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Original article

Life-long body mass index trajectories and mortality in two generations

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ABSTRACT

Purpose: To identify life-long body mass index (BMI) trajectories across two related generations and estimate their associated mortality risks and population attributable deaths.

Methods: We use prospective cohort data from the Framingham Heart Study (1948–2011) original (4576 individuals, 3913 deaths) and offspring (3753 individuals, 967 deaths) cohorts and latent trajectory models to model BMI trajectories from age 31 to 80 years. Survival models are used to estimate trajectory-specific mortality risk.

Results: We define seven BMI trajectories among original cohort and six among offspring cohort. Among original cohort, people who are normal weight at age 31 years and gradually move to overweight status in middle or later adulthood have the lowest mortality risk even compared to those who maintain normal weight throughout adulthood, followed by overweight stable, lower level of normal weight, overweight downward, class I obese upward, and class II/III upward trajectories. Mortality risks associated with obesity trajectories have declined across cohorts, while the prevalence of high-risk trajectories has increased.

Conclusions: The mortality impact of weight gain depends on an individual's BMI trajectory. Population attributable deaths associated with unhealthy weight trajectories have grown over generations because the prevalence has increased, offsetting the decline in trajectory-specific mortality risks.

As one of the most urgent epidemics in many societies, obesity has emerged as a key risk factor for many illnesses (e.g., diabetes, cardiovascular disease, stroke, and certain cancers), morbidities, functional limitation, and mortality [1–16]. The extent of obesity's negative impact accumulates over the life course and depends on timing of onset of obesity and duration of excess body mass [12, 16]. Therefore, it is essential to utilize life history information on body mass index (BMI; weight (kg)/height $(m)^2$) to estimate the impact of obesity on disease and mortality. A growing body of literature has done so and highlighted that: (1) a dynamic measure capturing weight status changes (e.g., weight loss, large weight gain) is more predictive of disease and mortality than a static measure of weight status (e.g., baseline BMI) [1–11]; (2) obesity increases the risk of mortality more profoundly when it persists over the life course [3, 12]; and (3) attributable mortality risk due to obesity is larger when using obesity trajectories rather than a static measure of obesity [3]. These literatures are insightful in emphasizing the importance of dynamic BMI history on health and mortality, but life-course BMI dynamics have remained poorly characterized and it remains unclear how such dynamics relate to health and mortality.

Several strategies to model the impact of weight status histories on mortality have been utilized [10–24], for example, strictly adding BMI statuses from different lifetime points in the hazard model, constructing duration of obesity, and specifying the amount of weight changes. These approaches usually utilize limited time points of BMI information and are based on strong assumptions,

Abbreviations: BMI, body mass index; FHS, Framingham Heart Study; PAF, population attributable mortality risk fraction; HR, hazard ratio; CI, confidence interval.

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for example, BMI statuses from different lifetime points independently affect mortality, the effect of duration of obesity does not depend on timing of onset of obesity, or cutoff points in weight change are specified arbitrarily [10]. Some approaches recognize that obesity levels from different lifetime points may be interactive in their effects and include interactions among BMI statuses to the models [22–24]. Including interactions among BMI status at different times in the life course improves model fit, but the interpretation of these interactions is not straightforward, especially when BMI history includes multiple time points.

Recent studies have employed an alternative modeling strategy, namely the implementation of semiparametric group-based trajectory models (mixture models) [25–27], to capture latent BMI trajectories throughout the life course. This strategy considers the complex structure of BMI histories by accounting for initial BMI status, and linear and nonlinear trajectories. It can easily take advantage of BMI statuses from multiple time points, avoid arbitrary cutoff points in weight changes, capture the onset and duration of each BMI status, recognize the linkage among these BMI statuses over the life course, and segregate individuals into distinct life history trajectories. These studies, however, have focused either on older [3, 28, 29] or younger populations [30, 31] due to data limitations. To extend these studies, we use the same analytical approach but employ relatively complete cohort data beginning at age 31 from the Framingham Heart Study (FHS) original and offspring cohorts to model life-long BMI trajectories and estimate trajectory-specific mortality risks. This study is the first to examine the association of life-long BMI trajectories with mortality and the first to do this across two generations, which should uncover how BMI evolves over the whole adulthood, provide a more accurate estimate of the mortality consequence of obesity than prior studies, and yield insights on the dynamics of this relationship over time.

