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ORIGINAL RESEARCH

Body Mass Index and Association With Cardiovascular Outcomes in Patients With Stable Coronary Heart Disease – A STABILITY Substudy

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BACKGROUND: The obesity paradox states that patients with higher body mass index (BMI) and cardiovascular disease may experience better prognosis. However, this is less clear in patients with coronary heart disease.

METHODS AND RESULTS: The prospective STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial included 15 828 patients with stable coronary heart disease with 3 to 5 years' follow-up on optimal secondary preventive treatment. BMI was measured at baseline (n=15 785). Associations between BMI and cardiovascular outcomes were evaluated by Cox regression analyses with multivariable adjustments. Mean age was 64±9 years and 19% women. Most risk markers (diabetes, hypertension, inflammatory biomarkers, triglycerides) showed a graded association with higher BMI. The frequency of smoking, levels of high-density lipoprotein, growth differentiation factor 15, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) were higher at lower BMI. Low BMI (<20 kg/m^2; n=244 [1.5%]) was associated with doubled risk of total death (hazard ratio [HR], 2.27; 95% CI, 1.60–3.22), cardiovascular death (HR, 2.26; 95% CI, 1.46–3.49), and heart failure (HR, 2.51; 95% CI, 1.35–4.68) compared with BMI of 25 to <30 kg/m^2 (n=6752 [42.8%]) as reference. Similarly, high BMI of ≥35 kg/m^2 (n=1768 [11.2%]) was associated with increased risk of the same outcomes. A BMI between 20 and <25 kg/m^2 was associated with increased risk of cardiovascular death (HR, 1.26; 95% CI, 1.03–1.54) and total death (HR, 1.21; 95% CI, 1.03–1.42).

CONCLUSIONS: Patients with stable coronary heart disease showed a graded increase in cardiometabolic and inflammatory risk factors with increasing BMI category >25 kg/m^2. All-cause and cardiovascular mortality were lowest at BMI of 25 to 35 kg/m^2. Underweight with BMI of <20 kg/m^2 and very high BMI of ≥35 kg/m^2 were strong risk markers for poor prognosis.

REGISTRATION: URL: https://clinicaltrials.gov/; Unique identifier NCT00799903.

Key Words: coronary artery disease ■ obesity ■ risk factors

Overweight is an increasingly common phenomenon in most parts of the world.[1,2] Obesity, assessed using body mass index (BMI) >30 kg/m^2, is an established risk factor for development of coronary heart disease (CHD) in healthy individuals.[3] Furthermore, obesity is associated with many of the known cardiovascular risk factors, such as hypertension and dyslipidemia.[4] However, in some epidemiological studies, increased obesity has not been associated with a lower risk. Studies have

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CLINICAL PERSPECTIVE

What Is New?

- Patients with stable coronary heart disease had a graded increase in cardiometabolic and inflammatory risk factors with increasing body mass index (BMI) category >25 kg/m^2.
- All-cause and cardiovascular mortality were lowest at a BMI between 25 and 35 kg/m^2, which is somewhat higher than what is currently recommended in prevention guidelines.
- Underweight with BMI <20 kg/m^2 and very high BMI ≥35 kg/m^2 were strong risk markers for poor prognosis.

What Are the Clinical Implications?

- We need to better establish the ideal BMI for patients with coronary heart disease and determine if recommendations should be revised.
- It is important to identify underweight and extreme overweight as strong markers of poor prognosis.

Nonstandard Abbreviations and Acronyms

GDF-15	growth differentiation factor 15
STABILITY	Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy

demonstrated that in patients with heart failure, acute coronary syndromes,[5–7] atrial fibrillation,[8] cardiovascular disease with diabetes,[9] or after coronary revascularization[10] there may be an "overweight paradox" phenomenon, with better cardiovascular prognosis among patients with higher BMI.[8,11] The association between BMI and cardiovascular outcomes in patients with stable CHD seems inconsistent and complex. In a recent retrospective study of >15 000 patients with stable coronary artery disease with long-term follow-up, obesity was independently associated with increased mortality, whereas overweight was not.[12] There is limited and partly conflicting data on the ideal weight and BMI in patients with known CHD in secondary prevention. The aim of the current substudy, a post hoc analysis of the prospective STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial was to explore associations between BMI and clinical outcomes in patients with stable CHD, and possibly identify an optimal BMI for the risk of cardiovascular events. In addition, we aimed to better understand potential mechanisms behind the associations.

METHODS

The data underlying this article can be shared on reasonable request from www.clinicalstudydatarequest.com.

Study Design, Population, and Clinical End Points

The prospective STABILITY trial was a randomized placebo-controlled study evaluating the effects of a lipoprotein-associated phospholipase A2 inhibitor darapladib and included 15 828 patients with stable CHD with a follow-up of 3 to 5 (median, 3.7) years on optimal secondary preventive treatment.[13] The study design, baseline characteristics, and main results have been presented previously.[14,15] In brief, patients with CHD, as documented by at least 1 of the following: previous myocardial infarction (MI), previous percutaneous coronary intervention or coronary artery bypass grafting, or multivessel coronary artery disease were eligible. In addition, at least 1 specified risk indicator was required. The study was performed in accordance with the Declaration of Helsinki, approved by institutional review boards, and all patients provided written informed consent.

Primary outcomes were the composite of cardiovascular death, MI, and stroke. Secondary outcomes were the individual major adverse cardiovascular event components, urgent coronary revascularization, stroke, all-cause mortality, hospitalization for heart failure, and new cancer diagnosis. All end points were centrally adjudicated to minimize variability. Details of the end point definitions have been published elsewhere.[14]

Analyses

BMI and waist circumference were measured at baseline (n=15 785). BMI was divided into 5 categories, based on standard cutoff values for normal weight (20 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obesity (30 to <35 kg/m^2), extreme obesity (≥35 kg/m^2), and underweight (<20 kg/m^2). Venous blood samples were obtained at inclusion in the morning after 9 hours of fasting. EDTA plasma aliquots were stored at −80°C until biochemical analyses. Established biochemical assays for NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity cardiac troponin T, high-sensitivity C-reactive protein, interleukin-6, growth differentiation factor 15 (GDF-15), and lipoprotein-associated phospholipase A2 were centrally performed as previously published.[16–21] Physical activity at baseline was assessed on the basis of a lifestyle questionnaire.

