

# The obesity paradox exists in Asia: A systematic review and meta-analysis of body mass index effects on clinical outcomes following percutaneous coronary intervention in Asia

Andrianto\*, Chabib Fachry Albab, Nandha Pratama Mahardika

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Dr. Soetomo General Academic Hospital, Universitas Airlangga, Surabaya, Indonesia

# Abstract

coronary intervention

Cardiovascular diseases (CVDs) are major contributors to illness and death globally. Body mass index (BMI) is a well-established prognostic factor on cardiovascular risk outcome. Numerous investigations have provided evidence for the existence of the obesity paradox after percutaneous coronary intervention (PCI). However, the association between BMI and the results following PCI has not been extensively investigated in Asian populations. The research aims to fill the current void in understanding by investigating the association between BMI and clinical consequences following PCI, with a particular focus on Asian individuals. A systematic search was conducted through PubMed, ScienceDirect, and Cochrane Library to identify studies examining the effect of BMI on clinical outcome after PCI in Asia. R Studio 4.3.2 software was used to carry out the analysis of the data. A total of 182,110 patients who had gone through PCI were found in the 5 included cohorts. A meta-analysis conducted on the subjects revealed that patients who were overweight (odds ratio [OR] = 0.60, 95% confidence interval [CI] [0.57, 0.63], P < 0.0001) had a lower risk of all-cause mortality compared to individuals with a healthy weight and patients with obesity (OR = 0.65, 95% CI [0.41, 1.05], P = 0.006) had a lower risk of all-cause mortality than healthy weight individuals. The study also found that overweight patients (OR = 0.60, 95% CI [0.39, 0.91], P = 0.02) had a lower risk of cardiac mortality. In addition, obese patients (OR = 0.41, 95% CI [0.19, 0.88], P = 0.02) had a lower risk of noncardiac mortality. However, the study found that there were no differences in major adverse cardiovascular event, myocardial infarction, and bleeding between all patient groups. This meta-analysis supports the presence of an obesity paradox after PCI in Asian populations. The obesity paradox was evident in all-cause mortality, cardiac mortality, and noncardiac mortality.

**Keywords:** Asia, Body mass index, Clinical outcome, Obesity paradox, Percutaneous

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INTRODUCTION

Cardiovascular diseases (CVDs) remain a prominent contributor to illness and death on a global scale, with a substantial burden on health-care systems [1]. Percutaneous coronary intervention (PCI) plays a crucial role in managing coronary artery diseases [2]. With the rising prevalence of coronary artery diseases in Asia [3], understanding the factors influencing clinical outcomes after PCI becomes important for optimizing patient care.

Numerous studies have explored the "obesity paradox," a phenomenon where individuals with higher body mass

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index (BMI) exhibit better survival outcomes than those with lower BMI following certain cardiovascular procedures [4]. The BMI is notorious as a significant course for evaluating the susceptibility to CVDs [5,6]. Extensive documentation exists on the correlation between obesity and adverse cardiovascular events in Western populations. However, the relevance of

\*Address for correspondence: Dr. Andrianto, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, JI. Prof. Dr. Moestopo No. 47, Pacar Kembang, Kec. Tambaksari, Surabaya, Jawa Timur 60132, Indonesia. E-mail: andrianto@fk.unair.ac.id

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this paradox in the Asian population remains underexplored. Several studies have yielded mixed results, highlighting the need for a more comprehensive investigation into the interplay between BMI and various clinical factors in Asian populations on post-PCI outcomes [7,8]. In addition, the intricate interplay between BMI and various clinical factors, such as diabetes, hypertension, and lipid profiles, in influencing PCI outcomes in Asia requires comprehensive investigation [9-11].

Understanding the BMI-related nuances in post-PCI outcomes is crucial for tailoring therapeutic strategies and optimizing patient care in diverse populations. Filling the current void in understanding of the association of BMI and clinical consequences following PCI is the main focus of this research, in particular on Asian individuals. By elucidating the role of BMI in influencing outcomes, this study seeks to contribute valuable insights that can inform clinical decision-making, enhance risk stratification, and improve overall cardiovascular care in the Asian population undergoing PCI.

#### **Methods**

This study was organized by following the protocols outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Ethical approval was not necessary since there was no direct participation of patients in this study, and all utilized data had been previously published. We have registered our protocol in PROSPERO (CRD42023463250).

#### Eligibility

We conducted a systematic search focusing on observational studies that analyzed the influence of BMI on clinical effects following PCI in Asia has been examined. Studies conducted outside of Asia were deliberately excluded. There was no restriction on the publication year, but studies not written in English, those without available full text, and those involving nonhuman subjects were excluded. Duplicate articles were addressed prior to the screening of titles and abstracts.

#### Search strategy and selection of studies

We performed an extensive systematic database search independently by two authors in PubMed, ScienceDirect, and the Cochrane Library on September 25, 2023. The keywords that will be used are derived from "body mass index" AND "percutaneous coronary intervention," together with their corresponding MeSH terms, synonyms, and detailed explanations [Supplementary Files: Search strategy in each database]. Review articles will be omitted, but their citations will be scrutinized to identify any potentially overlooked relevant studies. Independent examination of titles and abstracts of the articles was carried out for a comprehensive screening of titles and abstracts.

The criteria for inclusion (which serve as guidelines for selecting eligible studies for inclusion in the analysis) and exclusion criteria were determined as follows.

## Inclusion criteria

The following are the inclusion criteria in this study: (1) study population: individuals undergoing PCI; (2) intervention

criteria: participants were categorized into different groups following their weight status, namely, underweight (<18.5), normal (18.5–23), overweight (23.0–27.5), and obese (>27.5). A variation of 2 kg/m<sup>2</sup> in BMI considered to be within an acceptable range; (3) outcome measures: the study focused on all-cause mortality, cardiac and noncardiac mortality, major adverse cardiovascular events (MACEs), myocardial infarction (MI), bleeding, and revascularization, with at least one of these indicators included in the analysis; and (4) study design: the selected studies were observational.

