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Association of body mass index with kidney function and mortality in high cardiovascular risk population: A nationwide prospective cohort study

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ABSTRACT

Background: There is increasing awareness of the impact of obesity and underweight on cardiovascular (CV) disease, chronic kidney disease (CKD) and mortality. Abnormal body mass index (BMI) might be associated with worse clinical outcomes, including CKD progression, but limited evidence exists among Asian patients with high CV risk.

Objective: To investigate the association of BMI with progressive loss of kidney function and all-cause mortality in Thai patients with high CV risk.

Methods: In a national cohort of 5887 high CV risk subjects, we assessed the association of high BMI with the composite renal outcome (estimated glomerular filtration rate [eGFR] decline over 40%, eGFR less than 15 mL/min/1.73 m^2, doubling of serum creatinine, initiation of dialysis and death related to renal causes) and with all-cause mortality in Cox proportional hazards models.

Results: A total of 5887 participants (3217 male and 2670 female) with high CV risk were enrolled. Participants were classified into five groups by their baseline BMI; <20 kg/m^2 ($n = 482$), 20–24.9 kg/m^2 ($n = 2437$), 25–29.9 kg/m^2 ($n = 2140$), 30–34.9 kg/m^2 ($n = 665$) and 35 kg/m^2 ($n = 163$), respectively. On multivariate analysis of Cox proportional hazards models, adjusted for other covariates, baseline BMI ≥35 kg/m^2 was an independent predictor of loss of kidney function (HR 1.60, 95% CI 1.04–2.40) and all-cause mortality (HR 2.68, 95% CI 1.50–4.80). Baseline BMI <20 kg/m^2 was an independent predictor of all-cause mortality as well (adjusted HR 2.26, 95% CI 1.50–3.42).

Conclusion: In the high CV risk Thai population, a BMI of 35 kg/m^2 or more is associated with loss of kidney function and mortality. On the other hand, a BMI less than 20 kg/m^2 is also associated with all-cause mortality.

KEYWORDS
body mass index, end-stage renal disease, glomerular filtration rate, high cardiovascular risk, mortality, obesity

SUMMARY AT A GLANCE

A nationwide prospective cohort study was conducted to evaluate the association between BMI and clinical outcomes in Asian patients with high CV risks. A BMI of 35 kg/m^2 or more is

related to loss of kidney function and mortality, whereas a BMI of less than 20 kg/m^2 is also associated with all-cause mortality.

1 | INTRODUCTION

Obesity has been increasing in recent decades and is considered a significant contributor to poor health in most countries.[1] In 2015, there were approximately 604 million adults with obesity worldwide. Based upon data collected for The National Health and Nutrition Examination Survey, estimates of the overall age-adjusted prevalence of obesity in the United States from 1988–1994, 1999–2000 and 2017–2018 increased progressively from 22.9% to 30.5% to 42.4%.[2]

The global prevalence of obesity results from multifactorial factors of genetic predisposition, increased accessibility to high-calorie foods, and decreased physical activity, leading to increased risk of atherosclerosis-related diseases such as diabetes, dyslipidemia, hypertension, chronic kidney disease (CKD) and cardiovascular (CV) morbidity and mortality.[3–9] A high body mass index (BMI) is also associated with an increased risk of end-stage renal disease (ESRD).[10–12]

Previous studies conducted in the United States described a strong relationship between the risk of developing advanced CKD and an increased BMI, especially for those with BMI >25 kg/m^2, regardless of age, sex and race, and the presence of underlying renal disease, diabetes or hypertension.[11,13] Not only is obesity a risk factor for impaired renal function, but being underweight is found to be a risk as well. A recent national diabetes cohort from Korea showed that participants with BMI less than 18.5 kg/m^2 were associated with an increased hazard ratio of ESRD.[14] Evidence also demonstrated that either high (>25 kg/m^2) or low BMI (<22.5 kg/m^2) were associated with increased mortality from all and CV causes.[15–18]

Although a high BMI may relate to the incidence of CKD and CKD progression, some studies suggested that elevated BMI may improve survival among individuals with CKD[19] and ESRD.[20,21] However, there is limited evidence showing how BMI affects renal outcome and mortality among the Asian population, which has a different definition of obesity according to BMI criteria.[22,23] Thus, this study explores the association between BMI and renal outcomes and mortality among Thai patients at high CV risk.

2 | MATERIALS AND METHODS

The national study, entitled 'Cohort of Patients with High Risk for Cardiovascular Events (CORE-Thailand) Registry', is a multicentre prospective cohort. It was conducted in 25 hospitals ranging from secondary to tertiary-care levels in Thailand. The Joint Research Ethics Committee and Ministry of Public Health, Thailand, approved the study protocol. Written informed consent was obtained from all participants.

2.1 | Study population

Enrolled during April 2011–March 2014, the participants included patients aged 45 years or older with established coronary artery disease (CAD), or cerebrovascular disease (CVD), or peripheral arterial disease (PAD), or with three CV risk factors; male aged 55 years or older, or female aged 65 years or older, or diabetes (type 1 or type 2 diabetes mellitus or currently receiving hypoglycemic agents), or impaired fasting glucose (fasting plasma glucose 100–125 mg/dL), or hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or currently receiving antihypertensive agents), or dyslipidemia (total cholesterol >200 mg/dL or low-density lipoprotein (LDL) >130 mg/dL or triglycerides >150 mg/dL or high-density lipoprotein (HDL) <40 mg/dL or currently receiving antihyperlipidemic agents), or CKD (persistent proteinuria or estimated GFR 15–60 mL/min/1.73m^2 over 3 months), or current smoking (>1 cigarette per day), or family history of premature atherosclerosis (any first-degree relatives with myocardial infarction or coronary angioplasty or coronary artery bypass surgery before the age of 55 among males and 65 among females).

