Original Investigation | Public Health

Association of Weight Loss Between Early Adulthood and Midlife With All-Cause Mortality Risk in the US

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Abstract

IMPORTANCE Describing potential mortality risk reduction associated with weight loss between early adulthood and midlife is important for informing primary and secondary prevention efforts for obesity.

OBJECTIVE To examine the risk of all-cause mortality among adults who lost weight between early adulthood and midlife compared with adults who were persistently obese over the same period.

DESIGN, SETTING, AND PARTICIPANTS Combined repeated cross-sectional analysis was conducted using data from the National Health and Nutrition Examination Survey III (1988-1994) and continuous waves collected in 2-year cycles between 1999 and 2014. The data analysis was conducted from February 10, 2019, to April 20, 2020. Individuals aged 40 to 74 years at the time of survey (baseline) were included in the analyses (n = 24 205).

EXPOSURES Weight history was assessed by self-reported weight at age 25 years, at 10 years before baseline (midlife: mean age, 44 years; interquartile range, 37-55), and measured weight at baseline. Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) at each time was categorized as normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0). Weight change patterns were assessed from age 25 years (early adulthood) to 10 years before baseline (midlife).

MAIN OUTCOMES AND MEASURES Incident all-cause mortality using linked data from the National Death Index.

RESULTS Of the 24 205 participants, 11 617 were women (49.0%) and 11 567 were non-Hispanic White (76.9%). The mean (SD) BMI was 29.0 (6.1) at baseline. During a mean (SD) follow-up of 10.7 (7.2) years, 5846 deaths occurred. Weight loss from obese to overweight was associated with a 54% (hazard ratio, 0.46; 95% CI, 0.27-0.77) reduction in mortality risk compared with individuals with stable obesity between early adulthood and midlife. An estimated 3.2% (95% CI, 1.6%-4.9%) of early deaths could have been avoided if those who maintained an obese BMI instead lost weight to an overweight BMI by midlife. Overall, an estimated 12.4% (95% CI, 8.1%-16.5%) of early deaths may be attributable to having weight in excess of the normal BMI range at any point between early and mid-adulthood.

CONCLUSIONS AND RELEVANCE In this study, weight loss from obesity to overweight between early adulthood through midlife appeared to be associated with a mortality risk reduction compared with persistent obesity. These findings support the importance of population-based approaches to

(continued)

Key Points

Question Is weight loss between early adulthood and midlife associated with reduced mortality risk later in life compared with persistent obesity?

Findings In this combined, repeated cross-sectional analysis of a nationally representative cohort of 24 205 US adults followed up for a mean of 10.7 years, participants who lost weight from an obese body mass index in early adulthood to overweight in midlife had a 54% reduction in mortality risk relative to those who maintained an obese body mass index. An estimated 3.2% of early deaths could have been avoided if those who maintained an obese BMI instead lost weight to an overweight BMI by midlife.

Meaning Findings from this study suggest that population-based approaches to preventing weight gain and treating obesity early in life may have important mortality reduction benefits.

+ **Supplemental content**

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Abstract (continued)

preventing weight gain across the life course and a need for greater emphasis on treating obesity early in life.

Introduction

The prevalence of obesity has increased rapidly in the US and globally over the past several decades.[1,2] In addition to this general trend, recent birth cohorts in the US are reaching a higher prevalence of obesity earlier in the life course.[3] As a result, younger generations are experiencing a greater cumulative exposure to excess adiposity during their lifetime. Relying on a snapshot of obesity status assessed at one specific time in the life course, previous studies have generally found a U-shaped or J-shaped association between body mass index (BMI) and mortality.[4-8] However, by including only a single measurement of BMI, these studies do not acknowledge the dynamic aspect of weight progression over time and are subject to measurement errors related to individual differences in body frame size and lean mass.[9]

Studies that consider weight progression across adulthood in association with mortality have found that weight gain from early adulthood to midlife is associated with increased risk.[9-12] A study by Chen et al[12] using data from the National Health and Nutrition Examination Survey (NHANES) reported that weight gain in adulthood significantly increased all-cause mortality risk. While Chen et al[12] provided evidence on the mortality risk of weight change compared with stable normal weight, they did not estimate the potential mortality risk reductions associated with weight loss among adults with obesity. Few other studies have investigated the association of weight loss with mortality, and the results are inconsistent.[13-17] Specifically, it remains unclear whether people with measures of BMI above normal in early adulthood who later lose weight reduce their mortality risk or whether there is residual risk due to irreversible pathologic processes resulting from carrying excess weight earlier in life.