#### **Exclusion criteria**

The exclusion criteria in this study were as follows: (1) the study appears to contain inconsistencies within either its design or application of intervention methods; (2) the initial research does not contain the vital data needed to be included in this meta-analysis; (3) there is a recurrence of publications for the same studies; (4) the criteria for diagnosis or the measures for determining the outcome are not well defined; (5) review articles, case reports, reviews, abstracts of scientific meetings, and letters to editor; and (6) study in non-English languages.

#### **Article extraction**

We autonomously gathered pertinent articles from the encompassed studies using a structured and standardized template. We took some data, such as author, country, sample size, mean age, female sex, BMI, any comorbidities, intervention, outcome, and duration of follow-up. Any inconsistencies will be addressed through a consensus among all authors participating in the data extraction procedure.

#### **Quality assessment**

We performed bias assessment using the *Newcastle Ottawa Scale (NOS)*. The bias risk assessment was independently conducted by at least two authors. To resolve any disagreements, a senior author was involved in the process of reaching a consensus.

### Quantitative data synthesis and publication bias

Meta-analyses were conducted and displayed in the form of a forest plot. The odds ratio (OR) was determined by analyzing the data pertaining to the frequency of events and the cumulative sum of each outcome. Either the random-effect or fixed-effect model was used to pool aggregate data from each study depending on interstudy heterogeneity. Heterogeneity was considered significant if Cochran's Q had P < 0.1 or  $I^2 > 50\%$ . Assessment of publication bias in this study used Begg's funnel plot. Hartung Knapp (HK) adjustment approaches were performed due to the small number of selected studies.

#### RESULTS

#### Search results and study characteristics

A systematic search was carried out and found 3638 studies for review, and a manual search identified no additional studies. After review, 5 observational studies that met the inclusion criteria were incorporated into the analysis [Figure 1].

Our final analysis comprised 183,921 patients in total, with a maximum mean age of 67.17 years. All studies

were conducted in Asia. Two studies were conducted in Korea, and one encompassed several ASEAN countries. The follow-up duration minimally was 12 months, and the longest was 60 months. In every study, the most commonly occurring comorbidities were hypertension, diabetes mellitus, smoking, and hyperlipidemia. The outline of the demographic characteristics of the included patients is detailed in Table 1.

#### Risk of bias among included studies

All included studies demonstrated a reliable selection process, as the study populations adequately representing the influence of BMI on clinical effect following PCI in Asia. In addition, good comparative and exposure aspects were observed. The final evaluation using the NOS revealed a mean score above 7, signifying satisfactory follow-up duration and the reasonably low dropout rates [Supplementary Files: Newcastle Ottawa Scale].

# All-cause mortality after percutaneous coronary intervention

A meta-analysis of all-cause mortality after PCI was carried out using data from five included studies. The pooled analysis after HK adjustment approaches revealed that healthy weight patients had a greater all-cause mortality rate compared to underweight patients [OR = 3.04, 95% (1.72, 5.38), P < 0.00001; Figure 2a]. Overweight individuals had a significantly lower overall mortality rate than individuals with a healthy weight [OR = 0.60, 95% (0.57, 0.63), P < 0.00001; Figure 2b]. Similarly, the

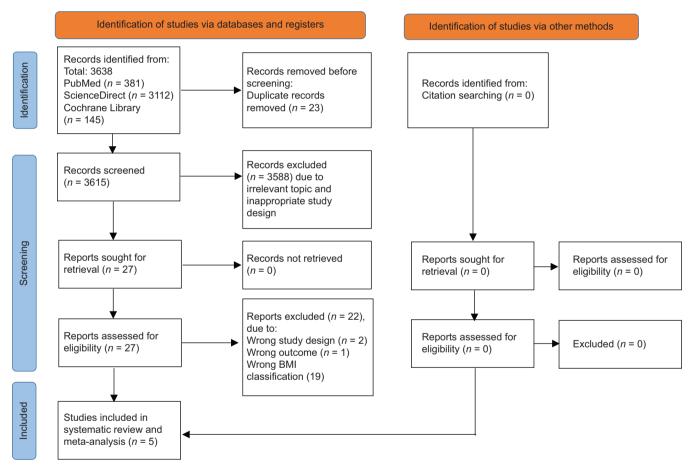


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of selection studies. BMI: Body mass index

Table 1: Characteristics	s of studi	es						
Author	Country	Sample	Mean age	Female	Comorbidity(s)	Duration of follow	Study	Quality
		size (n)	(years)	(%)		up (months)	design	score
Kang et al., 2010 [12]	Korea	3824	62.57	24.26	HT, DM, smoking, hyperlipidemia	12	Non-RCT	8
Numasawa et al., 2015 [13]	Japan	10,142	67.17	20.50	HT, DM, smoking, hyperlipidemia	12	Non-RCT	8
Azhari et al., 2017 [14]	ASEAN	28,742	58.75	17.19	HT, DM, smoking, hyperlipidemia, renal	12	Non-RCT	7
					impairment			
Wang et al., 2017 [15]	China	10,723	59.75	22.87	HT, DM, smoking, hyperlipidemia, COPD	24	Non-RCT	7
Song et al., 2021 [16]	Korea	130,490	64.35	27.52	HT, DM, smoking, dyslipidemia, drink, CKD	60	Non-RCT	8

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, RCT: Randomized control trial, ASEAN: Association of Southeast Asian Nations

