



Research Paper

Body mass index trajectories during mid to late life and risks of mortality and cardiovascular outcomes: Results from four prospective cohorts

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ABSTRACT

Background: Our understanding of the weight-outcome association mainly comes from single-time body mass index (BMI) measurement. However, data on long-term trajectories of within-person changes in BMI on diverse study outcomes are sparse. Therefore, this study is to determine the associations of individual BMI trajectories and cardiovascular outcomes.

Methods: The present analysis was based on data from 4 large prospective cohorts and restricted to participants aged ≥ 45 years with at least two BMI measurements. Hazard ratios (HR) and 95% confidence intervals (95%CI) for each outcome according to different BMI trajectories were calculated in Cox regression models.

Findings: The final sample comprised 29,311 individuals (mean age 58.31 years, and 77.31% were white), with a median 4 BMI measurements used in this study. During a median follow-up of 21.16 years, there were a total of 10,192 major adverse cardiovascular events (MACE) and 11,589 deaths. A U-shaped relation was seen with all study outcomes. Compared with maintaining stable weight, the multivariate adjusted HR for MACE were 1.53 (95%CI 1.40–1.66), 1.26 (95%CI 1.16–1.37) and 1.08 (95%CI 1.02–1.15) respectively for rapid, moderate and slow weight loss; 1.01 (95%CI 0.95–1.07), 1.13 (95%CI 1.05–1.21) and 1.29 (95%CI 1.20–1.40) respectively for slow, moderate and rapid weight gain. Identical patterns of association were observed for all other outcomes. The development of BMI differed markedly between the outcome-free individuals and those who went on to experience adverse events, generally beginning to diverge 10 years before the occurrence of the events.

Interpretation: Our findings may signal an underlying high-risk population and inspire future studies on weight management.

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1. Introduction

In light of the obesity epidemic [1,2], it is imperative to understand the relationship of weight to the risks of mortality and cardiovascular diseases (CVD). Although this relation is well documented in previous researches, most of them were based on single-time assessment of body weight (or body mass index, BMI) [3–8]. As noted, the relation of single-time BMI measurement to adverse outcomes

changed during the observation period [9]. Specifically, the magnitude of this association weakens among middle-aged and elderly populations [10,11].

Further, using single-time BMI may fail to recognize the effect of weight change on the associated risks. Weight changes are highly variable over the life course [12–15]. Both weight loss and gain in middle-aged adults rendered increased risk of all-cause and CVD mortality [4,16–19]. However, the patterns of BMI change may differ among individuals; thus, a life-course perspective is essential. Mapping the longitudinal trajectory of BMI may directly capture the within-person change in BMI, and better characterize the associated risks.

Although increasing number of studies have investigated the relationship of BMI trajectories and cardiovascular outcomes, most were

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Research in context

Evidence before this study

We searched Pubmed for articles published in English assessing risk of cardiovascular disease and all-cause mortality in relation to BMI and BMI trajectories, using the search terms “BMI”, “change in BMI”, “BMI trajectories”, “cardiovascular diseases”, “major adverse cardiovascular events”, “death”, “mortality”, “coronary heart disease”, “stroke”, “heart failure”, “myocardial infarction” and “risk”, from the inception to December 15, 2020. We found numerous studies discussing the associations of single time BMI measurements and cardiovascular risks, but few of them explored the associations of individual change trajectories and adverse outcomes.

Added value of this study

In this large population-based study, a U-shaped relation was observed between BMI trajectories and subsequent risk of different health outcomes. Both weight gain and weight loss conferred increased risks for cardiovascular events and all-cause mortality. In addition, we found for the first time that falling off the BMI trajectory could be a warning sign for future occurrence of adverse events.

Implications of all the available evidence

Our findings may signal an underlying high-risk population and underscore the importance of maintaining body weight over the middle to late adulthood.

Details of the design of each study are reported in Appendix 1. The present analysis was restricted to participants aged ≥ 45 years at baseline or during follow-up. For example, if a person initially entered the cohort at 35 years old, then we would collect data 10 years after his enrollment, at the time when he was 45 years old. The included participants should have at least two non-missing values for BMI. Participants who were lost to follow-up were excluded in this study. The final sample size comprised 29,311 individuals.

2.2. Ethical approval statement

The institutional review board approved individual study from the original cohorts, and all participants provided written informed consent in each study. As only deidentified data were used without any additional patient contact in the current study, additional ethical approval or patient consent was not required.

2.3. BMI and trajectories definition

Participants were routinely followed up since baseline enrollment. Weight and height were obtained from the health examination records during the follow-up periods, which were both measured under a standardized protocol within each study (Appendix 1). BMI was calculated as weight divided by the square of height (kg/m^2). In this study, BMI measurements were recorded with identical time interval within each cohort (2 to 5 years for individual cohort). To explore the characteristics of BMI change by age, we first estimated a series of trajectories by assuming linear, quadratic and cubic patterns of change in BMI over time. Finally, linear trajectories provided the optimal fit to our data (data shown in Appendix 2), so we applied the linear mixed-effects model to calculate the slope [44,45]. BMI-slope can be thought of as BMI change per year or annual change in BMI, implying the direction and magnitude of the change in a subject's BMI over the time period. A positive value indicates weight gain over time, whereas a negative value indicates weight loss. We defined the categories of BMI trajectories as: rapid gain ($>0.5 \text{ kg}/\text{m}^2/\text{year}$), moderate gain ($0.3\text{--}0.5 \text{ kg}/\text{m}^2/\text{year}$), slow gain ($0.1\text{--}0.3 \text{ kg}/\text{m}^2/\text{year}$), stable ($\pm 0.1 \text{ kg}/\text{m}^2/\text{year}$), slow loss ($0.1\text{--}0.3 \text{ kg}/\text{m}^2/\text{year}$), moderate loss ($0.3\text{--}0.5 \text{ kg}/\text{m}^2/\text{year}$) and rapid loss ($>0.5 \text{ kg}/\text{m}^2/\text{year}$). In addition, weight variability was computed to assess fluctuation around the trend in BMI over the period, using the coefficient variation (CoV) [46].

2.4. Covariates

The available socio-demographic characteristics in the current study included age, sex, race, education level, marital status, smoking status, income, physical activity, consumption of fruits and vegetables, baseline BMI, baseline blood pressure, history of hypertension, diabetes, chronic obstructive pulmonary disease (COPD), stroke, coronary heart disease (CHD), chronic heart failure (CHF) and cancer, serum level of glucose, total cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC) and triglyceride. For covariates reported differently across the 4 cohorts, standardized categories were used to harmonize data across the cohorts as follows: race (white or non-white), marital status (married, separated/divorced/widowed or never married), smoking status (never, former or current smoker), education level (less than high school, high school graduate, some college or college and above) and current alcohol use (yes or no).

