学位論文

Validation of the obesity paradox by body mass index and waist circumference in patients undergoing percutaneous coronary intervention
（経皮的冠動脈インターベンションを受けた患者における BMI と腹囲による肥満パラドックスの検証）

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Original Articles

Validation of the Obesity Paradox by Body Mass Index and Waist Circumference in Patients Undergoing Percutaneous Coronary Intervention

Short title: Obesity paradox in CAD patients

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The authors confirm contribution to the paper as follows: study conception and design: Y. Shirahama, N. Tabata, K.Sakamoto, R. Sato, K. Yamanaga, K. Tsujita; data collection: S.

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Data Availability Statement:

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

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Abstract

BACKGROUND:

The paradoxical association of obesity with mortality, named the "obesity paradox", has been inconsistent, possibly due to a difference between body mass index (BMI) and central obesity, estimated by waist circumference (WC) as patterns of adiposity.

SUBJECTS/METHODS:

We enrolled 8 513 participants from the Kumamoto Intervention Conference Study, a multicenter registry that included consecutive patients undergoing percutaneous coronary intervention (PCI) at 18 centers between 2008 and 2017 in Japan. Patients were divided into quartiles in ascending order of the BMI or WC. The primary endpoints were all-cause mortality and cardiovascular death within a year.

RESULTS:

There were 186 deaths (case fatality rate, 22.1/1000 person-years) during the follow-up period. The lowest group (1st quartile) of BMI or WC had the worst prognosis among the quartiles (1st quartile, 4.2%; 2nd quartile, 1.9%; 3rd quartile, 1.5%; 4th quartile, 1.1%; $P < 0.001$ (χ^2) and 1st quartile, 4.1%; 2nd quartile, 2.3%; 3rd quartile, 1.2%; 4th quartile, 1.5%; $P < 0.001$ (χ^2), respectively). Similar results were obtained for cardiovascular death. In a multivariable analysis adjusted by nine conventional factors, the lowest group (1st quartile) of BMI (hazards ratio, 2.748; 95% confidence interval [CI], 1.712-4.411) and WC (hazards ratio, 2.340; 95% CI, 1.525-3.589) were independent prognostic factors for all-cause mortality. By dividing the participants into two groups according to either the BMI or WC based on the National Cholesterol Education Program Adult Treatment Panel III and World Health Organization classification, the highest mortality was observed in the lower group. However, the C-statistic after adding BMI (quartile) to conventional factors was found to be slightly higher than BMI (two categories) and WC (two categories) (0.735 vs. 0.734).

CONCLUSIONS:

The obesity paradox was observed in patients after PCI, and single-use of BMI (or WC) was sufficient to predict the prognosis of patients after PCI.

Introduction

Obesity is a growing public health problem, and its prevalence is increasing worldwide [1]. In Asian countries, as well as Western countries, obesity has increased over the last few decades as a result of the Westernization of lifestyles [2]. Obesity is associated with cardiovascular risk in the general population, whether defined by body mass index (BMI) or waist circumference (WC) [3,4]. However, a counterintuitive association between obesity and mortality, termed the “obesity paradox”, was reported previously [5]. Although the protective effects of obesity have been reported in coronary artery disease (CAD) patients, evidence for an obesity paradox in past studies has been less consistent. BMI is a popular measure of body fat, and most previous studies have focused on BMI to investigate the “obesity paradox”. However, WC may more accurately reflect visceral adiposity than BMI [6], and a previous study thus supported the use of WC in addition to BMI in assessing the risk of death [7].

We hypothesized that the inconsistency of the “obesity paradox” may be due, in part, to a difference between BMI and central obesity, estimated by WC, as patterns of adiposity. Thus, we aimed to investigate the additive impact of WC on BMI on clinical outcome in CAD patients.

Materials/Subjects and Methods

Study population

This was a multicenter observational cohort study. Details of the Kumamoto Intervention Conference Study registry have been previously described [8]. From August 2008 to March 2017, 18 495 consecutive participants were enrolled, and the exclusion criteria were as follows: (1) no data on the BMI or WC (n = 9452) and (2) unidentified prognosis within a 1-year follow-up (n = 530). We enrolled 8 513 participants with complete WC and BMI data to examine the impact of obesity. Each institutional ethics committee approved the study, and informed consent was obtained from all participants. This study complied with the Declaration of Helsinki.

Clinical parameters

Height, body weight, and WC were measured at the initial referral. WC was measured at the midpoint between the lowest rib and the iliac crest. Patients were divided into quartiles in ascending order of the BMI or WC. Other clinical parameters have been previously described [8]. In brief, diabetes was defined as any fasting plasma glucose concentration of ≥ 126 mg/dL or a plasma glucose concentration of ≥ 200 mg/dL after 2 h from the oral glucose tolerance test or diabetes treatment. The definition of hypertension was a blood pressure of ≥ 140/90 mmHg or hypertension treatment. Dyslipidemia was defined as low-density lipoprotein of ≥ 140 mg/dL (≥ 3.63 mmol/L), high-density lipoprotein < 40

mg/dL (<1.04 mmol/L), triglycerides ≥150 mg/dL (≥1.7 mmol/L), or the use of lipid-lowering therapy. The smoking history was determined through an interview. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of < 60 mL/min per 1.73 m^2. Peripheral arterial disease was defined as an ankle-brachial index value of < 0.9 in either leg or a history of the treatment of peripheral vascular disease. Acute coronary syndrome (ACS) was defined as ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina pectoris.

Clinical endpoints

The primary endpoints were 1) all-cause mortality and 2) cardiovascular death within 1 year; it is reported that patients at risk of atherothrombosis may have cardiac events within a year [9]. After the interventional procedure, each institution prospectively followed up with the patients, and events were reported based on medical records and confirmed by direct contact with the patients and/or their families. Cardiovascular death was defined as death due to myocardial infarction, congestive heart failure, or documented sudden cardiac death.

Statistical analysis

Continuous variables with a normal distribution are expressed as the mean ± standard deviation, and categorical data are presented as numbers (proportions). Fisher's exact test and the chi-square test

were used to test differences between the four groups for categorical variables. Analysis of variance was used to analyze the differences in continuous variables between the four groups. The Kaplan–Meier method and log-rank test were used to estimate the event probabilities at 365 days and compare survival times, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the clinical outcome were calculated using Cox proportional hazards analysis, forced inclusion methods were used for multivariable analyses, and conventional risk factors such as age, sex, diabetes, current smoking, CKD, peripheral arterial disease, old myocardial infarction, ACS, and heart failure (nine prognostic factors) were the variables used. The incremental effects of adding BMI or WC to the prognostic factors were evaluated using continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [10]. A C-statistic of > 0.7 was considered an acceptable discriminatory power, > 0.8 excellent, and > 0.9 outstanding. The improvement in the C-statistic for a model containing a new marker is defined simply; however, this increase is often very small in magnitude. Therefore, improvements in the C-statistic, IDI, and NRI were evaluated in the present study. C-statistics were calculated using the pROC package in R. NRI and IDI were computed using the PredictABEL package. A P-value of < 0.05 was considered to denote statistical significance. All statistical tests were two-sided. Statistical analyses were performed using IBM SPSS Statistics for Mac, Version 26 (IBM Corp., Armonk, NY, USA) and R, version 2.7.0 (Toukei Kagaku Kenkyujo Co. Ltd., Japan).

Results

Clinical characteristics

A total of 8 513 patients who underwent PCI were enrolled in the present study (Figure 1). The median age of the patients was 71.0 (interquartile range: 63.0-78.0) years, and 27% were females. The distributions of the BMI and WC of the patients are shown in Figure 2. The median BMI was 23.9 [21.8-26.1] kg/m^2 (Figure 2A), and the median WC was 87.0 [82.0-93.0] cm for males and 85.0 [77.5-92.9] cm for females (Figure 2B). The baseline characteristics of the cohort stratified by the BMI and WC are summarized in Tables 1A and 1B, respectively. The BMI and WC cohorts shared similar clinical findings, and in both cohorts, the lowest group (1st quartile) was associated with a higher age; lower proportions of diabetes, hypertension, dyslipidemia, current smoking, previous myocardial infarction, and prior PCI; and higher rates of CKD (including the need for hemodialysis) and ACS.

Primary endpoints at the follow-up

Overall, 186 deaths were recorded during the follow-up period, and the case fatality rate was 22.1/1000 person-years. The causes of death among the four groups are shown in Table 2. The lowest group (1st quartile) of BMI had the highest mortality (4.2%) compared with the other three categories (Figure 3A, upper left; 2nd quartile, 1.9%; 3rd quartile, 1.5%; or 4th quartile, 1.1%) ($P < 0.001$ (χ^2)). The lowest

group (1st quartile) of BMI also had the highest rate of cardiovascular death (1.3%) (Figure 3A, upper right; 2nd quartile, 0.7%; 3rd quartile, 0.6%; or 4th quartile, 0.5%) (P = 0.016 (χ^2)). We performed Kaplan–Meier analysis and observed that there was a significant difference in all-cause mortality among the four categories (Figure 3A, lower left; log-rank P < 0.001). The difference was also statistically significant for cardiovascular death (Figure 3A, lower right; log-rank P = 0.015). Similar results were obtained for WC; however, the relationship between mortality, cardiovascular death, and WC appeared to be reverse J-shaped; the mortality rate was the lowest in the 3rd quartile (Figure 3B). Moreover, we examined all-cause mortality (Supplemental Figures 1A and 1C) and cardiovascular death (Supplemental Figures 1B and 1D) within 1-month and from 1-month to 1-year. In terms of the BMI and WC, the lowest group was significantly associated with all-cause mortality and cardiovascular death from 1-month to 1-year (Supplemental Figures 2A to 2D).

Cox proportional hazards analysis

The results of the univariable and multivariable Cox proportional hazards analyses for all-cause mortality are summarized in Table 3. In the multivariable analysis adjusted by nine prognostic factors, the lowest group (1st quartile) of BMI and WC were independently associated with 1-year mortality (Table 3; HR, 2.748; 95% CI, 1.712-4.411; P < 0.001 and HR, 2.340; 95% CI, 1.525-3.589; P < 0.001, respectively). Even after including BMI and WC as continuous variables, BMI (HR, 0.851; 95% CI,

192 0.811-0.893; P < 0.001) and WC (HR, 0.956; 95% CI, 0.941-0.971; P < 0.001) were independent
193 prognostic factors for all-cause mortality. Neither the BMI nor the WC quartiles were associated with
194 cardiovascular death in the multivariable analyses (data not shown).
195
196 ***C-statistic for regression models, continuous NRI, and IDI***
197 C-statistic values were calculated for all-cause mortality within the 1-year follow-up. The C-statistic
198 of the variables, including nine prognostic factors, was 0.719 (95% CI, 0.680-0.758) vs. 0.735 (95%
199 CI, 0.696-0.774) after including the BMI quartile; the continuous NRI and IDI were 0.294 (0.151-
200 0.438; P < 0.001) and 0.0055 (0.0003-0.0078; P < 0.001), respectively (Table 4). The C-statistic
201 increased from 0.735 to 0.739 by adding the WC quartile to these factors; the continuous NRI and
202 IDI were 0.358 (0.218-0.499; P < 0.001) and 0.001 (-0.001-0.0022; P = 0.076), respectively (Table
203 4). The receiver operating characteristic curve is shown in Supplemental Figure 2.
204
205 ***BMI/WC in two categories divided by National Cholesterol Education Program Adult Treatment***
206 ***Panel III and World Health Organization classification***
207 Patients were supplementarily divided by the modified National Cholesterol Education Program Adult
208 Treatment Panel III criteria with ethnic-specific values and the World Health Organization
209 classification for the general definition of obesity. Patients with a BMI of ≥ 25 kg/m^2 were defined as

having an obese BMI, and those with a WC of ≥ 85 cm for men or ≥ 90 cm for women were defined as having an obese WC.

The clinical parameters of the two groups are shown in Supplemental Tables 1A and 1B. Similar to previous results (Tables 1A and 1B), the higher group was associated with younger age; higher proportions of males and participants with diabetes, hypertension, dyslipidemia, current smoking, and prior PCI; and lower rates of CKD (including the need for hemodialysis) and ACS.

We performed a Kaplan–Meier analysis among the two categories of BMI or WC, and as a result, non-obese BMI and non-obese WC showed the highest mortality (Supplemental Figures 3A and 3B upper left; 2.6% vs. 1.4%; $P < 0.001$ and 3.0% vs. 1.4%; $P < 0.001$, respectively).

The C-statistic of the nine prognostic factors + the BMI value was 0.724 (95% CI, 0.685-0.764) and continuous NRI and IDI were 0.277 (0.154-0.400; $P < 0.001$) and 0.0013 (0.0003-0.0023; $P = 0.010$), respectively (Supplemental Table 2). The C-statistic increased from 0.724 to 0.734 by adding the WC value to these factors; the continuous NRI and IDI were 0.402 (0.265-0.539; $P < 0.001$) and 0.0028 (0.001-0.0047; $P = 0.002$), respectively (Supplemental Table 2).

