

# Influence of Underlying Diseases and Age on the Association between Obesity and All-Cause Mortality in Post-Middle Age

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## Abstract

**Background:** Studies on the association between obesity and all-cause mortality have found that the degree of obesity is directly proportional to all-cause mortality. In contrast, there have been studies indicating that obese people with underlying diseases have a higher survival rate. We hypothesized that age and underlying diseases lead to such contrasting results. Therefore, we conducted a study to clarify the influence of post-middle age obesity and underlying diseases on all-cause mortality. **Methods:** This study used data from longitudinal studies in the United States, which conducted follow-up for 19 years on 33,708 participants in different age groups:  $\geq 45$ , 45 - 64, and  $\geq 65$  years. Hazard ratio (HR) was determined using the Cox proportional hazards model to analyze a group consisting of all participants, a group of those with underlying diseases, and a group of those without underlying diseases, considering age, gender, education history, marital status, household income, smoking history, and BMI category as covariates. **Results:** In the group aged  $\geq 65$  without underlying diseases, HR was almost 1 in those with BMI 25 - <30, 30 - <35, and BMI > 35 kg/m<sup>2</sup>. Further, HR was higher in the 45 - 64 age group without underlying diseases if BMI was >35 kg/m<sup>2</sup>. However, HR was approximately 1 in the  $\geq 65$  age group. **Conclusions:** The study revealed that among individuals aged  $\geq 65$  years without underlying diseases, there was no association between obesity and all-cause mortality. Among individuals without underlying diseases, HR was higher in the 45 - 64 age group with BMI > 35 kg/m<sup>2</sup> but was approximately 1 among those aged  $\geq 65$  years. Therefore, an interaction based on age was detected. These findings may lead to recommendations regarding the need to modify the advice and education provided to obese individuals in different age groups.

## Keywords

Underlying Diseases, Obesity, All-Cause Mortality, Post-Middle Age

## 1. Introduction

Approximately one-third of the world's population is considered obese. In particular, the number of obese people is known to be increasing in high-income countries in North America and Europe [1] [2] [3] [4]. Because obesity is thought to increase the risk of underlying diseases [5]-[13], maintaining average body proportion and avoiding obesity are important issues in health maintenance.

Several studies have indicated that a greater degree of obesity correlates with higher all-cause mortality [14]-[27]. On the other hand, obese individuals with diseases such as heart failure and hypertension have been reported to have a higher survival rate than non-obese individuals [28]-[37]. Because mortality among young obese individuals is higher than that among elderly obese individuals [38] [39], age has also been reported to influence the association between obesity and all-cause mortality rate.

Differing results in obesity and all-cause mortality studies may be due to differences in target populations or bias correction methods such as inclusion and exclusion criteria set at the start of the studies [40]. However, details of the influence of different criteria and conditions on results of studies have not been clarified. In this study, we focused on age and underlying diseases as conditions that can affect results regarding correlations between Body Mass Index (BMI), which represents the degree of obesity, and all-cause mortality rate, with the aim of clarifying the influence of post-middle age obesity and underlying diseases on all-cause mortality rate. Most of the previous work on the relationship between obesity and all-cause mortality used a survival analysis such as the Cox proportional hazard model. Therefore, also in this study, the relationship between obesity and all-cause mortality was analyzed using the Cox proportional hazard model.

## 2. Methods

### 2.1. About HRS Data

The Health and Retirement Study (HRS) is a nationally representative elderly panel survey led by Michigan University sampled using a multi-stage extraction method focused on American nationals aged  $\geq 50$  years including a total of 37,000 people from 23,000 households in the United States. With the aim to understand the actual living conditions of the elderly, data were collected every 2 years since 1992, and the survey had been conducted for a total of 11 times up to 2012.

HRS data obtained over a long period were gathered. An initial HRS cohort data of 1992 consisted of individuals born between 1931 and 1941 (aged 51 - 61 years at the time of the study) and their spouses. Next, using data from the "AHEAD" study, which was conducted separately from HRS, cohort data of those born between 1890 and 1923 (aged  $\geq 70$  years) was integrated into the HRS data in 1998. HRS incorporated 2 new cohort data sets, one of those born between 1924 and 1930 and the other of those born between 1942 and 1947, with the goal to create a complete sample data set of American populations aged  $\geq 50$

years. Further, HRS incorporated additional data as follows: in 1998, data of those born between 1942 and 1947; in 2004, data of those born between 1948 and 1953; and in 2010, data of those born between 1954 and 1959.