Statistical Analysis

To investigate differences across the 5 BMI groups, categorical variables were presented as count and

proportion and continuous variables as mean and SD. Groups were compared with the chi-square test. Continuous variables were compared with Kruskal-Wallis nonparametric tests. Associations between BMI and clinical outcomes were evaluated using Cox proportional hazards regression models and expressed with hazard ratios (HRs) and 95% CIs, presented in tables or with forest plots. Survival curves for cardiovascular death, all-cause death, MI, and hospitalization for heart failure were performed by using the Kaplan-Meier method (not shown). The underlying proportional hazards assumptions of the Cox proportional hazard models were verified by visual inspection of Kaplan-Meier graphs and Schoenfeld residual plots. The basic model was adjusted for age, sex, and randomized treatment. In the multivariable model, we adjusted for age, sex, randomized treatment, prior percutaneous coronary intervention/coronary artery bypass grafting, prior MI, renal dysfunction, polyvascular disease, diabetes, smoking, stroke/transient ischemic attack, congestive heart failure, systolic blood pressure, geographic region, chronic obstructive pulmonary disease, cancer diagnosis, and Asian/Japanese origin. Spline plots with 4 knots were constructed to show relations between BMI study outcomes. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). A 2-sided *P* value of <0.05 was considered statistically significant. There was no adjustment for multiplicity.

RESULTS

A summary of baseline characteristics and demographics is shown in Table 1. Mean age was 64±9 years, and 18.7% were women. In total, 244 (1.5%) patients had a BMI of <20 kg/m^2, 3060 (19.4%) a BMI of 20 kg/m^2 to <25 kg/m^2, 6752 (42.8%) a BMI of 25 kg/m^2 to <30 kg/m^2, 3961 (25.1%) a BMI of 30 kg/m^2 to <35 kg/m^2, and 1768 (11.2%) with BMI of ≥35 kg/m^2, respectively. Severe underweight (BMI of <18.5 kg/m^2) was observed in 79 patients (0.5%). Several established risk markers, such as diabetes, hypertension, previous revascularization, and levels of both inflammatory biomarkers and triglycerides showed an increased and graded association with higher BMI. In addition, both systolic and diastolic blood pressure were higher with higher BMI category. The prevalence of smoking, and serum levels of high-density lipoprotein, GDF-15, and NT-proBNP were higher at lower BMI. Patients with a high BMI of >30 kg/m^2, classified as obese, were slightly younger, more often women, and more often of White race than those classified as having normal weight or overweight. The association between BMI and biomarkers of special interest (interleukin-6, high-sensitivity cardiac troponin T, NT-proBNP and GDF-15) are shown in Figure 1. Interleukin-, GDF-15, and high-sensitivity cardiac troponin were highest in the low and high end of BMI categories. NT-proBNP was highest among patients with very low BMI and were lowest among patients with highest BMI. Physical activity assessed as metabolic equivalents of task h/week was lowest among patients with BMI of <25 kg/m^2.

BMI and Association With Clinical Outcomes

The associations between BMI and risk of major adverse cardiovascular event, total death, cardiovascular death, and heart failure hospitalization are presented in Table 2 and Figure 2. For cardiovascular and total mortality and heart failure, the event rates (Table 2) were lowest in the BMI category of 25 to <30 kg/m^2. Spline plots for clinical outcomes (cardiovascular and total mortality, heart failure, MI, and stroke) showed the lowest risk at a BMI of around 27 kg/m^2 (Figure 2A). Spline plots were also created for the Asian and non-Asian populations, separately (Figures 2B and 2C). The U-shaped curve was more pronounced in the Asian population than in the non-Asian population. The HR and 95% CI for total and cardiovascular death and for hospitalization for heart failure are presented in Figure S1A and S1B and Figure 2A and 2B), in the respective populations. In the Asian population, the risk of cardiovascular death was significantly higher among those with the lowest BMI (<20 kg/m^2; HR, 2.87; 95% CI, 1.56–5.26), and with a BMI of >35 kg/m^2 (HR, 3.35; 95% CI, 1.36–8.26). The corresponding risks for heart failure hospitalization were HR of 3.02 (95% CI, 1.33–6.85) and HR of 3.23 (95% CI, 1.13–9.24), respectively.

The associations between BMI and clinical outcomes in all patients (basic adjustment model) are shown in Figure 3A. After multivariable adjustments, as shown in Figure 3B, there remained a significantly increased risk of cardiovascular death in patients with a BMI of 20 to <25 kg/m^2 (HR, 1.26; 95% CI, 1.03–1.54) with a BMI of 25 to <30 kg/m^2 as reference, and the risk was more than doubled in those with very low BMI (<20 kg/m^2; HR, 2.26; 95% CI, 1.46–3.49). However, the risk of cardiovascular death in patients with a BMI of 30 to <35 kg/m^2 and ≥35 kg/m^2, respectively, was numerically higher but not statistically significant.

Similarly, total death was increased among patients with very low BMI (<20 kg/m^2) (HR, 2.27; 95% CI, 1.60–3.22) but not for those with higher BMI categories. For heart failure hospitalization, the risk among patients with very low BMI was increased with HR of 2.51 (95% CI, 1.35–4.68) but not significantly increased