Discussion

The main findings of this study were as follows: (1) the lowest BMI or WC groups were associated with worse outcomes, and 1st quartiles of BMI and WC were independent prognostic factors of all-cause mortality by the multivariable analyses; (2) significant predictive model improvements by significant NRI were observed after adding the BMI and then the WC quartiles to the model of conventional factors; (3) significant IDI was also observed after adding the BMI quartile to the model of conventional factors but not after adding the WC quartile to the model of conventional factors and the BMI quartile; (4) similar results were obtained by dividing the participants into two groups according to BMI or WC by the National Cholesterol Education Program Adult Treatment Panel III criteria and the World Health Organization classification, and the highest mortality was observed in the lower group; (5) the C-statistic after adding BMI (quartile) to the conventional factors was found to be slightly better than the BMI (two categories) and WC (two categories) (0.735 vs. 0.734).

Effect of BMI and WC in the obesity paradox

BMI is the most popular criterion of obesity and is associated with total body fat [11,12], and there have been many reports of the “obesity paradox” using the BMI of patients with coronary artery

243 disease (CAD) [13]. However, BMI is just a surrogate measure of body fat, and the validity of the
244 “obesity paradox” using BMI has been called into question [14] because BMI does not distinguish
245 between lean and fat mass. Abdominal obesity has been reported to be significantly different in any
246 BMI category [15]. Gaining lean body mass is generally a "health index" and predictor of better
247 outcomes in humans without cardiovascular disease.
248 WC, which is the perimeter of the abdomen, is an alternative index of obesity that may be more
249 specific for visceral fat. A paradoxical link between obesity defined by WC and favorable prognosis
250 has also been demonstrated in patients with heart failure [16, 17] and atrial fibrillation [18].
251 Furthermore, Ono et al. enrolled 1 799 patients with left main CAD or three-vessel disease and
252 reported that body composition should be assessed by BMI and WC in the appropriate evaluation of
253 the long-term risk of obesity [19].
254 The present study included 8 513 patients, and we believe this is the largest study to verify the
255 “obesity paradox” in patients with CAD requiring PCI using the BMI or WC, and our results suggest
256 that higher WC is correlated with better outcomes in patients with CAD. As previously reported, this
257 study showed that the “obesity paradox” in patients with CAD could apply to the WC. Although WC
258 is a better indicator of central obesity, it is still a proxy of obesity, and as such, it can also be
259 subjected to biases since it appears that the relative proportion of lean vs. fat mass appears to be the
260 causative factor behind this “paradoxical protective effect of obesity.”

In contrast to previous work, in the present study, the participants were divided into quartiles according to their BMI and WC, and it was found that patients in the lowest group of BMI and WC had the worst prognosis following PCI. It can be stated that this study confirms that other anthropometric indices such as the WC provide evidence supporting the idea that after acute and chronic atherothrombotic and cardiovascular diseases, it appears that some body mass is necessary to face the challenges of survival. However, mortality and cardiovascular death were linear in terms of the BMI but reverse J-shaped in terms of the WC. This indicates that excessive visceral fat might increase mortality, suggesting that the paradoxical effect of obesity is not incremental.

Moreover, it was found that adding the BMI quartile improved prognosis prediction with significant NRI and IDI; however, after adding the WC quartile, the increase in C-statistics was very small (from 0.735 to 0.739), and its IDI was not significant (P = 0.076) (Table 4). In addition, the C-statistic of the nine prognostic factors + BMI (two categories) + WC (two categories) was 0.734, whereas the C-statistic of the nine prognostic factors + BMI (quartile) was 0.735 (Table 4 and Supplemental Table 2). This indicates that the addition of BMI (quartile) is only slightly better than the addition of BMI (two categories) and WC (two categories) for prognosis prediction after PCI. Therefore, for prognosis prediction after PCI, measurement of BMI or WC may be sufficient (measurements of both BMI and WC are not always necessary).

Possible explanations for the protective effect of obesity

Several reports have addressed the mechanisms of the "obesity paradox:" (1) plasma lipoproteins decrease inflammatory cytokines [20]; (2) people with obesity have more energy than people without obesity to move their bodies due to their increased weight, and myocardial ischemic symptoms tend to occur earlier [21]; (3) antithrombotic and/or antiplatelet drugs increase the risk of adverse events at extremely low body weights, resulting in increased bleeding events in the non-obesity group [22]; (4) anatomical differences might contribute to the benefit of people with obesity, as petite patients usually have smaller coronary arteries and might suffer from an increased risk of stent thrombosis after PCI [23]. Therefore, lean body mass might explain why people without obesity have increased mortality and why overweight patients have better outcomes [24]. In contrast to visceral (abdominal) fat, abdominal subcutaneous fat accumulation results in beneficial systemic metabolism and cardiovascular protective effects [25].

In the present study, we additionally investigated all-cause mortality and cardiovascular death within 1 month and from 1 month to 1 year. We found that the difference in the survival rate among the four groups became clear after 1 month (Supplemental Figure 1). Therefore, it could be said that obesity is involved in long-term survival, and is not a problem during the PCI perioperative period. It is possible that advances in PCI devices and techniques have brought about this result, and the number of cardiovascular deaths reported in the present study in 1-year were as few as 64.

297 The underweight group had a higher rate of cardiovascular death (Figure 3); however, many non-
298 cardiovascular events also caused death. One possible explanation is that people without obesity
299 may be frail and cachexic and may suffer from non-cardiac diseases such as cancer, sepsis, and
300 hemorrhagic events. In fact, when we investigated the cause of death, we found that the lowest group
301 tended to die from various causes such as sepsis, bleeding, cancer, and multiple organ failure (Table
302 2). For such patients, a reduction to 2.5 mg may be considered for low doses of prasugrel to reduce
303 bleeding events.
304
305 ***Study limitations***
306 The present study has several limitations. First, we enrolled only Japanese patients, and our results
307 may not be generalizable worldwide. Second, 9 982 patients (54%) were excluded from the study
308 due to the lack of BMI, WC, and follow-up data within 1 year. Comparing the excluded and
309 analyzed cohorts, there were significant differences in sex; age; weight; height; BMI; WC;
310 hypertension; dyslipidemia; smoking; CKD; old myocardial infarction; ACS; and the rate of use of
311 aspirin, clopidogrel, cilostazol, ticlopidine, and sarpogrelate. Therefore, selection bias may have
312 occurred. Third, WC and BMI were assessed at one point; however, the degree of obesity and loss of
313 muscle mass may represent the progression of chronic disease. In addition, the lowest BMI or WC
314 group may include poorly nourished patients and those with cancer history; however, the present

study is based on a multicenter registry, and the present data lacked nutritional indicators (such as albumin and lymphocyte counts) and cancer details. Moreover, we did not directly quantify or measure fat mass, such as with dual-energy X-ray absorptiometry or computed tomography. In addition, there were no data on cytokines or adipokines. In addition, WC is one of the most difficult anthropometric measures in terms of consistency between evaluators, and since this is a multicenter study, we cannot discard the possibility that variations in measurements across institutions might introduce some bias into the statistical analyses. In addition, the fact that neither BMI quartile nor WC quartile was associated with cardiovascular death in the multivariable analyses suggests that there may be some biases in this dataset.

Conclusion

The obesity paradox was observed in patients after PCI, and single-use of BMI (or WC) was sufficient to predict the prognosis of patients after PCI, lending further support to the paradoxical effect of obesity.

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Figure legends

Figure 1. Study flow chart.

From August 2008 to March 2017, 18 495 consecutive participants were recorded in this registry, and we excluded patients without the BMI or WC data and those with unidentified prognoses during the 1-year follow-up. As a result, 8 513 patients who underwent PCI were included in this study. Patients were divided into quartiles in ascending order of the BMI or WC.

BMI, body mass index; WC, waist circumference; PCI, percutaneous coronary intervention

Figure 2. Histogram of BMI (A) and WC (B) in all patients.

The median BMI was 23.9 [21.8-26.1] kg/m^2, and the median WC was 87.0 [82.0-93.0] cm for males and 85.0 [77.5-92.9] cm for females.

BMI, body mass index; WC, waist circumference

Figure 3. Event rates among the four groups according to the BMI (A) and WC (B) in the quartile.

The survival rate was examined using the BMI and WC in the quartile, respectively. The lowest group (1st quartile) of BMI had the highest mortality (4.2%) compared with the three other categories (Figure 3A, upper left; 2nd quartile, 1.9%; 3rd quartile, 1.5%; or 4th quartile, 1.1%) ($P < 0.001(\chi^2)$). The lowest

group (1st quartile) of BMI also had the highest rate of cardiovascular death (1.3%) (Figure 3A, upper right; 2nd quartile, 0.7%; 3rd quartile, 0.6%; or 4th quartile, 0.5%) (P = 0.016(χ^2)). We performed Kaplan–Meier analysis and observed that there was a significant difference in all-cause mortality among the four categories (Figure 3A, lower left; log-rank P < 0.001). The difference was also statistically significant for cardiovascular death (Figure 3A, lower right; log-rank P = 0.015). Similar results were obtained for WC (Figure 3B).

BMI, body mass index; WC, waist circumference

Table 1A. Baseline Characteristics Stratified by Body Mass Index in Quartile

	1st quartile BMI<21.84 (n = 2136)	2nd quartile 21.84≦BMI<23.94 (n = 2114)	3rd quartile 23.94≦BMI<26.10 (n = 2135)	4th quartile 26.10≦BMI (n = 2128)	*P value*
Age in years (median)	75.0 (67.0 – 81.0)	72.0 (64.0 – 79.0)	70.0 (62.0 – 77.0)	67.0 (59.0 – 75.0)	<0.001
Female, n (%)	741 (34.7)	524 (24.8)	482 (22.6)	506 (23.8)	<0.001
Height (cm)	158.0 ± 9.6	160.0 ± 9.0	160.9 ± 9.0	161.2 ± 9.5	<0.001
Weight (kg)	50.2 ± 7.5	58.9 ± 6.8	64.7 ± 7.3	74.7 ± 10.9	<0.001
BMI (kg/㎠)	20.0 ± 1.5	22.9 ± 0.6	24.9 ± 0.6	28.7 ± 2.6	<0.001
Waist Circumference (cm)	77.7 ± 7.1	84.3 ± 5.9	88.9 ± 6.0	96.7 ± 8.4	<0.001
eGFR mL/min/1.73 m^2	59.1 ± 25.6	61.1 ± 22.3	63.8 ± 21.7	64.1 ± 23.7	<0.001
HbA1c (%)	6.2 ± 1.2	6.3 ± 1.1	6.4 ± 1.2	6.7 ± 2.7	<0.001
Diabetes, n (%)	778 (36.4)	809 (38.3)	906 (42.4)	1076 (50.6)	<0.001
Hypertension, n (%)	1587 (74.3)	1658 (78.4)	1703 (79.8)	1805 (84.8)	<0.001
Dyslipidaemia, n (%)	1158 (54.2)	1332 (63.0)	1467 (68.7)	1565 (73.5)	<0.001
Smoking, n (%)	424 (19.9)	438 (20.7)	479 (22.4)	530 (24.9)	0.003
CKD, n (%)	1002 (46.9)	937 (44.3)	857 (40.1)	851 (40.0)	<0.001
On HD, n (%)	172 (8.1)	100 (4.7)	71 (3.3)	69 (3.2)	<0.001
Prior MI, n (%)	340 (15.9)	397 (18.8)	383 (17.9)	418 (19.6)	0.040
Prior PCI, n (%)	476 (22.3)	556 (26.3)	583 (27.3)	600 (28.2)	<0.001
Prior CABG, n (%)	95 (4.4)	90 (4.3)	84 (3.9)	94 (4.4)	0.811
Composite of PAD, n (%)	224 (10.5)	166 (7.9)	164 (7.7)	132 (6.2)	<0.001
ACS, n (%)	987 (46.2)	964 (45.6)	870 (40.7)	876 (41.2)	<0.001
DES, n (%)	1589 (74.4)	1585 (75.0)	1599 (74.9)	1606 (75.5)	0.882
Anti thrombotic agents after PCI					

Aspirin, n (%)	2120 (99.3)	2088 (98.8)	2115 (99.1)	2108 (99.1)	0.560
Clopidogrel, n (%)	1541 (72.1)	1517 (71.8)	1519 (71.1)	1499 (70.4)	0.489
Prasugrel, n (%)	285 (13.3)	267 (12.6)	279 (13.1)	292 (13.7)	0.539
Cilostazol, n (%)	49 (2.3)	54 (2.6)	48 (2.2)	44 (2.1)	0.694
Ticlopidine, n (%)	268 (12.5)	285 (13.5)	286 (13.4)	294 (13.8)	0.709
Sarpogrelate, n (%)	13 (0.6)	16 (0.8)	17 (0.8)	17 (0.8)	0.713
DOAC, n (%)	62 (2.9)	46 (2.2)	55 (2.6)	48 (2.3)	0.453
Warfarin, n (%)	182 (8.5)	150 (7.1)	141 (6.6)	151 (7.1)	0.339