2.5. Outcomes

All reported cases were systemically validated through medical review and adjudicated using each cohort's specific protocol (Appendix 1). All participants were followed up to the event of interest or until censoring at the end date of individual cohort. The primary

assuming the population lies within a mixture of latent groups, using either growth curve model or group-based latent model [11,20–29]. These models are largely based on subgroup means over a specific period of time and might be imprecise. Till now, there are at least 2 to 6 different BMI trajectory patterns being reported [11,20–30], even using the same dataset [20,26].

Therefore, in order to obtain a more precise association between BMI trajectory and cardiovascular outcomes, we here used the original BMI slope from each individual to represent individual BMI change trajectory. As far as we know, less than ten papers have reported the value of BMI slope in cardiovascular system [13,14,31–37]. Most of them investigated the association of BMI slope and change in cardiovascular risk factors [14,31,33–36]. Only two researches illustrated its association with cardiovascular outcomes [13,32]. However, models were not fully adjusted and differences on weight change direction were not taken into consideration.

Therefore, in our current study, we separated weight gain and weight loss by different degrees of change to comprehensively illustrate the relation of individual BMI trajectory to diverse study outcomes. As a second aim, we explored and characterized the developmental paths of BMI prior to individual outcomes.

2. Methods

2.1. Study design and cohort

The present analysis was based on data from 4 large, community-based, prospective cohort studies: 1) the ARIC (Atherosclerosis Risk In Communities) Study [38]; 2) the CHS study (Cardiovascular Health Study) [39]; 3) the MESA study (Multi-Ethnic study of atherosclerosis) [40]; and 4) the FHS study (Framingham Heart Study) [41]. We obtained the cohort data sets from the NIH Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) [42,43].

outcomes of interest for our analysis were myocardial infarction (MI), CHF, stroke, and a composite of major adverse cardiovascular events (MACE, including CVD death, MI, CHF and stroke). The secondary outcomes were all-cause death, CVD death, non-CVD death and CHD death.

2.6. Statistics analysis

Clinical characteristics are presented as means (standard deviation) or median (interquartile range) for continuous variables and by frequency (percentage) for categorical variables. For comparison of baseline characteristic among different BMI trajectories, we applied the analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables.

Because the time of follow-up differed between participants, we estimated person-time incidence rates for the outcomes of interest. The event rates were calculated by dividing the number of events by the accumulated person-time of follow-up for participants in a given BMI trajectory category. We report the rates per 1000 person-years adjusted by age distribution within each exposure category.

Hazard ratios (HR) and 95% confidence intervals (95%CI) for each outcome according to different BMI trajectories were calculated in Cox regression models, using the stable category as reference and adjusted (a) for age, sex and race (minimum adjustment) and (b) for age, sex, race, smoking, education marital status, current alcoholic drinking status, education level, income, physical activity, consumption of fruits and vegetables, history of hypertension, diabetes, CHD, CHF, stroke, COPD, cancer, serum glucose level and lipid profiles (full or multivariate adjustment model). The proportional hazards assumption was checked by plotting the $\log(-\log(\text{survival}))$ versus $\log(\text{survival time})$ and by using Schoenfeld residuals. We did not find evidence suggesting potential violation for any exposure-outcome associations. In addition, restricted cubic spline models were used to visualize the relationship of annual BMI change to different study outcomes.

Missing data were handled using full information maximum likelihood under the missing-at-random assumption in our main analysis. The proportion of missing values was presented in supplementary Table 1 (Appendix 3). Missing values on all socio-demographic covariates were handled by Markov Chain Monte Carlo multiple imputation method before their inclusion in the full adjusted models. The variables entered in the imputation method were serum glucose, lipid profiles (LDLC, HDLC, triglyceride, total cholesterol), baseline BMI, systolic and diastolic blood pressure, physical activity and consumption of fruits and vegetables. Finally, results from 10 multiple imputation cycles were combined together to draw a final output.

To evaluate the characteristics of BMI trajectories prior to adverse outcomes, we estimated the mean BMI during the last 20 years before events of interest or the end date or censored date of individual study. We fitted second-order fractional polynomial models using mean BMI values for each participant. Robust variance estimates were used to account for clustering of observations by participant. Models were fitted using the `mfp` command in STATA. Predicted values and their confidence intervals were estimated using the `fracpred` command.

To mitigate the potential bias, the following sensitivity analyses were performed: 1) we excluded participants with missing data on baseline covariates (i.e. complete-case regression analyses), with pre-existing illness at baseline (including history of CHD, CHF, stroke, COPD or cancer), or with the highest weight variability; 2) we repeated the main analysis separately in each cohort; 3) we used the change in BMI relative to baseline BMI as the exposure variable (percent change of BMI) to evaluate the corresponding risks. Percent change of BMI was calculated as $(\text{last time BMI} - \text{baseline BMI}) / \text{baseline BMI}$ [47]. Furthermore, subgroup analyses were conducted to evaluate whether the relationship between different BMI trajectories and outcomes differed by age (<60 or ≥ 60 years), sex, race (white

or non-white), smoking status (never, current or former smokers) and baseline BMI (normal, overweight or with obesity). Potential effect modifications by these variables were examined by introducing a product term of the stratified variable and BMI trajectories to the final model and determined by the likelihood ratio test result. Particularly, to better distinguish intentional and unintentional weight loss, we further stratified the three weight loss categories into low, moderate and high variability subgroups, in which the highest variability subgroup represents intentional weight loss subcategory.

We did all these analyses with STATA/SE 15.1 (Stata Corp, College Station, TX, USA). All statistical tests were 2-sided with a significance threshold of 0.05.

2.7. Role of the funding source

All sources of funding had no involvement in study design, in the collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the paper for publication. DL, YC, CZ and WS have full access to all the data in this study and take full responsibility as guarantors for the integrity of the data and the accuracy of the data analysis.