Patients with one of the following were excluded: having CV events in the past 3 months, having severe aortic aneurysm indicated for surgery, participating in a blinded clinical trial, having limited life expectancy within 3 years from a non-CV condition such as cancer or documented human immunodeficiency virus infection, or having difficulty returning for a follow-up visit. Figure 1 showed that 9390 participants were eligible for the inclusion and exclusion criteria of the CORE-Thailand study. In addition to the CORE-Thailand study, 3503 patients with renal endpoints, missing information of serum creatinine or BMI were excluded. Therefore, this cohort's total eligible participants were 5887.

The primary composite outcome focused on renal endpoints consisted of estimated GFR decline over 40%, eGFR less than 15 mL/min/1.73m^2, doubling of serum creatinine and initiation of dialysis, and death related to renal causes. The secondary outcomes were rapid renal progression, all-cause mortality and CV mortality.

2.2 | Data collection

Data from each hospital were collected using a standardized case report form. The case report form focused on demographic data, including age, sex, smoking history, exercise, family history of premature atherosclerosis, medications and comorbidities. Anthropometric and laboratory measurements were recorded among participants, including blood pressure (BP), waist circumference, BMI, serum creatinine, eGFR, total cholesterol, HDL, LDL, triglycerides, fasting plasma glucose, haemoglobin A1c (HbA1c) and urine protein. The eGFR was

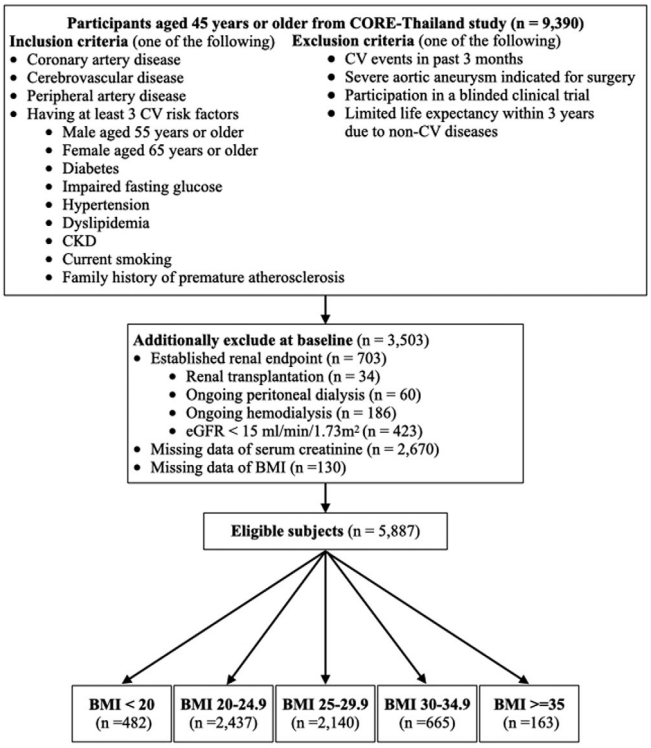


FIGURE 1 Enrollment flowchart. Coronary artery disease consisted of one of the followings: a history of chronic stable angina, unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery. Cerebrovascular disease consisted of one of the followings: a history of transient ischemic attack, ischemic stroke, carotid stenting or carotid endarterectomy. Peripheral artery disease consisted of one of the followings: a history of intermittent claudication with ABI <0.9, aortic dissection/surgery, peripheral artery angioplasty/stenting/bypass graft, amputation of ischemic limbs. BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate

calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[24] Participants were appointed for clinical and laboratory re-evaluation at 6, 12, 24, 36, 48, and 60 months after the first visit.

2.3 | Definitions

The established CV diseases, CAD, CVD, and PAD, were defined as one or more of their events. CAD consisted of stable or unstable angina with evidence of CAD by non-invasive study or coronary angiogram, myocardial infarction (MI), history of percutaneous coronary intervention, or history of coronary artery bypass graft surgery (CABG). CVD consisted of transient ischemic attack, ischemic stroke, history of carotid stenting or carotid endarterectomy. PAD consisted of intermittent claudication with ABI <0.9, aortic dissection/surgery, peripheral artery angioplasty/stenting/bypass graft or amputation of ischemic limbs. Rapid renal progression was defined as a decline of eGFR at least 5 mL/min/1.73m^2 per year.

For multivariate analysis, covariates of model 1 included age, sex, systolic BP, diastolic BP, hypertension, dyslipidemia, diabetes, history of smoking, regular exercise and eGFR. Covariates of model 2 included age, sex, systolic BP, diastolic BP, hypertension, dyslipidemia, diabetes, history of smoking, regular exercise, eGFR, antiplatelet agents, ACEI/ARBs, insulin and statin.

2.4 | Statistical analyses

For descriptive analyses, continuous variables were expressed as mean with standard deviation and compared between the BMI groups by one-way analysis of variance (ANOVA). Categorical variables were expressed as a frequency with column percentage (%) and compared between BMI groups by Chi-square test. Univariate and multivariate analyses were performed with the hazard ratio (HR) with 95% confidence intervals (CI), involving survival time to each subject's first event. The Kaplan–Meier model and log-rank statistics were used to analyse the outcomes according to BMI groups. Statistical significance was considered as a two-tailed probability of less than .05. Statistical analysis was performed using SPSS 26.0 (SPSS, Chicago, IL).

3 | RESULTS

3.1 | Baseline characteristics

A total of 5887 participants (3217 male and 2670 female) older than 44 years with high CV risk were enrolled, with the mean age of 66.1 ± 9.8 years. The mean BMI was 25.5 ± 4.5 kg/m^2, and the mean eGFR was 66.1 ± 23.2 mL/min/1.73m^2. The participants were categorized into five groups by their baseline BMI; <20 kg/m^2 (n = 482), 20–24.9 kg/m^2 (n = 2437), 25–29.9 kg/m^2 (n = 2140), 30–34.9 kg/m^2 (n = 665) and 35 kg/m^2 (n = 163), respectively.

