

Body mass index and cardiovascular outcomes in patients with acute coronary syndrome by diabetic status: Korean cohort study

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Abstract

Background: The “obesity paradox” has not been elucidated in the long-term outcomes of acute coronary syndrome (ACS). Therefore, we investigated the association between obesity and cardiovascular (CV) outcomes in ACS patients with and without diabetes.

Methods: We identified 6,978 patients with ACS aged 40–79 years from the Korean National Health Insurance Service-Health Screening Cohort between 2003 and 2015. Baseline body mass index (BMI) was categorized as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}22.9 \text{ kg/m}^2$), overweight ($23.0\text{--}24.9 \text{ kg/m}^2$), obese class I ($25.0\text{--}29.9 \text{ kg/m}^2$), and obese class II ($\geq 30.0 \text{ kg/m}^2$). The primary outcome was major adverse CV events (MACE)—CV death, myocardial infarction (MI), and stroke. The secondary outcomes were the individual components of MACE, hospitalization for heart failure (HHF), and all-cause death.

Results: The study included 3,989 patients with and 2,989 without diabetes. Compared to normal-weight patients without diabetes (reference group), those with diabetes had a higher risk of MACE (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.07–1.56). Obese patients without diabetes had a lower risk of MACE (HR, 0.78; 95% CI, 0.62–0.97) than those with diabetes (HR, 0.95; 95% CI 0.78–1.14). In patients without diabetes, obese BMI decreased the risk of HHF (HR, 0.62; 95% CI, 0.42–0.92) and stroke (HR, 0.61; 95% CI, 0.42–0.88), but not in those with diabetes.

Conclusion: Among patients with ACS, obesity had rather protective effect on CV outcomes compared to normal weight, while this was not evident in patients with diabetes.

Background

Obesity is a well-established risk factor for cardiovascular (CV) disease that increases the risk of CV mortality [1,2]. However, several studies have reported that obese patients with high body mass index (BMI) have a better prognosis than patients with normal BMI [3]. However, the mechanism of this phenomenon, called “obesity paradox” is unclear.

Diabetes mellitus has been known to increase the risk of CV disease, and patients with diabetes experience worse CV outcomes than those without diabetes [4]. In a prospective cohort study, diabetes increased the risk of mortality by 140% in patients with previous myocardial infarction (MI) [5]. According to the Korean registry data, diabetes is an independent risk factor for 1-year mortality in patients undergoing percutaneous coronary intervention with MI [6].

There has been an ongoing debate regarding the relationship between obesity and CV outcomes according to the presence of diabetes. In a large-scale population study regarding diabetes mellitus, overweight or obese patients had a lower risk of major adverse CV events (MACE) and all-cause mortality than those with normal-weight patients [7]. However, there is limited evidence regarding the long-term

prognosis in patients with established CV disease. Therefore, we investigated the association of obesity and diabetes mellitus with the clinical outcomes in patients treated with acute coronary syndrome (ACS).

Methods

Study population

This study used data from the nationwide administrative claims-based databases of the Korean National Health Insurance Service (NHIS), which covers > 98% of the entire Korean population. The NHIS-Health Screening Cohort is a dataset with a random sample of 10% of the population aged 40–79 years who completed a National Health Screening test in 2002 or 2003. The database provides information regarding the demographic characteristics, medical claims (including diagnostic and treatment codes), health surveys, physical examinations, and biochemical tests of 514,866 participants. The diagnostic codes are based on the International Classification of Diseases, 10th revision (ICD-10) [8].

This study included patients who were hospitalized with ACS (ICD-10: I20–I22) between 2003 and 2015. Patients with a previous history of ACS or cancer were excluded. Patients whose data were unavailable for analysis or not received the health screening test within 1 year were also excluded (Figure 1). The follow-up period was defined as the time from the date of the health screening test to the first outcome event, date of death, or end of the study period (December 31, 2015), whichever came first. The study protocol was reviewed and approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-EXP-17-253). The requirement for informed consent was waived as the data used in the database were deidentified.