	Experi	imental		Control				
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weigh
BMI = Underweight vs	Healthy V	Veight						
Kang et al, 2010	11	69	21	648		- 5.66	[2.60; 12.32]	4.49
Numasawa et al, 2015	27	462	127	5945		2.84	[1.86; 4.36]	5.49
Wang et al. 2017	2	90	46	2672		1.30	[0.31; 5.43]	2.79
Azhari et al, 2017	6	435	50	5168		1.43	[0.61; 3.36]	4.19
Song et al, 2020	504	1860	6689	70593			[3.20; 3.95]	5.99
Random effects model		2916		85026	$\diamond$	3.04	[1.72; 5.38]	22.5%
Heterogeneity: $I^2 = 53\%$ , $\tau^2$	<sup>2</sup> = 0.0687,	p = 0.07	7					
BMI = Overweight vs H	ealthy We	eight						
Kang et al, 2010	27	1041	21	648		0.80	[0.45; 1.42]	5.0%
Numasawa et al, 2015	38	3100	127	5945			[0.39; 0.82]	5.59
Wang et al, 2017	58	5404	46	2672		0.62	[0.42; 0.91]	5.59
Azhari et al. 2017	89	12605	50	5168		0.73	[0.51; 1.03]	5.69
Song et al. 2020	3043	52012	6689	70593			[0.57: 0.62]	6.09
Random effects model		74162		85026	•		[0.57; 0.63]	27.5%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	67						
)								
BMI = Obesity vs Health	hy Weigh	t						
Kang et al, 2010	3	255	21	648		0.36	[0.11; 1.20]	3.19
Numasawa et al, 2015	17	635	127	5945		1.26	[0.75; 2.10]	5.29
Wang et al, 2017	25	2557	46	2672			[0.35; 0.92]	5.29
Azhari et al, 2017	68	10534	50	5168		0.67	[0.46; 0.96]	5.5%
Song et al. 2020	324	6025	6689	70593		0.54	[0.48; 0.61]	5.9%
Random effects model		20006		85026	$\diamond$		[0.41; 1.05]	25.0%
<u>H</u> eterogeneity: $I^2 = 64\%$ , $\tau^2$	$^{2} = 0.0769$	p = 0.03	3					
2								
BMI = Obesity vs Overv	veight							
Kang et al, 2010	3	255	27	1041		0.45	[0.13; 1.49]	3.29
Numasawa et al, 2015	17	635	38	3100		2.22	[1.24; 3.95]	5.09
Wang et al, 2017	25	2557	58	5404		0.91	[0.57; 1.46]	5.39
Azhari et al, 2017	68	10534	89	12605			[0.67; 1.25]	5.69
Song et al, 2020	324	6025	3043	52012			[0.81; 1.03]	5.99
Random effects model		20006		74162	$\diamond$		[0.59; 1.73]	25.0%
Heterogeneity: $I^2 = 61\%$ , $\tau^2$	$^{2} = 0.0822,$	p = 0.04	1					
Random effects model		117090		329240	<>	1.00	[0.72; 1.40]	100.0%
Heterogeneity: $I^2 = 98\%$ , $\tau^2$	2 = 0.4254	$p < 0.0^{\circ}$	1			1		
Test for subgroup difference	es: $\gamma_{2}^{2} = 6$	9.80, df =	= 3 (p < 0.	01) (	0.1 0.5 1 2	10		

Figure 2: Forest plot for all-cause mortality of patients after percutaneous coronary intervention in (a) underweight and healthy weight patients; (b) overweight and healthy weight patients; (c) obese and healthy weight patients; and (d) obese and overweight patients. BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

overall mortality rate for individuals with obesity was lower than that for overweight individuals [OR = 0.65, 95% (0.41, 1.05), P = 0.006; Figure 2c], and there was no notable disparity in overall mortality rates between patients with overweight and obesity. [OR = 1.01, 95% (0.59, 1.73), P = 0.98; Figure 2d].

#### Cardiac mortality after percutaneous coronary intervention

A meta-analysis on cardiac mortality after PCI was performed using data from two included studies. The pooled analysis after HK adjustment approaches revealed that cardiac mortality of healthy weight patients was greater than underweight patients [OR = 2.88, 95% (1.21, 6.88), P = 0.04; Figure 3a]. Overweight individuals had a lower risk of cardiovascular mortality compared to individuals with a healthy weight [OR = 0.60, 95% (0.39, 0.91), P = 0.02; Figure 3b]. No notable distinction was found in cardiovascular mortality between patients with obesity and those with healthy weight [OR = 0.59, 95% (0.30, 1.19), P = 0.07; Figure 3c]. In addition, the cardiac mortality rates revealed no significant distinction between patients with overweight and patients with obesity [OR = 1.02, 95% (0.57, 1.83), P = 1.73; Figure 3d].

#### Noncardiac mortality after percutaneous coronary intervention

A meta-analysis on noncardiac mortality after PCI was performed using data from two included studies. Pooled analysis after the HK adjustment approach revealed that healthy weight patients had no difference in non-cardiac mortality compared with underweight patients [OR = 4.45, 95% (0.67, 29.48), P = 0.1 Figure 4a]. There was no notable distinction in noncardiac mortality between overweight and healthy patients [OR = 0.82, 95% (0.40, 1.66), P = 0.30; Figure 4b]. The noncardiac mortality among individuals with obesity was lower compared to individuals with a healthy weight [OR = 0.41, 95% (0.19, 0.88), P = 0.02; Figure 4c]. In addition, there was no notable distinction in noncardiac mortality between patients with overweight and patients with obesity [OR = 0.58,95% (0.28, 1.22), P = 0.14; Figure 4d].