3. Results

3.1. Baseline characteristics of the study population

Baseline characteristics of the participants are presented by cohorts (supplementary Table 2 in Appendix 3) and different BMI trajectories (Table 1). The average age of study participants at enrollment was 58.31 (9.77) years, men composed 45.02% of all participants, and 77.31% self-identified as white. Overall, 25.26% of participants had obesity, 40.41% were overweight while 34.33% were of normal BMI at baseline. All of them had at least 2 measures of BMI within a median interval of 8.78 (4.24) years. The majority of participants (83.24%) contributed more than 3 measurements of BMI over time (median 4, IQR 3–4). Finally, 43.8% (12,825/29,311) of the overall study population had gained weight, whereas roughly 24.6% (7203/29,311) fell into the three weight-loss categories during follow-up.

Participants with greatest weight loss were those with highest BMI at baseline, were more likely to have preexisting comorbidities, and were more prone to be single (separated or never married). On the other hand, participants who gained most weight were younger, more likely to be current smokers and majority were female.

3.2. BMI trajectories and risks of adverse outcomes

During a median follow-up of 21.16 (IQR 14.07–23.55) years, there were a total of 10,192 MACE and 11,589 deaths, of which 4532 were due to CVD. Table 2 shows the age-adjusted rates per 1000 person-years for all study outcomes and the hazards adjusted for different covariates.

3.2.1. Primary outcomes

Compared with maintaining stable weight, the multivariate adjusted HRs for MACE were 1.53 (95%CI 1.40–1.66), 1.26 (95%CI 1.16–1.37) and 1.08 (95%CI 1.02–1.15) respectively for rapid, moderate and slow weight loss; 1.01 (95%CI 0.95–1.07), 1.13 (95%CI 1.05–1.21) and 1.29 (95%CI 1.20–1.40) respectively for slow, moderate and rapid weight gain. Models examining the associations with outcomes of MI and CHF yielded similar results as MACE. While for stroke, the hazard was significantly increased in participants with moderate-to-rapid weight loss and moderate weight gain, but for slow weight loss or slow weight gain, the association was insignificant (Table 2). Consistently, Fig. 1-A shows a U-shaped relation of the entire range of annual BMI change to individual cardiovascular outcomes in the cubic spline models.

Table 1

Baseline characteristic of participants according to different BMI trajectories.

	Total	Rapid loss >0.5 kg/m ² /year	Moderate loss 0.3–0.5 kg/m ² /year	Slow loss 0.1–0.3 kg/m ² /year	Stable ±0.1 kg/m ² /year	Slow gain 0.1–0.3 kg/m ² /year	Moderate gain 0.3–0.5 kg/m ² /year	Rapid gain >0.5 kg/m ² /year	P value
No. of participants	29,311	1682	1795	4330	8213	6822	3470	2999	
Age, years	58.31 (9.77)	59.84 (10.38)	60.38 (10.28)	60.01 (10.15)	59.25 (10.16)	57.59 (9.22)	56.35 (8.81)	55.05 (8.24)	<0.001
Sex, male	13,195 (45.02%)	649 (38.59%)	835 (46.52%)	2085 (48.15%)	4062 (49.46%)	3266 (47.87%)	1359 (39.16%)	939 (31.31%)	<0.001
Race									<0.001
White	22,661 (77.31%)	1137 (67.60%)	1329 (74.04%)	3359 (77.58%)	6381 (77.69%)	5503 (80.67%)	2730 (78.67%)	2222 (74.09%)	
Non-white	6650 (22.69%)	545 (32.40%)	466 (25.96%)	971 (22.42%)	1832 (22.31%)	1319 (19.33%)	740 (21.33%)	777 (25.91%)	
Baseline BMI, kg/m ²	27.42 (5.03)	30.54 (5.81)	28.87 (5.19)	27.72 (4.87)	26.50 (4.51)	26.59 (4.59)	27.38 (4.88)	28.76 (5.86)	<0.001
Blood pressure, mmHg									
Systolic	128.58 (21.32)	136.13 (23.24)	134.65 (22.52)	132.18 (21.03)	129.39 (21.38)	125.97 (20.12)	125.02 (20.42)	123.83 (20.58)	<0.001
Diastolic	75.55 (12.24)	79.21 (13.80)	77.19 (12.95)	76.79 (12.91)	75.51 (11.99)	74.81 (11.76)	74.44 (11.61)	74.02 (11.79)	<0.001
Education level									<0.001
Less than high school	6820 (23.27%)	488 (29.01%)	469 (26.13%)	1088 (25.13%)	1854 (22.57%)	1439 (21.09%)	779 (22.45%)	703 (23.44%)	
High school graduate	13,004 (44.37%)	745 (44.29%)	789 (43.96%)	1900 (43.88%)	3672 (44.71%)	3037 (44.52%)	1502 (43.29%)	1359 (45.32%)	
Some college or college+	9487 (32.37%)	449 (26.69%)	537 (29.92%)	1342 (30.99%)	2687 (32.72%)	2346 (34.39%)	1189 (34.27%)	937 (31.24%)	
Marital status									<0.001
Married	18,525 (63.20%)	890 (52.91%)	1055 (58.77%)	2632 (60.79%)	5104 (62.15%)	4578 (67.11%)	2345 (67.58%)	1921 (64.05%)	
Separated/divorced/widowed	6107 (20.84%)	473 (28.12%)	445 (24.79%)	921 (21.27%)	1589 (19.35%)	1253 (18.37%)	685 (19.74%)	741 (24.71%)	
Never married	4679 (15.96%)	319 (18.97%)	295 (16.43%)	777 (17.94%)	1520 (18.51%)	991 (14.53%)	440 (12.68%)	337 (11.24%)	
Smoking status									<0.001
Never	15,483 (52.82%)	977 (58.09%)	1024 (57.05%)	2309 (53.33%)	4247 (51.71%)	3538 (51.86%)	1858 (53.54%)	1530 (51.02%)	
Former	7301 (24.91%)	307 (18.25%)	397 (22.12%)	1036 (23.93%)	2121 (25.82%)	1853 (27.16%)	885 (25.50%)	702 (23.41%)	
Current	6527 (22.27%)	398 (23.66%)	374 (20.84%)	985 (22.75%)	1845 (22.46%)	1431 (20.98%)	727 (20.95%)	767 (25.58%)	
Current alcohol use	16,734 (57.09%)	836 (49.70%)	957 (53.31%)	2405 (55.54%)	4875 (59.36%)	4076 (59.75%)	1965 (56.63%)	1620 (54.02%)	<0.001
Physical activity, met-min/week	1621 (1868)	1314 (1381)	1547 (1829)	1643 (1903)	1608 (1836)	1719 (2014)	1667 (1855)	1562 (1806)	<0.001
Fruits and vegetables, cups/day	3.91 (2.36)	4.05 (3.03)	3.94 (2.12)	3.92 (2.34)	3.89 (2.29)	3.86 (2.30)	3.89 (2.38)	3.95 (2.34)	<0.001
History									
Diabetes	2772 (9.46%)	278 (16.53%)	283 (15.77%)	529 (12.22%)	675 (8.22%)	463 (6.79%)	264 (7.61%)	280 (9.34%)	<0.001
Hypertension	10,166 (34.68%)	834 (49.58%)	802 (44.68%)	1610 (37.18%)	2698 (32.85%)	2059 (30.18%)	1107 (31.90%)	1056 (35.21%)	<0.001
CHD	1524 (5.20%)	90 (5.35%)	115 (6.41%)	263 (6.07%)	448 (5.45%)	326 (4.78%)	145 (4.18%)	137 (4.57%)	<0.001
CHF	765 (2.61%)	62 (3.69%)	62 (3.45%)	105 (2.42%)	159 (1.94%)	152 (2.23%)	100 (2.88%)	125 (4.17%)	<0.001
Stroke	401 (1.37%)	32 (1.90%)	30 (1.67%)	71 (1.64%)	102 (1.24%)	79 (1.16%)	41 (1.18%)	46 (1.53%)	0.07
COPD	1550 (5.29%)	99 (5.89%)	89 (4.96%)	234 (5.40%)	450 (5.48%)	329 (4.82%)	196 (5.65%)	153 (5.10%)	0.38
Cancer	1966 (6.71%)	126 (7.49%)	130 (7.24%)	327 (7.55%)	573 (6.98%)	428 (6.27%)	207 (5.97%)	175 (5.84%)	0.009
Glucose, mmol/l	5.68 (1.97)	6.11 (2.57)	6.03 (2.39)	5.79 (2.03)	5.54 (1.73)	5.53 (1.62)	5.68 (2.11)	5.73 (2.26)	<0.001
Total cholesterol, mg/dL	5.47 (1.08)	5.45 (1.16)	5.48 (1.13)	5.53 (1.10)	5.48 (1.06)	5.45 (1.05)	5.46 (1.09)	5.41 (1.10)	<0.001
HDL cholesterol, mg/dL	1.34 (0.42)	1.27 (0.41)	1.29 (0.40)	1.32 (0.42)	1.35 (0.43)	1.35 (0.42)	1.36 (0.42)	1.36 (0.41)	0.009
LDL cholesterol, mg/dL	3.43 (0.98)	3.38 (1.02)	3.42 (1.01)	3.46 (0.99)	3.43 (0.96)	3.44 (0.95)	3.44 (1.00)	3.42 (1.03)	<0.001
Triglyceride, mg/dL	1.52 (0.99)	1.71 (1.42)	1.70 (1.19)	1.61 (1.02)	1.51 (0.95)	1.45 (0.83)	1.46 (0.96)	1.41 (0.94)	<0.001

