Original Article

The U-shaped relationship between BMI and all-cause mortality contrasts with a progressive increase in medical expenditure: a prospective cohort study

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The U-shaped relationship between body mass index (BMI) and all-cause mortality has generated uncertainty about optimal BMI. For clarification, we have related BMI to both mortality and medical expenditure. The MJ Health examination cohort of 111,949 examinees established during 1994-1996 was followed with endpoint information derived from death certificates and National Health Insurance records from 1996 to 2007. Age- and gender-specific relative risks between BMI groups were estimated by Cox and logistic regressions. The BMI and all-cause mortality relationship is U-shaped with the concave regions sitting in the region of BMI 22-26, butshifted rightward for the elderly. After excluding smokers and cancer patients at baseline, the low mortality region moved leftward to BMI 20-22. Cause-specific mortalities from respiratory disease, injury, and senility increased in the underweight group (BMI <18.5). Above 18.5, BMI was negatively associated with mortality from respiratory diseases and senility, but not with others. In contrast, irrespective of age and gender, the overall median and mean medical expenditures progressively increased with BMI, particularly beyond 22. Expenditures for injury, respiratory, circulatory diseases and senility all increased with BMI. The U-shaped BMI-mortality relation was a result of elevated death rate at both ends of the BMI scale. Increased mortality at the low end did not contribute to higher medical expenditure, maybe because the lean and frail deceased tend to die abruptly before large amount of medical expenditure was consumed. Our findings suggest that current recommendations to maintain BMI at the lower end of the desirable range remain tenable for the apparently healthy general public.

Key Words: cohort studies, body mass index, mortality, expenditure, Asians

INTRODUCTION

Obesity is associated with an increased burden of disease and higher risks of multiple health problems, notably cardiometabolic diseases,[1-3] asthma,[4] sleep apnea,[5] and certain forms of cancers.[6-8] Body mass index (BMI), as weight (kg)/height^2 (m^2), is widely used to determine whether individuals are overweight or obese.[9] However, in many populations, the relation between all-cause mortality and BMI is U-shaped, including the findings of the Prospective Studies Collaboration,[10] the Asian Cohort Consortium[11] and the National Cancer Institute Cohort Consortium.[12] This phenomenon is more prominent in the elderly,[13-15] in smokers,[10,16] and in patients with major cardiovascular events and chronic kidney failure [17] than their counterparts and sometimes inverse J-shaped relations are observed. It is hypothesized and has been partially demonstrated [10] that smoking status and terminal illnesses might contribute to weight loss and thus increased mortality in underweight people. However, in several studies where smokers and people who died in the first several years of follow-up were not considered, the curvilinear relationship between BMI and mortality is persistent.[10,12,15,16]

Death statistics reflect not only the critical life-threatening events which have occurred, but also how well the events are managed; which means cause of death is not a straightforward indicator of health burden. Being

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overweight or obese is associated not only with mortality, but also with the encumbrance of various illnesses and sub-clinical disorders that require management. There is need to evaluate the relationships between indices of obesity and morbidity, at least by age and gender and compare these to those with mortality, so that both outcomes are taken into account clinically and in public health. To this end, we have used medical expenditure, important in its own right, as a surrogate for a weighted morbidity index. Previous economic studies [18-20] which examined BMI-morbidity-cost relationships have generally not explored the gradients and separations by demographic subgroups to allow for necessary comparisons with BMI and mortality; or have not made direct mortality comparison.

With near-complete coverage of the population, medical expenditure estimates ascertained from the National Health Insurance (NHI) system in Taiwan can serve as a summary indicator of illness and provides a way to explore the relationship between BMI and disease burden, as a basis for health policy. We report baseline BMI and subsequent medical expenditures as an estimate of morbidity, along with mortality for comparison, in a large cohort of Taiwanese adults.

METHODS

Studied population

This study utilized a database of health examination data from the privately-owned nationwide MJ Health Screening Centers in Taiwan.[21-23] Included were a total of 140,860 adults who had a physical examination in 1994-1996. A structured questionnaire was used to gather information on demographics, medical history, medications, and personal behaviors. Measurements of body weight and height were made. Detail description of data for those health examinees and their socio-economic distribution have been described in our previous report.[24]

Death certificate data from the Department of Health in Taiwan were used to ascertain the date and cause of death. Individuals who died before January 1, 1996 were excluded, yielding 140,619 individuals. Data were then linked to NHI database (1996-2007).[25,26] During the linkage process, the government's confidentiality regulations were followed. The personal identification numbers were encrypted and thus no privacy data from the study individuals could be identified. There were 589 persons in the dataset (about 0.4 %) without NHI records; these individuals were excluded. Those who died within 5 years of the baseline examination (n=2,535) and those without smoking status data (n=25,546) were excluded.

This study was approved by the Institutional Review Board of MJ Life Enterprises Taiwan Ltd. To provide evidence-based guidelines for the definition of obesity in Taiwanese adults, BMI data from this project were linked with the NHI database, with the approval and under the auspices of the Bureau of Food Hygiene and Bureau of Health Promotion, Department of Health, Taiwan. This linkage was terminated in December, 2011.

Medical expenditures

Total medical care expenditure was derived from the NHI claim database, including inpatient, outpatient, emergency, and rehabilitation services, examination and laboratory test, prescription medication, and co-payment of all medical conditions. Expenditures in New Taiwan Dollars (NT$) were summed per year for each subject. To eliminate bias from the unusually high expenses of critical care, medical charges during the last month of life were not included. Average annual medical expenditures were calculated as the sum of all the inflation-adjusted expenditures divided by follow-up time. We adjusted expenditures using Consumer Price Indices (CPI) to measure expenditures in the constant NT$ of 2007, as the Taiwan government adjusts NHI payment schemes from time to time largely based on CPI as well as prices of selected services. We did not further adjust these expense measures using the real interest rate in the market, because medical expenditures were used as a surrogate of a weighted morbidity index and we adopted a zero-discount rate for health effects. The follow-up time was defined as the number of years that a subject was covered by the NHI system (i.e., from January 1, 1996 to either the date of death or to December 31, 2007).