# Major adverse cardiovascular event after percutaneous coronary intervention

A meta-analysis of MACE after PCI was performed using data from two included studies. The pooled analysis after HK adjustment approaches revealed that there were no noteworthy differences in MACE between all patient groups: underweight versus healthy weight patients [OR = 1.13, 95% (0.09, 14.82), P = 0.68; Figure 5a], overweight

	Experin	nental	С	ontrol				
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
BMI = Underweight vs	Healthy V	Veight			1			
Kang et al, 2010	6	69	17	648		3.54	[1.35; 9.29]	11.9%
Wang et al, 2017	1	90	25	2672		1.19	[0.16; 8.88]	4.4%
Random effects model		159		3320	$\sim$	2.88	[1.21; 6.88]	16.3%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	34						
a								
BMI = Overweight vs H					_			
Kang et al, 2010		1041	17	648	- <u></u>		[0.29; 1.15]	16.0%
Wang et al, 2017		5404	25	2672			[0.36; 1.04]	18.7%
Random effects model		6445		3320	$\diamond$	0.60	[0.39; 0.91]	34.7%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	91						
b BMI = Obesity vs Healtl	hy Weigh	÷						
Kang et al, 2010	2	255	17	648		0.29	[0.07; 1.28]	7.1%
Wang et al, 2017	17		25	2672			[0.38; 1.32]	17.2%
Random effects model		2812	20	3320			[0.30; 1.19]	24.3%
Heterogeneity: $I^2 = 15\%$ , $\tau^2$			28	0020		0.00	[0.00, 1.10]	24.07
BMI = Obesity vs Overv	veight							
Kang et al, 2010	2	255	16	1041		0.51	[0.12; 2.22]	7.0%
Wang et al, 2017	17	2557	31	5404			[0.64; 2.10]	17.6%
Random effects model		2812	•.	6445	~		[0.57; 1.83]	24.7%
Heterogeneity: $I^2 = 4\%$ , $\tau^2$			1		T		L	
d					1			
Random effects model		12228		16405		0.83	[0.52; 1.32]	100.0%
Heterogeneity: $I^2 = 53\%$ , $\tau^2$	= 0.2249	p = 0.0	04					
Test for subgroup difference	$es: \chi_3^2 = 1$	1.52, df	= 3 (p < 0	0.01)	0.1 0.5 1 2 10			

Figure 3: Forest plot for cardiac mortality of patients after percutaneous coronary intervention in (a) patients with underweight and healthy weight; (b) patients with overweight and healthy weight; (c) patients with obesity and healthy weight; and (d) obese and overweight patients. BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

	Experin	nental	C	ontrol				
Study	Events			Total	Odds Ratio	OR	95%-CI	Weigh
BMI = Underweight vs I	Healthy V	Veight						
Kang et al, 2010	5	69	5	648		- 10.05	[2.83; 35.63]	12.6%
Wang et al, 2017	1	90	21	2672		1.42	[0.19; 10.66]	8.29
Random effects model		159		3320		- 4.45	[0.67; 29.48]	20.8%
Heterogeneity: $I^2 = 61\%, \tau^2$	<sup>2</sup> = 1.1781,	p = 0.1	11					
a								
BMI = Overweight vs H								
Kang et al, 2010		1041	5	648		1.37	[0.48; 3.97]	
Wang et al, 2017		5404		2672		0.63		
Random effects model		6445		3320	$\sim$	0.82	[0.40; 1.66]	31.6%
Heterogeneity: $I^2 = 37\%$ , $\tau^2$	<sup>2</sup> = 0.1096,	p = 0.2	21					
b								
BMI = Obesity vs Health	hy Weigh							
Kang et al, 2010	1	255		648		0.51	[0.06; 4.35]	
Wang et al, 2017	8	2557	21	2672		0.40	[0.18; 0.90]	15.99
Random effects model		2812		3320	$\sim$	0.41	[0.19; 0.88]	23.5%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	83						
BMI = Obesity vs Overv	veight							
Kang et al. 2010	1	255	11	1041	<u>z</u>	0.37	[0.05; 2.87]	8.09
Wang et al, 2017	8	2557	27	5404		0.63	[0.28; 1.38]	16.19
Random effects model		2812		6445		0.58	[0.28; 1.22]	24.19
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	64					. / .	
l Random effects model		12228		16405		0.93	[0.44; 1.99]	100.09
Heterogeneity: $I^2 = 67\%$ , $\tau^2$	$^{2} = 0.7672$	p < 00	01					
Test for subgroup difference				12)	0.1 0.5 1 2 10			

Figure 4: Forest plot for noncardiac mortality of patients after percutaneous coronary intervention in (a) underweight and patients with healthy weight; (b) overweight and patients with healthy weight; (c) obese and patients with healthy weight; and (d) obese and overweight patients. BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

versus healthy weight patients [OR = 0.87, 95% (0.54, 1.39), P = 0.16; Figure 5b], obesity versus healthy weight patients [OR = 0.92, 95% (0.53, 1.62), P = 0.52; Figure 5c], and overweight versus obesity patients [OR = 1.04, 95% (0.41, 2.66), P = 0.71; Figure 5d].

# Myocardial infarction after percutaneous coronary intervention

A meta-analysis of MI after PCI was performed using data from two included studies. The pooled analysis after HK adjustment approaches revealed no notable differences between MI across all patient groups: underweight versus healthy weight patients [OR = 2.12, 95% (0.82, 5.49), P = 0.12; Figure 6a], overweight versus healthy weight patients [OR = 0.84, 95% (0.35, 2.06), P = 0.64; Figure 6b], obesity versus healthy weight patients [OR = 1.01, 95% (0.69, 1.49), P = 0.96; Figure 6c], and overweight versus obesity patients [OR = 1.15, 95% (0.46, 2.86), P = 0.55; Figure 6d].