Table 1. Summary of Demographic and Baseline Characteristics by BMI Category

Baseline characteristics		<20 kg/m² N=244	20 < 25 kg/m² N=3060	25 < 30 kg/m² N=6752	30 < 35 kg/m² N=3961	≥35 kg/m² N=1768	Total N=15 785	*P* value for overall tests
Age at randomization (years)	Median (Q1–Q3)	68.0 (58.5–75.0)	66.0 (59.0–72.0)	65.0 (59.0–71.0)	64.0 (58.0–70.0)	63.0 (58.0–69.0)	65.0 (59.0– 71.0)	<0.0001
Sex, n (%)	Female	78 (32.0)	614 (20.1)	1061 (15.7)	757 (19.1)	448 (25.3)	2958 (18.7)	<0.0001
Race, n (%)	Black	5 (2.0)	51 (1.7)	144 (2.1)	99 (2.5)	63 (3.6)	362 (2.3)	<0.0001
	Central/South/ Southeast Asian	92 (37.7)	479 (15.7)	485 (7.2)	108 (2.7)	25 (1.4)	1189 (7.5)	<0.0001
	East Asian/Japanese	49 (20.1)	686 (22.4)	674 (10.0)	103 (2.6)	10 (0.6)	1522 (9.6)	<0.0001
	Other	4 (1.6)	57 (1.9)	164 (2.4)	79 (2.0)	37 (2.1)	341 (2.2)	<0.0001
	White	94 (38.5)	1787 (58.4)	5285 (78.3)	3572 (90.2)	1633 (92.4)	12 371 (78.4)	<0.0001
Geographic region, n (%)	Asia/Pacific	150 (61.5)	1204 (39.3)	1337 (19.8)	312 (7.9)	80 (4.5)	3083 (19.5)	<0.0001
	Eastern Europe	28 (11.5)	484 (15.8)	1587 (23.5)	1061 (26.8)	370 (20.9)	3530 (22.4)	<0.0001
	North America	27 (11.1)	478 (15.6)	1471 (21.8)	1215 (30.7)	820 (46.4)	4011 (25.4)	<0.0001
	South America	10 (4.1)	206 (6.7)	575 (8.5)	304 (7.7)	101 (5.7)	1196 (7.6)	<0.0001
	Western Europe	29 (11.9)	688 (22.5)	1782 (26.4)	1069 (27.0)	397 (22.5)	3965 (25.1)	<0.0001
BMI	Median (Q1–Q3)	19.0 (18.2–19.5)	23.5 (22.4–24.3)	27.5 (26.2–28.7)	31.9 (30.9–33.2)	37.6 (36.1–40.3)	28.3 (25.5–31.7)	<0.0001
Weight, kg	Median (Q1–Q3)	52.0 (47.0–55.3)	66.0 (60.0–72.0)	80.0 (73.1–86.0)	93.5 (86.0–100.5)	110.2 (101.0–121.0)	82.0 (71.6–94.0)	<0.0001
Waist/Hip ratio at randomization, n (%)	Level 1: Males: ≤0.90, Females: ≤0.83	118 (48.4)	861 (28.1)	717 (10.6)	190 (4.8)	71 (4.0)	1957 (12.4)	<0.0001
	Level 2: Men: >0.90 to ≤0.95; Women: >0.83 to ≤0.9	63 (25.8)	987 (32.3)	1879 (27.8)	712 (18.0)	257 (14.5)	3898 (24.7)	<0.0001
	Level 3: Men: >0.95; Women: >0.90	62 (25.4)	1183 (38.7)	4085 (60.5)	3003 (75.8)	1419 (80.3)	9752 (61.8)	<0.0001
Physical activity MET h/wk	Median (Q1–Q3)	28.0 (14.0–52.0)	40.0 (18.0–70.0)	42.0 (20.0–76.0)	40.0 (20.0–74.0)	32.0 (14.0–66.0)	40.0 (18.0–72.0)	<0.0001
Diabetes, n (%)		58 (23.8)	848 (27.7)	2326 (34.4)	1814 (45.8)	1078 (61.0)	6124 (38.8)	<0.0001
Smoking status, n (%)	Never smoked	88 (36.1)	1060 (34.6)	2104 (31.2)	1124 (28.4)	501 (28.3)	4877 (30.9)	<0.0001
	Current smoker	66 (27.0)	628 (20.5)	1255 (18.6)	650 (16.4)	255 (14.4)	2854 (18.1)	<0.0001
	Former smoker	90 (36.9%)	1372 (44.8%)	3392 (50.2%)	2187 (55.2%)	1012 (57.2%)	8053 (51.0%)	<0.0001
Systolic blood pressure (mm Hg)	Median (Q1–Q3)	125.5 (112.0–141.0)	129.0 (117.0–141.0)	131.0 (121.0–142.0)	132.0 (122.0–143.0)	132.0 (122.0–144.0)	131.0 (120.0–142.0)	<0.0001
Diastolic blood pressure (mm Hg)	Median (Q1–Q3)	75.0 (66.0–84.0)	76.0 (69.0–84.0)	79.0 (72.0–86.0)	80.0 (73.0–86.0)	80.0 (73.0–87.0)	79.0 (72.0–85.0)	<0.0001
Diagnosis of hypertension, n (%)		132 (54.1)	1861 (60.8)	4722 (69.9)	3052 (77.1)	1517 (85.8)	11 284 (71.5)	<0.0001
Prior MI, n (%)		169 (69.3)	1823 (59.6)	4028 (59.7)	2329 (58.8)	947 (53.6)	9296 (58.9)	<0.0001
Prior PCI or CABG, n (%)		148 (60.7)	2272 (74.2)	5064 (75.0)	2968 (74.9)	1380 (78.1)	11 832 (75.0)	<0.0001
Multivessel CHD, n (%)		45 (18.4)	447 (14.6)	1028 (15.2)	582 (14.7)	276 (15.6)	2378 (15.1)	0.4554

(*Continued*)