Abbreviation: BMI, body mass index; CHD, coronary heart disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2

Hazard ratios (95%CI) of clinical outcomes with different BMI trajectories.

	Stable	Rapid loss	Moderate loss	Slow loss	Slow gain	Moderate gain	Rapid gain
Primary outcomes							
MACE							
No. event/person-years	2941/155,792	713/23,906	707/27,767	1655/74,524	2160/130,208	1084/64,851	932/53,592
Age-adjusted rate /1000 person-years	18.97(18.28,19.67)	35.60(32.28,39.15)	24.67(22.88,26.57)	18.97(17.98,20.00)	17.33(19.31)	16.84(15.84,17.88)	15.05(14.02,16.13)
Model 1	Ref	1.84(1.70,2.00)	1.44(1.33,1.57)	1.19(1.12,1.26)	1.00(0.95,1.06)	1.17(1.09,1.26)	1.42(1.32,1.53)
Model 2	Ref	1.53(1.40,1.66)	1.26(1.16,1.37)	1.08(1.02,1.15)	1.01(0.95,1.07)	1.13(1.05,1.21)	1.29(1.20,1.40)
MI							
No. event/person-years	1037/164,637	233/26,207	265/29,853	586/79,578	791/136,751	397/68,746	311/56,890
Age-adjusted rate/1000 person-years	6.24(5.81,6.69)	10.43(8.84,12.21)	9.94(8.55,11.47)	5.91(5.30,6.56)	6.15(5.68,6.65)	5.29(4.76,5.86)	6.43(5.63,7.31)
Model 1	Ref	1.67(1.45,1.93)	1.49(1.30,1.71)	1.18(1.07,1.31)	1.02(0.93,1.12)	1.18(1.05,1.32)	1.29(1.13,1.46)
Model 2	Ref	1.43(1.24,1.66)	1.31(1.14,1.50)	1.09(0.98,1.21)	1.03(0.94,1.13)	1.15(1.02,1.29)	1.19(1.04,1.35)
CHF							
No. event/person-years	1475/165,743	383/25,838	362/29,849	909/79,935	1093/137,804	562/69,059	546/56,590
Age-adjusted rate/1000 person-years	9.97(9.32,10.65)	16.61(14.93,18.43)	9.92(8.73,11.21)	10.16(9.44,10.91)	7.02(6.53,7.54)	7.74(7.10,8.43)	14.10(12.62,15.69)
Model 1	Ref	1.96(1.75,2.20)	1.47(1.31,1.65)	1.30(1.20,1.41)	1.04(0.96,1.12)	1.23(1.11,1.35)	1.73(1.57,1.92)
Model 2	Ref	1.52(1.36,1.71)	1.22(1.09,1.37)	1.15(1.06,1.25)	1.04(0.96,1.12)	1.14(1.03,1.26)	1.45(1.31,1.61)
Stroke							
No. event/person-years	976/166,810	231/26,187	214/30,260	468/80,978	655/139,017	368/69,593	259/57,704
Age-adjusted rate/1000 person-years	5.79(5.28,6.34)	7.92(6.84,9.11)	6.29(5.42,7.25)	6.24(5.61,6.92)	7.07(6.27,7.93)	5.51(4.80,6.30)	5.30(4.58,6.10)
Model 1	Ref	1.69(1.47,1.96)	1.30(1.12,1.51)	0.99(0.89,1.11)	0.94(0.85,1.04)	1.20(1.06,1.35)	1.17(1.02,1.34)
Model 2	Ref	1.47(1.27,1.71)	1.16(1.00,1.35)	0.92(0.82,1.03)	0.96(0.86,1.06)	1.20(1.06,1.36)	1.13(0.99,1.31)
Secondary outcomes							
All-cause death							
No. event/person-years	3295/173,469	957/28,221	858/32,156	2011/84,666	2341/143,867	1133/72,616	994/60,559
Age-adjusted rate/1000 person-years	28.08(26.77,29.44)	32.51(30.40,34.72)	21.35(19.73,23.05)	19.73(18.81,20.68)	14.75(14.13,15.38)	13.79(12.98,14.63)	29.01(26.62,31.55)
Model 1	Ref	2.16(2.00,2.32)	1.49(1.39,1.61)	1.24(1.18,1.32)	0.97(0.92,1.03)	1.07(1.00,1.15)	1.36(1.27,1.46)
Model 2	Ref	1.98(1.83,2.13)	1.38(1.28,1.49)	1.18(1.12,1.25)	0.99(0.93,1.04)	1.08(1.01,1.15)	1.29(1.20,1.38)
CVD death							
No. event/person-years	1358/173,469	347/28,221	344/32,156	752/84,666	944/143,867	427/72,616	360/60,559
Age-adjusted rate/1000 person-years	11.17(10.38,11.99)	11.53(10.28,12.89)	9.05(8.00,10.18)	8.44(7.82,9.10)	10.37(9.28,11.55)	6.34(5.69,7.05)	6.05(5.41,6.75)
Model 1	Ref	2.09(1.85,2.35)	1.63(1.44,1.83)	1.19(1.08,1.30)	1.01(0.93,1.10)	1.08(0.97,1.21)	1.35(1.20,1.52)
Model 2	Ref	1.75(1.55,1.98)	1.39(1.23,1.57)	1.08(0.99,1.18)	1.03(0.95,1.13)	1.10(0.98,1.23)	1.27(1.13,1.44)
Non-CVD death							
No. event/person-years	2111/173,469	636/28,221	539/32,156	1337/84,666	1532/143,867	758/72,616	672/60,559
Age-adjusted rate/1000 person-years	10.80(10.29,11.33)	22.56(20.71,24.52)	17.40(15.74,19.17)	16.00(15.03,17.00)	15.94(15.03,16.88)	7.64(7.02,8.29)	11.93(10.96,12.97)
Model 1	Ref	2.24(2.05,2.45)	1.47(1.33,1.61)	1.29(1.21,1.38)	0.99(0.92,1.05)	1.10(1.01,1.20)	1.41(1.29,1.54)
Model 2	Ref	2.16(1.97,2.36)	1.41(1.28,1.55)	1.25(1.17,1.34)	0.99(0.93,1.06)	1.10(1.01,1.19)	1.33(1.22,1.46)
CHD death							
No. event/person-years	788/173,469	186/28,221	208/32,156	433/84,666	554/143,867	238/72,616	182/60,559
Age-adjusted rate/1000 person-years	5.74(5.28,6.23)	7.25(5.95,8.72)	6.04(5.22,6.94)	4.10(3.64,4.60)	3.64(3.32,3.98)	4.06(3.35,4.89)	3.15(2.70,3.66)
Model 1	Ref	1.92(1.64,2.26)	1.63(1.40,1.90)	1.16(1.03,1.30)	1.02(0.92,1.14)	1.05(0.91,1.22)	1.22(1.04,1.44)
Model 2	Ref	1.57(1.33,1.85)	1.36(1.17,1.59)	1.04(0.93,1.17)	1.04(0.94,1.16)	1.05(0.91,1.22)	1.11(0.94,1.31)