#### Bleeding after percutaneous coronary intervention

A meta-analysis of bleeding after PCI was performed using data from two included studies. The pooled analysis revealed after HK adjustment approaches that healthy weight patients had a higher risk of bleeding after PCI compared to underweight patients [OR = 2.41, 95% (1.15, 5.05), P = 0.004; Figure 7a]. However, no difference was found in terms of bleeding between

Li	Experi	mental	c	ontrol	an and the life	itai.		
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
BMI = Underweight vs	Healthy	Weight			1			
Kang et al, 2010	13	69	98	648		1.30	[0.69; 2.47]	3.4%
Azhari et al, 2017	5	435	70	5168		0.85	[0.34; 2.11]	1.7%
Random effects model		504		5816		1.13	[0.09; 14.82]	5.1%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, <i>p</i> = 0	.45						
BMI = Overweight vs H	ealthy W	eiaht						
Kang et al, 2010		1041	98	648	-	0.84	[0.63; 1.11]	17.9%
Azhari et al, 2017	154	12605	70	5168		0.90	[0.68; 1.20]	17.4%
Random effects model		13646		5816	$\triangleleft$	0.87	[0.54; 1.39]	35.3%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$		.72						
BMI = Obesity vs Health	hv Weigh	nt						
Kang et al, 2010	38	255	98	648		0.98	[0.65; 1.48]	8.5%
Azhari et al. 2017	128	10000000000000000000000000000000000000	70	5168	*	0.90	[0.67; 1.20]	16.4%
Random effects model		10789		5816	$ \rightarrow $	0.92	[0.53; 1.62]	24.9%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$				0010		0.01	[0.00, 1.02]	24.070
BMI = Obesity vs Overv	veight							
Kang et al. 2010	38	255	135	1041		1.18	[0.80; 1.73]	9.3%
Azhari et al, 2017		10534		12605		0.99	[0.79; 1.26]	25.3%
Random effects model		10789	104	13646		1.04	[0.41; 2.66]	34.6%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$				10040		1.04	[0.41, 2.00]	04.070
d	- 0, <i>p</i> - 0	.47						
Random effects model		35728		31094		0.95	[0.86; 1.05]	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.85						
Test for subgroup difference	es: $\chi_3^2 = 6$	3.19, df =	= 3 (p = 0	.10)	0.1 0.5 1 2 10			

Figure 5: Forest plot for major adverse cardiovascular event of patients after percutaneous coronary intervention in (a) underweight and patients with healthy weight; (b) overweight and patients with healthy weight; (c) obese and patients with healthy weight; and (d) obese and overweight patients. BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

	Experir	nental	c	ontrol				
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weigh
BMI = Underweight vs	Healthy V	Veight			Ĩ			
Kang et al, 2010	2	69	7	648		2.73	[0.56; 13.42]	1.59
Wang et al, 2017	3	90	49	2672		1.85	[0.56; 6.04]	2.79
Random effects model		159		3320		2.12	[0.82; 5.49]	4.2%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, <i>p</i> = 0.	70						
BMI = Overweight vs H	ealthy W	eight						
Kang et al, 2010	5	1041	7	648		0.44	[0.14; 1.40]	2.99
Wang et al, 2017	115	5404	49	2672		1.16	[0.83; 1.63]	33.39
Random effects model		6445		3320		0.84	[0.35; 2.06]	36.2%
Heterogeneity: $I^2 = 60\%$ , $\tau^2$	$^{2} = 0.2813$	p = 0.1	1					
BMI = Obesity vs Health	hy Weigh	t						
Kang et al, 2010	3	255	7	648		1.09	[0.28; 4.25]	2.19
Wang et al, 2017	47	2557	49	2672	-		[0.67; 1.50]	
Random effects model		2812		3320	4		[0.69; 1.49]	25.4%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, <i>p</i> = 0.	91						
BMI = Obesity vs Overv	veight							
Kang et al, 2010	3	255	5	1041		2.47	[0.59; 10.39]	1.89
Wang et al, 2017	47	2557	115	5404			[0.61; 1.21]	32.49
Random effects model		2812		6445			[0.46; 2.86]	34.2%
Heterogeneity: $I^2 = 49\%$ , $\tau^2$	<sup>2</sup> = 0.2693	, <i>p</i> = 0.1	6				. ,	
Random effects model		12228		16405		1.03	[0.85; 1.25]	100.09
Heterogeneity: $I^2 = 6\%$ , $\tau^2$								
Test for subgroup difference	es: $\chi_{2}^{2} = 2$	.37, df =	= 3(p = 0.	50)	0.1 0.5 1 2 10			

Figure 6: Forest plot for myocardial infarction of patients after percutaneous coronary intervention in (a) underweight and patients with healthy weight; (b) overweight and patients with healthy weight; (c) patients with obesity and healthy weight; and (d) patients with obesity and overweight. BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

Study	Experin Events			ontrol Total	Odds Ratio	OR	95%-CI	Weight
BMI = Underweight vs I	Jealthy V	Veight			1			
Numasawa et al. 2015	12 12	462	64	5945		2 45	[1.31; 4.57]	16.0%
Wang et al, 2017	1	90	15				[0.26; 15.23]	
Random effects model		552	15	8617			[1.15; 5.05]	
Heterogeneity: $I^2 = 0\%$ , $\tau^2$				0017		2.41	[1.10, 0.00]	10.47
BMI = Overweight vs H	ealthy W	eight						
Numasawa et al, 2015	20	3100	64	5945		0.60	[0.36; 0.99]	18.59
Wang et al, 2017	22	5404	15	2672		0.72	[0.38; 1.40]	15.39
Random effects model		8504		8617			[0.20; 2.10]	
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	65						
BMI = Obesity vs Health								
Numasawa et al. 2015			64	5945		0.58	[0.21; 1.60]	9.8%
Wang et al. 2017		2557	15	2672			[0.39; 1.79]	
Random effects model		3192		8617			[0.08; 6.61]	23.3%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$					_	0.10	[0.00, 0.01]	2010 /
BMI = Obesity vs Overv	veight							
Numasawa et al, 2015	4	635	20	3100		0.98	[0.33; 2.87]	9.1%
Wang et al, 2017	12	2557	22	5404	- <u>F</u>	1.15	[0.57; 2.33]	14.5%
Random effects model		3192		8504		1.10	[0.42; 2.90]	23.5%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, <i>p</i> = 0.	80						
Random effects model		15440		34355		0.96	[0.62; 1.50]	100.0%
Heterogeneity: $I^2 = 52\%$ , $\tau^2$					1 1 1 1			
Test for subgroup difference	es: $\chi_3^2 = 1$	80.45, 0	f = 3 (p <	0.01)	0.1 0.5 1 2 10			