Compared to those with lower BMI, participants with higher BMI had younger age and a higher proportion of females. The higher BMI groups tended to have higher waist circumference, BP, fasting plasma glucose, HbA1c, triglycerides, and have a higher percentage of diabetes, hypertension, dyslipidemia, ACEI/ARBs, CCBs, diuretic, statin, ezetimibe, hypoglycemic medications and vasodilators. Inversely, participants with higher BMI tended to have slightly lower HDL and a lower proportion of current smokers, CAD and CVD.

Compared with the overall trend, it was noticeable that the highest BMI group (BMI ≥35 kg/m^2) had a reverse direction of some variables, such as triglycerides, HDL, statin and vasodilators. A U-shaped association was found among a percentage of warfarin use. An inverted U-shapes association was found among a percentage of non-proteinuria. There were no significant differences among other variables between the five BMI groups (Table 1).

TABLE 1 Baseline characteristics

	BMI					
	<20 (*n* = 482)	**20–24.9 (*n* = 2437)**	**25–29.9 (*n* = 2140)**	**30–34.9 (*n* = 665)**	**≥35 (*n* = 163)**	***p*-value**
Age (years)	71.16 ± 10.03	66.98 ± 9.79	65.03 ± 9.31	63.3 ± 9.38	62.21 ± 9.88	<.001
Female (N, %)	231 (47.93%)	1049 (43.04%)	930 (43.46%)	348 (52.33%)	112 (68.71%)	<.001
BMI (kg/m^2)	18.16 ± 1.53	22.88 ± 1.4	27.19 ± 1.35	31.82 ± 1.28	38.68 ± 4.25	<.001
Waist circumference (cm)	73.41 ± 8.04	83.91 ± 7.57	93.2 ± 7.63	101.06 ± 8.44	110.26 ± 11.53	<.001
Systolic BP (mmHg)	127.82 ± 18.83	131.8 ± 18.74	133.4 ± 17.28	136.44 ± 16.06	136.39 ± 18.5	<.001
Diastolic BP (mmHg)	70.23 ± 11.1	73.34 ± 10.93	75.63 ± 10.43	77.79 ± 10.3	76.92 ± 11.45	<.001
Diabetes (N, %)	185 (38.38%)	1351 (55.44%)	1368 (63.93%)	525 (78.95%)	141 (86.5%)	<.001
Hypertension (N, %)	443 (91.91%)	2315 (94.99%)	2081 (97.24%)	654 (98.35%)	159 (97.55%)	<.001
Dyslipidemia (N, %)	370 (76.76%)	2114 (86.75%)	1951 (91.17%)	631 (94.89%)	152 (93.25%)	<.001
Exercise (*N*, %)	406 (84.23%)	2033 (83.42%)	1771 (82.76%)	565 (84.96%)	140 (85.89%)	.598
History of smoking (*N*, %)	103 (21.37%)	585 (24%)	557 (26.03%)	186 (27.97%)	41 (25.15%)	.061
Current smoking (*N*, %)	45 (9.34%)	121 (4.97%)	90 (4.21%)	26 (3.91%)	7 (4.29%)	<.001
Family history of premature atherosclerosis (*N*, %)	43 (8.92%)	194 (7.96%)	171 (7.99%)	49 (7.37%)	12 (7.36%)	.909
Coronary artery disease (*N*, %)	245 (50.83%)	1159 (47.56%)	892 (41.68%)	227 (34.14%)	45 (27.61%)	<.001
Cerebrovascular disease (*N*, %)	55 (11.41%)	249 (10.22%)	145 (6.78%)	39 (5.86%)	9 (5.52%)	<.001
Peripheral artery disease (*N*, %)	45 (9.54%)	64 (2.63%)	36 (1.68%)	7 (1.05%)	2 (1.23%)	<.001
LVEF (%)	52.09 ± 17.05	56.42 ± 16.06	57.49 ± 15.7	60.59 ± 16.76	60.44 ± 13.99	<.001
Fasting plasma glucose (mg/dL)	116.39 ± 46.11	121.46 ± 43.68	128.5 ± 52.76	133.57 ± 47.42	145.45 ± 79.06	<.001
HbA1c (%)	7.01 ± 1.6	7.02 ± 1.48	7.23 ± 1.58	7.38 ± 1.62	7.4 ± 1.72	<.001
Total cholesterol (mg/dL)	168.33 ± 38.17	168.06 ± 39.05	169.59 ± 41.59	171.31 ± 40.87	171.65 ± 32.39	.482
Triglyceride (mg/dL)	119.28 ± 61.51	133.69 ± 78.7	145.2 ± 81.77	158.32 ± 122.81	140.39 ± 56.43	<.001
HDL (mg/dL)	50.77 ± 16.77	50.65 ± 14.79	48.67 ± 13.59	48.38 ± 12.08	50.5 ± 13.61	<.001
LDL (mg/dL)	95.3 ± 29.65	95.02 ± 33.26	96.94 ± 35.14	97.94 ± 34.12	97.7 ± 29.95	.289
Serum creatinine (mg/dL)	1.16 ± 0.48	1.15 ± 0.46	1.16 ± 0.47	1.18 ± 0.53	1.14 ± 0.58	.838
eGFR (mL/min/1.73m^2)	63.28 ± 23.64	66.1 ± 22.71	66.38 ± 22.55	66.64 ± 24.82	68.44 ± 28.31	.05
Urine protein (N, %) Negative	69 (76.67%)	488 (78.84%)	485 (78.48%)	154 (70.64%)	46 (70.77%)	<.001
1+	11 (12.22%)	68 (10.99%)	72 (11.65%)	30 (13.76%)	7 (10.77%)	
2+	8 (8.89%)	38 (6.14%)	35 (5.66%)	27 (12.39%)	6 (9.23%)	
3+	0 (0%)	21 (3.39%)	23 (3.72%)	6 (2.75%)	5 (7.69%)	
4+	2 (2.22%)	4 (0.65%)	3 (0.49%)	1 (0.46%)	1 (1.54%)	
Antiplatelet agents (*N*, %)	372 (77.18%)	1815 (74.48%)	1547 (72.29%)	478 (71.88%)	111 (68.1%)	.051
Warfarin (*N*, %)	30 (6.22%)	114 (4.68%)	71 (3.32%)	26 (3.91%)	12 (7.36%)	.007
Beta-blockers (*N*, %)	268 (55.6%)	1339 (54.94%)	1191 (55.65%)	364 (54.74%)	84 (51.53%)	.877
ACEI/ARBs (*N*, %)	271 (56.22%)	1568 (64.34%)	1511 (70.61%)	495 (74.44%)	134 (82.21%)	<.001
CCBs (*N*, %)	157 (32.57%)	933 (38.28%)	918 (42.9%)	335 (50.38%)	81 (49.69%)	<.001
Diuretics (*N*, %)	123 (25.52%)	625 (25.65%)	621 (29.02%)	281 (42.26%)	75 (46.01%)	<.001
Statin (*N*, %)	412 (85.48%)	2152 (88.31%)	1919 (89.67%)	602 (90.53%)	138 (84.66%)	.015
Ezetimibe (*N*, %)	6 (1.24%)	94 (3.86%)	122 (5.7%)	41 (6.17%)	11 (6.75%)	<.001
Insulin (*N*, %)	26 (5.39%)	216 (8.86%)	270 (12.62%)	126 (18.95%)	39 (23.93%)	<.001
Sulfonylurea (*N*, %)	81 (16.8%)	596 (24.46%)	641 (29.95%)	239 (35.94%)	69 (42.33%)	<.001
Metformin (*N*, %)	84 (17.43%)	774 (31.76%)	829 (38.74%)	329 (49.47%)	90 (55.21%)	<.001
Thiazolidinedione (*N*, %)	9 (1.87%)	134 (5.5%)	185 (8.64%)	97 (14.59%)	29 (17.79%)	<.001

