BMI Trajectory In Relation to Cause-Specific Mortality In Taiwan's Adult Population.

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Research

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Abstract

Background: A dynamic change in weight over time has been known as an important factor that impacts mortality risk. However, it is currently unknown how the dynamic change of body mass index (BMI) contributes to the cause-specific mortality risk.

Methods: In this cohort study, we obtained data from a large prospective cohort study in Taiwan between 1998 and 2019, which was linked to National Death Registry for death information. The database accumulated 290,279 participants who were born before 1977. We excluded those who were less than 40 years old at 1998 (n=51,731), less than two waves follow-up (n=145,270), and who had ever been diagnosed at baseline with any of the following self-reported conditions: cancer, stroke (n=3392) with a final 89,886 participants.

Results: This study shows that different trajectories are associated with mortality suggests that the mortality risk differs in each trajectory group and in each age and gender stratification. It appears that obesity is a protective factor in cancer-related mortality in females but not in males in the group of old age; low-normal weight is a risk factor in respiratory-related mortality in all participants.

Conclusions: Our findings can be used to define the appropriate BMI in each age and gender groups and thereby earlier health interventions can be taken to avoid mortality.

Background

A dynamic change in weight over time has been known as an important factor of mortality risk, especially among older adults(1). BMI trajectory studies can highlight the importance of initial weight status and the amount of weight gain in relation to mortality. In a study that examined BMI trajectory in an elder adult sample in the United States (US), small weight gain was not associated with increasing mortality risk, regardless of the initial BMI; however, when the initial BMI was greater than 35, a large weight gain increased mortality risk(2). However, most of the trajectory studies focused on all-cause mortality. It is important to investigate different causes of death among groups of different weight because cancer and cardiovascular disease (CVD) death may be related to BMI(3, 4).

The association between change of BMI and mortality risk has been reported as a “reverse J shape” since underweight and obesity were associated with increased mortality risk(5). Overweight, however, was sometimes found to have a protective effect among the elderly, which was known as the “obesity paradox”(6–8). Overweight groups had the lowest risk of death in both Japanese and Western populations(5). In several US samples, the association differed by the amount of weight change. Modest weight gains were associated with a significantly decreased mortality risk, whereas excessive weight gains predicted a significantly increased mortality risk(5). The literature regarding the obesity paradox was not consistent. Some studies presented evidence against this phenomenon(9) and considered it to be a phenomenon of reverse causality that low BMI populations may incur illnesses such as cancer or severe infection.

All of the previous research mixed different ages into one population group; however, differences in physiological statuses, patterns of weight change, and causes of death were found in different age groups(10). Also, very few of the studies focused on Asian populations, and some found gender differences on this issue. Since males and females have differences in hormones, body composition and incidence of various diseases, our study emphasizes the gender differences.

To better access the threat of weight pattern changes over time, it is essential to examine the all-cause and cause-specific mortality risk consequences of BMI trajectories. Identification of cause-specific mortality risk in different BMI trajectories can facilitate our understanding of the details behind the “obesity paradox.” The present study has two specific aims: First, we applied group-based trajectory models to obtain the heterogeneity of the BMI trajectory throughout eighteen years in adulthood by gender and age groups among Taiwanese adults; second, we examined the relationship between the trajectories of BMI and all-cause and cause-specific mortality.

Method

Participants

This research was conducted using the Taiwan MJ cohort resource—a longitudinal, population-based health dataset run by the MJ Health Management Institution, Taiwan(11). The details of the MJ cohort population and data collection are reported elsewhere(12–15). Briefly, the MJ cohort has enrolled about 600,000 Taiwanese individuals since 1994.

Participants
in the MJ cohort were healthy individuals who received health examinations including a self-reported questionnaire on medical, social and family history as well as demographic information and underwent a series of medical tests and physical examinations.

The details of participant selection for the present study are shown in Fig.
1. The database accumulated 290,279 participants who were born before 1977 and were first included in the MJ cohort between 1998 and 2006. We obtained all of the included participants’ data that had been collected from the year they were first included in MJ cohort to year 2017. Setting three years as an interval, we built a 7-wave longitudinal dataset (The interval of seventh wave has only 2 years, 2016–2017). If two or more measurements for one person were accessible within one interval, the measurement closest to the center of the interval was chosen. We excluded those who were less than 40 years old at 1998 (n = 51,731), less than two waves follow-up (n = 145,270), and who had ever been diagnosed at baseline with any of the following self-reported conditions: cancer, stroke (n = 3392). The final study sample included 89,886 participants.

