Adherence to healthy lifestyle improved clinical outcomes in coronary artery disease patients after coronary intervention

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Abstract

Background: Lifestyle modification is suggested for patients with coronary artery disease (CAD), but the impact of adherence to a healthy lifestyle remains undetermined. The aim of this study is to investigate the association of adherence to a healthy lifestyle with future outcomes and biochemical markers in CAD patients.

Methods: The Biosignature CAD study examined 716 CAD patients who underwent a percutaneous coronary intervention (PCI). Information was collected on whether these patients adhered to a healthier lifestyle after PCI, including healthy diet, not smoking, and exercise. The clinical outcomes included major cardiovascular events and unplanned revascularization procedures, hospitalization for refractory or unstable angina, and other causes

Results: The average follow-up period was 26.8 ± 8.1 months, during which 175 (24.4%) patients experienced at least one event. The combination of healthy lifestyle factors was associated with lower risk, and the maximum risk reduction reached 50% (hazard ratio: 0.50, 95% confidence interval: 0.25-0.99). As the number of healthy lifestyle factors increased, there were decreases in inflammatory markers, C-reactive protein, waist circumference, low-density lipoprotein cholesterol, and the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol ($p < 0.05$). The benefits of modifiable healthy lifestyle factors were especially observed in the younger population, males, patients with HDL <40 mg/dL, those with reduced left ventricular ejection fraction, and those receiving statin therapy.

Conclusion: Adherence to a healthy lifestyle is independently associated with a lower risk of future adverse events in CAD patients and plays an important role in secondary prevention in the era of interventional cardiology.

Keywords: Coronary artery disease; Lifestyle modification; Secondary prevention

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1. INTRODUCTION

Coronary artery disease (CAD) is associated with an increased risk of morbidity and mortality. To reduce future cardiovascular complications, patients are encouraged to adopt lifestyle modifications and undergo pharmacological therapy to prevent atherosclerotic complications. Great efforts have been made to prevent cardiovascular disease (CVD), but the occurrence of adverse events remains a concern, including acute coronary syndrome, stroke, revascularization procedures, and cardiovascular death. Furthermore, there is particular concern for patients who have received coronary angioplasty. Therefore, it is important to reduce residual risk in this high-risk population.

Most studies have focused on the effectiveness of pharmacological treatment for secondary prevention in the context of CAD. Recently, adherence to a healthy lifestyle has attracted attention and has been encouraged for primary prevention of CVD. Low-risk healthy lifestyle factors have been associated with a lower risk of developing cardiovascular events, and the combined benefit has been observed in the primary prevention for CVD in Caucasian populations.[1,2] Such factors include not smoking, physical activity, and healthy diet habits. Recently, Lv et al[3] reported that adherence to healthier modifiable lifestyle factors is also associated with a lower CVD burden in primary prevention in Chinese individuals. Thus, a healthy lifestyle is important for CVD prevention in Asian populations well.

Interestingly, most observations have been on the benefits of combined healthy lifestyle factors in primary prevention, but there is limited information about their effects in secondary prevention. Furthermore, after coronary intervention, it is recommended that patients receive aggressive medical therapy, such as statins and antiplatelet therapy, but the risk of developing adverse events remains higher than in the general population. Although education for lifestyle modification is usually provided for CAD patients in daily practice, the impact of maintaining a healthy lifestyle for secondary prevention in stable CAD patients has remained undetermined, and the information is limited for Asian populations.[4,5] Additionally, the relationship between a healthy lifestyle and biochemical profiles in CAD patients is also unclear.

In the current study, we prospectively examined the joint association of healthy lifestyle factors with the future risk of adverse cardiovascular events in an Asian cohort of CAD patients after coronary intervention – the Taiwan Biosignature CAD study.[6–9] The long-term cardiovascular outcomes were analyzed to evaluate whether adherence to healthy lifestyle factors are independently associated with reduced risk of future events. Our findings could provide real-world evidence of the impact of a healthy lifestyle on secondary prevention in CAD patients after percutaneous coronary intervention (PCI).

2. METHODS

2.1. Study population

The Biosignature study was a nationwide prospective cohort study that was conducted to identify risk factors among CVD patients who were in stable condition at baseline.[8,9] In brief, a series of stable CAD patients were evaluated at nine different medical centers located in Northern, Central, Southern, and Eastern Taiwan. The patients were evaluated if they had a history of significant CAD documented by coronary angiogram, a history of myocardial infarction (MI), or a history of angina with ischemic ECG changes or a positive response to a stress test.

The patients were enrolled according to the following criteria: (1) successful PCI with either coronary stenting or balloon angioplasty at least once and (2) stability on medical treatment for at least 1 month before enrollment. To collect biochemical parameters in stable condition, patients were excluded if (1) they had acute-phase cardiovascular events, including hospitalization for unstable angina, acute coronary syndrome, acute MI, acute cerebrovascular events, or other acute cardiovascular events within 3 months before enrollment; (2) they planned to receive further coronary revascularization or interventional procedures for another condition in the following year; (3) they had significant malignancy or tumors requiring advanced medical or surgical therapy in the following year; (4) they had other major systemic CVDs requiring hospitalization or operation in the following year; or (5) they were unable or unwilling to be followed-up in the following year. This study was approved by the institutional research boards and ethics committees in each hospital. All patients gave written informed consent before entering the study.

2.2. Baseline data collection

After enrollment, specially trained study nurses and qualified cardiologists collected all data prospectively whenever feasible. Baseline characteristics were collected and included risk factors such as the history of hypertension, diabetes, smoking habits, and medications used. In addition, biochemical profiles were recorded, including blood glucose, lipid profile, and renal function. Dietary information and exercise frequency were determined at baseline using a structured questionnaire. Healthy lifestyle factors were analyzed and included a healthy diet, not smoking, and regular exercise habits.

