ESC European Society of Cardiology

European Journal of Preventive Cardiology
https://doi.org/10.1093/eurjpc/zwab190

FULL RESEARCH PAPER

Continuing regular physical activity and maintaining body weight have a synergistic interaction in improving survival: a population-based cohort study including 6.5 million people

Chang-Hoon Lee[1], Kyung-Do Han[2], Da Hye Kim[3], and Min-Sun Kwak [4,*]

[1]Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea; [2]Department of Statistics and Actuarial Science, Soongsil University, Sangdo-ro, Dongjak-gu, Seoul 06978, Republic of Korea; [3]Department of Biomedicine and Health Science, Catholic University of Korea, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea; and [4]Department of Internal Medicine, Healthcare Research Institute, Healthcare System Gangnam Center, Seoul National University Hospital, 39FL., Gangnam Finance Center 737, Yeoksam-Dong, Gangnam-gu, Seoul 06236, Republic of Korea

Received 3 June 2021; revised 14 October 2021; editorial decision 27 October 2021accepted 29 October 2021

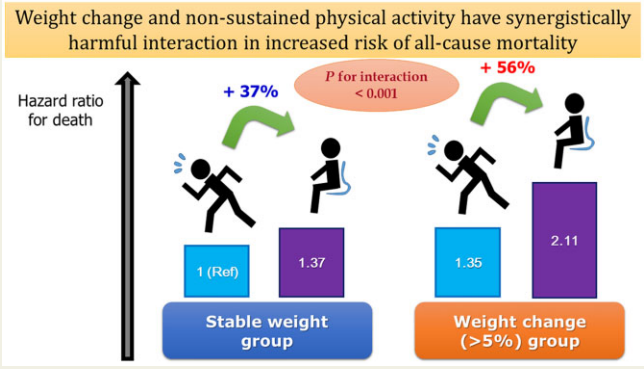
Aims Continuing physical activity (PA) and maintaining body weight are tightly intertwined; however, no study investigated whether these two factors have interactions in terms of the mortality. The aim of this study is to elucidate whether continuing regular PA and maintaining body weight have interactions in terms of all-cause mortality risk.

Methods and results Participants with health screening from both 2009 and 2011 without underlying cancer or cardiovascular disease were included. Physical activity change was grouped as remained active, inactive-to-active, active-to-inactive, or remained inactive. Body weight change was categorized as stable (weight change < 5%), weight gain, or loss. Outcome included all-cause mortality. Of 6 572 984 total participants, 91 347 deaths occurred during a median 7.4-year follow-up. Compared with the remained active and stable weight group, most other groups had a higher mortality risk. The weight loss and remained inactive group [adjusted hazard ratio (aHR), 2.30; 95% confidence interval (CI), 2.22–2.38] and the weight gain and remained inactive group (aHR, 2.17; 95% CI, 2.09–2.25) showed the highest mortality risks. Among stable weight participants, the ranking of the groups from highest to lowest in terms of mortality risk was as follows: remained inactive (aHR, 1.46; 95% CI, 1.41–1.50), active-to-inactive (aHR, 1.24; 95% CI, 1.19–1.29), inactive-to-active (aHR, 1.15; 95% CI, 1.11–1.20), and remained active (reference). Remaining active and maintaining a stable body weight had a synergistic interaction on decreasing all-cause mortality risk (multiplicative *P* for interaction < 0.001; relative excess risk due to interaction, 0.38; 95% CI, 0.31–0.46; attributable proportion, 0.18; 95% CI, 0.15–0.22).

Conclusions Continuing regular PA as recommended and maintaining body weight have multiplicative and additive interactions on reducing all-cause mortality. Healthcare providers should emphasize the importance of both regular PA and body weight maintenance for the general public.

* Corresponding author. Tel: +82 2 2112 5690, Fax: +82 2 2112 5635, Email: rasberry0309@gmail.com

Graphical Abstract



Keywords Physical activity • Exercise • Body weight • Mortality

Introduction

Physical activity (PA) is beneficial for reducing all-cause mortality,[1,2] and expert guidelines recommend consistent PA of at least 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic PA for adults.[3,4] Continuing regular PA as recommended over time results in more survival benefits.[5,6]

Maintenance of body weight has also been reported to be associated with improved survival. A stable body weight is associated with decreased mortality risk,[7–10] while weight variability is related to an increased risk of mortality.[11–15]

Thus, both continuing regular PA and maintaining body weight are important factors in improving survival. These two factors are tightly intertwined. Physical activity plays an important role in body weight regulation,[16,17] and weight gain is associated with future physical inactivity.[18] Therefore, a change in PA and a change in body weight cannot be considered independently. However, how a continuing regular PA and maintaining body weight interact is not clear. Although there were a few studies focusing on the combined effects of PA and body mass index (BMI) on mortality,[19–21] no study clearly demonstrated any significant interactions.

Therefore, the aim of this study is to elucidate whether continuing regular PA and maintaining body weight have interactions in terms of the risk of all-cause mortality.

Methods

Data source of the National Health Insurance Service

We used the database of the National Health Insurance Service (NHIS), which is managed by the Korean government. The NHIS covers nearly all Koreans (97.2% of the Korean population).[22] The NHIS provides annual or biennial standardized health check-ups for all insured Koreans older than 40 years and employees older than 20 years. The NHIS contains the following information for each participant: demographic information including PA questionnaire, anthropometric measurement, examination, claims for disease diagnosis codes of the International Classification of Diseases (ICD-10), and treatments including procedures performed and medication prescribed.[23]

This study protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (H-2002-004-1097). The requirement for informed consent from participants was waived because of the retrospective design of the study, and the researchers accessed only de-identified clinical data for analytical purposes.