Estimating the population consequences of elevated BMI is complicated by the complex interactions of BMI with age, smoking, and other risk factors and the lack of understanding of healthy weight trajectories over the life course.[18] As a result, the proportion of total deaths that are attributable to obesity reported by previous studies varies widely.[6,19] Additional empirical estimates derived from nationally representative data sources are needed to assess the population-level effects of obesity prevention and treatment on mortality risk reduction across the life course.

Using data from the NHANES, the present study evaluates the all-cause mortality risk associated with patterns of BMI change between early adulthood and midlife. We tested whether individuals who were overweight or obese in early adulthood but lost weight to lower BMI levels by midlife were at reduced risk of mortality compared with individuals who maintained a stable overweight or obese BMI (the risk reduction hypothesis) and at an increased risk of mortality compared with individuals who remained at lower BMI levels over the same time (the residual risk hypothesis). We also estimated the implications for overall US mortality based on population counterfactuals for primary and secondary obesity prevention across the life course.

Methods

The NHANES consists of a series of cross-sectional, nationally representative surveys of civilian, noninstitutionalized US adults. Using a complex, stratified, multistage probability cluster sampling design, NHANES data were collected periodically before 1999 and continuously thereafter in 2-year cycles. Interviews were conducted in respondents' homes, and laboratory and health measurements were performed by trained technicians in mobile examination centers. Written informed consent

was obtained from all NHANES participants. The present investigation relied on deidentified publicly available data and was therefore exempted from review by the Boston University Medical Center Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We incorporated data on adult participants aged 40 to 74 years at the time of survey (baseline) from both the NHANES III (1988-1994) and continuous NHANES (1999-2014). Data analysis was conducted from February 10, 2019, to April 20, 2020. We included individuals with complete data on vital status, self-reported weight at age 25 years and 10 years before baseline, measured weight at baseline, and relevant covariates (n = 24 205). Participants with unreliable BMI self-reports, defined as a discrepancy between measured and self-reported BMI at baseline outside the first to 99th percentile range, were excluded. The procedure to obtain the analytic sample is depicted in eFigure 1 in the Supplement.

Vital status was obtained from the NHANES Linked Mortality File, in which eligible participants were matched to the National Death Index through December 31, 2015. A description of the methods has been published elsewhere.[20] We calculated the follow-up time for each individual from the time of baseline to the date of death or censoring at the last date at which vital status was ascertained.

Weight Change Measures and Covariates

Participants were asked to recall weight at age 25 years (early adulthood) and weight 10 years before their age at baseline (midlife). Baseline weight and height were measured at the time of the medical examination. To calculate BMI, we used measured height at baseline for participants younger than 50 years and recalled height at age 25 years for participants aged 50 years and older. Recalled height at age 25 years was not recorded in the NHANES III; thus, the use of recalled height was limited to respondents from 1999 to 2014 who were older than 50 years.

Body mass index was calculated as weight in kilograms divided by height in meters squared. The BMI values at each time were categorized as normal weight (18.5-24.9), overweight (25.0-29.9), and obese ($\geq$30.0), consistent with established definitions.[21] We examined weight change patterns from age 25 years (early adulthood) to 10 years before baseline (midlife; mean age, 44 years; interquartile range, 37-55). For each time interval, 9 weight change patterns were created in 3 broad categories: (1) weight maintenance (normal-normal, overweight-overweight, obese-obese), (2) weight gain (normal-overweight, normal-obese, overweight-obese), and (3) weight loss (overweight-normal, obese-normal, obese-overweight) as described in eTable 1 in the Supplement.