Figure 1 Patient attrition and cohort selection. Inclusion and exclusion criteria show cohort selection for the MJ cohort dataset.</fig>

Death information was based on the National Death Registry obtained from the Ministry of Health and Welfare, Taiwan, and was linked to the MJ cohort. All deaths were identified from death certificates and confirmed by trained physicians. Follow-up time for mortality started at the date of each participant's first measurement and was censored by October 31, 2019, the date when we linked death information to the MJ cohort. We categorized the cause of mortality into three leading causes: "cancer" (including all kinds of cancer), "cardiovascular disease", and "respiratory disease." All other causes of death were grouped into the category "Other."

Outcome measures

This analysis focused on three separate outcome measures: (1) change of BMI across time, (2) hazard of all-cause mortality in distinct groups, and (3) hazard of cause-specific mortality in distinct groups.

Exposure

Body height and weight for each participant were measured at every follow-up visit and BMI was calculated.
According to the BMI classification by the World Health Organization (WHO), BMI above 30 should be classified as obesity, BMI between 25 and 30 should be classified as overweight, and BMI below 18.5 should be classified as underweight(16).

Covariate variables

Age, smoking status, alcohol consumption, educational level, and physical activity at baseline were obtained from the self-reported questionnaire from the MJ cohort and were incorporated as covariates in the present study. Age was defined at the year of 1998. Smoking status and alcohol consumption were both classified into three categories: never smoker/drinker, former smoker/drinker, and current smoker/drinker. Educational level was classified into two categories: high school or less, and college or above. Physical activity was classified into three categories: seldom (exercise less than two hours a week), sometimes (exercise between two and five hours a week) and frequent (exercise more than five hours a week).

Statistical Methods

We separated the participants into 4 groups by gender (male or female) and age (40 to 60-year-old and more than 60 years old).
Descriptive statistics (mean, standard deviation, and percentages) were used to summarize the participants' demographic and clinical characteristics. We used a group-based trajectory model with maximum likelihood estimation to identify distinct trajectories of changes in BMI(17) using the SAS PROC TRAJ program (SAS Institute, Inc., Cary, North Carolina). As recommended, we estimated models with 2–5 trajectories by assuming linear, quadratic, and cubic patterns of change in BMI over time; the best-fitting model (the number of distinct trajectories and the patterns of change in BMI) was determined on the basis of Bayesian Information Criterion (BIC) scores(18).

The hazard ratio (HR) of all-cause mortality was analyzed using a Cox proportional hazards model, including BMI trajectory groups, and covariates (age, smoking status, alcohol consumption, educational level and physical activity). In this study, the time from baseline was used as the time scale to parameterize the baseline hazard function(19) because different birth cohorts were observed at different ages. The analyses were performed using the SAS PROC PHREG program.

A cause-specific hazards model was used to assess the HR of cause-specific mortality. This model can be estimated by censoring participants with the competing event and then fitting the standard Cox proportional hazards model(20). The analyses were performed using the SAS PROC PHREG program.

Results

Of all 89,886 participants, 53.3% were female, 82.5% were aged between 40 and 60 (Table 1). Mean age was 55.2 and mean BMI was 24.1.

The mean follow-up time was 16.8 years: 14.2 years for participants aged over 60 and 17.3 years for participants aged between 40 and 60.
A quarter of participants had a college degree, but a much lower proportion of women aged over 60 had a college degree (3.8%).
In terms of lifestyle factors, women were more likely to be never smokers or never drinkers, regardless of age groups. Overall, 38.3% had a seldom level of physical activity, 18.6% were sometimes and 35.5% were frequent.

Table 1
Baseline characteristics by subgroups and classified by gender and age

	Males aged over 60	Males aged 40–60	Females aged over 60	Females aged 40–60
People count	8,140	33,790	7,621	40,335
Age, mean(SD), years	70.1 (5.3)	51.9 (6.5)	69.5 (5.3)	52.3 (6.2)
Person-year, mean(SD), years	14.2 (5.4)	17.2 (3.6)	15.5 (4.9)	17.4 (3.3)
Number of death	4498	3987	3100	2863
Cancer(%)	1,366 (30.4)	1,805 (45.3)	813 (26.2)	1,437 (50.2)
Cardiovascular disease(%)	1,062 (23.6)	748 (18.8)	801 (25.8)	438 (15.3)
Respiratory disease(%)	652 (14.5)	197 (4.9)	286 (9.2)	110 (3.8)
Others(%)	1,418 (31.5)	1,237 (31)	1,200 (38.7)	878 (30.7)
BMI, mean(SD), kg/m^2	23.7 (3.1)	24.4 (3.0)	24.6 (3.5)	23.7 (3.4)
Smoking status, number(%)				
Never	3,504 (43)	15,611 (46.2)	6,893 (90.4)	36,416 (90.3)
Former	1,648 (20.2)	4,114 (12.2)	111 (1.5)	312 (0.8)
Current	2,535 (31.1)	12,351 (36.6)	215 (2.8)	1475 (3.7)
Missing data	453 (5.6)	1,714 (5.1)	402 (5.3)	2132 (5.3)
Alcohol consumption, number(%)				
Never	4,546 (55.8)	18,526 (54.8)	6,459 (84.8)	32,556 (80.7)
Former	886 (10.9)	2,058 (6.1)	97 (1.3)	629 (1.6)
Current	1,981 (24.3)	1,077 (31.9)	189 (2.5)	2,254 (5.6)
Missing data	727 (8.9)	2,431 (7.2)	876 (11.5)	4,896 (12.1)
Education level, number(%)				
High school or less	6,046 (74.3)	18,720 (55.4)	6,950 (91.2)	31,500 (78.1)
College or above	1,604 (19.7)	13,487 (39.9)	288 (3.8)	7,088 (17.6)
Missing data	490 (6)	1,583 (4.7)	383 (5)	1,747 (4.3)

