Association of Changes in Physical Activity and Adiposity With Mortality and Incidence of Cardiovascular Disease: Longitudinal Findings From the UK Biobank

Matthew N. Ahmadi, PhD; Jason M.R. Gill, PhD; and Emmanuel Stamatakis, PhD

Abstract

Objective: To examine the association of changes in physical activity and adiposity with all-cause mortality and incident cardiovascular disease (CVD).

Methods: Physical activity, body mass index (BMI), body fat percentage, waist circumference, and waist to hip ratio changes were categorized on the basis of public health and clinical guidelines. Among 29,610 participants (mean ± SD follow-up, 5.1±2.1 years), 545 deaths and 2970 CVD events occurred. Participants were observed from baseline (March 13, 2006, to October 10, 2010) and follow-up (August 1, 2012 to November 9, 2018) assessment through March 31, 2021.

Results: Compared with stable-insufficient physical activity, increasing physical activity to meet guidelines at follow-up was associated with lower all-cause mortality (hazard ratio, 0.64 [0.49 to 0.85]) and CVD (0.83 [0.72 to 0.96]) risk. This risk was similar to that of those who achieved physical activity guidelines at both time points (all-cause mortality, 0.74 [0.60 to 0.92]; CVD, 0.88 [0.79 to 0.99]). For obese and overweight participants, decreasing BMI category was associated with a lower CVD risk (0.70 [0.47 to 1.04]) similar to the risk of those who had a healthy weight at both time points (0.85 [0.76 to 0.96]). In the joint analyses, the only combination that lowered all-cause mortality and CVD risk was physical activity increase and adiposity decrease over time (eg, CVD risk: BMI, 0.64 [0.42 to 0.96]; body fat percentage, 0.76 [0.55 to 0.97]; waist circumference, 0.66 [0.48 to 0.89]; waist to hip ratio, 0.78 [0.62 to 0.97]) compared with the reference group (stable physical activity and adiposity).

Conclusion: Increases in physical activity to meet guidelines lowered all-cause mortality and CVD risk equal to that of those who continually met guidelines. The risk was effectively eliminated in those who had concurrent adiposity decrease.

Both insufficient physical activity and high levels of adiposity are modifiable risk factors associated with increased risk of all-cause mortality and the development of cardiovascular disease (CVD).1-3 Most of the public health evidence arises from studies assessing a person’s physical activity or adiposity at a single time point with subsequent morbidity and mortality outcomes several years later. From 1975 to 2016, more than 90% of epidemiologic investigations on physical activity used a single—time point assessment to investigate relationships with health outcomes.4 Likewise, most of the evidence for the relationship of adiposity with morbidity and mortality is based on single-assessment studies.5,7 Such investigations assume that physical activity or adiposity is constant over time or that the rank order stays the same if changes occur; however, this may not always be a valid assumption, and the extent to which changes in physical activity or adiposity over time affect CVD risk is unclear. This may have implications for public health messaging and policy.
Several single-time point assessment studies have proposed that physical activity can attenuate or even eliminate adiposity-associated morbidity and mortality.\(^8\)\(^9\)\(^10\) The preponderance of evidence based on single-time point assessments is susceptible to misclassification of a participant’s physical activity or adiposity level. This can bias the associations toward the null and will impair understanding of the true effects of the physical activity and adiposity.\(^11\)\(^12\) Thus, the generalizability and interpretation of the physical activity and adiposity relationship would be enhanced by measurements at more than 1 time point.\(^13\) Indeed, the 2020 World Health Organization (WHO) Physical Activity and Sedentary Behaviour Guidelines Development Group and other scientific authorities have urged more studies on the longitudinal relationship of physical activity and adiposity with clinical end points.\(^2\)\(^14\)\(^15\)\(^16\)

Most prospective studies and clinical trials have found that an inverse relationship between physical activity and mortality or CVD risk persists after adjustment for overall and central adiposity.\(^17\)\(^18\) This suggests that physical activity—associated mortality and cardiovascular health are, at least in part, independent of adiposity. It is possible that long-term changes in physical activity and adiposity might synergistically affect CVD risks. However, most existing studies that investigated the combined associations of physical activity and adiposity have been limited to single baseline assessments or nonconcurrent measurements at follow-up.\(^17\)\(^19\)\(^22\)

The aim of our study was to estimate the separate and combined associations of changes in physical activity and indicators of adiposity with all-cause mortality and CVD incidence and to determine whether this depended on baseline levels of physical activity and adiposity in the UK Biobank study.

