Changes in physical activity and adiposity with mortality and incidence of cardiovascular disease: longitudinal findings from the UK Biobank

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Abstract

Objective: To examine the association of changes in physical activity (PA) and adiposity with all-cause mortality (ACM) and incident cardiovascular disease (CVD). The majority of underpinning evidence comes from baseline assessment studies. We have a limited understanding of how changes, particularly in combination, affect CVD risk.

Patients and Methods: PA, body mass index (BMI), body fat percentage (BF%), waist circumference (WC), and waist to hip ratio (WHR) changes were categorised based on public health and clinical guidelines. Among 29,610 participants (mean±SD follow-up= 5.1±2.1y) 545 deaths and 2,970 CVD events occurred. Participants were followed through March 31st, 2021.

Results: Compared to stable-insufficient PA, increasing PA to meet guidelines at follow-up was associated with lower ACM (HR= 0.64; [0.49, 0.85]) and CVD (0.83; [0.72, 0.96]) risk. This risk was similar to those who achieved PA guidelines at both timepoints (ACM= 0.74; [0.60, 0.92]; CVD= 0.88; [0.79, 0.99]). For obese and overweight participants, decreasing BMI category was associated with a lower CVD risk (0.70; [0.47, 1.04]) similar to those who had a healthy weight at both timepoints (0.85 [0.76, 0.96]). In the joint analyses, PA increase and adiposity decrease over-time was the only combination that lowered ACM and CVD risk (e.g:CVD risk: BMI= 0.64 [0.42, 0.96]; BF%= 0.76 [0.55, 0.97]; WC= 0.66 [0.48,0.89]; WHR= 0.78 [0.62, 0.97]) compared to the reference group (stable PA and adiposity).

Conclusion: Increases in PA to meet guidelines lowered ACM and CVD risk equal to those who continually met guidelines. The risk was effectively eliminated in those who had concurrent adiposity decrease.

Abbreviations: BF%, body fat percentage; BMI, Body mass index; CVD, cardiovascular disease; WC, waist circumference; WHR, waist-to-hip ratio

Introduction

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).[1–5] Most of the public health evidence arises from studies assessing a person's physical activity or adiposity at a single timepoint with subsequent morbidity and mortality outcomes several years later. From 1975 to 2016, more than 90% of epidemiological investigations on physical activity used a single timepoint assessments to investigate relationships with health outcomes.[6] Likewise, the majority 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 are constant over time, or if changes occur, the rank order stays the same, however, this may not always be a valid assumption, and it is unclear the extent to which changes in physical activity or adiposity over time affects CVD risk. This may have implications for public health messaging and policy.

Several single timepoint assessment studies have proposed physical activity can attenuate or even eliminate adiposity associated morbidity and mortality.[8–10]The preponderance of evidence based on single timepoint assessments is susceptible to misclassify a participants' physical activity or adiposity level. This can bias the associations towards the null and will impair understanding of the true effects of the physical activity and adiposity.[11,12] Thus the generalisability and interpretation of the physical activity and adiposity relationship would be enhanced by measurements at more than one timepoint.[13] Indeed, the 2020 WHO Physical Activity and Sedentary Behaviour Guidelines Development Group as well as other scientific authorities have

urged more studies on the longitudinal relationship of physical activity and adiposity with clinical endpoints. [2,14–16]

The majority of prospective studies and clinical trials have found that an inverse relationship between physical activity and mortality or CVD risk persist after adjustment for overall and central adiposity.[17,18] This suggests 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, the majority of existing studies that investigated the combined associations of physical activity and adiposity have been limited to single baseline assessments or non-concurrent 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 40-69 years between 2006 and 2010 from 22 centres across the UK 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 UK's National Health