A healthy diet pattern was determined according to the guidelines of the American Heart Association and the American College of Cardiology on lifestyle management to reduce cardiovascular risk.[10] These guidelines emphasize an increased intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts), as well as nontropical vegetable oils, along with limited intake of sweets, sugar-sweetened beverages, and red meats. The healthy diet pattern was assessed using a food frequency questionnaire according to the recommended Food Score developed in 2000 by Kant et al,[11] which follows the guidelines mentioned.

Nonsmoking status was assigned to those who had never smoked or had quit smoking >6 months prior.[3] Regular active exercise was defined as exercise episodes lasting for at least 30 minutes and occurring more than five times a week.[12] Patients without any of these three healthy lifestyle factors were defined as the unhealthy lifestyle group. Subjects were evaluated at 3-month intervals in an outpatient clinic. Subjects with a healthy lifestyle were defined as those who adhered to lifestyle factors (not smoking, healthy diet, and adequate exercise) during the follow-up period for >50% of the time. A similar definition of dietary habit adherence has been reported previously.[7] The information about lifestyle factors was collected and confirmed regularly by the same study nurses throughout the follow-up period.

2.3. Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the appropriate Health Authorities, independent Ethics Committees, the Joint IRB Ethics Committee Review Board in Taiwan, and Independent Review Boards in each hospital (Taipei Veterans General Hospital, Taipei, Taiwan; Cheng-Hsin General Hospital, Taipei, Taiwan; E-Da Hospital, Kaohsiung, Taiwan; Far Eastern Memorial Hospital, New Taipei City, Taiwan; Kaohsiung Medical University Hospital and Kaohsiung Medical University, Kaohsiung, Taiwan; Mackay Memorial Hospital, Mackay Medical College, New Taipei City, Taiwan; China Medical University Hospital, Taichung, Taiwan; Buddhist Tzu-Chi General Hospital, Tzu-Chi University, Hualien, Taiwan; National Taiwan University College of Medicine and Hospital, Taipei, Taiwan). All patients had to provide written informed consent before enrollment.

2.4. Clinical follow-up for adverse cardiovascular events

Each patient was initially in stable condition under medical treatment and was prospectively followed up in individual hospital clinics at regular 3-month intervals for at least 1 year after enrollment. The development of adverse cardiovascular

events was identified and recorded during follow-up. Such events included cardiovascular death, nonfatal MI, nonfatal stroke, unplanned revascularization procedures, hospitalization for refractory or unstable angina, and hospitalization for other causes (including stroke, transient ischemic attack, and peripheral arterial occlusive disorder).

MI was confirmed if ischemic symptoms presented with elevated serum levels of cardiac enzyme or characteristic ECG changes. Coronary revascularization procedures with either PCI or coronary artery bypass grafting (CABG) were confirmed by reviewing medical records. Stroke was defined as a new neurological deficit lasting for at least 24 hours with definite image evidence of a cerebrovascular accident according to magnetic resonance imaging or computed tomography scans. The protocol for the follow-up of cardiovascular events was similar to those reported in previous studies.[8,9,13,14]

2.5. Statistics

Data are expressed as the means ± SDs for numerical variables and as numbers (percentages) for categorical variables. Continuous variables were compared between groups through an analysis of variance. Bonferroni correction was used to adjust for multiple tests. Subgroup comparisons of categorical variables were conducted using a χ^2 test or Fisher's exact test. Patients with event occurrence were compared to those without events. A multivariate Cox regression analysis was performed to estimate the association of individual healthy lifestyle factors and joint effects with the risk of future adverse events after adjusting for variables including age, gender, body mass index (BMI), hypertension, diabetes, stroke, CAD severity, medications, lipid profiles, and inflammatory markers.

3. RESULTS

3.1. Patient characteristics

The study enrolled a total of 716 CAD patients who underwent a coronary intervention and had information on lifestyle factors. There were 610 (85.2%) male patients, 466 (65.1%) patients who had hypertension, 264 (36.9%) patients who had diabetes, 16 (2.23%) patients who had stroke, and 177 (24.7%) patients who had a family history of hypertensive CVD. Table 1 shows the patients' baseline characteristics.

With regard to lifestyle issues, 444 (62%) patients adhered to dietary suggestions for CAD patients, including eating low-fat diets with more vegetables, fruit, fish, whole grains, and olive oil during the follow-up period. Furthermore, 330 (46.1%) patients were nonsmokers, and 347 (48.5%) patients had regular exercise habits of at least 30 minutes per day for >5 days per week. Pharmacologic treatments included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) (66.2%), β-blockers (58.9%), calcium channel blockers (35.9%), diuretics (12.7%), and statins (70.5%).

Table 2 shows the events that occurred in the average follow-up period of 26.8 ± 8.11 months. A total of 175 (24.4%) of the 716 patients experienced at least one event. The major clinical events that occurred during follow-up are summarized in Table 2. There were 12 cardiac deaths, 22 nonfatal MIs, and 123 readmissions for revascularization procedures. Furthermore, four patients developed stroke, and 14 patients suffered congestive heart failure.

Table 3 compares the baseline characteristics between those who had adverse cardiovascular events and those who did not. Patients with events had fewer nonsmokers (35% vs 49%, $p = 0.001$), less active exercise (38.3% vs 51.8%, $p = 0.002$), less ACE inhibitor/ARB use (60% vs 68%, $p = 0.046$), and higher rates of triple vessel disease (40.1% vs 27.5%, $p = 0.005$) and diuretic use (17.7% vs 11.1%, $p = 0.022$). Although the results did not achieve statistical significance, patients without events tended to have healthy diet habits (63.6% vs 57.1%, $p = 0.127$).