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; HD, haemodialysis; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass; PAD, peripheral arterial disease; ACS, acute coronary syndrome; DES, drug-eluting stent; DOAC, direct oral anticoagulants

Table 1B. Baseline Characteristics Stratified by Waist Circumference in Quartile

	1st quartile WC<80 cm (n = 1792)	2nd quartile 80 cm≦WC<87cm (n = 2438)	3rd quartile 87cm≦WC<93cm (n = 2066)	4th quartile 93 cm≦WC (n = 2217)	*P value*
Age in years (median)	75.0 (66.0 – 81.0)	72.0 (64.0 – 79.0)	70.0 (62.0 – 77.0)	68.0 (60.0 – 76.0)	<0.001
Female, n (%)	710 (39.6)	600 (24.6)	435 (21.1)	508 (22.9)	0.017
Height (cm)	156.0 ± 9.3	159.4 ± 8.8	161.3 ± 8.7	162.7 ± 9.3	<0.001
Weight (kg)	50.6 ± 8.4	58.6 ± 7.8	64.4 ± 8.4	73.3 ± 11.6	<0.001
BMI (kg/㎡)	20.7 ± 2.5	23.0 ± 2.1	24.7 ± 2.2	27.6 ± 3.2	<0.001
Waist Circumference (cm)	73.9 ± 4.7	83.2 ± 2.1	89.5 ± 1.7	99.0 ± 6.1	<0.001
eGFR mL/min/1.73 m^2	59.3 ± 25.2	62.5 ± 22.3	63.5 ± 22.2	62.4 ± 24.2	<0.001
HbA1c (%)	6.2 ± 1.1	6.3 ± 1.1	6.5 ± 2.7	6.6 ± 1.3	<0.001
Diabetes, n (%)	599 (33.4)	924 (37.9)	910 (44.0)	1136 (51.2)	<0.001
Hypertension, n (%)	1339 (74.7)	1889 (77.5)	1664 (80.5)	1861 (83.9)	<0.001
Dyslipidaemia, n (%)	981 (54.7)	1513 (62.1)	1406 (68.1)	1622 (73.2)	<0.001
Smoking, n (%)	322 (18.0)	514 (21.1)	477 (23.1)	558 (25.2)	0.001
CKD, n (%)	835 (46.6)	1029 (42.2)	838 (40.6)	945 (42.6)	0.004
On HD, n (%)	143 (8.0)	102 (4.2)	72 (3.5)	95 (4.3)	<0.001
Prior MI, n (%)	279 (15.6)	437 (17.9)	366 (17.7)	456 (20.6)	0.004
Prior PCI, n (%)	418 (23.3)	619 (25.4)	545 (26.4)	633 (28.6)	0.006
Prior CABG, n (%)	76 (4.2)	120 (4.9)	79 (3.8)	88 (4.0)	0.302
Composite of PAD, n (%)	169 (9.4)	193 (7.9)	151 (7.3)	173 (7.8)	0.071
ACS, n (%)	804 (44.9)	1093 (44.8)	884 (42.8)	916 (41.3)	0.050
DES, n (%)	1364 (76.1)	1814 (74.4)	1505 (72.8)	1696 (76.5)	0.025
Anti thrombotic agents after PCI					

Aspirin, n (%)	1780 (99.3)	2405 (98.6)	2049 (99.2)	2197 (99.1)	0.308
Clopidogrel, n (%)	1279 (71.4)	1753 (71.9)	1489 (72.1)	1555 (70.1)	0.837
Prasugrel, n (%)	243 (13.6)	299 (12.3)	262 (12.7)	319 (14.4)	0.002
Cilostazol, n (%)	27 (1.5)	63 (2.6)	53 (2.6)	52 (2.3)	0.141
Ticlopidine, n (%)	241 (13.4)	325 (13.3)	269 (13.0)	298 (13.4)	0.580
Sarpogrelate, n (%)	10 (0.6)	18 (0.7)	18 (0.9)	17 (0.8)	0.726
DOAC, n (%)	44 (2.5)	55 (2.3)	57 (2.8)	55 (2.5)	0.010
Warfarin, n (%)	129 (7.2)	180 (7.4)	145 (7.0)	170 (7.7)	0.785

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; HD, haemodialysis; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass; PAD, peripheral arterial disease; ACS, acute coronary syndrome; DES, drug-eluting stent; DOAC, direct oral anticoagulants

Table 2A. Cause of Death for the quartile on BMI

	1st quartile (n = 2136)	2nd quartile (n = 2114)	3rd quartile (n = 2135)	4th quartile (n = 2128)
Cardiac, n (%)	27 (1.3)	14 (0.7)	12 (0.6)	11 (0.5)
Stroke, n (%)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)
Sepsis, n (%)	18 (0.8)	6 (0.3)	1 (0.0)	2 (0.1)
Bleeding, n (%)	10 (0.5)	3 (0.1)	8 (0.4)	1 (0.0)
Cancer, n (%)	12 (0.6)	7 (0.3)	4 (0.2)	5 (0.2)
MOF, n (%)	9 (0.4)	2 (0.1)	3 (0.2)	0 (0.0)
Sepsis, n (%)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Renal failure, n (%)	4 (0.2)	1 (0.0)	0 (0.0)	0 (0.0)
DIC, n (%)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NOMI, n (%)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Unknown, n (%)	3 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Others, n (%)	13 (0.6)	7 (0.3)	5 (0.2)	4 (0.2)
Total	89 (4.2)	40 (1.9)	33 (1.5)	24 (1.1)

Abbreviations: MOF, multiple organ failure; DIC, disseminated intravascular coagulation; NOMI, non-occlusive mesenteric ischemia

Table 2B. Cause of Death for the quartile on WC

	1st quartile (n = 1792)	2nd quartile (n = 2438)	3rd quartile (n = 2066)	4th quartile (n = 2217)
Cardiac, n (%)	21 (1.2)	21 (0.9)	8 (0.4)	14 (0.6)
Stroke, n (%)	1 (0.1)	0 (0)	0 (0.0)	1 (0.0)
Sepsis, n (%)	16 (0.9)	7 (0.3)	1 (0.0)	3 (0.1)
Bleeding, n (%)	7 (0.4)	8 (0.3)	5 (0.2)	2 (0.1)
Cancer, n (%)	10 (0.6)	9 (0.4)	4 (0.2)	5 (0.2)
MOF, n (%)	8 (0.4)	1 (0.0)	5 (0.2)	0 (0.0)
Sepsis, n (%)	1 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Renal failure, n (%)	3 (0.2)	1 (0.0)	1 (0.0)	0 (0.0)
DIC, n (%)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
NOMI, n (%)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Unknown, n (%)	3 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Others, n (%)	10 (0.6)	9 (0.4)	2 (0.1)	8 (0.4)
Total	73 (4.1)	55 (2.3)	25 (1.2)	33 (1.5)

Abbreviations: MOF, multiple organ failure; DIC, disseminated intravascular coagulation; NOMI, non-occlusive mesenteric ischemia

Table 3. Cox proportional hazard analysis for all-cause mortality in 4 categories of BMI or WC

	Univariable Regression			Multivariable Regression Model ①			Multivariable Regression Model ②		
Variable	HR	95% CI	*P value*	HR	95% CI	*P value*	HR	95% CI	*P value*
BMI									
4th quartile		Reference			Reference				
3rd quartile	1.375	0.813 – 1.326	0.235	1.273	0.743 – 2.179	0.379			
2nd quartile	1.684	1.015 – 2.794	0.043	1.440	0.858 – 2.417	0.168			
1st quartile	3.751	2.390 – 5.887	<0.001	2.748	1.712 – 4.411	<0.001			
WC									
4th quartile		Reference						Reference	
3rd quartile	0.813	0.483 – 1.367	0.435				0.760	0.447 – 1.293	0.312
2nd quartile	1.523	0.989 – 2.344	0.056				1.407	0.905 – 2.189	0.130
1st quartile	2.771	1.837 – 4.180	<0.001				2.340	1.525 – 3.589	<0.001
Sex	0.878	0.640 – 1.206	0.422	1.232	0.877 – 1.730	0.229	1.291	0.919 – 1.815	0.141
Age	1.060	1.043 – 1.076	<0.001	1.041	1.023 – 1.059	<0.001	1.045	1.027 – 1.063	<0.001
CKD	2.574	1.899 – 3.491	<0.001	1.820	1.319 – 2.512	<0.001	1.790	1.297 - 2.468	<0.001
ACS	1.707	1.277 – 2.281	<0.001	1.656	1.215 – 2.257	0.001	1.669	1.225 – 2.274	0.001
OMI	1.493	1.070 – 2.084	0.018	1.524	1.083 – 2.145	0.016	1.530	1.086 – 2.155	0.015
DM	1.203	0.901 – 1.605	0.211	1.385	1.027 – 1.867	0.033	1.433	1.061 – 1.935	0.019
Smoking	0.878	0.612 – 1.258	0.478	1.291	0.872 – 1.913	0.202	1.327	0.896 – 1.965	0.159
HF	2.615	1.942 – 3.521	<0.001	1.803	1.318 – 2.466	<0.001	1.861	1.362 – 2.543	<0.001
PAD	2.120	1.426 – 3.150	<0.001	1.776	1181 – 2.671	0.006	1.804	1.201 – 2.710	0.004

Adjusted by age, sex, chronic kidney disease, acute coronary syndrome, old myocardial infarction, diabetes, current smoking, heart failure, and peripheral arterial disease. Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; CKD, chronic kidney disease; ACS, acute coronary syndrome; OMI, old myocardial infraction; DM, diabetes; HF, heart failure; PAD, peripheral arterial disease; ACS, acute coronary syndrome;

Table 4. NRI and IDI by adding quartiles of BMI and WC to 9 prognostic factors

Variable	C-statistics	NRI	*P value*	IDI	*P value*
Factor 9	0.719				
Factor 9 + BMI (quartile)	0.735	0.294 (0.151-0.438)	< 0.001	0.0055 (0.0003-0.0078)	<0.001
Factor 9 + BMI + WC (quartile)	0.739	0.358 (0.218-0.499)	< 0.001	0.001 (-0.001-0.0022)	0.076

Abbreviations: Factor 9 (age, sex, chronic kidney disease, acute coronary syndrome, old myocardial infarction, diabetes, current smoking, heart failure, and peripheral arterial disease); NRI, net reclassification improvement; IDI, integrated discrimination improvement; BMI, body mass index; WC, waist circumference

