)	1.01 (0.95 to 1.07)	0.96 (0.91 to 1.02)
30-34.9	1.28 (1.19 to 1.37)	1.26 (1.17 to 1.35)	1.10 (1.02 to 1.19)
≥35	1.78 (1.62 to 1.95)	1.72 (1.56 to 1.89)	1.34 (1.21 to 1.49)
Waist circumference, cm			
<88 Women, <102 men	1 (reference)	1 (reference)	1 (reference)
≥88 Women, ≥102 men	1.41 (1.34 to 1.48)	1.38 (1.31 to 1.45)	1.21 (1.14 to 1.27)
BF[e]			
Low	1 (reference)	1 (reference)	1 (reference)
Medium-low	1.05 (0.99 to 1.11)	1.04 (0.98 to 1.11)	0.99 (0.93 to 1.05)
Medium-high	1.32 (1.23 to 1.42)	1.29 (1.20 to 1.39)	1.13 (1.05 to 1.22)
High	1.71 (1.56 to 1.88)	1.66 (1.51 to 1.82)	1.30 (1.18 to 1.44)

[a]BF, body fat percentage; BMI, body mass index; PA, physical activity.
[b]Model 1 was adjusted for age (as time-scale in model) and sex.
[c]Model 1a was adjusted as Model 1 plus BF-categories in the case of PA and plus PA-quintiles in the case of BMI, waist circumference or BF (mutual adjustment).
[d]Model 3a was adjusted as Model 1a plus ethnicity, education, marital status, employment, Townsend Deprivation Index, diet pattern, salt intake, alcohol intake, smoking status, screen time, asthma, depression, hormone replace therapy (women only), diabetes, hypertension and statins medication.
[e]The four BF groups were created maintaining the sex-specific distribution in the normal-weight, overweight, obese type 1, and obese type 2 BMI categories as: low, medium-low, medium-high, and high BF.

mortality for physical activity, BMI, WC, and BF ("independent" associations) are presented in Table 2.

Figure 1 displays joint PA-BMI, PA-WC, and PA-BF associations with all-cause mortality. The likelihood ratio tests of interaction were not significant irrespective of the adiposity measure used ($P>0.08$ for model 1 and $P>0.18$ for model 3). Generally, the magnitude of associations was similar in the crude (age- and sex-adjusted) model compared with the multivariable-adjusted model. In the multivariable-adjusted model, the highest risk (HR, 1.54; 95% CI, 1.33 to 1.79) was observed in the low PA and high BF group, compared with the reference (high PA and low BF). The magnitude of associations were similar when combining PA with BMI (HR for low PA and high BMI, 1.52; 95% CI, 1.30 to 1.78) and WC (HR for low PA and high WC, 1.55; 95% CI, 1.32 to 1.57) (see Supplementary Table 3 [available online at http://www.mayoclinicproceedings.org] for n/deaths in each PA-adiposity category). The lowest risk of premature mortality was observed in the referent group (high PA combined with a low level of adiposity), but there was a consistent pattern of attenuated HRs with high PA across levels of adiposity, irrespective of the adiposity metric used, although PA did not attenuate the higher risk associated with a BMI greater than or equal to 35 kg/m^2. For example, HRs for high PA in the most-obese category, compared with the reference, were 1.24 (95% CI, 1.04 to 1.49) and 1.19 (95% CI, 1.10 to 1.30) for high BF and WC, respectively, but 1.45 (95% CI, 1.21 to 1.73) for BMI. When restricting the joint-associations analyses to never-smokers (n=168,654), the