Outcomes and covariates

The following demographic and anthropometric data were collected 1 year before the index date: age, sex, height, weight, and blood pressure. BMI was defined as weight (kg) divided by height in meter squared (m^2) and categorized according to the Asian-specific criteria as [9]: underweight ($<18.5\text{ kg}/m^2$), normal weight ($18.5\text{--}22.9\text{ kg}/m^2$), overweight ($23.0\text{--}24.9\text{ kg}/m^2$), obese class I ($25.0\text{--}29.9\text{ kg}/m^2$), and obese class II ($\geq30.0\text{ kg}/m^2$). Total cholesterol and glucose levels were collected from baseline fasting blood analysis. Smoking status (smoker, former smoker, or nonsmoker), alcohol consumption (low, middle, or high), and physical activity (low, middle, or high) were obtained from self-reported questionnaires. Household income was categorized into three groups (lowest 30%, middle 40%, and highest 30%). The prescribed drugs were categorized using the Anatomical Therapeutic Chemical (ATC) codes: antihypertensive agents (C07–C09), statins (C10AA), and antiplatelet agents (B01A). Baseline comorbidities included a previous history of stroke (ICD-10: I50) and heart failure (ICD-10: I60–I64). Diabetes mellitus was defined using the following criteria: diagnosed with ICD-10 codes (E10–E14) more than twice, receiving glucose-lowering agents (ATC: A10B) for > 30 days, receiving insulin (ATC: A10A) as an outpatient, or fasting blood glucose level of $\geq 126\text{ mg/dL}$.

The primary outcome was MACE–CV death (ICD-10: I00–I99), MI (ICD-10: I21–I22), and stroke (ICD-10: I60–I64). The secondary outcomes were individual components of MACE, hospitalization for heart failure (HHF; ICD-10: I50), and all-cause death. All-cause and CV death were defined by death status in the NHIS database, which was linked to the National Death Registry using unique resident registration numbers.

Statistical analysis

All categorical variables are presented as frequencies and percentages. Normally distributed data were presented as mean ± standard deviation, whereas nonparametric data are presented as median and interquartile range by BMI. Cox proportional hazard regression analyses were performed to identify the association of BMI with the primary and secondary outcomes according to the presence of diabetes, calculating hazard ratio (HR) and 95% confidence interval (CI) and adjusting for the following potential confounders: sex, age, systolic blood pressure, fasting glucose level, total cholesterol level, drinking status, smoking status, physical exercise, household income, use of antihypertensive agents, use of statins, use of antiplatelet agents, previous history of heart failure, previous history of stroke, and index year. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The study initially enrolled 26,597 patients who were diagnosed with ACS, and 6,978 participants fulfilled the inclusion criteria (Figure 1). The baseline characteristics according to the presence of diabetes mellitus are summarized in Table 1. Compared with patients without diabetes, those with diabetes ($n = 3989$, 57.1%) were older, were more likely to be females, and had higher BMI and systolic blood pressures. Patients with diabetes were less likely to be current smokers and had low alcohol consumption compared with those without diabetes; however, they had more frequent comorbidities and more frequently used concomitant medications. The baseline characteristics of patients with and without diabetes stratified by BMI are summarized (Additional file 1: Supplementary Table 1). Obese patients were more likely to be younger, males, and physically active, and current smokers and more frequently used medications than normal-weighted patients.

Table 1. Baseline characteristics according to the presence of diabetes mellitus

	Without diabetes (n = 2,989)	With diabetes (n = 3,989)	P-value
Age, years	60.8 ± 9.7	64.4 ± 9.5	<0.001
Women, n (%)	1,038 (34.7)	1,528 (38.3)	0.002
Body mass index, kg/m ²	24.2 ± 2.9	24.6 ± 3.1	<0.001
SBP, mmHg	130.1 ± 17.7	131.7 ± 17.9	<0.001
DBP, mmHg	80.4 ± 11.3	80.0 ± 11.0	0.073
Total cholesterol, mg/dL	203.7 ± 40.1	201.5 ± 44.6	0.030
Fasting glucose, mg/dL	94.0 (86.0–102.0)	106.0 (92.0–131.0)	<0.001
Clinical diagnosis, n (%)			0.003
MI	1,565 (52.4)	1,946 (48.8)	
Unstable angina	1,424 (47.6)	2,043 (51.2)	
Smoking status, n (%)			
Never	1,745 (58.4)	2,463 (61.7)	<0.001
Former	429 (14.3)	630 (15.8)	
Current	815 (27.3)	896 (22.5)	
Alcohol consumption, n (%)			
Low	2,032 (68.0)	2,996 (75.1)	<0.001
Middle	874 (29.2)	904 (22.7)	
High	83 (2.8)	89 (2.2)	
Physical activity, n (%)			
Low	1,007 (33.7)	1,066 (26.7)	<0.001
Middle	1,567 (52.4)	2,366 (59.3)	
High	415 (13.9)	557 (14.0)	
Household income, n (%)			
Lower 30%	611 (20.4)	921 (23.1)	0.030
Mid 40%	996 (33.3)	1,283 (32.2)	
Upper 30%	1,382 (46.2)	1,785 (44.7)	
Comorbidities, n (%)			
HF	376 (12.6)	830 (20.8)	<0.001
Stroke	445 (14.9)	967 (24.2)	<0.001
Concurrent medication, n (%)			
ACEi or ARB	2,166 (72.5)	3,377 (84.7)	<0.001
Beta-blockers	2,268 (75.9)	3,383 (84.8)	<0.001
Calcium channel blocker	2,120 (70.9)	3,229 (80.9)	<0.001