Table 1. Continued

Baseline characteristics		<20 kg/m² N=244	20 < 25 kg/m² N=3060	25 < 30 kg/m² N=6752	30 < 35 kg/m² N=3961	≥35 kg/m² N=1768	Total N=15 785	*P* value for overall tests
Time from CHD event to randomization, n (%)	Remote	172 (70.5)	2172 (71.0)	5093 (75.4)	3114 (78.6)	1393 (78.8)	11 944 (75.7)	<0.0001
	Recent	72 (29.5)	879 (28.7)	1647 (24.4)	838 (21.2)	368 (20.8)	3804 (24.1)	<0.0001
Family history of premature CHD, n (%)		35 (14.4)	615 (20.1)	1654 (24.6)	1119 (28.3)	627 (35.5)	4050 (25.7)	<0.0001
Polyvascular disease, n (%)		35 (14.3)	444 (14.5)	946 (14.0)	651 (16.4)	289 (16.3)	2365 (15.0)	0.0052
NYHA class, n (%)	Class I	27 (42.2)	277 (43.1)	516 (34.5)	297 (28.8)	116 (24.6)	1233 (33.3)	<0.0001
	Class II	24 (37.5)	302 (47.0)	835 (55.8)	617 (59.8)	276 (58.6)	2054 (55.4)	<0.0001
	Class III	7 (10.9)	48 (7.5)	87 (5.8)	72 (7.0)	61 (13.0)	275 (7.4)	<0.0001
	Class IV	6 (9.4)	16 (2.5)	58 (3.9)	45 (4.4)	18 (3.8)	143 (3.9)	<0.0001
COPD or asthma, n (%)		26 (10.8)	258 (8.5)	566 (8.5)	410 (10.5)	276 (15.8)	1536 (9.8)	<0.0001
Aspirin at randomization, n (%)		219 (89.8)	2824 (92.3)	6267 (92.8)	3662 (92.5)	1615 (91.3)	14 587 (92.4)	0.1371
ACE inhibitor or ARB at randomization, n (%)		170 (69.7)	2150 (70.3)	5148 (76.2)	3218 (81.2)	1486 (84.0)	12 172 (77.1)	<0.0001
Statin at randomization, n (%)		235 (96.3)	2972 (97.1)	6604 (97.8)	3836 (96.8)	1710 (96.7)	15 357 (97.3)	0.0102
Beta blocker at randomization, n (%)		172 (70.5)	2230 (72.9)	5340 (79.1)	3258 (82.3)	1479 (83.7)	12 479 (79.1)	<0.0001
P2Y12 at randomization, n (%)		110 (45.1)	1224 (40.0)	2244 (33.2)	1217 (30.7)	592 (33.5)	5387 (34.1)	<0.0001
LDL-C, mmol/L, n (%)	Median (Q1–Q3)	2.01 (1.52–2.55)	2.06 (1.61–2.60)	2.10 (1.65–2.65)	2.08 (1.62–2.63)	1.97 (1.55–2.48)	2.07 (1.62–2.62)	<0.0001
HDL-C, mmol/L, n (%)	Median (Q1–Q3)	1.42 (1.13–1.73)	1.25 (1.05–1.50)	1.17 (1.00–1.39)	1.12 (0.96– 1.31)	1.09 (0.94–1.25)	1.15 (1.00–1.38)	<0.0001
Triglycerides, mmol/L, n (%)	Median (Q1–Q3)	1.11 (0.86–1.42)	1.29 (0.96–1.78)	1.49 (1.09–2.06)	1.68 (1.24–2.34)	1.80 (1.34–2.52)	1.52 (1.10–2.13)	<0.0001
eGFR (CKD-EPI)	Median (Q1–Q3)	73.7 (59.5–89.0)	76.0 (62.9–88.5)	74.3 (61.5–86.2)	73.9 (61.8–86.5)	73.4 (59.8–86.7)	74.4 (61.7–86.7)	<0.0001
Creatinine, µmol/L	Median (Q1–Q3)	87.0 (73.5–104.5)	88.0 (78.0–100.0)	89.0 (80.0–105.0)	90.0 (80.0–105.0)	90.0 (80.0–106.0)	89.0 (80.0–105.0)	<0.0001
Significant renal dysfunction, n (%)		73 (29.9)	795 (26.0)	1959 (29.0)	1257 (31.7)	682 (38.6)	4766 (30.2)	<0.0001
Hemoglobin, g/L	Median (Q1–Q3)	135.0 (123.0–146.0)	141.0 (132.0–150.0)	144.0 (135.0–152.0)	145.0 (135.0–153.0)	142.0 (132.0–151.0)	144.0 (134.0–152.0)	<0.0001
WBC, GI/L	Median (Q1–Q3)	6.55 (5.40–7.80)	6.40 (5.30–7.70)	6.50 (5.50–7.70)	6.70 (5.70–7.90)	6.80 (5.70–8.10)	6.60 (5.50–7.80)	<0.0001
hsCRP, mg/L	Median (Q1–Q3)	0.90 (0.40–2.60)	0.90 (0.40–2.20)	1.20 (0.60–2.60)	1.70 (0.80–3.60)	2.50 (1.20–4.90)	1.30 (0.60–3.10)	<0.0001
hsTroponin T, ng/L	Median (Q1–Q3)	9.2 (6.0–15.3)	8.6 (5.8–13.0)	9.0 (6.1–13.8)	9.5 (6.4–14.6)	10.6 (7.0–16.8)	9.3 (6.2–14.2)	<0.0001
NT-proBNP, ng/L	Median (Q1–Q3)	346 (143–857)	194 (93–443)	172 (83–376)	160 (77–329)	172 (75–356)	173 (83–379)	<0.0001
Interleukin -6, ng/L	Median (Q1–Q3)	2.10 (1.30–4.05)	1.80 (1.20–2.90)	2.00 (1.40–3.00)	2.20 (1.50–3.30)	2.70 (1.90–3.90)	2.10 (1.40–3.20)	<0.0001
Cystatin C, mg/L	Median (Q1–Q3)	1.12 (0.94–1.35)	0.99 (0.86–1.16)	0.99 (0.86–1.16)	0.98 (0.86–1.16)	1.04 (0.90–1.25)	0.99 (0.86–1.18)	<0.0001
GDF-15, ng/L	Median (Q1–Q3)	1573 (1044–2435)	1271 (935–1847)	1235 (898–1778)	1208 (886–1781)	1359 (982–1966)	1253 (914–1826)	<0.0001
LpPLA2 activity, µmol/min per L	Median (Q1–Q3)	164.3 (131.6–197.0)	169.8 (137.9–203.5)	173.4 (145.3–204.5)	173.5 (145.4–205.8)	171.3 (142.0–202.4)	172.5 (143.1–204.3)	<0.0001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CDK-EPI, Chronic Kidney Disease Epidemiology Collaboration; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LpPLA2, lipoprotein-associated phospholipase A2; MET h, Metabolic Equivalents of Task, hours per week; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; Q, quartile; and WBC, white blood cell.

Percentages calculated with patients with data as denominator. P value calculated for difference between groups.

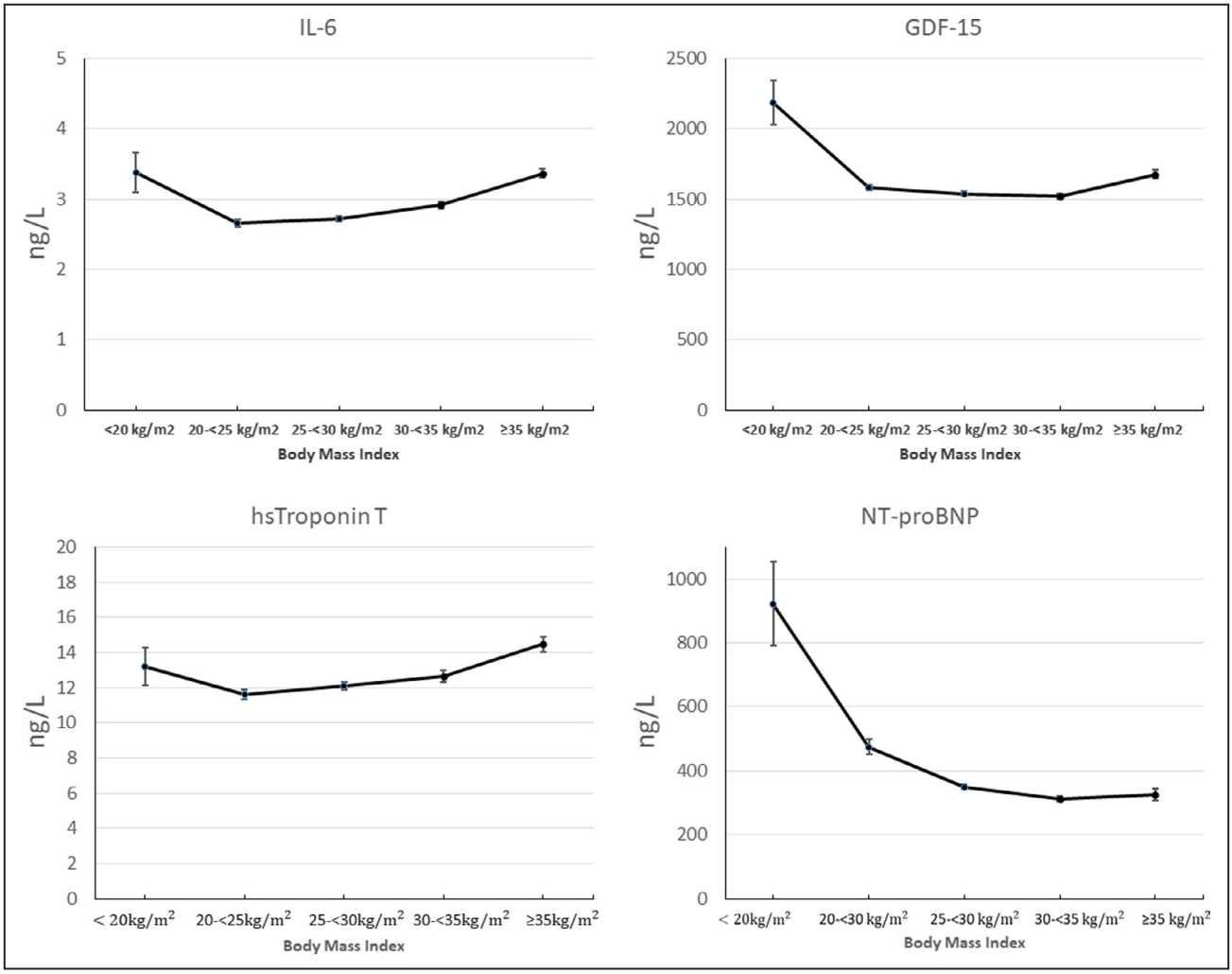


Figure 1. Levels of biomarkers (interleukin -6, GDF-15, Troponin T and NT-proBNP) in relation to categories of BMI.
BMI indicates body mass index; GDF-15, growth differentiation factor 15; hsTroponin T, high-sensitivity cardiac troponin T; IL-6, interleukin 6; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