	Males aged over 60	Males aged 40–60	Females aged over 60	Females aged 40–60
Physical activity, number(%)				
Seldom	2,372 (29.1)	12,370 (36.6)	2,612 (34.3)	17,065 (42.3)
Sometimes	1,113 (13.7)	6,798 (20.1)	1,201 (15.8)	7,631 (18.9)
Frequent	3,952 (48.6)	11,983 (35.5)	3,243 (42.6)	12,526 (31.1)
Missing data	703 (8.6)	2,639 (7.8)	565 (7.4)	3,113 (7.7)

As shown in Table 1, 14,448 participants (16.1%) died during follow-up; the majority of deaths were caused by cancer (37.5%), followed by others (32.7%), CVD (21.1%), and respiratory disease (8.6%). Both males and females in the 40–60 age group had a higher proportion of cancer deaths than their counterparts in the 60 or above age group (Male: 45.3% [aged 40–60] vs. 30.4% [aged over 60]; female: 50.2% [aged 40–60] vs. 26.2% [aged over 60]).

In the trajectory analysis, of the four groups, each was identified by four trajectory groups based on BIC. In Table 2, we presented the intercept, slope and group membership for each trajectory group by age and gender. Figure 2a to Fig. 2d illustrate the trajectories of BMI in four distinct groups derived from group-based trajectory models; solid lines indicate the mean values of BMI. We differentiated the four trajectory groups as obesity, overweight, mid-normal weight, and low-normal weight based on the intercept displayed in Table 2. The linear slope was used to differentiate a stable or increasing trend. Mid-normal weight, regardless of a stable or increasing trend, was the largest trajectory group for each age and gender group: 42.7%-47.2% (Table 2). Obesity was the smallest trajectory group, but still comprised 4.4%-7.3% of the study population. The second largest trajectory group was the overweight group, except for females aged 40–60, in which low-normal weight was the second largest group.

Table 2
Estimates of growth curve parameters for body mass index trajectories

Male aged over 60	**Intercept, kg/m^2**		**Linear Slope, kg/m^2**		**Group membership, %**
	Estimate	**95% CI**	**Estimate**	**95% CI**	
Obesity, stable	30.1	26.5, 33.7	0.001	-0.029, 0.031	7.3
Overweight, stable	25.9	23.6, 28.2	0.01	-0.004, 0.023	36.1
Mid-normal weight, stable	22.5	20.2, 24.7	-0.007	-0.02, 0.006	42.7
Low-normal weight, stable	18.8	16.2, 21.4	0.008	-0.016, 0.031	13.9
Males aged 40–60	Intercept, kg/m^2		Linear Slope, kg/m^2		Group membership, %
	Estimate	95% CI	Estimate	95% CI	
Obesity, increasing	31.1	27.1, 35.0	0.026	0.014, 0.038	6.1
Overweight, increasing	26.7	24.4, 29.0	0.035	0.03, 0.041	31.5
Mid-normal weight, increasing	23.5	21.2, 25.7	0.025	0.021, 0.029	46.6
Low-normal weight, increasing	19.9	17.4, 22.5	0.031	0.024, 0.038	15.7
Females aged over 60	Intercept, kg/m^2		Linear Slope, kg/m^2		Group membership, %
	Estimate	95% CI	Estimate	95% CI	
Obesity, increasing	32.7	28.4, 36.9	0.043	0.004, 0.082	5.8
Overweight, stable	27.6	24.9, 30.3	0.018	-0.002, 0.039	28.1
Mid-normal weight, stable	23.7	21.2, 26.3	0.0002	-0.015, 0.016	47.2
Low-normal weight, stable	19.8	16.9, 22.8	-0.017	-0.048, 0.006	18.9
Female aged 40–60	Intercept, kg/m^2		Linear Slope, kg/m^2		Group membership, %
	Estimate	95% CI	Estimate	95% CI	
Obesity, increasing	32.5	27.7, 37.3	0.079	0.064, 0.095	4.4