Figure 1

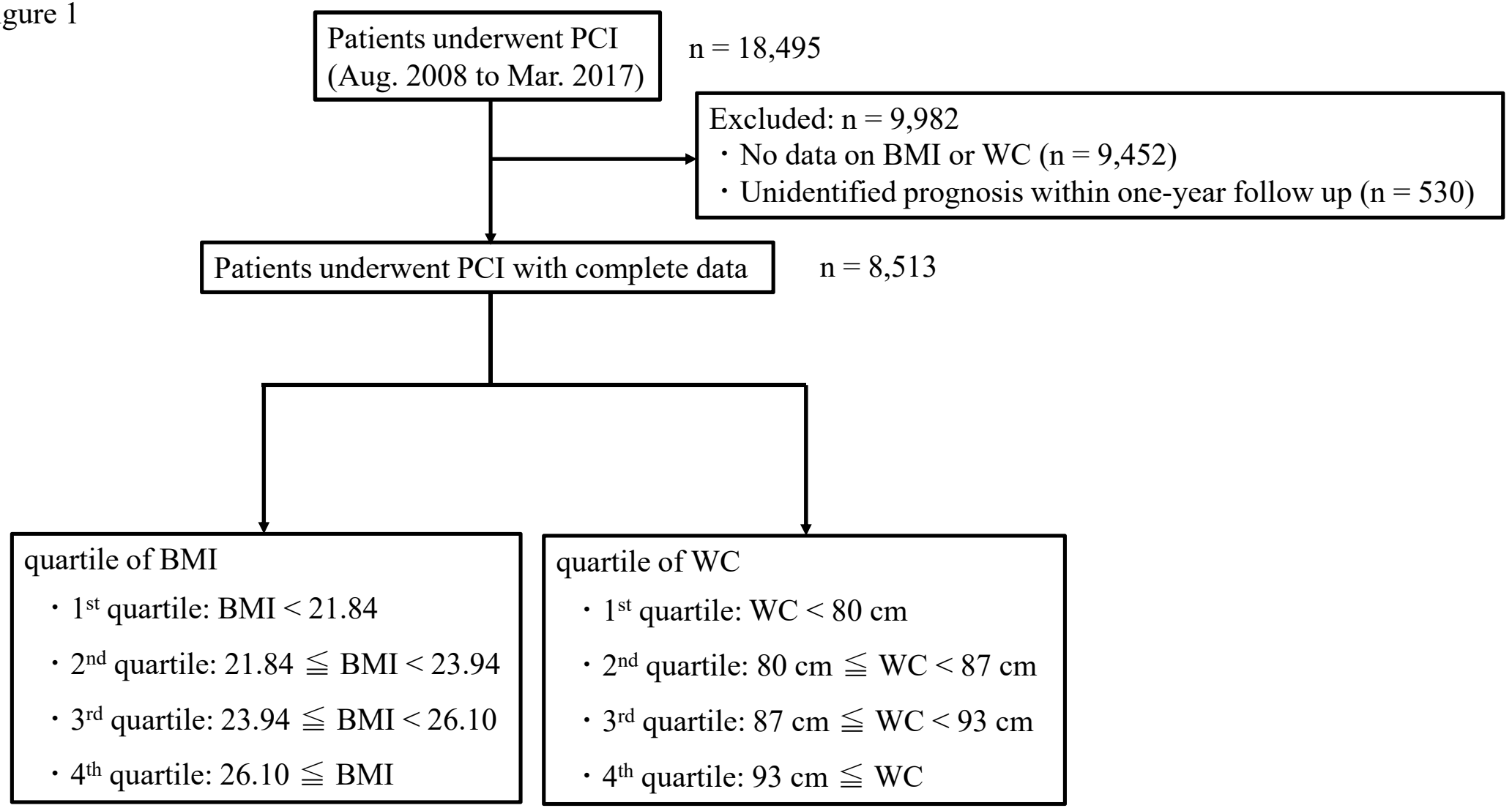

Patients underwent PCI
(Aug. 2008 to Mar. 2017)
n = 18,495
Excluded: n = 9,982
・No data on BMI or WC (n = 9,452)
・Unidentified prognosis within one-year follow up (n = 530)
Patients underwent PCI with complete data
n = 8,513
quartile of BMI
・1st quartile: BMI < 21.84
・2nd quartile: 21.84 ≦ BMI < 23.94
・3rd quartile: 23.94 ≦ BMI < 26.10
・4th quartile: 26.10 ≦ BMI
quartile of WC
・1st quartile: WC < 80 cm
・2nd quartile: 80 cm ≦ WC < 87 cm
・3rd quartile: 87 cm ≦ WC < 93 cm
・4th quartile: 93 cm ≦ WC

Figure 2A

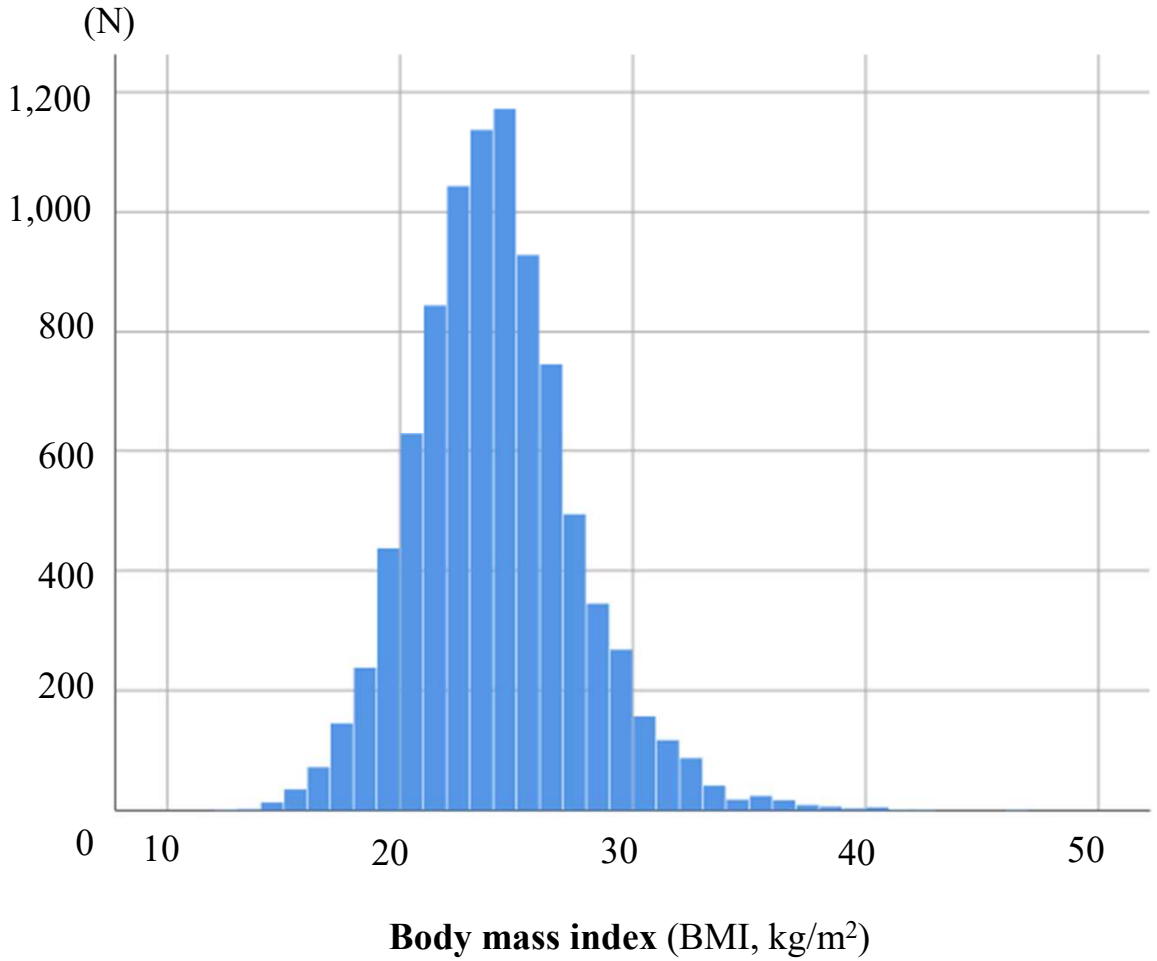
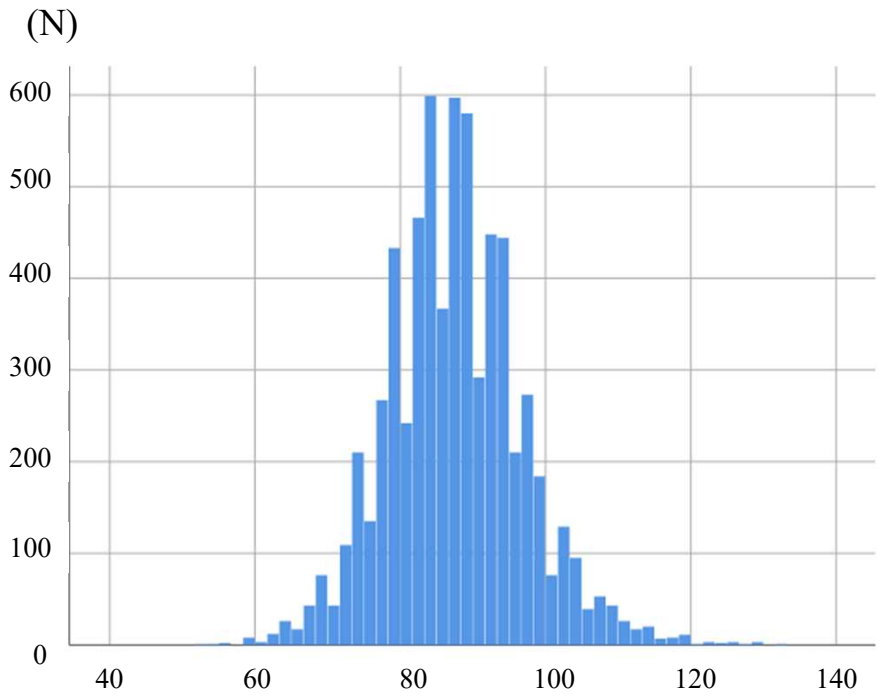
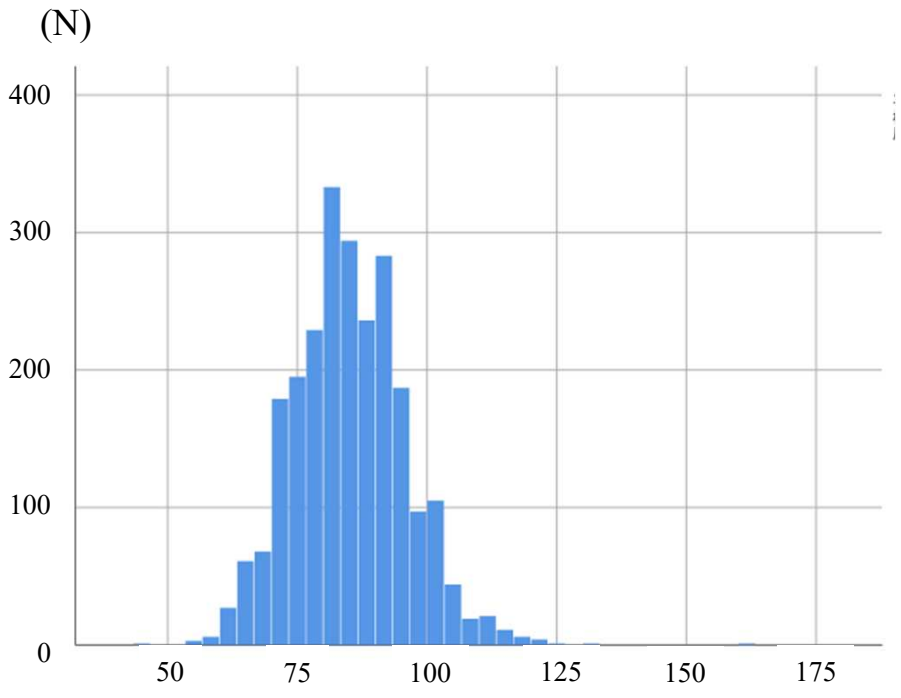

(N)
1,200
1,000
800
600
400
200
0
10
20
30
40
50
Body mass index (BMI, kg/m2)