Service, National Research Ethics Service (Ref 11/NW/0382). 40,949 participants had two measurements of physical activity and adiposity. For the core sample, we excluded participants who were clinically underweight (body mass index <18.5 kg/m^2; n = 142) at the first assessment.[23,24] Participants with diagnosed cardiovascular disease prior to their first assessment (n = 3,840) or follow-up assessment (n = 3,334), or had missing covariate data (n = 1,025), were additionally excluded. Participants who were outliers for sex-specific body mass index change (>2SD) in the sample, indicative of occult illness, were further excluded (men = 764; female = 851). To minimise the risk of reverse causality, we further excluded participants who had an event within the first two 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 using a modified International Physical Activity Questionnaire (IPAQ) short form and included items on frequency and duration of walking, moderate intensity activity, and vigorous intensity activity.[25] Physical activity was expressed as MET mins/week and based on the IPAQ scoring procedure. We categorized physical activity around the current WHO guidelines as: inactive (0 minutes of MVPA; 0 MET mins/week): insufficient (> 0 to <150 minutes of MVPA; (> 0 to <600 MET mins/week); and sufficient ($\geq$ 150 minutes of MVPA; ≥ 600 MET mins/week). [3] Physical activity changes were categorised as decreased (moved category downward), stable (stayed in the same category) or increased (moved category upward).

Body weight (kg), height (cm), body fat (BF%), waist circumference (cm), and hip circumference (cm), were measured according to standardized procedures without

shoes by trained staff.[26] Body weight and BF% were measured with a Tanita BC418ma bioimpedance device (Tanita, Tokyo, Japan) to the nearest 0.1kg and 0.1%. Height was measured with the Seca 202 stadiometer (Seca, Hamburg, Germany) to the nearest 0.1cm. 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 using a Wessex non-stretchable sprung tape with the participant in the resting-standing position to the nearest 0.1cm. We used ethnicity specific cut-offs for adiposity categories.[27–29] The majority of the sample was Western European and the cut-offs for these participants were as follows: based on body mass index (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).[23,24] In the absence of widely accepted population-based risk categories or cut-offs for BF%, groups were based on sex-specific distributions of BMI categories in accordance with prior published research[30] and classified as: high (≥29.0% for men and ≥42.0% for women), moderate (<29.0% to ≥22.0% for men and <42.0% to ≥35.2% for women), and low (<22.0% for men and <35.2% for women). Based on sex-specific waist circumference (WC) measurements participants were classified as: high (> 102cm for men and >88cm for women), moderate (≤102cm to > 94cm for men and ≤88cm to > 80cm for women) and low (≤94cm for men and ≤80cm for women).[27] Based on sex-specific waist to hip ratio (WHR) measurements participants were classified as: high (≥ 1.0 for men and ≥ 0.86 for women), moderate (<1.0 to ≥ 0.96 for men and <0.86 to ≥ 0.81 for women) and low (< 0.96 for men and < 0.81 for women).[27] BMI, BF%, WC, and WHR were categorised 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 based on their change in physical activity (decreased, stable, increased) and indicator of adiposity (decreased, stable, increased) between baseline and follow-up.

Assessment of mortality and cardiovascular disease

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. Due to 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 I00-I99) as diseases of the circulatory system and included non-fatal and fatal events; non-fatal 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 (NHS) Digital of England and Wales or the NHS Central Register and National Records of Scotland. The inpatient hospitalization data were provided by either 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, 10th revision.

Covariates

Information about participants and their lifestyle-related risk factors were measured at both baseline and follow-up and included: age, sex, smoking status (never, current, former), alcohol consumption (units/week; 1 unit = 8 g of pure ethanol), ethnicity (White, Asian, Black, other), sleep pattern (defined as the count of healthy sleep characteristics: morning chronotype, adequate sleep duration (7-8

hours/night), never or rare insomnia, never or rare snoring and infrequent daytime sleepiness; and categorized into three groups (healthy, ≥ 4; intermediate, 2-3; and poor: ≤ 1)[31], education (university/college degree, A-levels, O-levels, CSEs, none of the above) fruits and vegetables consumption (servings/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)[32], and physician diagnosed cancer (self-reported and cancer registry). Baseline physical activity and adiposity categories were also included as covariates.

Analysis

Hazard ratios (HR) and 95% confidence interval ((95% CI) for all-cause mortality were estimated for each of the joint exposure groups, using Cox proportional hazards regression models. We used Fine-Gray subdistribution hazard models to estimate HR and 95% CI for CVD incidence, where mortality from other causes were considered a competing risk.[33] 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 physical activity, indicators of adiposity changes with all-cause mortality and CVD incidence. The timescale 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.[34,35] For all-cause mortality, we performed additional analyses by excluding participants with prevalent cancer.

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

We performed all analysis using R statistical software with the rms and survival packages.[36,37] We reported this study as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (**Supplemental STROBE Statement**).