Statistical analyses

Gender and age specific analyses were carried out. Participants were stratified into young (20-39 years old), middle (40-59 years old), and elder age (≥60 years old) groups by their age at entry. Baseline smoking status was classified into five categories: never, abstain, occasionally, frequently and daily. Baseline BMI was first categorized into four groups of overall adiposity according to the Taiwanese definition: <18.5 as underweight, 18.5-23.9 as normal, 24.0-26.9 as overweight, and ≥27.0 as obese. To analyze relationships in more details, we also categorized subjects into seven groups by their BMI: <18.5, 18.5-19.9, 20.0-21.9, 22.0-23.9, 24.0-25.9, 26.0-27.9 and ≥28.0. We did not create additional categories above BMI 28 because relatively small proportion of people had a BMI >30 in this cohort. The mean, the median and the inter-quartile range of average annual medical expenditures for each BMI group were estimated.

Subjects with average annual medical expenditures greater than the 75th percentile in their gender/age group were defined as high medical expenders. Logistic regression model was used to estimate the odds ratio (OR) of being a high expender. In the logistic regression analysis, adjustments were made for baseline age, age^2 and smoking status (5 categories), since mean age and proportion of smokers varied across BMI groups. With regard to the analysis of all-cause mortality, the Cox proportional-hazards model was used to estimate the hazard ratio (HR), while age and smoking adjustments were made in the same way as the above. The proportional-hazards assumption was examined using the Kaplan-Meier plots, which show no cross over in survival probability. Therefore, the proportionality assumption across the BMI is valid for the analysis. The underweight (BMI <18.5) group was designated as the reference group for both models.

We explored the relationship between baseline BMI and cause-specific mortality and medical expenditure. Cause of death, based on the ICD-9-CM codes on death certificate, was used to identify deaths from lung cancer (ICD-9-CM: 162), other cancers (ICD-9-CM: 140~208,

Table 1. Characteristics of the subjects by gender, MJ cohort

Characteristics	Men		Women		Both	
	n	(%)	n	(%)	n	(%)
Sample size	53177	(47.5) †	58772	(52.5)	111949	
Age (years)	42.7 (14.3) ‡		42.9 (14.4)		42.5 (14.1)	
20-39	27441	(51.6)	29624	(50.4)	57065	(51.0)
40-59	16999	(32.0)	20992	(35.7)	37991	(33.9)
≥60	8737	(16.4)	8156	(13.9)	16893	(15.1)
Smoking status						
Never	17835	(33.5)	50644	(86.2)	68479	(61.2)
Abstain	7563	(14.2)	1114	(1.9)	8677	(7.8)
Occasionally	4623	(8.7)	1783	(3.0)	6406	(5.7)
Frequently	2925	(5.5)	2725	(4.6)	5650	(5.1)
Every day	20231	(38.0)	2506	(4.3)	22737	(20.3)
BMI (kg/m^2)	23.3±3.9		23.8±3.3		23.0±4.3	
<18.5	2171	(4.1)	4702	(8.0)	6873	(6.1)
18.5-19.9	4290	(8.1)	7738	(13.2)	12028	(10.7)
20-21.9	9744	(18.3)	13719	(23.3)	23463	(21.0)
22-23.9	12899	(24.3)	12464	(21.2)	25363	(22.7)
24-25.9	11839	(22.3)	9083	(15.5)	20922	(18.7)
26-27.9	7175	(13.5)	5680	(9.7)	12855	(11.5)
≥28	5059	(9.5)	5386	(9.2)	10445	(9.3)
No of death	3211	(6.0)	2134	(3.6)	5345	(4.9)
Years covered by NHI§	11.7 (0.9)		11.6 (1.0)		11.7 (0.8)	

After excluding those died within 5 years of baseline.
† Percentage of the total study population.
‡ Mean (SD)
§ National Health Insurance database.

except 162), circulatory diseases (ICD-9-CM: 390-459 and 250), respiratory diseases (ICD-9-CM: 460-466 or 470-478 or 480-499), digestive diseases (ICD-9-CM: 526-579, but not 540-543 and not 550-553), genitourinary diseases (ICD-9-CM: 580-630), injury/poisoning (ICD-9-CM: 800-1000), tuberculosis (ICD-9-CM: 10-18 or 137), and senility (ICD-9-CM: 797). The differences in cause-specific mortality across BMI categories were tested using logistic regression models, BMI 18.5-19.9 as the reference. For medical expenditure, we used the same ICD code groups to identify insurance claims for those disease(s) and the associated costs. Least-square means of cause-specific medical expenditure by baseline BMI were calculated based on general linear models controlling for age, age^2, sex, age-sex interaction and smoking status (5 categories). We further tested the differences in log-transformed medical cost across BMI categories based on linear models, while log-transformed zero expenditure was imputed by value zero.

The statistical analyses were performed with the SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC, USA), and statistical significance was defined as $p < 0.05$.

RESULTS

Characteristics of the studied populations

Table 1 shows the sample size of this study; slightly more than half of the subjects were female. Mean baseline age was around 43 years and the mean BMI was 23.3±3.9 and 23.8±3.3, respectively, for males and females. According to the Taiwanese obesity definition (BMI ≥27), the overall prevalence was 15.1% in males and 13.3% in females. According to the WHO definition (BMI ≥30), obesity prevalence was 3.5% and 4.1% in men and in women, respectively. The proportions of cigarette smokers and ex-smokers were higher in men than in women. During 11.7 years of follow-up from 1996 to 2007, there were 7,880 deaths of which 2,535 were excluded, because they died within 5 years of baseline BMI determination. However, results are similar whether these people are included or not in the analysis.