Statin	2,208 (73.9)	3,382 (84.8)	<0.001
Antiplatelet agents	2,056 (68.8)	3,204 (80.3)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HF, heart failure; MI, myocardial infarction; SBP, systolic blood pressure

During a mean follow-up of 5.4 ± 3.7 years (median, 4.9 years), 1,633 MACE and 1,023 deaths occurred (Table 2). In patients with ACS, diabetes increased the risk of MACE (event rates 5.81 vs. 4.01 per 100 person-years, HR 1.49, 95% CI 1.34–1.65). Patients with diabetes had higher risks of stroke, CV death, and MI than those without diabetes (stroke: HR 2.06, 95% CI 1.75–2.42; CV death: HR 1.25, 95% CI 1.03–1.53; MI: HR 1.26, 95% CI 1.09–1.50). Patients with diabetes also had higher event rates and risks of HHF and all-cause death than those without diabetes (HHF: event rates 2.40 vs. 1.15, HR 2.13, 95% CI 1.79–2.55; all-cause death: event rates 3.05 vs. 2.25, HR 1.40, 95% CI 1.23–1.60). After the adjustment with confounding variables, patients with diabetes had a higher risk of MACE than those without diabetes (HR 1.22, 95% CI 1.09–1.37); the risk of stroke was significantly higher (HR 1.50, 95% CI 1.26–1.79), but that of CV death and MI was not (CV death: HR 1.15, 95% CI 0.92–1.43; MI: HR 1.05, 95% CI 0.89–1.23). Further, patients with diabetes had higher risks of HHF and all-cause death than those without diabetes (HHF: HR 1.47, 95% CI 1.22–1.78; all-cause death: HR 1.28, 95% CI 1.11–1.49).

Table 2. Clinical outcomes of patients with and without diabetes mellitus

	Without diabetes (n = 2,989)			With diabetes (n = 3,989)			Unadjusted	Adjusted
	Person-years	No. of events	Event rate (per 100 PY)	Person-years	No. of events	Event rate (per 100 PY)	HR (95% CI)	HR (95% CI)*
MACE	13,057	524	4.01	19,096	1,109	5.81	1.49 (1.34–1.65)	1.22 (1.09–1.37)
CV death	14,471	153	1.06	22,913	286	1.25	1.25 (1.03–1.53)	1.15 (0.92–1.43)
MI	13,542	272	2.01	20,734	500	2.41	1.26 (1.09–1.50)	1.05 (0.89–1.23)
Stroke	13,863	196	1.41	20,812	592	2.84	2.06 (1.75–2.42)	1.50 (1.26–1.79)
HHF	14,103	162	1.15	21,385	513	2.40	2.13 (1.79–2.55)	1.47 (1.22–1.78)
All-cause death	14,471	325	2.25	22,913	698	3.05	1.40 (1.23–1.60)	1.28 (1.11–1.49)

*Adjusted for sex, age, body mass index (categorical), systolic blood pressure, fasting glucose, total cholesterol, drinking status, smoking status, physical exercise, household income, concurrent medications, comorbidities, and index year.

CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; PY, person-years

The risk of the primary outcome across the BMI groups in post-ACS patients are described in Figure 2. Compared to normal-weight patients without diabetes (reference group), those with diabetes had a higher risk of MACE (HR 1.29, 95% CI 1.07–1.56). Obese patients without diabetes had a lower risk of the primary outcome (HR 0.78, 95% CI 0.62–0.97) than those with diabetes (HR 0.95, 95% CI 0.78–1.14). The risk of MACE was highest in the underweight group with diabetes (HR 1.79, 95% CI 1.24–2.58); it was not obvious in underweight group without diabetes (HR 1.23, 95% CI 0.77–1.97).

Among the secondary outcomes, obesity decreased the risk of stroke (HR 0.61, 95% CI 0.61–1.11) and HHF (HR 0.62, 95% CI 0.42–0.92) in patients without diabetes (Additional file 2: Supplementary Figure 1). However, the obese group with diabetes had similar risks of events to the reference group (stroke: HR 1.11, 95% CI 0.84–1.47; HHF: HR 1.04, 95% CI 0.76–1.40, respectively). The risks of death (CV and all-cause) and MI tended to be lower in the obese group with and without diabetes than in the reference group, although there was no statistical significance.

The subgroup analyses stratified by age, sex, smoking, and clinical diagnosis are shown in Supplementary Figure 2 (Additional file 3). Obese female and elderly (≥ 65 years) patients without diabetes had a lower rate of MACE, while diabetes mellitus increased the risk of the primary outcome of the under- or normal-weight patients in male, younger (<65 years), and MI groups. In the smoking subgroup, there was no difference according to BMI and the presence of diabetes mellitus.

Discussion

This study showed that obesity and diabetes mellitus affected the long-term outcomes of patients with ACS. While diabetes mellitus deteriorated the clinical outcomes, obesity ameliorated the results; the “obesity paradox” was obvious in post-ACS patients regardless of the presence of diabetes. Obesity decreased the risk of MACE driven primarily by stroke and reduced the rate of HHF exclusively in patients without diabetes mellitus. These were more evident in female and elderly patients without diabetes. However, patients with diabetes did not show such benefit. All-cause and CV mortality seemed to be lowered in overweight and obese patients with and without diabetes.

As the prevalence of diabetes mellitus has increased worldwide, the prevalence also correspondingly increased in Korea, accounting for approximately 5.1 million people with diabetes in 2016 [10]. Patients with diabetes not only have a higher risk for developing coronary heart disease, but their prognosis worsens after acute MI [11,12]. In a previous cohort study, patients with diabetes had a lower socioeconomic status than those without diabetes, which would also affect the adverse CV results [5]. The present study also showed similar findings.

Obesity increases the risk of CV disease via dysregulated metabolism sharing the common mechanism with diabetes (e.g., insulin resistance and inflammation) [13]. BMI increases the prevalence of diabetes mellitus up to 5 times depending on the race [14,15]. However, in contrast to the biological effect of obesity, overweight or obese patients show a better prognosis than normal-weight patients, which is called the “obesity paradox” [13]. In a systematic review for the general population, all-cause mortality was the lowest in the overweight BMI group [16]. In a meta-analysis study, obese patients with coronary artery disease had no increased risk for all-cause and CV death, which was most evident in BMI 25.0–29.9 kg/m² [17]. A study including 12 million Koreans also reported the inverse relationship between BMI and all-cause mortality. The optimal BMI for lowering all-cause death was higher in men than in women and was increased with aging, which corresponded to the overweight or obese BMI categories [18]. Our study showed that overweight or obese patients did not have an increased risk of all-cause and CV mortality compared with normal-weight patients, regardless of the presence of diabetes. In the overall population, the risk of all-cause and CV mortality mortalities was significantly lower in the overweight and obese groups than in the reference group (Additional file 1: Supplementary Table 2). As observed in the present study, obese patients had a favorable outcome of MACE with lower event rates of stroke and HHF compared with the normal-weight group. Stroke was more prevalent in obese patients, but the “obesity

paradox" has remained. In the REACH study, the higher BMI groups had a comparable risk of stroke in patients with established CV disease than the reference group [19]. A study of 5,202 patients with a previous history of CV disease reported a consistent finding that obesity was protective for clinical outcomes including stroke and HHF. The risks of stroke and HHF increased by 10% and 5%, respectively, with the decreased weight [20].