Methods

Data

FHS began in 1948 with a sample of adults in Framingham, Massachusetts [32–34]. Beginning in 1971, the children of the original cohort and their spouses were enrolled and constituted the offspring cohort. The original and offspring cohorts are mostly non-Hispanic Whites. Blacks, Hispanics, and other minorities are part of the Omni cohort (506 individuals), which are not included in this analysis. The original cohort consisted of 5079 men and women, 28–74 years of age at the onset of the study. Participants were examined every 2–3 years from 1948 to 2010, for a total of 30 exams. Height and weight were measured at each clinical exam. Participants in the offspring cohort were examined every 3–4 years from 1971 to 2014, for a total of nine exams. However, detailed height and weight information was collected across exams 2–7 (1979–2001) and our analysis was restricted to these six exams. The offspring cohort consisted of 5013 participants, 22–67 years of age at the onset of exam 2, the first study exam used here. After removing individuals with missing data on the key variables, we arrived at a final sample size of 4576 individuals for the original cohort and 3753 individuals for the offspring cohort. Supporting Information 1 provides the descriptive characteristics of the excluded sample, which is generally similar to those included in the study (Table 1).

Due to the small number of observations before age 31 years and in order to remain consistent with the trajectory and survival analysis for both cohorts, we restricted the analysis to observations that were 31 years of age or older. FHS collected information on deaths through newspapers, personal physician communications, or coroner reports. As of 2011, 3913 individuals in the original cohort and 967 individuals in the offspring cohort died. FHS supplied the days since exam 1 as the date of death, allowing us to compute the time spent at risk. For respondents who died, exposure to mortality risk was calculated as the duration from age 31 years until their date of death (in years). For the surviving respondents, we computed exposure to mortality risk as the duration from age 31 years until date of last contact or the last exam these individuals participated in. We reshaped the data to a person-year format left truncated at age 31 years or age at first survey (for those older than age 31 years) and right-censored at the age of death or last survey/contact. The total number of observations for the original and offspring cohort was 44,261 and 19,067, respectively.

Predictors of mortality

BMI trajectory. Due to small sample sizes at very old age, we constructed BMI trajectories between ages 31 and 80 years.

Sociodemographic and behavioral factors. We use education as a proxy for an individual's socioeconomic status, which is negatively associated with BMI and mortality. So, it is a potential confounder in BMI-mortality relationship. Educational attainment consists of four categories: less than high school, high school graduate, some college, and college graduate. Smoking tends to be negatively related to BMI while positively associated with mortality, so it also confounds the BMI-mortality link. Smoking status at each exam is based on the average number of cigarettes respondents smoked per day. It includes four categories: nonsmoker, low smoking (1–9 cigarettes), moderate smoking (10–19 cigarettes), and heavy smoking (20 or more cigarettes). Smoking is treated as a time varying variable. We could not differentiate between never and former smokers because smoking information was collected in every exam and respondents might have smoked before the first exam or in-between while did not smoke at the year of exam. Birth cohorts are controlled because prior studies have reported substantial cohort-based pattern in obesity [37], obesity-related mortality [38], and mortality of all causes [39]. We constructed six categorical birth cohorts for the original cohort (i.e., 1876–1894, 1895–1899, 1900–1904, 1905–1909, 1910–1914, and 1915 and above), and seven for the offspring cohort (i.e., 1903–1924, 1925–1929, 1930–1934, 1935–1939, 1940–1944, 1945–1949, 1950 and above).

Health and medical history. Respondents were examined by teams of doctors and nurses at each exam. They were also asked if they took any medication to treat a health condition and if they were diagnosed with or had any disease. We created a dummy variable to indicate whether the participant had any chronic disease, for example, degenerative arthritis, gouty arthritis, rheumatoid arthritis, asthma or wheezing, prostate trouble, prostate disease, heart disease, hypertension, rheumatic heart disease, hypertensive cardiovascular disease, arrhythmia, aortic disease, mitral valve disease, vascular brain disease, pulmonary disease, gallbladder disease, urinary tract disease, renal disease, neurological disease, or thyroid disease. We also coded the dummy variable as 1 if the participant took medication to treat cardiovascular/heart diseases, arthritis, thyroid disease, or diabetes. We did not create a summary index of diseases because the number of diseases examined changed across exams. Diseases can be the causal pathway linking obesity to mortality but may also confound the BMI-mortality relationship because they are correlated with BMI status and the risk of dying.