Table 1

Baseline characteristics of CAD patients with coronary intervention

	n = 716
Age (year)	66.5 ± 12.1
Male, n (%)	610 (85.2)
BMI (Kg/m^2)	26.29 ± 4.76
Hypertension, n (%)	466 (65.08)
DM, n (%)	264 (36.9)
Family history of CAD, n (%)	177 (24.7)
History of stroke, n (%)	16 (2.2)
Waist (cm)	93.92 ± 9.85
Adherence to healthy lifestyle	
Healthy diet, n (%)	444 (62.01)
No smoking, n (%)	330 (46.09)
Active exercise, n (%)	347 (48.46)
Systolic BP (mmHg)	129.49 ± 17.15
Diastolic BP (mmHg)	73.53 ± 12.30
LVEF (%)	55.22 ± 12.47
Glucose (mg/dL)	120.62 ± 45.87
Cholesterol (mg/dL)	161.08 ± 34.16
LDL-C (mg/dL)	93.23 ± 28.00
HDL-C (mg/dL)	42.21 ± 11.00
Triglyceride (mg/dL)	130.17 ± 80.49
TC/HDL-C ratio	4.02 ± 1.19
CAD severity	
LM, n (%)	42 (7.7)
LAD, n (%)	434 (79.3)
LCX, n (%)	298 (54.5)
RCA, n (%)	325 (59.4)
SVD, n (%)	178 (32.5)
DVD, n (%)	186 (34.0)
TVD, n (%)	169 (30.9)
Stent (n)	1.59 ± 0.91
Average length of stent (mm)	22.12 ± 6.09
Average diameter of stent (mm)	3.11 ± 0.55
Medication	
Anti-platelet, n (%)	653 (91.20)
ACE inhibitor/ARB, n (%)	474 (66.20)
β-blocker, n (%)	422 (58.94)
Calcium channel blocker, n (%)	257 (35.89)
Diuretics, n (%)	91 (12.71)
Statin, n (%)	505 (70.53)

Values are mean ± SD, or n (%).

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; DVD = double vessel disease; HDL-C = high density lipoprotein cholesterol; LAD = left anterior descending; LCX = left circumflex; LDL-C = low density lipoprotein cholesterol; LM = left main; LVEF = left ventricle ejection fraction; RCA = right coronary artery; SVD = single vessel disease; TC = total cholesterol; TVD = triple vessel disease.

Table 2

Cardiovascular events during follow-up

Clinical events	n
Cardiac death	12
Nonfatal myocardial infarction	22
Nonfatal stroke	4
Revascularization	123
Congestive heart failure	14
All cardiovascular events	175

Table 3

Comparison of patients with and without future cardiovascular events

	Event (–), n = 541		Event (+), n = 175		
	N	%	N	%	*p*
Age					0.493
0–64	251	46.4	87	49.7	
65–74	132	24.4	45	25.7	
≧75	158	29.2	43	24.6	
Male gender	463	85.6	147	84	0.608
Hypertension	354	65.4	112	64	0.729
DM	193	35.7	71	40.6	0.243
Family history of CAD	132	24.4	45	25.7	0.726
History of stroke	10	1.8	6	3.4	0.219
CAD severity					
SVD	135	33.8	43	29.3	0.320
DVD	142	35.5	44	29.9	0.223
TVD	110	27.5	59	40.1	0.005
Lifestyle parameters					
Healthy diet	344	63.6	100	57.1	0.127
No cigarette smoking	268	49.5	62	35.4	0.001
Active exercise	280	51.8	67	38.3	0.002
Medication					
Anti-platelet	490	90.6	163	93.1	0.297
ACE inhibitor/ARB	369	68.2	105	60	0.046
β-blocker	313	57.9	109	62.3	0.300
Calcium channel blocker	203	37.5	54	30.9	0.110
Diuretics	60	11.1	31	17.7	0.022
Statin	385	71.2	120	68.6	0.513

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; DVD = double vessel disease; SVD = single vessel disease; TVD = triple vessel disease.

3.2. Effects of healthy lifestyle factors on biochemical and inflammatory profiles

Table 4 shows the baseline characteristics, biochemical profiles, and inflammatory markers according to the number of healthy lifestyle factors adhered to in the study population. There was a significant trend of lower serum levels of high-sensitivity C-reactive protein as the number of healthy lifestyle factors increased. Notably, waist circumference, low-density lipoprotein (LDL) cholesterol, and the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol also decreased gradually as the number of healthy lifestyle factors increased ($p < 0.05$) (Fig. 1). The modifiable healthy lifestyle factors were associated with improved inflammatory status and biomedical profiles with a dosing effect. In addition, patients with more healthy lifestyle factors tended to be female and older. Regarding CAD severity, although patients without HLF had more triple vessel disease, there was no significant difference in the number of affected sites of coronary vessels among the various HLF groups.

3.3. Effects of healthy lifestyle factors on the risk of future cardiovascular events

To further investigate the potential impact of different lifestyle factors on future risk, the effects of modifiable healthy lifestyle factors were analyzed in all study patients, including healthy diet, active exercise, and no cigarette smoking. Table 5 shows the combined effects of healthy lifestyle factors in relation to the future risk of cardiovascular events adjusted for comorbidities, age, gender, history of hypertension, diabetes and medications (statins, ACE inhibitors/ARB, β-blockers, calcium channel blockers, and diuretics). Not smoking (hazard ratio [HR]: 0.59, 95% confidence interval [CI]: 0.41-0.83) and active exercise (HR: 0.66, 95% CI: 0.48-0.90) were independently associated with lower risks of future events in CAD patients after PCI.

Regarding the joint effects of a healthy lifestyle, the risk of future events decreased gradually as the number of healthy lifestyle factors increased, and all three healthy lifestyle factors were associated with a maximum risk reduction of 38% for future adverse events (HR: 0.38, 95% CI: 0.20-0.72) (Fig. 2). The subgroup analysis showed that the benefits of combined modifiable healthy lifestyle factors are especially pronounced in younger patients, males, patients with HDL <40 mg/dL, those reduced left ventricular ejection fraction (LVEF < 50%), and those receiving statin therapy. These findings indicate that adherence to a healthy lifestyle was associated with lower risk of future coronary heart disease in high-risk CAD patients (Fig. 3A and B).