Potential confounders included age, sex, race/ethnicity, educational level, country of birth, smoking status, and survey year. We used a parsimonious set of covariates to avoid overadjustment for potential intermediates, such as leisure time, physical activity level, and self-reported health status at baseline.

Statistical Analysis

Survival Analysis

Cox proportional hazards regression models were used to estimate the association between weight change patterns and all-cause mortality in the total sample and among never smokers, adjusting for the covariates described above. There were 5846 deaths over a mean (SD) of 10.7 (7.2) years (288 590 person-years) of follow-up, or a rate of 20.3 deaths per 1000 person-years. The proportional hazards assumption was tested with Schoenfeld residuals,[22] and no significant deviation from proportionality in hazards over time was detected.

We tested 2 hypotheses concerning weight loss using adjusted models with different reference categories. First, we investigated whether individuals who lost weight were at a reduced risk of death compared with those who remained overweight or obese. To test this risk reduction hypothesis, we estimated the hazards for the overweight-normal group compared with the overweight-overweight group and the obese-overweight group relative to the obese-obese group. Second, we investigated whether individuals with weight loss were at increased risk relative to those who maintained lower

weight over time to examine whether there is residual risk associated with having previously been heavier. To test this residual risk hypothesis, we compared the mortality risk for the obese-overweight group with the overweight-overweight group and the overweight-normal group with the normal-normal group.

Consistent with a prior study,[23] we estimated the proportion of early deaths attributable to obesity progression under 4 hypothetical scenarios using the following equation[24] for the population-attributable fraction (PAF): $\Sigma pd_i[(HR_i - 1)/HR_i]$, where pd_i is the proportion of total incident deaths observed in the ith obesity progression category and HR_i is the hazard ratio (HR) associated with that category. The PAFs represent the proportion of early deaths that would not have occurred if members of that weight change category were redistributed to another lower risk category, assuming that the observed associations represent causal effects. Confidence intervals for PAFs were calculated using the delta method for complex survey design, accounting for multiple sources of uncertainty.[24]

Secondary Analyses

In secondary analyses, we stratified our Cox proportional hazards regression models by sex and baseline age (<65 and ≥65 years) to examine effect modification. Next, we repeated the survival analyses in a second observation interval from 10 years before baseline (midlife: mean age, 44 years; interquartile range, 37-55) to baseline (mean age, 55 years; interquartile range, 47-65). We also tested the mortality risk reduction and residual risk hypotheses for weight change patterns that occurred during the second observation interval.

Stata, version 14 (StataCorp LLC) was used for data management and analyses. All estimates were adjusted for complex survey design, including NHANES examination sample weights, primary sampling unit, and strata. The PAFs were calculated using the Stata package punafcc.[24] Statistical significance was determined by a 2-sided P value <.05.

Results

Descriptive statistics for the participants are reported in **Table 1**. With weighted percentages shown, of the 24 205 participants, 11 617 were women (49.0%) and 12 588 were men (51.0%). At baseline, the mean (SD) age of the participants was 54.2 (9.6) years. The mean (SD) recalled BMI was 23.7 (4.1) at age 25 years and 27.2 (5.7) at 10 years before baseline. The mean (SD) BMI was 29.0 (6.1) at baseline. The proportions of race/ethnicity were 76.9% for non-Hispanic White, 10.0% for non-Hispanic Black, and 13.1% for Hispanic and other non-Hispanic individuals. Overall, 10 787 of the sample (55.7%) reported having more than a high school education at baseline, and 19 167 individuals (87.6%) were born in the US.

With respect to weight change patterns between age 25 years (early adulthood) and 10 years before baseline (midlife), 56.2% of the respondents maintained their BMI categories. The proportions of the population who maintained body weight were 38.5% at normal weight, 12.1% at overweight, and 5.6% at obese levels. Weight loss was rare in the study population. Only 1.3% of the individuals who were overweight at age 25 years lost weight to a normal BMI 10 years before baseline, 0.8% lost weight from obese to overweight, and 0.2% lost weight from obese to normal.