Mean age and outcomes of interest by 4 BMI categories

When participants were separated into BMI groups corresponding to underweight, normal, overweight and obese (Table 2), the highest crude mortality was seen in the underweight group for middle-aged men and elderly, but in the obese group for young men and women. The relationship between age and adiposity also varied by age stratum. In the 20- to 39-years-old group, the overweight and obese groups were older than their leaner counterparts, whereas in the elder group the underweight groups were older than their counterparts. The lowest hazard ratio for all cause mortality was seen at BMI 18.5-23.9 in the young and the middle-aged, but at BMI 24-26.9, in the elders, with significance only evident for the latter.

With respect to medical expenditures, the median expenditure and odds ratio of spending greater than the 75th percentile increased from underweight to obese status in all gender/age groups (except young age underweight). The average annual medical expenditure for men older than 60 was greater than their female counterparts. In contrast, women had greater medical expenditures than men in all other age and BMI groups. To examine in detail the association between BMI and outcomes, we divided subjects into seven groups according to their BMI.

Medical expenditures by narrow BMI groups

In all gender-age groups, J-shaped patterns were observed for BMI to mean medical expenditure curves, indicating

Table 2. Mean age, sample size and outcomes stratified by gender, age and BMI, MJ cohort

Age group (years)	20-39				40-59				≥60			
BMI (kg/m^2)	Under-weight <18.5	Normal 18.5-23.9	Overweight 24-26.9	Obese ≥27	Under weight <18.5	Normal 18.5-23.9	Overweight 24-26.9	Obese ≥27	Under weight <18.5	Normal 18.5-23.9	Overweight 24-26.9	Obese ≥27
MALES												
Sample size	1459 (5.3%)†	15327 (55.9%)	7103 (25.9%)	3552 (12.9%)	327 (1.9%)	7412 (43.6%)	6076 (35.7%)	3184 (18.7%)	385 (4.4%)	4194 (48.0%)	2855 (32.7%)	1303 (14.9%)
Age (mean(SD))	29.4 (5.0)	30.6 (5.1)	32.4 (4.7)	32.5 (4.9)	49.6 (6.6)	49.4 (6.2)	49.2 (6.1)	48.9 (6.0)	68.4 (5.8)	67.1 (5.2)	66.7 (4.9)	66.6 (4.9)
Smoker‡%	64.5%	63.7%	66.7%	70.0%	69.1%	64.7%	64.0%	68.2%	75.1%	74.3%	70.4%	69.9%
Mean annual medical expenditures (NT§)	8441	7057	8321	10781	18537	19912	22616	27148	45548	49438	52717	61134
Median annual medical expenditures (NT)	3055	3507	4338	5291	8175	9036	11124	15200	24707	28734	36437	45197
OR¶ (95% CI)	1.00	0.90 (0.79-1.03)	1.19 (1.03-1.36)	1.76 (1.52-2.03)	1.00	1.13 (0.85-1.51)	1.57 (1.18-2.10)	2.51 (1.87-3.37)	1.00	1.03 (0.80-1.33)	1.37 (1.06-1.78)	1.91 (1.46- 2.50)
Number of deaths	15	126	72	51	25	369	300	182	122	1011	634	304
Follow-up years†† (mean (SD))	12.2 (0.8)	12.3 (0.8)	12.3 (0.8)	12.2 (0.8)	12.2 (1.2)	12.2 (1.2)	12.2 (1.1)	12.1 (1.2)	11.1 (2.3)	11.5 (1.9)	11.6 (1.8)	11.5 (1.9)
Crude mortality (/1000 person years)	0.84	0.67	0.83	1.17	6.29	4.10	4.06	4.71	28.66	21.00	19.18	20.25
HR (95% CI)	1.00	0.77 (0.45-1.32)	0.86 (0.49-1.51)	1.18 (0.66-2.11)	1.00	0.73 (0.49-1.10)	0.76 (0.51-1.15)	0.91 (0.60-1.38)	1.00	0.81 (0.67-0.97)	0.78 (0.64-0.94)	0.83 (0.67-1.02)
FEMALES												
Sample size	4047 (13.7%)	20735 (70.0%)	3275 (11.1%)	1567 (5.3%)	438 (2.1%)	9936 (47.3%)	6353 (30.3%)	4265 (20.3%)	217 (2.7%)	3250 (39.9%)	2714 (33.3%)	1975 (24.2%)
Age (mean (SD))	28.2 (4.7)	30.7 (5.1)	32.4 (5.0)	32.7 (5.1)	48.2 (6.2)	49.0 (6.0)	50.6 (5.7)	51.2 (5.5)	67.6 (5.8)	66.6 (5.2)	66.3 (4.9)	66.2 (4.9)
Smoker%	18.9%	16.5%	16.7%	17.7%	13.0%	10.4%	9.9%	11.1%	14.3%	11.8%	11.0%	11.3%
Mean annual medical expenditures (NT)	10031	9698	11241	14025	19342	20536	24453	33220	38842	41361	46736	55070
Median annual medical expenditures (NT)	6788	6815	7031	8060	9755	11223	14483	19286	20693	26281	32342	39119
OR (95% CI)	1.00	1.05 (0.97-1.14)	1.20 (1.07-1.33)	1.73 (1.52-1.97)	1.00	1.30 (0.99-1.72)	1.80 (1.36-2.38)	3.04 (2.30-4.03)	1.00	1.85 (1.23-2.79)	2.52 (1.67-3.79)	3.54 (2.35-5.35)
Number of deaths	21	93	28	15	17	259	218	193	60	516	389	325
Follow-up years (mean (SD))	12.2 (0.8)	12.3 (0.8)	12.3 (0.8)	12.3 (0.8)	12.2 (1.0)	12.3 (0.9)	12.2 (1.0)	12.2 (1.1)	11.3 (2.0)	11.8 (1.7)	11.9 (1.6)	11.8 (1.7)
Crude mortality (/1000 person years)	0.42	0.36	0.69	0.78	3.18	2.12	2.80	3.70	24.36	13.42	12.05	13.92
HR (95% CI)	1.00	0.76 (0.47-1.23)	1.32 (0.74-2.36)	1.44 (0.73-2.83)	1.00	0.65 (0.40-1.06)	0.77 (0.47-1.26)	0.96 (0.59-1.59)	1.00	0.58 (0.44-0.75)	0.54 (0.41-0.71)	0.64 (0.49-0.85)