Study population

Participants older than 20 years who had undergone the Korean Health Screening in 2009 and underwent follow-up health check-ups in 2011 were initially included. Among them, participants with missing data were excluded. Participants who were diagnosed with any cancer before 2011 were excluded based on ICD-10 C-codes and registration programmes for serious diseases. The Korean government provides co-payment for registered cancer patients with a cancer diagnosis confirmed by a physician. Participants who were diagnosed with major cardiovascular disease [myocardial infarction (I21, I22) or stroke (I63, I64)] or who had a history of major cardiovascular disease (heart disease or stroke) based on a questionnaire were additionally excluded. The included participants were followed up until December 2018 (*Figure 1* and Supplementary material online, *Figure S1*).

Physical activity measurements

The PA questionnaire used by the Korean National Health Insurance Service (KNHIS) in 2009 and 2011 was a modified Korean version of the International Physical Activity Questionnaire (IPAQ), a well-validated questionnaire, including frequency, duration, and intensity (walking, moderate intensity, or vigorous intensity) of PA. 'Regular PA' was defined as meeting any one of the following two criteria: (i) three or more days/week of vigorous activity of at least 20 min per day or (ii) five or more days/week of moderate-intensity activity of at least 30 min per day.[3,4]

The same questionnaires were used in 2009 and 2011, and participants were divided into four groups as follows: 'remained inactive' (no regular

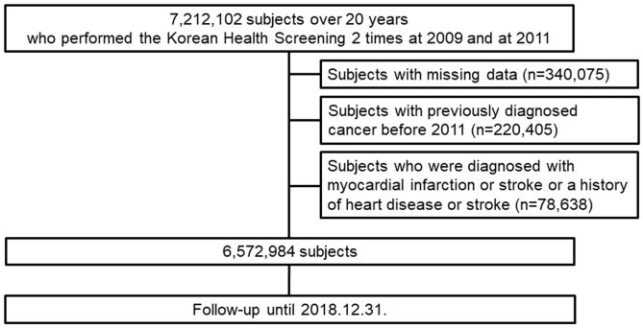


Figure 1 Flow chart of study enrolment.

exercise both in 2009 and 2011), 'remained active' (regular exercise at both times), 'active-to-inactive' (regular PA in 2009, then no regular PA in 2011), and 'inactive-to-active' (no regular PA in 2009, then regular PA in 2011). The active-to-inactive group and inactive-to-active group are also categorized into the 'changed PA' group. 'Not remained active' group includes 'remained inactive', 'active-to-inactive', and 'inactive-to-active' groups.

Body weight change

Body weight change was calculated as the difference in weight between 2009 and 2011. Based on previous studies,[24,25] we categorized the 'stable weight' group as individuals with a weight change within 5%, the 'weight loss' group as individuals with a weight loss ≥5%, and the 'weight gain' group as individuals with a weight gain ≥5%. The 'weight loss' group and 'weight gain' group are also categorized into the 'changed weight' group.

Measurement of clinical parameters and biochemical analysis

Standardized self-administered questionnaires were collected. The questionnaires included age, sex, alcohol consumption (frequency and amount), smoking (current, former, and never), annual income, regular PA, and underlying diseases. Heavy alcohol consumption was defined as ingesting more than 21 standard alcohol drinks/week based on the self-administered questionnaire.[26]

Height (m) and body weight (kg) were measured using an electronic scale. Body mass index was calculated as follows: BMI = body weight (kg)/height^2 (m^2). The waist circumference was measured using a tape measure at the midpoint between the iliac crest and the lower costal margin by a trained examiner. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 min of rest.

Blood samples were collected from each participant after overnight fasting. The laboratory examinations included assessments of serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and fasting glucose. All biochemical analyses were carried out using standardized laboratory methods.

The diagnoses of hypertension, dyslipidaemia, and diabetes mellitus (DM) were defined using anthropometric measurements and laboratory data (SBP 140 mmHg or DBP 90 mmHg; total cholesterol levels ≥ 240 mg/dL; fasting glucose level ≥ 126 mg/dL) or ICD codes (ICD I10 to I13 or I15; E78; E11 to E14) and medication use, including antihypertensive medication, dyslipidaemia medication, insulin, or oral hypoglycaemic agents.

Outcomes

The primary outcome was all-cause mortality during the follow-up period. The NHIS database includes whether a person died or not during the follow-up duration of the study (until 31 December 2018) and the death date if he or she died. The causes of death were not included in our database.

Statistical analysis

Continuous variables are expressed as the means ± standard deviations, and categorical variables are expressed as numbers and percentages. Between-group comparisons were performed using χ^2 tests for categorical variables and Student's *t*-test or one-way analysis of variance for continuous variables. For non-normally distributed variables, log transformation was performed.

All-cause mortality was calculated as the number of events divided by total person-years (per 1000). To adjust for covariates, multivariable Cox proportional hazards regression analyses were performed. Subgroup analysis according to BMI was performed to evaluate whether BMI had any effect on the combined impact of PA and body weight change on mortality.

To investigate whether there was any interaction between PA and weight change, we applied two by two categories: 'stable weight' group and 'changed weight' group for weight change and 'remained active group' and 'not remained active' group for PA change. The interaction term of 'change in body weight' × 'change in PA' was analysed to evaluate whether there was a multiplicative interaction effect between change in body weight and change in PA on all-cause mortality. Measures of additive interaction included relative excess risk due to interaction (RERI) and attributable proportion (AP).

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

In total, 6 572 984 participants (mean age, 48.4 ± 13.4 years; 56.7% were male) were included in the analysis. The flowchart of the study enrolment is presented in *Figure 1*. The baseline characteristics of the total population and participants according to change in PA are presented in *Table 1*. The baseline characteristics according to body weight change are presented in Supplementary material online, *Table S1*.