**METHODS**

**Study Population**
The UK Biobank is a large population-based prospective cohort study. Invitations were sent to recruit participants aged 40 to 69 years between 2006 and 2010 from 22 centers across the United Kingdom to reflect a diverse socioeconomic demographic and mixture of urban and rural residents. Two follow-up visits took place between 2012 and 2018. We used data from the most recent follow-up. All participants provided informed written consent, and ethical approval was provided by the United Kingdom’s National Health Service, National Research Ethics Service (Ref 11/NW/0382). There were 40,949 participants who had 2 measurements of physical activity and adiposity. For the core sample, we excluded participants who were clinically underweight (body mass index [BMI] <18.5 kg/m\(^2\); n=142) at the first assessment.\(^23\)\(^24\) Participants with diagnosed CVD before the first assessment (n=3,840) or follow-up assessment (n=3,334) or who had missing covariate data (n=1,025) were additionally excluded. Participants who were outliers for sex-specific BMI change (>2 SD) in the sample, indicative of occult illness, were further excluded (men, 764; women, 851). To minimize the risk of reverse causality, we further excluded participants who had an event within the first 2 years of follow-up (all-cause mortality, 146; fatal CVD, 32; nonfatal CVD, 1,237).

**Assessment of Physical Activity and Indicators of Adiposity**
Physical activity was measured with a modified International Physical Activity Questionnaire short form and included items on frequency and duration of walking, moderate-intensity activity, and vigorous-intensity activity.\(^25\) Physical activity was expressed as metabolic equivalent of task (MET) minutes per week and based on the International Physical Activity Questionnaire scoring procedure. We categorized physical activity around the current WHO guidelines as inactive (0 minutes of moderate- to vigorous-intensity physical activity [MVPA]; 0 MET-min/wk), insufficient (>0 to <150 minutes of MVPA; >0 to <600 MET-min/wk), and sufficient (≥150 minutes of MVPA; ≥600 MET-min/wk).\(^3\) Physical activity changes were categorized as decreased
(moved category downward), stable (stayed in the same category), or increased (moved category upward).

Body weight, height, body fat percentage (BF%), waist circumference (WC), and hip circumference were measured according to standardized procedures without shoes by trained staff. Body weight and BF% were measured with a Tanita BC-418MA bio-impedance device to the nearest 0.1 kg and 0.1%. Height was measured with the Seca 202 stadiometer to the nearest 0.1 cm. Waist circumference was measured at the level of the umbilicus and hip circumference was measured just over the buttocks at the point of maximum circumference by a Wessex non-stretchable sprung tape with the participant in the resting-standing position to the nearest 0.1 cm. We used ethnicity-specific cutoffs for adiposity categories. Most of the sample was Western European, and the cutoffs for these participants were as follows. Based on BMI, participants were classified as obese ($\geq 30$ kg/m$^2$), overweight ($\geq 25$ to $<30$ kg/m$^2$), or healthy ($\geq 18.5$ to $<25$ kg/m$^2$). In the absence of widely accepted population-based risk categories or cutoffs for BF%, groups were based on sex-specific distributions of BMI categories and classified as high ($\geq 29.0$% for men and $\geq 42.0$% for women), moderate ($<29.0$ to $\geq 22.0$% for men and $<42.0$ to $\geq 35.2$% for women), and low ($<22.0$% for men and $<35.2$% for women). Based on sex-specific WC measurements, participants were classified as high ($>102$ cm for men and $>88$ cm for women), moderate ($\leq 102$ cm to $>94$ cm for men and $\leq 88$ cm to $>80$ cm for women), and low ($\leq 94$ cm for men and $\leq 80$ cm for women).

Based on sex-specific waist to hip ratio (WHR) measurements, participants were classified as high ($\geq 1.0$ for men and $\geq 0.86$ for women), moderate ($<1.0$ to $\geq 0.96$ for men and $<0.86$ to $\geq 0.81$ for women), and low ($<0.96$ for men and $<0.81$ for women).

The BMI, BF%, WC, and WHR were categorized as decreased (moved category downward), stable (stayed in the same category), or increased (moved category upward).

Participants were classified into 1 of 9 mutually exclusive groups on the basis of their change in physical activity (decreased, stable, increased) and indicator of adiposity (decreased, stable, increased) between baseline and follow-up.

