# Association and Time-Varying Effects of Body Mass Index on All-Cause Mortality in Patients With Hypertension

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# Abstract

Background

The relationship between body mass index (BMI) and mortality in hypertension patients remains controversial. This study aimed to evaluate the association and the time-varying effects of different BMI categories on the risk of all-cause mortality in hypertension patients.

Methods

This retrospective cohort study was conducted among 212,394 Chinese people with hypertension. All deaths were identified based on Shanghai Vital Statistics. Cox model combined with time-by-covariate interactions was used to estimate the association and the time-varying effects of BMI on the risk of all-cause mortality. The potential non-linear effects across follow-up period for BMI were examined by the application of restricted cubic spline (RCS).

Results

Overall, 31,130 deaths occurred (14.7%) within an average follow-up of 8.24 years. Underweight (<18.5 $kg/m^2$) showed a progressively weakening negative effect on all-cause mortality over time. For both sexes, overweight (23.0-24.9 $kg/m^2$) and class I obesity (25.0-29.9 $kg/m^2$) showed protective effects within 5 years after registration, but these became insignificant in later years. There was no significant difference in the effect on all-cause mortality between class II obesity (≥30.0 $kg/m^2$) and normal weight. in the elderly patients, overweight, class I obesity and class II obesity had continuous protective effects on mortality.

Conclusions

Although the effect of baseline body mass index on the risk of all-cause mortality varied at different follow-up periods, underweight persistently remained a risk factor for all-cause mortality in hypertension, whereas overweight and class I obesity had protective effects. Thus, in the long-term management of hypertension, more attention should be given to underweight patients.


# Background

Hypertension is a major risk factor for cardiovascular disease and premature death, and its increasing prevalence has caused a heavy burden on healthcare not only in Western countries, but also in Asian countries.[1-4] Obesity as a rapidly growing public health problem has been proven to be associated with higher risk of hypertension.[5, 6] In this context, all major international guidelines recommend weight loss as part of the treatment for hypertension. However, the relationship between body mass index (BMI) and mortality in hypertension patients remains controversial.[7, 8] Liu et al. reported that compared with normal weight, overweight and obesity can reduce the risk of all-cause mortality.[9] In contrast, other retrospective cohort studies of adult hypertension showed no difference in mortality between those with overweight and

normal BMI.[10, 11] These conflicting correlations may be partly due to the difference in the design, sample size, and BMI classification criteria among the studies.

In addition, these previous studies all used the Cox proportional hazard (PH) model to illustrate the relationship between BMI and death in hypertension patients. This model based on the following fundamental assumption: the proportionality of hazards, which means that the factors investigated have a sustained impact on the hazard - or risk - over time.Therefore, biased estimates will be obtained if time-varying factors that violate the PH assumption are included as time-independent factors. Moreover, if the variable only has an effect on the outcomes during a certain follow-up period and has no effect during the rest of the follow-up period, then this effect may also be missed when using the Cox regression model. Therefore, detecting and accounting for time-varying effects are essential in the modeling process and helpful for providing valuable information about the effects of changes over time.[12-14] However, there have been few studies on the time-varying effects of BMI on mortality in patients with long-standing hypertension.

Based on a comprehensive network health information system, standardized management of hypertension patients as a basic community medical service has been carried out. The Community Health Service Center collects and records the basic information of these participants in the electronic health record (eHR) database since 2007 in Minhang District, Shanghai, including demographic information, self-reported height and weight, drugs for the treatment of hypertension, family history of major chronic diseases, diabetic comorbidities and daily physical exercise, smoking, and drinking.[15, 16]The purpose of this study was to assess the association and the time-varying effects of different levels of BMI on all-cause mortality based on the standardized management system of hypertension in Shanghai, China.

# Methods

### Study design and subjects

This was a retrospective cohort study of hypertension patients aged 20-85 years in Shanghai, China. Hypertension is defined as systolic blood pressure (SBP) ≥140mmHg or diastolic blood pressure (DBP) ≥90mmHg according to the guidelines of the World Health Organization(WHO).Between 2007 and 2015, 260,416 patients with hypertension received in standardized management from general practitioners. Of them, we excluded 48,022 patients with missing demographic data (n=2,361), permanent residents who were not registered in Shanghai (n=27,978), baseline age <20 or ≥85 years (n=8,114), follow-up time of less than 3 months (n=3,788), missing data on height/weight or those with extreme BMI (≥40.0 $kg/m^2$) (n=5,001), and those with missing data on any other risk factors (n=780). Finally, 212,394 (99,038 men and 113,356 women) participants were included in the analysis.

### Definition of Variables

BMI was calculated by dividing the body weight (kg) with the square of the height (m). We used a modified BMI classification for Asians recently recommended by the WHO as follows: underweight, 18.5 $kg/m^2$;

normal, 18.5-22.9 kg/$m^2$; overweight, 23-24.9 kg/$m^2$; obese grade I, 25-29.9 kg/$m^2$; and obese grade II, ≥30 kg/$m^2$).[17] Diabetes was diagnosed based on the current WHO diagnostic criteria: fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2-h plasma glucose ≥11.1 mmol/L (200 mg/dl). Smoking was classified as never smoking or smoking, defined as smoking at least one year per day, including quitting. Drinking was divided into never drinkers; occasional drinkers; and regular drinkers, defined as drinking at least twice a week for more than 1 year. Exercise is divided into rarely exercise; occasional exercise; and regular exercise, defined as engaging in at least 150 minutes of moderate-intensity physical activity a week, or at least 75 minutes of high-intensity activity a week.

### Outcome Assessment

The primary study endpoint was deaths from all-causes. All-cause mortality included death due to any reason. The observation period ended on December 31, 2018. Each participant was followed up to record all-cause mortality, which was verified using specific identification numbers from the Shanghai Vital Statistics Bureau. The Shanghai Vital Statistics System is a population-based registration system that receives the death certificates from more than 400 hospitals in Shanghai. These certificates are in turn routinely verified by the district and Shanghai CDC.