The **Figure** and eFigure 2 in the Supplement show the adjusted cumulative hazard curves of all-cause mortality for weight change patterns for all individuals and for never smokers. The adjusted HRs for each weight change pattern are presented in **Table 2**. For all participants, maintaining an obese BMI from early adulthood to midlife increased the risk of all-cause mortality compared with stable normal weight, with an HR of 2.17 (95% CI, 1.85-2.53). While weight gain from a normal to overweight BMI was not associated with risk, normal-obese (HR, 1.32; 95% CI, 1.15-1.52) and overweight-obese (HR, 1.47; 95% CI, 1.28-1.69) weight changes were associated with elevated mortality risks. Similar associations were observed among never smokers (normal-obese: HR, 1.37; 95% CI, 1.08-1.74; overweight-obese: HR, 1.75; 95% CI, 1.39-2.22).

With the risk reduction hypothesis, we found that adults who lost weight from obese to overweight by midlife had a 54% lower risk of all-cause mortality (HR, 0.46; 95% CI, 0.27-0.77) compared with adults who were stable obese (**Table 3**). Adults who lost weight from overweight in early adulthood to normal weight by midlife did not have reduced mortality risk (HR, 1.12; 95% CI, 0.86-1.45). Associations were similar in never smokers.

In the residual risk hypothesis, higher mortality was observed for adults with normal weight at midlife who were previously overweight in early adulthood (HR, 1.29; 95% CI, 1.02-1.64) compared with those who maintained stable normal weight. A significant residual risk was also found in never smokers who were previously overweight (HR, 1.58; 95% CI, 1.12-2.21). There was no significant residual risk for adults with overweight who were previously obese (HR, 0.86; 95% CI, 0.53-1.41). We also found no significant risk among never smokers.

Table 4 presents the PAFs calculated under 4 hypothetical population weight change scenarios. The first scenario describes the potential health implications of a treatment strategy in which adults who maintained an obese BMI instead lost weight to overweight by midlife. In this scenario, an estimated 3.2% (95% CI, 1.6%-4.9%) of early deaths could be averted. We also estimated that 12.4% (95% CI, 8.1%-16.5%) of early deaths could be avoided if the entire population with a BMI above normal weight instead had a normal BMI from age 25 years through midlife.