## 2.2. Ethical Considerations

The HRS data that we used for our analysis was collected from 37,317 people between 1992 and 2012 who agreed to participate in the study via informed consent after approval from the University of Michigan Ethics Committee (IRB) was obtained. The HRS data is available for public use via web-based access following the instructions provided on the HRS website ([hrsonline.isr.umich.edu/index.php](http://hrsonline.isr.umich.edu/index.php)). Although there are some restrictions on the answers to sensitive and restricted questionnaires, data are made available based on appropriate procedures. For the present study, we applied for data user registration on the HRS website and obtained approval to use the data from the HRS group. Thereafter, we were provided publicly available data files that we used to perform our analysis.

## 2.3. Subjects and Variables

Among 37,317 individuals who participated in HRS between 1992 and 2012, those aged  $\geq 45$  years were chosen as study subjects. To compare the subjects with and without underlying diseases, those who suffered from at least 1 of 6 chronic diseases, diabetes mellitus, chronic respiratory disease, chronic heart disease, malignant tumors, high blood pressure, or stroke, were identified as a group with underlying diseases. Those who denied having any of the above 6 diseases at study initiation were identified as a group without underlying diseases. Analysis was performed on the following groups: all participants, a group with underlying diseases, and a group without underlying diseases. Subjects were also stratified into different age groups comprising those aged  $\geq 45$ , 45 - 64 (middle-aged and above), and  $\geq 65$  (the elderly).

The degree of obesity is defined by WHO standards [41] as follows: underweight (BMI  $< 18.5$  kg/m<sup>2</sup>), normal range (BMI 18.5 -  $< 25$  kg/m<sup>2</sup>), pre-obese (BMI 25 -  $< 30$  kg/m<sup>2</sup>), class I obese (BMI 30 -  $< 35$  kg/m<sup>2</sup>), class II obese (BMI 35 -  $< 40$  kg/m<sup>2</sup>), and class III obese (BMI  $\geq 40$  kg/m<sup>2</sup>). We stratified the participants into 6 groups based on the WHO criteria of degree of obesity: BMI  $< 18.5$  kg/m<sup>2</sup>, BMI 18.5 -  $< 22.5$  kg/m<sup>2</sup>, BMI 22.5 -  $< 25$  kg/m<sup>2</sup>, BMI 25 -  $< 30$  kg/m<sup>2</sup>, BMI 30 -  $< 35$  kg/m<sup>2</sup>, and BMI  $\geq 35$  kg/m<sup>2</sup>. BMI 22.5 -  $< 25$  kg/m<sup>2</sup>, which was associated with the lowest mortality rate, was defined as a reference based on a previous study that involved data of 900,000 individuals [18] and one that was conducted on the data of 30,300,000 individuals [26]. The variables were as follows: age at baseline, gender (male or female), race (white or nonwhite), education history (high school/higher graduate or less than a high school education), marital status (married/de factor relationship or unmarried), household income (annual household income  $\geq$  \$30,000 or  $<$  \$30,000), smoking history (with or without smoking history), BMI (BMI  $< 18.5$  kg/m<sup>2</sup>, BMI 18.5 -  $< 22.5$  kg/m<sup>2</sup>, BMI 22.5 -

<25 kg/m<sup>2</sup>, BMI 25 - <30 kg/m<sup>2</sup>, BMI 30 - <35 kg/m<sup>2</sup>, and BMI ≥ 35 kg/m<sup>2</sup>), and underlying diseases (with or without underlying diseases). Subjects were excluded from the study if any information was missing regarding age, gender, race, educational history, marital status, annual household income, smoking history, BMI, or disease morbidity, or if they were aged ≤44 at the start of the study. Because data from the National Death Index up to 2011 obtained by the RAND Institute was used to track the death year, the follow-up period of this study was 19 years, from 1992 to 2011. In addition, HRS data and those preprocessed by the RAND Institute were used.