### Statistical analysis

The participants were divided into five groups according to the WHO BMI classification for Asians described above. The baseline participant characteristics were compared using variance (ANOVA)analysis for continuous variables and the $\chi^2$ test for categorical variables. Survival curves by BMI group and sex were generated using the Kaplan-Meier method and compared using the log-rank test. The possible risk factors for all-cause mortality included age, sex (male/female), SBP, diabetic comorbidities (yes/no), family history of cardiovascular disease (yes/no), family history of diabetes (yes/no), family history of stroke (yes/no), family history of hypertension (yes/no), BMI (<18.5/18.5-22.9/23-24.9/25.0-29.9/≥30.0 kg/$m^2$), participation in exercise (rare/occasional/frequent), smoking status (yes/no), and drinking status (never/occasional/regular). Multivariate analysis using forward stepwise regression procedures were performed to identify the risk factors of all-cause mortality, excluding the family history of stroke. The polytomous variables were processed using dummy variables while binary variables entered the model directly.

We first examined the PH hypothesis of the variables in the Cox PH model by fitting the interaction between each variable and time as a 3-knot restricted cubic splines (RCS) function.[18]The hazard function, denoted by h(t), is given using the following formula:

$$h(t)=h_0(t)\exp[\beta_1 x+\beta_2 xt+\beta_3 xS(t)]$$

where x equals the factor value; t, time; and S (t), the non-linear part of the cubic spline time function. Three statistical tests were performed during this process, corresponding to three invalid hypotheses and *P*-values.

(1) $H_0$: β1=β2=β3=0 and "*P* for overall association;" *P*<0.05 indicated that this variable was a risk factor for death. (2)$H_0$: β2=β3=0and "*P* for PH assumption;" *P*<0.05 indicated that the variable does not meet the PH hypothesis, and the HR of the variable changes with time. (3) $H_0$:β3=0and "*P* for non-linearity." If the variable violated the PH hypothesis, then P<0.05 indicated that the influence of the variable is non-linear and the macro% RCS was needed, the knots were set at the $10^{th}$, $50^{th}$, and $90^{th}$ percentiles. Otherwise, when the effect of the variable shows a linear change trend, the formula was reduced to $h(t)=h_0(t)\exp[\beta_1 x+\beta_2 xt)$. [19, 20]Then, we conducted a stratified analysis of sex and age, incorporated the adjusted variables that did not meet the PH hypothesis into the model, and compared the relationship between different BMI categories and all-cause mortality after controlling for sex and age. Patients who died within 2 years after enrollment were excluded from the sensitivity analysis to solve possible causal inversion. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA). All test were two-sided, and P<0.05 was considered significant.

# Results

### Patient characteristics

The average participant age was 63.3 years (range, 20-85 years), and the average follow-up period was 8.2 years. In total, 99,038 participants were men (46.6%) and 113,356 were women (53.4%), and the total follow-up time was 797,272 person-years and 952,266 person-years, respectively. Overall, 31,130 patients (14.7%) died during the follow-up; of these, 16,600 and 14,530 were men and women, respectively.

Table 1 shows the baseline characteristics of the study population by BMI group. There were significant differences in demographic characteristics, lifestyle, clinical characteristics, and family history of chronic disease between the five groups. In total, 80% of the participants in the underweight group were elderly. In addition, the underweight group also showed a lower proportion of diabetic comorbidities, family history of chronic diseases, smoking, and drinking than did the other BMI groups. Meanwhile, the proportion of deaths was significantly higher in the underweight group than that in the other BMI groups.

### Survival and time-varying effect analysis

Figure 1 shows the survival rates of the BMI groups by sex. In both sexes, the cumulative survival rate of underweight patients was significantly lower than that of the other BMI groups. Meanwhile, the cumulative survival rates of the overweight and obese group were higher than that of the normal weight group.

With respect to the time-varying effect, the results showed that BMI did not meet the PH hypothesis and showed a linear trend over time (variable*time). Table 2 shows the adjusted HRs of all-cause mortality at 1, 5, and 10 years after registration. As shown, the time-varying effects were similar for both sexes. The risk of all-cause mortality in the underweight group was markedly higher than that in the other BMI groups, and its risk effects decreased over time. Compared with normal weight, overweight and class I obesity had a protective effect against all-cause mortality. In the first 5 years after registration, the protective effect of overweight in male patients increased from 0.84 (95% CI: 0.79-0.90) at 1 year after registry to 0.87 (95% CI:

0.84-0.91) at 5 years after registry. Overweight was protective in the first 5 years after registration for women, but its effect turned insignificant in 10 years after registration. The HRs for class I obesity exhibited an upward trend. In men, it increased from 0.73 (95% CI: 0.68-0.79) at 1 year after registry to 0.82 (95% CI: 0.79-0.86) at 5 years after registry. In women, it increased from 0.82 (95% CI: 0.76-0.89) to 0.92 (95% CI: 0.89-0.96), respectively. However, the protective effect of class I obesity on all-cause mortality decreased 10 years after registration, and there was no longer any significant difference from normal weight. The effect of class II obesity on all-cause mortality was not significantly different from that of normal weight. However, in the late follow-up period of female patients, class II obesity was shown to increase the risk of all-cause mortality. The results of the sensitivity analysis were basically the same, but after 10 years of registration, the effect of class II obesity for women on death became insignificant. Visual demonstrations of the time-varying effects of BMI are presented in Figure 2.

We also conducted a stratified analysis of age to explore the time-varying effect of different BMI classifications on all-cause mortality in hypertension patients in different age groups. The age cut-off was set to 60 years. As shown in Table 3, underweight had a negative impact on death among patients of all age groups, but this effect gradually decreases over time. Elderly patients (≥60 years) dropped from the initial HR 1.89 (95% CI: 1.73-2.07)to 1.50 (95% CI: 1.35-1.67) 10 years after registration; while young and middle-aged patients ( Age<60 years) declined from HR 2.34 (95% CI: 1.58-3.47) at 1 year after registration to 1.99 (95% CI: 1.23-3.20) at 10 years after registration.Overweight and class I obesity were protective factors, but in young and middle-aged patients, their effects also reduced over time. It was worth noting that compared with young and middle-aged patients, overweight and obesity had sustained protective effects in the elderly. The results of the sensitivity analysis remained unchanged. Figure 3 shows more visual results. The sensitivity analysis results of sex and age were shown in figure 4 and table 4, figure 5 and table 5 respectively.