Table 1 Baseline characteristics (at 2011) according to the change of physical activity

Physical activity	Total	Remained active	Inactive-to-active	Active-to-inactive	Remained inactive	*P*-value
N	6 572 984	516 148	813 218	711 718	4 531 900	
Age, years	48.44 ± 13.35	50.79 ± 12.23	49.32 ± 12.96	50.38 ± 13.24	47.71 ± 13.48	<0.001
Men	3 728 358 (56.7)	348 345 (67.5)	480 464 (59.1)	420 636 (59.1)	2 478 913 (54.7)	<0.001
Smoking						<0.001
Non-smoker	3 851 136 (58.6)	270 766 (52.5)	468 328 (57.6)	418 729 (58.8)	2 693 313 (59.4)	
Ex-smoker	1 101 795 (16.8)	135 977 (26.3)	161 957(19.9)	131 927 (18.5)	671 934 (14.8)	
Current	1 620 053 (24.7)	109 405 (21.2)	182 933 (22.5)	161 062 (22.6)	1 166 653 (25.7)	
Alcohol drinking						<0.001
Non	3 295 333 (50.1)	227 688 (44.1)	399 413 (49.1)	364 160 (51.2)	2 304 072 (50.8)	
Mild	2 799 696 (42.6)	244 139 (47.3)	354 141 (43.6)	295 540 (41.5)	1 905 876 (42.1)	
Heavy	477 955 (7.3)	44 321(8.6)	59 664 (7.3)	52 018 (7.3)	321 952 (7.1)	
Lowest quartile of income (Q1)	1 318 244 (20.1)	105 108 (20.4)	180 139 (22.2)	149 076 (21.0)	883 921 (19.5)	<0.001
BMI (kg/m^2)	23.8 ± 3.2	24.2 ± 2.9	24.0 ± 3.0	24.1 ± 3.1	23.7 ± 3.3	<0.001
WC (cm)	80.6 ± 9.0	81.4 ± 8.2	80.8 ± 8.6	81.4 ± 8.7	80.3 ± 9.2	<0.001
Body weight (kg)	64.6 ± 11.7	66.8 ± 11.1	65.2 ± 11.4	65.4 ± 11.6	64.1 ± 11.8	<0.001
SBP (mmHg)	122.4 ± 14.5	123.9 ± 14.1	122.8 ± 14.3	123.4 ± 14.5	122.0 ± 14.6	<0.001
DBP (mmHg)	76.3 ± 9.8	77.1 ± 9.6	76.5 ± 9.7	76.8 ± 9.8	76.1 ± 9.8	<0.001
Hypertension	1 781 147 (27.1)	161 666 (31.3)	232 889 (28.6)	218 596 (30.7)	1 167 996 (25.8)	<0.001
Dyslipidaemia	1 305 443 (19.9)	112 318 (21.8)	167 718 (20.6)	157 457 (22.1)	867 950 (19.2)	<0.001
Diabetes mellitus	579 050 (8.8)	55 950 (10.8)	78 625(9.7)	75 364 (10.6)	369 111 (8.1)	<0.001
Fasting glucose (mg/dL)	97.2 ± 21.8	98.7 ± 22.0	97.6 ± 21.6	98.5 ± 22.9	96.8 ± 21.6	<0.001
Total cholesterol (mg/dL)	195.3 ± 35.9	195.6 ± 35.3	194.7 ± 35.6	196.3 ± 36.2	195.2 ± 36.0	<0.001
Triglyceride (mg/dL)[a]	111.63 (111.58–111.68)	107.77 (107.61–107.93)	113.91 (113.77–114.06)	108.00 (107.88–108.13)	112.39 (112.33–112.44)	<0.001
LDL (mg/dL)	114.3 ± 33.0	114.7 ± 32.6	114.2 ± 32.8	115.1 ± 33.3	114.1 ± 33.0	<0.001
HDL (mg/dL)	55.1 ± 14.5	55.9 ± 14.5	55.4 ± 14.6	54.8 ± 14.3	55.0 ± 14.4	<0.001

Categorical variables are expressed as number (%); continuous variables are expressed mean ± standard deviation.
BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; WC, waist circumference.
[a]Geometric means (95% confidence interval).

The median follow-up duration of this cohort was 7.4 years (interquartile range, 7.2–7.6). A total of 91 347 (1.89 incidence rate per 1000 person-years) participants died during follow-up. Supplementary material online, *Table S2* shows that the 'remained inactive' group had a significantly higher risk of all-cause mortality than the 'remained active' group and 'changed PA' groups after adjustment for covariates including age, sex, smoking, alcohol consumption, income, hypertension, dyslipidaemia, DM, and BMI. Regarding weight change, approximately 15% of participants experienced weight gain, and approximately 11% of participants experienced weight loss. In multivariate analysis, the 'weight loss' or 'weight gain' group had a more than 50% higher risk for all-cause mortality than the 'stable weight' group (Supplementary material online, *Table S3*).

Table 2 and *Figure 2* show the combined effect between the change in PA and the change in body weight on all-cause mortality. Compared with those who remained active and had a stable weight, most other categories had a higher risk of mortality. Those who were categorized into both the weight loss group and the remained inactive group showed the highest risks of mortality [adjusted hazard ratio (aHR), 2.30; 95% confidence interval (CI), 2.22–2.38], and those who were categorized into both the weight gain group and the remained inactive group showed the comparably highest risks of mortality (aHR, 2.17; 95% CI, 2.09–2.25). Although the stable weight group had lower risks of mortality than the weight loss or weight gain group, regardless of weight stability, the ranking of the groups from highest to lowest risk of mortality was as follows: remained inactive, active-to-inactive, inactive-to-active, and remained active.

When the group was divided into four simpler groups depending on the weight stability and change in PA (*Table 3*, *Figure 3*, and Supplementary material online, *Figure S2*), the stable weight group that remained active had the lowest risk of all-cause mortality, and the changed weight group with not remained active group had the highest risk of all-cause mortality (aHR, 2.11; 95% CI, 2.04–2.18). The 'stable weight with changed PA group' and 'remained active but changed weight group' had similarly increased risk for mortality (aHR, 1.37; 95% CI, 1.33–1.41 and aHR 1.35; 95% CI 1.27–1.43) compared to that of the group that maintained a stable weight and remained active. There was a significant multiplicative interaction (*P* for interaction < 0.001). A significant additive interaction was also observed (RERI, 0.38; 95% CI, 0.31–0.46; AP, 0.18; 95% CI, 0.15–0.22).