## 2.4. Exclusion Period

To exclude individuals who died from rapid deterioration in their condition soon after study participation or those who were already in a poor condition, those who died within 2 years after study participation were excluded.

## 2.5. Statistical Analysis

Using the Cox proportional hazards model, the hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated for the BMI categories using all-cause mortality as an outcome. In the analysis, age, sex, race, marital status, educational history, household income, smoking history, BMI category were included as covariates. A univariate analysis was performed for each variable. Cross tables were prepared for variables, and associations between the variables were examined using the chi-square test. For variables with strong relevance between variables, an interaction term was created; this term was used as an adjustment variable. In addition, proportional hazards of each variable were confirmed to be maintained using log-log plot survival curves. Covariates and interaction terms were introduced in the Cox proportional hazards model, and HR was obtained while confirming the impact of HR between variables.

The software package JMP Pro11.2 (SAS Institute Inc., Cary, NC, USA) was used for analysis. SPSS20.0 (SPSS Inc., Chicago, IL, USA) was used for plotting log-log survival curves that could not be analyzed using JMP Pro11.2.

The general form of the cox proportional hazards model was:

$$h(t; x) = h_0(t) \cdot \exp(\beta_1 x_1 + \dots + \beta_p x_p)$$

where  $h(t)$  is the hazard function at time  $t$  for a subject with covariate values  $x_1, \dots, x_p$ ,  $h_0(t)$  is the baseline hazard function, *i.e.*, the hazard function when all covariates equal zero.  $\exp$  is the exponential function ( $\exp(x) = e^x$ ),  $x_i$  is the  $i^{\text{th}}$  covariate in the model, and  $\beta_i$  is the regression coefficient for the  $i^{\text{th}}$  covariate,  $x_i$ .

For a single dichotomous covariate, such as values  $j$  and  $i$ , the hazard ratio (HR) was

$$\begin{aligned} HR &= \frac{h(t; x_i)}{h(t; x_j)} = \frac{h_0(t) \exp\{\beta_1 x_{i1} + \dots + \beta_p x_{ip}\}}{h_0(t) \exp\{\beta_1 x_{j1} + \dots + \beta_p x_{jp}\}} \\ &= \exp\{\beta_1(x_{i1} - x_{j1}) + \dots + \beta_p(x_{ip} - x_{jp})\} \end{aligned}$$

HR does not depend on time and is always constant.

### 3. Results

Demographic features of the study participants are shown in **Table 1**.

The number of participants aged  $\geq 45$  years excluding those who died within 2 years after the start of the study was 33,708, and females accounted for 56% of all participants. The median age was 56 years, and the mean age was 60.14 years. The median BMI was 26.6 kg/m<sup>2</sup>, and the mean BMI was 27.45 kg/m<sup>2</sup>. During the 19 years of follow-up, the observation period was 335,219 person years and the mean follow-up period was 9.94 years. The number of deaths during the follow-up period was 10,104, and the mean follow-up period only for death events was 9.91 years. The mean follow-up period from the start of the study until death of the 6942 individuals who had at least one underlying disease and were aged  $\geq 45$  years was 9.46 years, and the mean follow-up period from the start of the study until death of the 3162 individuals without underlying diseases and were aged  $\geq 45$  years was 10.9 years (**Table 2**).

The number of participants aged 45 - 64 years excluding those who died within 2 years after the start of the study was 23,730, and females accounted for 54% of all participants. The median age was 54 years, and the mean age was 54.02 years. The median BMI was 27.1 kg/m<sup>2</sup>, and the mean BMI was 28.04 kg/m<sup>2</sup>. During the 19 years of follow-up, the observation period was 234,192 person years and the mean follow-up period was 9.87 years. The number of deaths during the follow-up period was 3556, and the mean follow-up period only for death events was 11.51 years. The mean follow-up period until death of the 2281 individuals aged 45 - 64 years who had at least one underlying disease was 11.02 years, and the mean follow-up period of the 1275 individuals without underlying diseases was 12.38 years (**Table 3**).