Model 1, adjusted for age, gender and race; Model 2, adjusted for age, gender, race, smoking status, current alcoholic use, education level, marital status, income, physical activity, consumption of fruits and vegetables, history of hypertension, diabetes, HF, CHD, cancer, COPD and stroke, baseline BMI, serum level of glucose, total cholesterol, LDLC, HDLC and triglyceride.

Abbreviation: MACE, major adverse cardiovascular events; MI, myocardial infarction; CHF, chronic heart failure; CVD, cardiovascular disease; Non-CVD, non-cardiovascular disease; CHD, coronary heart disease.

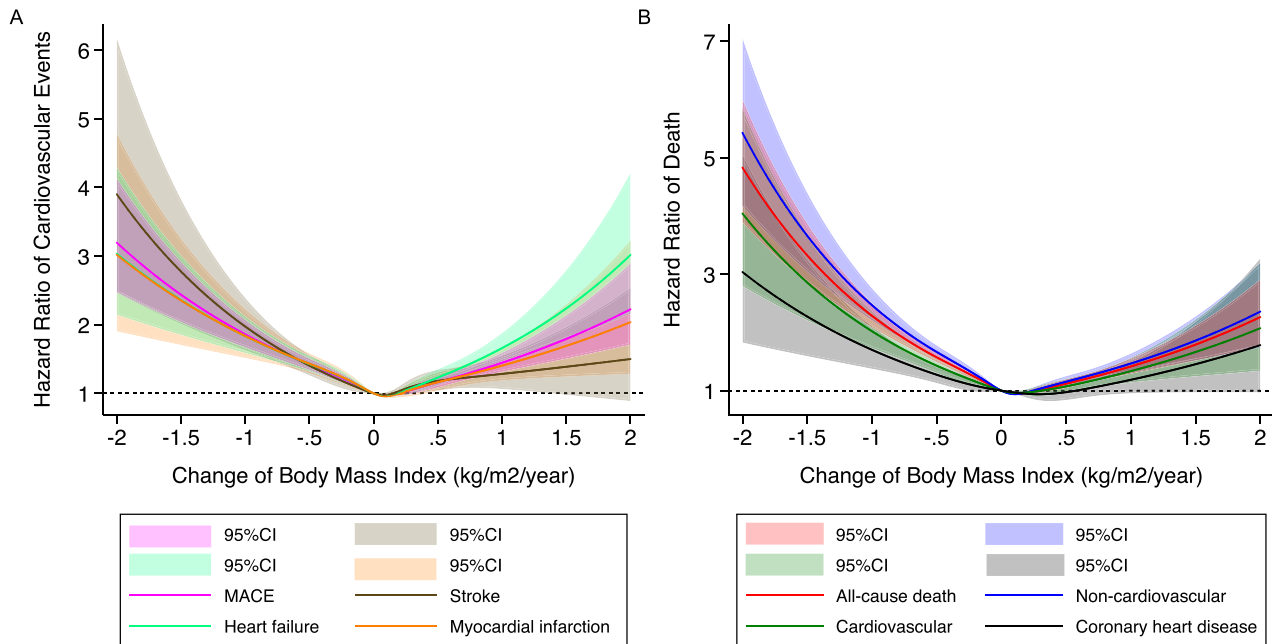


Fig. 1. U-shaped association between annual change in BMI and different study outcomes. Associations were examined by multivariable Cox regression models based on restricted cubic splines. Solid line represents estimates of hazard ratios and dashed line represents 95%CI. Each color represents one outcome of interest. A. Association between annual change in BMI and cardiovascular outcomes. MACE (purple), stroke (light grey), heart failure (light green) and myocardial infarction (orange). B. Association between annual change in BMI and death outcomes. All-cause death (red), non-cardiovascular death (blue), cardiovascular death (dark green) and death due to coronary heart disease (dark grey). MACE, major adverse cardiovascular events. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2.2. Secondary outcomes