Male aged over 60	Intercept, kg/m^2		Linear Slope, kg/m^2		Group membership, %
	Estimate	95% CI	Estimate	95% CI	
Overweight, increasing	27.3	24.6, 30.1	0.051	0.044, 0.058	21.9
Mid-normal weight, increasing	23.6	21.2, 25.9	0.032	0.027, 0.037	44
Low-normal weight, increasing	20.2	17.8, 22.7	0.012	0.007, 0.018	29.7
Abbreviations : CI, confidence interval					

HRs for overall mortality are displayed in Table 3 using the “mid-normal weight” trajectory group as the referent. Model 1 represents the model without any adjustment whereas model 2 was fully adjusted for age, educational level, smoking status, alcohol consumption and physical activity. Regardless of age and gender, the obesity group had the highest adjusted HR (aHR) (Male aged over 60: aHR = 1.26[Confidence interval (CI) = 1.12–1.42]; Male aged 40–60: aHR = 1.40[CI = 1.24–1.58]; Female aged over 60: aHR = 1.24[CI = 1.06–1.45]; Female aged 40–60: aHR = 1.33[CI = 1.14–1.57]). For males aged over 60, overweight was a protective factor in the unadjusted model (HR = 0.93, 95%CI = 0.87–0.99), but the significant effect disappeared after adjusting for lifestyle factors, age and education. Low-normal weight was significantly associated with mortality for all age and gender groups, except for females aged 40–60.

Table 3
Association between body mass index trajectories and all-cause mortality

Male aged over 60	**Death, number of death/number of total participants %**	**Model 1[a]**		**Model 2[b]**	
		HR	**95% CI**	**HR**	**95% CI**
Obesity, stable	324/549, 59%	1.14*	1.01, 1.28	1.26***	1.12, 1.42
Overweight, stable	1,544/2,958, 52%	0.93*	0.87, 0.99	0.98	0.91, 1.04
Mid-normal weight, stable	1,947/3,582, 54%	1	referent	1	referent
Low-normal weight, stable	683/1,057, 65%	1.31***	1.20, 1.43	1.21***	1.11, 1.32
Males aged 40–60	Death, number of death/ number of total participants %	Model 1[a]		Model 2[b]	
		HR	95% CI	HR	95% CI
Obesity, increasing	298/1,983, 15%	1.46***	1.29, 1.65	1.40***	1.24, 1.58
Overweight, increasing	1,255/10,557, 12%	1.11**	1.03, 1.20	1.11**	1.04, 1.20
Mid-normal weight, increasing	1,754/10,357, 17%	1	referent	1	referent
Low-normal weight, increasing	680/4,943, 14%	1.30***	1.19, 1.42	1.21***	1.11, 1.32
Females aged over 60	Death, number of death/ number of total participants %	Model 1[a]		Model 2[b]	
		HR	95% CI	HR	95% CI
Obesity, stable	180/417, 43%	1.16	0.99, 1.35	1.24**	1.06, 1.45
Overweight, stable	867/2,089, 42%	1.10**	1.01, 1.20	1.02	0.93, 1.11
Mid-normal weight, stable	1,455/3,785, 38%	1	referent	1	referent
Low-normal weight, decreasing	598/1,330, 45%	1.24***	1.13, 1.37	1.15**	1.04, 1.26
Females aged 40–60	Death, number of death/ number of total participants %	Model 1[a]		Model 2[b]	
		HR	95% CI	HR	95% CI
Obesity, increasing	170/1,710, 10%	1.53***	1.30, 1.80	1.33**	1.14, 1.57

Male aged over 60	Death, number of death/number of total participants %	Model 1[a]		Model 2[b]	
		HR	95% CI	HR	95% CI
Overweight, increasing	760/8,641, 9%	1.32***	1.21, 1.45	1.16**	1.06, 1.27
Mid-normal weight, increasing	1,232/18,273, 7%	1	referent	1	referent
Low-normal weight, increasing	701/11,711, 6%	0.88**	0.80, 0.96	1.05	0.96, 1.15

Abbreviations : CI, confidence interval;HR, Hazard ratio

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$

[a]Unadjusted model

[b]Fully adjusted model: adjusted for age, educational level, smoking status, alcohol consumption and physical activity.