TABLE 1 (Continued)

	BMI					
	<20 ($n = 482$)	20–24.9 ($n = 2437$)	25–29.9 ($n = 2140$)	30–34.9 ($n = 665$)	≥35 ($n = 163$)	*p*-value
DPP-4 inhibitors (*N*, %)	8 (1.66%)	76 (3.12%)	98 (4.58%)	36 (5.41%)	19 (11.66%)	<.001
Vasodilators (*N*, %)	10 (2.07%)	72 (2.95%)	64 (2.99%)	35 (5.26%)	4 (2.45%)	.015

Note: Data are presented as mean ± *SD* and number with column percentage. Diuretics consisted of hydrochlorothiazide, furosemide and spironolactone. Vasodilators consisted of doxazosin, alfuzosin, prazosin, hydralazine, minoxidil and methyldopa. Antiplatelet agents consisted of aspirin, ticlopidine, clopidogrel, ticagrelor and cilostazol. Coronary artery disease consisted of one of the followings: a history of chronic stable angina, unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery. Cerebrovascular disease consisted of one of the followings: a history of transient ischemic attack, ischemic stroke, carotid stenting or carotid endarterectomy. Peripheral artery disease consisted of one of the followings: a history of intermittent claudication with ABI <0.9, aortic dissection/surgery, peripheral artery angioplasty/stenting/bypass graft, amputation of ischemic limbs.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CCBs, calcium-channel blockers; DPP-4 inhibitors, dipeptidyl-peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobinA1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

TABLE 2 Incidence of primary and secondary outcomes

	BMI					
	<20 ($n = 482$)	20–24.9 ($n = 2437$)	25–29.9 ($n = 2140$)	30–34.9 ($n = 665$)	≥35 ($n = 163$)	*p*-value
eGFR decline over 40%	25 (5.19%)	184 (7.55%)	163 (7.62%)	55 (8.27%)	25 (15.34%)A,B,C,D	.001
eGFR less than 15 mL/min/1.73 m^2	9 (1.87%)	75 (3.08%)	64 (2.99%)	39 (5.86%)A,B,C	11 (6.75%)A	<.001
Doubling of serum creatinine	14 (2.9%)	81 (3.32%)	76 (3.55%)	33 (4.96%)	14 (8.59%)A,B,C	.003
Initiation of dialysis	1 (0.21%)	5 (0.21%)	2 (0.09%)	2 (0.3%)	1 (0.61%)	.279
Death related to renal causes	0 (0%)	6 (0.25%)	5 (0.23%)	0 (0%)	0 (0%)	.743
Primary composite outcome	27 (5.6%)	200 (8.21%)	176 (8.22%)	63 (9.47%)	26 (15.95%)A,B,C	.001
All-cause mortality	39 (8.09%)	110 (4.51%)A	72 (3.36%)A	18 (2.71%)A	14 (8.59%)C,D	<.001
CV mortality	11 (2.28%)	38 (1.56%)	29 (1.36%)	9 (1.35%)	3 (1.84%)	.644
Rapid renal progression	156 (32.37%)	900 (36.93%)	837 (39.11%)	278 (41.8%)A	63 (38.65%)	.012

Note: Data are presented as number with column percentage. Primary composite outcome consists of eGFR decline over 40%, eGFR less than 15 mL/min/1.73 m^2, doubling of serum creatinine, initial dialysis and death related to renal cause. Rapid renal progression defined as eGFR decline over 5 mL/min/1.73 ˝2 per year. The mean difference is significant at the .05 level. A: compared with BMI <20 kg/m^2, B: compared with BMI 20–24.9 kg/m^2, C: compared with BMI 25.29.9 kg/m^2, D: compared with BMI 30–34.9 kg/m^2.

Abbreviations: CV mortality; cardiovascular mortality; eGFR; estimated glomerular filtration rate.

3.2 | Primary and secondary outcomes

Participants with higher BMI had a higher incidence of the primary composite outcome. Table 2 demonstrated that 5.6%, 8.21%, 8.22%, 9.47% and 15.95% participants from BMI <20, 20–24.9, 25–29.9, 30–34.9 and ≥35 kg/m^2, respectively, had events of the primary composite outcome. For each primary outcome, having eGFR decline over 40%, eGFR less than 15 mL/min/1.73 m^2 and doubling serum creatinine differed among the BMI groups significantly.