# Discussion

In this study, we explored the association and the time-varying effects of BMI on mortality in patients with hypertension in a large retrospective cohort. Being underweight was associated with a higher risk of all-cause mortality, but the adverse effects of underweight gradually diminished over time. Meanwhile, overweight and class 1 obesity had a protective effect on death in both sexes, but its beneficial effects were also only observed in the first 5 years after registration. However in the elderly, overweight, class I obesity and class II obesity had continuous protective effects on mortality. To the best of our knowledge, this is the first study to evaluate the time-varying effects of BMI on all-cause mortality in people with hypertension within a long-term follow-up period. Our findings provide useful data for guiding the long-term management of hypertension patients.

Hypertension is a major public health concern worldwide, and thus the risk factors for all-cause mortality in patients with hypertension have become the subject of many studies. Our findings are consistent with those of previous studies that explored the relationship between BMI and all-cause mortality in hypertension patients and found that underweight is a risk factor for all-cause mortality, whereas

overweight and obesity have protective effects on survival.[16, 21, 22] Xu et al. found a higher risk of mortality among patients who were underweight (<18.5 kg/$m^2$) than their normal weight counterparts (18.5-24.9 kg/$m^2$) (HR=1.75, 95% CI: 1.63-1.87).[11] Several prospective studies conducted in Japan and other Asian countries have also reached similar conclusions.[23, 24]These findings could be because chronic disease, prior to the diagnosis of hypertension, may lead to weight loss and an increased risk of death. However, the time-varying changes in the HRs of BMI have not been evaluated.

Based on previous studies, this study explored the effects of different BMI categories on the long-term survival of hypertension patients using a time-dependent Cox regression model in a relatively large sample and long-term follow-up cohort. At 1 year after registration, the risk of death for underweight patients was higher than that at 5 and 10 years after registration. This may be because hypertension patients nearing death have poor physical condition and thus seek more aggressive medical management. Thus, more patients were identified and received treatment. Underweight patients who survived medical management may consciously gain weight in search of a higher survival rate, which may explain the weakening of the role of underweight on mortality over time. In addition, at different follow-up time points, even 10 years after registration, the risk of all-cause mortality in underweight patients with hypertension was higher than that of normal weight patients. This ruled out the possible causal inversion of weight loss when impending death in studies of underweight patients with high mortality.[25]

Evidence of the obesity paradox has been found in many cardiovascular disease studies——that is, compared with patients of normal weight, measured by all-cause mortality，overweight and obese patients have improved short-term and long-term survival——including coronary heart disease, myocardial infarction, atrial fibrillation, heart failure as well as hypertension. Most of these studies were conducted in patient cohorts recruited from elderly subjects.[22, 26-30]In 1985, Barrett-Connor and Khaw conducted an index study on 1,727 male patients with hypertension between the ages of 50 and 79, and for the first time proposed that overweight and obesity reduced all-cause mortality.[31]Yang et al. evaluated 20694 hypertension patients aged 45-75 years in China and found that compared with those with normal weight (BMI, 18.5-23.9 kg/$m^2$), the risk for mortality was lower in those who were overweight (BMI, 24.0-27.9 kg/$m^2$) (HR=0.78) and obese (BMI ≥28 kg/$m^2$) (HR=0.64).[32] Jayedi et al. conducted a meta-analysis of a prospective and retrospective cohort study to investigate the relationship between BMI and all-cause mortality in hypertension patients and found the lowest mortality rate in those with a BMI of 27.5-30 kg/$m^2$.[33]Consistent findings were found in the current study that overweight and obesity had protective effects on mortality especially in elderly patients. One of the physiological explanations emphasized that patients who are defined as obese according to the BMI cut-off point may have healthy metabolic characteristics. Compared with non-obese individuals with many risk factors (such as dyslipidemia), obese individuals with healthy metabolic characteristics may have a lower risk of mortality.[34, 35]In addition, a prospective study that measured sympathetic nerve activity in heart failure using the cardiac norepinephrine spillover method found higher activity in normal weight hypertension patients than their obese counterparts. This supports that obese hypertension patients do not experience the toxic effects of sympathetic nerve activation.[30, 36, 37]

Compared with the young and middle-aged patients, relatively stable protective effects of overweight and obesity were shown in the elderly over time. One possible reason is that aging is related to fat redistribution. Although there is evidence that there is a biological advantage in excess fat storage during disease. Body fat may play a role in reducing oxidative stress and inflammation, lowering the level of B-type natriuretic peptide, and improving the secretion of amino acids and adipokines, which may improve the survival rate of obese individuals.[38-40]But with age, body composition will change as fat mass increases and muscle mass decreases. In other words, even if the weight and BMI are the same, the elderly may have more fat mass than the young and middle-aged.[41]Adipose tissue can also produce soluble TNF-α receptor to neutralize the adverse effects of TNF-α, which is related to the worse prognosis of these patients.[42, 43] In addition, aging is related to a significant decrease in energy expenditure and fat oxidation, a decrease in skeletal muscle mass, and an increase in visceral fat accumulation. Therefore, the protective effect of nutritional status in overweight and obese elderly may be the reason for this phenomenon.[44]Besides, it is worth noting that in our study, with the exclusion of the elderly, overweight and class I obesity no longer had significant protective effects compared with normal weight at 10 years after registration. Although overweight still had a protective effect in men at 10 years after registration, the time-varying effects of BMI for both sexes were similar, and the HRs that changed with time increased linearly. Sensitivity analysis also yielded similar results. A possible reason is that the good survival of overweight patients may be related to the high prevalence of relatively benign comorbidities (e.g., well-controlled hypertension). As the follow-up time is extended, the condition deteriorates, and overweight patients no longer have survival advantages. Given that previous studies explaining the obesity paradox did not reveal the time-varying effects of overweight and class I obesity on all-cause mortality in hypertension patients over time, whether overweight and obesity can achieve long-term survival advantages in young and middle-aged patients needs further verification. It is necessary to treat obesity as a time-varying exposure and take into account changes in weight status to understand the relationship between true obesity and mortality.