Table 4

with a fully adjusted model. Likewise, the “mid-normal weight” trajectory was treated as referent for each age and gender group. Regardless of age and gender

Male aged over 60	low-normal weight, stable	Mid-normal weight, stable	Overweight, stable	Obesity, stable
Cancer	1.06 (0.90, 1.25)	1	1.01 (0.89, 1.13)	1.336*** (1.09, 1.64)
Cardiovascular disease	0.94 (0.77, 1.15)	1	0.994 (0.87, 1.14)	1.336*** (1.06, 1.69)
Respiratory disease	1.70*** (1.39, 2.08)	1	0.817** (0.68, 0.98)	1.027 (0.73, 1.46)
Others	1.33** (1.14, 1.55)	1	1.004 (0.89, 1.13)	1.232 (0.99, 1.53)
Males aged 40–60	low-normal weight, increasing	Mid-normal weight, increasing	Overweight, increasing	Obesity, increasing
Cancer	1.02 (0.92, 1.30)	1	1.061 (0.95, 1.18)	1.205 (0.99, 1.46)
Cardiovascular disease	1.12 (0.90, 1.40)	1	1.363** (1.16, 1.61)	2.079*** (1.61, 2.68)
Respiratory disease	1.85*** (1.31, 2.61)	1	1.002 (0.71, 1.41)	0.699 (0.32, 1.51)
Others	1.25** (1.07, 1.46)	1	1.07 (0.94, 1.22)	1.425** (1.15, 1.77)
Females aged over 60	low-normal weight, increasing	Mid-normal weight, increasing	Overweight, increasing	Obesity, increasing
Cancer	0.92 (0.75, 1.12)	1	1.01 (0.86, 1.19)	0.75*** (0.60, 0.93)
Cardiovascular disease	1.08 (0.89, 1.31)	1	1.10 (0.96, 1.22)	1.35* (1.02, 1.81)
Respiratory disease	1.94*** (1.45, 2.58)	1	1.19 (0.94, 1.21)	1.24 (0.70, 2.22)
Others	1.21* (1.04, 1.40)	1	1.10 (0.95, 1.26)	1.56** (1.24, 1.96)
Females aged 40–60	low-normal weight, increasing	Mid-normal weight, increasing	Overweight, increasing	Obesity, increasing
Cancer	0.96 (0.84, 1.09)	1	1.04 (0.91, 1.18)	1.02 (0.79, 1.32)
Cardiovascular disease	1.15 (0.90, 1.48)	1	1.50** (1.19, 1.88)	1.62* (1.09, 2.41)

Male aged over 60	low-normal weight, stable	Mid-normal weight, stable	Overweight, stable	Obesity, stable
Respiratory disease	1.74*** (1.10, 2.74)	1	1.11 (0.68, 1.82)	2.03 (0.98, 4.19)
Others	1.09 (0.92, 1.30)	1	1.23* (1.04, 1.45)	1.68** (1.29, 2.19)

[a]Fully adjusted model: adjusted for age, educational level, smoking status, alcohol consumption and physical activity

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$

Cause-specific analysis was performed for competing risk analysis and the aHR are shown in Table 4 with a fully adjusted model. Likewise, the “mid-normal weight” trajectory was treated as referent for each age and gender group. Regardless of age and gender, respiratory disease has a significantly increasing mortality risk in low-normal weight groups (males aged over 60: aHR = 1.70[CI = 1.39–2.08[; males aged 40–60: aHR = 1.85[CI = 1.31–2.61]; females aged over 60: aHR = 1.94(CI = 1.45–2.58); females aged 40–60: aHR = 1.74(CI = 1.10–2.74)). In addition, a significantly increasing risk of mortality of cCVD in the obesity trajectory group was also found in all age and gender groups (males aged over 60: aHR = 1.34[CI = 1.06–1.69]; males aged 40–60: aHR = 2.08[CI = 1.61–2.68]; females aged over 60: aHR = 1.35[CI = 1.02–1.81]; females aged 40–60: aHR = 1.62[CI = 1.09–2.41]).

The obesity trajectory group had a contrary mortality risk of cancer disease compared to males and females aged over 60. For males, the “obesity, stable” group had a higher cancer mortality risk (aHR = 1.34, 95% CI = 1.09, 1.64), but for females, the “obesity, decreasing” group had a decreased risk compared to the referent (aHR = 0.75, CI = 0.60, 0.93).

Discussion

The present study identified BMI trajectories over 18 years in a large sample of adults older than 40 years of age, and examined the association of various BMI trajectory groups with all-cause and cause-specific mortality risk. With almost twenty years of follow-up, this is one of the largest studies to examine the grouping of BMI changes in adulthood. There are several key findings in our study. First, the distribution of the population into different trajectory groups and the change of patterns of trajectory groups over time are different from Western populations. Second, obesity or overweight is not a protective factor for mortality in middle aged males and females. Third, obesity is a protective factor in cancer-related mortality in females but not in males in the old age group. Fourth, low-normal weight is a risk factor in respiratory-related mortality. Last, the mortality risk of chronic obesity differed by cause of death, which is rarely discussed in the literature. Particularly, we found that an increased risk of CVD cause of death in all age and gender groups; an increased risk of cancer cause of death was found only in males over 60 of age.