4. DISCUSSION

The major findings of the present study show that adherence to healthy lifestyle factors, especially not smoking and active physical activity, could be associated with significantly decreased risk of future cardiovascular events in an Asian cohort of stable CAD patients after PCI. Furthermore, the risk decreased as the number of healthy lifestyle factors increased. Additionally, inflammatory markers, waist circumference, LDL cholesterol, and the ratio of total cholesterol to HDL cholesterol gradually decreased as the number of healthy lifestyle factors increased.

These findings showed a dose-dependent beneficial effect of combined healthy lifestyle factors in secondary prevention for CAD. The subgroup analysis showed that the benefits of combined modifiable healthy lifestyle factors are especially pronounced in the younger population, males, those with HDL <40 mg/dL, those with reduced LVEF, and those receiving statin therapy. These results indicate that adherence to a healthy lifestyle was associated with lower risk of future coronary heart disease in high-risk CAD patients.

Adherence to healthy lifestyles has been suggested to reduce clinical risk factors. Intensive lifestyle modification by nurse managers with a treatment protocol was examined in the COURGE trial. The intervention decreased the proportion of smokers (from 23% to 19%), increased physical activity (walk ≥150 minutes per week from 58% to 66%), increased the rate of consuming <7% of calories from saturated fat from 46% to 80%, and significantly decreased blood pressure and LDL.[15] In another study in India, a community worker-based intervention for adherence to drug and lifestyle changes after acute coronary syndrome resulted in improvement of clinical risk markers as well (BP, weight, lipid profiles, and BMI).[16] Both of these studies showed that lifestyle modification significantly improved clinical parameters that are considered to contribute to adverse outcomes.

The current study is just an observational study and not an intervention study with a lifestyle-modification protocol. Nevertheless, we observed benefits if patients with CAD maintained recommended healthy lifestyles (healthier diet, not smoking, and actively exercise). Similarly, Booth et al[17] observed that adherence to healthy lifestyles (especially smoking cessation, physical activity, and Mediterranean diet) was associated with a lower risk of recurrent CHD and death in patients after MI, PCI, and CABG. The present not only showed an association between lower risk of future adverse outcomes and maintaining healthy lifestyle, but also an association between increasing healthy behaviors and improvement of clinical risk factors and inflammatory markers. These results provide evidence linking lifestyle modification and benefits of CV risk reduction.

Table 4

Baseline characteristics of CAD patients according to the adherence of healthy lifestyle factors (HLF)

	No HLF	One HLF	Two HLFs	Three HLFs		
	n = 82	n = 239	n = 303	n = 92	*p	**p for trend
Age	61.3 ± 14.3	66.0 ± 12.1	67.02 ± 11.28	70.30 ± 11.39	<0.0001	<0.0001
Male, n (%)	79 (96.3)	204 (85.4)	257 (84.82)	70 (76.09)	0.0027	0.001
BMI (Kg/m^2)	26.3 ± 3.9	26.9 ± 6.3	25.98 ± 3.63	25.77 ± 4.02	0.1299	0.0801
Hypertension, n (%)	49 (59.8)	156 (65.3)	198 (65.35)	63 (68.48)	0.6814	0.296
Diabetes, n (%)	32 (39.0)	95 (39.8)	111 (36.63)	26 (28.26)	0.2668	0.0975
Waist (cm)	95.8 ± 9.9	94.7 ± 10.9	93.50 ± 9.23	91.57 ± 8.51	0.0168	0.0016
CAD severity						
SVD, n (%)	20 (31.8)	57 (31.3)	81 (35.37)	20 (27.40)	0.6025	0.9554
DVD, n (%)	12 (19.1)	73 (40.1)	70 (30.6)	31 (42.5)	0.005	0.1458
TVD, n (%)	29 (46.03)	50 (27.5)	72 (31.4)	18 (24.7)	0.0277	0.0624
Number of affected sites (n)	2.17 ± 1.10	2.02 ± 0.87	2.00 ± 0.94	1.90 ± 0.82	0.3958	0.1172
Systolic BP (mmHg)	127.9 ± 19.4	128.9 ± 16.8	130.72 ± 17.39	128.35 ± 15.07	0.3982	0.4509
Diastolic BP (mmHg)	72.1 ± 12.5	73.0 ± 12.3	74.62 ± 12.56	72.63 ± 11.11	0.2151	0.3157
LVEF (%)	54.0 ± 14.4	56.0 ± 13.9	54.74 ± 11.48	56.08 ± 10.48	0.8368	0.7958
Glucose (mg/dL)	127.5 ± 49.7	122.0 ± 48.3	119.84 ± 46.31	113.47 ± 32.20	0.2242	0.0441
Cholesterol (mg/dL)	160.6 ± 34.4	164.2 ± 34.5	157.89 ± 33.23	163.88 ± 35.58	0.1552	0.6049
LDL-C (mg/dL)	95.6 ± 25.0	96.7 ± 29.3	89.97 ± 27.29	92.73 ± 28.60	0.0378	0.0476
HDL-C (mg/dL)	38.5 ± 8.9	41.5 ± 9.9	42.83 ± 11.84	45.27 ± 11.52	0.0003	<0.0001
Triglyceride (mg/dL)	139.5 ± 88.7	134.2 ± 77.4	127.39 ± 79.49	120.60 ± 83.76	0.3409	0.0676
TC/HDL-C ratio	4.4 ± 1.3	4.12 ± 1.18	3.91 ± 1.18	3.81 ± 1.14	0.0037	0.0003
Creatinine	1.7 ± 2.2	1.43 ± 1.62	1.29 ± 1.27	1.17 ± 1.11	0.0515	0.0073
CRP	0.19 (0.02-6.41)	0.16 (0.02-13.08)	0.13 (0.02-13.08)	0.11 (0.02-2.73)	0.1414	0.0228
Medication						
ACE inhibitor/ARB, n (%)	49 (59.76)	161 (67.36)	204 (67.33)	60 (65.22)	0.5981	0.5249
β-blocker, n (%)	53 (64.63)	135 (56.49)	188 (62.05)	46 (50.00)	0.1146	0.299
Calcium channel blocker, n (%)	27 (32.93)	81 (33.89)	117 (38.61)	32 (34.78)	0.625	0.432
Diuretics, n (%)	14 (17.07)	30 (12.55)	38 (12.54)	9 (9.78)	0.5457	0.2147
Statin, n (%)	59 (71.95)	173 (72.38)	210 (69.31)	63 (68.48)	0.8303	0.4074
All cardiovascular events, n (%)	32 (39.02)	71 (29.71)	58 (19.14)	14 (15.22)	<0.0001	<0.0001
Cardiac death, n (%)	1 (1.22)	6 (2.51)	4 (1.32)	1 (1.09)	0.673	0.5436
Nonfatal MI, n (%)	5 (6.10)	7 (2.93)	7 (2.31)	3 (3.26)	0.3708	0.2623
Nonfatal stroke, n (%)	1 (1.22)	1 (0.42)	2 (0.66)	—	—	—
Revascularization, n (%)	25 (30.49)	47 (19.67)	41 (13.53)	10 (10.87)	0.0008	0.0001