† Percentage of the total study population.
‡ Including those who abstained from smoking, smoked occasionally, smoked frequently or daily.
§ New Taiwan Dollars.
¶ Odds Ratio of being a high medical expender (average annual medical expenditures greater than the 75th percentile in their gender/age group). Baseline age, age^2 and smoking status (5 categories) was adjusted in the logistic regression model.
†† From baseline to either the date of death or to December 31, 2007.
Hazard Ratio: The proportional hazard model was used to estimate the hazard ratio of all-cause mortality, adjusting for baseline age, age^2 and smoking status(5 categories).

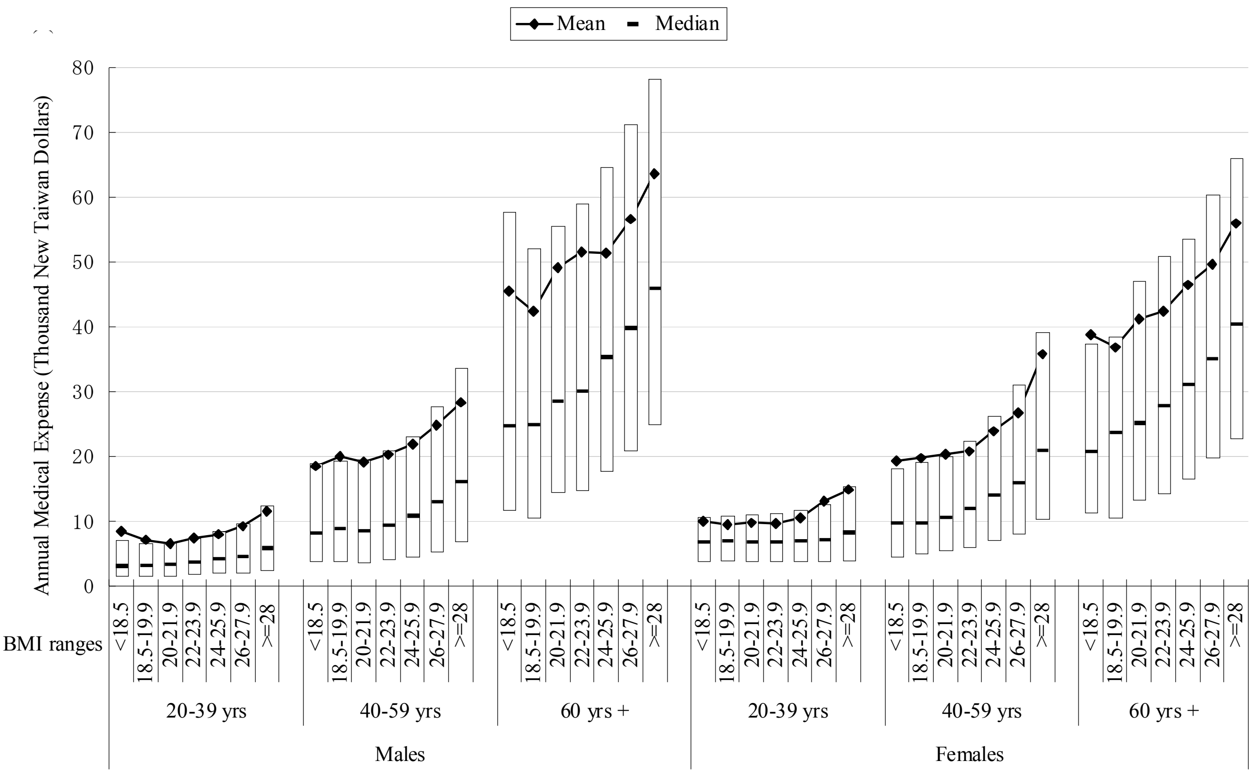

Figure 1. The mean, median and inter-quartile range of annual medical expenditure according BMI levels, by gender and by age. The upper and lower ends of the bars denote for the upper and lower quartiles.