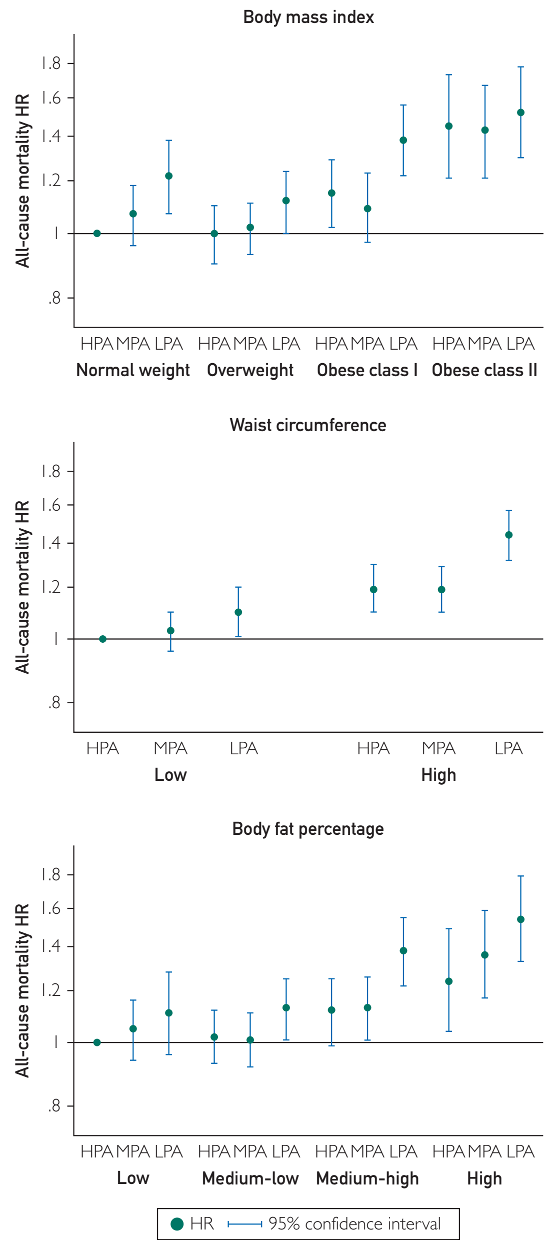

FIGURE 1. Joint associations between all-cause mortality and groups of physical activity in relation to body mass index, waist circumference, and body fat percentage strata. Values are hazard ratios (HRs) and 95% CIs. For waist circumference, low means less than 88 cm in women and 102 cm in men, and high greater than or equal to 88 cm in women and greater than or equal to 102 cm in men. The four body fat percentage groups were created maintaining the sex-specific distribution in the normal weight, overweight, obese class 1, and obese class 2 body mass index categories as: low, medium-low, medium-high, and high body fat percentage. Results are from model 3, adjusted for age (as time-scale in model), sex, ethnicity, education, marital status, employment, Townsend deprivation index, diet pattern, salt intake, alcohol intake, smoking status, screen time, asthma, depression, hormone replace therapy (women only), diabetes, hypertension, and statins medication. HPA = high physical activity, group created by combining quintiles 4 and 5; LPA = low physical activity, group including the first quintile; MPA, medium physical activity, group created by combining quintiles 2 and 3.

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associations were generally attenuated for the low- and accentuated for the high-adiposity categories compared with the full sample (Supplementary Table 4, available online at http://www.mayoclinicproceedings.org).

In the stratified analysis (Table 3), higher levels of PA were associated with a lower risk of all-cause mortality in all strata of BMI except for those with obesity class II, irrespective of the level of adjustment, although some of the 95% CIs overlapped 1 (eg, those with low BF). The most pronounced risk reductions were generally observed when comparing the least active (reference) and the second quintile of physical activity for all measures of adiposity. Similar to the joint-associations analyses, the magnitude of associations was analogous in the crude (age- and sex-adjusted) model (Supplementary Table 5, available online at http://www.mayoclinicproceedings.org) compared with the multivariable-adjusted model. In the multivariable-adjusted model, being in the most active quintile was associated with a 19% lower all-cause mortality risk compared with the least-active category in the normal weight stratum (HR, 0.81; 95% CI, 0.70 to 0.93) and the risk reduction was approximately 15% in the overweight (HR, 0.85; 95% CI, 0.76 to 0.96) and obese I (HR, 0.84; 95% CI, 0.71 to 0.98) strata. Being in the most active quintile did not reduce all-cause mortality risk in those with BMI greater than or equal to 35 kg/m^2 (HR, 0.94; 95% CI, 0.71 to 1.23). Among those with a high WC, the risk for all-cause mortality was 19% lower (HR, 0.81; 95% CI, 0.72 to 0.92) in the most-active compared with those in the least-active quintile. A lower risk of death with higher levels of PA was also observed in all strata of BF, except for those with low BF, with the greatest risk reduction in individuals with high BF (HR, 0.70; 95% CI, 0.53 to 0.94 when comparing the most-active to the least-active quintile).

When the analysis was restricted to never-smokers (Supplementary Table 6, available online at http://www.mayoclinicproceedings.org), the effect sizes were generally attenuated with nonsignificant associations across normal weight and overweight BMI. In contrast, PA remained significantly and inversely associated with all-cause mortality in the obese BMI categories, those with high abdominal adiposity (WC) and medium-high and high body fat.