**Assessment of Mortality and CVD**

Participants were followed up prospectively from study entry (between March 2006 and October 2010) until an event (death or incident disease) or the censoring date, whichever came first. Because of the nature of rolling updates of the data linkage, censoring dates varied between resources (between February 2021 and March 2021). We defined CVD (International Classification of Diseases codes 100 to 199) as diseases of the circulatory system and included nonfatal and fatal events; nonfatal events were obtained through hospital inpatient admission records. The date and the cause of death (both primary and contributory) were obtained through the data linkage with either the National Health Service Digital of England and Wales or the National Health Service Central Register and National Records of Scotland. The inpatient hospitalization data were provided by the Hospital Episode Statistics for England, the Patient Episode Database for Wales, or the Scottish Morbidity Record for Scotland. Both the cause of death and the inpatient admission were coded with the International Classification of Diseases, Tenth Revision.

**Covariates**

Characteristics of the participants and their lifestyle-related risk factors were measured at both baseline and follow-up. These included age, sex, smoking status (never, current, former), alcohol consumption (units per week; 1 unit $= 8$ g of pure ethanol), and ethnicity (White, Asian, Black, other); sleep pattern, defined as the count of healthy sleep characteristics (morning chronotype, adequate sleep duration [7 to 8 hours per night], never or rare insomnia, never or rare snoring, and infrequent daytime sleepiness) and categorized into 3 groups (healthy, $\geq 4$; intermediate, 2 or 3; and poor, $\leq 1$); education (university/college degree, Certificate of Secondary
Education, none of these); fruit and vegetable consumption (servings per day); Townsend area deprivation index (obtained from postcode of residence and derived using aggregated data on unemployment, car and home ownership, and household overcrowding; assessed at baseline only); and physician-diagnosed cancer (self-reported and cancer registry). Baseline physical activity and adiposity categories were also included as covariates.

**Statistical Analyses**

Hazard ratios (HRs) and 95% CIs for all-cause mortality were estimated for each of the joint exposure groups by Cox proportional hazards regression models. We used Fine-Gray subdistribution hazard models to estimate HR and 95% CI for CVD incidence, in which mortality from other causes was considered a competing risk. For the separate analysis of changes in physical activity and indicators of adiposity, the referent group was insufficient-stable physical activity or overweight/moderate-stable adiposity. For joint physical activity-adiposity change analysis, the referent group was stable physical activity and stable adiposity. We performed analyses to test the independent association of changes in physical activity and indicators of adiposity with all-cause mortality and CVD incidence. The time scale was in calendar time (months) for all analysis. We adjusted all models for baseline and follow-up age, sex, education, sleep pattern, smoking status, alcohol use, ethnicity, deprivation index, and cancer. Baseline physical activity and adiposity were included as covariates in the joint and independent association analyses. For all sets of analyses, we calculated E-values to estimate the plausibility of bias from unmeasured confounding. The E-values indicate the minimum strength of association that an unmeasured confounder would need with both exposure and outcome to explain away the observed association. For all-cause mortality, we performed additional analyses by excluding participants with prevalent cancer.

To improve comparability of our results with existing literature in which only baseline assessments of physical activity or adiposity were made (not baseline and follow-up assessments, as in this study), we carried out additional analyses for the association between baseline physical activity or baseline adiposity with mortality and CVD incidence.

We performed all analysis using R statistical software with the rms and survival packages. We reported this study per the Strengthening the Reporting of Observational Studies in Epidemiology guideline (Supplemental STROBE Statement, available online at http://www.mayoclinicproceedings.org).

**RESULTS**

A total of 545 deaths and 2,970 incident CVD events occurred among 29,610 participants (mean age ± SD, 55.1±7.5 years; female, 52.8%) in our core analyses. Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org) provides a flow diagram of participant exclusion. Supplemental Figures 2 and 3 (available online at http://www.mayoclinicproceedings.org) show the proportions and combinations of eligible participants with missing or complete covariate data. There was an average of 7.0 (2.2) years between baseline and follow-up of physical activity and adiposity measurements. Across physical activity change categories, 4,157 (14.0%) decreased physical activity, 18,949 (64.0%) had stable physical activity, and 6,504 (22.0%) increased physical activity. Across BMI change categories, 1,967 (6.6%) decreased BMI, 24,388 (82.4%) had stable BMI, and 3,255 (11.0%) increased BMI. Across BF% change categories, 2,902 (10.1%) decreased BF%, 20,946 (72.8%) had stable BF%, and 4,920 (17.1%) increased BF%. Across WC change categories, 3,728 (12.6%) decreased WC, 18,530 (62.6%) had stable WC, and 7,352 (24.8%) increased WC. Across WHR change categories, 3,728 (12.6%) decreased WHR, 18,530 (62.6%) had stable WHR, and 7,352 (24.8%) increased WHR. Participants’ characteristics...
FIGURE 1. Separate association of physical activity, body mass index, and body fat percentage baseline changes with all-cause mortality risk (physical activity, body mass index: n=29,610; body fat percentage: n=28,768). Physical activity: inactive, 0 minutes of moderate- to vigorous-intensity physical activity (MVPA); insufficient, >0 to <150 minutes of MVPA; and sufficient, ≥150 minutes of MVPA. Body mass index: obese, ≥30 kg/m²; overweight, <30 to ≥25 kg/m²; or healthy weight, <18.5 kg/m². Body fat percentage: high, ≥29% for men and ≥42% for women; moderate, <29% to ≥22% for men and <42% to ≥35.2% for women; and low, <22% for men and <35.2% for women. Adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruit and vegetable consumption, deprivation index, physical activity baseline and change group (or body mass index baseline and change group for physical activity as an exposure), and cancer diagnosis. X-axis is on log scale.
at baseline are displayed in Table 1, and follow-up characteristics are presented in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