Figure 7: Forest plot for bleeding of patients after percutaneous coronary intervention in (a) underweight and patients with healthy weight; (b) overweight and patients with healthy weight; (c) obese and patients with healthy weight; and (d) obese and overweight patients. BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

overweight and healthy weight patients [OR = 0.64, 95% (0.20, 2.10), P = 0.3; Figure 7b]. There were no notable differences in bleeding after PCI risk between patients with obesity and healthy weight [OR = 0.73, 95% (0.08, 6.61), P = 0.28; Figure 7c]. No noteworthy differences were found between overweight and obese patients in bleeding after PCI [OR = 1.10, 95% (0.42, 2.90), P = 0.76; Figure 7d].

# DISCUSSION

The obesity paradox in Asia after PCI refers to the counterintuitive observation that overweight or obese individuals undergoing PCI for coronary artery disease tend to exhibit better outcomes than their normal-weight counterparts. While obesity is well-known as a contributing element to the development of CVD, some studies in Asian populations suggest a smaller risk of adverse events, such as mortality or major cardiovascular events, among obese patients following PCI. This paradox highlights the complex interplay of factors influencing cardiovascular outcomes in diverse populations. Deeper research is needed in examining the fundamental process and clinical implications in the Asian setting. Five cohort studies were included in this study. Three studies stated that there was an obesity paradox in outcomes after PCI [12-14], while the other two studies stated the opposite [15,16]. The five existing studies involved patients with almost similar comorbidities, namely, hypertension, diabetes mellitus, smoking, and hyperlipidemia. In addition, the presentation of patients involved in all studies was predominantly male. Therefore, confounding factors from comorbidities and gender can be ignored.

This study is the initial meta-analysis to discuss the obesity paradox in Asia. In this study, patients with overweight and

obesity have lower all-cause mortality than healthy weight patients. Our findings demonstrate the presence of the "obesity paradox" within the Asian PCI-treated patient population. This is in accordance with the results of Liu et al.'s meta-analysis in 2022, although it did not specifically involve Asian patients. The study reports that patients classified as overweight and obese exhibited a smaller inhospital mortality than individuals with a healthy weight. Overweight and obese individuals have also exhibited a decreased possibility of short-term mortality compared to those who maintain a healthy weight. Furthermore, overweight individuals and obese individuals were observed to have lower long-term mortality than individuals with a healthy weight [17]. Several mechanisms have been suggested to explain the observed obesity paradox in coronary heart disease. As BMI rises, there is a proportional increase in the size of coronary arteries. In addition, adverse outcomes following PCI and coronary artery bypass grafting are linked to smaller coronary arteries [18]. Obese individuals may also have a protective advantage due to greater cardiac remodeling after MI compared to underweight patients. The substantial calorie reserve in obese patients proves to be beneficial in scenarios where CVD triggers cachexia. The onset of postprocedure cachexia can significantly impair the overall health of patients [19]. Furthermore, individuals with obesity and heart disease are inclined to adopt lifestyle modifications encompassing improved dietary habits, caloric restrictions, and regular physical activity. These changes can contribute to a favorable shift in the prognosis of the condition. The altered levels of cytokines and hormones associated with obesity could offer protection for the heart by offsetting the damaging impacts of other biological factors that are increased in both acute and chronic heart diseases. The high concentrations of inflammatory tumor necrosis factor-alpha (TNF- $\alpha$ ) can be

alleviated due to the plentiful existence of TNF- $\alpha$  receptors on adipose tissues [20]. Moreover, it has been demonstrated that individuals with obesity exhibit notably reduced circulating levels of natriuretic peptides, which are associated with the pathophysiology of heart failure [21]. The increased concentrations of free lipoproteins in obese individuals aid in obstructing lipopolysaccharide and other inflammatory cytokines [22].

Another significant discovery indicates that there was no substantial dissimilarity between overweight and obesity in all-cause mortality, cardiac mortality, noncardiac mortality, MACE, MI, and bleeding after PCI. This finding indicates that better outcomes may not be the result of a higher BMI value. Hence, there might exist a nonlinear connection between BMI and mortality, potentially manifesting as a J-or U-shaped curve. A meta-analysis in 2013 by Li et al. which investigated the relationship between BMI and mortality in patients who underwent PCI for CAD for more than 5 years showed an almost similar result. The analysis from the study showed a J-shaped relationship between BMI and total mortality, with underweight patients who had the highest mortality risk, followed by obese patients, and the lowest mortality risk from overweight patients [23]. A recent study by Braekkan et al. supports our findings [24]. Their results revealed that following the adjustment for several elements, such as age and complications, different BMI classifications exhibited a J-shaped correlation with long-term mortality hazard ratios (HRs). In addition, the research conducted by Timóteo et al. provides evidence to support the existence of a bimodal association between BMI and mortality in patients with ST-elevation MI (STEMI) who had gone through PCI. These results were the same as a study with Sinjini's results [25]. This suggests that the BMI index, to some degree, provides a safeguard against all-cause mortality.