Results

A total of 545 deaths and 2,970 incident CVD events occurred among 29,610 participants (mean age ± SD = 55.1 ± 7.5; female = 52.8%) in our core analyses. **Supplemental Figure 1** provides a flow diagram of participant exclusion. 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 their physical activity, 18,949 (64.0%) had stable physical activity, and 6,504 (22.0%) increased their physical activity. Across BMI change categories, 1,967 (6.6%) decreased their BMI, 24,388 (82.4%) had stable BMI, and 3,255 (11.0%) increased their BMI. Across BF% change categories, 2,902 (10.1%) decreased

BF%, 20,946 (72.8%) had stable BF%, and 4,920 (17.1%) increased their BF%. Across WC change categories, 3,728 (12.6%) decreased their WC, 18,530 (62.6%) had stable WC, and 7,352 (24.8%) increased their WC. Across WHR change categories, 3,728 (12.6%) decreased their WHR, 18,530 (62.6%) had stable WHR, and 7,352 (24.8%) increased their WHR. Participant characteristics at baseline are displayed in **Table 1** and follow-up characteristics are presented in **Supplemental Table 1**.

Independent associations of changes in physical activity and adiposity with all-cause mortality and CVD incidence

Compared to those with stable physical activity, participants who increased their physical activity had a lower risk for all-cause mortality (HR [95%CI]: 0.78 [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 2 and 3**).

Separate associations of changes in physical activity and changes in adiposity by baseline levels

Figure 1, and **Supplemental Figure 4-5** presents the multivariable adjusted associations of changes in physical activity (Fig 1A), BMI (Fig 1B), BF% (Fig 1C), WHR (**Supp Fig 4A**), and WC (**Supp Fig 5A**) with mortality risk. Sequential covariate adjustment models are shown in **Supplemental Table 2**. Compared to 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 timepoints (1.53 [1.12 to 1.92]) had similarly higher mortality risk.

The associations for adiposity changes were less consistent. For example, compared to being overweight at both timepoints, participants who were overweight at baseline, and decreased their BMI category, had a HR of 0.64 (0.40 to 1.02), whilst 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 to stable moderate WHR. Those with high adiposity at both timepoints (i.e.: obese, high BF%/WC/WHR) had higher mortality risk than those who were overweight or had moderate BF%/WC/WHR at both timepoints. 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.

--Insert Figure 1 near here--

Figure 2, **Supplemental Table 3** and **Supplemental Figure 4-5** shows the multivariable adjusted associations of changes in physical activity (**Fig 2A**), BMI (**Fig 2B**), BF% (**Fig 2C**), WHR (**Supp Fig 4B**), and WC (**Supp Fig 5B**) with risk of CVD. For physical activity, patterns were similar to those observed for risk of mortality. Compared to those with insufficient physical activity at both timepoints, those with initial insufficient physical activity who increased activity and those who were sufficiently active at both timepoints 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 to those who were overweight at both timepoint, those who were overweight and decreased their BMI and those with a healthy weight at both timepoints 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 all 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]), 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, had a high BF% or WC at both timepoints had higher CVD risk than the stable overweight, or moderate BF% or WC reference groups.

--Insert Figure 2 near here--

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 3-4**), 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 Figure 6-7**). 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/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, 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.

--Insert Figures 3 and 4 near here--

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/low adiposity, although the association was not statistically significant for BF%. For mortality, this relationship was not consistent for BMI (**Supplemental Figure 8 and 9**). Exclusion of prevalent cancer did not appreciably change the associations of changes for all-cause mortality (**Supplemental Tables 4-5**). The E-values (**Supplemental Tables 6-9**) 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 cardiovascular disease incidence suggests

that an unmeasured confounder would need to be associated with the joint physical activity-body mass index 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, and the largest to examine separate and concurrent changes in both factors, on all-cause mortality and CVD incidence. 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 that was equivalent to those whose level of activity met WHO guidelines at both timepoints. Thus, it appears that the relationship between physical activity and mortality/CVD risk is largely a function of relatively recent, rather than past, physical activity. These associations were consistent across all three BMI and BF% change categories. In contrast, adiposity decreases over time were not always associated with lower mortality or CVD risk compared to 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 particularly relevant for middle-aged adults who generally experience a 3-fold absolute decrease in physical activity as they transition to older adult life.[38]. The vast majority of 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 showed 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 against such biases and allows the effects of change to be ascertained. Studies in other populations assessing leisure time physical activity trajectories[39,40] or MVPA changes [41–44] 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 based on distributions shifts, or did not consider baseline levels, or grouped activity changes as "mixed patterns". Others assessed changes over a very short period, e.g. 1-2 years.[45,46] 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 gets progressively stronger at 18 years.[47,48] In most groups, we found decreasing adiposity was generally associated with a lower risk of CVD. This finding partially contrasts several prior investigations including those in the Framingham Heart Study and NHANES.[17,49–52] 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