Table 2 The combined effect of change of PA and change of body weight on all-cause mortality after adjustment for age, sex, smoking, drinking, yearly income, diabetes, hypertension, dyslipidaemia, and body mass index

Change of weight	Change of PA	Number (%)	IR per 1000	Univariate model HR (95% CI)	Multivariate model 1 HR (95% CI)	Multivariate model 2 HR (95% CI)
Weight loss (≥5%)	Remained active	53 754 (0.82)	2.348	1.68 (1.57–1.81)	1.54 (1.44–1.66)	1.31 (1.22–1.40)
	Inactive-to-active	106 447 (1.62)	3.995	1.77 (1.68–1.87)	1.95 (1.85–2.06)	1.61 (1.53–1.70)
	Active-to-inactive	74 057 (1.13)	2.468	2.85 (2.71–3.01)	2.31 (2.20–2.44)	1.87 (1.77–1.97)
	Remained inactive	498 745 (7.59)	4.314	3.09 (2.99–3.20)	2.94 (2.84–3.04)	2.30 (2.22–2.38)
Stable weight (<5%)	Remained active	400 855 (6.10)	1.399	1 (reference)	1 (reference)	1 (reference)
	Inactive-to-active	603 069 (9.17)	1.767	1.04 (1.00–1.08)	1.19 (1.14–1.24)	1.15 (1.11–1.20)
	Active-to-inactive	529 757 (8.06)	1.457	1.26 (1.21–1.31)	1.29 (1.24–1.34)	1.24 (1.19–1.29)
	Remained inactive	3 336 252 (50.76)	1.645	1.18 (1.14–1.22)	1.56 (1.51–1.61)	1.46 (1.41–1.50)
Weight gain (≥5%)	Remained active	61 539 (0.94)	1.398	1 (0.92–1.09)	1.38 (1.27–1.50)	1.43 (1.31–1.55)
	Inactive-to-active	103 702 (1.58)	1.827	1.13 (1.06–1.21)	1.68 (1.57–1.79)	1.68 (1.57–1.79)
	Active-to-inactive	107 904 (1.64)	1.584	1.31 (1.23–1.39)	1.88 (1.77–2.00)	1.90 (1.79–2.02)
	Remained inactive	696 903 (10.60)	1.820	1.30 (1.26–1.35)	2.23 (2.15–2.31)	2.17 (2.09–2.25)

Multivariate model 1: age, sex adjusted model.
Multivariate model 2: age, sex, smoking, drinking, income, diabetes, hypertension, dyslipidaemia, and body mass index adjusted model.
CI, confidence interval; HR, hazard ratio; IR, incidence rate; PA, physical activity.

In the subgroup analysis, the effect of PA and weight stability on mortality was similar regardless of BMI subgroup. Weight stability was more beneficial than weight loss of more than 5%, even in the severe obesity subgroup (Supplementary material online, *Table S4* and *Figure S3*). The effect of PA and weight stability on mortality was similar regardless of subgroups according to the age, sex, smoking, alcohol drinking, diabetes, dyslipidaemia, and hypertension (Supplementary material online, *Table S5*).

Discussion

This large population-based cohort study showed that both continuing regular PA and maintaining body weight are associated with a decreased risk of all-cause mortality. Additionally, continuing regular PA and maintaining body weight have multiplicative and additive interactions on reducing mortality.

We showed that both continuing regular PA and maintaining body weight are associated with a decreased risk of all-cause mortality. These results are in line with previous reports.[1–3,5,6,27] Furthermore, to our knowledge, this study is the first to reveal that continuing regular PA and maintaining body weight have synergistic benefits in reducing the risk of all-cause mortality. The synergistic effect was demonstrated by both a significant multiplicative interaction (P for interaction < 0.001) and a significant additive interaction (RERI, 0.38; 95% CI, 0.31–0.46; AP, 0.18; 95% CI, 0.15–0.22). The stable weight group that remained active had the lowest risk of all-cause mortality. The 'stable weight with changed PA group' and 'remained active but changed weight group' had similarly increased risk for mortality (aHR, 1.37; 95% CI, 1.33–1.41 and aHR 1.35; 95% CI 1.27–1.43) compared to that of the group that maintained a stable weight and remained active. The changed weight with not remained active group had the highest risk of all-cause mortality (aHR, 2.11; 95% CI, 2.04–2.18).

The biological mechanism by which continuing regular PA and maintaining body weight have a synergistic interaction on survival is unclear. However, there are many data supporting that both are beneficial for improved survival. First, both contribute to healthier body composition. It has been known that an increased fat mass is associated with an increased risk of mortality, and an increased lean body mass is related to a reduced mortality.[28] Weight gain leads to increased fat mass,[29] and weight loss or weight fluctuation results in decreased lean body mass.[30,31] Physical activity decreases fat mass[32] and increases lean body mass.[3,33] Thus, both continuing regular PA and maintaining body weight could have enhanced beneficial effects on survival through healthier changes in body composition. Second, both can protect against telomere shortening. Physical activity can protect against telomere shortening via various mechanisms, including increased telomerase activity and decreased oxidative stress and systemic inflammation.[34] Obesity is related to telomere shortening,[35] and weight gain and weight variability are also associated with telomere shortening.[36] A study reported that a high level of diet restriction that could result in weight loss was associated with telomere shortening.[37] In addition, psychological stress has also been shown to affect telomere shortening,[37] and regular PA reduces stress. Third, both contribute to favourable metabolic profiles. Blood pressure, insulin resistance, and lipid profile are metabolic profiles closely associated with cardiovascular disease.[38] Body weight fluctuation is associated with worse metabolic profiles than weight stability,[39] and PA is known to improve these profiles.[40,41] Thus, weight stability and PA might synergistically improve metabolic indicators, reducing the risk of cardiovascular disease and contributing to longevity benefits. Fourth, both PA and weight stability reduce inflammation and oxidative stress,[42,43] which can lead to cardiovascular diseases or cancer.[44,45] Weight gain, obesity, and underweight[46] are all known to be associated with increased systemic inflammation and oxidative stress.[47] The reduction in oxidative stress and chronic inflammation