Analytical models

We used a semiparametric group-based trajectory model to capture the latent BMI trajectories between ages 31 and 80 years. This model uses a multinomial mixture modeling strategy and identifies relatively homogeneous clusters of trajectories of change

Table 1
Descriptive characteristics of analytic sample, Framingham Heart Study

	N	Mean (or %)		N	Mean (or %)
Original cohort			Offspring cohort		
Time-invariant variables (N = 4576 individuals)			Time-invariant variables (N = 3753 individuals)		
Birth cohorts			Birth cohorts		
1876 to 1894	524	11.45%	1903 to 1924	500	13.32%
1895 to 1899	676	14.77%	1925 to 1929	539	14.36%
1900 to 1904	690	15.08%	1930 to 1934	571	15.21%
1905 to 1909	818	17.88%	1935 to 1939	536	14.28%
1910 to 1914	920	20.10%	1940 to 1944	676	18.01%
1915 and above	948	20.72%	1945 to 1949	555	14.79%
			1950 and above	376	10.02%
Gender			Gender		
Male	2079	45.43%	Male	1813	48.31%
Female	2497	54.57%	Female	1940	51.69%
Educational attainment			Years of education		
Less than high school	1930	42.18%	0–11	292	7.78%
High school graduate	1358	29.68%	12	1293	34.45%
Some college	713	15.58%	13–15	1007	26.83%
College graduate	575	12.57%	16 and above	1161	30.94%
Time-variant variables (N = 44,261 observations)			Time-variant variables (N = 19,067 observations)		
BMI*†	39,736	26.12	BMI*†	18,822	27.01
Body type categories*			Body type categories*		
Underweight‡	601	1.51%	Underweight‡	158	0.84%
Normal weight§	16,428	41.34%	Normal weight§	6860	36.45%
Overweight‖	16,503	41.53%	Overweight‖	7597	40.36%
Class I obesity¶	4941	12.43%	Class I obesity¶	3030	16.10%
Class II/III obesity#	1263	3.18%	Class II/III obesity#	1177	6.25%
Age	44,261	64.73	Age	19,067	53.56
Smoking behavior			Smoking behavior		
Nonsmoker	29,805	67.34%	Nonsmoker	14,680	76.99%
Low smoking (1–9 cigarettes)	2842	6.42%	Low smoking (1–9 cigarettes)	636	3.34%
Moderate smoking (10–19 cigarettes)	3072	6.94%	Moderate smoking (10–19 cigarettes)	770	4.04%
Heavy smoking (20 or more cigarettes)	8542	19.30%	Heavy smoking (20 or more cigarettes)	2981	15.63%
Disease index	44,261	70.20%	Disease index	19,067	80.20%

*Total sample size is different because this variable was constructed using reported BMIs (Original N = 39,736; Offspring N = 18,822).
†Weight (kg)/height(m)^2.
‡Underweight was defined as having less than 18.5 kg/m^2.
§Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m^2.
‖Overweight was defined as having a BMI between 25 and 29.9 kg/m^2.
¶Class I obesity was defined as having a BMI between 30 and 34.9 kg/m^2.
#Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m^2.

over time in the presence of repeated observations on analytic units [35, 36]. Different from other growth curve models (e.g., latent growth curve model, hierarchical growth curve analysis), this model does not remove missing data, but instead includes individuals with missing data at any time point in the modeling procedure, which then mitigates attrition bias. Supporting Information 2 provides the technical details of this model. We used the R lcmm package to estimate the model. As the distribution of BMI was right skewed, we modeled the logarithm of BMI (log(BMI)). We conducted latent class trajectory analysis for the original and offspring cohorts separately to reveal the differences between the cohorts and assess the time/cohort trends. After obtaining the latent trajectories for these two cohorts, we fit a Cox hazard model for each cohort adjusted for sociodemographic, smoking behavior, diseases, and medical history to calculate the relative mortality risk of each trajectory, using attained age as the time metric. Considering time-varying disease characteristics as both potential confounders and mediators, we proceeded by fitting models both with and without adjustment for these factors. After obtaining the hazard ratios (HRs) of death associated with BMI trajectories, we calculated the population attributable mortality risk fraction (Supporting Information 3 provides the technical details). Overall patterns were similar by gender despite small difference in the number of individuals in each trajectory and the size of coefficient estimate of the effect of each trajectory on mortality. For this reason and for the sake of space, we report the findings for whole sample without breaking down gender.

Results

Table 1 shows the descriptive statistics. Compared to the original cohort, the offspring cohort has a smaller proportion of observations that are smokers, but a larger proportion of observations that have any disease. We define four BMI groups using World Health Organization classifications: normal (BMI of 18.5–24.9 kg/m^2), overweight (BMI of 25–29.9 kg/m^2), class I obese (BMI of 30–34.9 kg/m^2), and class II/III obese (BMI greater than or equal to 35 kg/m^2). The proportion of observations that are class I obesity and class II/III obesity increases from 12.45% to 16.10%, 3.18% to 6.25%, respectively, from the original to offspring cohort.