Independent Associations of Changes in Physical Activity and Adiposity With All-Cause Mortality and CVD Incidence
Compared with those with stable physical activity, participants who increased their physical activity had a lower risk for all-cause mortality (HR, 0.78 [95% CI, 0.62 to 0.98]) and CVD incidence (0.80 [0.70 to 0.91]). When adiposity decreased, we observed an attenuated risk for all-cause mortality (0.67 [0.49 to 0.93] for BMI; 0.85 [0.68 to 1.07] for BF%; 0.78 [0.59 to 1.04] for WC) and CVD incidence (0.87 [0.74 to 1.01] for BMI; 0.89 [0.73 to 1.10] for BF%; 0.73 [0.63 to 0.87] for WC), except for WHR (Supplemental Figures 4 and 5, available online at http://www.mayoclinicproceedings.org).

Separate Associations of Changes in Physical Activity and Changes in Adiposity by Baseline Levels
Figure 1 and Supplemental Figures 6 and 7 (available online at http://www.mayoclinicproceedings.org) present the multivariable adjusted associations of changes in physical activity (Figure 1A), BMI (Figure 1B), BF% (Figure 1C), WHR (Supplemental Figure 6A), and WC (Supplemental Figure 7A) with mortality risk. Sequential covariate adjustment models are shown in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org). Compared with the reference group of stable-insufficient physical activity, those with insufficient physical activity at baseline who increased their activity level (0.64 [0.49 to 0.85]) and those who had stable-sufficient physical activity (0.74 [0.60 to 0.92]) had similarly lower mortality risk in the final adjusted model. Those who were inactive at baseline and increased activity levels had a lower mortality risk, but this association was not statistically significant (0.71 [0.47 to 1.09]). Those with sufficient activity at baseline who decreased their activity level had similar risk to those with stable-insufficient activity (1.00 [0.78 to 1.29]), and those with insufficient activity who decreased their activity level (1.39 [1.05 to 1.87]) and those who were inactive at both time points (1.53 [1.12 to 1.92]) had similarly higher mortality risk.

The associations for adiposity changes were less consistent. For example, compared with being overweight at both time points, participants who were overweight at baseline and decreased their BMI category had an HR of 0.64 (0.40 to 1.02), whereas those who were obese and decreased their BMI category had an HR of 0.97 (0.61 to 1.55). We observed a similar pattern for WC decrease among the high (1.18 [0.80 to 1.74]) and moderate (0.73 [0.48 to 1.12]) groups. When BF% category decreased, mortality risk was lower for those with initially high BF% (0.69 [0.40 to 0.98]), with no appreciable change in those initially in the moderate BF% category (0.96 [0.69 to 1.34]). The decreased WHR category was not associated with a lower risk of mortality compared with stable-moderate WHR. Those with high adiposity at both time points (ie, obese; high BF%, WC, or WHR) had higher mortality risk than those who were overweight or had moderate BF%, WC, or WHR at both time points. Mortality risk was also higher when adiposity increased among overweight (1.27 [0.83 to 1.95]), moderate BF% (1.15 [0.78 to 1.70]), moderate WC (1.12 [0.76 to 1.64]), and moderate WHR (1.51 [1.02 to 2.23]) groups.
FIGURE 2. Separate association of physical activity, body mass index, and body fat percentage baseline changes with cardiovascular disease risk (physical activity, body mass index: n=29,610; body fat percentage: n=28,768). Physical activity: inactive, 0 minutes of moderate- to vigorous-intensity physical activity (MVPA); insufficient, >0 to <150 minutes of MVPA; and sufficient, ≥150 minutes of MVPA. Body mass index: obese, ≥30 kg/m²; overweight, <30 to ≥25 kg/m²; or healthy weight, ≥18.5 kg/m². Body fat percentage: high, ≥29% for men and ≥42% for women; moderate, <29% to ≥22% for men and <42% to ≥35.2% for women; and low, <22% for men and <35.2% for women. Adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruit and vegetable consumption, deprivation index, physical activity baseline and change group (or body mass index baseline and change group for physical activity as an exposure), and cancer diagnosis. X-axis is on log scale.

