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A Two-Decade Population-Based Study on the Effect of Hypertension in the General Population with Obesity in the United States

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Data Availability

Data were retrieved from the National Health and Nutrition Examination Survey Registry.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from IRB review as no confidential patient information was involved.

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All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables has not been previously published and that the manuscript is not under consideration elsewhere.

Authors' Contributions

All authors approve the final version of the manuscript, including the authorship list and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

STUDY IMPORTANCE QUESTIONS

What is already known about this subject?

- Hypertension significantly increases the risk of mortality, cardiovascular diseases and stroke compared to those without hypertension in the general population with obesity.

What are the new findings in your manuscript?

- Nearly 50% of all patients with obesity have hypertension, half of whom have uncontrolled hypertension.
- There is a stepwise incremental risk of mortality in controlled and uncontrolled hypertension, compared to the normotensive counterparts, irrespective of sex, age and diabetes status. This trend is observed across the normal weight, overweight, and obese groups.

How might your results change the direction of research or the focus of clinical practice?

- Healthcare providers should aim to optimise the level of hypertension control and advocate weight loss through lifestyle and pharmacological interventions to achieve better outcomes for people with obesity.

ABSTRACT

Background

With rising prevalence of hypertension and obesity, the effect of hypertension in obesity remains an important global issue. We examined the prognosis of the US general population with obesity based on hypertension control.

Methods

This study examined participants from the National Health and Nutrition Examination Survey (NHANES) between 1999-2018. Patients with obesity were stratified into no hypertension, controlled hypertension, uncontrolled hypertension. The study outcome was all-cause mortality. Cox regression of all-cause mortality was adjusted for age, sex, ethnicity, diabetes, and previous myocardial infarction.

Results

Of 16,386 patients with obesity, 53.1% had no hypertension, 24.7% had controlled hypertension and 22.2% had uncontrolled hypertension. All-cause mortality rates were significantly higher in uncontrolled hypertension (17.1%) followed by controlled hypertension (14.8%) and no hypertension (4.0%). Uncontrolled hypertension had the highest mortality risk (HR1.34, 95%CI:1.13-1.59, p=0.001), followed by controlled hypertension (HR1.21, 95%CI:1.10-1.34, p<0.001), compared to no hypertension after adjustment. The excess mortality trend was more pronounced in females, diabetics and the elderly.

Conclusion

The incremental mortality risk in controlled and uncontrolled hypertension, compared to the normotensive counterparts, irrespective of sex, age and diabetes status, should urge healthcare providers to optimise hypertension control and advocate weight loss to achieve better outcomes for people with obesity.

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INTRODUCTION

Hypertension has long been recognised as a key public health issue(1), with an overall prevalence of 29.3% in the United States (US).(2) The increased prevalence of hypertension has been associated with increasing body mass index (BMI)(2), with recent studies(3) demonstrating a linear relationship of obesity with blood pressure across both developed and developing countries(1, 4, 5). For every 10-pound weight gain, systolic blood pressure was raised by an average of 4.5 mmHg(5).

Obesity is a major risk factor for hypertension, hyperlipidemia, diabetes mellitus(6, 7, 8), and adverse cardiovascular events such as acute myocardial infarction (AMI) and heart failure(9, 10). The complex pathophysiological mechanisms underlying obesity and hypertension involve the interplay of impaired renal sodium reabsorption, renin-angiotensin and sympathetic nervous systems, neurohumoral vascular function and altered metabolism(11, 12). Borgeraas et al.(13) demonstrated 1.8 and 1.6 times elevated risk of incident AMI and cardiovascular death in individuals with obesity compared to normal weight respectively. Moreover, incident hypertension increases with obesity, and suboptimal hypertension control rates are more prevalent in patients with obesity as well(14).

The effect of hypertension in individuals with obesity remains an important topic especially with the global rise in the prevalence of both diseases in the past few decades(2, 15). The need for targeted clinical guidelines for the management of obesity-related hypertension(14) is of utmost importance given that both cardiovascular risk factors are reversible and can mitigate major cardiovascular adverse outcomes(16, 17, 18). While studies have described the prevalence of hypertension in obesity(14, 19, 20), there is a lack of data on the prognostic outcomes of patients with obesity based on the degree of hypertension control in a population-based study. Hence, we sought to examine the clinical characteristics and prognostic outcomes based on the presence of hypertension and the extent of hypertension control in a general population with obesity.