with higher BMI categories. For patients with very high BMI (≥35 kg/m^2), the adjusted risk of heart failure hospitalization did not reach statistical significance (HR, 1.35; 95% CI, 0.98–1.87). The risk of the composite major adverse cardiovascular event (cardiovascular death, MI, and stroke) was not significantly associated

Table 2. Clinical Outcomes During Follow-up by BMI Category

Clinical outcome, n (%)	<20 kg/m^2 N=244	20 to <25 kg/m^2 N=3060	25 to <30 kg/m^2 N=6752	30 to <35 kg/m^2 N=3961	≥35 kg/m^2 N=1768	Total N=15 785	*P* value
MACE (cardiovascular death, MI and stroke)	34 (13.9)	298 (9.7)	658 (9.7)	386 (9.7)	205 (11.6)	1581 (10.0)	0.0375
All-cause death	37 (15.2)	242 (7.9)	465 (6.9)	260 (6.6)	146 (8.3)	1150 (7.3)	<0.0001
Cardiovascular death	24 (9.8)	157 (5.1)	287 (4.3)	171 (4.3)	90 (5.1)	729 (4.6)	0.0004
Hospitalization for heart failure	12 (4.9)	45 (1.5)	135 (2.0)	91 (2.3)	64 (3.6)	347 (2.2)	<0.0001
MI	11 (4.5)	127 (4.2)	310 (4.6)	210 (5.3)	105 (5.9)	763 (4.8)	0.0314
Major coronary event	32 (13.1)	273 (8.9)	635 (9.4)	405 (10.2)	200 (11.3)	1545 (9.8)	0.0153
Stroke	5 (2.0)	58 (1.9)	145 (2.1)	61 (1.5)	35 (2.0)	304 (1.9)	0.2935
Cancer during the study	11 (4.5)	189 (6.2)	491 (7.3)	272 (6.9)	143 (8.1)	1106 (7.0)	0.0478

BMI indicates body mass index; MACE, major cardiovascular event; and MI, myocardial infarction.
P value calculated for difference between groups.

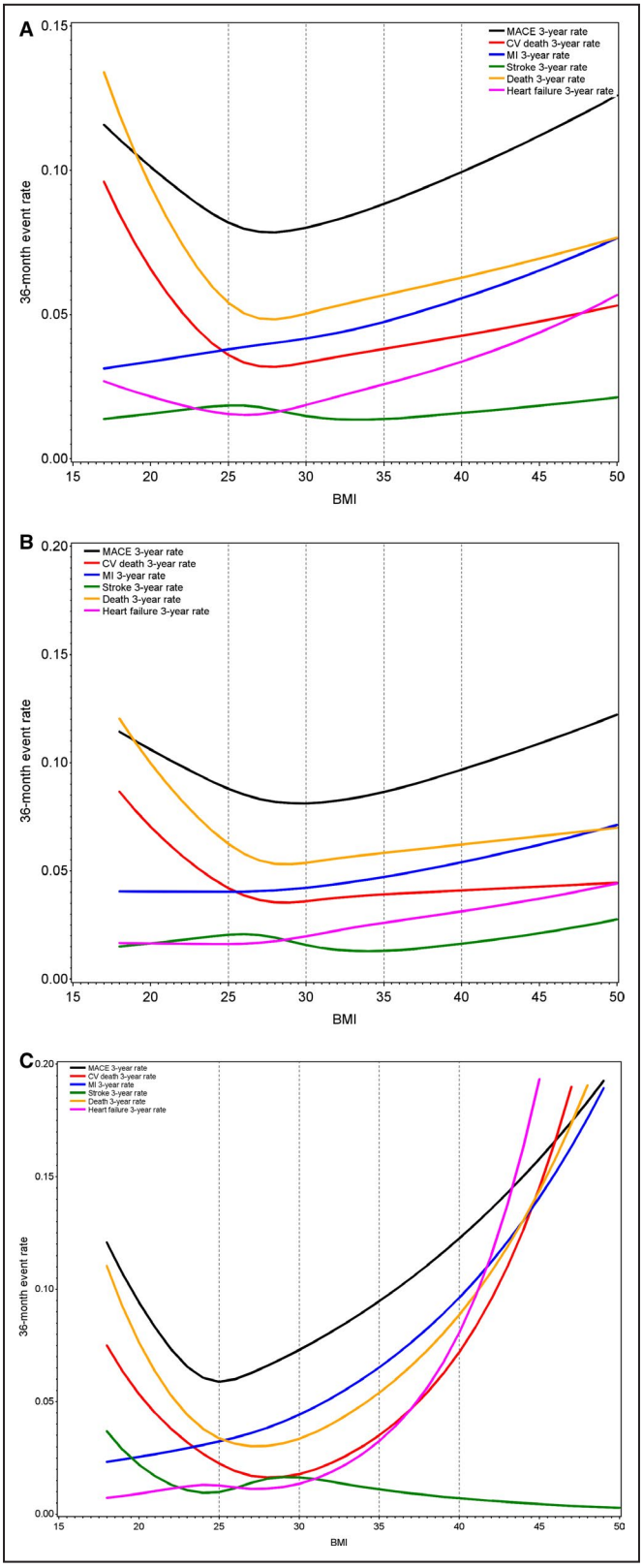
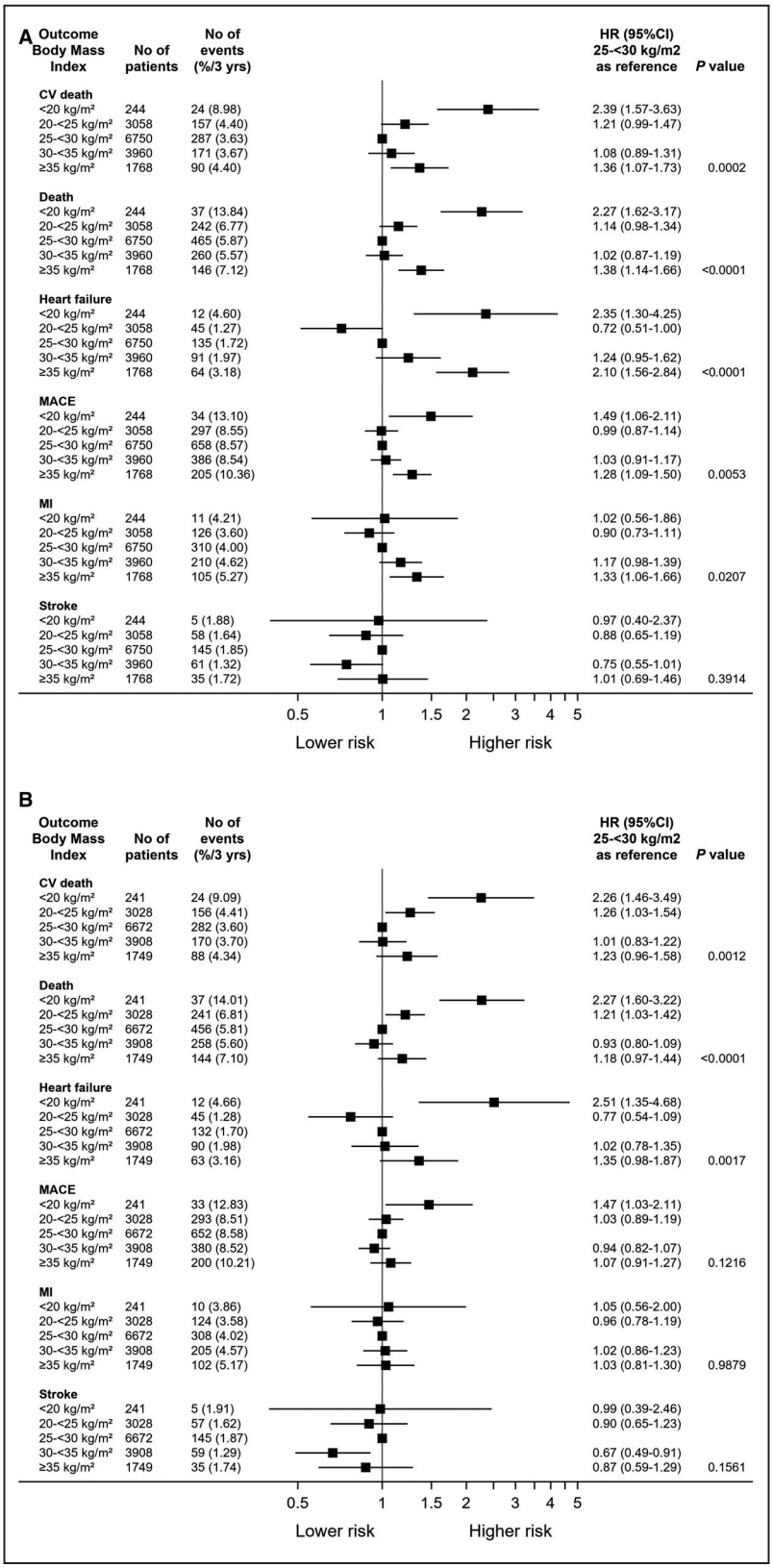