When comparing the BMI trajectory in our sample and Western populations, there are some major differences. First, the distribution of population concentrates in the mid-normal weight group in Taiwan, whereas in Western population, such as in the US and Austria, trajectories of overweight and obesity often account for 70–80% of the sample(21–23). Our data are similar to other Asian countries such as Japan(5), where the mid-normal weight group comprises 67.1% of the population. Second, body weight status does not seem to vary across the lifetime in our sample, which is similar to studies in Japan(5), but different in US and Austrian studies(22–24). Asian populations may be different from Western populations on the issue of BMI trajectory. Third, we showed an increasing pattern from groups between 40 and 60 years of age, which was not demonstrated in previous studies because those studies that examined BMI trajectory and mortality only used data from older adults, such as aged over 60(21).

The result of all-cause mortality among older populations in our study is comparable to studies that showed the lowest mortality risk in normal and overweight trajectory groups(5). Older populations tend to have a reverse J-shaped association of BMI with all-cause mortality, which indicates that underweight and obesity are both important risk factors of mortality(25–27). This so-called “obesity paradox”—higher BMI has protective association with all-cause mortality in older population(6, 28)—was also found in our sample of Taiwanese populations. Combining our finding of obesity as not being a protective factor for mid-aged adults in our sample, one possible mechanism may be selection bias. Obese mid-aged adults might be more likely to die from CVD death if they have severe obesity-related CVD. This may result in a sample biased toward less risk of obesity-associated CVD deaths. Our sample also confirmed an association between CVD death and obesity in mid-aged adults.

In the present study, obesity was a protective factor in cancer-related mortality in females but not in males in the older age group. Gender differences might occur due to the following reasons: (1) Estrogens could inhibit the growth of tumors, such as for the esophageal cancer(29), liver cancer(30, 31), and colon cancer(32, 33). Cancer cell progression rates are associated with sex hormones and the altered hormone environment in obesity state(34). After menopause, the level of estrogen decreases in women with normal weight; however, in overweight or obese women, the adipose tissue can secrete estrogen. The level of estrogen is significantly higher in postmenopausal obese women than in postmenopausal, normal-weight women and is also higher than in men(35), and may in turn protect obese older women from cancer. (2) Sex-related differences at the genetic and molecular levels can affect the differences in the degree of response to chemotherapy(36, 37). Several commonly used chemotherapy agents—including 5-fluorouracil, doxorubicin, cisplatin, and paclitaxel—all have lower clearance rates in females, which leads to higher therapeutic efficacy, but the agents also have more severe toxicity(38), such as in lung cancer(37, 39), colon cancer(37), gastric and pancreatic cancer(37). Gender differences in cancer-related mortality may result from better prognosis of cancer treatments in obese women.

In the present study, low-normal weight was a risk factor in respiratory-related mortality in all four groups. Several studies stated similar results. A meta-analysis(40) found that, compared to adults with normal BMI, underweight adults with COPD had an increased risk of mortality. This was because lower BMI was associated with accelerated lung function decline in adults, resulting in higher likelihood for COPD(40),

and other respiratory diseases as well, such as cystic fibrosis, asthma, and pneumonia(41, 42). A possible explanation is that reduced skeletal muscle mass, especially reduced diaphragmatic muscle mass, is associated with low pulmonary function because of the decreased strength of respiratory muscles(43). In a study of healthy adults in Korea(44), the parameter which represented pulmonary function—forced expiratory volume in 1 second (FEV1)—was decreased in underweight populations compared to normal weight populations (Odds Ratio (OR) = 2.10, 95% CI = 1.98–2.21). Underweight adults who were at risk for respiratory diseases may have considered pulmonary rehabilitation programs that aimed to improve their lung function(44) in addition to increasing their weight. Another explanation may be that genetic factors modulate both BMI and lung function; for example, several studies(45, 46) found a significant association between BMI and the fat mass and obesity-associated (FTO) genes in many general population studies(47). Among the FTO genes, rs8050136 minor alleles were associated with both higher BMI and better lung function(47).

The present study has several limitations. First, the interim between the measurements was 3 years, limiting information about changes in between. However, in our results, there was a limited change of BMI over each three years; we do not think this limitation will affect the results of our trajectory analysis. Second, although BMI is the most commonly used measure of adiposity, it has been criticized as not being able to distinguish between excess fat, muscle, water or bone mass(48), nor does it provide any indication of the distribution of fat in an individual, such as visceral fat or cutaneous fat(48). This may lead to misclassification bias. The term *normal weight obesity* (NWO) has been used since 2008; about 15% of people were classified as NWO(49). However, this relatively small percentage of the population may not lead to severe bias since some studies that pay attention to the representativeness of BMI to obesity suggest that BMI is still a good index for cardiometabolic risk(50). However, it is still important for further research to pay attention to the representativeness of BMI to obesity. Third, our dataset did not measure some confounders that are associated with both BMI trajectory and certain causes of death, such as common genetic factors such as FTO genes. The effect of causal inference cannot be fully established.