The percentages of all-cause mortality and rapid renal progression significantly differed among the five BMI groups. The highest incidence of all-cause mortality was 8.59% from the highest BMI group (BMI ≥35 kg/m^2). The highest incidence of rapid renal progression was 39.11% from BMI 25–29.9 kg/m^2 group. There were no significant differences in CV mortality between the BMI groups.

3.3 | Incidence rate and Cox regression analyses

The incidence rate per 100 person-years (95% CI) of primary composite outcome among the BMI <20, 20–24.9, 25–29.9, 30–34.9 and ≥35 kg/m^2 groups were 2.02 (1.38–2.94), 2.58 (2.24–2.96), 2.50 (2.16–2.90), 2.98 (2.33–3.81), 5.04 (3.43–7.40), respectively. Cox regression model showed an association between the BMI groups and primary composite outcomes. Compared with the reference group (BMI 25–29.9 kg/m^2), the unadjusted HR in the BMI <20, 20–24.9, 30–34.9 and ≥35 kg/m^2 groups had 0.75-fold (95% CI 0.50–1.12), 1.01-fold (95% CI 0.83–1.24), 1.20-fold (95% CI 0.90–1.60) and 2.09-fold (95% CI 1.39–3.16), respectively. Only the BMI ≥35 kg/m^2 group indicated a statistical significance. After adding covariates from model 1, the BMI ≥35 kg/m^2 group only had a significantly higher risk of the primary composite outcome at adjusted HR 1.61 (95% CI 1.06–2.45). After adding covariates from model 2, the BMI ≥35 kg/m^2 group still had a significantly higher

TABLE 3 Incidence rate and hazard ratio of primary and secondary outcomes

BMI (kg/m^2)	Events (*n*)	Person-time (years)	Incidence rate per100 person-years (95% CI)	Univariate		Multivariate			
						Model 1		Model 2	
				Crude HR (95%CI)	*p*-value	Adjusted HR (95%CI)	*p*-value	Adjusted HR (95%CI)	*p*-value
HR for primary composite outcome									
<20	27	1337.63	2.02 (1.38–2.94)	0.75 (0.50–1.12)	.155	0.90 (0.60–1.36)	.623	0.94 (0.62–1.42)	.763
20–24.9	200	7766.65	2.58 (2.24–2.96)	1.01 (0.83–1.24)	.889	1.10 (0.90–1.36)	.351	1.13 (0.92–1.38)	.264
25–29.9	176	7029.79	2.50 (2.16–2.90)	Reference	1	Reference	1	Reference	1
30–34.9	63	2114.16	2.98 (2.33–3.81)	1.20 (0.90–1.60)	.212	1.05 (0.79–1.41)	.723	1.04 (0.77–1.38)	.817
≥35	26	516.01	5.04 (3.43–7.40)	2.09 (1.39–3.16)	<.001	1.61 (1.06–2.45)	.025	1.60 (1.04–2.40)	.032
HR for all-cause mortality									
<20	39	1315.77	2.96 (2.17–4.06)	3.03 (2.05–4.47)	<.001	2.15 (1.43–3.23)	<.001	2.26 (1.50–3.42)	<.001
20–24.9	110	7842.93	1.40 (1.16–1.69)	1.39 (1.04–1.88)	.029	1.23 (0.91–1.66)	.187	1.25 (0.92–1.69)	.157
25–29.9	72	7170.93	1.00 (0.80–1.26)	Reference	1	Reference	1	Reference	1
30–34.9	18	2135.45	0.84 (0.53–1.34)	0.84 (0.50–1.41)	.503	0.95 (0.57–1.60)	.851	0.92 (0.55–1.55)	.749
≥35	14	556.26	2.52 (1.49–4.25)	2.49 (1.40–4.41)	.002	2.67 (1.47–4.72)	.001	2.68 (1.50–4.80)	.001
HR for CV mortality									
<20	11	1395.63	0.79 (0.44–1.42)	2.08 (1.04–4.17)	.039	1.55 (0.76–3.20)	.231	1.74 (0.84–3.61)	.134
20–24.9	38	8207.76	0.46 (0.34–0.64)	1.19 (0.74–1.93)	.476	1.05 (0.65–1.72)	.837	1.08 (0.66–1.77)	.761
25–29.9	29	7459.10	0.39 (0.270–0.56)	Reference	1	Reference	1	Reference	1
30–34.9	9	2259.99	0.40 (0.21–0.77)	1.03 (0.49–2.17)	.945	1.11 (0.52–2.37)	.780	1.07 (0.50–2.27)	.869
≥35	3	584.99	0.51 (0.17–1.59)	1.30 (0.40–4.28)	.662	1.28 (0.38–4.25)	.678	1.30 (0.39–4.33)	.663
HR for rapid renal progression									
<20	156	1131.43	13.79 (11.79–16.13)	0.98 (0.82–1.16)	.781	1.01 (0.85–1.20)	.940	1.02 (0.85–1.21)	.847
20–24.9	899	1703.54	13.95 (13.07–14.89)	0.97 (0.88–1.06)	.481	0.98 (0.90–1.08)	.747	0.99 (0.90–1.09)	.814
25–29.9	873	5816.97	14.39 (13.45–15.40)	Reference	1	Reference	1	Reference	1
30–34.9	278	1703.54	16.31 (14.51–18.35)	1.14 (0.99–1.30)	.060	1.13 (0.99–1.30)	.080	1.14 (0.99–1,31)	.065
≥35	63	440.72	14.29 (11.17–18.30)	1.01 (0.78–1.31)	.936	1.02 (0.79–1.32)	.881	1.02 (0.74–1.32)	.905

Note: Primary composite outcome consists of eGFR decline over 40%, eGFR less than 15 mL/min/1.73 m^2, doubling of serum creatinine, initial dialysis and death related to renal cause. Model 1 adjusted by; age, sex, systolic BP, diastolic BP, hypertension, dyslipidemia, diabetes, history of smoking, regular exercise and eGFR. Model 2 adjusted by: age, sex, systolic BP, diastolic BP, hypertension, dyslipidemia, diabetes, history of smoking, regular exercise, eGFR, antiplatelet agents, ACEI/ARBs, insulin and statin. All variables are at baseline.