For the original cohort, seven quadratic latent trajectories best fit the data as shown in Figure 1 (Supporting Information 4–7 describe the model selection). Since we model the trajectories based on log(BMI), we back-transform the trajectories to the original scale for presentation purpose. The topmost trajectory (open triangles, 1.88% of the sample) starts with class I obesity at age 31 years (BMI = 34.31 kg/m^2) and increases to a BMI of approximately 40.37 kg/m^2 at age 60. From this point onward, the trajectory decreases slightly. We call this the “class II/III obese” trajectory. The trajectory marked by solid circles (8.35% of the sample) starts with an overweight status at age 31 years (BMI = 29.21 kg/m^2) and increases to the class I obese status. We call this trajectory “class I obese.” The next trajectory marked by open circles (20.89% of the sample) starts with a BMI of 26.27 kg/m^2 and slowly increases, but it remains within the overweight category by

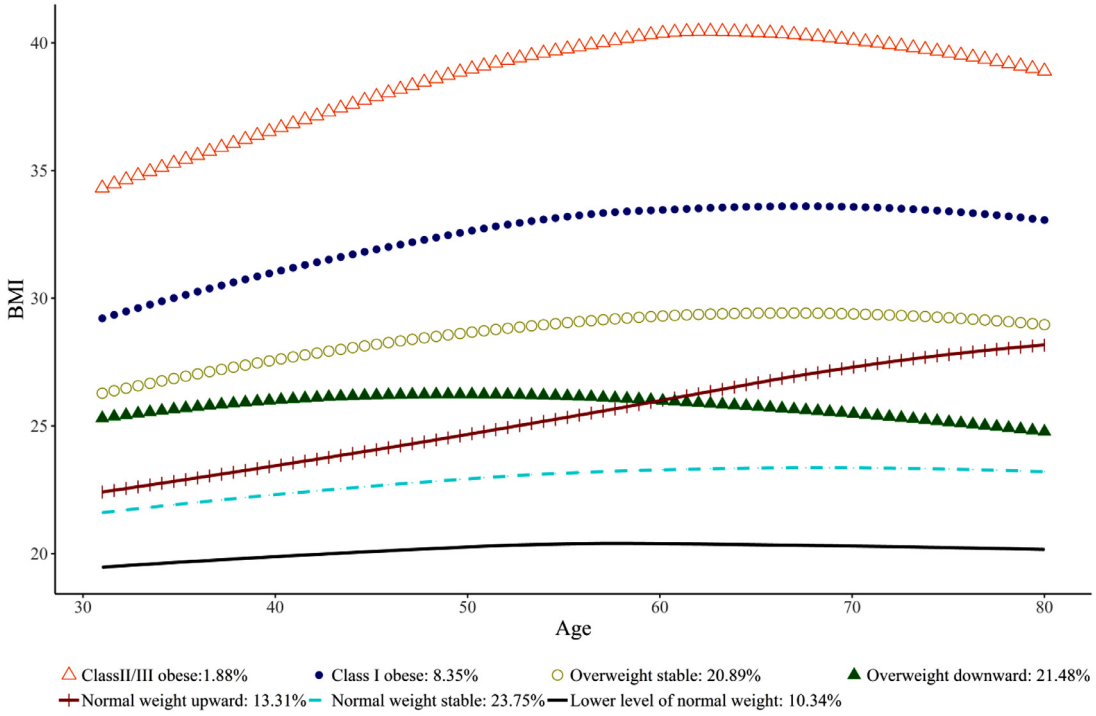

Fig. 1. Seven latent BMI trajectories from 31 to 80 years of age in the Framingham Heart Study original cohort 1948–2010.

age 80 years. We refer to this category as the "overweight stable." The trajectory marked by closed triangles (21.48% of the sample) starts with a BMI of 25.90 kg/m^2 at age 31 years but gradually decreases by age 80. We refer to this trajectory as "overweight downward." Although we label it as an "overweight downward" trajectory, it can be understood as a general downward trajectory as "overweight" is the expected mean value for initial BMI for this trajectory and may include a range of BMIs. The trajectory marked by plus signs (13.31% individuals) starts with a normal weight status (BMI = 22.41 kg/m^2) and increases to an overweight status around age 55 years. We call this trajectory "normal weight upward." The trajectory marked by a dashed line (23.75% individuals) starts with a BMI of 21.60 kg/m^2 and remains in normal weight up to age 80 years. We call this trajectory "normal weight stable." The bottommost trajectory (solid line, 10.34% of the sample) starts with a BMI of 19.47 kg/m^2. We refer to it as "lower level of normal weight."