Table 1. Sample Characteristics by Weight Change Patterns From Age 25 Years to 10 Years Before Baseline, NHANES 1988-1994 and 1999-2014
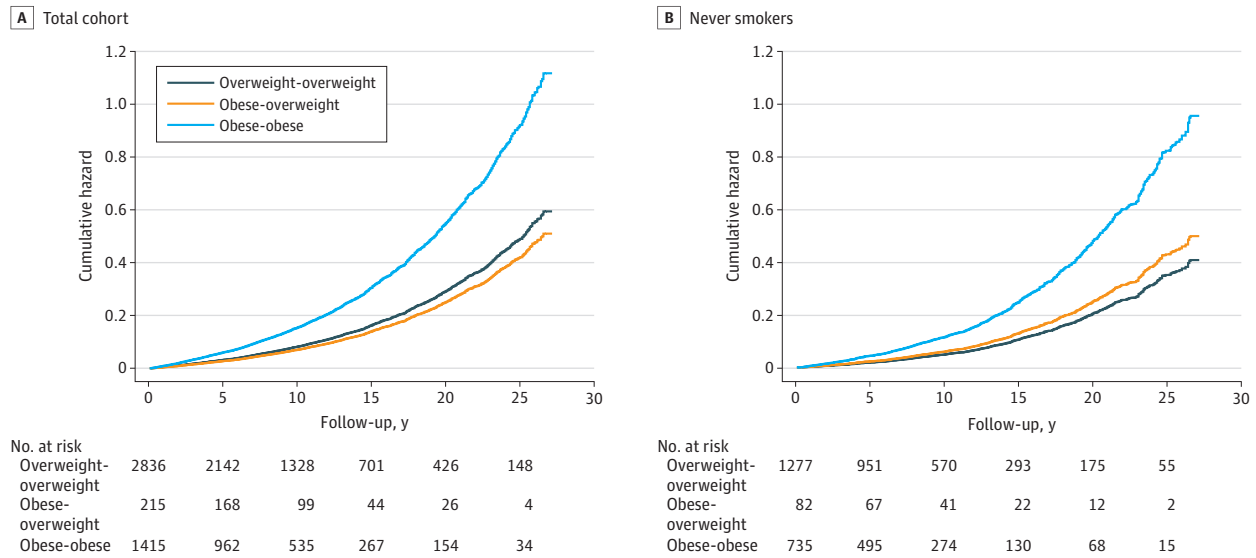
Characteristics[a]	Total	Maintenance			Gain			Loss		
		Normal-normal	Overweight-overweight	Obese-obese	Normal-overweight	Normal-obese	Overweight-obese	Overweight-normal	Obese-Normal	Obese-overweight
No. (%)	24 205 (100)	8363 (38.5)	2811 (12.1)	1405 (5.6)	6329 (24.1)	2279 (7.9)	2394 (9.4)	351 (1.3)	59 (0.2)	214 (0.8)
Age, mean (SD), y	54.2 (9.6)	52.5 (9.4)	52.0 (9.2)	51.1 (8.8)	56.6 (9.6)	59.0 (9.0)	54.6 (9.3)	54.1 (9.4)	51.4 (9.5)	53.1 (9.6)
Sex										
Female	11 617 (49.0)	4808 (61.4)	634 (19.6)	676 (45.1)	2960 (47.0)	1417 (65.3)	887 (33.7)	129 (37.6)	32 (55.4)	74 (32.2)
Male	12 588 (51.0)	3555 (38.6)	2177 (80.4)	729 (54.9)	3369 (53.0)	862 (34.7)	1507 (66.3)	222 (62.4)	27 (44.6)	140 (67.9)
Race/ethnicity										
Non-Hispanic										
White	11 567 (76.9)	4268 (78.2)	1349 (78.2)	625 (74.2)	2934 (75.8)	994 (75.7)	1120 (76.4)	146 (72.8)	26 (71.7)	105 (77.8)
Black	5619 (10.0)	1766 (8.5)	661 (10.0)	451 (15.2)	1367 (9.7)	587 (12.2)	631 (11.3)	97 (12.3)	16 (14.6)	43 (9.8)
Hispanic and non-Hispanic other	7019 (13.1)	2329 (13.2)	801 (11.9)	329 (10.6)	2028 (14.5)	698 (12.1)	643 (12.3)	108 (15.0)	17 (13.7)	66 (12.4)
Education										
<High school	6144 (14.9)	1809 (12.8)	719 (13.8)	370 (15.8)	1690 (16.4)	738 (19.0)	609 (15.4)	115 (18.2)	16 (19.6)	78 (22.0)
High school	7274 (29.4)	2519 (28.2)	815 (28.6)	433 (31.8)	1889 (29.7)	689 (32.0)	739 (30.7)	115 (31.6)	20 (29.2)	55 (26.9)
>High school	10 787 (55.7)	4035 (57.6)	1277 (57.6)	602 (52.5)	2750 (53.9)	852 (49.0)	1046 (53.9)	121 (50.3)	23 (51.2)	81 (51.1)
Country of birth										
US	19 167 (87.6)	6469 (85.7)	2235 (89.3)	1253 (93.9)	4850 (85.7)	1843 (90.6)	2025 (90.9)	273 (86.9)	49 (86.4)	170 (91.8)
Other	5038 (12.4)	1894 (14.3)	576 (10.7)	152 (6.1)	1479 (14.3)	436 (9.4)	369 (9.1)	78 (13.1)	10 (13.6)	44 (8.2)
Smoking status										
Never	11 635 (49.0)	3956 (48.5)	1270 (47.0)	731 (53.5)	3124 (49.9)	1174 (52.9)	1150 (47.1)	135 (43.6)	13 (22.8)	82 (41.4)
Former	7212 (29.9)	2232 (27.5)	828 (29.9)	359 (26.9)	2049 (32.4)	753 (32.5)	792 (32.7)	97 (27.5)	23 (47.7)	79 (32.0)
Current	5358 (21.1)	2175 (24.0)	713 (23.1)	315 (19.6)	1156 (17.8)	352 (14.7)	452 (20.1)	119 (28.9)	23 (29.3)	53 (26.7)
BMI, mean (SD)										
At age 25 y	23.7 (4.1)	21.2 (1.6)	26.4 (1.2)	34.6 (4.9)	22.4 (1.7)	22.6 (1.6)	27.3 (1.4)	26.4 (1.3)	34.4 (5.7)	33.1 (3.7)
10 y prior to baseline	27.2 (5.7)	22.6 (1.6)	27.7 (1.4)	38.6 (7.4)	27.0 (1.4)	33.8 (4.4)	34.1 (4.3)	23.4 (1.3)	23.2 (1.5)	27.9 (1.4)
At baseline	29.0 (6.1)	24.9 (3.6)	29.7 (4.1)	38.7 (7.8)	29.2 (4.0)	34.1 (5.5)	34.7 (5.4)	25.9 (4.5)	29.4 (7.8)	30.7 (6.2)
BMI change, mean (SD)	3.5 (4.3)	1.4 (1.6)	1.2 (1.6)	4.0 (6.3)	4.5 (2.1)	11.3 (4.6)	6.8 (4.4)	−3.0 (1.9)	−11.2 (6.0)	−5.2 (3.9)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NHANES, National Health and Nutrition Examination Survey.