The primary strength of this study was that a large sample population was followed up for 8 years. The electronic health records of residents in Minhang District provide comprehensive and accurate retrospective cohort data, including demographic information and physiological indicators. Because this is a long-term follow-up study, the Cox PH model with time-varying coefficients may be more suitable for data analysis than the Cox model. The use of RCS to assess time-by-covariate interactions also allowed us to evaluate the PH assumption and evaluate whether the factor's HR changes linearly or non-linearly with time, which violated the assumption, and then graphically display the correlation between the risk factor and the research outcomes. Furthermore, we adopted the standard BMI classification for Asians, which differs greatly from the Western population in body composition. At a given BMI, the proportion of body fat in the Asian population tends to be higher, thus making them susceptible to cardiovascular disease.[17]Therefore, the results of studies may vary under different populations, races, or BMI classification standards. The BMI classification standard adopted in this study is more suitable for this research population to obtain more accurate conclusions. In addition, we conducted a stratified analysis based on sex and age to eliminate potential confounding effects and further revealed the association between BMI and outcomes in hypertension patients of different sexes and ages.

However, this study also has some limitations. First, the BMI index alone cannot distinguish central obesity from abdominal obesity. Robustness and obesity may also lead to the same BMI, and thus the interpretation of the results may be biased. Second, the number of patients who were underweight or overweight was relatively small, especially after stratified analysis of age. This reduced the statistical power of BMI in different age groups on the time-varying effect of all-cause mortality. Third,the possibility of a selection bias, which may have influenced the results, could not be ruled. Obese patients are more likely to seek treatment and disease management and thus may achieve a higher survival rate. In the future, when further studying the relationship between BMI and mortality in patients with hypertension, we should consider the changes in dynamic BMI or include the body fat percentage in the analysis.

# Conclusions

We propose that the association and time-varying effects of different BMI categories on the risk of all-cause mortality in hypertension patients. Study can guide medical staff and primary medical institutions to manage hypertension patients, and also provides a basis for the revision and promotion of guidelines for weight management of patients with hypertension. The BMI should be studied as an intervention in patients with hypertension, especially underweight or overweight patients, to determine the long-term effects of optimal weight on prognosis in this patient group.

# Abbreviations

BMI: body mass index; BP: blood pressure; DBP: diastolic blood pressure; her: electronic health record; ICD: International Classification of Diseases; PH: proportional hazard; RCS: restricted cubic splines; SBP: systolic blood pressure; WHO: World Health Organization

# Declarations


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### Authors' contributions

GYQ and HLX conceived the idea and was responsible for the primary design of the study. JJZ and HLX conducted data extraction and statistical analyses. JJZ and XHL developed the first draft of the manuscript. JLZ, JL and LLC involved in data acquisition and check. GYQ and HLX contributed to data interpretation. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.


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### Availability of data and materials

The datasets generated and analyzed in the study are not publicly available but are available from the corresponding authors on reasonable request.

### Ethics approval and consent to participate

The study was approved by the Institutional Review Board of center for disease control and prevention in Minhang District, Shanghai (NO: EC-P-2019-009). Informed consent from participants involved in the study was waived due to the fact that anonymized data compiled from electronic medical records was applied in the study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that there is no duality of interest associated with this manuscript.