METHODS

Study Population

This study analysed the results of NHANES, a cross-sectional survey conducted from 1999 to 2018 in the US. Using a stratified, multistage, clustered probability sampling design, the survey collected data representative of the general non-institutionalised population. The NHANES study also consisted of a structured interview in the patients' home with subsequent standardised health examination at a mobile examination centre for physical examinations and laboratory tests. The national death index was used to collect longitudinal outcomes of mortality. The original survey was approved by the National Centre for Health Statistics Research Ethics Review Board. Institutional Review Board for the present analysis was waived as the data used in analysis is publicly available and de-identified.

Participants were included if they were ≥18 years of age and obese. Obesity was defined as a body mass index (BMI) ≥30kg/m^2 as per the World Health Organisation recommendation(21). Patients with obesity were stratified into 3 groups based on the presence of hypertension, and the level of hypertension control – 1) no hypertension, 2) controlled hypertension, 3) uncontrolled hypertension. Hypertension was defined as a systolic blood pressure reading of ≥140mmHg, diastolic blood pressure reading of ≥90 mmHg, or the use of anti-hypertensives, in accordance to established hypertension studies using the NHANES cohort(22, 23). Controlled hypertension was defined as blood pressure <140/90 mmHg with anti-hypertensive use, and uncontrolled hypertension as blood pressure ≥140/90 mmHg with and without anti-hypertensive use. Diabetes was defined as self-reported diagnosis of diabetes, glycated hemoglobin ≥6.5%, fasting plasma glucose ≥7mmol/l, or the use of anti-diabetic medications. Chronic kidney disease (CKD) was defined as the presence of kidney damage or an estimated glomerular filtration rate of less than 60mL/min/1.73 m^2 under the Modification of Diet in Renal Disease (MDRD) equation.(24)

Study Outcomes

The study outcomes include cardiovascular mortality and all-cause mortality. Cardiovascular mortality was defined as any death attributable to any cardiovascular cause. All-cause mortality was death due to any cause.

Statistical Analysis

All statistical analysis was conducted in STATA (17.0). Continuous variables were examined with Wilcoxon ranked sum test and Kruskal–Wallis analysis of variance while binary variables were examined with chi-square test and fisher exact where appropriate. A risk ratio (RR) was used to examine the independent predictors of hypertension in the study population with obesity, adjusted for age, sex, ethnicity, diabetes mellitus and BMI. Multivariable Cox models were constructed to examine the association of hypertension and all-cause mortality, adjusted for age, sex, ethnicity, diabetes mellitus, and previous myocardial infarction. Violations of the Cox proportional model was examined with Schoenfeld residuals and log-log plot. We also fitted a multivariable competing risk analysis to estimate the risk of cardiovascular mortality with the Fine-Gray Sub-distribution hazard ratio (SHR). Subgroup analyses were performed to examine the level of hypertension control and cardiovascular mortality in patients with obesity, based on weight group, sex, ethnicity, age and diabetic status. Adjusted hazards ratio was also plotted in a predicted margins plot for weight, age, and sex, in relation to systolic blood pressure.

RESULTS

Baseline Characteristics

From 1999 to 2018, there was a total of 49,099 patients recruited in the NHANES study, of which 35.6% with obesity. Of 17,511 patients with obesity, 93.6% (N=16.386) had available data on blood pressure and were included in the primary analysis. The median follow-up duration was 7.3 years (interquartile range [IQR] 4.1–11.4). Patients with obesity were more likely older, female and had significantly higher prevalence of hypertension, chronic kidney disease, diabetes mellitus, and history of myocardial infarction compared to non-obese. The obese group had a significantly higher proportion of patients with controlled and uncontrolled hypertension compared to the non-obese group (Supplementary Table 1).

Among participants with obesity, 53.1% had no hypertension, 24.7% had controlled hypertension and 22.2% had uncontrolled hypertension. Patients with hypertension were older, predominantly male, had a higher BMI, prevalence of chronic kidney disease, diabetes mellitus and previous myocardial infarction, compared to those with no hypertension (Table 1).