339 weight from 10 to 37 years prior or potential reverse causation (i.e. the presence of
340 disease leading to a change in physical activity or weight status) from not excluding
341 participants with early events, who would have had increased likelihood of having
342 undiagnosed disease at baseline. A key strength with the present study is that, in
343 addition to excluding participants with a history of major chronic illness at baseline,
344 we also excluded participants with events within the first two years of follow up,
345 which minimised the potential for reverse causation that may have contributed to the
346 protective associations of excess adiposity observed in previous studies.[15,53]

347 The combination of both increasing physical activity and decreasing adiposity was
348 the only group that substantially reduced the risk of mortality and CVD compared to
349 stable physical activity and stable adiposity. It is possible that the beneficial
350 relationship occurs from physical activity and adiposity independently modulating
351 many of the same inflammatory and metabolic markers that contribute to associated
352 morbidity and mortality.[54–56] This would also explain why positive changes in only
353 one exposure (increasing physical activity or decreasing adiposity) attenuated, but
354 did not fully offset, the risk of mortality and morbidity. Our findings contrast other
355 studies that found that a physical activity increase was not associated with lower
356 mortality when combined with a weight/adiposity decrease.[57,58] The differences may
357 be due, at least in part, to previous studies using different physical activity and
358 weight/adiposity change definitions and change evaluation methods. Our longitudinal
359 results based on clinical standards indicate that there is a beneficial relationship
360 between physical activity and adiposity that supersedes improvements in each risk
361 factor separately. Investing resources on strategies that facilitate sustained long-term
362 improvements in both physical activity and adiposity levels at the population level
363 may bring better health outcomes.

Differences in adiposity measures may have differential effects on the association with mortality and CVD risk. [59–61] BMI by definition 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 (i.e. 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 biological changes that affect BMI and BF% independent of adiposity changes. Such biological changes as muscular atrophy which increases with age would have opposing effects on BMI (decrease) and BF% (increase) levels.[62] Our analyses of WHR changes showed less consistent patterns than the WC associations. Unlike waist circumference, hip circumference changes overtime can occur due to changes in subcutaneous fat, gluteal muscle mass, or both.[63] As a consequence, long term changes in WHR may be reflective of different aspects of body composition which makes interpretation less clear than WC changes, especially in older adults who commonly experience sarcopenia.[64,65]

Strengths and limitations

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 [66] whereby the associations are attenuated due to changes over time that was shown in our joint baseline analyses. To reduce the risk of reverse causality, we removed CVD and mortality events occurring in the first two 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 for 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 its 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 over several years have low feasibility and have not been successful.[67] In the general population, time to event induction would necessitate randomized controlled trials to be impracticably large to have sufficient power.[68] The UK Biobank may be prone to healthy volunteer selection bias due to a low response rate, although recent empirical evidence has shown that this doesn't affect the physical activity-disease relationships.[69,70] Our physical activity measures were self-reported, likely suffering from social desirability bias. Social desirability, would have likely led to an overestimation of the exposures in the positive direction and thus attenuated the associations between physical activity and mortality or CVD.

Conclusions

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 were similar to those who had high levels of physical activity at both timepoints, 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 timepoints. Thus, public health

messaging could emphasize that it is never too late to improve physical activity and weight to reduce mortality and CVD risk.

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638

Figure Titles and Legends:

Figure 1:

Title: 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]).

Legend: Physical activity: inactive (0 minutes of MVPA), Insufficient (>0 to < 150 minutes of MVPA), Sufficient (≥ 150 minutes of MVPA); Body mass index: obese (≥ 30 kg/m^2), overweight (<30 to ≥ 25 kg/m^2), healthy weight (≥ 18.5 kg/m^2; body fat percentage: high (≥29% for men and ≥42% for women), moderate (<29% to ≥22% for men and <42% to ≥35.2% for women), low (<22% for men and <35.2% for women).; adjusted for age, sex, smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables 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.