The patterns of associations were similar in men and women, although the magnitude of associations appeared more pronounced in women (Supplementary Tables 7 and 8, available online at http://www.mayoclinicproceedings.org).

Results of analysis using cause-specific mortality (Figure 2) showed that high levels of PA attenuated the risk of CVD mortality in all strata of adiposity (Supplementary Table 9, available online at http://www.mayoclinicproceedings.org), whereas attenuation was less pronounced for cancer-related mortality (Supplementary Table 10, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

We found that high levels of PA attenuated the increased risk of all-cause mortality with increasing levels of BMI, WC, and BF, except for BMI greater than 35 kg/m^2 where the risk was increased regardless of activity levels. High PA was also associated with lower risk of all-cause mortality in nearly all strata of adiposity, irrespective of the adiposity measure used, with the exceptions of BMI greater than 35 kg/m^2 and low-BF.

Our findings echo previous studies based on self-reported anthropometric data, which have reported that PA attenuated the increased risk of high BMI on all-cause mortality.[10,11,38] Our study also extends these previous results by including BMI and WC from clinical assessments, as well as BF as a direct measure of adiposity.

In general, the associations between PA and all-cause mortality observed from the stratified analyses are smaller in magnitude compared with previous observations.[10,11,17,38] This may partly be explained by how the reference group was defined in each study because the levels of PA in the least or most active group can vary in some extent across these studies.

Our findings are also in accordance with evidence from self-report[38] and device-measured[2] PA data indicating that the greatest reductions in all-cause mortality are usually observed when increasing activity from an initially low level. The absolute difference in PA observed between the least and the second-least active (second quintile) groups (corresponding to 600 MET-min) (Table 1) is equivalent to the current recommendations for public health of 150 min/week of moderate PA.[39] No further risk reductions were observed with higher levels of PA, especially when BMI and WC were modelled as adiposity indicators. This suggests that the PA levels needed to obtain health benefits should be achievable for most individuals irrespective of their level of adiposity. We observed that moderate levels of PA also conferred benefits in reducing mortality risk, regardless of the actual BMI or BF, except in those categorized by BMI as obesity class 2. In the stratified analysis, we observed the greatest risk reduction in the most-active group with high BF (median PA levels, 5918 MET-min/week; equivalent to approximately 256 minutes of daily walking), compared with the least-active-high BF referent group (median PA levels, 990 MET-min/week; corresponding to approximately 43 minutes of daily walking). The attenuating effect of high levels of PA across levels of adiposity was similar regardless of whether adiposity was measured by anthropometric measures or as body fat assessed by bio-impedance, except among individuals with a BMI greater than or equal to 35 kg/m^2. Nevertheless, the joint associations analysis showed that, in those with high BF, high levels of PA (median PA levels, 4032 MET-min/week; approximately 175 minutes of daily walking) substantially attenuated the detrimental association between BF and mortality. However, the importance of maintaining a healthy weight is also evident from the joint analyses as individuals with low adiposity and low PA had lower mortality risk than those with high adiposity, irrespective of their level of PA. Taken together, our results suggest that a combination of PA and maintenance of a healthy body weight, which may not be achieved through PA alone,[5] is needed to manage the risk of premature mortality. From these results, two aspects should be particularly highlighted. First, the patterns of the associations using BMI or BF are not identical. Previous research has reported that BMI is a stronger predictor of mortality than BF,[40] and the potential underlying mechanisms could be related to the fact that BMI takes into account fat and fat-free mass, both commonly high in obese BMI categories, whereas BF is only adiposity. Therefore, this may partially explain the different patterns. On the other hand, this suggests that, besides the benefits of PA in almost all adiposity strata, high levels of PA may be even more beneficial in those with high amounts of body fat.