Figure 2. Spline plot shows rates of major cardiovascular event (MACE), cardiovascular (CV) death, myocardial infarction (MI), stroke, total death, hospitalization for heart failure by body mass index (BMI).
(**A**) Total population. (**B**) Non-Asian population. (**C**) Asian population.



(*P*=0.11) with BMI, indicating that the driver of major adverse cardiovascular events was mainly cardiovascular death both in the low and high ranges of BMI. For the risk of MI, there was no significant association with BMI. Consistently, there was no association with BMI with the risk of stroke.

Figure 3. The association of body mass index (BMI) with clinical outcomes.
(**A**) Basic adjustment model. (**B**) Fully adjusted. (**A**) BMI 25 < 30 kg/m^2 as reference. Adjusted for age, sex, and randomized treatment. *P* value denotes difference between groups. (**B**) BMI of 25 < 30 kg/m^2 as reference. Adjusted for age, sex, and randomized treatment, prior percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG), prior MI, renal dysfunction, polyvascular disease, diabetes, smoking, stroke/transient ischemic attack (TIA), congestive heart failure, systolic blood pressure, geographic region, chronic obstructive pulmonary disease (COPD), cancer diagnosis and Asian/Japanese origin. *P* value denotes difference between groups. CV indicates cardiovascular; MACE, major adverse cardiovascular event; and MI, myocardial infarction.

Subgroup and Sensitivity Analyses

Several prespecified subgroups, such as age, sex, diabetes, and type of MI were analyzed. Similar findings with a U-shaped curve were found also in these subgroups (data not shown). The curves were consistent with the main study results, and there was no significant interaction with age, sex, diabetes, or type of MI (type 1 versus types 2–5). A sensitivity analysis of patients after exclusion of patients with low BMI (<20 kg/m^2) showed consistent results with a U-shaped risk curve as with the main analysis. Figure 2A and 2B show that the association between BMI and outcomes were more pronounced in both the low and high end of BMI in the Asian subgroup and the risk curves among non-Asians were flatter in the higher end of BMI range. The HR and 95% CI are shown in Figure S1A and S1B.

DISCUSSION

In this contemporary study of patients with stable CHD, high levels of standard of care and a long-term follow-up of 3.7 years, we report the associations between BMI and clinical cardiovascular outcomes. The main findings from these analyses were that (1) almost 75% of the patients were overweight or obese and (2) the risk curve for cardiovascular death, total death, and hospitalization for heart failure was U-shaped, with the highest risk in the low and high ends of BMI. The lowest risk was observed in patients with a BMI of 27 kg/m^2. Of note, this is considered as overweight in most secondary prevention guidelines.[22] In contrast, for patients with underweight (<20 kg/m^2), the risk of cardiovascular and total death was more than doubled. In addition, we could not confirm the appearance of an overweight paradox in our study, with lower risk in the higher BMI levels, as has been shown for patients with other cardiovascular conditions.[5,7,23–25] Of note, international guidelines on prevention[22] recommend a target BMI of 20 to <25 kg/m^2. Our results do not provide firm support for this interval as being optimal, but suggests that a slightly higher BMI may be optimal with respect to risk of clinical outcomes. Although speculative, a slightly higher BMI than recommended might indicate greater reserves when developing CHD, which may be beneficial. The ideal BMI in terms of risk of cardiovascular events in patients with stable CHD cannot be established on the basis of our study. However, our data could be interpreted as maintaining a BMI in the range of what is considered as slightly overweight appears to be optimal for cardiovascular prognosis.