Predictors of Hypertension in Obesity

The independent predictors of hypertension in patients with obesity were older age (RR 1.03, 95%CI: 1.03 to 1.03), male (RR: 1.04, CI: 1.02 to 1.05), BMI (RR 1.02, 95%CI: 1.01 to 1.02), and presence of diabetes mellitus (RR 1.22, 95%CI: 1.18 to 1.26). White (RR: 1.08, CI: 1.05 to 1.11), Black (RR: 1.25, CI: 1.20 to 1.31) and other Hispanics (RR: 1.09, CI: 1.04 to 1.14) were at higher risk of hypertension relative to Mexican Americans (Supplementary Table 2).

Effect of Hypertension on Mortality in Patients with Obesity

Among patients with obesity, all-cause mortality was significantly higher in uncontrolled hypertension (17.1%) followed by controlled hypertension (14.8%) and no hypertension (4.0%). Similarly, cardiovascular mortality was significantly higher in patients with controlled hypertension (3.8%) and uncontrolled hypertension (3.5%), compared to those with no hypertension (1.2%) (Table 2).

The presence of hypertension increased the risk of all-cause mortality by 28% (HR 1.28, 95%CI: 1.14 to 1.44) and the risk of cardiovascular mortality by 151% (SHR 2.51, 95%CI: 1.62 to 3.90) after adjusting for important confounders (Figure 1; Supplementary Table 3). In the multivariable model, uncontrolled hypertension had the highest risk of all-cause mortality (HR 1.34, 95%CI: 1.13 to 1.59, p=0.001), followed by controlled hypertension

(HR 1.21, 95%CI: 1.10 to 1.34, p<0.001), compared to no hypertension. Similarly, uncontrolled hypertension had the highest risk of cardiovascular mortality (SHR: 2.96, 95%CI: 1.91 to 4.60, p<0.001) followed by controlled hypertension (SHR: 2.06, 95%CI: 1.39 to 3.06, p<0.001), compared to those with no hypertension after adjustment (Table 3, Figure 2).

Effect of hypertension on mortality stratified across different weight groups, sex, age and ethnicity

Compared to those with no hypertension, uncontrolled hypertension had the highest cardiovascular mortality risk followed by controlled hypertension. This trend was observed across all weight groups, with the mortality risk most pronounced in obese group, followed by overweight and normal weight groups (Table 4; Supplementary Figure 1).

Compared to those with no hypertension, a higher risk of cardiovascular mortality was observed in the uncontrolled hypertension group followed by the controlled hypertension group regardless of sex (Supplementary Figure 2) or diabetes status (Supplementary Figure 3), with larger effect sizes seen in females and presence of diabetes. Middle-aged or elderly participants had higher risk of cardiovascular mortality in the uncontrolled hypertensive group, followed by the controlled hypertensive group, with more pronounced effect sizes noted in the elderly compared to middle-aged group (Supplementary Figure 4). A similar trend in increased cardiovascular mortality risk by hypertension status was observed among White and Black but not in the Mexican Americans (Supplementary Table 4; Supplementary Figure 5).

The effects of increasing systolic blood pressure on cardiovascular mortality were demonstrated on predicted margins plots, stratified across weight groups (Supplementary Figure 6), age (Supplementary Figure 7) and sex (Supplementary figure 8). Systolic blood pressure above 140mmHg had a larger increase in cardiovascular mortality risk for all weight categories and sex. A similar trend was noted in the elderly, but not in the middle age or young groups.

DISCUSSION

Evidence have shown that hypertension and obesity significantly increase the risk of cardiovascular mortality, cardiovascular diseases and stroke compared to those without hypertension and/or obesity in the general population(25, 26). However, little is known about the prognostic outcomes of hypertension within the general population with obesity, based on the degree of hypertension control. This study of 49,099 participants highlights that nearly 50% of all patients with obesity had hypertension, which is higher than previous estimates of 35.7%(27). This study also demonstrated the stepwise incremental risk of cardiovascular mortality with controlled and uncontrolled hypertension, and this trend is observed across the normal weight, overweight, and obese groups.

Obesity significantly increases the prevalence of cardiometabolic risk factors such as hypertension, diabetes mellitus and chronic kidney disease(28, 29, 30), and these risk factors synergistically elevate the risk of incident cardiovascular disease and cardiovascular mortality(25, 26). A key study by Thomas *et al* suggested that the presence of hypertension in obesity was the key driving factor of the increased cardiovascular risk(31). In fact, they found that hypertension in overweight subjects significantly increased cardiovascular mortality risk, but not in those overweight with hypercholesterolemia or diabetes alone(31). Long-term data from population cohorts also found that the cardiovascular mortality rate doubled in patients with hypertension and obesity compared to their non-hypertensive counterparts with the same BMI(32). Our findings extend the current notion that even though a large proportion of patients with obesity have well-controlled hypertension, they are still at a higher cardiovascular mortality risk compared to those without hypertension(33). This emphasizes the paramount importance in preserving metabolic health and prevent the development of hypertension in patients with obesity. Concerted efforts in early screening and preventive strategies for patients with obesity at risk of developing hypertension should be given its due consideration.