[b] Weight change patterns are defined in eTable 1 in the Supplement.

[a] Unweighted frequencies and weighted means/percentages are presented.

In secondary analyses, we found that stable obesity from 10 years before baseline to baseline increased the risk of all-cause mortality, with HRs of 1.54 (95% CI, 1.37-1.73) compared with stable normal weight (eTable 2 in the Supplement). There was no evidence of risk reduction for adults who lost weight from obese to overweight or overweight to normal weight. We found that adults who lost weight from obese to overweight experienced residual risk (HR, 1.64; 95% CI, 1.38-1.95) along with adults who lost weight from overweight to normal weight (HR, 1.44; 95% CI, 1.19-1.75) (eTable 3 in the Supplement).

Figure. Adjusted Cumulative Hazard Curves of All-Cause Mortality for Selected Weight Change Patterns From Early Adulthood to Midlife

A | Total cohort

B | Never smokers

No. at risk						
Overweight-overweight	2836	2142	1328	701	426	148
Obese-overweight	215	168	99	44	26	4
Obese-obese	1415	962	535	267	154	34

No. at risk						
Overweight-overweight	1277	951	570	293	175	55
Obese-overweight	82	67	41	22	12	2
Obese-obese	735	495	274	130	68	15

Patterns shown for total cohort (A) and never smokers (B).

Table 2. Adjusted Hazard Ratios of All-Cause Mortality for Weight Change Patterns From Young Adulthood to Midlife

Characteristic	Weight change patterns							
	Maintenance			Gain			Loss[a]	
	Normal-normal	Overweight-overweight	Obese-obese	Normal-overweight	Normal-obese	Overweight-obese	Overweight-normal	Obese-overweight
Full sample								
No. of events	1631	592	322	1375	544	531	119	64
Events/1000 py	16.4	19.6	24.8	20.1	25.4	23.0	28.6	28.9
Age-adjusted HR (95% CI)[b]	1 [Reference]	1.31 (1.17-1.46)	2.20 (1.88-2.57)	1.07 (0.98-1.17)	1.25 (1.09-1.44)	1.56 (1.37-1.78)	1.56 (1.22-1.99)	1.19 (0.78-1.80)
Multivariable adjusted HR (95% CI)[c]	1 [Reference]	1.15 (1.02-1.31)	2.17 (1.85-2.53)	1.05 (0.97-1.15)	1.32 (1.15-1.52)	1.47 (1.28-1.69)	1.29 (1.02-1.64)	1.00 (0.62-1.60)
Never smokers								
No. of events	453	169	130	486	218	195	28	19
Events/1000 py	9.8	12.8	19.6	14.6	19.1	17.7	17.4	20.7
Age-adjusted HR (95% CI)[b]	1 [Reference]	1.37 (1.06-1.76)	3.29 (2.55-4.23)	1.24 (1.04-1.46)	1.47 (1.17-1.86)	1.98 (1.56-2.50)	1.62 (1.11-2.35)	1.39 (0.71-2.70)
Multivariable adjusted HR (95% CI)[c]	1 [Reference]	1.20 (0.93-1.56)	2.82 (2.16-3.67)	1.16 (0.98-1.37)	1.37 (1.08-1.74)	1.75 (1.39-2.22)	1.58 (1.13-2.21)	1.46 (0.81-2.65)