ASSOCIATION OF PHYSICAL ACTIVITY AND ADIPOSITY CHANGES WITH CVD

www.mayoclinicproceedings.org

853
activity and those who were sufficiently active at both time points had similarly lower CVD risk. Those who were inactive at baseline and increased activity also had a lower risk of CVD, but this association was not statistically significant (0.85 [0.69 to 1.06]). Decreasing physical activity was associated with higher CVD risk in all groups, ranging from 1.10 (0.95 to 1.27) to 1.42 (1.02 to 1.98), although the effect estimates were less precise with wider 95% CIs.

Compared with those who were overweight at both time points, those who were overweight and decreased their BMI and those with a healthy weight at both time points had lower CVD risk (Figure 2; Supplemental Table 3). Participants who were initially overweight or obese and decreased their BMI and those with a stable healthy weight had similar HRs for CVD risk. Decreasing BF%, WC, and WHR attenuated CVD risk when BF% (0.81 [0.62 to 1.08]), WC (0.74 [0.56 to 0.96]), and WHR (0.83 [0.67 to 1.03] were moderate at baseline. Increasing adiposity was not associated with higher CVD risk among the healthy weight (0.88 [0.71 to 1.09]) and low BF% (0.89 [0.76 to 1.05]), WC (0.82 [0.70 to 0.95]), or WHR (0.74 [0.62 to 0.87]) groups. Those who were obese or had a high BF% or WC at both time points had higher CVD risk than the stable overweight or moderate BF% or WC reference groups.

**Joint Association of Changes in Physical Activity and Indicators of Adiposity**

Increasing physical activity while BF% was stable or decreased was associated with lower risk of mortality and CVD (Figures 3 and 4), with the magnitude of the lowered risk being more pronounced when BF% also decreased. Broadly similar findings were observed when BMI or WC was used as the index of adiposity but not for WHR (Supplemental Figures 8 and 9, available online at http://www.mayoclinicproceedings.org). When physical activity was stable, increases or decreases in BF%, BMI, or WC did not appreciably change CVD risk relative to the referent group (stable physical activity and stable BF%, BMI, or WC). However, mortality risk was lower when physical activity was stable and BMI (0.71 [0.48 to 1.05]), BF% (0.79 [0.59 to 0.99]), or WC (0.82 [0.61 to 1.04]) decreased. There was a higher risk of mortality and CVD when physical activity decreased across WHR change categories. Decreasing physical activity was not associated with higher risk of mortality or CVD when BF%, BMI, or WC also decreased.

In our analyses of joint baseline physical activity and adiposity (BMI, BF%, WC, and WHR), there was a consistently reduced risk of CVD when sufficient physical activity was combined with healthy or low adiposity, although the association was not statistically significant for BF%. For mortality, this relationship was not consistent for BMI (Supplemental Figures 10 and 11, available online at http://www.mayoclinicproceedings.org). Exclusion of prevalent cancer did not appreciably change the associations of changes for all-cause mortality (Supplemental Tables 4 and 5, available online at http://www.mayoclinicproceedings.org). The E-values (Supplemental Tables 6 to 9, available online at http://www.mayoclinicproceedings.org) indicated that a substantial degree of unmeasured confounding would be required to reduce the observed association to the null for increased physical activity and decreased adiposity. For example, the E-value for CVD incidence suggests that an unmeasured confounder would need to be associated with the joint physical activity—BMI exposure and outcome with at least a 2.5-fold increase in risk to explain away the observed association.