Figure 2:

Title: Separate association of physical activity, body mass index, and body fat percentage baseline changes with cardiovascular disease incidence risk (physical activity, body mass index [n=29,610]; body fat percentage [n=28,768]).

Legend: Physical activity: inactive (0 minutes of MVPA), Insufficient (>0 to < 150 minutes of MVPA), Sufficient (≥ 150 minutes of MVPA); Body mass index: obese (≥ 30 kg/m^2), overweight (<30 to ≥ 25 kg/m^2), or healthy weight (≥ 18.5 kg/m^2; %body fat:: 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, fruits and vegetables 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.

Figure 3:

Title: 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]).

Legend: Adjusted for age, sex, baseline physical activity, baseline body mass index (or body fat percentage); smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis.

Figure 4:

Title: 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]).

Legend: Adjusted for age, sex, baseline physical activity, baseline body mass index (or body fat percentage); smoking status, alcohol consumption, ethnicity, sleep pattern, education, fruits and vegetables consumption, deprivation index, and cancer diagnosis.

Table 1: Participant baseline characteristics categorized by physical activity and body mass index groups (n = 29,610)

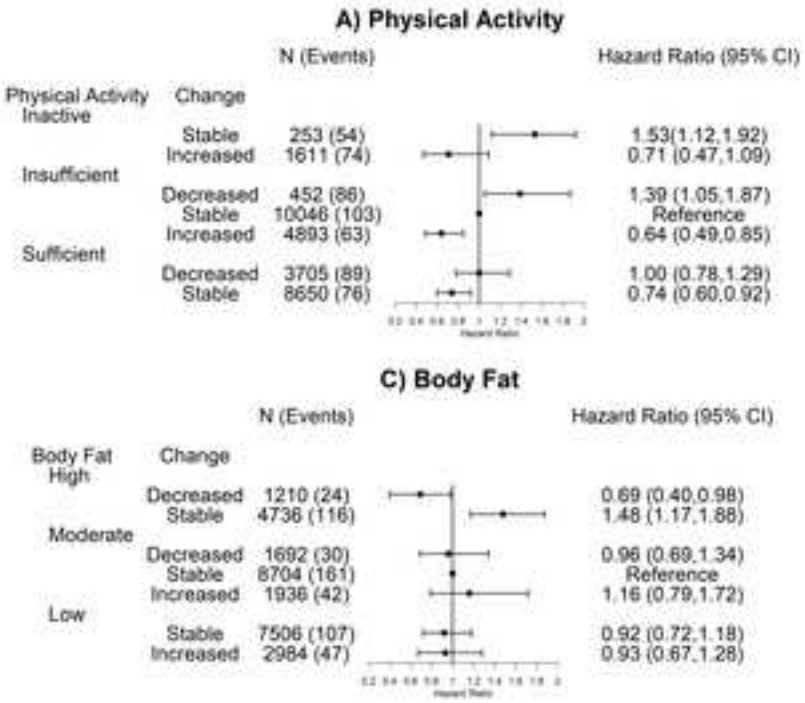
Physical activity group	Increase			Stable			Decrease		
BMI group	Decrease	Stable	Increase	Decrease	Stable	Increase	Decrease	Stable	Increase
N	514	5,354	636	1,074	15,813	2,062	379	3,221	557
PA, MET-min/week	640.60 (372.82)	671.60 (378.13)	651.07 (372.29)	640.33 (235.27)	650.49 (240.35)	610.93 (220.24)	690.35 (360.58)	600.18 (310.74)	653.62 (300.91)
PA change	137.9 (469.9)	222.98 (416.58)	301.03 (475.75	7.94 (486.46)	10.75 (442.76)	-6.39 (424.78)	-118.99 (469.83)	-225.96 (403.85)	-177.98 (465.63)
BMI, kg/m	27.09 (2.35)	26.20 (4.22)	25.76 (2.44)	26.94 (2.33)	26.21 (4.28)	25.95 (2.44)	27.16 (2.41)	26.61 (4.43)	26.06 (2.53)
BMI change	-0.18 (0.08)	0.02 (0.19)	0.32 (0.25)	-0.18 (0.08)	0.04 (0.20)	0.34 (0.27)	-0.17 (0.08)	0.07 (0.22)	0.39 (0.28)
Body fat, %	30.02 (8.07)	31.43 (7.50)	30.56 (7.36)	30.29 (7.73)	29.39 (8.26)	29.96 (7.54)	31.7 (7.85)	30.25 (8.23)	30.44 (7.54)
Body fat change	-1.40 (2.43)	0.86 (2.76)	4.04 (2.98)	-1.01 (2.50)	1.21 (2.78)	4.13 (3.06)	-0.68 (2.44)	1.57 (2.85)	4.47 (3.34)
Waist circumference, cm	89.53 (9.46)	86.94 (12.59)	84.90 (10.01)	89.45 (9.54)	87.06 (12.67)	85.83 (9.93)	89.09 (8.95)	87.86 (12.74)	85.94 (10.13)
Waist circumference change	-2.83 (5.60)	0.75 (6.27)	6.04 (6.69)	-2.94 (5.88)	1.25 (6.16)	6.07 (6.90)	-1.81 (5.90)	1.86 (6.47)	7.13 (6.86)
Waist to hip ratio	0.87 (0.08)	0.85 (0.09)	0.84 (0.08)	0.87 (0.08)	0.86 (0.09)	0.85 (0.08)	0.87 (0.08)	0.86 (0.09)	0.85 (0.08)
Waist to hip ratio change	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.01 (0.01)	0.00 (0.01)	0.00 (0.01)	0.01 (0.01)
Age	55.29 (6.88)	54.77 (7.30)	53.33 (7.66)	55.93 (7.36)	55.30 (7.61)	53.63 (7.70)	56.72 (6.89)	55.68 (7.82)	54.30 (7.79)
Male, N (%)	246	2405	241	568	7660	905	80	1592	234