Similarly, the HRs for all-cause mortality were 1.98 (95%CI 1.83–2.13), 1.38 (95%CI 1.28–1.49) and 1.18 (95%CI 1.12–1.25) respectively for rapid, moderate and slow weight loss; 0.99 (95%CI 0.93–1.04), 1.08 (95%CI 1.01–1.15) and 1.29 (95%CI 1.20–1.38) respectively for slow, moderate and rapid weight gain, when compared to maintaining stable weight. Identical patterns of association were observed for CVD, non-CVD and CHD death (Table 2). Likewise, in the restricted cubic spline models, we detected a U-shaped relationship between annual BMI change and mortality risk, with a nadir around 0 kg/m²/year (Fig. 1-B).

3.3. BMI trajectories prior to different outcomes

Fig. 2 is an illustrative drawing to represent the general developmental patterns of BMI prior to different outcomes. We found that the development of BMI differed markedly between the outcome-free individuals and those who went on to experience adverse events. Trajectories appeared similar for the outcomes of MACE, all-cause, CVD and non-CVD death. The outcome-free participants followed a trajectory where the average BMI levels rise initially, remain stable or steadily decreased throughout follow-up. Those who went on to experience events generally showed lower baseline levels of BMI,

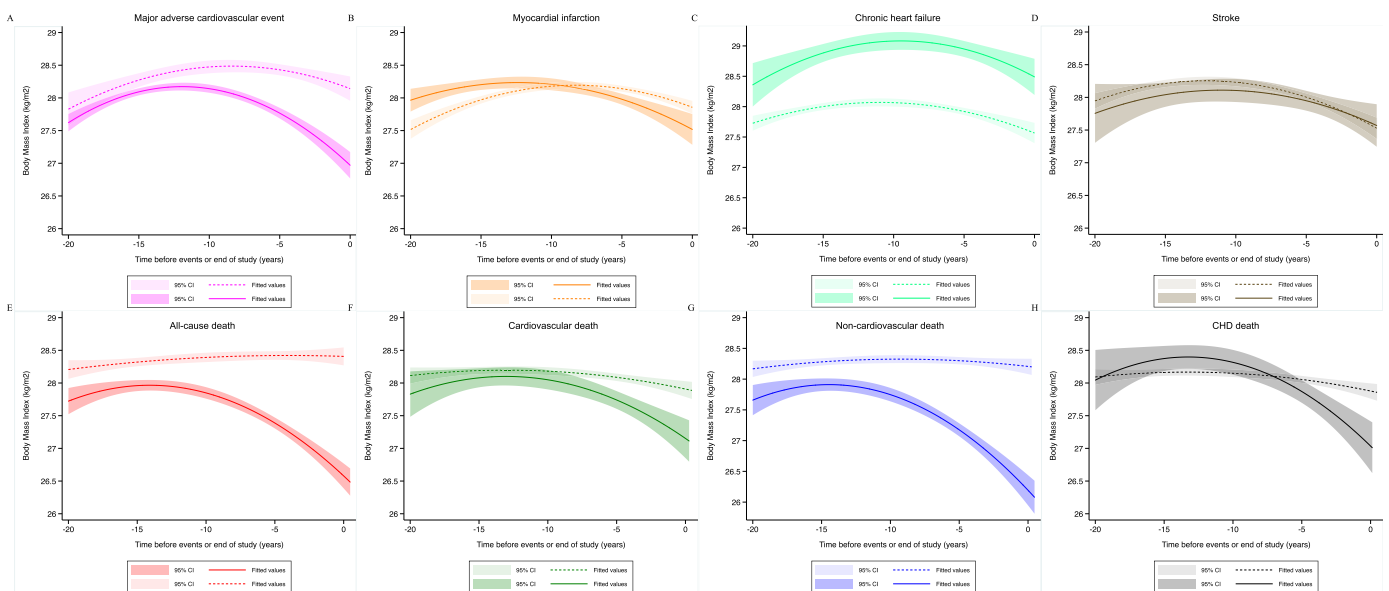


Fig. 2. Distinct trajectory patterns of BMI between the outcome-free individuals (dashed line) and those who went on to experience adverse events (solid line). The corresponding shaded area represents 95%CI. Each color represents one outcome of interest. A. Major adverse cardiovascular events (purple). B. Myocardial infarction (orange). C. Chronic heart failure (light green). D. Stroke (light grey). E. All-cause death (red). F. Cardiovascular death (dark green). G. Non-cardiovascular death (blue). H. CHD death (dark grey). CHD, coronary heart disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

steeper rise initially and faster fall before the occurrence of the events. With regards to MI and CHD death, the average BMI level was comparable in participants with or without the outcomes, but an accelerated decline was observed in those who died or experienced the events. Interestingly, although the developmental trend was identical among participants with and without CHF, those who experienced CHF had a generally higher BMI level during their life. With respect to the outcome of stroke, the BMI trajectories were less distinctive between groups.

3.4. Additional information and stratified analysis

We repeated the primary analyses in a series of sensitivity analyses. Excluding participants with missing values on baseline covariates (supplementary Table 3 in Appendix 3), with preexisting illnesses at

baseline (supplementary Table 4 in Appendix 3), or with highest weight variability during follow-up (supplementary Table 5 in Appendix 3) did not appreciably change the results. In terms of percent change of BMI, the association patterns for cardiovascular outcomes were identical to our primary analysis (supplementary Table 6 in Appendix 3). But for the death outcomes, we only found significant increased risk in weight loss quintiles (quintile 1 and 2). When separating the primary analysis by individual cohort, consistent findings were observed (supplementary Table 7 in Appendix 3).