Abbreviations: HR, hazard ratio; py, person-years.

[a] Results for weight loss pattern obese-normal were suppressed because of few incident events (<10).

[b] Age at baseline (continuous).

[c] Adjusted for age at baseline (years), sex (male, female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic other), educational level (less than high school, high school or equivalent, and college and above), nativity (US born, non-US born), smoking status (never, former, and current), and survey year (continuous).

Stratified analyses by baseline age and sex are shown in eFigure 3 in the Supplement. We found significant interactions between weight change categories and baseline age, but not between weight change and sex. For the weight gain and stable obese categories, the associations appeared to be stronger among participants who were younger than 65 years at baseline compared with those 65 years or older.

Discussion

This nationally representative study of US adults revealed significant associations between patterns of BMI change across the life course and risks of all-cause mortality. From early to middle adulthood, the lowest mortality risk was observed among individuals who entered adulthood with a normal BMI and maintained a BMI within the normal range through middle adulthood. Individuals who lost or gained weight over this interval were at intermediate risk, whereas individuals who maintained BMI in the obese range were at the highest risk.

While these results are broadly consistent with a recent study by Chen et al[12] that used NHANES data, we tested 2 different hypotheses concerning weight loss. First, we found evidence in support of a risk reduction hypothesis. Weight loss from obese to overweight in individuals between early and middle adulthood was associated with more than a 50% reduction in mortality risk relative to those who remained obese throughout the period. In contrast, the same weight loss pattern in a later weight change interval was not associated with risk reduction. The discrepancy likely reflects the different nature of weight loss at an earlier vs later life course. Weight loss at an older age is often unintentional, associated with underlying health conditions and/or age-related loss of muscle mass,[25] whereas weight loss earlier in life tends to capture changes in fat mass and is less likely to be affected by the onset of chronic diseases.[9] The 10-year period between the earlier weight change interval and baseline may have also minimized a reverse association (ie, the influence of disease on

Table 3. Adjusted Hazard Ratios of All-Cause Mortality for Risk Reduction and Residual Risk Hypotheses

Hypothesis	HR (95% CI)[a]	
	Full sample	Never smokers
Risk reduction		
Obese-overweight	0.46 (0.27-0.77)	0.52 (0.28-0.97)
Obese-obese	1 [Reference]	1 [Reference]
Overweight-normal	1.12 (0.86-1.45)	1.31 (0.90-1.92)
Overweight-overweight	1 [Reference]	1 [Reference]
Residual risk		
Obese-overweight	0.86 (0.53-1.41)	1.22 (0.65-2.30)
Overweight-overweight	1 [Reference]	[1 Reference]
Overweight-normal	1.29 (1.02-1.64)	1.58 (1.12-2.21)
Normal-normal	1 [Reference]	1 [Reference]

Abbreviation: HR, hazard ratio.

[a] Adjusted for age at baseline (years), sex (male and female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic other), educational level (less than high school, high school or equivalent, and college and above), nativity (US born, non-US born), smoking status (never, former, and current), and survey year (continuous).