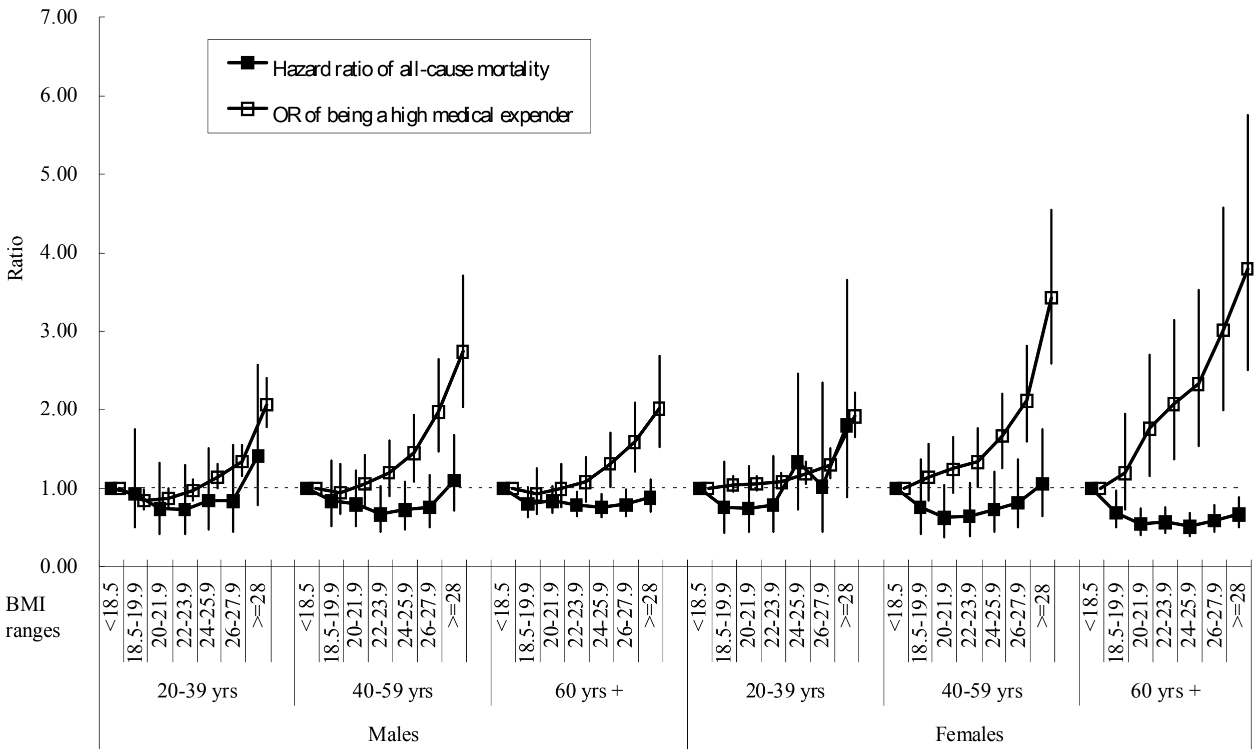

Figure 2. Relative risk of all-cause mortality and of high medical expenditure comparing various BMI groups with BMI <18.5, by gender and by age, adjusting for age (continuous), age^2 and smoking status (5 categories).

that mean annual medical expenditures (Figure 1) increased in general with BMI values and were lowest in the groups with BMIs between 18.5 and 22.0. Median annual medical expenditures were much lower than the means (Figure 1). The medians, a statistic of centrality, of annual expenditures rose steadily with BMI. To take age and smoking status into account, we applied a logistic regression to estimate OR of a subject being a high medical expender. The odds ratio of being a high medical expender generally increased with BMI (Figure 2). Those with the lowest risk were either at BMI <18.5 or at BMI 18.5-19.9, after adjustment for age and smoking.

All-cause mortality by narrow BMI group (Figure 2)

The relationship between BMI and mortality was generally U-shaped or reversed J-shape for all gender-age groups. In women, the lowest mortality rates were between BMI 18.5 to 22, 20 to 22, and 24 to 26 for the young, middle-aged, and elderly age groups, respectively. In men, they were between BMI 20 to 24, 22 to 24, and 24 to 26 in the young, middle-aged, and the elderly. There was a rightward shift with age for the concave regions.

Cause-specific analysis for mortality and medical expenditure

Table 3 shows mean cause-specific mortality and medical expenditure by BMI groups and compare them between BMI groups after age, sex, and smoking status were adjusted. People with BMI <18.5 had significantly higher mortality than those at BMI 18.5-19.9 for injury, tuberculosis (TB), other respiratory disease, and senility. For people in the range of BMI >18.5, no clear association was seen for BMI and mortality from cancer, injury, TB, genitourinary or digestive tract diseases; but there was a negative association between BMI and mortality from respiratory disease or from senility, and a positive association between BMI and circulatory disease mortality. Although we did not find any association between BMI and lung cancer when all age groups were combined, a negative association and a positive association were observed for those aged ≥60 and those between 20-39, respectively (data not shown).

In contrast, increasing medical expenditure was seen with BMI increments for circulatory diseases, respiratory diseases, injury, and senility. Further, no association was found between BMI and cancer, digestive tract or genitourinary diseases. The relationship between BMI and disease burden from respiratory disease, injury, and senility indicated by medical expenditure is in the opposite direction to that for mortality. The only exception is on decreasing medical costs with incremental BMI for TB.

In Figure 3, BMI-medical expenditure and BMI-mortality relationships in all subjects are compared.

Overall BMI-Mortality relationship

Taking all six age-sex groups together (Figure 3), HRs for all cause mortality were the lowest at BMI 22-26. However, if we excluded smokers and those with cancer at baseline and also adjusted for age, age^2, age×sex, sex and smoking status, the concave region shifted to BMI 20-22.

Overall BMI-expenditure relationship

The odds ratio for high medical expenditure was very close for BMI 18.5-19.9 and for BMI 20-21.9. The OR for high medical expending was significantly greater than one by 23% (1.15 to 1.31) for BMI 24- 25.9, compared to BMI <18.5. After excluding people with a cancer history or who were smokers at baseline, the OR became 1.31 (1.20 to 1.43) for those at BMI 24-25.9 while those at BMI <18.5, 18.5-19.9, and 20-21.9 were flat.