As depicted in Fig. 3, the associations of BMI trajectories and MACE were generally consistent in stratified analyses by sex, race and smoking status. It should be noted that the BMI-MACE association was significantly modified by age and borderline by baseline BMI. The hazards for MACE were significantly higher in those younger than 60 years, but lower in those who were initially with obesity.

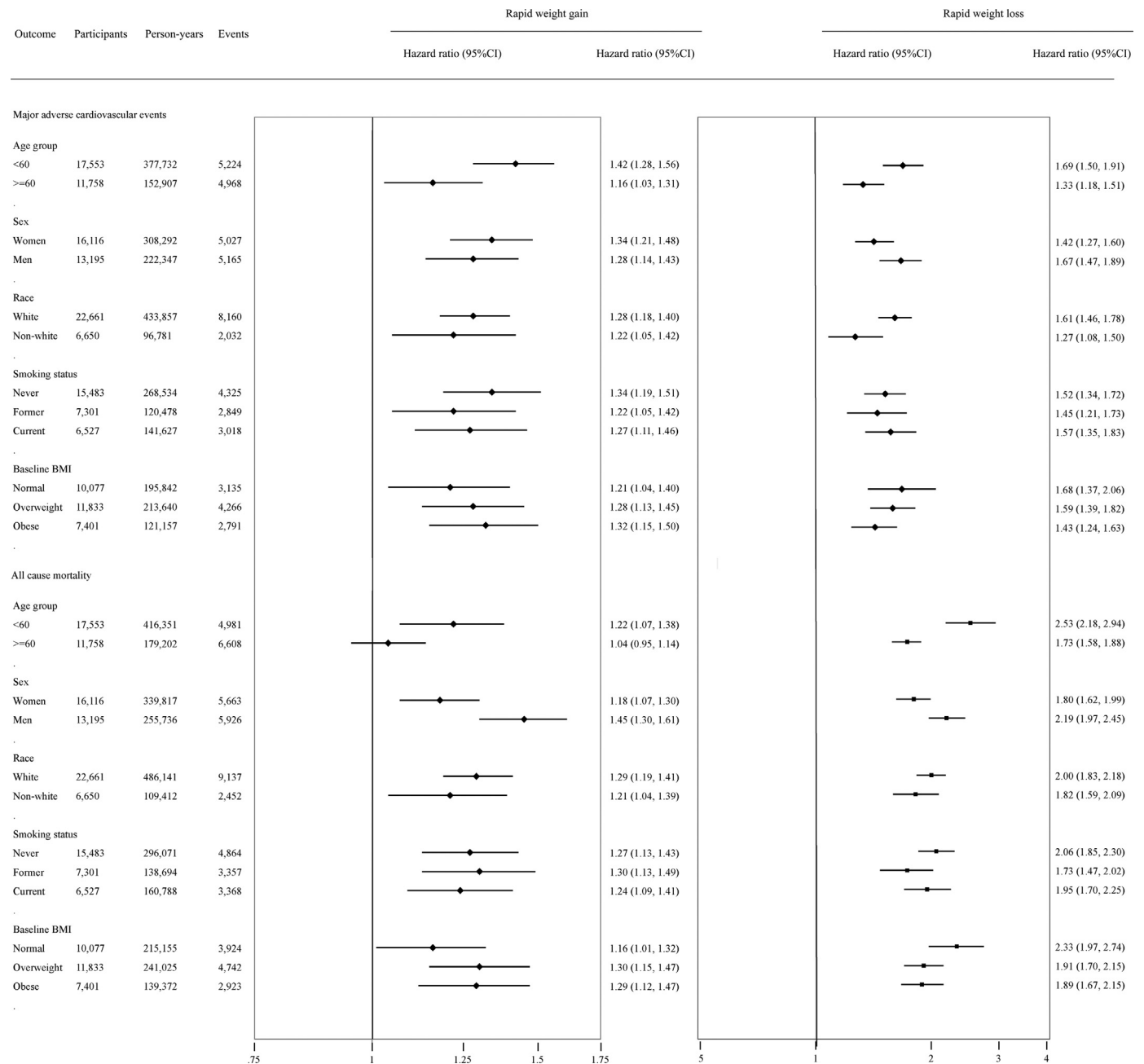


Fig. 3. Associations of BMI trajectories with major adverse cardiovascular events (MACE) and all-cause mortality, stratified by age group, sex, race, smoking status and baseline BMI. Hazard ratios are adjusted for age, gender, race, smoking status, current alcoholic use, education level, marital status, income, physical activity, consumption of fruits and vegetables, history of hypertension, diabetes, HF, CHD, cancer, COPD and stroke, baseline BMI, serum level of glucose, total cholesterol, LDLC, HDLC and triglyceride.

For all-cause mortality, the associations with BMI trajectories were generally consistent in white or non-white population and significantly modified by age, sex, and smoking status. It's revealed that male and individuals younger than 60 years had higher hazards for death. But surprisingly, the hazards were lower in the smoker subgroups. Similar to the MACE outcome, the hazards for death were lower in subgroup with obesity, but the modification effect by baseline BMI was insignificant. The association of BMI trajectories and other outcomes across the predefined subgroups are provided in supplementary Table 8 and Table 9 (Appendix 3).

Interestingly, when stratifying the three weight loss categories into low, moderate and high variability subgroups, different findings were observed. As presented in supplementary Table 10 (Appendix 3), the association patterns of weight loss and the studied outcomes were similar to the primary analysis in the lower two quantiles (low and moderate variability), while the associations became insignificant in the highest quantile. However, with regards to all-cause and non-cardiovascular death, the weight-loss-mortality association persisted.

4. Discussion

In our analyses of the overall cohort of 29,311 participants, a U-shaped relation was observed between BMI trajectories and subsequent risk of cardiovascular events and all-cause mortality. Significant increase of risks for MACE and all-cause death were noted for people assigned in weight loss or weight gain categories. The hazard risks for adverse outcomes were consistently lowest among individuals maintaining their body weight. Although effect modification was observed in several subgroups, our findings were generally robust in a number of sensitivity analysis. Furthermore, our study for the first time delineates the characteristics of BMI trajectories prior to different health outcomes, showing an accelerated decline in BMI almost ten years before the occurrence of the events.