In the outcomes of MACE and MI after PCI, in our meta-analysis, we found that overweight and obesity had lower MACE than healthy weight, but it was not significant. Firman et al.'s research, which states that BMI, emerged as a standalone prognosticator for MACEs and the incident of recurrent infarction (OR 2.322 [95% confidence interval 1.505–3.584; P < 0.001]). The likelihood of MACE decreases with increasing weight, reaching its lowest risk reduction point for MACE at 28-29.0 kg/m<sup>2</sup>. Beyond this range, the risk curve increases, yet it remains below the risk linked to a BMI of 23 kg/m<sup>2</sup> [26]. An investigation involving 6978 patients in Korea revealed that obesity exerted a safeguarding influence on MACEs, particularly in individuals without diabetes [27]. In the multivariable analysis, elevated BMI levels were linked to a reduced risk of subsequent MACEs, peripheral vascular disease, cardiovascular-related death, and all-cause mortality when compared to individuals with a normal BMI [28]. MACEs and cardiac death were less prevalent in the group with obesity than the other groups over the 1-year follow-up period [29].

Another interesting finding is that the all-cause mortality, cardiac mortality, and bleeding after PCI in underweight patients have more favorable consequences than healthy weight patients. These results are new, and few studies have

addressed this outcome. Among patients who underwent coronary angiography, being underweight and having obesity class III are linked to a higher risk of mortality, with the lowest mortality observed in the preobesity class [30]. A meta-analysis by Lin *et al.* in 2013 investigates the relationship between BMI and bleeding complications in CAD patients who underwent PCI. The study showed a J-shaped relationship between BMI and bleeding, in which underweight patients had a higher risk of bleeding complications compared to normal weight. In addition, overweight and class I/II obese patients had a lower risk of bleeding compared to normal-weight and underweight patients [31].

Another interesting study by Lin et al. investigates the relationship between BMI and mortality in CAD patients who underwent PCI with drug-eluting stents (DESs). The study reported that in 30 days, overweight and obese patients had a lower mortality risk compared to normal-weight patients, but this paradox disappeared in studies where DESs were used in all patients. Familiar trends were also found for MACE and mortality with longer follow-up duration (1-3 years). Over 3 years of follow-up showed that overweight and obese patients still had a lower risk of mortality compared to normal-weight patients, but the benefit was smaller [32]. Individuals with underweight and those who are morbidly obese often show signs of sarcopenia and reduced ratios of fat-free mass to fat mass, increasing their susceptibility to critical illness. In a retrospective study conducted by De Schutter et al., calculations were made for lean mass index, body fat, and BMI. The findings indicated that lean mass offers a protective effect; however, this survival advantage is diminished in the presence of sarcopenic obesity [33].

This study has several limitations. The type of PCI generation used was not differentiated. Apart from that, indications for PCI, such as STEMI or other, were still not considered. The BMI classification used in the world of health varies for each center, many studies could not be included even though they were carried out in Asia. The last limitation for the adjusted ORs was inflation may be caused by spare effect. Future studies should accommodate these limitations to provide a better picture of the obesity contradiction, or paradox in Asia.

# CONCLUSION

This meta-analysis showed the presence of an obesity paradox after PCI in Asia. The obesity paradox was evident in all-cause mortality, cardiac mortality, and noncardiac mortality.

## Acknowledgment

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## Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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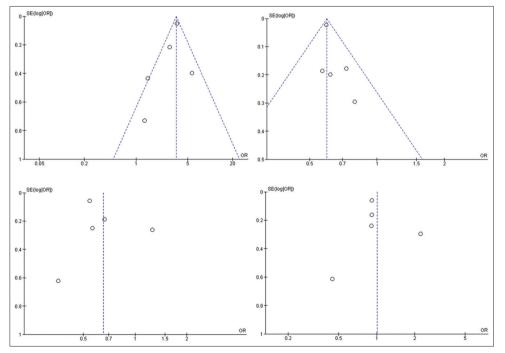
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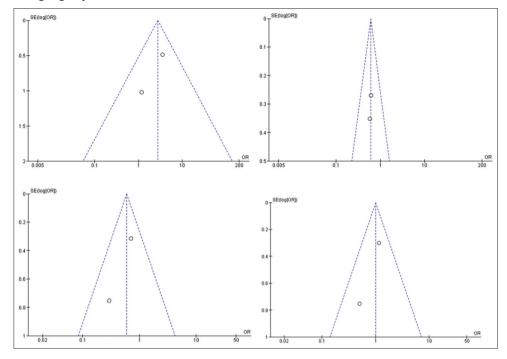
# SUPPLEMENTARY FILES

Database	Search strategy in each database Search strategy
Pubmed	#1: (Body Mass Index [MeSH Terms]) OR (Body Mass Index [Title/Abstract]) OR (BMI [Title/Abstract])
	<ul><li>#2: (Percutaneous Coronary Intervention [MeSH Terms])</li><li>OR (Percutaneous Coronary Intervention [Title/Abstract])</li><li>OR (PCI [Title/Abstract])</li></ul>
	#3: (Observation [MeSH Terms]) OR (Observation [All Fields] OR (Cohort [All Fields])
	#6: #1 AND #2 AND #3
Science	#1: 'Body Mass Index'/exp
Direct	#2: 'BMI'/exp
	#3: #1 OR #2
	#4: 'Percutaneous Coronary Intervention'/exp
	#5: 'PCI'/exp
	#6: #4 OR #5
	#7: 'Observation'/exp
	#8: `Cohort`/exp
	#9: #7 OR #8
	#10: #3 AND #5 AND #9
The	#1: MeSH descriptor: [Body Mass Index] this term only
Cochrane	#2: MeSH descriptor: [BMI] this term only
Library	#3: #1 OR #2
	#4: MeSH descriptor: [Percutaneous Coronary Intervention] this term only
	#5: MeSH descriptor: [PCI] this term only
	#6: #4 OR#5
	#7: MeSH descriptor: [Observation] this term only
	#8: MeSH descriptor: [Cohort] this term only
	#9: #7 OR #8
	#10: #3 AND #6 AND #9