	(48.1)	(45.1)	(38.0)	(53.1)	(48.6)	(44.1)	(45.2)	(46.7)	(42.1)
Ethnicity = white, N (%)	494 (96.7)	5182 (97.1)	622 (98.0)	1039 (97.2)	15321 (97.3)	1988 (96.9)	169 (95.5)	3301 (96.9)	543 (97.7)
Education = college/university, N (%)	235 (46.0)	2736 (51.3)	365 (57.5)	569 (53.2)	8178 (51.9)	1184 (57.7)	101 (57.1)	1913 (56.1)	342 (61.5)
Smoking, N (%)									
never	319 (62.7)	3427 (64.4)	358 (56.6)	661 (61.9)	10082 (64.1)	1284 (62.7)	112 (63.3)	2116 (62.2)	326 (58.7)
previous	164 (32.2)	1712 (32.2)	249 (39.3)	384 (36.0)	5012 (31.9)	679 (33.2)	56 (31.6)	1119 (32.9)	203 (36.6)
current	26 (5.1)	184 (3.5)	26 (4.1)	22 (2.1)	628 (4.0)	84 (4.1)	9 (5.1)	167 (4.9)	26 (4.7)
Alcohol consumption, units/week[2]	4.35 (1.11)	4.25 (1.12)	4.25 (1.17)	4.37 (1.13)	4.27 (1.14)	4.21 (1.20)	4.23 (1.08)	4.22 (1.18)	4.11 (1.21)
Fruits and vegetables, servings/day	5.86 (6.14)	5.85 (7.21)	5.14 (7.69)	6.87 (7.43)	6.27 (7.63)	5.96 (7.99)	5.75 (7.10)	5.79 (7.49)	5.99 (7.05)
Sleep pattern, N (%)[3]									
Poor	3 (1.3)	37 (1.4)	13 (3.9)	3 (0.5)	109 (1.2)	26 (1.9)	1 (1.3)	17 (1.0)	5 (1.5)
Intermediate	85 (36.0)	923 (34.6)	114 (4.1)	190 (32.9)	3070 (32.5)	521 (37.1)	26 (33.8)	558 (33.9)	125 (36.5)
Healthy	148 (62.7)	1707 (64.0)	207 (62.0)	385 (66.6)	6277 (66.4)	857 (61.0)	50 (64.9)	1073 (65.1)	212 (62.0)
Deprivation Index[4]	-2.09 (2.68)	-2.08 (2.61)	-2.06 (2.68)	-2.03 (2.62)	-2.11 (2.60)	-2.01 (2.67)	-2.15 (2.55)	-1.93 (2.71)	-1.89 (2.76)
Cancer, N (%)[5]	41 (8.0)	338 (6.3)	37 (5.8)	77 (7.2)	958 (6.1)	135 (6.5)	41 (8.0)	223 (6.5)	47 (8.4)