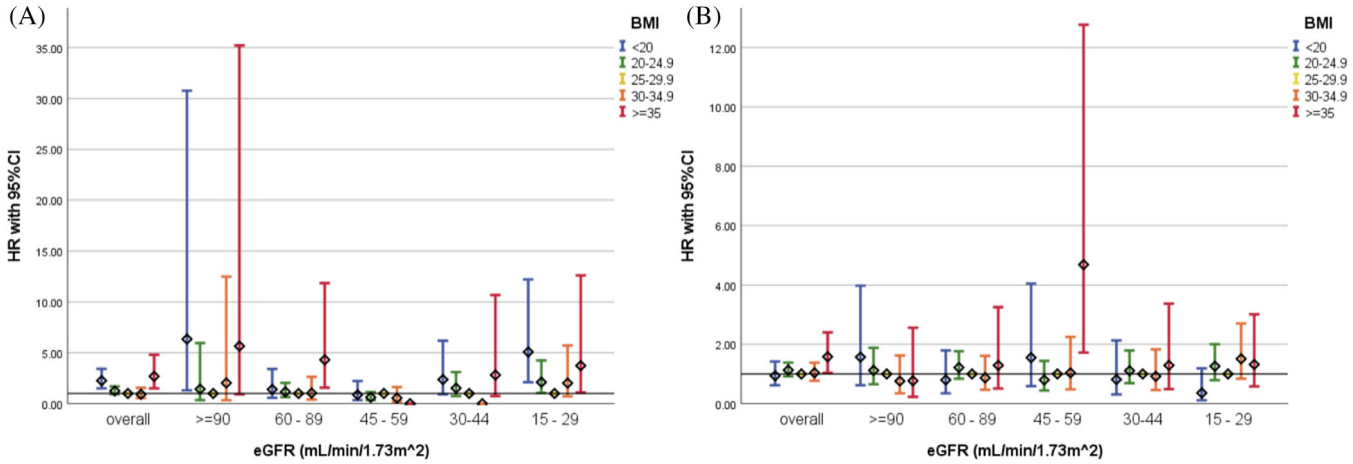
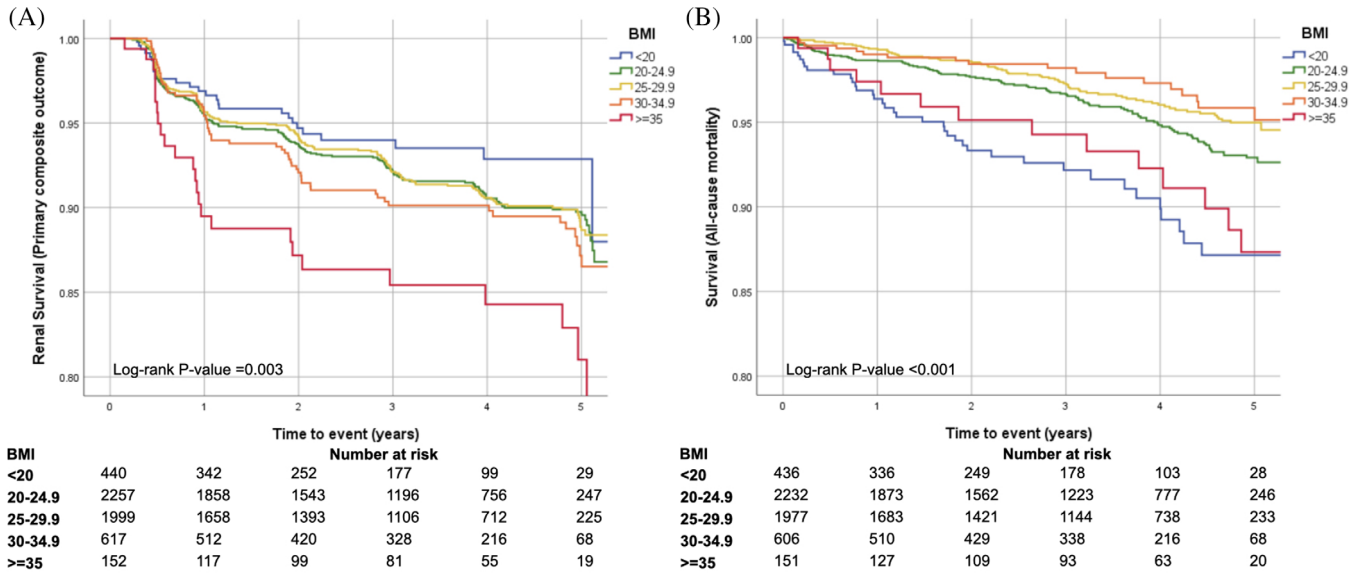


FIGURE 2 (A) Subgroup analysis of primary composite outcome according to eGFR and BMI groups after adjusting with covariates from model 2. According to five subgroups by baseline eGFR (mL/min/1.73m^2); ≥90 ($n = 1074$), 60–89 ($n = 2460$), 45–59 ($n = 1121$), 30–44 ($n = 821$) and 15–29 ($n = 411$), the total numbers of events in each eGFR subgroup were 77 (7.17%), 144 (5.85%), 67 (5.98%), 95 (11.57%) and 109 (26.52%), respectively. (B) Subgroup analysis of all-cause mortality according to eGFR and BMI groups after adjusting with covariates from model 2. According to five subgroups by baseline eGFR (mL/min/1.73m^2); ≥90 ($n = 1074$), 60–89 ($n = 2460$), 45–59 ($n = 1121$), 30–44 ($n = 821$) and 15–29 ($n = 411$), the total numbers of events in each eGFR subgroup were 18 (1.68%), 69 (2.80%), 56 (5.00%), 48 (5.85%) and 62 (15.09%), respectively