The number of participants aged  $\geq 65$  years excluding those who died within 2 years after the start of the study was 9978, and females accounted for 59% of all participants. The median age was 73 years, and the mean age was 74.7 years. The median BMI was 25.6 kg/m<sup>2</sup>, and the mean BMI was 26.05 kg/m<sup>2</sup>. During the 19 years of follow-up, the observation period was 101,027 person years and the mean follow-up period was 10.12 years. The number of deaths during the follow-up period was 6548, and the mean follow-up period only for death events was 9.04 years. The mean follow-up period until death of the 4661 individuals aged  $\geq 65$  years who had at least one underlying disease was 8.69 years, and the mean follow-up period of the 1887 individuals without underlying diseases was 9.9 years (**Table 4**).

An interaction term was created for each variable among age, gender, race, education history, marital status, household income, smoking history, and BMI categories that showed association using chi-square test and was input as a covariate in the Cox proportional hazards model. No results showed that HR was significantly influenced before and after input of the interaction term. In addition, the proportional hazards for each variable could be confirmed.

**Table 1.** Sociodemographic characteristics.

	≥45 years old						45 - 64 years old						≥65 years old					
	All participants N = 33,708		Underlying disease N = 18,006		Without underlying diseases N = 15,702		All participants N = 23,730		Underlying disease N = 11,338		Without underlying diseases N = 12,392		All participants N = 9978		Underlying disease N = 6668		Without underlying diseases N = 3310	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<b>Gender</b>																		
<b>Female</b>	18,754	56	9906	55	8848	56	12,834	54	6031	53	6803	55	5920	59	3875	58	2045	62
<b>Male</b>	14,954	44	8100	45	6854	44	10,896	46	5307	47	5589	45	4058	41	2793	42	1265	38
<b>Race</b>																		
<b>Non-white</b>	8191	24	5021	28	3170	20	6668	28	3944	35	2724	22	1523	15	1077	16	446	14
<b>White</b>	25,517	76	12,985	72	12,532	80	17,062	72	7394	65	9668	78	8455	85	5591	84	2864	86
<b>Education history</b>																		
<b>Less than a high school education</b>	7916	23	3631	20	4285	27	6348	27	2657	23	3691	30	1568	16	974	15	594	18
<b>High school/higher graduate</b>	25,792	77	14,375	80	11417	73	17,382	73	8681	77	8701	70	8410	84	5694	85	2716	82
<b>Marital status</b>																		
<b>Unmarried</b>	9414	28	5667	31	3747	24	5575	23	3074	27	2501	20	3839	38	2593	39	1246	38
<b>Married/de facto relationship</b>	24,294	72	12,339	69	11955	76	18,155	77	8264	73	9891	80	6139	62	4075	61	2064	62
<b>Annual household income</b>																		
<b>&lt;\$30000</b>	15,071	45	9199	51	5872	37	8273	35	4563	40	3710	30	6798	68	4636	70	2162	65
<b>≥\$30000</b>	18,637	55	8807	49	9830	63	15,457	65	6775	60	8682	70	3180	32	2032	30	1148	35
<b>Smoking history</b>																		
<b>Without smoking history</b>	14,089	42	7236	40	6853	44	9492	40	4265	38	5227	42	4597	46	2971	45	1626	49
<b>With smoking history</b>	19,619	58	10,770	60	8849	56	14,238	60	7073	62	7165	58	5381	54	3697	55	1684	51
<b>BMI category</b>																		
<b>&lt;18.5</b>	504	1	270	2	234	1	255	1	110	1	145	1	249	3	160	2	89	3
<b>18.5 - &lt;22.5</b>	4759	14	1940	11	2819	18	2982	13	899	8	2083	17	1777	18	1041	16	736	22
<b>22.5 - &lt;25</b>	6355	19	2938	16	3417	22	4075	17	1470	13	2605	21	2280	23	1468	22	812	25
<b>25 - &lt;30</b>	13,262	39	6986	39	6276	40	9282	39	4286	38	4996	40	3980	40	2700	40	1280	39
<b>30 - &lt;35</b>	5812	17	3657	20	2155	14	4532	19	2687	24	1845	15	1280	13	970	15	310	9
<b>≥35</b>	3016	9	2215	12	801	5	2604	11	1886	17	718	6	412	4	329	5	83	3

\*Exclude those who died within 2 years of starting tracking.