All values represent Mean (SD) unless noted otherwise; BMI = body mass index; WHR = waist to hip ratio
[1]%Body fat analytic sample was 28,768
[2] 1 unit = 8 g of ethanol
[3]sleep patterns were determined based on the method proposed by Fan M. et al (24). In brief, participants were categorized by how many healthy sleep characteristics (morning chronotype, adequate sleep duration (7-8 hr./d), never or rare insomnia, never or rare snoring, and infrequent daytime sleepiness) they displayed into three groups (healthy: ≥ 4; intermediate: 2-3; poor: ≤ 1)
[4]scores ranged from -6.3 to 10.6; higher index score implies a greater degree of deprivation
[5]Physician diagnosed (self-reported and cancer registry) before baseline.

Figure 1

Click here to access/download;Figure;Fig 1 comb ACM.tiff



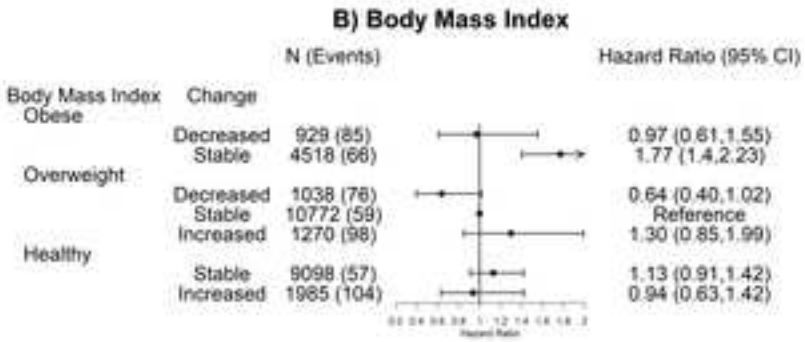
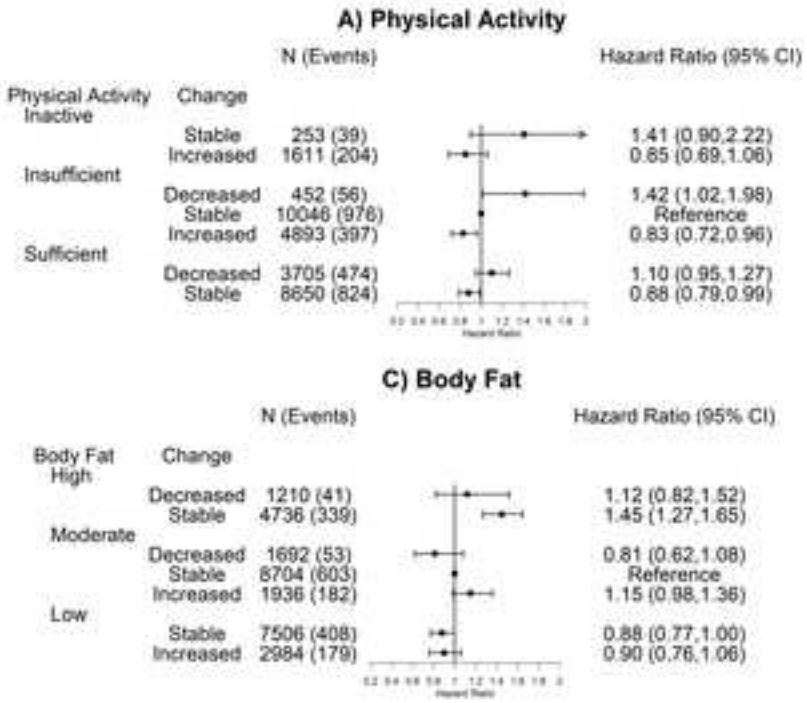


