

Association Between Obesity Grade and the Age of the First Acute Coronary Syndrome: Cross-sectional Observational Study

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1 **Association between obesity grade and the age of the first acute coronary syndrome:**
2 **cross-sectional observational study**

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13 **Abstract**

14 **Background:** The study evaluates how obesity grade is associated with age during the first
15 acute coronary syndrome (ACS) and examines the effect of cardiovascular (CV) risk factors
16 and the age of first ACS in patients with severe obesity. The effect of the degree of obesity on
17 the age of first ACS may disappear in the absence of other CV risk factors

18 **Methods:** We enrolled consecutive patients diagnosed with first episode of ACS between
19 2014 and 2019, and categorized them by body mass indices (BMI). Independent variables
20 affecting the age of first ACS were examined by linear regression analysis.

21 **Results:** A total of 1005 patients (mean age, 57.5 ± 12.3 years; 19.3% female) were included.
22 Patients with ACS with severe obesity were younger than those with ACS in the grade-I
23 obesity, overweight, and normal-weight groups (52.8 ± 9.9 vs. 55.3 ± 10.9 , 56.8 ± 11.4 , and

24 61.4 ± 4.2, respectively, $p < 0.001$). BMI had a strong, inverse linear relationship with earlier
25 age of first ACS. After adjustment CV risk factors, patients with severe obesity may
26 experience first ACS sooner than those with normal-weight, overweight, and grade-I obesity
27 (-3.4, -5.6, and -7.1 years, respectively; $p < 0.001$). However, males and females with severe
28 obesity without CV risk factors experienced first ACS episode 22 and 27 years later,
29 respectively.

30 **Conclusion:** Patients with severe obesity experience first ACS episode 7.1 years earlier than
31 those with normal-weight. Absence of CV risk factors in people with obesity can improve the
32 potential negative effect of obesity on the ACS age.

33 **Trial registration:** NCT04578964, 08 October 2020

34 **Keywords:** acute coronary syndrome; age; coronary artery disease; obesity; risk factor

35 **Introduction**

36 Obesity is a highly preventable cause of death and an independent risk factor for
37 cardiovascular diseases (CVD) [1]. Although cardiovascular (CV) events have decreased in
38 the last 2 decades, premature atherosclerotic events have increased in younger individuals [2].
39 This phenomenon is mainly caused by the increasing prevalence of CV risk factors, such as
40 obesity, hypertension, and diabetes mellitus (DM). Furthermore, the increasing rate of
41 tobacco use as well as secondhand smoke exposure in young adolescents in low- and middle-
42 income countries increases the incidence of premature CVD [3].