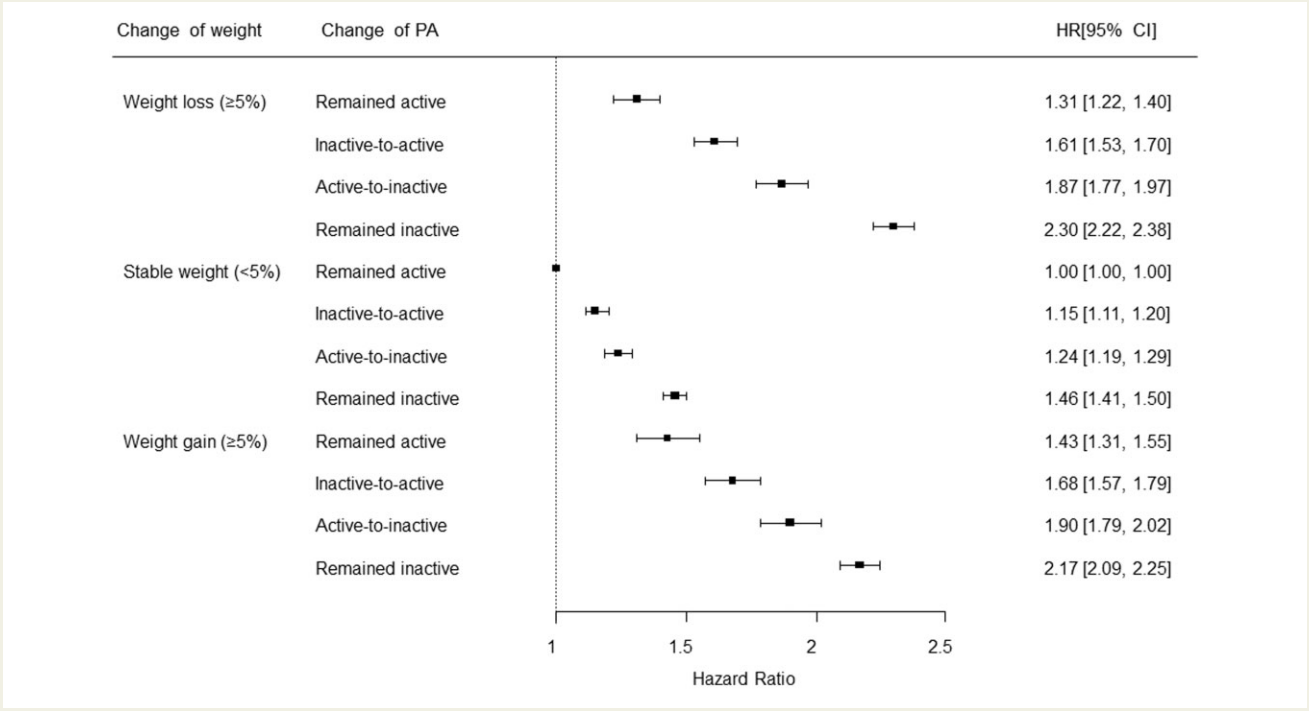


Figure 2 The combined effect of changes in physical activity and changes in body weight on all-cause mortality after adjustment for age, sex, smoking, alcohol consumption, annual income, diabetes mellitus, hypertension, dyslipidaemia, and body mass index.

Table 3 The combined effect of change of PA and change of body weight on all-cause mortality and interaction between PA and body weight on mortality

Weight change	Change of PA	IR_per1000	Univariate model HR (95% CI)	Multivariate model 1 HR (95% CI)	Multivariate model 2 HR (95% CI)	Interaction		
						RERI (95% CI)	AP (95% CI)	Multiplicative P for interaction
Stable weight	Remained active	1.399	1 (reference)	1 (reference)	1 (reference)	0.38 (0.31–0.46)	0.18 (0.15–0.22)	<0.001
	Not remained active[a]	1.634	1.17 (1.13–1.21)	1.46 (1.41–1.50)	1.37 (1.33–1.42)			
Changed weight	Remained active	1.840	1.32 (1.24–1.40)	1.47 (1.39–1.56)	1.35 (1.27–1.43)			
	Not remained active[a]	2.730	1.96 (1.90–2.02)	2.44 (2.36–2.52)	2.11 (2.04–2.18)			

Multivariate model 1: age, sex adjusted model.
Multivariate model 2: age, sex, smoking, drinking, income, diabetes, hypertension, dyslipidaemia, and body mass index adjusted model.
AP, attributable proportion; CI, confidence interval; HR, hazard ratio; IR, incidence rate; PA, physical activity; RERI, relative excess risk due to interaction.
[a]'Not remained active' includes 'remained inactive', 'active-to-inactive', and 'inactive-to-active' groups.

through PA and weight stability might decrease cardiovascular- or cancer-related death, reducing all-cause mortality.

Our study showed that the majority of the general population does not perform PA as recommended. More than two-thirds of the participants (69%) remained in the inactive group, and only 8% remained in the active group, which is similar to previous results.[48] This finding may reflect the increasing prevalence of sedentary lifestyles globally.[49] Additionally, half of the participants failed to maintain a stable body weight. Among them, 57% gained weight, which may reflect the increasing prevalence of obesity.[50,51] Intriguingly, more than half of those who maintained their body weight did not perform sufficient PA. Only 6% of participants both maintained a stable body weight and remained active.[52] These findings suggest that there are many people who might have longevity benefits with