More than 38.9% of US adults have obesity [1]; however, much of our understanding of the BMI-mortality association comes from single-time BMI measurement, without considering within-person variation over the long term. Since weight change is highly variable across adulthood, more studies are now focusing on BMI trajectories and different health outcomes [11,13,20-30,32]. However, most of these studies were grouping people using growth curve model or group-based latent model [11,20-29]. Using the above models, one can identify individuals with distinct BMI trajectories from the available data [25,48]. However, class membership is not determined with certainty for each individual since it relies on the selected models (linear, curvilinear, cubic and other forms) and probability of belonging [20,49]. Thus, misclassification is possible and the associated risk of adverse outcomes could be invalid. In articles published by Zeng H. et al. and Zajacova et al., the authors used the same data but identified different patterns of BMI trajectory [20,26]. As of now, at least two to six patterns of BMI trajectories have been reported in the general population and majority of them were depicting an ascending trend or paralleling with each other [21,26,28,50-52]. It is unrealistic that all participants were going the same way over the life course. There must be some groups of individuals experiencing gradual weight loss or even rapid loss in their weight. Furthermore, most of the existing studies differentiate the curves by studying changes in pre-defined BMI categories: defining a change within normal weight as "normal-stable" [28], or a change from overweight category to category with obesity as "overweight obesity" trajectory [26]. This crude categorization of BMI trajectories would probably yield over- or under-deterministic results. It should be noted that a variety of changes could occur within the same categories; even a small change in BMI could pose a significant deleterious effect on health [26]. Furthermore, the rate of change, the direction of change, or the slope of

the trajectory was all likely to make a difference in the negative outcomes [13,53].

Thus, from the current study, we derived an overall BMI trajectory (annual change in BMI or BMI slope) for each individual, giving further support to the associations of long term trajectories and diverse health outcomes. In our study, the slope of BMI throughout middle and older age, either positive or negative, rendered increased risks of MACE and mortality: the larger the changes the greater the risk. More specifically, BMI falling faster than 0.1 kg/m² per year resulted in at least 8% higher risks of MACE and 18% of death. On the other hand, increasing BMI by 0.3 kg/m² per year was associated with at least 13% higher hazards for MACE and 8% for death. Although several prior studies were conducted with a similar method, findings were mixed and inconsistent. As demonstrated in Framingham Heart Study, BMI slopes were inversely associated with the outcome of total mortality and morbidity due to CHD [13]. On the contrary, in the study of Chicago Western Electric Company, weight loss slope was significantly associated with total and cardiovascular mortality, while the weight gain slope showed nonsignificant increased risk of each endpoint for 25-year follow-up [32]. These inconsistencies may result from inadequate adjustment for potential cofounders and not considering the weight change direction.

Identical pattern of association was noted in subgroups of the population, after stratification for age, sex, race, smoking status and baseline BMI. However, effect modification of these stratification variables varied with respect to different outcomes. Generally, the hazardous effects of weight change and adverse outcomes were more pronounced in male participants and at younger age (<60 years). Two additional results should be noted. First, although previous studies have suggested that smoking status is a crucial modifier on the association of BMI and cardiovascular risks, we reveal that the hazards of cardiovascular outcomes were generally consistent in the three categories of smoking status. While for all-cause and non-CVD death, the association with weight loss were inconclusively modified by smoking status. The inconsistent observed relation could be the result of diverse weight change patterns associated with smoking or accounted for the unmeasured confounders [12,33]. Second, decreased weight in individuals with higher BMI (overweight or with obesity) may result in a better outcome when compared to those with normal weight at baseline, which could partially explain the phenomenon of "obesity paradox" [54]. The risk differences for weight gain among normal, overweight or individuals with obesity were less obvious.

In this study, we not only captured the characteristics of individual BMI change trajectory, but also directly evaluated the average BMI trajectories for those with and without specific outcomes. We found for the first time that patterns of change in BMI prior to different outcomes were different. Overall, the BMI trajectories appeared similar for most of the study outcomes: the outcome-free participants followed a trajectory where the average BMI levels remained relatively stable, while for those who went on to experience adverse events, the trajectories began to fall 10 years before the event. Although it's unclear whether the observed weight loss was the antecedent cause or the consequence of the outcome, these findings may signal an underlying high-risk population and underscore the importance of maintaining body weight over the middle to late adulthood.

The major strengths of this study include the availability of multiple BMI measurements within identical time interval and using the linear mixed model, which entails a more accurate assessment of individual BMI trajectory. Furthermore, although distinguishing intentional and unintentional weight loss is challenging, we try to separate them by using weight variability, in which the highest variability subgroup represents intentional weight loss subcategory. As a result, in weight loss participants with high weight variability, moderate and rapid weight loss was not significantly correlated with increased risk of cardiovascular events. But likewise, we did not

observe a beneficial effect in this group of population. One possible explanation for this is that weight rebound following intentional weight loss may offset the positive effect brought by losing weight [55]. Therefore, for weight loss individuals, it is imperative to first examine the reasons for weight loss: intentional or unintentional. If someone is losing weight intentionally, avoiding weight regain or achieving sustained weight loss may be the cornerstone of the accrued benefits brought by losing weight from a high BMI.

Despite of the strengths provided above, several limitations should be noted. Firstly, our findings relate solely to changes in BMI while the changes of fat mass, muscle mass and the general change of the body composition were unknown. In addition, since majority of the study participants were white US people, the results could not be generalized to more heterogeneous populations. Secondly, although we are trying to distinguish whether weight loss was intentional or unintentional in our sensitivity analysis, data on the causes of weight loss were unavailable in the current study. And thus, we could not confirm the above speculation and further studies are warranted.

In this large population-based study, a U-shaped relation was observed between BMI trajectories and subsequent risk of different health outcomes. Both weight gain and weight loss conferred increased risks for cardiovascular events and all-cause mortality. In addition, we found for the first time that patterns of change in BMI prior to different outcomes were different. Falling off the BMI trajectory could be a warning sign for future occurrence of adverse events; thus, maintaining body weight during the middle to late adulthood may be essential. Despite the observational nature of the current study, the trajectories and risk patterns identified here may inspire future studies on the cause and potentially weight management guidelines.

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Declaration of Competing Interest

We declare no competing interests.

Contributors

All authors contributed to the study concept and design. YC, CZ and WS contributed equally to this work. DL and YC are senior and corresponding authors who also contributed equally to this study. DL, YC, CZ and WS have full access to all the data in this study and take full responsibility as guarantors for the integrity of the data and the accuracy of the data analysis. CY, LD, CZ and WS contributed to the study design. CZ and WS contributed to analysis and data interpretation. CY and LD drafted the manuscript and contributed to the final approval of the manuscript. MW, YF and ZM contributed to critical revision of the manuscript for important intellectual content.

Data sharing statement

The cohort data sets were obtained from the NIH Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and could be applied to the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100790.

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