**Table 2.** BMI category for those  $\geq 45$  years old and HR for all-cause mortality.

	$\geq 45$ years; all participants				$\geq 45$ years; those with underlying disease				$\geq 45$ years; those without underlying disease			
The mean follow-up period (year)	9.94				9.11				10.9			
The mean follow-up period until death	9.91				9.46				10.9			
All participants/death (N)	33,708/10,104				18,006/6942				15,702/3162			
	n	No. of deaths	HR	95% CI	n	No. of deaths	HR	95% CI	n	No. of deaths	HR	95% CI
<b>BMI category</b>												
-18.5	504	279	<b>1.72</b>	<b>(1.51 - 1.95)*</b>	270	182	<b>1.84</b>	<b>(1.57 - 2.15)*</b>	234	97	<b>1.71</b>	<b>(1.37 - 2.11)*</b>
18.5 - 22.5	4759	1738	<b>1.17</b>	<b>(1.1 - 1.25)*</b>	1940	1044	<b>1.20</b>	<b>(1.10 - 1.30)*</b>	2819	694	<b>1.23</b>	<b>(1.11 - 1.37)*</b>
22.5 - 25	6355	2126	1.00	(ref)	2938	1397	1.00	(ref)	3417	729	1.00	(ref)
25 - 30	13,262	3937	0.96	(0.91 - 1.01)	6986	2733	<b>0.90</b>	<b>(0.85 - 0.96)*</b>	6276	1204	0.95	(0.87 - 1.05)
30 - 35	5812	1382	1.00	(0.94 - 1.08)	3657	1053	<b>0.88</b>	<b>(0.81 - 0.95)*</b>	2155	329	1.00	(0.87 - 1.13)
35-	3016	642	<b>1.45</b>	<b>(1.32 - 1.58)*</b>	2215	533	<b>1.20</b>	<b>(1.08 - 1.33)*</b>	801	109	<b>1.30</b>	<b>(1.05 - 1.58)*</b>

Statistically Significant \*, Within 2 years from commencement of tracking Exclusion from death, Covariates; Age, gender, race, marital status, academic background, annual household income, smoking history, BMI category.

**Table 3.** BMI category 45 - 64 years old and HR for all-cause mortality.

	45 - 64 years; all participants				45 - 64 years; with underlying disease				45 - 64 years; without underlying disease			
The mean follow-up period (year)	9.87				8.87				10.78			
The mean follow-up period until death	11.51				11.02				12.38			
All participants/death (N)	23,730/3556				11,338/2281				12,392/1275			
	n	No. of deaths	HR	95% CI	n	No. of deaths	HR	95% CI	n	No. of deaths	HR	95% CI
<b>BMI category</b>												
-18.5	255	74	<b>2.69</b>	<b>(2.09 - 3.40)*</b>	110	46	<b>2.94</b>	<b>(2.13 - 3.97)*</b>	145	28	<b>2.44</b>	<b>(1.61 - 3.55)*</b>
18.5 - 22.5	2982	473	<b>1.20</b>	<b>(1.06 - 1.36)*</b>	899	240	<b>1.25</b>	<b>(1.05 - 1.47)*</b>	2083	233	<b>1.28</b>	<b>(1.07 - 1.52)*</b>
22.5 - 25	4075	597	1.00	(ref)	1470	332	1.00	(ref)	2605	265	1.00	(ref)
25 - 30	9282	1408	1.02	(0.92 - 1.12)	4286	894	0.89	(0.79 - 1.02)	4996	514	1.00	(0.86 - 1.16)
30 - 35	4532	615	1.10	(0.98 - 1.23)	2687	447	0.87	(0.75 - 1.00)	1845	168	1.06	(0.87 - 1.29)
35-	2604	389	<b>1.75</b>	<b>(1.54 - 1.99)*</b>	1886	322	<b>1.26</b>	<b>(1.08 - 1.47)*</b>	718	67	<b>1.57</b>	<b>(1.19 - 2.04)*</b>

Statistically Significant \*, Within 2 years from commencement of tracking Exclusion from death, Covariates; Age, gender, race, marital status, academic background, annual household income, smoking history, BMI category.