Values are mean ± SD, or n (%).

*p-valve between groups; **p-value for trend for increasing healthy lifestyle parameters.

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CRP = C-reactive protein; DVD = double vessel disease; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; LVEF = left ventricle ejection fraction; MI = myocardial infarction; SVD = single vessel disease; TC = total cholesterol; TVD = triple vessel disease.

CVD is the leading cause of death in developed countries, and many treatment strategies have been suggested to reduce future events. Among the different treatment strategies, a healthy lifestyle has been encouraged for all patients, but the benefits are not easy to assess because of uncertainties regarding compliance. The EUROASPIRE IV study revealed that a large number of patients with coronary heart disease do not follow the guidelines for secondary prevention and have a high prevalence of persistent smoking, unhealthy diets, and physical inactivity.[18]

Our findings showed that greater lifestyle benefits with regard to CVD risk came from not smoking and exercise rather than from diet. Although a healthy diet was not found to be independently associated with reduced risk of adverse events, the three combined HLDs, including a healthy diet, still showed the maximum risk reduction of 50% when these three factors were all present. Interestingly, nearly all clinical trials from the 1960s through to the 1980s that examined diets with low total fat, low saturated fat, low dietary cholesterol, and increased polyunsaturated fat found significantly decreased serum cholesterol levels but failed to document a decrease in cardiovascular events.[19,20] This finding calls into question the importance of dietary control. However, recent studies on Mediterranean-style diets, which are characterized by vegetables, fruit, fish, whole grains, and olive oil, have shown that this approach reduces cardiovascular events to a greater degree than low-fat diets with benefits equal to or greater than statin therapies.[21] This suggests that a Mediterranean-style diet is helpful for secondary prevention in CAD patients.

Our observations showed that active physical activity was independently associated with a 32% risk reduction after considering comorbidities, disease severity, and medications, thus supporting the benefit of active physical activity for secondary prevention. Although there was strong evidence showing an inverse dose-response relationship between physical activity and mortality, the evidence for patients with preexisting CAD was still limited. Recently, Jeong et al[22] reported a benefit of physical activity on mortality reduction in an Asian population and showed that individuals with CVD may benefit from physical activity to a greater extent than healthy subjects without CVD. All of their findings supported that there is benefit in high-risk populations.

The association between nonsmoking and future risk followed the same trends. Among the three lifestyle factors, not smoking provided the highest risk reduction for patients with pre-existing CAD in the present study. The benefit is not limited to cardiovascular death: large-scale cohort studies have reported