Figure 2B

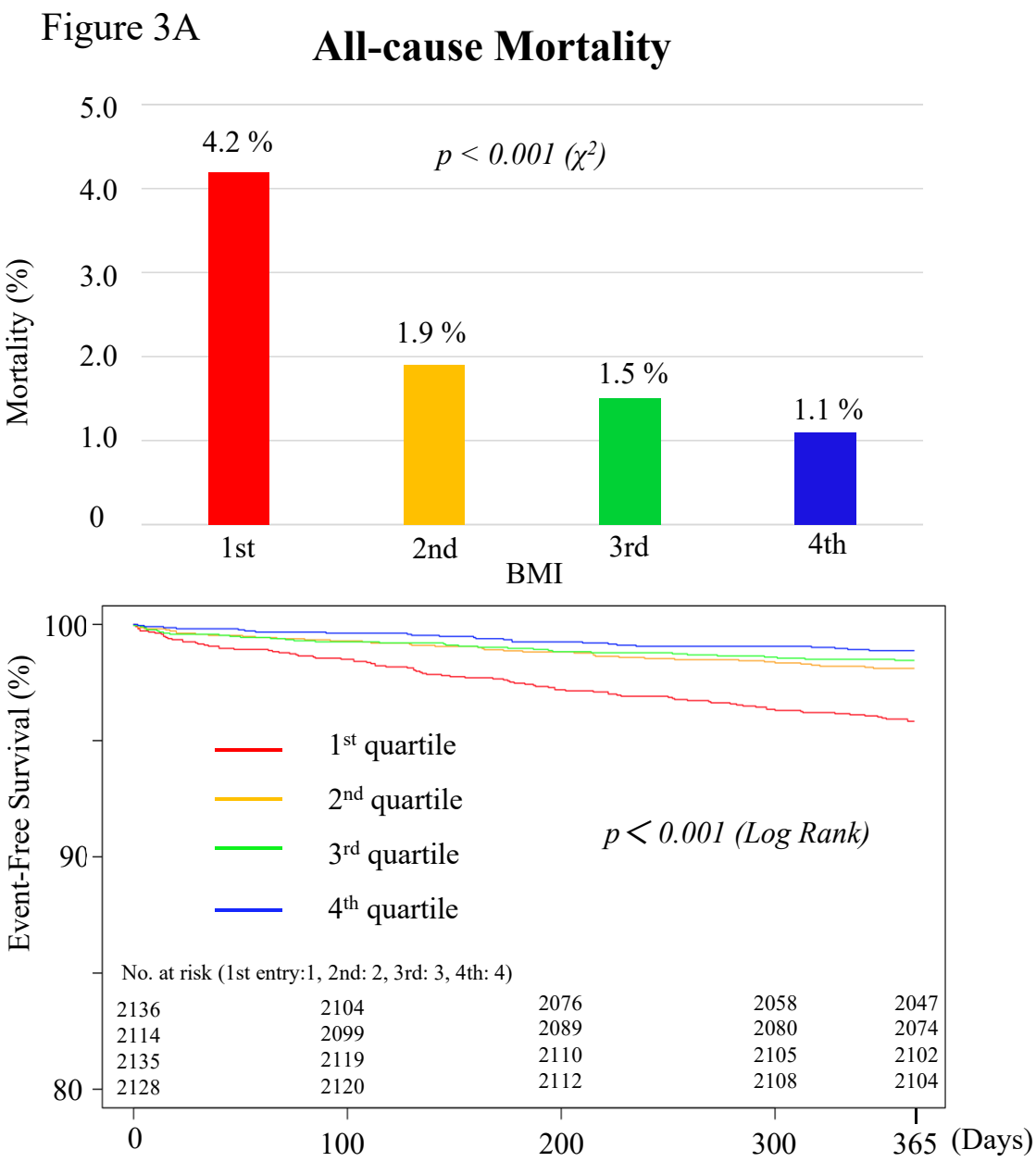


Male



Female

Figure 3A


All-cause Mortality
5.0
4.0
3.0
2.0
1.0
0
Mortality (%)
4.2 %
1.9 %
1.5 %
1.1 %
p < 0.001 (χ²)
1st
2nd
3rd
4th
BMI
100
90
80
Event-Free Survival (%)
1st quartile
2nd quartile
3rd quartile
4th quartile
p < 0.001 (Log Rank)
No. at risk (1st entry:1, 2nd: 2, 3rd: 3, 4th: 4)
2136 2104 2076 2058 2047
2114 2099 2089 2080 2074
2135 2119 2110 2105 2102
2128 2120 2112 2108 2104
0
100
200
300
365
(Days)

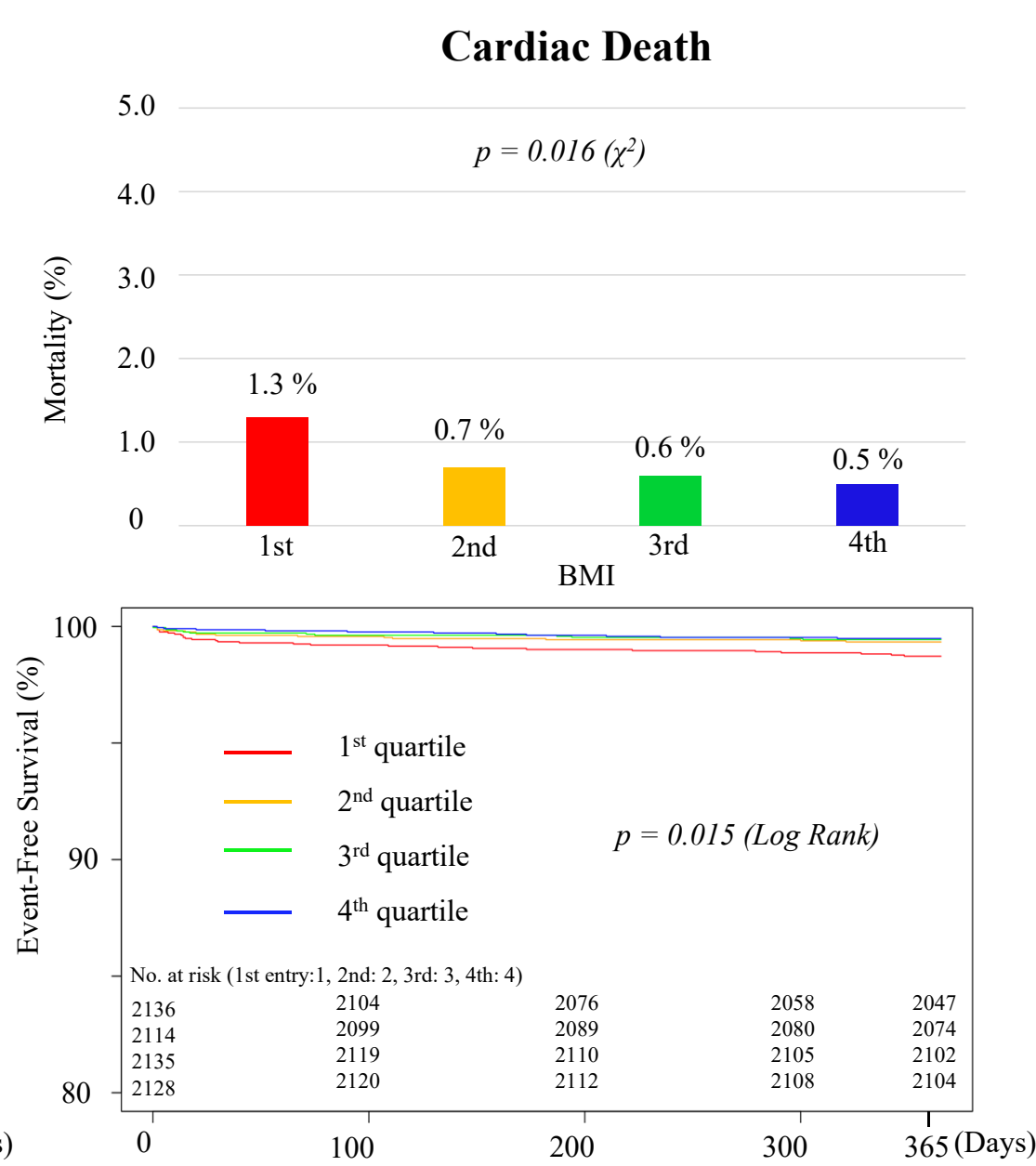
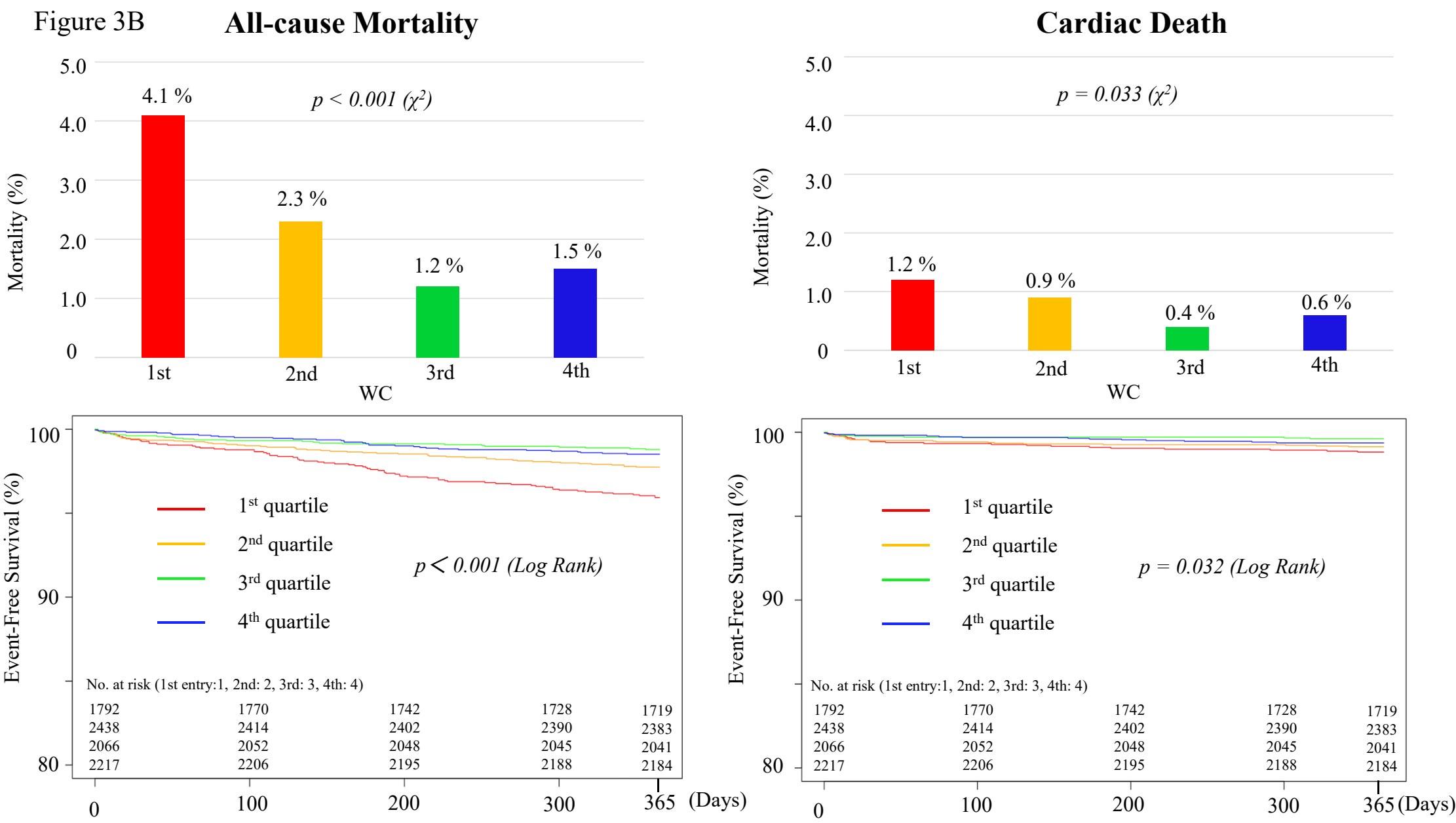

Cardiac Death
5.0
4.0
3.0
2.0
1.0
0
Mortality (%)
1.3 %
0.7 %
0.6 %
0.5 %
p = 0.016 (χ²)
1st
2nd
3rd
4th
BMI
100
90
80
Event-Free Survival (%)
1st quartile
2nd quartile
3rd quartile
4th quartile
p = 0.015 (Log Rank)
No. at risk (1st entry:1, 2nd: 2, 3rd: 3, 4th: 4)
2136 2104 2076 2058 2047
2114 2099 2089 2080 2074
2135 2119 2110 2105 2102
2128 2120 2112 2108 2104
0
100
200
300
365
(Days)

Figure 3B


All-cause Mortality
Mortality (%)
5.0
4.0
3.0
2.0
1.0
0
4.1 %
2.3 %
1.2 %
1.5 %
p < 0.001 (χ²)
1st
2nd
3rd
4th
WC
Event-Free Survival (%)
100
90
80
1st quartile
2nd quartile
3rd quartile
4th quartile
p < 0.001 (Log Rank)
No. at risk (1st entry:1, 2nd: 2, 3rd: 3, 4th: 4)
1792 1770 1742 1728 1719
2438 2414 2402 2390 2383
2066 2052 2048 2045 2041
2217 2206 2195 2188 2184
0
100
200
300
365 (Days)
Cardiac Death
Mortality (%)
5.0
4.0
3.0
2.0
1.0
0
1.2 %
0.9 %
0.4 %
0.6 %
p = 0.033 (χ²)
1st
2nd
3rd
4th
WC
Event-Free Survival (%)
100
90
80
1st quartile
2nd quartile
3rd quartile
4th quartile
p = 0.032 (Log Rank)
No. at risk (1st entry:1, 2nd: 2, 3rd: 3, 4th: 4)
1792 1770 1742 1728 1719
2438 2414 2402 2390 2383
2066 2052 2048 2045 2041
2217 2206 2195 2188 2184
0
100
200
300
365 (Days)

Supplemental table 1A. Baseline Characteristics Stratified by Body Mass Index-defined obesity