Of note, BMI was not associated with the risk of either MI or stroke, after multivariable adjustments, but rather to the risk of mortality and heart failure hospitalization. The reasons behind this lack of association are unknown and cannot be explained from this study. Our findings are corroborated by a recent study in patients with diabetes and prediabetes, in which similar associations were reported.[26] In contrast, in the INTERHEART study,[3] a cross-sectional case-control study, obesity assessed using BMI was associated with the risk of MI.

Many of the established risk markers for cardiovascular death were associated with increased BMI, as could be expected. In contrast, the levels of several biomarkers of special interest in terms of risk,[27] often related to mortality in other studies, such as interleukin-6, cystatin C, and GDF-15 showed a U-shaped association with BMI. However, NT-proBNP levels were highest in those with the lowest BMI and then increased, indicating that underlying explanations for the associations may differ in the low and high BMI range, respectively.

U-Shaped Curve Across Different Events

The U-shaped association between BMI and long-term risk of death and heart failure hospitalization is in contrast to others that have not confirmed such a relationship.[3,6] In a recent study[28] in elderly patients >80 years undergoing percutaneous coronary intervention, mortality was highest in the lowest BMI tertile in acute coronary syndromes, but this association was not confirmed in patients with stable CHD. Our study evaluated BMI with clinical outcomes, both as a continuous marker and based on clinically established categories, and clearly show an increased risk in patients with a BMI of 30 to <35 kg/m^2. We performed several subgroup analyses but could not confirm any interaction for either sex, age, diabetes, or type of MI. The results were consistent across all prespecified subgroups. We saw a different risk pattern when analyzing the Asian and non-Asian population separately. Asians have a different body composition and different risk levels of obesity for developing diabetes compared with other ethnicities. Other BMI cutoffs for obesity have thus been proposed by the World Health

Organization.[29] Applying the lower BMI cutoff values for overweight would lead to a higher proportion of Asians considered overweight in our study. The spline curves were clearly steeper and more pronounced in the Asian population in both the low and high end of BMI. In contrast, for non-Asians, the risk of death and heart failure hospitalization increased similarly in the low BMI region but increased only marginally in the high BMI categories.

Patients who are underweight and have very low BMI is an important group that deserves special focus. They often have comorbidities, such as current smoking, severe heart failure, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, or other severe diseases. Indeed, there were more smokers among the underweight group who also are at higher risk of smoking-related diseases such as chronic obstructive pulmonary disease. Thus, a possibility of collider bias may exist. Levels of NT-proBNP were higher in those who were underweight, indicating that heart failure with cachexia was more prevalent. Thus, a BMI of <20 kg/m^2 may be considered a proxy for other concomitant diseases and not seldom poor long-term prognosis. The results remained consistent despite adjustments for all known such factors, although hidden or unmeasured confounding may still partly explain some of the elevated risk in these patients. Our results stress the importance of a thorough diagnosing and treatment of patients who are underweight.

We chose to study the associations between BMI and clinical outcomes as a prespecified substudy. This information was easily available in this large global study. However, measures other than BMI may be considered more accurate, such as detailed measures of body composition, that is, waist-to-height ratio suggested by others[30] or truncal adiposity.[31] Also, biomarkers such as triglycerides to high-density lipoprotein-cholesterol ratio[32] and hypertriglyceridemic waist phenotype[33] has been suggested as a marker of increased atherosclerosis related risk. We also assessed waist circumference, which was strongly correlated with BMI and the associations to outcome were consistent with what was observed for BMI.

Limitations/Strengths

The strengths of the current study are that it is a large, prospective, randomized trial from 39 countries on a homogeneous cohort of patients with stable CHD with high-quality long-term follow-up of centrally adjudicated end points. There are some limitations. Despite the general recommendation to all patients to be physically active and reduce weight, our results are based on a single BMI baseline assessment, and we cannot provide data on variation over time, which has been shown by others to be associated with increased mortality and cardiovascular events.[34] However, patients were on a high standard of a modern secondary prevention regimen during follow-up including medication, smoking cessation, and advice on weight loss and regular physical exercise were provided. Despite performing multivariable adjustments in the analyses, unmeasured confounding cannot be fully excluded. Our results are observational and the associations are based on nonrandomized data. Results may thus not be used to claim any causal relationship. Since the follow-up time in this study was relatively short, the possibility of reverse causation cannot be excluded. Longer follow-up studies may be preferable[35] and more optimal, as has been shown in studies on a general population.

In conclusion, our study of a large prospective cohort of patients with stable CHD did not confirm an overweight paradox for cardiovascular clinical outcomes. After multivariable adjustments, the association between BMI and the risk of cardiovascular and total death as well as for hospitalization for heart failure had a U-shaped curve. Of note, the lowest risk was seen in patients with a BMI of around 27 kg/m^2, somewhat higher and in contrast to what is currently recommended in prevention guidelines. The highest risk was found among patients with very low BMI, indicating a specific high-risk group of note, as well as in patients with very high BMI. It is recommended to put special focus on these extreme groups to determine the underlying pathology and optimize treatment. Explanatory factors driving these differences may differ.