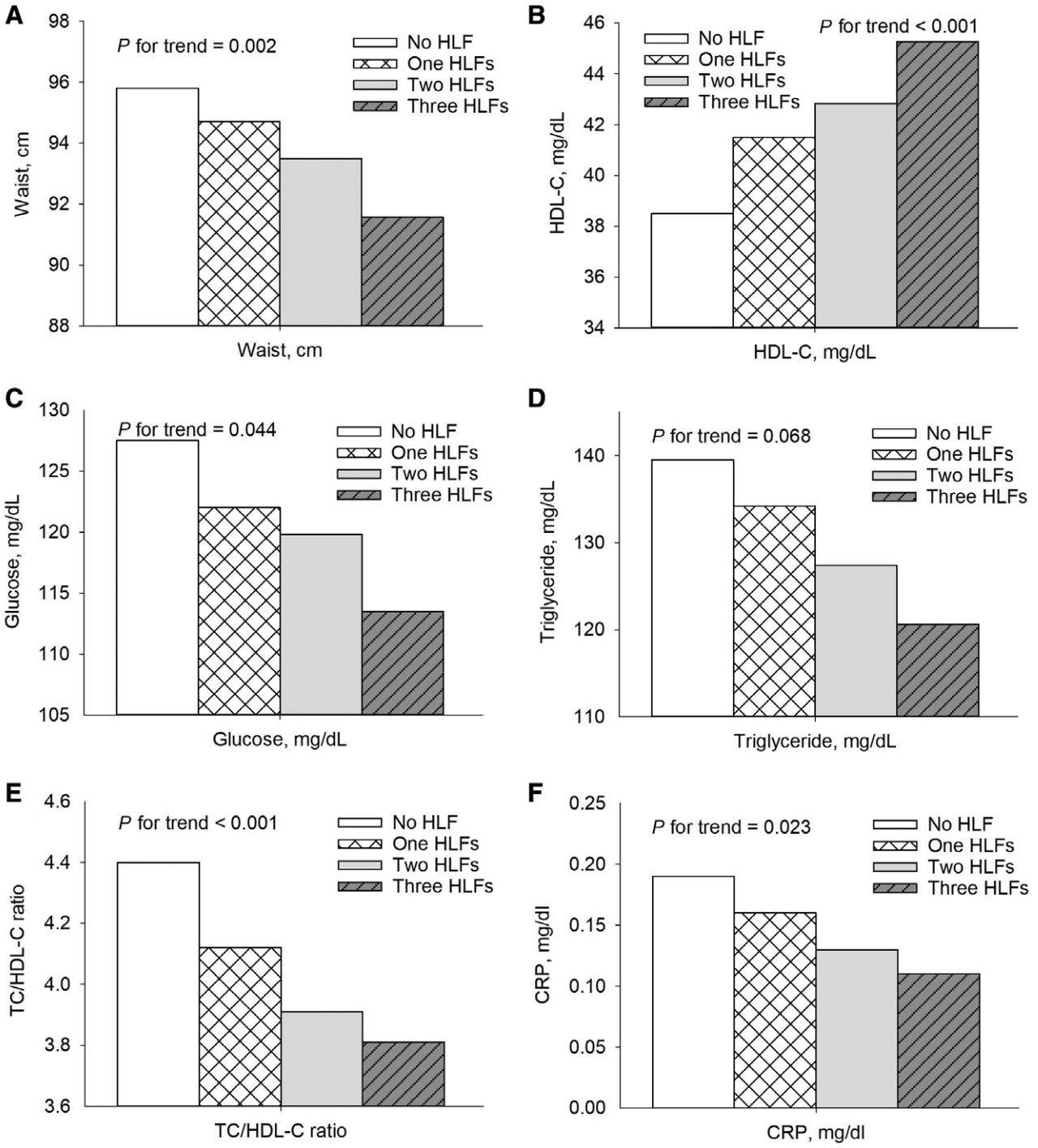

Fig. 1 Association of biomedical profiles and inflammation markers with the presence of healthy lifestyle factors: (A) waist; (B) glucose (mg/dL); (C) TC/HDL-C ratio; (D) HDL-C (mg/dL); (E) triglyceride (mg/dL); (F) CRP (mg/dL). CRP = C-reactive protein; HDL-C = high density lipoprotein cholesterol; TC = total cholesterol.

that smoking is related to deaths from various types of cancer, diabetes, chronic obstructive pulmonary disorder, and pneumonia.[23] Furthermore, the most important finding is that the risk declined as the number of years since quitting smoking increased among former smokers. This attests to the importance of smoking cessation, especially among high-risk CAD patients.

Our results demonstrated a joint effect of lifestyle modification, with the greatest risk reduction occurring in patients with high risk. This finding is in concordance with recent studies showing that CVD risk is inversely associated with the number of healthy behavior changes adopted by diabetic patients[24] and a Chinese population.[3] Our results supported the beneficial effects of healthy behaviors on cardiovascular risk reduction[1,25] for secondary prevention among CAD patients receiving PCI and further demonstrate the benefits for high-risk patients in particular.

It has been reported that diet and lifestyle can reduce CRP levels and the waist-to-hip ratio.[26] Patients with coronary heart disease and comorbid depression, behavioral interventions for

Table 5

Effects of healthy lifestyle factors (healthy diet, not smoking, and active exercise) on future risk of total cardiovascular events in patients with coronary artery disease

Healthy lifestyle factors	Event/persons (event rate %)	Crude HR	HR (95%CI) model 1	HR (95%CI), model 2
Healthy diet	100/444 (57.1%)	0.80 (0.59-1.07) $p = 0.13$	0.76 (0.56-1.02) $p = 0.07$	0.79 (0.58-1.07) $p = 0.13$
No smoking	62/340 (35.4%)	0.61 (0.44-0.83) $p < 0.01$	0.59 (0.41-0.83) $p < 0.01$	0.59 (0.41-0.83) $p < 0.01$
Active exercise	67/347 (38.3%)	0.61 (0.45-0.83) $p < 0.01$	0.65 (0.48-0.89) $p < 0.01$	0.66 (0.48-0.90) $p = 0.01$
With 0 healthy lifestyle factor	32/82 (39.2%)	1 (reference)	1 (reference)	1 (reference)
With 1 healthy lifestyle factor	71/239 (29.7%)	0.72 (0.47-1.09)	1.00 (1.00-1.00)	0.78 (0.51-1.19)
With 2 healthy lifestyle factor	58/303 (19.1%)	0.43 (0.28-0.67)	0.73 (0.48-1.11)	0.48 (0.31-0.75)
With 3 healthy lifestyle factor	14/92 (15.2%)	0.33 (0.18-0.62)	0.45 (0.29-0.70)	0.38 (0.20-0.72)
p-trend		<0.01	<0.01	<0.01

Crude HR: NO adjusted.

Model 1: adjusted with age, gender, history of hypertension, and diabetes.

Model 2: adjusted with age, gender, history of hypertension, diabetes, and medications (statin, ACE inhibitor/ARB, β-blocker, calcium channel blocker, diuretics).

CI = confidence interval; HR = hazard ratio.