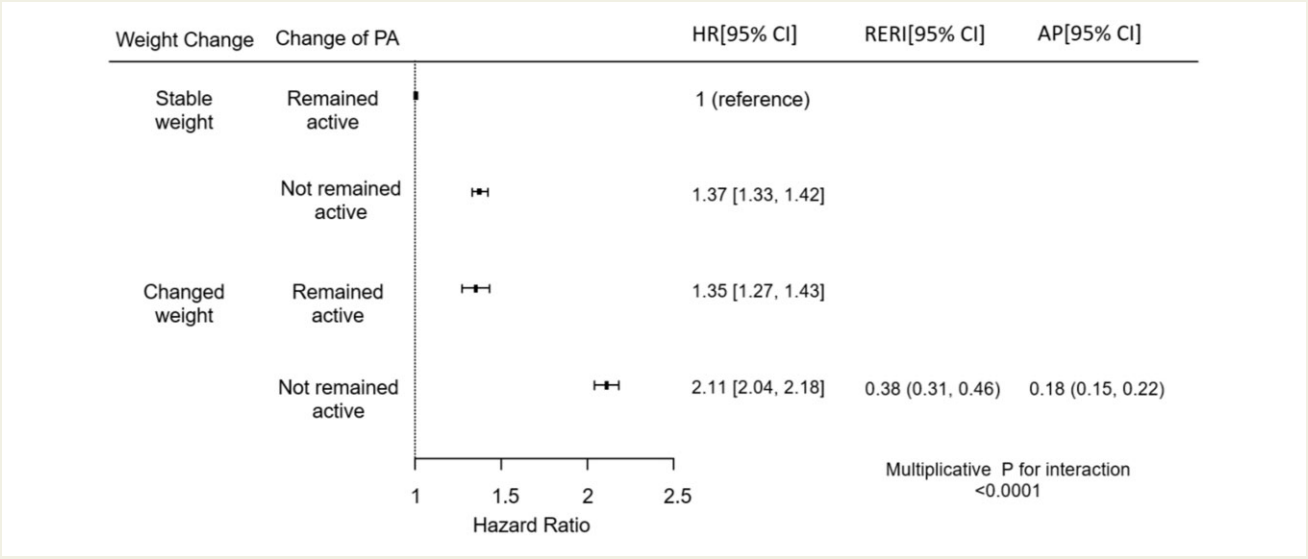


Figure 3 The combined effect of change in physical activity and change in body weight on all-cause mortality and the interaction between physical activity and body weight on mortality.

lifestyle modification of weight control and consistent exercise and that the recommendation of PA continuation and weight maintenance can be a valuable strategy for reducing the public health burden.

Our study evaluated the amount of PA two times with a 2-year interval. Interestingly, the changes in PA over 2 years resulted in a difference in all-cause mortality: the inactive-to-active group had better survival than the group that remained inactive, and the inactive-to-active group had better survival than the group that transitioned from active-to-inactive, regardless of weight change (*Table 2* and Supplementary material online, *Table S2*). This finding suggests the value of prompt lifestyle modification. It is worth recommending those who are inactive to 'just be active immediately' and those who are active to 'keep being active', irrespective of weight change.

Another unresolved issue concerning the effect of body weight and PA on mortality is whether weight loss in obese people is beneficial. In this study, subgroup analysis according to BMI showed no significant difference in PA and body weight change on mortality according to BMI. Even in the obese group, weight loss with sufficient PA or increased PA was associated with increased all-cause mortality compared to that of the weight stable group that maintained PA. This result is similar to many previous epidemiologic studies showing that weight loss in the obese group is associated with increased mortality.[11,53–55] In the same context, another study showed that sustained PA, not weight loss, is associated with survival benefit in terms of coronary heart disease.[56] These epidemiologic studies have limitations in that they cannot differentiate intentional weight loss from weight loss from other causes. On the other hand, a meta-analysis including randomized controlled trials showed that intentional weight loss is beneficial in obese people.[57] However, randomized controlled trials have limitations in that they are mostly small in size with relatively short-term interventions and follow-up durations. Cautious interpretation and further study is warranted in regard to the benefit of weight loss and PA in the obese group. At this point, physicians should focus on healthy lifestyle behaviours, including PA that contribute to weight stability rather than weight loss itself, even in obese subjects. This study has the following strengths: Firstly, this is a large-scale population-based study, which provides a strong statistical power to clearly demonstrate the interaction between continuing regular PA and maintaining body weight on the survival benefit. Secondly, various covariates including smoking, alcohol ingestion, income, BMI, DM, hypertension, and dyslipidaemia were adjusted in the multivariable model. It minimized the confounding effects. We admit several limitations. Firstly, our cohort consists of one ethnicity (Koreans). Thus, our results might not be generalizable to the whole world-wide population. Secondly, cause-specific death was not evaluated. Third, the level of PA was evaluated based on the self-declared questionnaire that depends on memory of the last 7 days, which could lead to recall bias. However, this 7-day recall survey has been well-validated and widely used in many previous researches.[58–60] Fourth, a question could be raised that the reason that remained active people and those with stable weight live longer is not only because PA and weight stability is healthful but also because they have other healthier conditions than other groups. However, even though the remained active people and stable weight group were not younger and were not healthier in smoking, alcohol intake, laboratory profiles, and comorbidities than other groups (*Table 1* and Supplementary material online, *Table S1*), they revealed the lowest crude mortality rate (Supplementary material online, *Tables S2* and *S3*). Thus, it is less likely that age and underlying health conditions affected the results. We also adjusted confounders in multivariable models as described above.

Conclusions

This large population-based study demonstrated that continuing regular PA as recommended and maintaining body weight have multiplicative and additive interactions on reducing all-cause mortality. Healthcare providers should emphasize both continuing regular PA and body weight maintenance for the general public.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Data availability

No additional data is available.

Funding

No funding.

Conflict of interest: none declared.