DISCUSSION

Our study showed that the BMI value is positively associated with medical expenditures irrespective of gender and age. Although a non-significant increase in mean medical expenditure was seen for those with BMI <18.5 compared to the BMI 18.5-19.9, no such increase was shown for median expenditure. BMI 18.5-19.9 and BMI 20-21.9 groups have the lowest mean or median medical expenditure levels in the whole BMI range from 18.5 and above. After removing smokers and people with some forms of cancer at baseline, the uprising trend of medical expenditure with BMI was even clearer. Our findings on BMI-medical expenditure relationship support the worldwide recommendation [27] for the public to maintain BMI in the lower end of the desirable BMI range.[28]

At the same time, we confirm that BMI has a U-shaped or reversed J-shaped relation with mortality in the Taiwanese population, consistent with the findings of other populations.[14,15,29] We found that the mortality increase in the low end of BMI scale was primarily due to that from injury,[30] respiratory disease,[16] tuberculosis, and senility in the BMI <18.5 group and an overall negative association between BMI and mortality from respiratory disease and from senility. The Prospective Studies Collaboration[10] also showed a negative association between BMI and mortality from respiratory disease, in particular chronic obstructive pulmonary disease (COPD). We confirmed in our study the same phenomenon for COPD (data not shown) which may cause weight loss over the long latent period and increased mortality. In addition, we did not observe a negative association between lung cancer mortality and BMI in all age groups combined, although a moderate positive association was seen for the young age group and a negative association for the elder group (data not shown). The opposite trends between the young and the old imply that the association between BMI and lung cancer mortality in the elderly may not be causal.

The relative risk of being a medical expender elevates significantly when BMI is higher than 24, although the relative risk of mortality against BMI seemed "flat" in the region near 24. Thus, the result supports the value of using 24 as a cut-off for overweight. Contrary to the medical expenditure as a summary indicator of health, all-cause mortality may not serve as an appropriate endpoint for determining the cut-points of BMI.

The U curve shifted to the right in elders in this study and others.[13] The older the population, the bottom of the U curve locates in the higher end of BMI distribution. The same right-shifting phenomenon has been shown in smokers [14,15] and in those with major diseases.[31] The Copenhagen City Heart Study [32] and a recent Indian study [33] demonstrated that weight loss, moderate or severe, is a predictor of death. If low BMI is a result of or compounded by involuntary weight loss due to disease, it is likely that higher mortality in the low BMI range is a consequence of disease or frailty.[34] The Leisure World Cohort study highlighted that being overweight or obese in young adulthood and underweight in later life was associated with an increased risk of old-age mortality.[35] The modest but positive association between BMI and medical expenditure of senility and no association between BMI and expenditure of respiratory disease suggests that those who died of these diseases may die before consuming large amount medical expenses. We did observe a consistent and negative association between BMI and TB mortality and/or TB medical expenditure. However,

Table 3. Cause-specific mortality (%) and mean annual medical expenditure (NT$) by BMI levels, MJ cohort, adjusted for age, sex, and smoking status.

BMI group		Total		Lung cancer		Other cancer		Circulatory disease		Respiratory disease	
No. of death		5345		399		1523		1518		338	
	n	mortality	*p*-value†	mortality	*p*-value	mortality	*p*-value	mortality	*p*-value	mortality	*p*-value
<18.5	6873	2.290	0.007	0.115	0.565	0.756	0.654	0.253	0.814	0.041	0.001
18.5-19.9	12028	1.790		0.138		0.700		0.242		0.020	
20-21.9	23463	1.654	0.252	0.112	0.358	0.731	0.724	0.252	0.763	0.014	0.117
22-23.9	25363	1.587	0.069	0.135	0.930	0.687	0.880	0.279	0.267	0.010	0.001
24-25.9	20922	1.624	0.144	0.123	0.587	0.764	0.461	0.285	0.208	0.008	< 0.001
26-27.9	12855	1.737	0.664	0.108	0.283	0.794	0.310	0.313	0.055	0.008	< 0.001
>=28	10445	2.236	0.002	0.113	0.409	0.888	0.062	0.444	0.000	0.010	0.005
	n	mean cost	*p*-value	mean cost	*p*-value	mean cost	*p*-value	mean cost	*p*-value	mean cost	*p*-value
<18.5	6873	19165	1.000	163	1.000	1490	0.584	2881	0.158	2147	0.894
18.5-19.9	12028	18508		185		1372		3112		1973	
20-21.9	23463	18774	0.992	150	0.938	1486	0.970	3320	0.002	2028	0.983
22-23.9	25363	19100	0.000	181	0.999	1397	0.950	3768	< 0.001	1908	0.119
24-25.9	20922	20514	0.000	212	1.000	1386	0.684	4821	< 0.001	1863	0.002
26-27.9	12855	23174	0.000	137	0.412	1599	0.936	6104	< 0.001	1882	0.003
>=28	10445	28334	0.000	184	0.308	1701	1.000	8192	< 0.001	2128	< 0.001