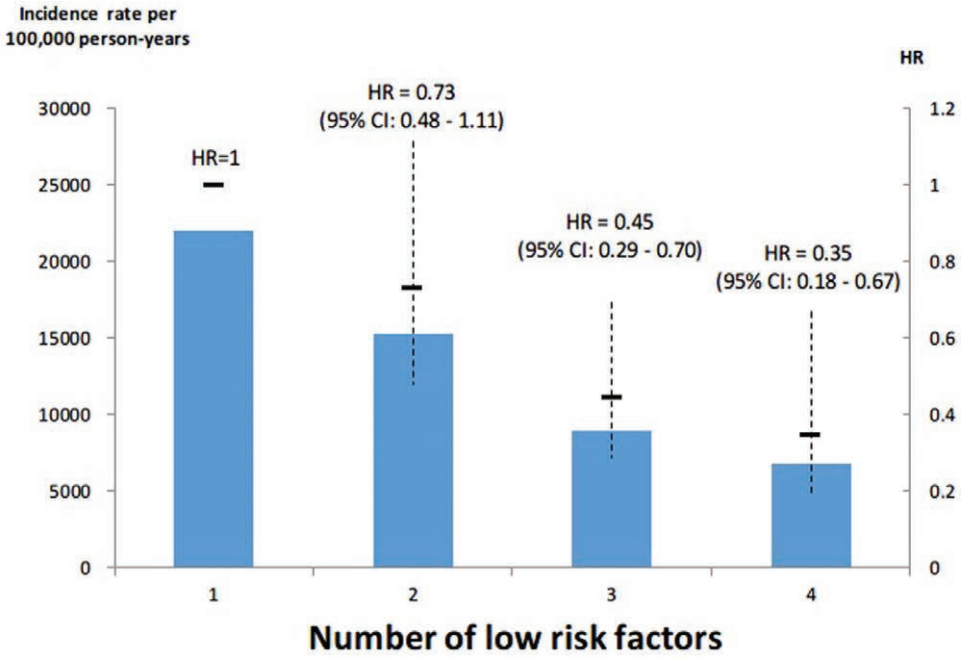

Fig. 2 Risk and incidence of total future cardiovascular events in patients according to adherence to healthy lifestyle factors including healthy diet, no cigarette smoking, and active exercise.

smoking, and lack of exercise may have significantly attenuated risk for MI or death.[27] In addition, the current findings further showed that serum triglycerides and the ratio of total cholesterol to HDL cholesterol decreased gradually as the number of healthy lifestyle factors increased ($p < 0.05$). This finding suggests an association between a healthy lifestyle and favorable lipid profiles.

Accordingly, a healthy lifestyle may be critical for baseline inflammation status and cardiovascular risk factors in either primary or secondary cohorts. Even when considering lipid profiles, medications, and inflammatory makers, lifestyle modification was still independently associated with a lower risk of future adverse events. Therefore, efforts to improve cardiovascular risk factors by adopting a healthy lifestyle could be essential for secondary prevention in all CAD patients for both Asian and Western people.

Our study has several limitations. First, a study nurse confirmed the adherence to lifestyle factors, especially dietary information, during the follow-up period. The diet components were not consumed in isolation, and multiple interacting food components and the consistency of adherence may have affected the dietary benefits for secondary prevention. Furthermore, the Western dietary recommendations were not designed for Taiwanese people.

Second, because the adherence to a healthy lifestyle was not randomized, a causal relationship between a healthy lifestyle and CVD risk cannot be established. Third, a healthy lifestyle and smoking cessation may change an individual's body weight. Although our study did not record body weight during each clinic visit, a recent study reported that smoking cessation was accompanied by substantial weight gain. Increasing body weight after smoking cessation increases the risk of type 2 diabetes, which peaks 5 to 7 years after quitting smoking and then gradually decreases.[28] However, the weight gain did not increase the mortality risk and did not mitigate the benefits of quitting smoking on reducing cardiovascular and all-cause mortality.[28]