**Table 4.** BMI category for those  $\geq 65$  years old and HR for all-cause mortality.

	$\geq 65$ years; all participants				$\geq 65$ years; underlying disease				$\geq 65$ years; without underlying disease			
The mean follow-up period (year)	10.12				9.52				11.3			
The mean follow-up period until death	9.04				8.69				9.9			
All participants/death (N)	9978/6548				6668/4661				3310/1887			
	n	No. of deaths	HR	95% CI	n	No. of deaths	HR	95% CI	n	No. of deaths	HR	95% CI
<b>BMI category</b>												
-18.5	249	205	<b>1.50</b>	<b>(1.29 - 1.74)*</b>	160	136	<b>1.60</b>	<b>(1.33 - 1.91)*</b>	89	69	<b>1.47</b>	<b>(1.13 - 1.89)*</b>
18.5 - 22.5	1777	1265	<b>1.15</b>	<b>(1.07 - 1.24)*</b>	1041	804	<b>1.18</b>	<b>(1.07 - 1.29)*</b>	736	461	<b>1.18</b>	<b>(1.04 - 1.35)*</b>
22.5 - 25	2280	1529	1.00	(ref)	1468	1065	1.00	(ref)	812	464	1.00	(ref)
25 - 30	3980	2529	<b>0.94</b>	<b>(0.88 - 1.00)*</b>	2700	1839	<b>0.92</b>	<b>(0.85 - 0.99)*</b>	1280	690	0.93	(0.82 - 1.04)
30 - 35	1280	767	0.97	(0.89 - 1.06)	970	606	0.91	(0.82 - 1.01)	310	161	0.96	(0.80 - 1.14)
35-	412	253	<b>1.22</b>	<b>(1.07 - 1.39)*</b>	329	211	1.16	(1.00 - 1.34)	83	42	1.04	(0.75 - 1.41)

Statistically Significant \*, Within 2 years from commencement of tracking Exclusion from death, Covariates; Age, gender, race, marital status, academic background, annual household income, smoking history, BMI category.

In each age group ( $\geq 45$ , 45 - 64, and  $\geq 65$  years), the Cox proportional hazards model was used to analyze a group comprising all subjects, a group with underlying diseases, and a group without underlying diseases, considering age, gender, race, education history, marital status, household income, smoking history, and BMI category as variables. BMI 22.5 - 25 kg/m<sup>2</sup> was set as a reference, and HR of the BMI category with 95% CI were calculated. The results showed that in the groups comprising all subjects, with underlying diseases, and without underlying diseases, HR was high if BMI was  $< 18.5$  kg/m<sup>2</sup>, and individuals with BMI 18.5 - 22.5 kg/m<sup>2</sup> who were relatively slim also had a slightly high HR. The 45 - 64 age group showed a higher HR than the  $\geq 65$  age group if BMI was  $< 18.5$  kg/m<sup>2</sup>.

All-subject groups aged 45 - 64 years had a HR  $> 1$  if BMI was 30 -  $< 35$  kg/m<sup>2</sup> or  $> 35$  kg/m<sup>2</sup>, and there was an association between obesity and all-cause mortality, but in all-subject groups aged  $\geq 65$  years; this association was found only if BMI was  $> 35$  kg/m<sup>2</sup>. Further, in any age group with underlying diseases, groups with BMI 25 -  $< 30$  kg/m<sup>2</sup> or 30 -  $< 35$  kg/m<sup>2</sup> had HR  $< 1$ , but if BMI was  $> 35$  kg/m<sup>2</sup>, HR was  $> 1$ , indicating an association between obesity and all-cause mortality.

However, in the subject groups aged  $\geq 65$  years without underlying diseases, with BMI 25 -  $< 30$  kg/m<sup>2</sup>, BMI 30 -  $< 35$  kg/m<sup>2</sup>, or BMI  $> 35$  kg/m<sup>2</sup>, HR was close to 1 and there was no association between obesity and all-cause mortality.