As obesity-related hypertension ensues, the level of control in blood pressure should be the main focus with favourable survival demonstrated in patients with controlled hypertension compared to those with uncontrolled hypertension. Indeed, it is alarming that only 52.7% of hypertensive patients had well-controlled blood pressure within the general population. This disparity in mortality between those with controlled and uncontrolled hypertension is even more pronounced in patients with obesity compared to those who are overweight and normal weight. This stepwise increment in mortality risk based on BMI category highlights the complex pathophysiologic effects of obesity-related hypertension on renal function and morphology(14). Uncontrolled hypertension may be attributed to adipose tissue that alters renal sodium reabsorption and impairment of

pressure natriuresis via the activation of the renin-angiotensin and sympathetic nervous systems(4, 34, 35), as well as the marked structural alterations in the kidneys resulting in the loss of nephron function and increase in arterial pressure(11). In addition, clinicians must remain cognizant when managing these patients with suboptimal blood pressure control, especially those with other vulnerable factors such as females, the elderly and diabetics. To date, clinical practice guidelines recommend specific blood pressure targets based on the individual's atherosclerotic cardiovascular disease (ASCVD) event risk and comorbidities. Our findings supports the current recommendations with the evident increase in cardiovascular mortality, particularly beyond the threshold of systolic blood pressure >140mmHg, regardless of BMI, sex and diabetic status(36)..

Our finding that BMI is the independent predictor of blood pressure control within the general population, which is consistent with the well-established positive relationship between elevated body weight and high blood pressure(4, 34), reemphasizes the importance in treatment strategies that target both obesity and hypertension. The Obesity Society and the American Society of Hypertension have outlined strategies(25) that focus on lifestyle modifications including exercise and dietary changes, weight loss and anti-hypertensive pharmacotherapy, which have combined effects in both weight loss and blood pressure control(25). Weight reduction has been shown to be the most effective method for the risk reduction of CVD in hypertensive obese(37), as it lowers blood pressure and prevents the development of hypertension in individuals with obesity(38, 39). The emerging interest on sodium-glucose cotransporter 2 inhibitors and its effects on blood pressure control(40, 41), weight loss(42, 43), and cardiorenal protection(44), appears promising particularly in addressing the metabolic milieu of patients with obesity-related hypertension.

Limitations

This large longitudinal cohort of multi-ethnic patients from the general US population extends the present knowledge that hypertension itself is the major driver for cardiovascular mortality, but the level of hypertension control in obesity also warrants further attention. However, there are several limitations. First, several confounding factors associated with obesity could have influenced the study outcomes. To address this, we used multivariable models adjusting for important prognostic factors such as age, sex and other cardiometabolic risk factors. Second, the population blood pressure was measured at a single timepoint during the clinic visit and may not accurately capture the variability in blood pressure. In addition, we could not account for patients who subsequently developed hypertension after the initial survey and clinic visit. Third, we used BMI to categorise obesity, which may not accurately distinguish between adipose tissue depot and muscle mass. Furthermore, due to BMI-ethnicity interactions, BMI cut-off values may differ among different ethnic

groups. Future studies using other measures of visceral fat, such as waist-hip ratio or waist circumference, will be of interest(45).

CONCLUSION

Nearly 50% of all patients with obesity have hypertension, half of whom have uncontrolled hypertension. There is a stepwise incremental risk of mortality in controlled and uncontrolled hypertension, compared to the normotensive counterparts, irrespective of sex, age and diabetes status. Healthcare providers should aim to optimise the level of hypertension control and advocate weight loss through lifestyle and pharmacological interventions to achieve better outcomes for people with obesity.

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FIGURE AND TABLE LEGENDS

Figure 1: Risk of cardiovascular mortality in obese group with controlled hypertension, uncontrolled hypertension and no hypertension.

Figure 2: Risk of all-cause mortality in obese group with controlled hypertension, uncontrolled hypertension and no hypertension.