**DISCUSSION**

This is one of the first prospective studies to investigate the association of longitudinal changes in physical activity and adiposity with all-cause mortality and CVD incidence and the largest to examine separate and concurrent changes in both risk factors. We found that participants who were inactive and insufficiently active at baseline and increased their physical activity had a lower
risk of all-cause mortality and CVD than their counterparts who did not increase their activity level and had a risk level equivalent to that of those whose level of activity met WHO guidelines at both time points. Thus, it appears that the relationship between physical activity and mortality or CVD risk is largely a function of relatively recent rather than past physical activity. These associations were consistent across all 3 BMI and BF% change categories. In contrast, adiposity decreases over time were not always associated with lower mortality or CVD risk compared with the stable overweight or moderate BF% group; however, decreasing adiposity attenuated the risks associated with decreased physical activity.

Our results suggest that it is never too late to start engaging in physical activity to improve long-term health. This is

FIGURE 3. Joint association of changes in physical activity and adiposity with all-cause mortality risk (body mass index: n = 29,610; body fat percentage: n = 28,768). Adjusted for age, sex, baseline physical activity, baseline body mass index (or body fat percentage), smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruit and vegetable consumption, deprivation index, and cancer diagnosis. X-axis is on log scale.

### Table A

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Body mass index</th>
<th>N (events)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased</td>
<td>Decreased</td>
<td>379 (56)</td>
<td>0.77 (0.32, 1.89)</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>3221 (91)</td>
<td>1.21 (0.94, 1.55)</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>557 (79)</td>
<td>1.18 (0.66, 2.11)</td>
</tr>
<tr>
<td>Stable</td>
<td>Decreased</td>
<td>1074 (64)</td>
<td>0.70 (0.47, 1.03)</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>15813 (49)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>2062 (68)</td>
<td>0.91 (0.63, 1.31)</td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>514 (41)</td>
<td>0.46 (0.23, 0.94)</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>5354 (42)</td>
<td>0.80 (0.63, 1.03)</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>636 (55)</td>
<td>0.79 (0.48, 1.03)</td>
</tr>
</tbody>
</table>

### Table B

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Body fat</th>
<th>N (events)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased</td>
<td>Decreased</td>
<td>363 (22)</td>
<td>0.83 (0.34, 1.35)</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>2190 (70)</td>
<td>1.24 (0.95, 1.61)</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>987 (51)</td>
<td>1.22 (0.78, 1.89)</td>
</tr>
<tr>
<td>Stable</td>
<td>Decreased</td>
<td>1757 (31)</td>
<td>0.79 (0.59, 1.06)</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>14360 (167)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>2807 (53)</td>
<td>0.98 (0.67, 1.42)</td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
<td>782 (28)</td>
<td>0.62 (0.31, 0.93)</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>4396 (72)</td>
<td>0.77 (0.59, 0.95)</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>1126 (33)</td>
<td>0.75 (0.45, 1.26)</td>
</tr>
</tbody>
</table>
particularly relevant for middle-aged adults, who generally experience a 3-fold absolute decrease in physical activity as they transition to older adult life. Most population studies have examined the association of single baseline assessments of physical activity with risk of mortality, which can bias the exposure-response relationship. Such studies assume that if physical activity or adiposity changes occur, the rank order stays the same. Our joint baseline analyses found that this assumption is not tenable and contributed to an attenuation of the associated risks. As a consequence, this can make the nuances of each risk factor indiscernible. By using baseline and follow-up assessments, our study mitigates such biases and allows the effects of change to be ascertained.