BMI is an indirect measure of adiposity and it does not take bone and muscle mass into consideration. Therefore, BMI has poor sensitivity and specificity when classifying obesity.[41] Additionally, the relation between BMI and BF is not linear and differs for men and women.[41] Anthropometric proxies for central obesity, such as WC, have been considered as better predictors of increased levels of health risk factors,[42,43] and some evidence suggests higher risk of mortality for high WC compared with BMI.[44-46] Nevertheless, just a few previous studies analyzed the associations between PA and mortality in strata of WC, all based on self-reported data,[10,11] restricted to single sex cohorts[11,13] or including a small number of deaths.[13] BF reflects better the serum lipid profile and its metabolic alterations than its anthropometric surrogates,[47] and this is closely related to coronary heart disease,[48] a leading cause of death in developed countries.[49]

It has previously been reported that smoking modifies the association between BMI and mortality by right-shifting the optimal BMI level into the overweight domain and that adjusting for smoking status is insufficient to remove this confounding.[11,50-52] Restricting our analysis to never-smokers attenuated the HRs, especially for those with low adiposity levels irrespective of the adiposity measure used. This may suggest residual confounding from smoking or smoking-related illness among

TABLE 3. Hazard Ratios for the Associations Between Physical Activity and All-Cause Mortality, by Adiposity Categories[a,b]

	Q1 (least active)	Q2	Q3	Q4	Q5 (most active)
BMI, kg/m^2					
18.5-24.9					
Model 3	1 (reference)	0.93 (0.81 to 1.08)	0.85 (0.73 to 0.99)	0.87 (0.75 to 1.00)	0.81 (0.70 to 0.93)
Total n/n deaths	16,205/342	19,863/378	21,314/368	22,415/399	22,573/401
25-29.9					
Model 3	1 (reference)	0.87 (0.77 to 0.97)	0.96 (0.85 to 1.07)	0.94 (0.84 to 1.06)	0.85 (0.76 to 0.96)
Total n/n deaths	24,921/614	25,960/547	26,197/600	25,852/602	25,709/561
30-34.9					
Model 3	1 (reference)	0.82 (0.70 to 0.97)	0.73 (0.61 to 0.86)	0.80 (0.68 to 0.94)	0.84 (0.71 to 0.98)
Total n/n deaths	12,149/393	9,841/257	8915/209	8496/227	8577/237
≥35					
Model 3	1 (reference)	0.96 (0.76 to 1.22)	0.91 (0.71 to 1.18)	0.97 (0.75 to 1.26)	0.94 (0.71 to 1.23)
Total n/n deaths	5,747/201	3517/111	2821/85	2493/80	2352/72
Waist circumference, cm					
Low: <88 women, <102 men					
Model 3	1 (reference)	0.94 (0.85 to 1.04)	0.94 (0.85 to 1.04)	0.95 (0.86 to 1.04)	0.88 (0.79 to 0.97)
Total n/n deaths	34,953/734	40,392/780	42,691/818	43,967/872	44,510/864
High: ≥88 women, ≥102 men					
Model 3	1 (reference)	0.83 (0.74 to 0.93)	0.81 (0.72 to 0.91)	0.84 (0.75 to 0.94)	0.81 (0.72 to 0.92)
Total n/n deaths	24,069/816	18,789/513	16,556/444	15,289/436	14,701/407
BF[c]					
Low					
Model 3	1 (reference)	0.96 (0.82 to 1.14)	0.95 (0.81 to 1.18)	0.87 (0.74 to 1.02)	0.94 (0.80 to 1.09)
Total n/n deaths	14,759/257	19,058/310	21,443/346	23,316/353	24,396/429
Medium-low					
Model 3	1 (reference)	0.90 (0.81 to 1.01)	0.90 (0.80 to 1.01)	0.99 (0.88 to 1.03)	0.84 (0.75 to 0.95)
Total n/n deaths	25,715/617	26,406/574	26,182/565	25,461/629	24,993/552
Medium-high					
Model 3	1 (reference)	0.80 (0.70 to 0.93)	0.81 (0.70 to 0.94)	0.80 (0.68 to 0.94)	0.80 (0.69 to 0.94)
Total n/n deaths	12,665/442	10,188/285	8799/255	8051/239	7684/229
High					
Model 3	1 (reference)	0.89 (0.71 to 1.10)	0.87 (0.68 to 1.10)	0.87 (0.68 to 1.11)	0.70 (0.53 to 0.94)
Total n/n deaths	5,883/234	3,529/124	2823/96	2428/87	2138/61

[a]BF, body fat percentage; BMI, body mass index; PA, physical activity; Q, quintile.

[b]Values are hazard ratios (95% CIs) unless stated otherwise.

[c]The four BF groups were created maintaining the sex-specific distribution in the normal-weight, overweight, obese type 1 and obese type 2 categories as: low, medium-low, medium-high and high BF.