Conclusion

In conclusion, these study findings highlight the impact of BMI trajectory on cause-specific mortality. In contrast to observations made regarding Western populations, BMI changes over time maintain unchanged in nearly all trajectory groups. In this research, both low-normal weight and obesity groups had significantly higher mortality risk than mid-normal weight groups in adults aged 40 to 60 among both genders, which indicates that no obesity paradox was found in this age group. In cause-specific mortality risk, low-normal weight was related to high risk of respiratory disease-related death, whereas obesity seemed to be a protective factor to cancer-related mortality risk in females over 60 years of age but not in males. Our research suggests that in mid-life it is still beneficial to maintain mid-normal weight to lower mortality risk; however, pulmonary rehabilitation intervention programs should be conducted for low-normal weight groups. These findings could provide both clinical and public health approaches to body-

weight management interventions conducive to improving the survival of adults both in their mid or later lives, particularly in Asian populations.

Abbreviations

aHR
adjusted hazard ratio
BIC
Bayesian Information Criterion
BMI
body mass index
CI
confidence interval
COPD
chronic obstructive pulmonary disease
CVD
cardiovascular disease
FEV1
forced expiratory volume in 1 second
FTO
Fat mass and obesity-associated
HR
hazard ratio
NWO
normal weight obesity
OR
odds ratio
US
United States
WHO
World Health Organization

Declarations

Ethics approval and consent to participate: This study protocol was reviewed with exemption and approved by the Institutional Review Board of National Cheng Kung University Hospital (IRB#: A-ER-109-011)

Consent for publication: Not applicable.

Availability of data and materials: In accordance with current national law, the data used in this study is only available for the researchers participating in this project. Thus, we are not allowed to distribute or make publicly available the data to other parties. However, researchers from public institutions can request data from the MJ resource center and Ministry of Health and Welfare, Taiwan if they comply with certain requirements.

Competing interests: All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions: All authors were involved in the study design. YT and PC performed the data management. PC conducted the statistical analyses and wrote the first draft of the manuscript. CS is the corresponding author who takes responsibility for the paper. All authors interpreted the results, contributed to drafting the article, and approved the final version of the manuscript.

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Figures

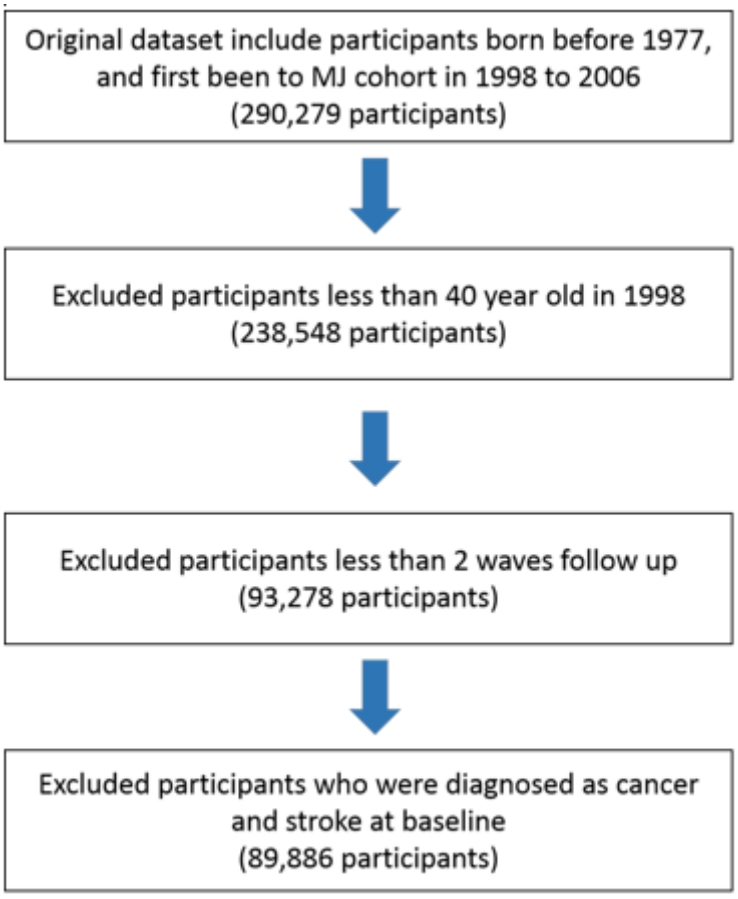

Figure 1

Patient attrition and cohort selection. Inclusion and exclusion criteria show cohort selection for the MJ cohort dataset.