Supplementary Figure 1. Adjusted cardiovascular mortality by the level of hypertension control in patients who are underweight, normal, overweight or obese.

Supplementary Figure 2. Adjusted cardiovascular mortality by the level of hypertension control in patients with obesity stratified according to sex.

Supplementary Figure 3. Adjusted cardiovascular mortality by the level of hypertension control in patients with obesity stratified according to diabetes status.

Supplementary Figure 4. Adjusted cardiovascular mortality by the level of hypertension control in patients with obesity stratified according to age group.

Supplementary Figure 5. Adjusted cardiovascular mortality by the level of hypertension control in patients with obesity stratified according to ethnicity.

Supplementary Figure 6. Predictive margins plot of adjusted subdistribution hazards ratio of cardiovascular mortality stratified by systolic blood pressure and weight amongst all patients.

Supplementary Figure 7. Predictive margins plot of adjusted subdistribution hazards ratio of cardiovascular mortality stratified by systolic blood pressure and age amongst all patients.

Supplementary Figure 8. Predictive margins plot of adjusted subdistribution hazards ratio of cardiovascular mortality stratified by systolic blood pressure and sex amongst all patients.

Table 1: Baseline characteristics of the study population with obesity, stratified based on no hypertension, controlled and uncontrolled hypertension.

Table 2: Outcomes of patients with obesity stratified by hypertension status.

Table 3: Multivariable analysis examining the association of the degree of hypertension control and all-cause or cardiovascular death in patients with obesity.

Table 4. Subgroup analysis of the adjusted cardiovascular mortality by the level of hypertension control in patients who are normal weight, overweight or obese

Supplementary Table 1. Baseline characteristics of the NHANES study population stratified based on the presence of obesity.

Supplementary Table 2. Independent predictors of hypertension in patients with obesity.

Supplementary Table 3. Multivariable analysis examining the association of the presence of hypertension and all-cause or cardiovascular mortality in patients with obesity.

Supplementary Table 4. Subgroup analysis of the adjusted cardiovascular mortality by the level of hypertension control in each sex, ethnicity, age group and diabetic status in patients with obesity.

Table 1: Baseline characteristics of the study population with obesity, stratified based on no hypertension, controlled and uncontrolled hypertension.

	No HTN (n=8703)	**Controlled HTN (n=4047)**	**Uncontrolled HTN (n=3636)**	**P-value**
Age	37 (28 to 47)	61 (52 to 70)	60 (47 to 70)	**<0.001**
BMI (kg/m^2)	33.8 (31.7 to 37.4)	34.6 (32.0 to 38.9)	34.4 (31.8 to 38.5)	**<0.001**
Weight (kg)	96.2 (85.9 to 108.3)	98.2 (87.3 to 110.7)	96.3 (85.8 to 110.2)	**<0.001**
Waist circumference (cm)	110 (103 to 118)	115 (108 to 124)	114 (107 to 122)	**<0.001**
Male	3692 (42.4)	1813 (44.8)	1743 (47.9)	**<0.001**
Ethnicity				**<0.001**
White	3312 (38.1)	1951 (48.2)	1396 (38.4)	
Black	1927 (22.1)	1108 (27.4)	1146 (31.5)	
Mexican American	2117 (24.3)	492 (12.2)	634 (17.4)	
Other Hispanic	818 (9.4)	310 (7.7)	292 (8.0)	
Others	529 (6.1)	186 (4.6)	168 (4.6)	
Chronic kidney disease	133 (1.6)	626 (16.3)	422 (12.3)	**<0.001**
Diabetes mellitus	913 (11.2)	1698 (44.7)	1157 (34.1)	**<0.001**
Previous myocardial infarction	85 (1.0)	451 (11.2)	258 (7.1)	**<0.001**
Systolic BP (mmHg)	118 (111 to 126)	124 (115 to 131)	148 (142 to 158)	**<0.001**
Diastolic BP (mmHg)	71 (64 to 77)	69 (61 to 76)	81 (70 to 91)	**<0.001**