## 4. Discussion

In the present study, over a 19-year follow-up period, subjects in age groups of  $\geq 45$ , 45 - 64, and  $\geq 65$  years were further grouped into subgroups comprising all subjects, those with underlying diseases, and those without underlying diseases. Covariates were used in a Cox proportional hazards model, and HR of each BMI category was calculated. The results revealed that in the group without underlying diseases, a characteristic association was noted between mortality and obesity in individuals aged 45 - 64 and  $\geq 65$  years.

Studies on the association between smoking history and all-cause mortality comparing healthy individuals without underlying diseases and those with underlying diseases have shown that healthy obese individuals who had neither a smoking history nor underlying diseases had higher all-cause mortality rates than obese individuals with a smoking history and underlying diseases [15] [19] [25] [26]. In the present study, individuals aged  $\geq 45$  and 45 - 64 years, individuals without underlying diseases with BMI 25 -  $<30$ , 30 -  $<35$ , or  $>35$  kg/m<sup>2</sup> had higher all-cause mortality rates than those with underlying diseases, which is consistent with previous studies. Despite the fact that previous studies have concluded that adjustment or exclusion of bias due to diseases was not effective when studying the association between obesity and all-cause mortality [23] [42] [43], the present study revealed that the association between obesity and all-cause mortality rate differs depending on the presence or absence of underlying diseases. This appears to confirm the necessity of adjusting for the influence of underlying diseases.

There have been reports that obese adults have higher all-cause mortality rates than the obese elderly [14] [38] and that mortality rates among the obese elderly are lower than those among obese youth [39]. Previous studies have demonstrated that age influences the association between obesity and all-cause mortality rates. However, we were unable to find any study that has analyzed the association between obesity and all-cause mortality rate focusing on underlying diseases and age. As we hypothesized that obesity and all-cause mortality may have an interaction based on age, we analyzed individuals aged 45 - 64 and  $\geq 65$  years in groups comprising all subjects, with underlying diseases, and without underlying diseases. The results indicated that in the all-subject group and in that with underlying diseases, individuals aged  $\geq 65$  years are likely to exhibit a weaker association between obesity with BMI of  $\geq 35$  kg/m<sup>2</sup> and all-cause mortality than those aged 45 - 64 years. Previous studies have reported that among individuals aged  $\geq 65$ , there is no association between obesity and the all-cause mortality rate [44] [45] [46]; however, none of these studies mentioned the influence of underlying diseases. In our study, the group without underlying diseases with BMI  $> 35$  kg/m<sup>2</sup> had a relatively high HR among those aged 45 - 64 years but had an HR of approximately 1 among those aged  $\geq 65$  years. This clearly indicated that age-related interactions were noted in obese individuals aged 45 - 64 years without underlying diseases and obese individuals aged  $\geq 65$  years without un-

derlying diseases. Because obesity increases the all-cause mortality rate, health professionals need to provide health advice and education to obese individuals. The present study suggested that such advice and education should be modified depending on the age of the individuals.

In the present study, questionnaire items were based on self-reported status of underlying diseases, height, weight, and BMI, which may have led to the underestimation of obesity [47]. While this study used self-reported BMI, because it has been reported that there is no significant difference between accurate BMI and self-reported BMI [48], we believe that the results of this study are sufficiently reliable.

In addition, because the mean BMI among Americans is much higher than the BMI defined by WHO as being normal, it is possible that BMI ranges in other nations may greatly differ from those among Americans. Due to a lack of information regarding muscle amount, it was impossible to distinguish between those with a large number of fat cells and those with significant muscle mass, and we were unable to exclude individuals who were not obese despite having a high BMI. Further, as neither the status of underlying diseases that occurred after the study started nor the rate of medical examinations was known, it was not clear whether a person was healthy and obese or was obese with underlying diseases. Moreover, as this study was performed in one country, the results may be different from those of other countries. Despite the above limitations, we consider the outcomes of the present study to be useful in creating strategies and content for health education and management among middle-aged and above obese individuals.

The results of the present study revealed that among obese individuals without underlying diseases, those aged 45 - 64 or  $\geq 65$  years exhibited age-related interactions between obesity and all-cause mortality. This suggests that health professionals may need to modify strategies and content with regard to health-related advice, health education, and health management given to obese middle-aged and above individuals, depending on their age.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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