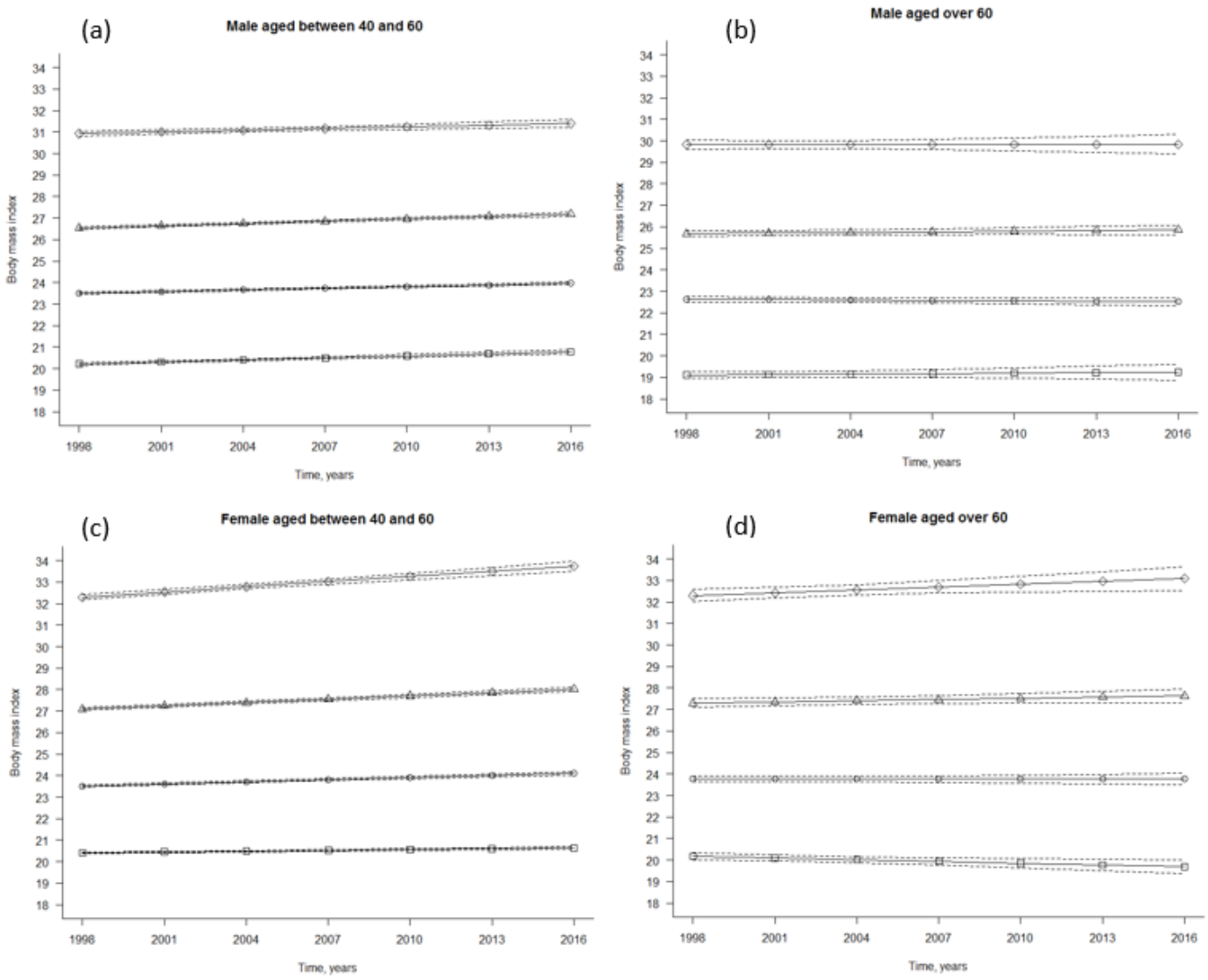

Figure 2

Body mass index trajectories for the 4-group model were over 19 years, adults from the MJ cohort, 1998–2017. Solid lines indicate the mean values of BMI (weight (kg)/height (m) 2) for participants in the groups; dashed lines = 95%confidence intervals. (a) Males aged between 40 and 60 years. The trajectories were as follows: diamond = obesity, increasing = triangle, overweight = increasing; circle = mid-normal weight, increasing; square = low-normal weight, increasing. (b) Males aged over 60 years. The trajectories were as follows: diamond = obesity, stable; triangle = overweight, stable; circle = mid-normal weight, stable; square = low-normal weight, stable. (c) Females aged between 40 and 60 years. The trajectories were as follows: diamond = obesity, increasing; triangle = overweight, increasing; circle = mid-normal weight, increasing; square = low-normal weight, increasing. (d) Females aged over 60 years. The trajectories were as follows: diamond = obesity, increasing; triangle = overweight = stable; circle = mid-normal weight, stable; square = low-normal weight, stable.