References

1. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986;**314**:605–613.
2. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality: the Finnish twin cohort. *JAMA* 1998;**279**:440–444.
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**:e127–e248.
4. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, Linet MS, Lee I-M, Matthews CE. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 2015;**175**:959–967.
5. Mok A, Khaw KT, Luben R, Wareham N, Brage S. Physical activity trajectories and mortality: population based cohort study. *BMJ* 2019;**365**:l2323.
6. Saint-Maurice PF, Coughlan D, Kelly SP, Keadle SK, Cook MB, Carlson SA, Fulton JE, Matthews CE. Association of leisure-time physical activity across the adult life course with all-cause and cause-specific mortality. *JAMA Netw Open* 2019;**2**:e190355.
7. Pan XF, Yuan JM, Koh WP, Pan A. Weight change in relation to mortality in middle-aged and elderly Chinese: the Singapore Chinese Health Study. *Int J Obes (Lond)* 2019;**43**:1590–1600.
8. Park SY, Wilkens LR, Maskarinec G, Haiman CA, Kolonel LN, Marchand LL. Weight change in older adults and mortality: the Multiethnic Cohort Study. *Int J Obes (Lond)* 2018;**42**:205–212.
9. Nordstoga AL, Zotcheva E, Svedahl ER, Nilsen TIL, Skarpsno ES. Long-term changes in body weight and physical activity in relation to all-cause and cardiovascular mortality: the HUNT study. *Int J Behav Nutr Phys Act* 2019;**16**:45.
10. Zajacova A, Ailshire J. Body mass trajectories and mortality among older adults: a joint growth mixture-discrete-time survival analysis. *Gerontologist* 2014;**54**:221–231.
11. De Stefani FDC, Pietraroia PS, Fernandes-Silva MM, Faria-Neto J, Baena CP. Observational evidence for unintentional weight loss in all-cause mortality and major cardiovascular events: a systematic review and meta-analysis. *Sci Rep* 2018;**8**:15447.
12. Reynolds MW, Fredman L, Langenberg P, Magaziner J. Weight, weight change, mortality in a random sample of older community-dwelling women. *J Am Geriatr Soc* 1999;**47**:1409–1414.
13. Cologne J, Takahashi I, French B, Nanri A, Misumi M, Sadakane A, Cullings HM, Araki Y, Mizoue T. Association of weight fluctuation with mortality in japanese adults. *JAMA Netw Open* 2019;**2**:e190731.
14. Zhang Y, Hou F, Li J, Yu H, Li L, Hu S, Shen G, Yatsuya H. The association between weight fluctuation and all-cause mortality: a systematic review and meta-analysis. *Medicine (Baltimore)* 2019;**98**:e17513.
15. Zou H, Yin P, Liu L, Liu W, Zhang Z, Yang Y, Li W, Zong Q, Yu X. Body-weight fluctuation was associated with increased risk for cardiovascular disease, all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2019;**10**:728.
16. Doucet E, King N, Levine JA, Ross R. Update on exercise and weight control. *J Obes* 2011;**2011**:358205.
17. Chaput JP, Klingenberg L, Rosenkilde M, Gilbert JA, Tremblay A, Sjodin A. Physical activity plays an important role in body weight regulation. *J Obes* 2011;**2011**:360257.
18. Golubic R, Ekelund U, Wijndaele K, Luben R, Khaw K-T, Wareham NJ, Brage S. Rate of weight gain predicts change in physical activity levels: a longitudinal analysis of the EPIC-Norfolk cohort. *Int J Obes (Lond)* 2013;**37**:404–409.
19. 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**:2694–2703.
20. Ekelund U, Ward HA, Norat T, Luan J, May AM, Weiderpass E, Sharp SJ, Overvad K, Østergaard JN, Tjønneland A, Johnsen NF, Mesrine S, Fournier A, Fagherazzi G, Trichopoulou A, Lagiou P, Trichopoulos D, Li K, Kaaks R, Ferrari P, Licaj I, Jenab M, Bergmann M, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Peeters PH, Monnikhof E, Bueno-de-Mesquita HB, Quirós JR, Agudo A, Sánchez M-J, Huerta JM, Ardanaz E, Arriola L, Hedblad B, Wirfält E, Sund M, Johansson M, Key TJ, Travis RC, Khaw K-T, Brage S, Wareham NJ, Riboli E. 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**:613–621.
21. Koster A, Harris TB, Moore SC, Schatzkin A, Hollenbeck AR, van Eijk JTM, Leitzmann MF. Joint associations of adiposity and physical activity with mortality: the National Institutes of Health-AARP Diet and Health Study. *Am J Epidemiol* 2009;**169**:1344–1351.
22. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort Profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017;**46**:e15.
23. Song SO, Jung CH, Song YD, Park C-Y, Kwon H-S, Cha BS, Park J-Y, Lee K-U, Ko KS, Lee B-W. Background and data configuration process of a nationwide population-based study using the Korean National Health Insurance System. *Diabetes Metab J* 2014;**38**:395–403.
24. Kritchevsky SB, Beavers KM, Miller ME, Shea MK, Houston DK, Kitzman DW, Nicklas BJ. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. *PLoS One* 2015;**10**:e0121993.
25. Kim Y-H, Kim SM, Han K-D, Son J-W, Lee S-S, Oh SW, Lee W-Y, Yoo SJ; on behalf of the Taskforce Team of the Obesity Fact Sheet of the Korean Society for the Study of Obesity. Change in weight and body mass index associated with all-cause mortality in Korea: a nationwide longitudinal study. *J Clin Endocrinol Metab* 2017;**102**:4041–4050.
26. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;**67**:328–357.
27. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL; 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc* 2019;**51**:1270–1281.
28. Lee DH, Keum NNa, Hu FB, Orav EJ, Rimm EB, Willett WC, Giovannucci EL. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *BMJ* 2018;**362**:k2575.
29. Itoh H, Kaneko H, Kiriyama H, Kamon T, Mizuno Y, Morita H, Yamamichi N, Komuro I. Association between changes in body weight and fat weight in middle age general population. *Int Heart J* 2020;**61**:15–20.
30. Newman AB, Lee JS, Visser M, Goodpaster BH, Kritchevsky SB, Tylavsky FA, Nevitt M, Harris TB. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr* 2005;**82**:872–878; quiz 915–6.
31. Lee JS, Visser M, Tylavsky FA, Kritchevsky SB, Schwartz AV, Sahyoun N, Harris TB, Newman AB; Health ABC Study. Weight loss and regain and effects on body composition: the Health, Aging, and Body Composition Study. *J Gerontol A Biol Sci Med Sci* 2010;**65**:78–83.
32. Slentz CA, Duscha BD, Johnson JL, Ketchum K, Aiken LB, Samsa GP, Houmard JA, Bales CW, Kraus WE. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE—a randomized controlled study. *Arch Intern Med* 2004;**164**:31–39.
33. Bann D, Kuh D, Wills AK, Adams J, Brage S, Cooper R; National Survey of Health and Development scientific and data collection team. Physical activity across adulthood in relation to fat and lean body mass in early old age: findings