BMI group		Digestive dis.		Genitourinary disease		Injury/poisoning		Tuberculosis		Senility	
No. of death		357		226		384		39		57	
	n	mortality	*p*-value	mortality	*p*-value	mortality	*p*-value	mortality	*p*-value	mortality	*p*-value
<18.5	6873	0.121	0.578	0.021	0.066	0.446	0.018	0.007	0.011	0.000026	0.180
18.5-19.9	12028	0.147		0.057		0.238		0.001		0.000014	
20-21.9	23463	0.138	0.787	0.044	0.380	0.229	0.859	0.002	0.302	0.000006	0.127
22-23.9	25363	0.111	0.226	0.042	0.278	0.264	0.645	0.001	0.725	0.000005	0.041
24-25.9	20922	0.096	0.075	0.043	0.288	0.298	0.311	0.001	0.601	0.000007	0.146
26-27.9	12855	0.138	0.785	0.041	0.278	0.297	0.353	0.001	0.720	0.000005	0.061
>=28	10445	0.196	0.221	0.066	0.613	0.229	0.874	0.001	0.795	0.000007	0.188
	n	mean cost	*p*-value	mean cost	*p*-value	mean cost	*p*-value	mean cost	*p*-value	mean cost	*p*-value
<18.5	6873	1550	0.150	2748	0.379	991	0.864	180	< 0.001	0.29	0.787
18.5-19.9	12028	1521		2693		913		79		0.15	
20-21.9	23463	1430	0.184	2650	0.001	951	0.047	71	< 0.001	0.15	0.999
22-23.9	25363	1437	0.022	2663	< 0.001	979	0.004	67	< 0.001	0.25	0.725
24-25.9	20922	1455	0.347	2598	< 0.001	946	0.000	35	< 0.001	0.27	0.972
26-27.9	12855	1576	1.000	2811	< 0.001	1028	0.000	38	< 0.001	0.75	0.225
>=28	10445	1724	0.996	3695	< 0.001	1232	0.000	35	< 0.001	0.49	0.100

†*p*-value is for comparing specific BMI group and the reference BMI group (18.5-19.9).

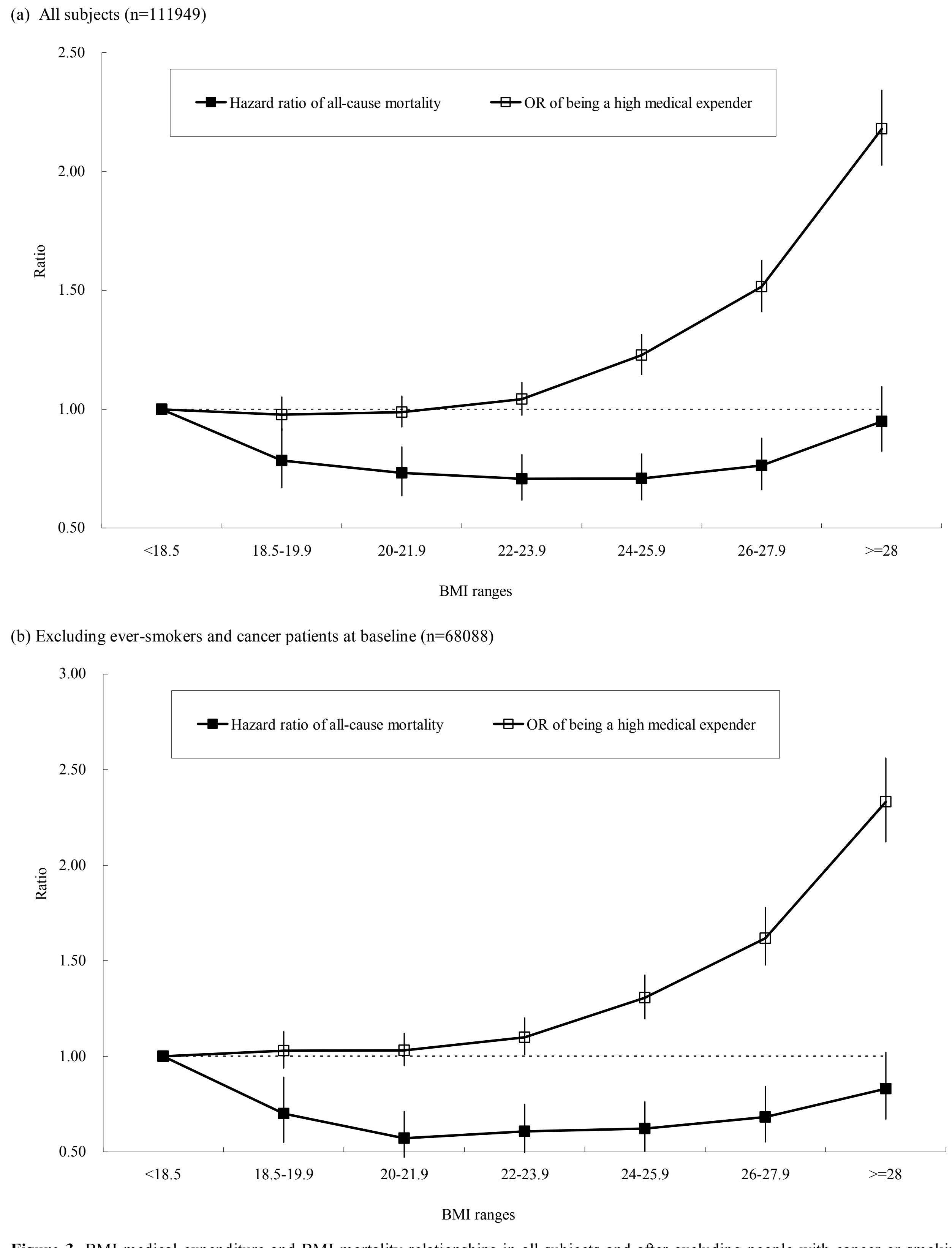

Figure 3. BMI-medical expenditure and BMI-mortality relationships in all subjects and after excluding people with cancer or smoking status at baseline, adjusting for gender, age, age^2, gender×age, smoking

since the latent TB infection is not uncommon,[36] it is possible that similar to COPD, TB caused weight loss and in turn TB death and it is difficult to exclude all of those infected with TB at baseline. Furthermore, TB infection may have contributed little to the overall BMI-disease burden relation due to its low prevalence in the present study.