Model 3 was adjusted for age (as time-scale), sex, ethnicity, education, marital status, employment, Townsend deprivation index, diet pattern, salt intake, alcohol intake, smoking status, screen time, asthma, depression, hormone replace therapy (women only), diabetes, hypertension, and statins medication.

lean individuals with low PA levels, a confounding structure which could also lead to lower PA levels (reverse causation). Joint-analysis among never-smokers suggested attenuated HRs among inactive lean individuals compared with active lean individuals but amplified the risk of mortality in those with obesity class II and low PA, consistent with the plausibility of an inflated mortality rate among the lean due to smoking-related confounding. Few previous studies have previously examined PA-adiposity-mortality interactions in never-smokers. Koster et al[10] observed a substantial increase in the risk of all-cause mortality among active obese when restricting their analysis to never-smokers but did not report the impact of this sensitivity analysis among lean individuals. Similarly, Ekelund et al[38] observed attenuated HRs with high PA among obese current and former smokers as compared with analysis among obese never-smokers.

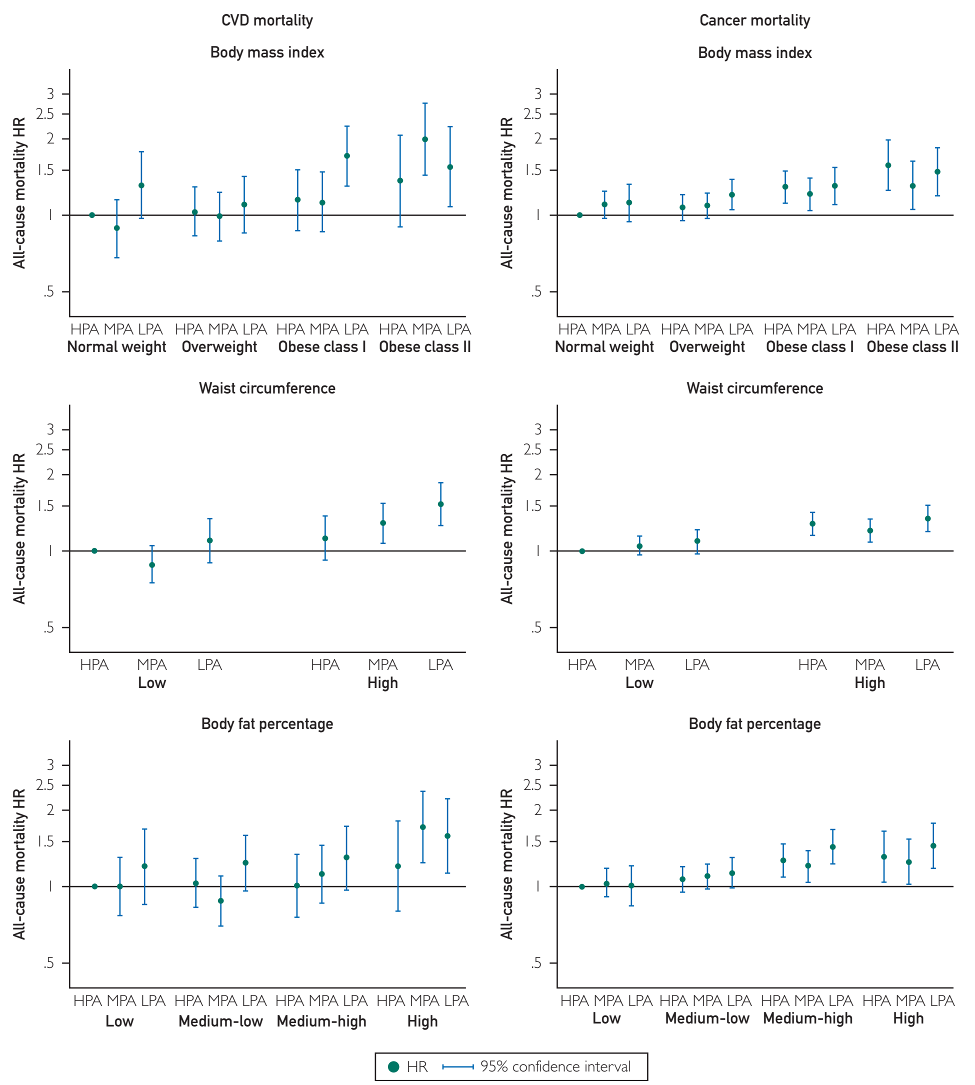

FIGURE 2. Joint associations between cardiovascular disease or cancer mortality and groups of physical activity in relation to body mass index, waist circumference and body fat percentage strata. Values are hazard ratios (HRs) and 95% CIs. For waist circumference, low means less than 88 cm in women and 102 cm in men, and high greater than or equal to 88 cm in women and greater than or equal to 102 cm in men. The four body fat percentage groups were created maintaining the sex-specific distribution in the normal-weight, overweight, obese type 1, and obese type 2 body mass index categories as: low, medium-low, medium-high and high body fat percentage. Results are from model 3, adjusted for age (as time-scale in model), sex, ethnicity, education, marital status, employment, Townsend deprivation index, diet pattern, salt intake, alcohol intake, smoking status, screen time, asthma, depression, hormone replace therapy (women only), diabetes, hypertension, and statins medication. HPA = high physical activity, group created by combining quintiles 4 and 5; LPA, low physical activity, group including the first quintile; MPA, medium physical activity, group created by combining quintiles 2 and 3.

The impact of residual confounding from smoking or smoking-related illness may differ across sample smoking prevalence and warrants further investigation.

When examining associations with cause-specific mortality we observed a larger attenuation and even elimination of the increased risk of adiposity from high PA on

CVD mortality but not on cancer mortality which is consistent with the findings from previous research[11] and supports the biological plausibility of our findings.