ARTICLE INFORMATION

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Supplemental Material

Figure S1

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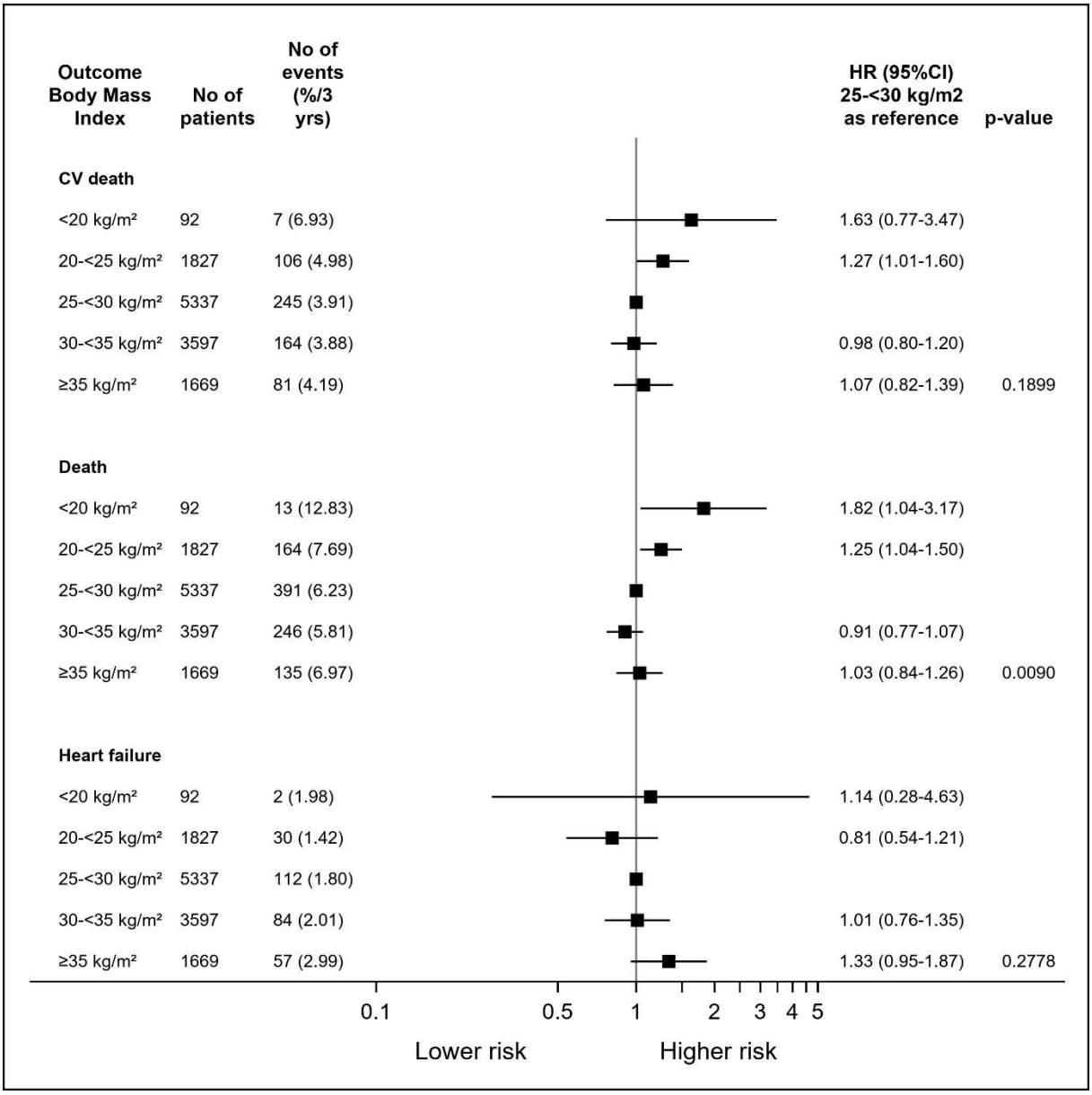
SUPPLEMENTAL MATERIAL

Figure S1A. The association of body mass index (BMI) with clinical outcomes (adjusted). Non-Asian population.



BMI 25<30 kg/m^2 as reference

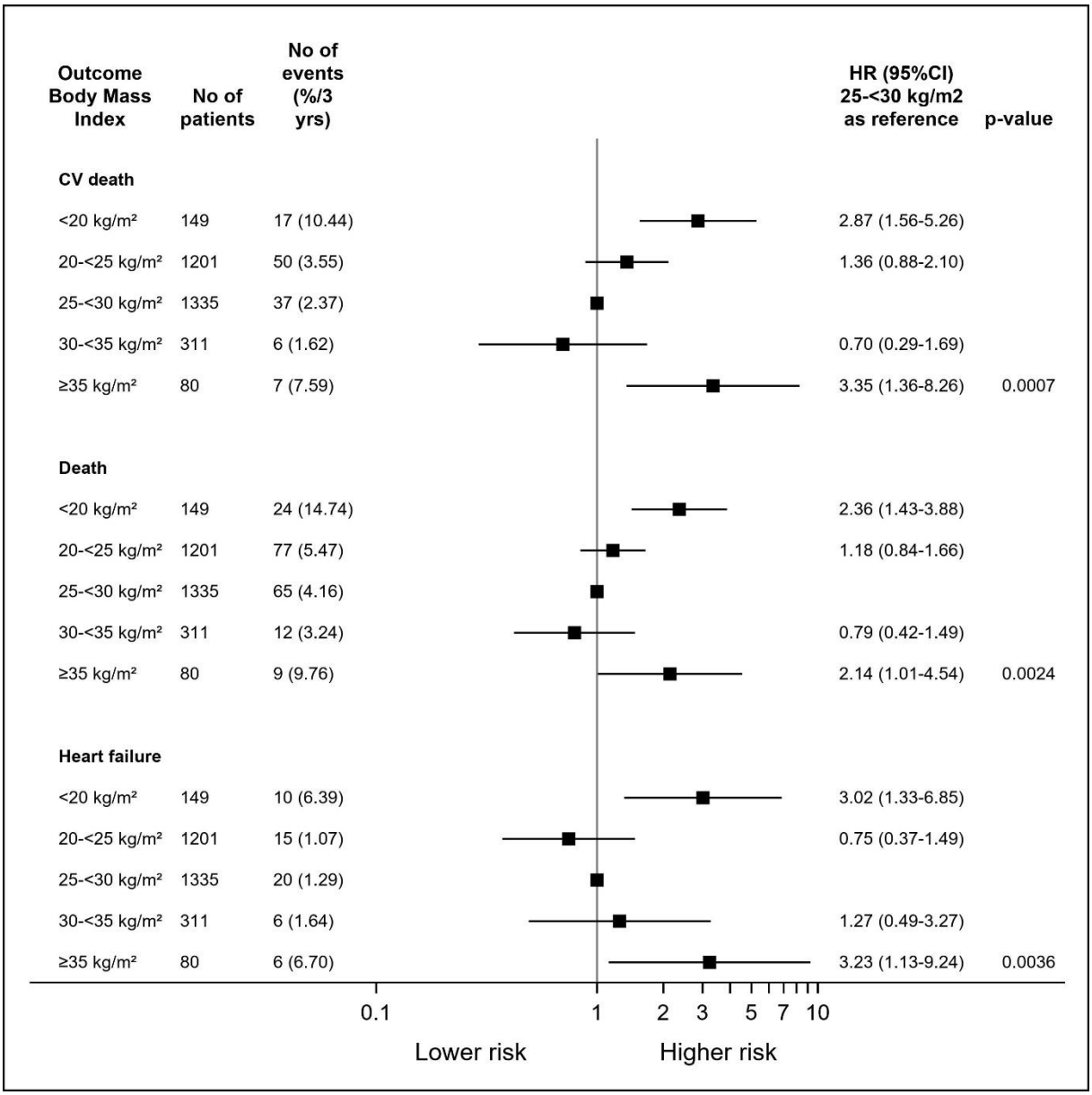
Adjusted for age, sex, randomized treatment, prior percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG), prior MI, renal dysfunction, polyvascular disease, diabetes, smoking, stroke/transient ischemic attack (TIA), congestive heart failure, systolic blood pressure, geographic region, chronic obstructive pulmonary disease (COPD), cancer diagnosis and Asian/Japanese origin.

P-value denotes difference between groups.

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Figure S1B. The association of body mass index (BMI) with clinical outcomes (adjusted).

Asian population.



BMI 25<30 kg/m^2 as reference

Adjusted for age, sex, randomized treatment, prior percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG), prior MI, renal dysfunction, polyvascular disease, diabetes, smoking, stroke/transient ischemic attack (TIA), congestive heart failure, systolic blood pressure, geographic region, chronic obstructive pulmonary disease (COPD), cancer diagnosis and Asian/Japanese origin.

P-value denotes difference between groups.

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.