Figure 2



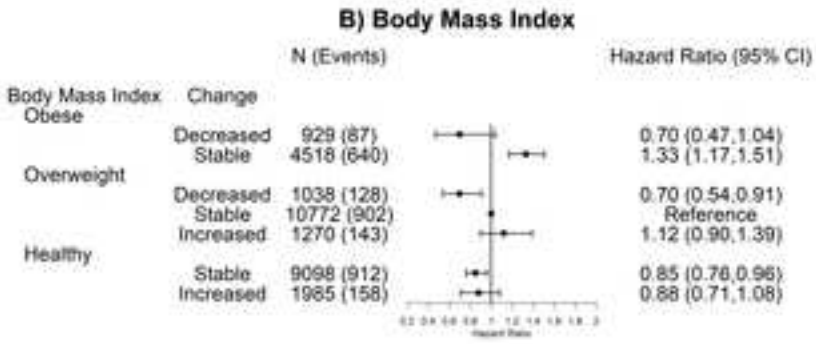
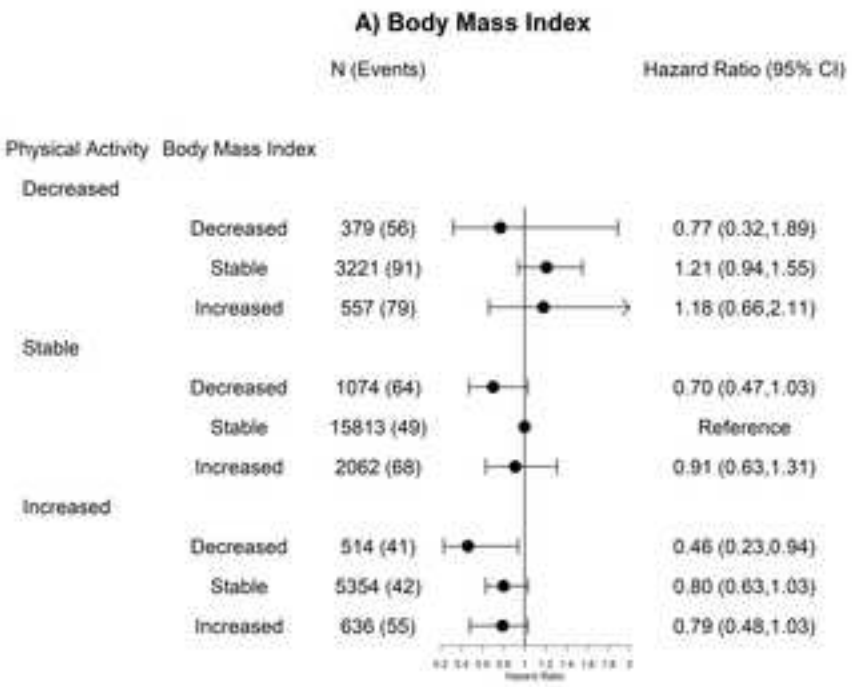


Figure 3



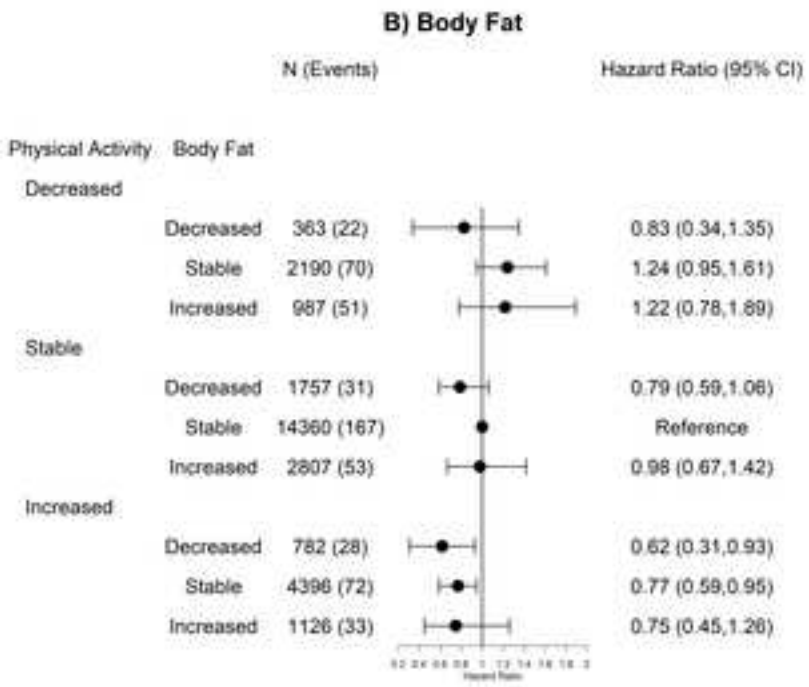


Figure 4