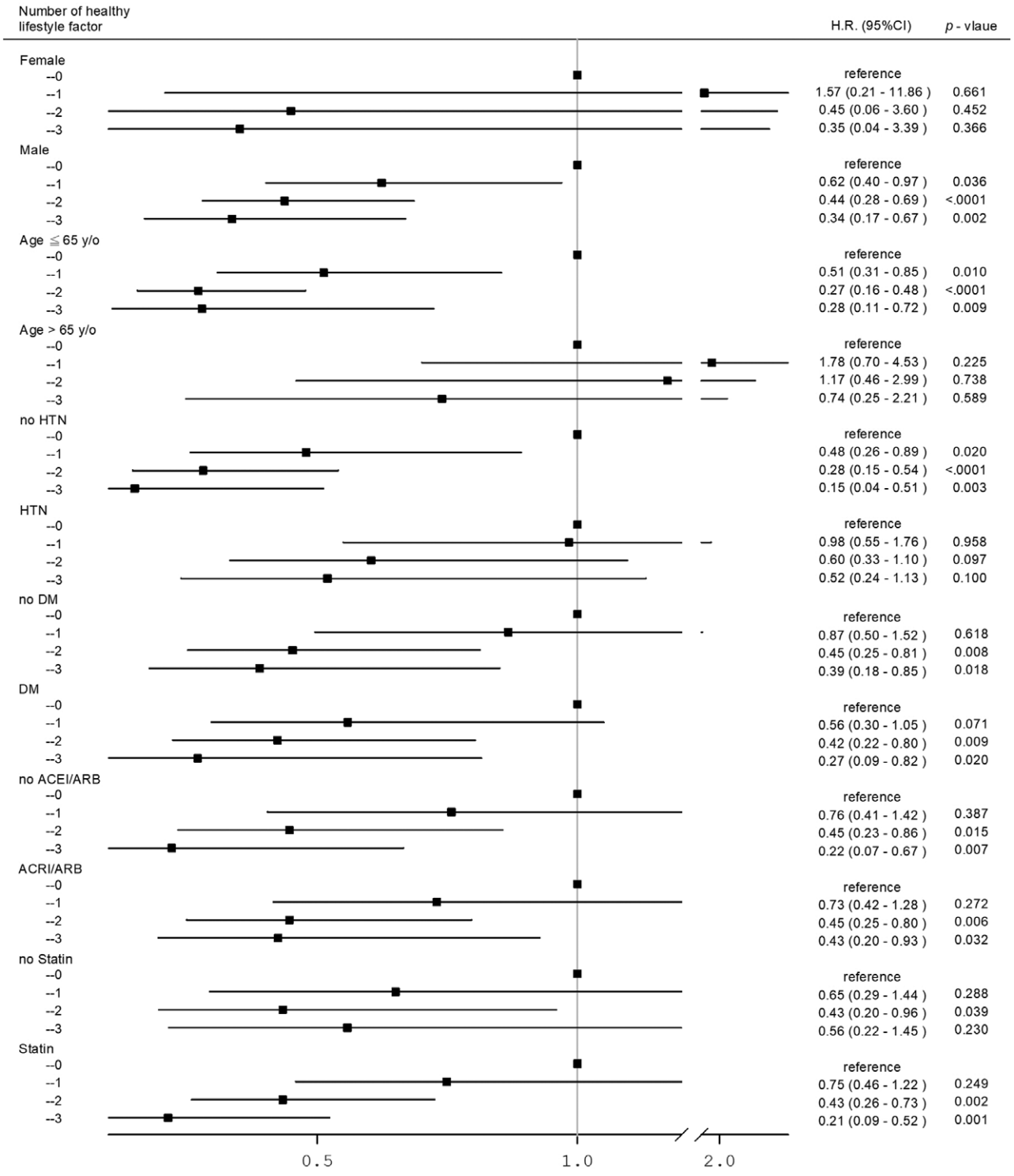

Fig. 3 Risk and number of healthy lifestyle factors among study population with variable subgroups (A and B).

The definition of regular exercise was modified from one suggestion of 150 minutes per week of moderate intensity. The definition may not represent all activities, and there is no consensus, especially for Asian CAD populations. Finally, the current study was an observational cohort study, not an intervention study. Thus, a rehabilitation program was not included, and the impact of cardiac rehabilitation was not estimated.

The evidence suggests that adherence to a healthy lifestyle, especially a healthy diet and not smoking, was associated with significantly reduced risk of future cardiovascular events in stable CAD patients. Furthermore, biomedical and inflammatory serum profiles were negatively correlated with an increased number of healthy lifestyle factors. Accordingly, a healthy lifestyle, even in the presence of standard medication, could be critical for

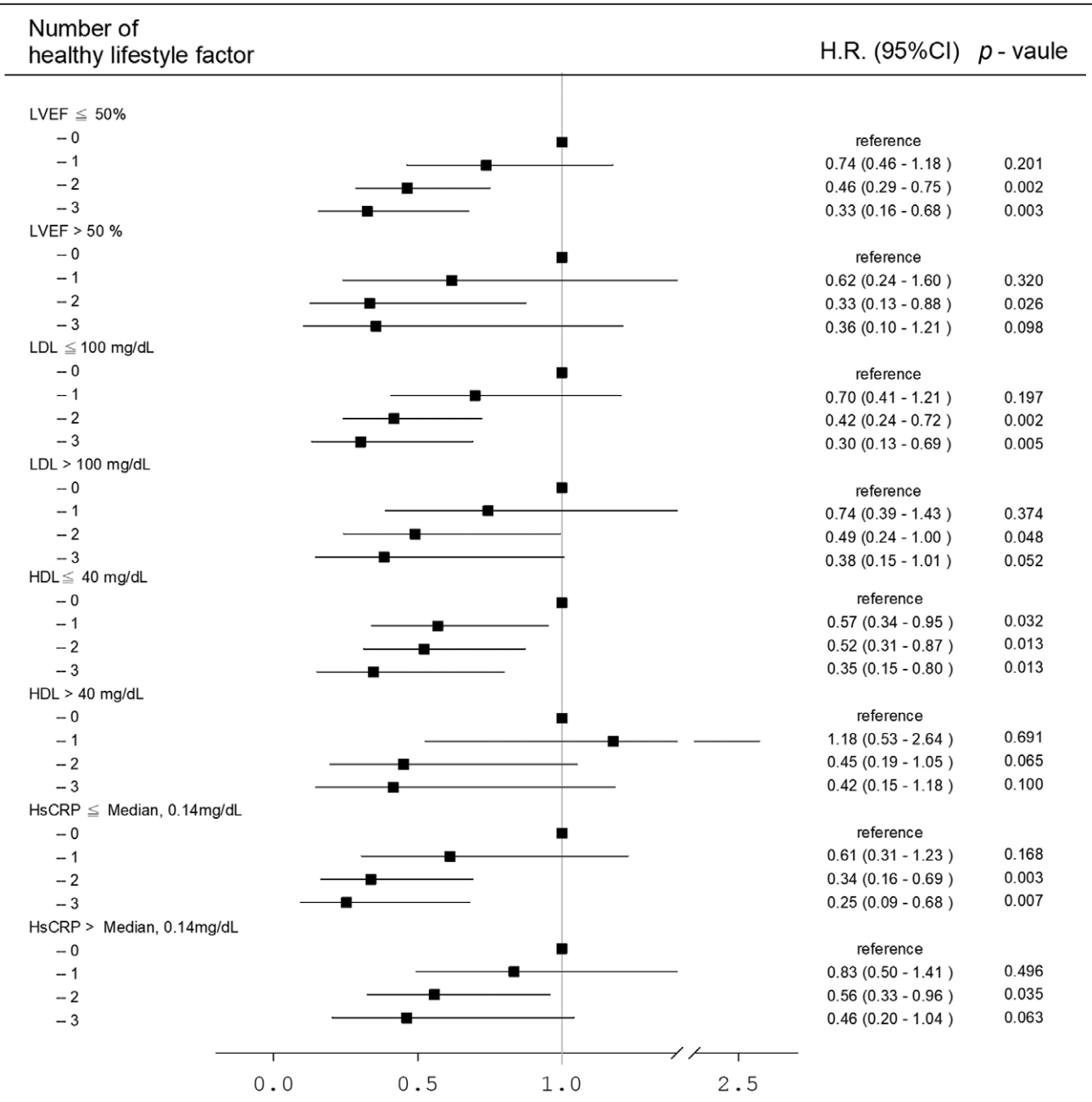

Fig. 3 Continued.

clinical outcomes in Chinese patients with PCI. A healthy lifestyle has prognostic significance beyond medical control in terms of biomedical and inflammatory profiles. Thus, future clinical studies should be conducted to refine the potential role of lifestyle modification for secondary prevention in patients with CVD.

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