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# Tables

**Table 1. Baseline characteristics according to BMI categories in people with hypertension**

| Characteristic | BMI (WHO category, kg/m$^2$) | | | | | *P* |
|---|---|---|---|---|---|---|
| | Underweight (N=5120) | Normal weight (N=70093) | Overweight (N=60437) | Class I obesity (N=68583) | Class II obesity (N=8161) | |
| Age ($\bar{x}$±SD, year) | 69.9±10.8 | 65.1±10.9 | 62.8±10.5 | 61.6±10.6 | 60.1±11.5 | <0.001 |
| 60 years | 1022(19.9) | 24324(34.7) | 25415(42.1) | 31808(46.4) | 3838(47.0) | <0.001 |
| ≥ 60 years | 4098(80.1) | 45769(65.3) | 35022(57.9) | 36775(53.6) | 4323(53.0) | |
| Follow-up time (years) | 7.5±3.2 | 8.1±2.8 | 8.3±2.7 | 8.4±2.7 | 8.2±2.7 | <0.001 |
| Sex (%) | | | | | | |
| Male | 2096(40.9) | 30992(44.2) | 29663(49.1) | 33123(48.3) | 3164(38.8) | <0.001 |
| Female | 3024(59.1) | 39101(55.8) | 30774(50.9) | 35460(51.7) | 4997(61.2) | |
| sbp ($\bar{x}$±SD) | 155.3±15.5 | 154.2±14.7 | 154.3±14.8 | 155.3±15.6 | 157.1±16.5 | <0.001 |
| dbp($\bar{x}$±SD) | 92.1±9.3 | 92.9±8.8 | 93.7±9.0 | 94.8±9.5 | 95.6±10.1 | <0.001 |
| Diabetic comorbidities | | | | | | |
| Yes | 697(13.6) | 11217(16.0) | 10471(17.3) | 13188(19.2) | 1854(22.7) | <0.001 |
| No | 4423(86.4) | 58876(84.0) | 49966(82.7) | 55395(80.8) | 6307(77.3) | |
| Death | | | | | | |
| Yes | 1738(33.9) | 12396(17.7) | 7905(13.1) | 8028(11.7) | 1063(13.0) | <0.001 |
| No | 3382(66.1) | 57697(82.3) | 52532(68.9) | 60555(88.3) | 7098(87.0) | |
| Family history of hp (%) | | | | | | |
| Yes | 1654(32.3) | 27635(39.4) | 26019(43.1) | 32659(47.6) | 4054(49.7) | <0.001 |
| No | 3466(67.7) | 42458(60.6) | 34418(56.9) | 35924(52.4) | 4107(50.3) | |
| Family history of cvd (%) | | | | | | |
| Yes | 110(2.2) | 1680(2.4) | 1539(2.6) | 2179(3.2) | 330(4.0) | <0.001 |
| No | 5010(97.8) | 68413(97.6) | 58898(97.4) | 66404(96.8) | 7831(96.0) | |
| Family history of stro (%) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yes | 110(2.2) | 1764(2.5) | 1621(2.7) | 2217(3.2) | 280(3.4) | <0.001 |
| No | 5010(97.8) | 68329(97.5) | 58816(97.3) | 66366(96.8) | 7881(96.6) | |
| Family history of dm (%) | | | | | | |
| Yes | 177(3.5) | 3223(4.6) | 3199(5.3) | 4607(6.7) | 615(7.5) | <0.001 |
| No | 4943(96.5) | 66870(95.4) | 57238(94.7) | 63976(93.3) | 7546(92.5) | |
| Exercise (%) | | | | | | |
| Never | 2043(39.9) | 22557(32.2) | 18779(31.1) | 22079(32.2) | 2926(35.9) | <0.001 |
| Sometimes | 2054(40.1) | 30941(44.1) | 26801(44.3) | 30191(44.0) | 3487(42.7) | |
| Everyday | 1023(20.0) | 16595(23.7) | 14857(24.6) | 16313(23.79) | 1748(21.4) | |
| Smoke (%) | | | | | | |
| Yes | 867(16.9) | 13042(18.6) | 13222(21.9) | 16108(23.5) | 1624(19.9) | <0.001 |
| Never | 4253(83.1) | 57051(81.4) | 47215(78.1) | 52475(76.5) | 6537(80.1) | |
| Drink (%) | | | | | | |
| Never | 4424(86.4) | 57359(81.8) | 46961(77.7) | 52218(76.1) | 6546(80.2) | <0.001 |
| Sometimes | 430(8.4) | 8407(12.0) | 8897(14.7) | 10332(15.1) | 978(12.0) | |
| Always | 266(5.2) | 4327(6.2) | 4579(7.6) | 6033(8.8) | 637(7.8) | |

**Table 2. Time-varying HRs and 95% CIs form risk factors of different sex in association with all-cause death from Multivariate Cox models.**

| BMI(kg/m$^2$) | HR(95%CI) | | |
|---|---|---|---|
| | all cause of death(N=212394,death=31130) | | |
| | 1-year | 5-year | 10-year |
| Male(N=99038) | | | |
| Underweight | 1.52(1.34-1.71) | 1.45(1.35-1.56) | 1.38(1.19-1.60) |
| Normal weight | 1 | | |
| Overweight | 0.84(0.79-0.90) | 0.87(0.84-0.91) | 0.92(0.85-0.98) |
| Class I obesity | 0.73(0.68-0.79) | 0.82(0.79-0.86) | 0.94(0.88-1.02) |
| Class II obesity | 0.90(0.75-1.09) | 0.95(0.86-1.05) | 1.01(0.83-1.24) |
| Female(N=113356) | | | |
| Underweight | 1.54(1.36-1.74) | 1.41(1.31-1.51) | 1.26(1.09-1.45) |
| Normal weight | 1 | | |
| Overweight | 0.84(0.78-0.91) | 0.91(0.87-0.95) | 0.99(0.91-1.07) |
| Class I obesity | 0.82(0.76-0.89) | 0.92(0.89-0.96) | 1.07(0.99-1.15) |
| Class II obesity | 1.12(0.97-1.30) | 1.14(1.05-1.24) | 1.17(1.01-1.36) |

*Adjust the age at diagnosis, systolic blood pressure, diastolic blood pressure, BMI, family history of diabetes, family history of hypertension, family history of cardiovascular disease, smoking status, drinking status and exercise status.

**Table 3. Time-varying HRs and 95% CIs form risk factors of different ages in association with all-cause death from Multivariate Cox models.**

| BMI(kg/m$^2$) | HR(95%CI) | | |
|---|---|---|---|
| | all cause of death(N=212394,death=31130) | | |
| | 1-year | 5-year | 10-year |
| Age<60(N=86407) | | | |
| Underweight | 2.34(1.58-3.47) | 2.18(1.72-2.74) | 1.99(1.23-3.20) |
| Normal weight | 1 | | |
| Overweight | 0.64(0.54-0.76) | 0.79(0.72-0.87) | 1.03(0.85-1.24) |
| Class I obesity | 0.59(0.50-0.70) | 0.75(0.69-0.83) | 1.01(0.85-1.21) |
| Class II obesity | 0.83(0.61-1.14) | 1.00(0.84-1.19) | 1.24(0.89-1.73) |
| Age≥ 60(N=125987) | | | |
| Underweight | 1.89(1.73-2.07) | 1.71(1.62-1.80) | 1.50(1.35-1.67) |
| Normal weight | 1 | | |
| Overweight | 0.74(0.70-0.78) | 0.78(0.76-0.80) | 0.83(0.78-0.88) |
| Class I obesity | 0.64(0.60-0.67) | 0.72(0.70-0.75) | 0.85(0.80-0.90) |
| Class II obesity | 0.80(0.70-0.90) | 0.82(0.77-0.88) | 0.86(0.76-0.98) |

*Adjust the sex, systolic blood pressure, diastolic blood pressure, BMI, family history of diabetes, family history of hypertension, family history of cardiovascular disease, smoking status, drinking status and exercise status.