For the offspring cohort, six quadratic latent trajectories best fit the data (Fig. 2). Overall pattern is similar to the original cohort with five differences. First, no downward trajectories are identified, which may be because the number of individuals with weight loss is too small to be captured in the model. Second, most trajectories in the offspring cohort slowly increase from age 31 to 80 years, while the upward trajectories in the original cohort start declining around age 60 years. Third, "normal weight upward" trajectory advances to overweight status at relatively younger age (age 45 years) in the offspring cohort compared to the corresponding trajectory in the original cohort. Fourth, different from "overweight stable" in the original cohort, we identify an "overweight obesity" trajectory in the offspring cohort. This trajectory starts with overweight at age 31 years and advances to obesity around age 60. Fifth, the proportion of the sample in higher BMI trajectories systematically increases from the original to the offspring cohort.

Next, we estimate the mortality hazards associated with these trajectories from a Cox model with "normal weight upward" as the reference group. Table 2 presents the results for the original cohort (Supporting Information 8 shows the complete table). After adjusting for birth cohort and gender, the highest mortality risk is for class II/III obese trajectory (HR = 2.15, 95% confidence interval [CI] = 1.72–2.69), followed by class I obese (HR = 1.56, 95% CI = 1.35–1.80). The lower level of normal weight trajectory is associated with a 48% (95% CI = 1.30–1.68) increase in the mortality risk. Overweight downward, overweight stable, and normal weight stable are associated with 37% (95% CI = 1.23–1.53), 32% (95% CI = 1.18–1.47), and 19% (95% CI = 1.07–1.32) increase in mortality risk, respectively. After further adjusting for educational attainment and smoking behavior, class II/III upward trajectory continues to be associated with the highest mortality risk (HR = 2.18, 95% CI = 1.69–2.82), followed by class I obese upward (HR = 1.58, 95% CI = 1.36–1.82), overweight downward (HR = 1.37, 95% CI = 1.23–1.53), lower level of normal weight (HR = 1.37, 95% CI = 1.20–1.56), overweight stable (HR = 1.34, 95% CI = 1.20–1.49), and normal weight stable (HR = 1.17, 95% CI = 1.06–1.30). In the final model that adjusts for disease index, the associations between obesity trajectories and mortality slightly weaken but remain in the same direction, which is because comorbidity profiles are more presented in these trajectories (Supporting Information 9).

Table 3 presents the adjusted HRs of the offspring cohort's BMI trajectories with the "normal weight upward" trajectory as the reference group (Supporting Information 10 shows the complete table). After adjusting for birth cohort, gender, education and smoking, class II/III obesity trajectory is associated with an 80% (95% CI = 1.21–2.64) increase in mortality risk, followed by class I obesity trajectory (HR = 1.43, 95% CI = 1.15–1.77), lower level of normal weight (HR = 1.24, 95% CI = 0.97, 1.59), normal weight stable (HR = 1.04, 95% CI = 0.88, 1.24), and overweight obesity (HR = 1.01, 95% CI = 0.84, 1.21). Compared to the original cohort, mortality risks associated with obesity trajectories have declined. In the fully adjusted model with disease index included, overall patterns remain the same.

Finally, we calculate the population attributable mortality risk fraction using HRs from the model adjusted for birth cohorts, gender, educational attainment, and smoking behavior. The mortality risk attributable to obese trajectories for the original cohort is 5.4%,