The findings of the present study have important public health implications as the 2018 US Physical Activity Guidelines Advisory Committee highlighted PA and mortality associations across weight strata as an under-researched area.[4] With a high prevalence of obesity in developed countries and increasing obesity prevalence in developing countries,[53] examining strata-specific associations are important to determine the need of tailored interventions. With the largest risk reductions observed when moving from the least-active quintile to the second quintile of PA irrespective of adiposity strata, recommending a minimum of 150 minutes of MVPA/week irrespective of weight seems reasonable to reduce all-cause mortality risk. Nevertheless, it is also essential to highlight the importance of achieving and maintaining a healthy weight and adiposity levels.

Study Limitations

Some strengths and limitations must be considered when interpreting the findings from our study. All adiposity measurements were collected by research staff, which reduces cognitive biases derived from self-administered measurements. The large sample size with a wide range of PA levels, BMI, WC, and BF included in our analyses produced effect estimates with narrow CIs. The large sample size allowed exclusion of participants with health conditions and deaths occurring within 2 years of follow-up to minimize reverse causation bias. Further, we adjusted our analyses for a range of potential confounders regarding lifestyle, health, and socioeconomic factors. Physical activity was assessed by a previously validated self-report instrument.[54] However, self-reported PA is less accurate than device-measured PA and may introduce bias. Random measurement error tends to attenuate the observed associations whereas a differential measurement error may either increase or attenuate the magnitude of association. It is possible that measurement error in self-reported PA, compared with device-measured activity, is larger in obese individuals.[55,56] This would dilute differences between PA categories within, but not between, adiposity categories. Also, the accuracy of bio-impedance for measuring BF is affected by the height, cross-sectional area, and ionic composition of the body,[57] and may not be equally valid across ethnicities.[58] In addition, UK Biobank participants are not representative of the entire UK population, and there is evidence of a healthy volunteer selection bias.[59] Nevertheless, the exposure-disease relationships may not be strongly affected by sample representativeness.[60]

Future studies may consider including even more precise measures of exposures such as accelerometer measures of PA and sedentary time and more precise measures of general and abdominal adiposity, such as magnetic resonance imaging.[61]

CONCLUSION

Low PA and adiposity were both associated with a higher risk of premature mortality, but high PA attenuated the increased risk with adiposity irrespective of adiposity metric, except in those with a BMI greater than or equal to 35 kg/m.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BF** = body fat percentage; **BMI** = body mass index; **CVD** = cardiovascular disease; **HR** = hazard ratio; **MET** = metabolic equivalent; **MVPA** = moderate-to-vigorous physical activity; **WC** = waist circumference