	Non-Obesity (Low BMI: n=5424)	Obesity (High BMI: n=3089)	*P value*
Age in years (median range)	73.0 (65.0 – 80.0)	68.0 (60.0 – 75.0)	<0.001
Female, n (%)	1519 (28.0)	734 (23.8)	<0.001
Height (cm)	159.4±9.3	161.1±9.4	<0.001
Weight (kg)	56.5±9.0	72.1±10.7	<0.001
BMI (kg/m^2)	22.1±2.1	27.7±2.6	<0.001
Waist Circumference (cm)	82.5±7.6	94.6±8.3	<0.001
eGFR mL/min/1.73 m^2	60.8±23.4	64.1±23.4	<0.001
HbA1c (%)	6.3±1.1	6.6±2.3	<0.001
Diabetes, n (%)	2082 (38.4)	1487 (48.2)	<0.001
Hypertension, n (%)	4183 (77.3)	2570 (83.3)	<0.001
Dyslipidaemia, n (%)	3295 (60.8)	2227 (72.2)	<0.001
Smoking, n (%)	1111 (20.5)	760 (24.7)	<0.001
CKD, n (%)	2415 (44.7)	1232 (40.0)	<0.001
On HD, n (%)	308 (5.7)	104 (3.4)	<0.001
Prior MI, n (%)	947 (17.5)	591 (19.2)	0.057
Prior PCI, n (%)	1364 (25.2)	851 (27.6)	0.016
Prior CABG, n (%)	230 (4.2)	133 (4.3)	0.911
Composite of PAD, n (%)	481 (8.9)	205 (6.6)	<0.001
ACS, n (%)	2410 (44.4)	1287 (41.7)	0.013
DES, n (%)	4060 (74.9)	2319 (75.1)	0.835
Anti thrombotic agents after PCI			
Aspirin, n (%)	5366 (99.1)	3060 (99.2)	0.811
Clopidogrel, n (%)	3891 (72.0)	2183 (70.9)	0.317
Prasugrel, n (%)	708 (37.0)	414 (38.1)	0.556
Cilostazol, n (%)	129 (2.4)	66 (2.1)	0.498
Ticlopidine, n (%)	702 (13.0)	429 (13.9)	0.219
Sarpogrelate, n (%)	40 (0.7)	23 (0.7)	1.000
DOAC, n (%)	138 (7.8)	73 (6.8)	0.604
Warfarin, n (%)	414 (7.6)	210 (6.8)	0.154

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; HD, haemodialysis; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass; PAD, peripheral arterial disease; ACS, acute coronary syndrome; DES, drug-eluting stent; BMS, bare metal stent; DOAC, direct oral anticoagulants

Supplemental table 1B. Baseline characteristics stratified by waist circumference-defined obesity

	Non-Obesity (Low WC: n=4180)	Obesity (High WC: n=4333)	*P value*
Age in years (median range)	73.0 (65.0 – 80.0)	69.0 (61.0 – 76.0)	<0.001
Female, n (%)	1606 (38.4)	647 (14.9)	<0.001
Height (cm)	157.0±9.3	163.0±8.4	<0.001
Weight (kg)	54.5±8.7	69.5±10.4	<0.001
BMI (kg/m^2)	22.1±2.6	26.1±3.1	<0.001
Waist Circumference (cm)	79.4±6.0	94.2±6.8	<0.001
eGFR mL/min/1.73 m^2	60.8±24.0	63.2±22.9	<0.001
HbA1c (%)	6.3±1.1	6.6±2.0	<0.001
Diabetes, n (%)	1538 (36.8)	2031 (47.0)	<0.001
Hypertension, n (%)	3215 (77.0)	3538 (81.8)	<0.001
Dyslipidaemia, n (%)	2485 (59.5)	3037 (70.2)	<0.001
Smoking, n (%)	757 (18.2)	1114 (25.8)	<0.001
CKD, n (%)	1872 (45.0)	1775 (41.1)	<0.001
On HD, n (%)	250 (6.0)	162 (3.7)	<0.001
Prior MI, n (%)	672 (16.1)	866 (20.0)	<0.001
Prior PCI, n (%)	955 (23.8)	1220 (28.2)	<0.001
Prior CABG, n (%)	194 (4.6)	169 (3.9)	0.096
Composite of PAD, n (%)	346 (8.3)	340 (7.9)	0.473
ACS, n (%)	1887 (44.9)	1820 (42.0)	0.007
DES, n (%)	3135 (75.0)	3244 (74.9)	0.900
Anti thrombotic agents after PCI			
Asprin, n (%)	4131 (99.0)	4295 (99.2)	0.206
Clopidogrel, n (%)	3020 (72.5)	3054 (70.7)	0.067
Prasugrel, n (%)	516 (37.2)	606 (37.6)	0.820
Cilostazol, n (%)	92 (2.2)	103 (2.4)	0.612
Ticlopidine, n (%)	550 (13.2)	581 (13.4)	0.749
Sarpogrelate, n (%)	29 (0.7)	34 (0.8)	0.705
DOAC, n (%)	99 (7.2)	112 (7.1)	0.886
Wafarin, n (%)	309 (7.4)	315 (7.3)	0.835

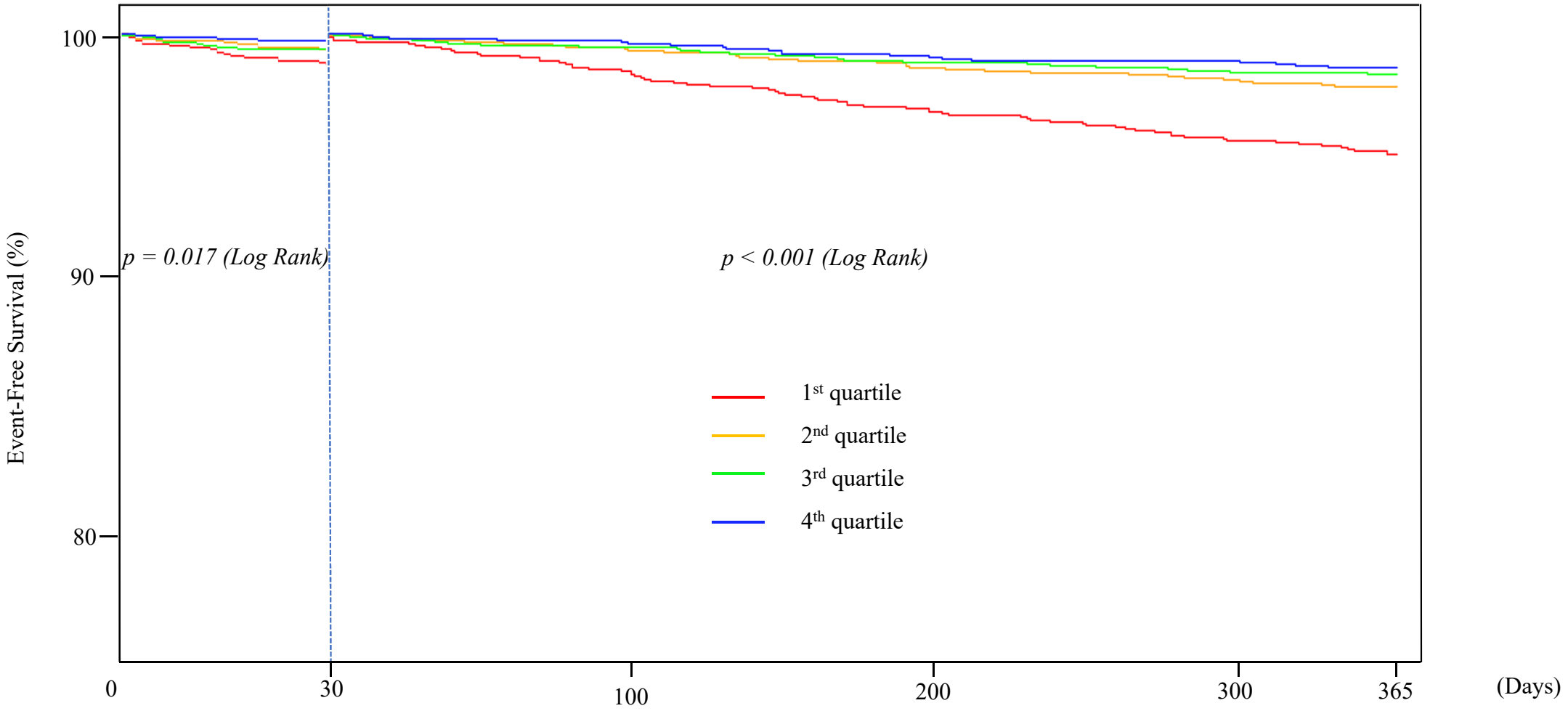
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; HD, haemodialysis; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass; PAD, peripheral arterial disease; ACS, acute coronary syndrome; DES, drug-eluting stent; BMS, bare metal stent; DOAC, direct oral anticoagulants

Supplemental table 2. NRI and IDI by adding BMI and WC to 9 prognostic factors

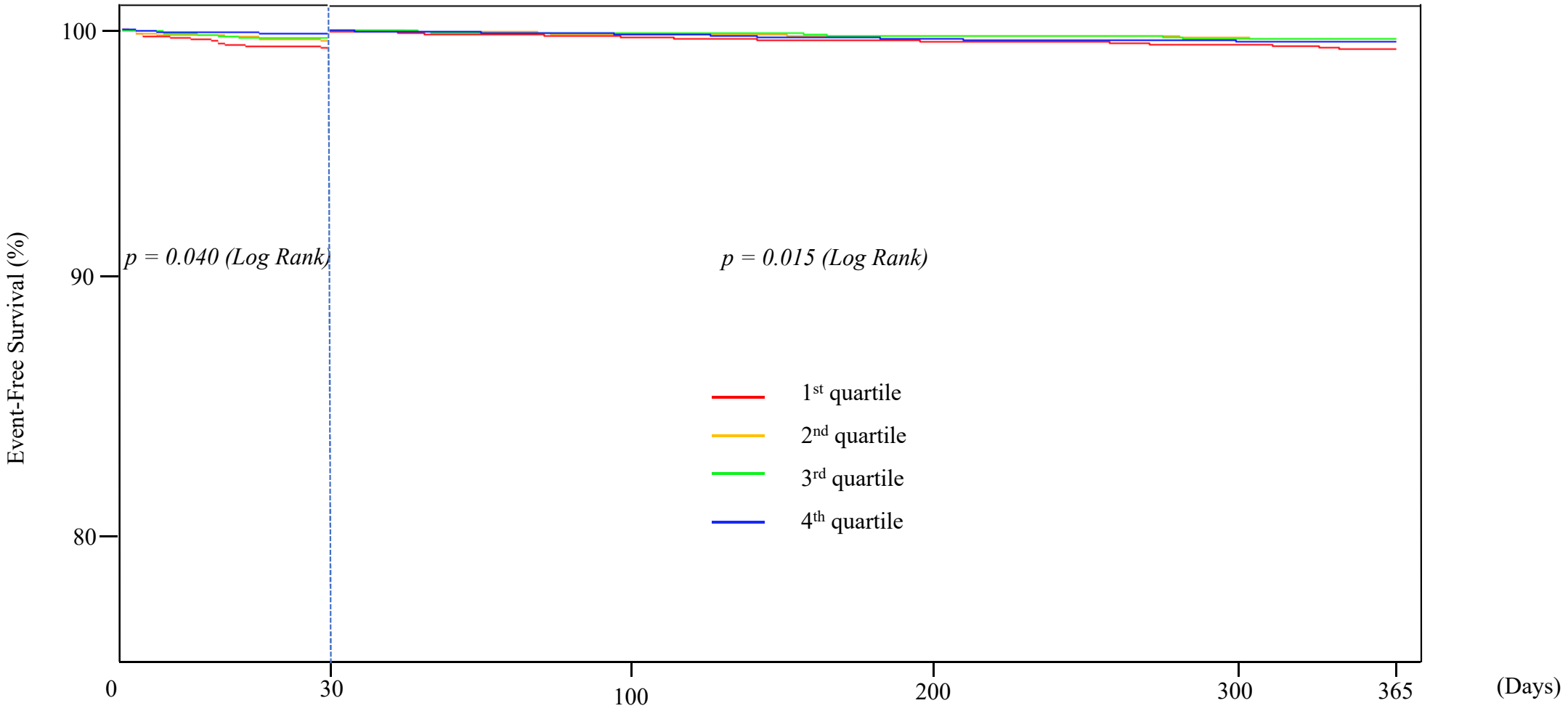
Variable	C-statistics	NRI	*P value*	IDI	*P value*
Factor 9	0.719				
Factor 9 + Low BMI	0.724	0.277 (0.154-0.400)	< 0.001	0.0013 (0.0003-0.0023)	0.01
Factor 9 + Low BMI + Low WC	0.734	0.402 (0.265-0.539)	< 0.001	0.0028 (0.001-0.0047)	0.002

Abbreviations: Factor 9 (age, sex, chronic kidney disease, acute coronary syndrome, old myocardial infarction, diabetes, current smoking, heart failure, and peripheral arterial disease); NRI, net reclassification improvement; IDI, integrated discrimination improvement; BMI, body mass index; WC, waist circumference