FIGURE 4. Joint association of changes in physical activity and adiposity with cardiovascular disease risk (body mass index n=29,610; body fat percentage: n=28,768). Adjusted for age, sex, baseline physical activity, baseline body mass index (or body fat percentage), smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruit and vegetable consumption, deprivation index, and cancer diagnosis. X-axis is on log scale.
<table>
<thead>
<tr>
<th>Physical activity group</th>
<th>Increase</th>
<th>Stable</th>
<th>Decrease</th>
<th>Increase</th>
<th>Stable</th>
<th>Decrease</th>
<th>Stable</th>
<th>Increase</th>
<th>Decrease</th>
<th>Stable</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>514</td>
<td>5,354</td>
<td>636</td>
<td>1,074</td>
<td>15,813</td>
<td>2,062</td>
<td>379</td>
<td>3,221</td>
<td>557</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA, MET-min/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>640.6 (372.8)</td>
<td></td>
<td></td>
<td></td>
<td>640.3 (235.2)</td>
<td></td>
<td>610.9 (220.2)</td>
<td>600.1 (310.7)</td>
<td></td>
<td>653.6 (300.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA change</td>
<td>137.9 (469.9)</td>
<td></td>
<td>7.94 (486.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>118.9 (469.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.0 (2.3)</td>
<td></td>
<td></td>
<td></td>
<td>301.0 (475.7)</td>
<td></td>
<td></td>
<td>225.9 (403.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI change</td>
<td>0.2 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3 (0.3)</td>
<td></td>
<td></td>
<td>0.2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fat (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30.0 (8.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fat change</td>
<td>0.2 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3 (0.3)</td>
<td></td>
<td></td>
<td>0.2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89.5 (9.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference change</td>
<td>0.2 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3 (0.3)</td>
<td></td>
<td></td>
<td>0.2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.87 (0.08)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR change</td>
<td>0.00 (0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01 (0.01)</td>
<td></td>
<td></td>
<td>0.00 (0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.2 (6.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53.6 (7.7)</td>
<td></td>
<td></td>
<td>56.7 (6.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>319 (62.7)</td>
<td></td>
<td>358 (56.6)</td>
<td></td>
<td></td>
<td>1,082 (64.1)</td>
<td></td>
<td></td>
<td>1,284 (62.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>164 (32.2)</td>
<td></td>
<td>384 (36.0)</td>
<td></td>
<td></td>
<td>501 (31.9)</td>
<td></td>
<td></td>
<td>679 (33.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption, units/week</td>
<td>4.3 (1.1)</td>
<td></td>
<td>4.2 (1.2)</td>
<td></td>
<td></td>
<td>4.2 (1.1)</td>
<td></td>
<td></td>
<td>4.2 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits and vegetables, servings/day</td>
<td>5.8 (6.1)</td>
<td></td>
<td>6.8 (7.4)</td>
<td></td>
<td></td>
<td>6.2 (7.6)</td>
<td></td>
<td></td>
<td>5.7 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>3 (1.3)</td>
<td></td>
<td></td>
<td>3 (0.5)</td>
<td></td>
<td>26 (1.9)</td>
<td></td>
<td>1 (1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>85 (36.0)</td>
<td></td>
<td>190 (32.9)</td>
<td></td>
<td></td>
<td>521 (37.1)</td>
<td></td>
<td></td>
<td>26 (33.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>148 (62.7)</td>
<td></td>
<td>385 (66.6)</td>
<td></td>
<td></td>
<td>857 (61.0)</td>
<td></td>
<td></td>
<td>50 (64.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deprivation index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>41 (8.0)</td>
<td></td>
<td></td>
<td>77 (7.2)</td>
<td></td>
<td>958 (6.1)</td>
<td></td>
<td>41 (8.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*BMI, body mass index; MET, metabolic equivalent of task; PA, physical activity; WHR, waist to hip ratio.

Categorical variables are presented as number (percentage). Continuous variables are presented as mean (standard deviation).

The body fat percentage analytic sample was 28,768.

One unit = 8 g of ethanol.

Scores ranged from 6.3 to 10.6; higher index score implies a greater degree of deprivation.

Physician diagnosed (self-reported and cancer registry) before baseline.
Studies in other populations assessing leisure-time physical activity trajectories\textsuperscript{37–38} or MVPA changes\textsuperscript{39–42} are broadly consistent with our findings. There was considerable heterogeneity in the operational definitions of the “changes” in physical activity over time in previous studies. Some classified physical activity change on the basis of distributions shifts, or did not consider baseline levels, or grouped activity changes as “mixed patterns.” Others assessed changes during a very short period (eg, 1 or 2 years).\textsuperscript{43,44} Expressing physical activity changes relative to public health guidelines provides information that can be readily translated into practice and future research.

Increasing adiposity accentuated associations with mortality and CVD, except for participants with a baseline healthy BMI or low BF%. The absence of an association with baseline healthy BMI or low BF% may be related to the effect of time. The relationship between excess adiposity and the development of chronic disease is curvilinear and becomes progressively stronger at 18 years.\textsuperscript{45,46} In most groups, we found that decreasing adiposity was generally associated with a lower risk of CVD. This finding partially contrasts with several prior investigations, including the Framingham Heart Study and National Health and Nutrition Examination Survey.\textsuperscript{17,47–50} These prior studies reported excess risk of CVD from weight loss, comparable to weight gain, that was independent of weight status at baseline. However, prior findings may have been affected by potential biases that arise from the use of self-reported weight and asking participants to recall their weight from 10 to 37 years earlier or potential reverse causation (ie, the presence of disease leading to a change in physical activity or weight status) from not excluding participants with events within the first 2 years of follow up, which minimized the potential for reverse causation that may have contributed to the protective associations of excess adiposity observed in previous studies.\textsuperscript{15,51}