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REFERENCES

1. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med*. 2009;43(1):1-2.
2. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ*. 2019;366:l4570.
3. US Department of Health and Human Services. *Physical Activity Guidelines for Americans*. 2nd Edition. Washington, DC: US Department of Health and Human Services; 2018.
4. 2018 Physical Activity Guidelines Advisory Comittee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. Washington, DC: US Department of Health and Human Services; 2018.
5. Jones PR, Ekelund U. Physical Activity in the Prevention of Weight Gain: the Impact of Measurement and Interpretation of Associations. *Curr Obes Rep*. 2019;8(2):66-76.
6. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. *BMJ Open Sport Exerc Med*. 2017;2(1):e000143.
7. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2(1):e004473.
8. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, Lu Y, Hajifathalian K, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet*. 2014;383(9921):970-983.
9. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*. 2012;9(11):e1001335.
10. Koster A, Harris TB, Moore SC, et al. Joint associations of adiposity and physical activity with mortality: the National Institutes of Health-AARP Diet and Health Study. *Am J Epidemiol*. 2009;169(11):1344-1351.
11. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as Compared with physical activity in predicting mortality among women. *N Engl J Med*. 2004;351(26):2694-2703.
12. Bellocco R, Jia C, Ye W, Lagerros YT. Effects of physical activity, body mass index, waist-to-hip ratio and waist circumference on total mortality risk in the Swedish National March Cohort. *Eur J Epidemiol*. 2010;25(11):777-788.
13. Katzmarzyk PT, Craig CL. Independent effects of waist circumference and physical activity on all-cause mortality in Canadian women. *Appl Physiol Nutr Metab*. 2006;31(3):271-276.
14. Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. *Nutr Today*. 2015;50(3):117-128.
15. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation on Obesity, Geneva, 3-5 June 1997 (No. WHO/NUT/NCD/98.1)*. Geneva, Switzerland: World Health Organization; 1998.
16. Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L, Hawkins M. Muscle mass, BMI, and mortality among adults in the United States: a population-based cohort study. *PLoS One*. 2018;13(4):e0194697.
17. Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P. The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women. *Int J Obes (Lond)*. 2005;29(8):894-902.
18. Hill A, Roberts J. Body mass index: a comparison between self-reported and measured height and weight. *J Public Health (Bangkok)*. 1998;20(2):206-210.
19. Flegal KM, Ioannidis JPA, Doehner W. Flawed methods and inappropriate conclusions for health policy on overweight and obesity: the Global BMI Mortality Collaboration meta-analysis. *J Cachexia Sarcopenia Muscle*. 2019;10(1):9-13.
20. Padwal R, Leslie WD, Lix LM, Majumdar SR. Relationship Among Body Fat Percentage, Body Mass Index, and All-Cause Mortality. *Ann Intern Med*. 2016;164(8):532.
21. Lee DH, Keum N, Hu FB, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *BMJ*. 2018;362:k2575.
22. Bigaard J, Frederiksen K, Tjønneland A, et al. Body fat and fat-free mass and all-cause mortality. *Obes Res*. 2004;12(7):1042-1049.
23. Auyeung TW, Lee JSW, Leung J, Kwok T, Leung PC, Woo J. Survival in older men may benefit from being slightly overweight and centrally obese — a 5-year follow-up study in 4,000 older adults using DXA. *J Gerontol Ser A Biol Sci Med Sci*. 2010;65(1):99-104.
24. Cesari M, Pahor M, Lauretani F, et al. Skeletal muscle and mortality results from the InCHIANTI study. *J Gerontol Ser A Biol Sci Med Sci*. 2009;64A(3):377-384.
25. Toss F, Wiklund P, Nordstrom P, Nordstrom A. Body composition and mortality risk in later life. *Age Ageing*. 2012;41(5):677-681.
26. Rolland Y, Gallini A, Cristini C, et al. Body-composition predictors of mortality in women aged ≥75 y: data from a large population-based cohort study with a 17-y follow-up. *Am J Clin Nutr*. 2014;100(5):1352-1360.
27. Wijnhoven HAH, Snijder MB, van Bokhorst-de van der Schueren MAE, Deeg DJH, Visser M. Region-specific fat mass and muscle mass and mortality in community-dwelling older men and women. *Gerontology*. 2012;58(1):32-40.
28. The UK Biobank. About UK Biobank. https://www.ukbiobank.ac.uk/about-biobank-uk/. Accessed January 27, 2020.
29. The UK Biobank. UK Biobank: protocol for a large-scale prospective epidemiological resource. https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf. Published 2007. Accessed September 23, 2019.
30. The IPAQ Group. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) — Short and Long Forms Contents. Biobank website, https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/ipaq_analysis.pdf. Accessed August 1, 2020.
31. Kokkinos P, Myers J, Franklin B, Narayan P, Lavie CJ, Faselis C. Cardiorespiratory fitness and health outcomes: a

call to standardize fitness categories. *Mayo Clin Proc*. 2018; 93(3):333-336.