from the Medical Research Council National Survey of Health and Development, 1946-2010. *Am J Epidemiol* 2014;**179**:1197–1207.
34. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L. Physical activity and telomere length: Impact of aging and potential mechanisms of action. *Oncotarget* 2017;**8**: 45008–45019.
35. Rode L, Nordestgaard BG, Weischer M, Bojesen SE. Increased body mass index, elevated C-reactive protein, and short telomere length. *J Clin Endocrinol Metab* 2014;**99**:E1671–E1675.
36. Kim S, Parks CG, DeRoo LA, Chen H, Taylor JA, Cawthon RM, Sandler DP. Obesity and weight gain in adulthood and telomere length. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:816–820.
37. Starkweather AR, Alhaeeri AA, Montpetit A, Brumelle J, Filler K, Montpetit M, Mohanraj L, Lyon DE, Jackson-Cook CK. An integrative review of factors associated with telomere length and implications for biobehavioral research. *Nurs Res* 2014;**63**:36–50.
38. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;**14**:173–194.
39. Zhang H, Tamakoshi K, Yatsuya H, Murata C, Wada K, Otsuka R, Nagasawa N, Ishikawa M, Sugiura K, Matsushita K, Hori Y, Kondo T, Toyoshima H. Long-term body weight fluctuation is associated with metabolic syndrome independent of current body mass index among Japanese men. *Circ J* 2005;**69**:13–18.
40. Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. *Lipids Health Dis* 2017;**16**:132.
41. Borjesson M, Onerup A, Lundqvist S, Dahlof B. Physical activity and exercise lower blood pressure in individuals with hypertension: narrative review of 27 RCTs. *Br J Sports Med* 2016;**50**:356–361.
42. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 2002;**162**:1286–1292.
43. Bouzid MA, Filaire E, Matran R, Robin S, Fabre C. Lifelong voluntary exercise modulates age-related changes in oxidative stress. *Int J Sports Med* 2018;**39**: 21–28.
44. Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vascul Pharmacol* 2015; **71**:40–56.
45. Weinberg F, Chandel NS. Reactive oxygen species-dependent signaling regulates cancer. *Cell Mol Life Sci* 2009;**66**:3663–3673.
46. Kahraman S, Yilmaz R, Akinci D, Arici M, Altun B, Erdem Y, Yasavul U, Turgan C. U-shaped association of body mass index with inflammation and atherosclerosis in hemodialysis patients. *J Ren Nutr* 2005;**15**:377–386.
47. Marseglia L, Manti S, D'Angelo G, Nicotera A, Parisi E, Di Rosa G, Gitto E, Arrigo T. Oxidative stress in obesity: a critical component in human diseases. *Int J Mol Sci* 2014;**16**:378–400.
48. An KY. Physical activity level in Korean adults: the Korea National Health and Nutrition Examination Survey 2017. *Epidemiol Health* 2019;**41**:e2019047.
49. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, Milani RV. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis* 2018;**61**:142–150.
50. Yiengprugsawan V, Rimpeekool W, Papier K, Banwell C, Seubsman SA, Sleigh AC. Relationship between 8-year weight change, body size, and health in a large cohort of adults in Thailand. *J Epidemiol* 2017;**27**:499–502.
51. Verkleij SP, Adriaanse MC, Wendel-Vos GC, Schuit AJ. Longitudinal relation between weight change and quality of life in a community-based population: a prospective cohort study. *Eur J Public Health* 2013;**23**:285–290.
52. Yang L, Cao C, Kantor ED, Nguyen LH, Zheng X, Park Y, Giovannucci EL, Matthews CE, Colditz GA, Cao Y. Trends in sedentary behavior among the US population, 2001-2016. *JAMA* 2019;**321**:1587–1597.
53. Beleigoli AM, Diniz M, Boersma E, Silva JL, Lima-Costa MF, Ribeiro AL. The effects of weight and waist change on the risk of long-term mortality in older adults—the Bambui (Brazil) Cohort Study of Aging. *J Nutr Health Aging* 2017;**21**: 861–866.
54. Dong S-Y, Wang M-L, Li Z-B, Dong Z, Liu Y-Q, Lu R-J, Li J-M, Tang R. Obesity, weight change, and mortality in older adults with metabolic abnormalities. *Nutr Metab Cardiovasc Dis* 2018;**28**:749–755.
55. Doehner W, Gerstein HC, Ried J, Jung H, Asbrand C, Hess S, Anker SD. Obesity and weight loss are inversely related to mortality and cardiovascular outcome in prediabetes and type 2 diabetes: data from the ORIGIN trial. *Eur Heart J* 2021; **41**:2668–2677.
56. Antonopoulos AS, Oikonomou EK, Antoniades C, Tousoulis D. From the BMI paradox to the obesity paradox: the obesity-mortality association in coronary heart disease. *Obes Rev* 2016;**17**:989–1000.
57. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ* 2017;**359**:j4849.
58. Kwon S, Lee H-J, Han K-D, Kim DH, Lee S-P, Hwang I-C, Yoon Y, Park J-B, Lee H, Kwak S, Yang S, Cho G-Y, Kim Y-J, Kim H-K, Ommen SR. Association of physical activity with all-cause and cardiovascular mortality in 7666 adults with hypertrophic cardiomyopathy (HCM): more physical activity is better. *Br J Sport Med* 2021;**55**:1034–1040.
59. Lee CH, Han KD, Yoo J, Kwak MS. Synergistic harmful interaction between sustained physical inactivity and hypertension/diabetes mellitus on the risk of all-cause mortality: a retrospective observational cohort study. *J Hypertens* 2021;**39**: 2058–2066.
60. Jeong S-W, Kim S-H, Kang S-H, Kim H-J, Yoon C-H, Youn T-J, Chae I-H. Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J* 2019;**40**:3547–3555.