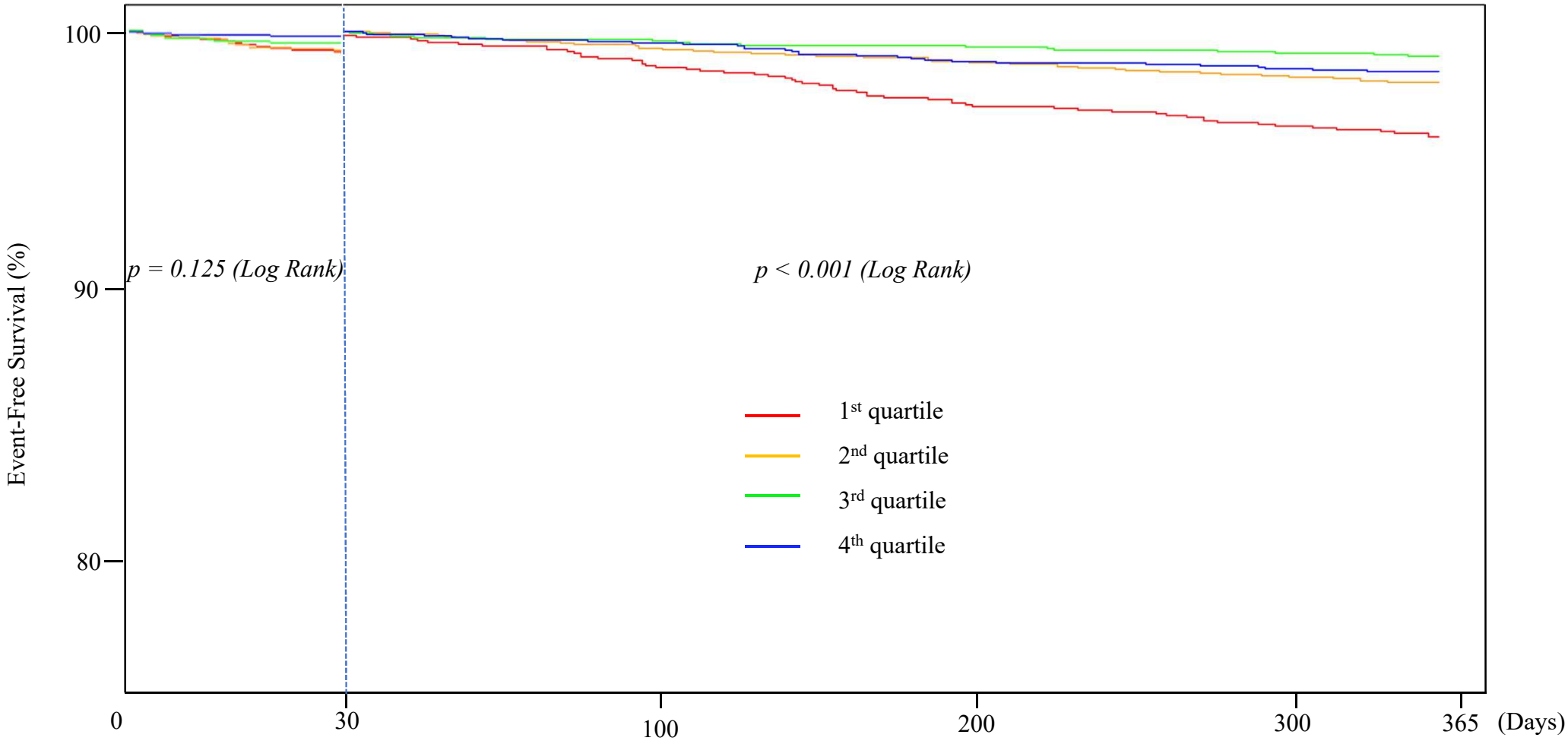
Supplemental figure 1A



Supplemental figure 1B



Supplemental figure 1C



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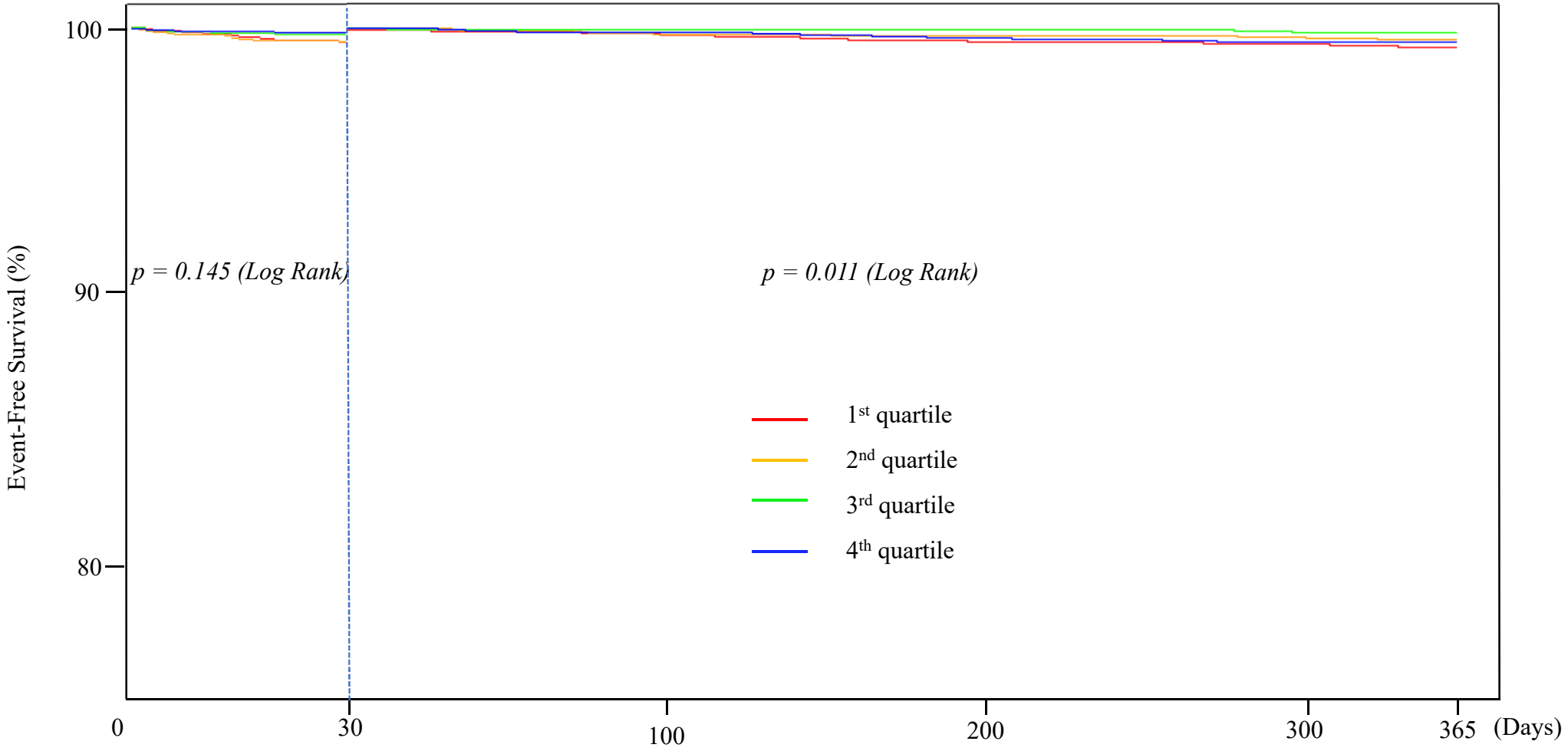
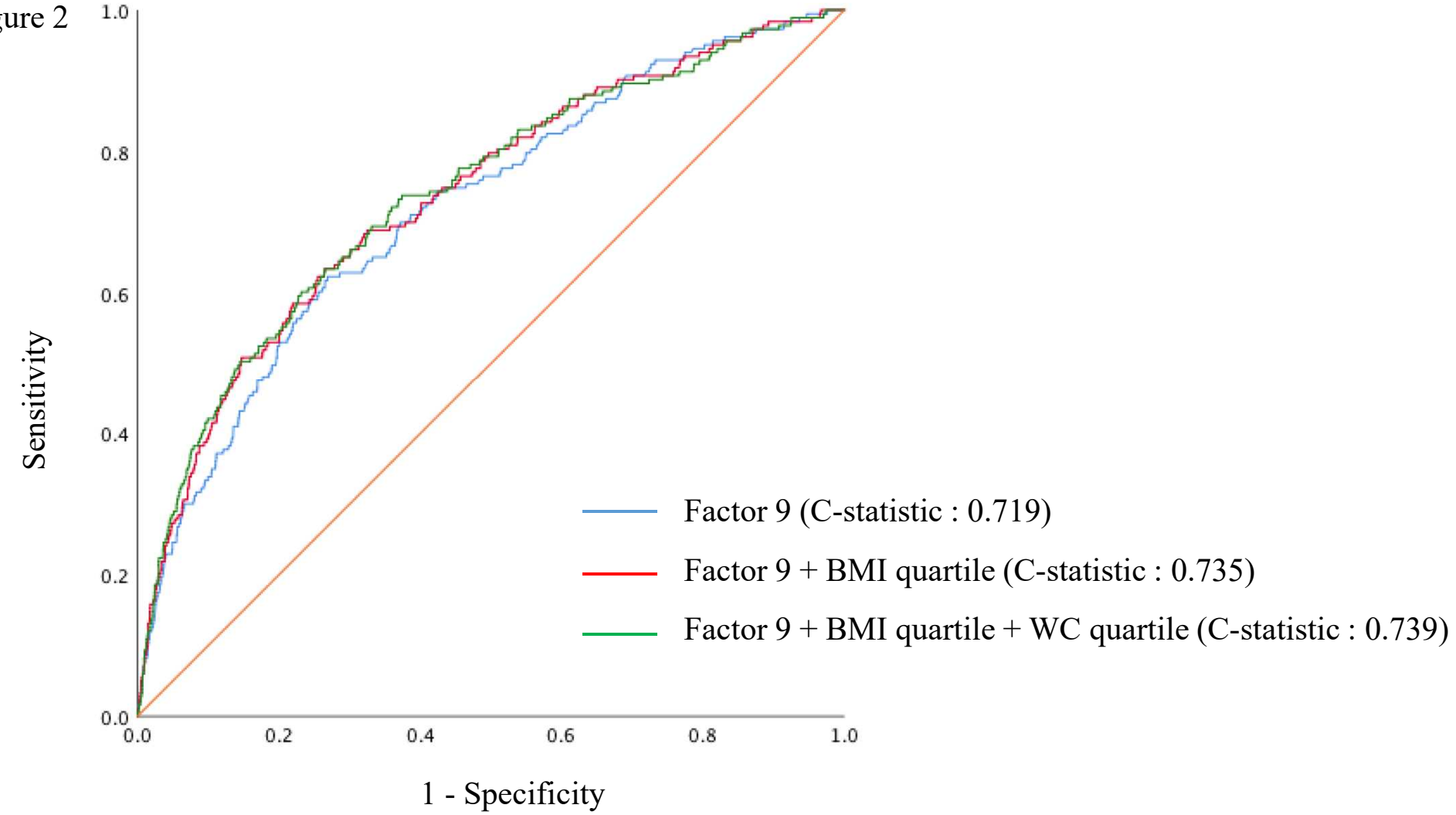