The association of BMI and long-term outcomes of patients with and without diabetes mellitus after CV events has not been recognized. In a study of 19,579 patients with diabetes and established CV disease, the increasing BMI enhanced the clinical outcomes during a 2-year follow-up [19]. The PROactive study revealed that the lowest mortality was seen in patients with a BMI of 30–35 kg/m². Patients with diabetes and CV comorbidity had the risk of all-cause and CV death, which increased by 13% and 7% for each 1% of weight loss [22]. The MONICA/KORA study with 4,504 patients after MI demonstrated the relationship between obesity and CV outcomes regarding the presence of diabetes during 6 years. Higher BMI decreased the risk of long-term survival in patients without diabetes, although diabetes attenuated the protective role of obesity [23].

The present study adds to the accumulating evidence that "obesity paradox" is obvious in patients with CV disease. It is a novel finding on the relationship between BMI and diabetes mellitus, that diabetes deteriorates the prognosis of ACS patients for the long-term duration in the Korean population while obesity was protective.

The cardiometabolic consequences of obesity have a more relevant impact on CV outcomes than obesity. A study on the population with CV disease demonstrated that the cardiometabolic dysfunction increased the risk of CV morbidity and all-cause mortality. Even in comparison with normal-weight patients with cardiometabolic dysfunction, overweight and obese patients had a comparable prognosis of CV disease [24]. A propensity-matched study of 7,788 patients with heart failure also reported a consistent result: the paramount difference in mortality between obese patients with and without diabetes [25]. The impaired cardiometabolic function, such as diabetes mellitus, might offset the protective role of obesity.

Most epidemiologic studies regarding "obesity paradox" used BMI as the obesity parameter. BMI is a simple and feasible measure, but it has some pitfalls. The HORIZONS-AMI trial including patients with ST-segment elevation MI showed that obese patients have more comorbidities, vulnerable features of the coronary lesions, and premature onset of MI. However, BMI did not predict the acute and long-term mortality [26]. The ethnic difference in BMI should also be considered. The pooled analysis for post-ACS patients reported that Asians had similar BMI between people with and without diabetes (24.7 vs. 24.2 kg/m²), whereas the Caucasians with diabetes had higher BMI than those without diabetes (29.3 vs. 27.2 kg/m²) [27]. The effect of obesity and diabetes for CV outcomes might be distinguishable between the ethnicities. In contrast to BMI, central obesity (e.g., waist-to-hip ratio) was more related to the clinical outcomes, and body fat distribution or epicardial fat were considered reliable measures for predicting the prognosis in CV disease [23]. A further study with these parameters is needed to clarify the interrelationship of diabetes mellitus and obesity in patients with CV disease.

Our findings showed that the aim of treatment in post-ACS patients with and without diabetes should be to prevent or control cardiometabolic complications and not merely weight reduction. Meanwhile, lowering the weight should not be underemphasized as intentional weight loss is still associated with an improvement of comorbidities and long-term prognosis in CV disease [19].

This study has some limitations. The data obtained from the claims data could not exclude the possibility of a diagnosis code inaccuracy, disease misclassification, or the bias of the observed difference-in-difference estimate toward the null. Additionally, this study was not able to consider the duration of diabetes, the quality or grade of diabetic treatment, and the information on the treatment of overweight or obesity. To identify the impact of obesity and diabetes on the long-term results of ACS patients, a well-designed prospective study is needed.

Conclusion

Obesity had a protective effect on MACE over normal weight in patients diagnosed with ACS, exclusively for stroke and HHF, but the presence of diabetes mellitus negated this effect. Especially for obese patients, the clinical practice might focus on improving the cardiometabolic profile rather than just losing the body weight for a better long-term prognosis.

Abbreviations

ACS: acute coronary syndrome; ATC Anatomical Therapeutic Chemical; BMI: body mass index; CI: confidence interval; CV: cardiovascular; HHF: hospitalization for heart failure; HR: hazard ratio; ICD: International Classification of Diseases; MACE: major adverse cardiovascular event; MI: myocardial infarction; NHIS: National Health Insurance Service

Declarations

Ethics approval and consent to participate

This cohort study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-EXP-17-253) and complied with the Declaration of Helsinki.

Consent for publication

Not applicable. The requirement for informed consent was waived as the data in this database were deidentified.