**Table 4. Time-varying HRs and 95% CIs form risk factors of different sex in association with all-cause death in sensitivity analysis.**

| BMI(kg/m$^2$) | HR(95%CI) | | |
|---|---|---|---|
| | all cause of death(N=212394,death=31130) | | |
| | 1-year | 5-year | 10-year |
| Male(N=99038) | | | |
| Underweight | 1.55(1.36-1.77) | 1.46(1.36-1.58) | 1.36(1.17-1.59) |
| Normal weight | 1 | | |
| Overweight | 0.81(0.76-0.88) | 0.86(0.83-0.90) | 0.93(0.86-1.00) |
| Class I obesity | 0.72(0.67-0.78) | 0.82(0.78-0.85) | 0.95(0.88-1.02) |
| Class II obesity | 0.91(0.74-1.11) | 0.95(0.85-1.06) | 1.01(0.82-1.24) |
| Female(N=113356) | | | |
| Underweight | 1.51(1.31-1.74) | 1.40(1.30-1.51) | 1.27(1.10-1.47) |
| Normal weight | 1 | | |
| Overweight | 0.86(0.79-0.94) | 0.91(0.87-0.96) | 0.98(0.90-1.06) |
| Class I obesity | 0.83(0.76-0.90) | 0.92(0.88-0.96) | 1.06(0.98-1.14) |
| Class II obesity | 1.16(0.98-1.36) | 1.15(1.06-1.26) | 1.15(0.99-1.34) |

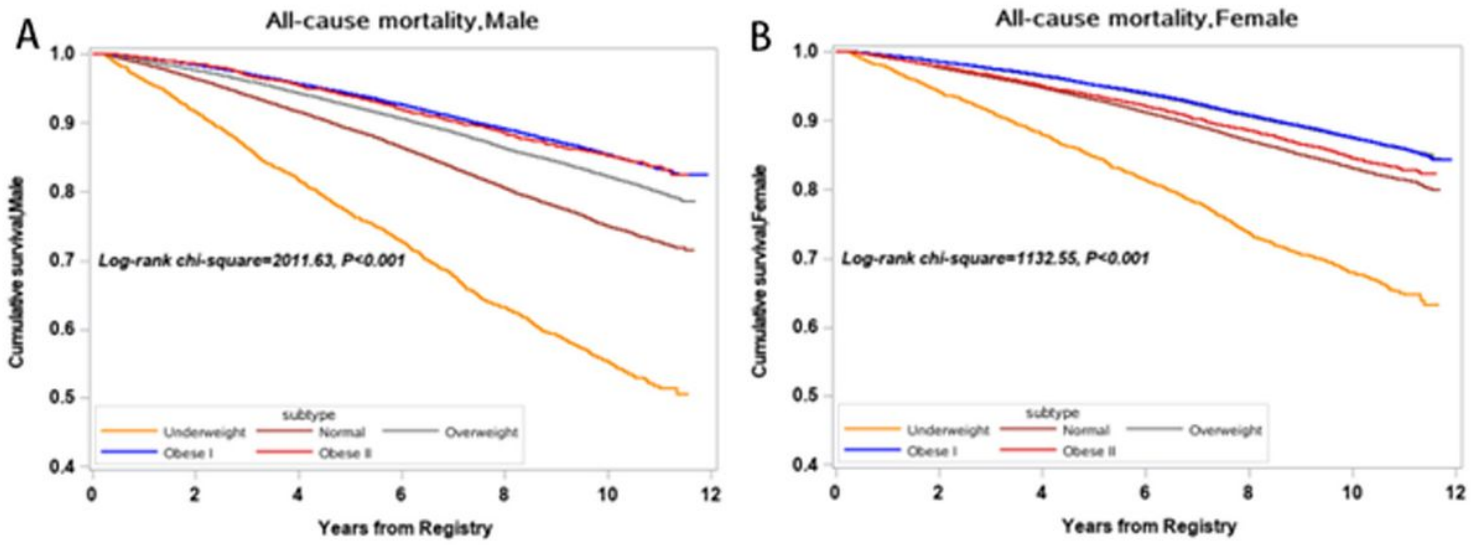
*Adjust the age at diagnosis, systolic blood pressure, diastolic blood pressure, BMI, family history of diabetes, family history of hypertension, family history of cardiovascular disease, smoking status, drinking status and exercise status.

**Table 5. Time-varying HRs and 95% CIs form risk factors of different ages in association with all-cause death in sensitivity analysis.**

| BMI(kg/m$^2$) | HR(95%CI) | | |
|---|---|---|---|
| | all cause of death(N=212394,death=31130) | | |
| | 1-year | 5-year | 10-year |
| Age<60(N=86407) | | | |
| Underweight | 2.56(1.69-3.88) | 2.24(1.77-2.84) | 1.90(1.17-3.10) |
| Normal weight | 1 | | |
| Overweight | 0.65(0.53-0.78) | 0.79(0.72-0.88) | 1.03(0.85-1.24) |
| Class I obesity | 0.58(0.48-0.69) | 0.75(0.68-0.82) | 1.03(0.86-1.23) |
| Class II obesity | 0.89(0.64-1.23) | 1.02(0.85-1.22) | 1.22(0.87-1.71) |
| Age≥ 60(N=125987) | | | |
| Underweight | 1.89(1.71-2.09) | 1.71(1.62-1.80) | 1.50(1.35-1.67) |
| Normal weight | 1 | | |
| Overweight | 0.74(0.69-0.78) | 0.78(0.75-0.80) | 0.83(0.79-0.88) |
| Class I obesity | 0.63(0.60-0.67) | 0.72(0.70-0.75) | 0.85(0.80-0.90) |
| Class II obesity | 0.80(0.69-0.91) | 0.82(0.77-0.89) | 0.86(0.76-0.98) |