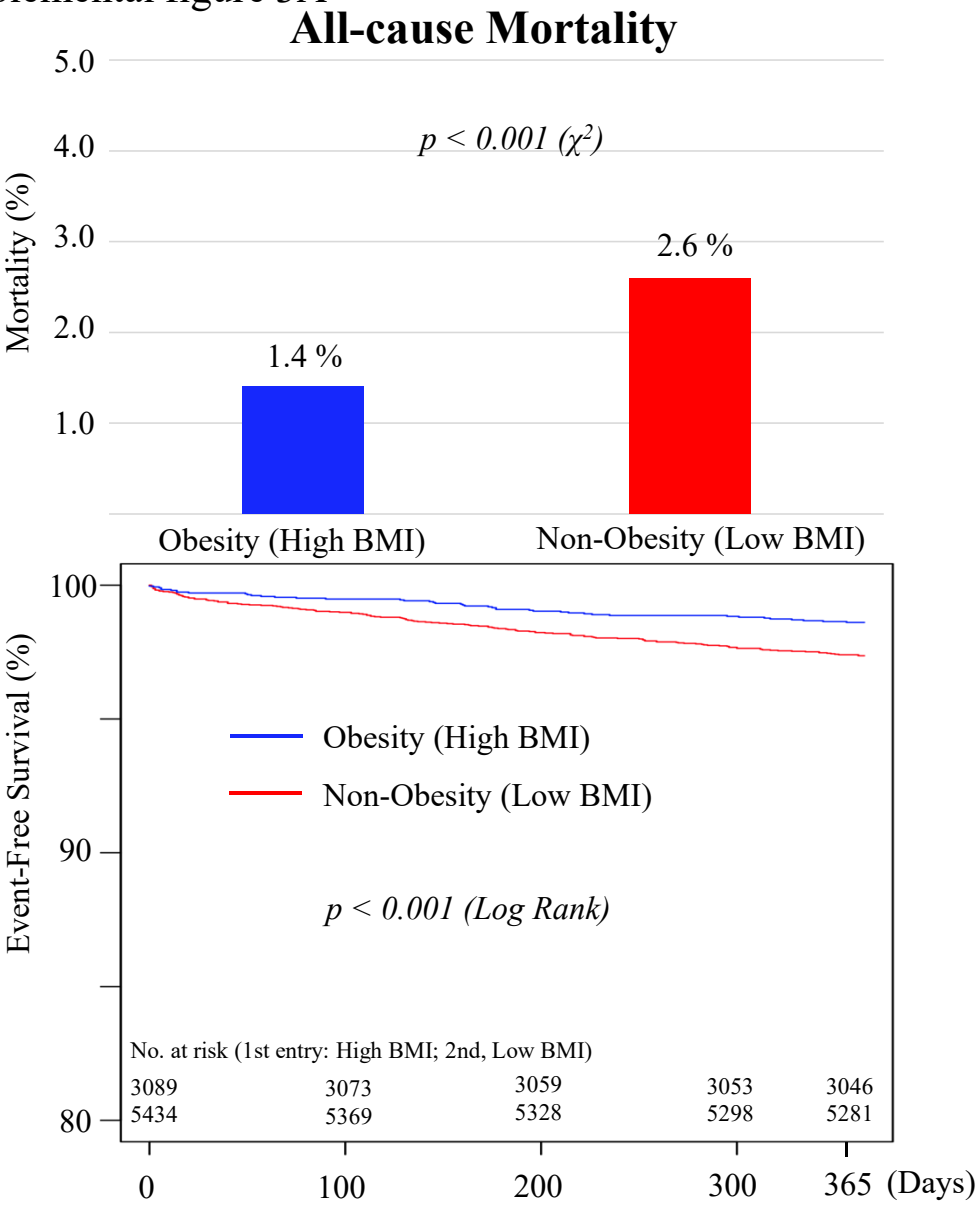
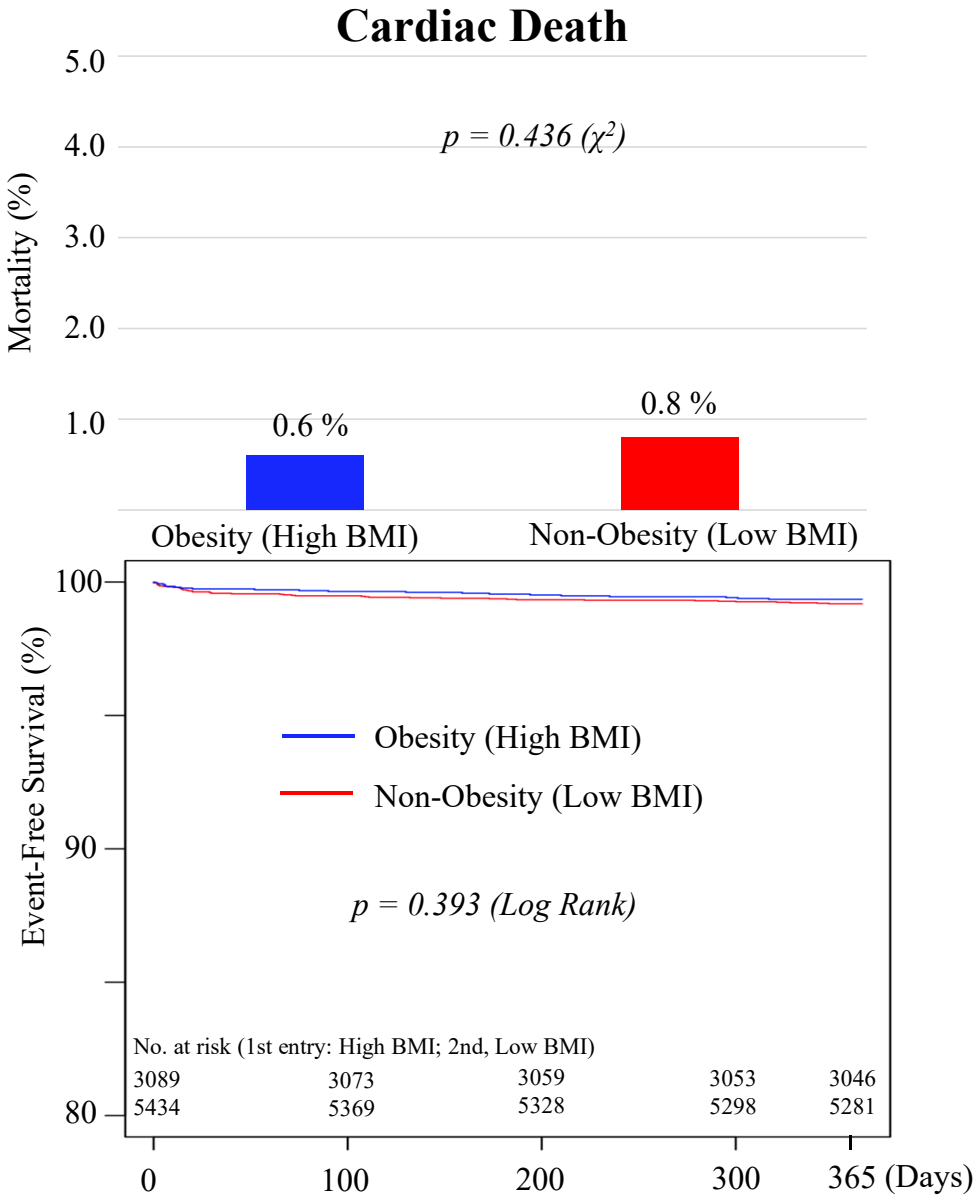
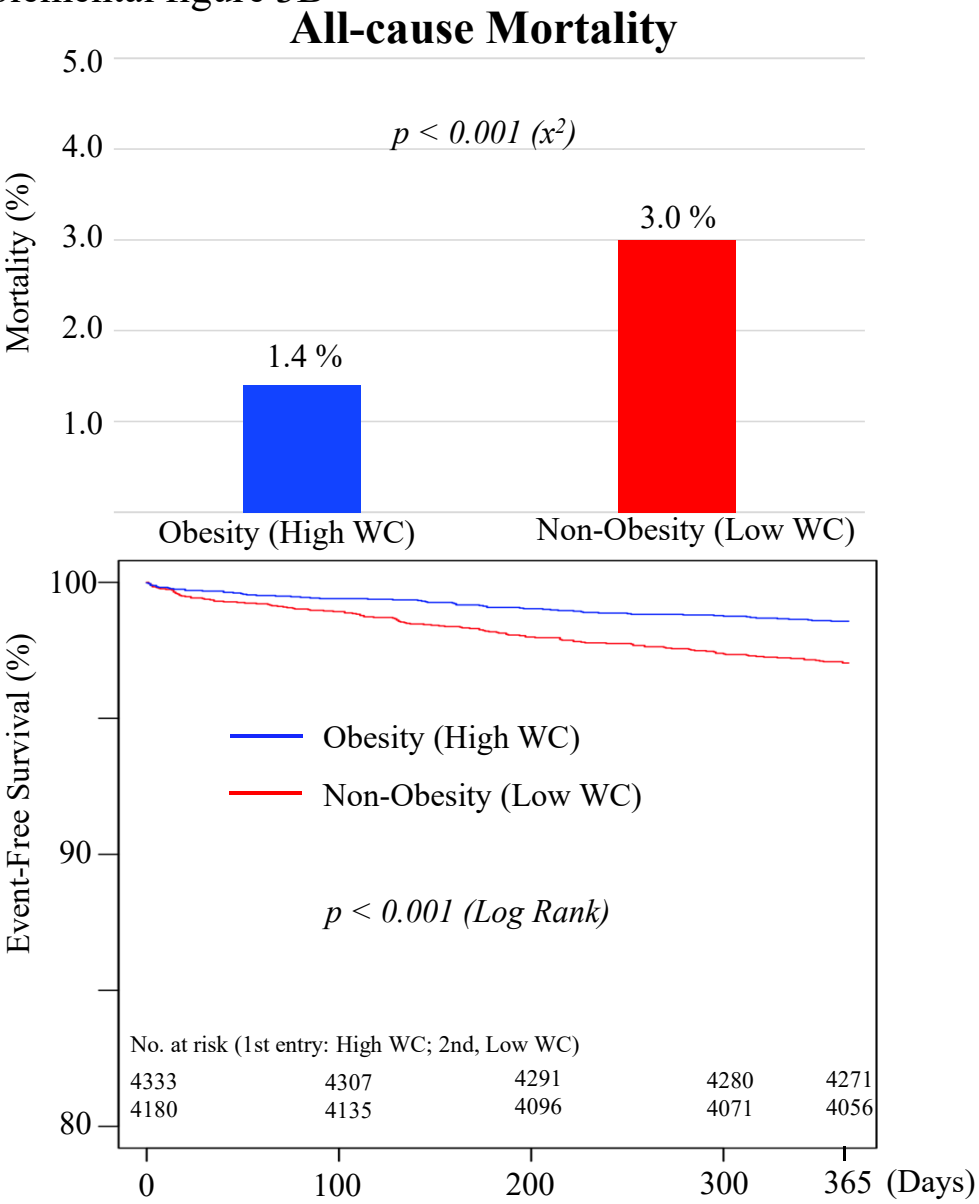
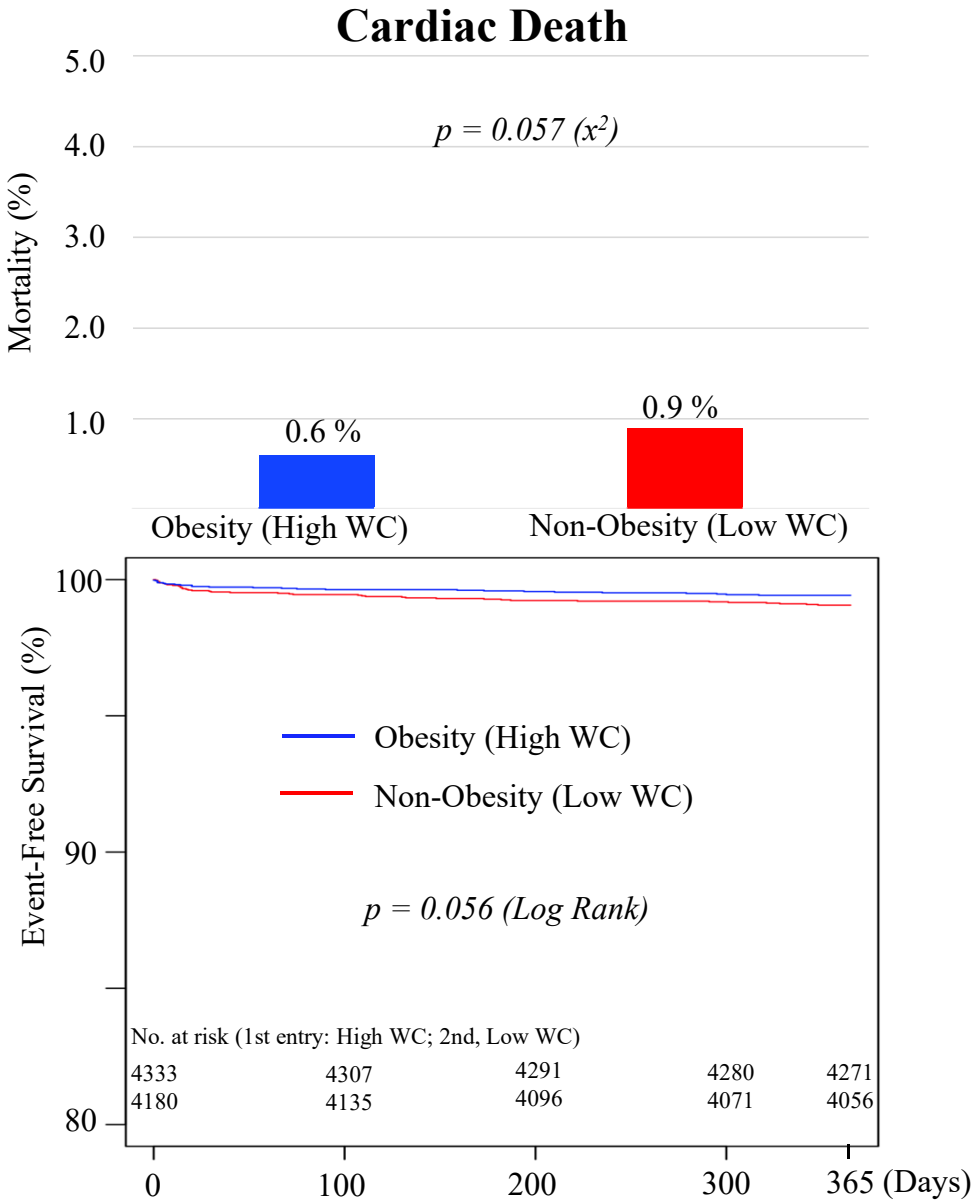


Supplemental figure 2



Supplemental figure 3A





Supplemental figure 3B