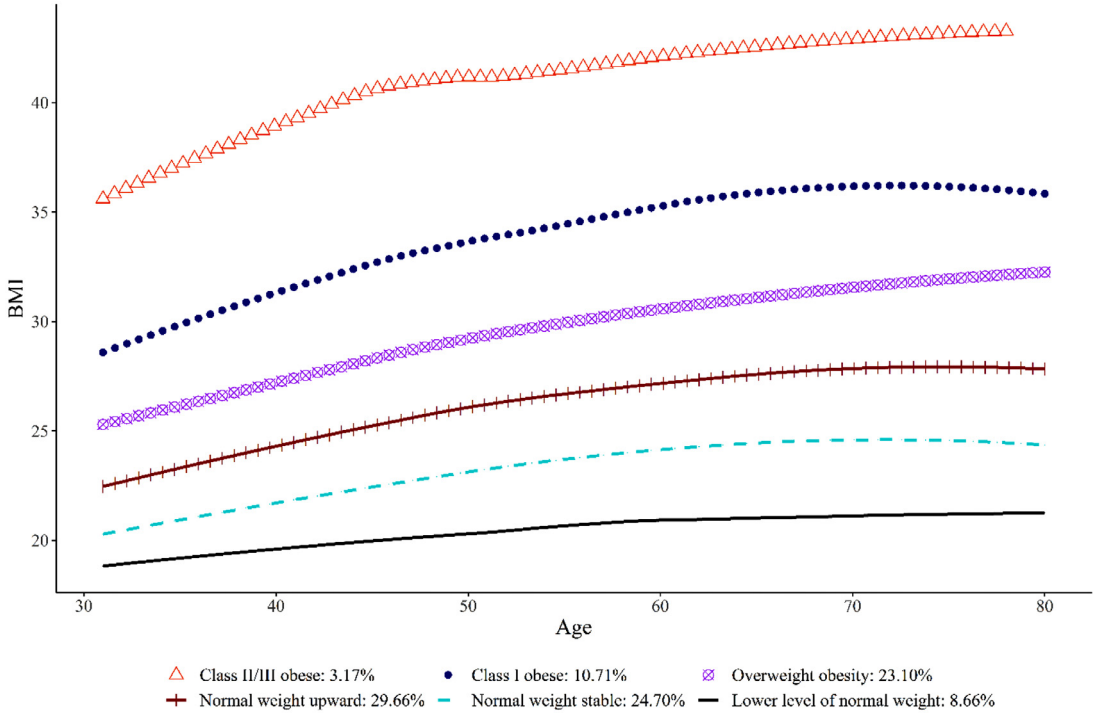

Fig. 2. Six latent BMI trajectories from 31 to 80 years of age in the Framingham Heart Study offspring cohort 1979–2001.

Table 2
Adjusted hazard ratios of BMI trajectories (ages 31–80) from Cox hazard models in Framingham Heart Study original cohort 1948–2010

	Number of persons	Number of deaths	Birth cohorts and gender adjusted HR (95% CI)	Education adjusted* HR (95% CI)	Behavioral factors adjusted† HR (95% CI)	Fully adjusted‡ HR (95% CI)
Body mass index trajectories						
Lower level of normal§ weight	473	404	1.48 (1.30, 1.68)	1.49 (1.31, 1.70)	1.37 (1.20, 1.56)	1.40 (1.23, 1.60)
Normal weight§ stable	1087	928	1.19 (1.07, 1.32)	1.21 (1.09, 1.34)	1.17 (1.06, 1.30)	1.19 (1.07, 1.32)
Normal weight§ upward	609	499	1.00	1.00	1.00	1.00
Overweight‖ downward	983	849	1.37 (1.23, 1.53)	1.38 (1.24, 1.54)	1.37 (1.23, 1.53)	1.38 (1.24, 1.53)
Overweight‖ stable	956	833	1.32 (1.18, 1.47)	1.32 (1.18, 1.46)	1.34 (1.20, 1.49)	1.34 (1.20, 1.49)
Class I obese¶	382	323	1.56 (1.35, 1.80)	1.53 (1.33, 1.77)	1.58 (1.36, 1.82)	1.55 (1.34, 1.79)
Class II/III obese#	86	77	2.15 (1.72, 2.69)	2.11 (1.68, 2.64)	2.18 (1.69, 2.82)	2.11 (1.63, 2.73)
AIC			56,589.88	56,581.22	56,446.30	56,397.36
BIC			56,665.15	56,675.30	56,559.20	56,516.53
Observations			44,261	44,261	44,261	44,261

*Adjusted for birth cohorts, gender, and education.
†Adjusted for birth cohorts, gender, education, and smoking behavior.
‡Adjusted for birth cohorts, gender, education, smoking behavior, and disease index.
§Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m².
‖Overweight was defined as having a BMI between 25 and 29.9 kg/m².
¶Class I obesity was defined as having a BMI between 30 and 34.9 kg/m².
#Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m².

but it rises to 6.4% for the offspring cohort. This increase in mortality attributable to obesity is a result of more individuals being in the high-risk trajectories, and this more than offsets the declining risk for specific trajectories.