The combination of increasing physical activity with decreasing adiposity was the only group that substantially reduced the risk of mortality and CVD compared with stable physical activity and stable adiposity. It is possible that the beneficial relationship occurs from physical activity and adiposity independently modulating many of the same inflammatory and metabolic markers that contribute to associated morbidity and mortality.\textsuperscript{52–54} This would also explain why positive changes in only 1 exposure (increasing physical activity or decreasing adiposity) attenuated but did not fully offset the risk of mortality and morbidity. Our findings contrast with other studies reporting that a physical activity increase is not associated with lower mortality when combined with a weight or adiposity decrease.\textsuperscript{55,56} The differences may be due, at least in part, to previous studies using different physical activity and weight or adiposity change definitions and change evaluation methods. Our longitudinal results based on clinical standards indicate that there is a beneficial relationship between physical activity and adiposity that supersedes improvements in each risk factor separately. Investing resources on strategies that facilitate sustained long-term improvements in both physical activity and adiposity at the population level may bring better health outcomes.

Differences in adiposity measures may have differential effects on the association with mortality and CVD risk.\textsuperscript{57–59} By definition, BMI does not differentiate fat mass from fat-free mass, and we expected that a more accurate measure of adiposity, such as BF%, would have clearer associations. Studies directly comparing longitudinal BMI and BF% changes (ie, categorizing both of them in an identical way so that results are comparable) are scarce. With the exception of minor variations, the joint association patterns we observed were relatively consistent whether the adiposity indicator was BMI or BF%. The minor variations may have been an effect of differences in biologic changes that affect BMI.
and BF% independent of adiposity changes. Biologic changes such as muscle atrophy that increase with age would have opposing effects on BMI (decrease) and BF% (increase) levels. Our analyses of WHR changes found less consistent patterns than with the WC associations. Unlike for WC, hip circumference changes over time can be due to changes in subcutaneous fat, gluteal muscle mass, or both. As a consequence, long-term changes in WHR may be reflective of different aspects of body composition, which makes interpretation less clear than for WC changes, especially in older adults, who commonly experience sarcopenia.

The strengths of our study included its longitudinal design and large number of participants, for whom measured physical activity, adiposity indicators, and covariate values spanned an average of 7 years between assessments. This reduces the possibility of regression dilution bias, whereby the associations are attenuated by changes over time as found in our joint baseline analyses. To reduce the risk of reverse causality, we removed CVD and mortality events occurring in the first 2 years of follow-up. To our knowledge, this is the first prospective study examining the joint relationship between changes in physical activity and adiposity in relation to clinically defined health risk categories. Such groupings allow more generalizable interpretations of our findings for uptake in clinical and public health research.

Due to the observational design, we cannot rule out the presence of unmeasured or poorly measured confounders, although the E-values suggested the impact is likely to be modest. In addition, population-level trials studying the effects of changes in risk factors, such as physical activity and adiposity, on mortality and disease during several years have low feasibility and have not been successful. In the general population, time to event induction would necessitate randomized controlled trials to be impractically large to have sufficient power. The UK Biobank may be prone to healthy volunteer selection bias because of a low response rate, although recent empirical evidence has found that this does not affect the physical activity–disease relationships. Our physical activity measures were self-reported, likely suffering from social desirability bias. Social desirability would probably have led to an overestimation of the exposures in the positive direction and thus attenuated the associations between physical activity and mortality or CVD.

**CONCLUSION**

We observed the greatest decrease in mortality and CVD risk in those who increased physical activity and decreased adiposity. Risk of CVD in those who increased their activity levels was similar to the risk in those who had high levels of physical activity at both time points, regardless of initial activity levels. The association for CVD risk when BMI decreased among obese and overweight participants was comparable to having a healthy BMI at both time points. Thus, public health messaging could emphasize that it is never too late to improve physical activity and weight to reduce mortality and CVD risk.

**ACKNOWLEDGMENTS**

The authors would like to thank all the participants and professionals contributing to the UK Biobank.

**SUPPLEMENTAL ONLINE MATERIAL**

Supplemental material can be found online at [http://www.mayoclinicproceedings.org](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; MVPA, moderate- to vigorous-intensity physical activity; WC, waist circumference; WHO, World Health Organization; WHR, waist to hip ratio

**Grant Support:** E.S. is funded by an Australian National Health and Medical Research Council Leadership 2 Fellowship (1194510).

**Potential Competing Interests:** The authors report no competing interests.
REFERENCES


ASSOCIATION OF PHYSICAL ACTIVITY AND ADIPOSITY CHANGES WITH CVD