Anti-hypertensive medications				
ACE inhibitor	-	1763 (43.6)	779 (21.4)	**<0.001**
ARB	-	958 (23.7)	516 (14.2)	**<0.001**
Beta-blockers	-	220 (15.4)	131 (17.4)	0.211
Calcium Channel Blockers	-	1127 (27.8)	702 (19.3)	**<0.001**
Diuretics	-	1836 (45.4)	910 (25.0)	**<0.001**
Laboratory variables				
Platelet (10^3/μL)	260 (220 to 305)	240 (201 to 287)	245 (205 to 290)	**<0.001**
Glycated hemoglobin (%)	5.5 (5.2 to 5.7)	5.9 (5.5 to 6.6)	5.8 (5.5 to 6.4)	**<0.001**
Fasting glucose (mmol/L)	5.5 (5.1 to 6.0)	6.2 (5.6 to 7.3)	6.0 (5.5 to 7.1)	**<0.001**
Total cholesterol (mg/dL)	193 (169 to 221)	185 (158 to 215)	198 (172 to 227)	**<0.001**
LDL-cholesterol (mg/dL)	118 (96 to 139)	106 (82 to 129)	115 (92 to 141)	**<0.001**
HDL-cholesterol (mg/dL)	46 (39 to 55)	46 (39 to 56)	47 (39 to 56)	**0.014**
Triglycerides (mg/dL)	134 (90 to 203)	147 (102 to 216)	146 (102 to 217)	**<0.001**
Total bilirubin (μmol/L)	10.3 (6.8 to 12.0	10.3 (8.6 to 13.7)	10.3 (8.6 to 13.7)	**<0.001**

Legend: ACE, Angiotensin-Converting Enzyme; ARB, Aldosterone Receptor Blockers; BMI, Body Mass Index; BP, Blood Pressure; HDL, High-density Lipoprotein; HTN, Hypertension; LDL, Low-density Lipoprotein
Continuous variables presented as median (interquartile range) and categorical variables presented as n (%).
P<0.05 denotes statistical significance (in bold).

Table 2: Outcomes of patients with obesity stratified by hypertension status.

	No HTN (n=8703)	Controlled HTN (n=4047)	Uncontrolled HTN (n=3636)	**P-value**
Cardiovascular mortality	82 (1.2)	115 (3.8)	96 (3.5)	**<0.001**
All-cause mortality	262 (4.0)	449 (14.8)	471 (17.1)	**<0.001**

Legend: HTN, Hypertension
Categorial variables presented as n (%).
P<0.05 denotes statistical significance (in bold).

Table 3: Multivariable analysis examining the association of the degree of hypertension control and all-cause or cardiovascular death in patients with obesity.

	All-cause mortality			Cardiovascular mortality		
	HR	95% CI	P-value	SHR	95% CI	P-value
Hypertension Status						
No HTN		Reference			Reference	
Controlled HTN	1.21	1.10 to 1.34	**<0.001**	2.06	1.39 to 3.06	**<0.001**
Uncontrolled HTN	1.34	1.13 to 1.59	**0.001**	2.96	1.91 to 4.60	**<0.001**
Age	1.06	1.06 to 1.08	**0.001**	1.08	1.06 to 1.09	**<0.001**
Male	1.46	1.36 to 1.57	**<0.001**	1.89	1.40 to 2.55	**<0.001**
Ethnicity						
Mexican American		Reference			Reference	
White	1.11	1.01 to 1.22	**0.023**	1.00	0.70 to 1.46	0.695
Black	1.01	0.79 to 1.30	0.916	1.13	0.60 to 2.15	0.600
Other Hispanic	0.77	0.54 to 1.09	0.145	0.63	0.18 to 2.13	0.454
Others	1.25	0.95 to 1.64	0.110	0.91	0.28 to 2.97	0.279
Diabetes mellitus	1.66	1.49 to 1.86	**<0.001**	1.47	1.05 to 2.05	**0.025**
Previous myocardial infarction	1.77	1.44 to 2.18	**<0.001**	2.05	1.67 to 2.51	**<0.001**

Legend: CI, Confidence Interval; HR, Hazard Ratio; HTN, Hypertension; SHR, Sub-distribution Hazard Ratio
P<0.05 denotes statistical significance (in bold).