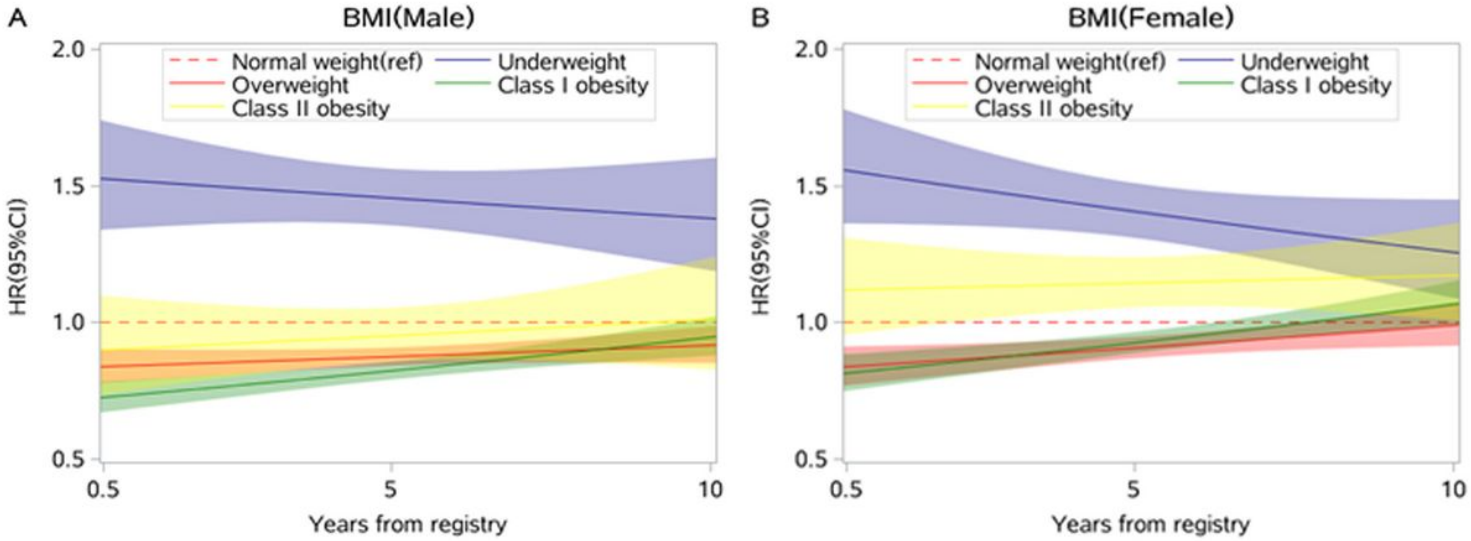
*Adjust the sex, systolic blood pressure, diastolic blood pressure, BMI, family history of diabetes, family history of hypertension, family history of cardiovascular disease, smoking status, drinking status and exercise status.

# Figures



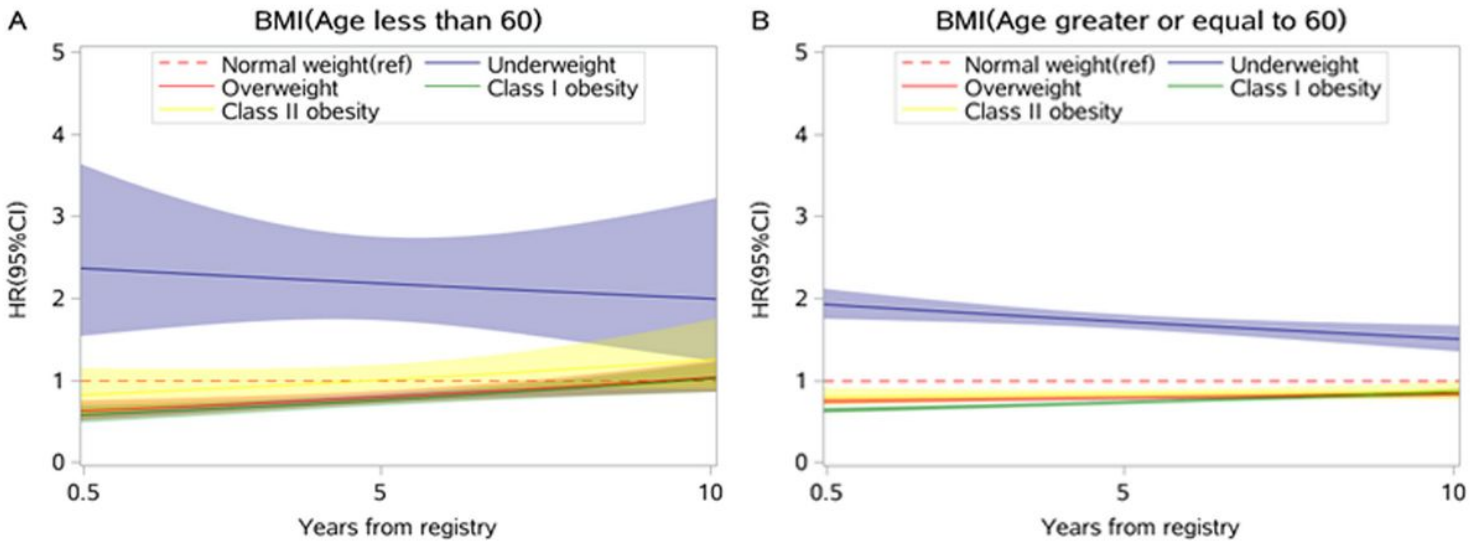
## Figure 1

Survival curves with regard to different categories of BMI in both sexes for all-cause mortality.