Discussion

Using relatively complete cohort data from the FHS original and offspring cohorts, we uncover the heterogeneity in life-long BMI trajectories across generations and estimate their associated mortality risks. We identify seven major trajectories among the original cohort including a downward trajectory, which is not identified in the offspring cohort. The overall trajectory patterns are similar between these two cohorts with some notable exceptions. First, the trajectories in the offspring cohort tend to shift upward at earlier ages relative to the original cohort. Second, the proportion of the sample in higher BMI trajectories is higher in the offspring cohort compared to the original cohort. Third, individuals in the higher weight trajectories experienced weight loss on average in the original cohort while this decline is less visible among the offspring cohort. The decline may be a result of diseased-induced weight loss, which may be better prevented and treated among the offspring cohort [40]. This diseases-induced weight loss does not cause misclassification of BMI trajectory as it may have done to static BMI status (i.e., normal weight group increasingly contains frail individuals over ages). In fact, these distinct trajectories are primarily determined by their baseline BMI status [41] and weight loss is captured within each trajectory. If weight loss has affected a good number of individuals since early adulthood, latent trajectory model can identify this group of individuals as a distinct trajectory (Fig. 1).

Table 3
Adjusted hazard ratios of BMI trajectories (ages 31–80) from Cox hazard models in Framingham Heart Study offspring cohort 1979–2001

	Number of persons	Number of deaths	Birth cohorts and gender adjusted HR (95% CI)	Education adjusted* HR (95% CI)	Behavioral factors adjusted† HR (95% CI)	Fully adjusted‡ HR (95% CI)
Body mass index trajectories						
Lower level of normal weight§	325	98	1.36 (1.07, 1.73)	1.43 (1.13, 1.83)	1.24 (0.97, 1.59)	1.26 (0.99, 1.61)
Normal weight§ stable	927	251	1.05 (0.89, 1.25)	1.09 (0.92, 1.30)	1.04 (0.88, 1.24)	1.05 (0.89, 1.25)
Normal weight§ upward	1113	293	1.00	1.00	1.00	1.00
Overweight‖ obesity	867	194	1.01 (0.84, 1.21)	1.02 (0.85, 1.22)	1.01 (0.84, 1.21)	1.00 (0.84, 1.20)
Class I obese¶	402	105	1.47 (1.19, 1.82)	1.42 (1.14, 1.76)	1.43 (1.15, 1.77)	1.41 (1.14, 1.75)
Class II/III obese#	119	26	1.84 (1.24, 2.74)	1.70 (1.14, 2.55)	1.79 (1.21, 2.64)	1.71 (1.16, 2.54)
AIC			13,858.68	13,828.27	13,713.75	13,703.77
BIC			13,917.17	13,901.38	13,801.49	13,796.38
Observations			19,067	19,067	19,067	19,067

*Adjusted for birth cohorts, gender, and education.
†Adjusted for birth cohorts, gender, education, and smoking behavior.
‡Adjusted for birth cohorts, gender, education, smoking behavior, and disease index.
§Normal weight was defined as having a BMI between 18.5 and 24.9 kg/m^2.
‖Overweight was defined as having a BMI between 25 and 29.9 kg/m^2.
¶Class I obesity was defined as having a BMI between 30 and 34.9 kg/m^2.
#Class II/III obesity was defined as having a BMI greater than or equal to 35 kg/m^2.

Among original cohort, people who are normal weight at age 31 years and gradually move to overweight status in middle or later adulthood have the lowest mortality risk even compared to those who maintain normal weight status throughout adulthood, followed by overweight stable, lower level of normal weight, overweight downward, class I obese upward and class II/III upward trajectories. Overall mortality patterns of these BMI trajectories are similar for offspring cohort except that some trajectories lose statistical significance (e.g., normal weight stable, overweight upward trajectory), which is probably due to smaller number of deaths. As of 2011, 3913 out of 4576 individuals in the original cohort died while only 967 out of 3753 individuals in the offspring cohort died. The overweight and obesity trajectories are more predictive of mortality than alternative measures of BMI history, including initial BMI status, maximum BMI, and BMI duration (Supporting Information 11), which further substantiates the utility of examining BMI trajectories.

This study complements a prior study that finds in later adulthood, people who started with overweight at age 51 years and remained in that status until age 77 had the lowest mortality risk [3]. Together, they implicate the complexity in the relationship between weight gain and mortality risk. Prior studies have recognized that the impact of weight gain depends on baseline BMI status [24] and magnitude of weight gain [4, 5, 9]. Our study further suggests that it depends on the timing of weight gain and its interaction with these two factors. For people with normal weight in early adulthood, moderate weight gain into overweight in later adulthood is associated with lower mortality risks compared to those who remain in the range of normal weight over the course of adulthood. But, for people with overweight or obesity status in early adulthood, weight gain is associated with excessive mortality risk.