32. World Health Organization. *Obesity : Preventing and Managing the Global Epidemic: Report of a WHO Consultation*. Geneva, Switzerland: World Health Organization; 2000.
33. World Health Organization. *Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008*. Geneva, Switzerland: World Health Organization; 2011.
34. Townsend P, Phillimore P, Beattie A. *Health and Deprivation : Inequality and the North*. London, United Kingdom: Croom Helm Ltd; 1988.
35. NHS. 8 tips for healthy eating. https://www.nhs.uk/live-well/eat-well/eight-tips-for-healthy-eating/. Accessed August 14, 2019.
36. Celis-Morales CA, Lyall DM, Steell L, et al. Associations of discretionary screen time with mortality, cardiovascular disease and cancer are attenuated by strength, fitness and physical activity: findings from the UK Biobank study. *BMC Med*. 2018; 16(1):77.
37. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446): 496-509.
38. Ekelund U, Ward HA, Norat T, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr*. 2015;101(3):613-621.
39. World Health Organisation. *Global Recommendations on Physical Activity for Health*. Geneva, Switzerland: World Health Organization; 2010.
40. Ortega FB, Sui X, Lavie CJ, Blair SN. Body mass index, the most widely used but also widely criticized index would a criterion standard measure of total body fat be a better predictor of cardiovascular disease mortality? *Mayo Clin Proc*. 2016;91(4):443-455.
41. Rothman KJ. BMI-related errors in the measurement of obesity. *Int J Obes*. 2008;32(Suppl 3):S56-S59.
42. Schneider HJ, Friedrich N, Klotsche J, et al. The predictive value of different measures of obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab*. 2010;95(4): 1777-1785.
43. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr*. 2004;79(3):379-384.
44. Staiano AE, Reeder BA, Elliott S, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes (Lond)*. 2012;36(11):1450-1454.
45. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008; 359(20):2105-2120.
46. Yusuf S, Hawken S, Ôunpuu S, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. *Lancet*. 2005;366(9497):1640-1649.
47. Nagaya T, Yoshida H, Takahashi H, Matsuda Y, Kawai M. Body mass index (weight/height2) or percentage body fat by bioelectrical impedance analysis: which variable better reflects serum lipid profile? *Int J Obes Relat Metab Disord*. 1999;23(7):771-774.
48. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease. *J Am Coll Cardiol*. 2009;53(21):1925-1932.
49. World Health Organization. Fact sheets: The Top 10 causes of death. WHO website, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Published May 24, 2018. Accessed August 1, 2020.
50. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med*. 1999;341(15):1097-1105.
51. Aune D, Sen A, Prasad M, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156.
52. Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016; 388(10046):776-786.
53. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. 2017;390(10113):2627-2642.
54. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Act*. 2011;8:115.
55. Dyrstad SM, Hansen BH, Holme IM, Anderssen SA. Comparison of self-reported versus accelerometer-measured physical activity. *Med Sci Sports Exerc*. 2014;46(1):99-106.
56. Warner ET, Wolin KY, Duncan DT, Heil DP, Askew S, Bennett GG. Differential accuracy of physical activity self-report by body mass index. *Am J Health Behav*. 2012;36(2):168-178.
57. Pietrobelli A, Heymsfield SB. Establishing body composition in obesity. *J Endocrinol Invest*. 2002;25(10):884-892.
58. Ward LC, Heitmann BL, Craig P, et al. Association between Ethnicity, Body Mass Index, and Bioelectrical Impedance: Implications for the Population Specificity of Prediction Equations. *Ann N Y Acad Sci*. 2000;904(1):199-202.
59. Fry A, Littlejohns T, Sudlow C, Doherty N, Allen N. The representativeness of the UK Biobank cohort on a range of sociodemographic, physical, lifestyle and health-related characteristics. *J Epidemiol Community Health*. 2016;70(suppl 1):A26.1-A26.
60. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026-1034.
61. Bergström G, Berglund G, Blomberg A, et al. The Swedish CArdioPulmonary BioImage Study: objectives and design. *J Intern Med*. 2015;278(6):645-659.