Availability of data and materials

Data cannot be shared publicly as the access of National Health Insurance Service (NHIS) data is available only at the NHIS center, Wonju, Republic of Korea. The contact information for the NHIS center of Republic of Korea is as follows: +82-33-736-2431-3 (Tel) and <https://nhiss.nhis.or.kr> (website).

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

DJK and SJP designed the data. KHH performed the data analysis. SJP and KHH wrote the manuscript. SJP interpreted the data regarding cardiovascular outcomes. KHH interpreted the data regarding epidemiologic and endocrinologic outcomes. DJK contributed to the discussion of the results and reviewed/edited the manuscript. All authors read and approved the final manuscript. SJP and KHH equally contributed to this work.

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Figures

**ACS patients with and without diabetes mellitus
in National Health Insurance Service-National Health Screening Cohort
from 2003 to 2015
(n=26,597)**

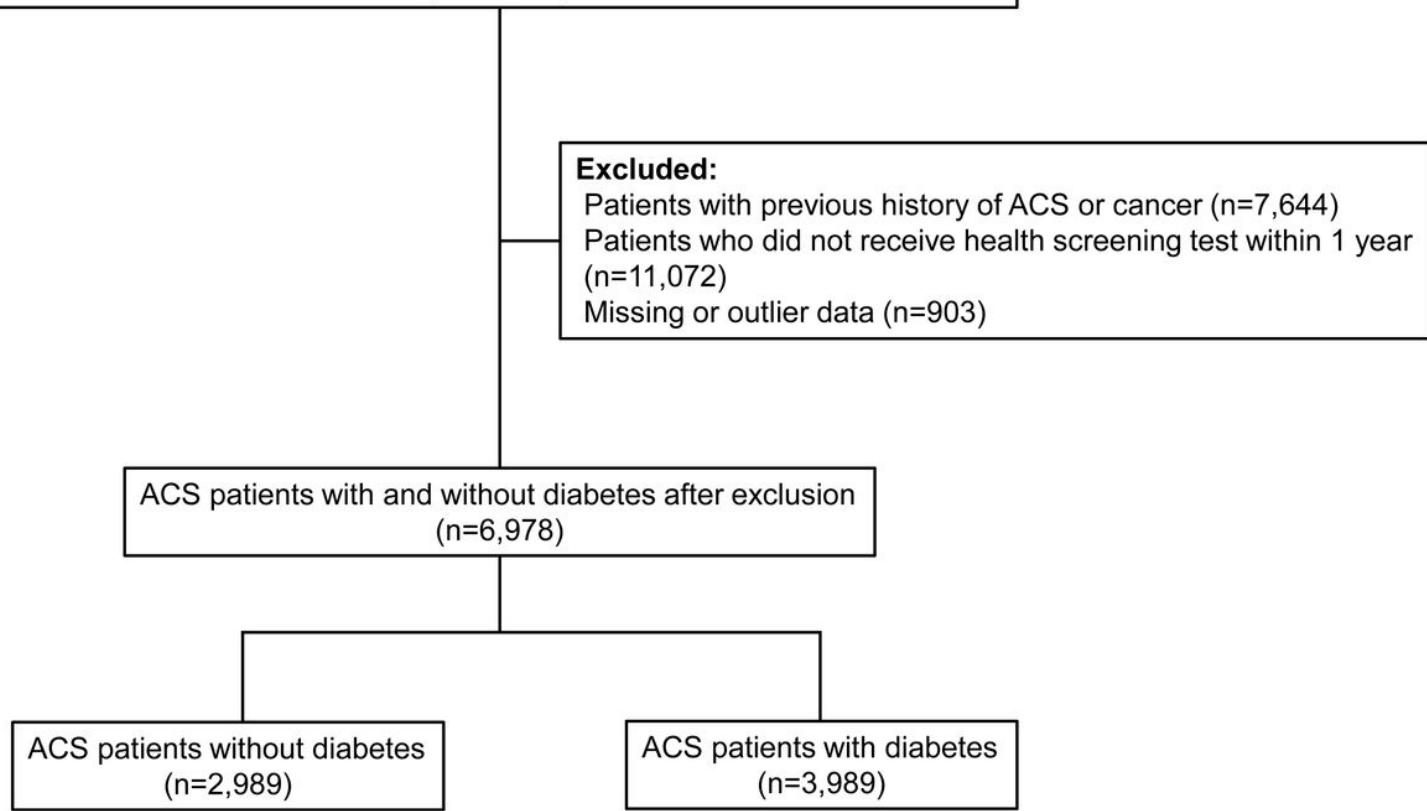
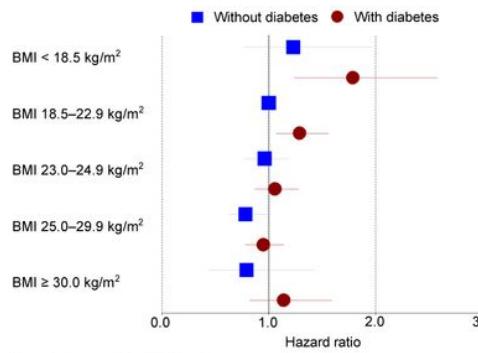
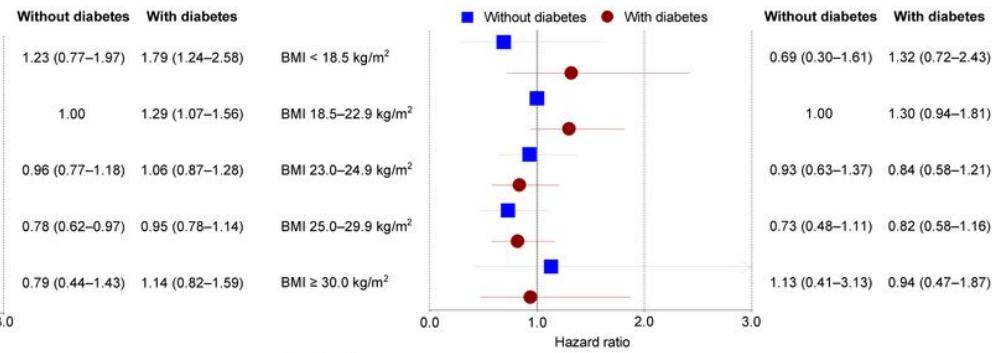
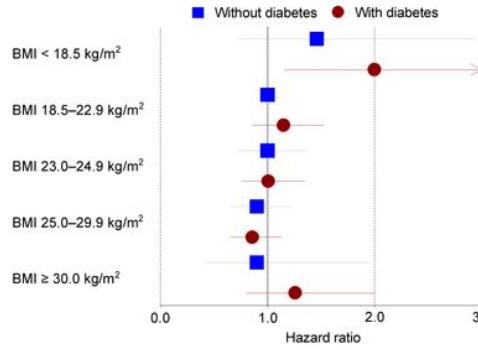
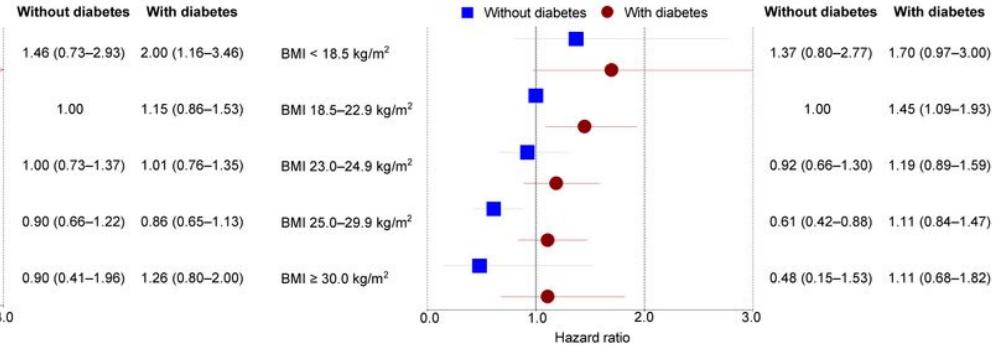


Figure 1

Flowchart of the study population ACS, acute coronary syndrome

a MACE**b Cardiovascular death****c Myocardial infarction****d Stroke****Figure 2**

Hazard ratio of (a) MACE, (b) CV death, (c) MI, and (d) stroke in patients with ACS according to the presence of diabetes mellitus and BMI ACS, acute coronary syndrome; BMI, body mass index; CV, cardiovascular; MI, myocardial infarction

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