Combination of these two important findings leads to a key implication: the impact of weight gain among overweight people in later adulthood depends on their baseline weight status in the early adulthood. If they were normal weight in early adulthood, a modest weight gain within the overweight range in later adulthood is beneficial for their survival [3]; but if they were already overweight in early adulthood, additional weight gain only brings extra harms. Moderate weight gain among those who are normal weight in early adulthood may confer some survival benefits, which is consistent with the view that modest extra body weight in old ages, including lean tissue mass and fat mass, might provide protection against nutritional and energy deficiencies, metabolic stresses, the development of wasting and frailty, and loss of muscle and bone density caused by chronic diseases such as heart failure [42–44]. But future research should continue this endeavor and fully explain this phenomenon.

Obesity upward trajectories have the highest mortality risks. Class I obesity upward and class II/III obesity upward trajectories in the original cohort are associated with 58% and 118% increases in mortality risk, respectively, without controlling for health factors. Among the offspring cohort, mortality risks associated with these two trajectories have declined to 43% and 80%, respectively. These declining mortality risks are not due to the change in reference group. For the same normal weight upward trajectory, the offspring cohort experiences a lower mortality risk compared to the original cohort (Supporting Information 12 shows the Cox models of the original and offspring cohorts combined). These findings are consistent with a prior study that has found a secular decline in the association between obesity and mortality in the United States [45].

This study has several limitations. First, FHS sample is rather homogeneous (i.e., Whites and within same families in one town). The advantage of the homogeneity of the sample is that it allows us to better mitigate any unmeasured confounding and better isolate the secular effects that may be influencing the obesity-mortality association over time in an epidemiological sample. The disadvantage concerns the representativeness of our sample and application of the findings to other racial groups. But FHS is the only U.S. data that has a long prospective follow-up on BMI and mortality. Therefore, replicating the analyses for other racial groups is not feasible at this point. Second, FHS original cohort and offspring cohort each comprise of a wide swath of birth cohorts with some overlap. But since the overlap in birth cohorts between original and offspring is small, the overall pattern across these two FHS cohorts can still portray a relatively clear cohort trend. Third, even though the latent trajectory model is a straightforward tool to uncover the underlying structure of developmental trajectories in the population, one caveat of this model is that the assignment of individuals to a distinct developmental pattern is based on their highest estimated group-membership probability to the identified pattern. Therefore, these latent patterns should not be considered as the actual developmental patterns but, rather, as approximations of more complex processes.

Fourth, we find that in the original cohort people in the weight loss trajectory face 37% increase in mortality risk compared to those in the normal weight upward trajectory, but we cannot dif-

ferentiate intentional weight loss from diseases-induced weight loss. However, prior studies have found that intentional weight loss has not always been observed to have putative beneficial effects on mortality [46–48]. Moreover, we have controlled for an age-varying disease index thereby reducing some of the confounding role of disease-induced weight loss. Fifth, we are unable to control for all confounding factors. To minimize potential confounding due to smoking, we constrained the sample to those who were nonsmokers at all waves and found the deleterious effects of overweight and obesity trajectories became greater (Supporting Information 13 and 14). This finding is especially salient for the original cohort because a larger proportion of that cohort was smokers. We could not conduct similar sensitivity analyses for those without any disease at all waves as the resulting sample is very small (259 individuals in original cohort and 10 individuals in offspring cohort). Moreover, as diseases are potentially the pathways from obesity to death especially in old age, such analysis controls away some of the risk of dying. Sixth, we did not conduct a detailed cause-specific hazard analysis because of the limited number of deaths in the offspring cohort. Supporting Information 15 and 16 show preliminary cause-specific results for cardiovascular disease and cancer. Obesity trajectories were linked to cardiovascular disease deaths but not deaths from cancer.

Improving upon prior studies, this study reveals the heterogeneity and mortality risk of life-long BMI trajectories across two related generations. We find that people in the normal weight upward trajectory have the lowest mortality risk, followed by normal weight stable, overweight stable/upward, lower level of normal weight, overweight downward (original cohort only), class I obese upward and class II/III upward trajectories. We further reveal the dynamics in the obesity—mortality relationship across generations. Even though the mortality risks associated with obesity trajectories have declined across cohorts, their contributions to population deaths increased from 5.4% in the original cohort to 6.4% in the offspring cohort due to the increasing proportion of individuals in these trajectories. These contributions are smaller than those found in younger birth cohorts [3]. These findings should have a broad implication on the current obesity epidemic in the United States, which should observe more obesity-related deaths at the population level in the years to come even though the mortality risk due to obesity has declined at the individual level.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2021.01.003.

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