Table 4. Subgroup analysis of the adjusted cardiovascular mortality by the level of hypertension control in patients who are normal weight, overweight or obese

	Normal weight	Overweight	Obese
Hypertension status			
No HTN	Reference	Reference	Reference
Controlled HTN	1.74 (95%CI 1.23-2.44, P=0.002)	1.56 (95%CI 1.19-2.04, P=0.001)	2.06 (95%CI 1.39-3.06, P<0.001)
Uncontrolled HTN	1.89 (95%CI 1.26-2.83, P=0.002)	1.93 (95%CI 1.70-2.19, P<0.001)	2.96 (95%CI 1.91-4.60, P<0.001)
Age	1.08 (95%CI 1.06-1.09, P<0.001)	1.07 (95%CI 1.06-1.08, P<0.001)	1.08 (95%CI 1.06-1.09, P<0.001)
Male	1.36 (95%CI 1.10-1.67, P=0.004)	1.69 (95%CI 1.28-2.25, P<0.001)	1.89 (95%CI 1.40-2.55, P<0.001)
Ethnicity			
Mexican American	Reference	Reference	Reference
White	0.66 (95%CI 0.47-0.94, P=0.020)	0.74 (95%CI 0.49-1.11, P=0.145)	1.01 (95%CI 0.70-1.46, P=0.969)
Black	0.73 (95%CI 0.43-1.24, P=0.245)	0.83 (95%CI 0.61-1.15, P=0.265)	1.13 (95%CI 0.60-2.15, P=0.697)
Other Hispanic	0.56 (95%CI 0.27-1.19, P=0.130)	0.43 (95%CI 0.28-0.64, P<0.001)	0.63 (95%CI 0.18-2.13, P=0.454)
Others	0.34 (95%CI 0.14-0.80, P=0.014)	0.38 (95%CI 0.13-1.08, P=0.070)	0.91 (95%CI 0.28-2.97, P=0.877)
Diabetes	1.68 (95%CI 1.16-2.42, P=0.006)	1.58 (95%CI 1.25-2.00, P<0.001)	1.47 (95%CI 1.05-2.05, P=0.025)
Previous myocardial infarction	2.32 (95%CI 1.38-3.91, P=0.002)	2.06 (95%CI 1.56-2.73, P<0.001)	2.05 (95%CI 1.67-2.51, P<0.001)

Legend: HTN, Hypertension
Data is presented as adjusted standard hazards ratio (95% confidence interval, P-value).
P<0.05 denotes statistical significance.

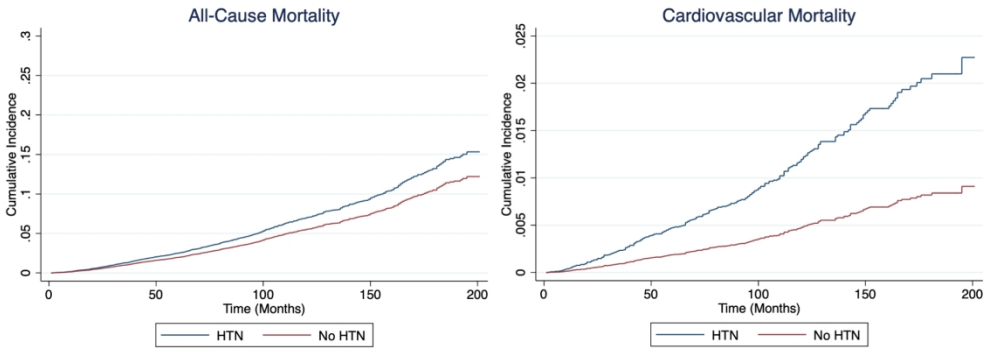

Figure 1

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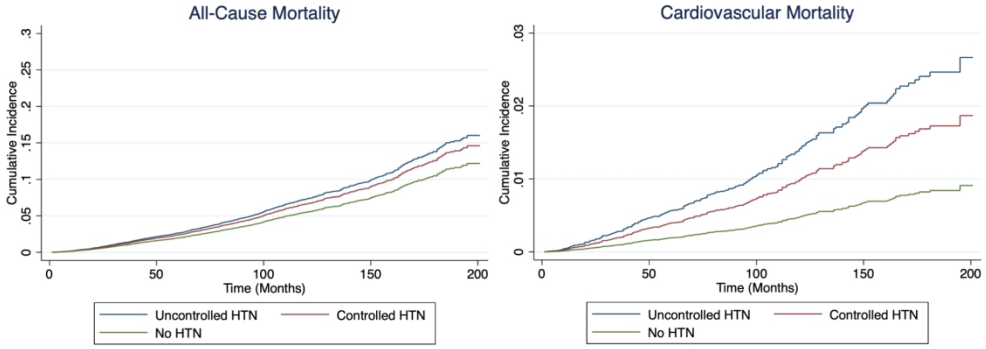

Figure 2

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3, 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.