BMI	Number at risk					
<20	440	342	252	177	99	29
20-24.9	2257	1858	1543	1196	756	247
25-29.9	1999	1658	1393	1106	712	225
30-34.9	617	512	420	328	216	68
>=35	152	117	99	81	55	19

BMI	Number at risk					
<20	436	336	249	178	103	28
20-24.9	2232	1873	1562	1223	777	246
25-29.9	1977	1683	1421	1144	738	233
30-34.9	606	510	429	338	216	68
>=35	151	127	109	93	63	20

FIGURE 3 (A) Kaplan–Meier survival curve for Primary Composite Outcome according to BMI groups (log-rank test, $p = .003$). (B) Kaplan–Meier survival curve for all-cause mortality according to BMI groups (log-rank test, $p < .001$)

risk at adjusted HR 1.60 (95%CI 1.04–2.40; Table 3). Subgroup analysis according to CKD stage, with adjusting in model 2, showed that an exposure–response relationship was found in those with eGFR 60–89, 30–44 and 15–29 mL/min/1.73m^2 with a slightly higher HR of the 20–24.9 kg/m^2 group than the 30–34.9 kg/m^2 group. An opposite trend was found in the group of eGFR ≥90 mL/min/1.73 m^2. A U-shaped association was found among patients with CKD stage IIIa, eGFR between 45 and 59 mL/min/1.73 m^2. Significant and prominent risk was found only in the highest BMI group of CKD stage IIIa with 4.66-fold HR (1.71–12.67; Figure 2A).

For all-cause mortality, the incidence rate per 100 person-years (95% CI) among the BMI <20, 20–24.9, 25–29.9, 30–34.9 and ≥35 kg/m^2 groups were 2.96 (2.17–4.06), 1.40 (1.16–1.69), 1.00 (0.80–1.26), 0.84 (0.53–1.34) and 2.52 (1.49–4.25), respectively. Cox regression analysis revealed that the unadjusted HR in the BMI <20, 20–24.9, 30–34.9 and ≥35 kg/m^2 groups had 3.03-fold (95% CI 2.05–4.47), 1.39-fold (95% CI 1.04–1.88), 0.84-fold (95% CI 0.50–1.41) and 2.49-fold (95% CI 1.40–4.41) higher risk, respectively, compared with the reference group (BMI 25–29.9 kg/m^2). The BMI <20, 20–24.9 and the BMI ≥35 kg/m^2 group had a significant association. After adding covariates from model 1, the lowest (BMI <20 kg/m^2) and highest

(BMI ≥35 kg/m^2) groups had a significantly higher risk of all-cause mortality at adjusted HR 2.15 (95% CI 1.43–3.23) and adjusted HR 2.67 (95% CI 1.47–4.72), respectively. After adjusting in model 2, the lowest and highest groups still had significant results with adjusted HR 2.26 (95% CI 1.50–3.42) and adjusted HR 2.68 (95% CI 1.50–4.80), respectively (Table 3). After dividing subjects according to eGFR, with adjusting in model 2, U-shaped associations of all-cause mortality still persisted in every eGFR subgroup, except the group of eGFR between 45 and 59 mL/min/1.73m^2. The highest risk of all-cause mortality was observed among a group of BMI <20 kg/m^2 with eGFR ≥90 mL/min/1.73 m^2 (Figure 2B).

After performing the analysis in CV mortality, the incidence rate (95% CI) among the BMI <20, 20–24.9, 25–29.9, 30–34.9 and ≥35 kg/m^2 groups were 0.79 (0.44–1.42), 0.46 (0.34–0.64), 0.39 (0.270–0.56), 0.40 (0.21–0.77) and 0.51 (0.17–1.59), respectively. There was only a significant association between the lowest BMI group and CV mortality in the unadjusted model with a 2.08-fold HR (95%CI 1.04–4.17). For the multivariate models, the hazard ratios were non-significant among all BMI groups. There were no significant associations after performing Cox regression analysis on the rapid renal progression (Table 3).

3.4 | Kaplan–Meier survival analyses

Kaplan–Meier survival curve of the primary composite outcome demonstrated worse renal survival in the higher BMI groups. The highest BMI group (BMI ≥35 kg/m^2) obviously had the worst outcome while the other BMI groups were slightly different. Log-rank test was considered significant at $p = .003$ (Figure 3A).

In contrast, the Kaplan–Meier survival curve of all-cause showed the best prognosis in the BMI 30–34.9 kg/m^2 group, followed by the 25–29.9, 20–24.9 and ≥35 kg/m^2 group, subsequently, with the worst prognosis in the lowest BMI (BMI <20 kg/m^2) group. Log-rank test was considered significant at $p < .001$ (Figure 3B). There were no significant differences in a log-rank test of CV mortality and rapid renal progression (data not shown).

4 | DISCUSSION

The nationwide prospective cohort demonstrated how abnormal BMI was related to composite renal outcomes and mortality in the Thai population with high atherosclerosis risk. An exposure–response relationship was found between BMI levels and the composite renal outcomes. After dividing subjects according to eGFR, a U-shaped association of the renal outcomes was found among the BMI groups of those who had baseline eGFR between 45 and 59 mL/min/1.73 m^2. The worst renal outcome was observed among patients who had BMI ≥35 kg/m^2 with eGFR between 45 and 59 mL/min/1.73 m^2. These findings were similar to related studies. A national cohort of 453 946 United States veterans with eGFR <60 mL/min/1.73 m^2 demonstrated a linear relationship between BMI groups and ESRD, especially in CKD stage IIIb to IV. A U-shaped association between BMI groups and CKD progression was seen in all CKD stages. It could be seen that the magnitude of renal outcomes in CKD stage IV was less than in stage III in this[25] and our study. However, this study was conducted among the U.S. population; their reference group was BMI 30–34.9 kg/m^2 that higher than our study, which was conducted among the Thai population. The renal outcomes, which is CKD progression, between the two studies were defined differently. A linear association between BMI and ESRD was also found in other cohorts, including both Asian and Western populations.[11,12]