Our data together with those in the literature suggest that when an individual, particularly elderly, presents with a low BMI in the desirable range (e.g., 18.5-22), it is not certain whether he or she is a healthy lean subject or someone who has certain underlying conditions and lost weight in the past. Therefore, attention should be given to weight loss due to frailty and chronic conditions such as cancer, TB, and COPD, before recommendation is made with regard to healthy body weight. Our overall medical expenditure findings are consistent with earlier findings in that co-morbidity of chronic diseases [37-39] and medical expenditures [20] both increase as BMI increases. Higher BMI values have also been correlated with a lower quality of life and more medical problems.[40,41] Conditions associated with obesity afflict the circulatory, gastrointestinal and musculoskeletal systems, leading to poor physical function.[40] Furthermore, increased BMI is associated with a significantly elevated risk for many cancers, and a certain percentage of most cancers can be attributed to being overweight or obese.[42,43] These chronic afflictions and the subsequent physical discomforts they produce not only increase the frequency of clinic visits [39,44] but also require long-term management. Our study did show a significant increase in expenditure from circulatory disease with BMI. Thus, it is not unexpected that medical expenditures, a summary index of poor health, increase with adiposity. On the other hand, medical expenditure could also be biased as an overall indicator of health when medical utilizing behaviors are determined by other unobserved factors. For example, some heavier senior women could be ones who were healthier and more physically able than the thinner ones so that they were more capable of “doctor shopping” for ageing-related issues. Future study is needed to confirm this issue.

There are several points of limitations and considerations in this study. First, using medical expenditures to represent poor health assumes that the diseases that cost more to treat are more serious. This assumption is subjective, because it represents only an economic viewpoint which is not completely satisfactory. Second, our study population is not a representative sample of the Taiwanese population. However, it has been reported that the socioeconomic distribution of these participants from multiple centers is close to that of Taiwanese people.[22] Third, socioeconomic status of subjects were not accounted for in this study because data is not available. It is possible that heavier people were wealthier and/or more health-conscious, so they may use more medical services. However, according to the literature, obesity (excess adiposity) is usually associated with poverty and lower education, rather than with wealth and knowledge. Forth, the Taiwanese population is leaner than Caucasian populations, and we did not have enough samples to create a BMI category above 28. Therefore, generalizability may be questioned. Nonetheless, since both Caucasian and Asian populations exhibit similar U-shaped BMI-mortality curves, with a progressively uprising trend at the upper end of the BMI distribution, we believe that this finding can be generalized to other populations. Fifth, we excluded subjects who died soon after the baseline, since this study aimed at examining the relationship between weight status and longer-term health outcomes. The exclusion may bias the estimates of mortality and expenditure. However, we found that exclusion or not did not change the results. Sixth, since the medical expenditure data is skewed to the right, log transformation was employed to make the distribution symmetric. However, for analyzing cause-specific expenditure, the standard error may be inflated for low prevalent diseases, since the expenditure distribution also has many zeros. We face the problem when the prevalence rates were not equally distributed in different BMI groups. Methods like Tobit model [45] or two part model are widely used for zero-inflated data. However, we can not perform this analyses due to designated termination date for the data linkage.

The temporal relationship between BMI and overall disease risk has been critically considered in establishing the BMI cut-off for obesity.[46,47] However, most studies used all-cause mortality as the endpoint. Integrated morbidity data is seldom available. Our study suggests that the U-shaped BMI-mortality relationship may be compounded by the effects of smoking, frailty, cancer, and weight loss associated with several respiratory diseases,[32-35] whereas medical expenditure medians and means increased monotonously with BMI in the normal BMI range and beyond, independent of age and sex. Elevation of medical expenditure starts at BMI 22-23.9 and become apparent at BMI 24-25.9 and above. With these caveats, the notion that one should maintain their BMI at the lower part of the normal range remains tenable.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Original Article

The U-shaped relationship between BMI and all-cause mortality contrasts with a progressive increase in medical expenditure: a prospective cohort study

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前瞻性世代研究顯示：身體質量指數與總死亡率的 U 型關係有異於其與醫療支出的持續上升關係

身體質量指數（BMI）與死亡率呈現 U 型關係，因而很難訂定最適 BMI 範圍。為了釐清這個問題，我們同時探討比較 BMI 和死亡率，以及醫療支出的關係。我們以美兆多中心診所在 1994 到 1996 年的 111,949 名健檢個案的資料，連結死亡及 1996 到 2007 年的健保資料作分析。各性別、年齡、BMI 層別的相對危險率以 Cox 及邏輯式回歸分析來估算。BMI 和總死亡率的關係確實是 U 型的，死亡率的最低點座落在 BMI 22 到 26 之間，而老年人的死亡率最低點有右移的現象。在去除了基線時的抽菸及癌症個案後，死亡率最低點往左移到了 BMI 20 到 22 之間。死於呼吸疾病、意外受傷、以及老化的比率在體重過輕（BMI<18.5）組別有增高的情形，但其他死因則都無此現象。相對的，在各性別年齡層的總體醫療支出平均值及中位數都隨著 BMI 的升高而增多，特別在 BMI 大於 22 時，尤為甚之。有關意外受傷、呼吸疾病、心血管疾病以及老化的醫療花費也都隨著 BMI 的升高而增加。BMI 與死亡率的 U 型關係源於曲線兩端的死亡率較高，而在 BMI 較低的曲線前端，並沒有醫療支出較高的情形，有可能是因為大部分極瘦的個案，因為體弱可能在很短的時間內就死亡，所以並不會使醫療支出提高。對於一般的健康民眾而言，建議其 BMI 維持在最適範圍內的較低點仍是合理的。

關鍵字：世代研究、身體質量指數、死亡率、支出、亞洲人