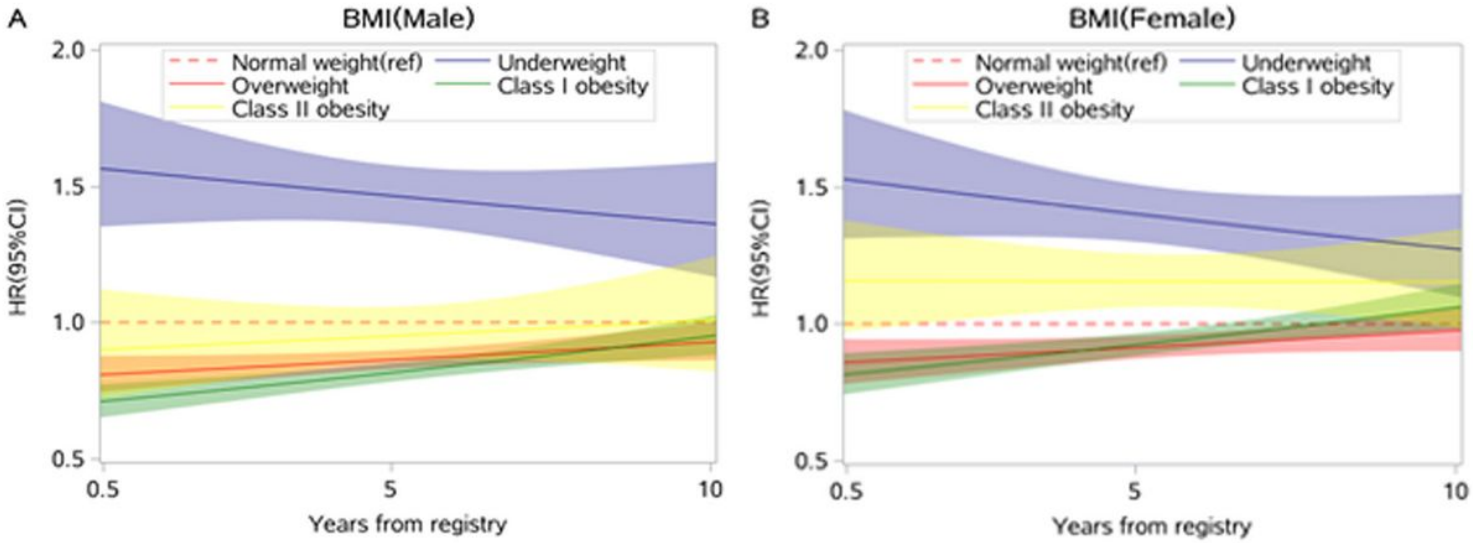

## Figure 2

Time-varying effects of BMI on all-cause mortality among hypertension patients of different sexes. The dashed red line indicates the reference value (HR = 1), and the light yellow, light red, light green, and light purple bands indicate 95% CI. Because the data is sparse, the curves are truncated at 0.5 and 10 years after diagnosis.



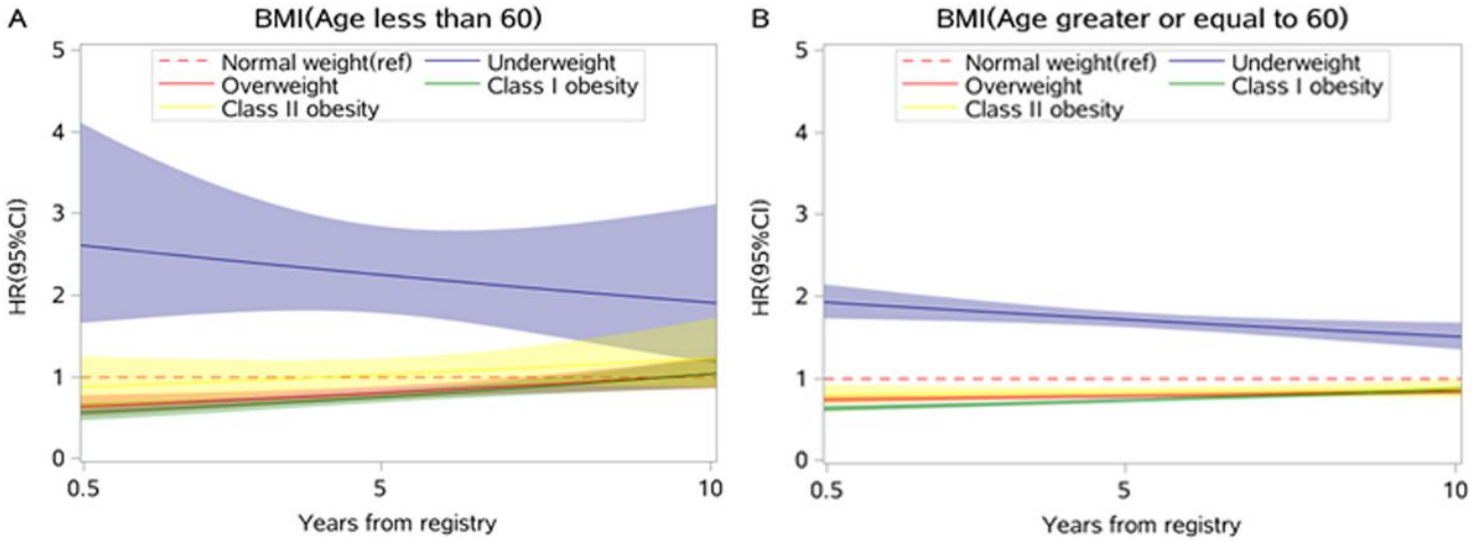

## Figure 3

Time-varying effects of BMI on all-cause mortality among hypertension patients of different ages. The dashed red line indicates the reference value (HR = 1), and the light yellow, light red, light green, and light purple bands indicate 95% CI. Because the data is sparse, the curve is truncated at 0.5 and 10 years after diagnosis.




## Figure 4

Time-varying effects of BMI on all-cause mortality in sensitivity analysis for sexes. The dashed red line indicates the reference value (HR = 1), and the light yellow, light red, light green, and light purple bands indicate 95% CI. Because the data is sparse, the curves are truncated at 0.5 and 10 years after diagnosis.




## Figure 5

Time-varying effects of BMI on all-cause mortality in sensitivity analysis for different ages. The dashed red line indicates the reference value (HR = 1), and the light yellow, light red, light green, and light purple bands indicate 95% CI. Because the data is sparse, the curve is truncated at 0.5 and 10 years after diagnosis.