Worsening of renal functions in those with BMI ≥35 kg/m^2 could be explained by obesity-related glomerulopathy (ORG), secondary form of focal segmental glomerulosclerosis (FSGS).[26–29] Serra et al. microscopically investigated the glomerular structure of extremely obese patients with normal renal function versus the control group.[26] They found that BMI was an independent predictor of glomerular lesions, and increased mesangial matrix, podocyte hypertrophy, mesangial cell proliferation and glomerulomegaly were more common in the obesity group.[26] However, ORG did not eventually develop in all obese patients. Other mechanisms could be explained by a chronic inflammatory state and metabolic dysregulation of obesity. Adipose tissue of obese patients can produce inflammatory cytokines, such as leptin, which resulted in insulin resistance, vascular and renal pathology.[30,31] Combined in vitro and in vivo studies demonstrated that leptin could induce transforming growth factor-beta1 (TGF-beta1), a profibrogenic factor, leading to kidney damage, characterized by endocapillary proliferation and subsequent glomerulosclerosis.[31] Hypoadiponectinemia, which was found in an obese patient, and excess caloric intake were related to podocyte effacement and albuminuria via a reduction of activated 5′-AMP activated protein kinase.[32]

For rapid renal progression, although the incidence of rapid renal progression between groups of BMI <20 kg/m^2 and BMI 30–34.9 kg/m^2 were different, the hazard ratios in both univariate and multivariate analysis did not demonstrate any significant relationship. We hypothesized that our study population, who had many risk factors for CKD progression at baseline, tended to have rapid eGFR decline in every BMI category. The rapid renal progression, defined as eGFR decline over 5 mL/min/1.73 m^2, had high sensitivity for every subject to meet the criteria. Unlike the primary outcome, which was composed of major renal endpoints, the subjects were less susceptible to meet the criteria. It also can indicate the severity of the renal function, which the representation is better than the rapid renal progression. Therefore, the different outcomes were illustrated.

Regarding all-cause mortality, the lowest and highest BMI groups were significantly associated with all-cause mortality. A U-shaped association was found between BMI levels. These results were similar to the U.S. cohorts.[25,33] A study by Flegal et al., among the U.S. general population, found that underweight patients were associated with increased mortality, from non-cancer and non-CV causes, while obese patients were associated with increased CV death.[33] This author also performed a systematic review and meta-analysis on the association between overweight, obesity and all-cause mortality. The results indicated that obesity, especially grade II and III, was

associated with increased all-cause mortality compared with BMI 18.5–<25 kg/m^2.[34]

Although obesity and overweight are risk factors of CKD, CV diseases and all-cause mortality, it has protective mechanisms against CKD-related and non-CV death.[33–36] It can be seen that participants with BMI ranged between 20 and 34.9 kg/m^2 had a better prognosis than both extremely higher or lower BMI groups. These results could partially explain by a phenomenon called the 'obesity paradox', the reverse epidemiology of CV risks. This phenomenon can happen to groups of patients who had malnutrition and the chronic inflammatory state as strong predictors for short-term mortality. An amount of muscle mass and body fat improve survival in obese patients. Underlying mechanisms which play a role in the obesity paradox consisted of hemodynamic stability of obesity, high lipoprotein concentration, which binds against circulating endotoxins, protective cytokine alterations, toxin sequestration by adipose tissues and anti-oxidative effects of muscles.[35] But, survival among the subjects of the extreme obesity group (BMI ≥35 kg/m^2) did not harmonize with this phenomenon. This group tended to have a higher prevalence of diabetes and hypoglycemic agent use and poorer glycemic control than overall subjects. Nevertheless, the results showed that their CV mortality did not significantly differ among BMI groups. Therefore, the cause of non-CV death should be further investigated.

The strength of this study comprised a great number of participants, generalizability across the country representing the Southeast Asian population with high CV risk and a 5-year prospective follow-up. However, several limitations exist. First, although we had many participants, subgroup analysis according to CKD stages and BMI groups revealed fewer significant results with a wider range of 95% CIs than the previous study.[25] The number of subjects in each subgroup might not yield enough power. Second, the results of subgroup analyses according to eGFR did not have the strength of evidence of outcomes tested for the entire population. Therefore, it should be interpreted with caution and used primarily to generate hypotheses. Third, variation of laboratory measurements was possible because specimens were collected and tested in different sites. Fourth, common investigations in the assessments of kidney function, such as blood urea nitrogen and albumin excretion rate, were unavailable. Many proteinuria results were missing at baseline. Therefore, we decided not to add proteinuria in the multivariate models. Otherwise, it would exclude 4267 of 5877 subjects from the analysis. Last, information about the cause of non-CV mortality, medication adherence, muscle mass and body fat was not assessed.

5 | CONCLUSION

In the high CV risk Thai population, an exposure–response relationship is found between BMI levels and renal outcomes. In contrast, a U-shaped association is found between BMI levels and all-cause mortality. A BMI of 35 kg/m^2 or more is related to deteriorated kidney function and mortality. On the other hand, a BMI less than 20 kg/m^2 is associated with mortality.

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CONFLICT OF INTEREST

The authors declare that no potential conflict of interest exists.

AUTHOR CONTRIBUTIONS

Noppawit Aiumtrakul, Annop Kittithaworn, and Bancha Satirapoj reviewed the literature, provided valuable input in designing the study, drafted the article and revised it critically. Ouppatham Supasyndh, Rungroj Krittayaphong, and Arintaya Phrommintikul provided literature review and revised the manuscript critically. All authors read and approved the manuscript and met the criteria for authorship.

ETHICS STATEMENT

The study protocol was approved by the Joint Research Ethics Committee and Ministry of Public Health, Thailand. Informed consent was obtained from all patients.

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