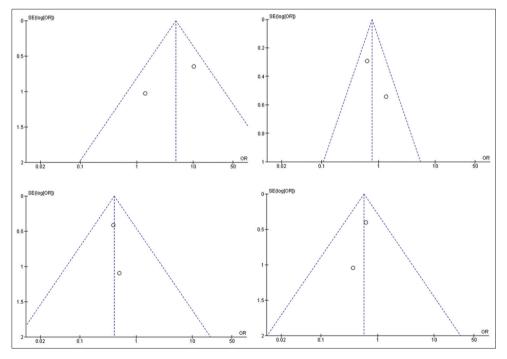
# **Funnel Plot for Included Studies**



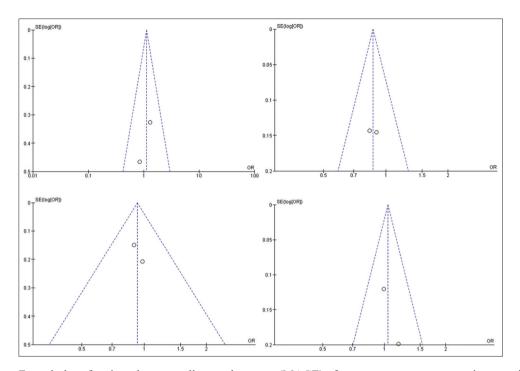
Funnel plot of all-cause mortality after percutaneous coronary intervention. (a) Funnel plot for all-cause mortality in underweight and healthy weight individuals. (b) Funnel plot for all-cause mortality in overweight and healthy weight individuals. (c) Funnel plot for all-cause mortality in obese and healthy weight individuals. (d) Funnel plot for all-cause mortality in the obesity and overweight groups. OR: Odds ratio



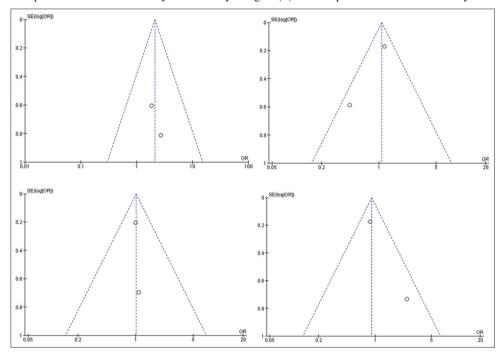
Funnel plot of cardiac mortality after percutaneous coronary intervention. (a) Funnel plot for cardiac mortality in underweight and healthy weight individuals. (b) Funnel plot for cardiac mortality in overweight and healthy weight individuals. (c) Funnel plot for cardiac mortality in obese and healthy weight individuals. (d) Funnel plot for cardiac mortality in obese and overweight individuals. OR: Odds ratio



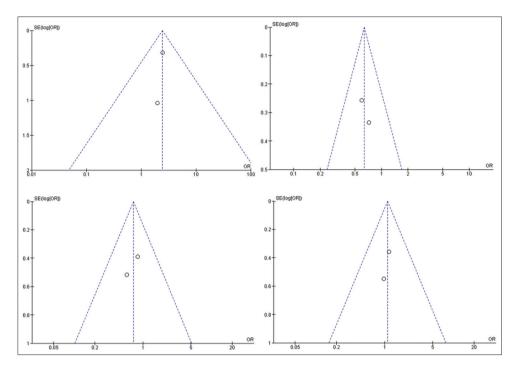
Funnel plot of noncardiac mortality after percutaneous coronary intervention. (a) Funnel plot for noncardiac mortality in underweight and healthy weight individuals. (b) Funnel plot for noncardiac mortality in overweight and healthy weight individuals. (c) Funnel plot for noncardiac mortality in obese and healthy weight individuals. (d) Funnel plot for noncardiac mortality in the obesity and overweight groups. OR: Odds ratio



Funnel plot of major adverse cardiovascular event (MACE) after percutaneous coronary intervention. (a) Funnel plot for MACE in underweight and healthy weight individuals. (b) Funnel plot for MACE in overweight and healthy weight individuals. (c) Funnel plot for MACE in obesity and healthy weight. (d) Funnel plot for MACE in obesity and overweight. OR: Odds ratio



Funnel plot of myocardial infarction (MI) after percutaneous coronary intervention. (a) Funnel plot for MI in underweight and healthy weight individuals. (b) Funnel plot for MI in overweight and healthy weight individuals. (c) Funnel plot for MI in obese and healthy weight individuals. (d) Funnel plot for MI in obese and overweight individuals. OR: Odds ratio



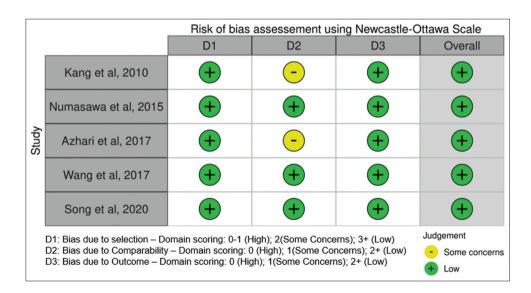
Funnel plot of bleeding after percutaneous coronary intervention. (a) Funnel plot for bleeding in underweight and healthy weight individuals. (b) Funnel plot for bleeding in overweight and healthy weight individuals. (c) Funnel plot for bleeding in obese and healthy weight individuals. (d) Funnel plot for bleeding in obese and overweight individuals. OR: Odds ratio

## Newcastle Ottawa Scale

Risk of bias plot of Newcastle Ottawa Scale

Authors	Selection	Comparatibility	Exposure	Total	
				score	
Kang et al., 2010 [12]	***	**	***	8	
Numasawa et al., 2015 [13]	***	**	***	8	
Azhari et al., 2017 [14]	***	**	**	7	
Wang et al., 2017 [15]	***	**	**	7	
Song et al., 2020 [16]	****	**	**	8	

Significance of total score, >=: high quality study; <= 7 low quality study, 0/\* : poor quality, \*\* : fair quality, \*\*\*/\*\*\*\* : good quality



Risk of bias summary plot of Newcastle Ottawa Scale