Table 4. PAFs for Population Counterfactuals

Population counterfactuals	Definition	PAF %, (95% CI)[a]
Weight loss	If those who maintained an obese BMI lost weight to an overweight BMI at midlife	3.2 (1.6-4.9)
Weight maintenance-overweight	If those who gained weight from overweight to obese instead remained overweight between age 25 y and midlife	2.3 (0.7-3.8)
Weight maintenance-normal	If those who gained weight from normal to obese instead remained normal between age 25 y and midlife	2.2 (1.0-3.3)
Comprehensive prevention	If the total population had a normal BMI from age 25 y through midlife	12.4 (8.1-16.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PAF, population-attributable fraction.

[a] PAFs and related 95% CIs were calculated by the Stata punafcc package using the formula $\Sigma pd_i[(HR_i - 1)/HR_i]$, where pd_i is the proportion of total incident deaths observed in the ith obesity progression category and HR_i is the hazard ratio (HR) associated with that category. PAFs were calculated using pd_i and HR_i estimated from the entire sample. All HR_i values were generated from Cox proportional hazards regression models adjusted for covariates (age at baseline, sex, race/ethnicity, educational level, nativity, and survey cycles) and postestimation analyses.

body weight), as one study indicated that weight loss accelerated an average of 9 years before death.[26]

The reduction in risk associated with weight loss from early to middle adulthood is contradictory to most previous observational studies, which showed an increased risk of death[11,14,16,27] or no reduction in risk.[9] The inconsistency may be a result of the period of the life course examined and/or incomplete adjustment for reverse associations in previous study designs. To evaluate mortality risks associated with weight loss and gain, studies often use stable weight as the reference category. Such a practice can obscure interpretation because stable weight may be maintained at different BMI levels with different risk implications.

The present study tested another hypothesis related to whether the imprint of early life obesity on mortality risk persists into midlife among those who lose weight. Compared with individuals who remained overweight between age 25 years and midlife, we did not observe higher risks of mortality in those who lost weight from obese to overweight. While small sample sizes prevented us from producing a precise estimate for this weight change pattern, such a finding would seem to suggest that the physiologic effects of early life obesity may be at least partially reversible. The finding that obesity limited to early or middle adulthood is associated with a lower mortality risk relative to persistent obesity but with a higher or comparable risk relative to stable normal weight is consistent with a life course perspective[28] and empirical evidence.[29,30]

When extrapolated to the population level, we found that 3.2% of early deaths may be attributable to maintaining weight in the stable obese range vs losing weight to an overweight BMI by midlife. These results indicate an opportunity to improve population health through enhanced targeting of evidence-based obesity treatments, including aggressive behavioral, lifestyle counseling, or other modalities, to young adults with obesity. In total, we estimated that 12.4% of early deaths were attributable to having weight in excess of the normal BMI range at any point between early and mid-adulthood.

Limitations

The present study had several limitations. First, to reconstruct weight change between early and midlife, we relied on recalled weight at age 25 years and 10 years before baseline. Despite validation studies that suggested a relatively strong concordance between recalled weight data and contemporaneous weight measures across a number of different populations and recall periods,[31-33] some misclassification has likely occurred.[34,35] A future analysis of weight loss and mortality risk could benefit from using a data source, such as the Framingham Heart Study, that has repeated objective measures of BMI over time. A second limitation is that we could not adjust for physical activity or diet in early adulthood because recall data on these variables were not collected. Third, the proportion of the sample that lost weight between early and midlife was small, limiting the precision of our estimates. Fourth, we had no data on the mechanism of weight change and whether it was intentional or unintentional; however, conditioning our analysis on 10-year survival after the midlife weight observation may reduce the likelihood of unintentional weight loss affecting the associations.[36]

Conclusions

In this nationally representative study of US adults, compared with remaining obese, weight loss from an obese BMI in early adulthood to an overweight BMI in midlife was associated with more than a 50% reduction in the subsequent risk of early death. At the population level, we estimated that weight loss from obese to overweight would prevent more than 3% of premature deaths, and preventing weight gain from normal weight could prevent more than 12% of premature deaths. Our findings support the importance of population-based approaches to preventing weight gain across the life course and a need for greater emphasis on treating obesity early in life.

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SUPPLEMENT.