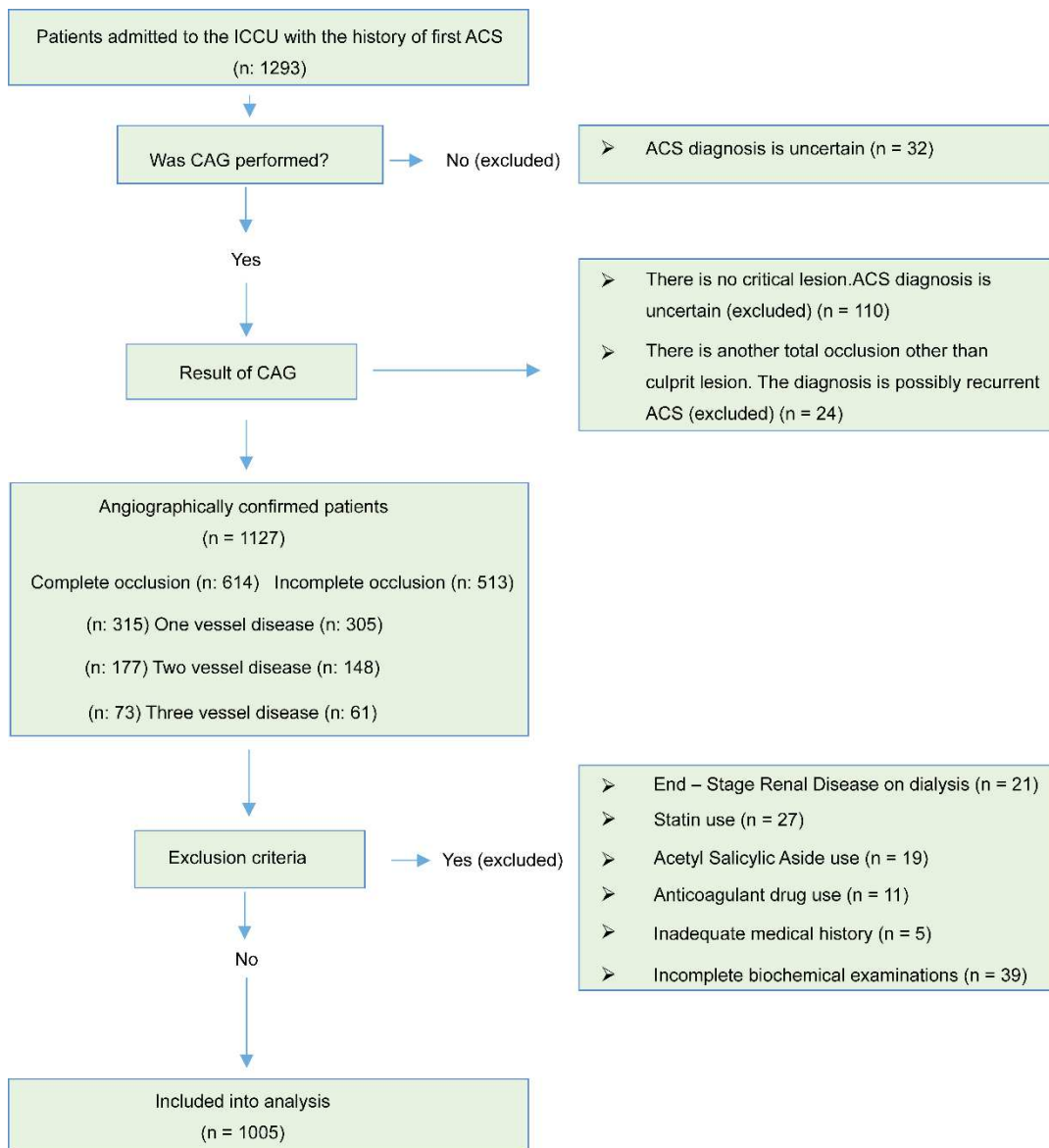
43 Obesity is characterized by an excess body fat associated with comorbid conditions
44 and increased mortality risk. A body mass index (BMI) ≥ 25 kg/m² defines overweight, BMI
45 ≥ 30 kg/m² defines obesity, and BMI ≥ 40 kg/m², or BMI ≥ 35 kg/m² with comorbidities,
46 defines severe obesity [4]. According the World Health Organization data, worldwide obesity
47 has nearly tripled since 1975 [5]. Overweight and obesity have reached epidemic levels
48 globally [6]. Compared with normal weight, severe obesity is associated with an elevated
49 ratio of total mortality and a marked decline in survival rates [7]. However, the metabolic risk
50 status of individuals with obesity demonstrates heterogeneity. Individuals with obesity that
51 seems to have no obesity-related metabolic complications are classified as metabolically
52 healthy obese (MHO), whereas those who have one of the four criteria of metabolic
53 syndrome (waist circumference excluded) are metabolically unhealthy obese (MUO).
54 Meanwhile, those individuals with metabolic obesity but have normal weights (MONW) are
55 characterized by insulin resistance and hyperinsulinism despite being not obese. CV events
56 are fewer in MHO people than in MONW and MUO patients [8].

57 The relationship between obesity and coronary artery disease is well documented [9],
58 but studies on the relationship between obesity grade and age during the first acute coronary

59 syndrome (ACS) episode are few. Obesity is associated with premature presentation of acute
60 myocardial infarction (MI) [10], and obesity grade inversely correlates with age of patients at
61 first NSTEMI episode [11]. Hence, obesity reduces the age of first ACS. However, obesity
62 was considered as a single-disease group in these studies. The MUO and MHO groups were
63 not examined separately, or the possible effect of the accompanying CV risk factors on the
64 age of ACS was not clearly examined. In the current study, we aimed to determine the
65 relationship between obesity grade and the age of first ACS and to examine the effect of CV
66 risk factors on the age of first ACS in people with severe obesity.

67 **Methods**

68 This cross-sectional observational study enrolled consecutive adult patients (>18
69 years) who were diagnosed with ACS for the first time and admitted to the intensive coronary
70 care unit of the Antalya Training and Research Hospital between 2014 and 2019. During the
71 hospitalization period, face-to-face interviews and physical examinations were performed,
72 and laboratory findings and CV risk factors were determined. The exclusion criteria were as
73 follows: CVD; chronic renal disease; chronic obstructive pulmonary disease; malignancy;
74 regular use of statins, antiplatelets, or anticoagulants; situations where oral communication
75 with the patient is impossible; situations where coronary angiography could not be
76 performed. Patients with findings that might be related to previous MI on electrocardiography
77 or echocardiography and total occlusion other than “culprit” lesion and no critical stenosis on
78 coronary angiography were also excluded (Supplementary Figure 1). Our study conformed to
79 the principles of the Declaration of Helsinki and was approved by the ethics committee of
80 Antalya Training and Research Hospital, University of Health Sciences (2014-097) (Clinical
81 trial number: NCT04578964). Written informed consent was obtained from all participants.



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95 **Supplementary Figure 1: Patient flowchart of the inclusion/exclusion procedure**

96 ACS: acute coronary syndrome, CAG: coronary angiography, ICCU: intensive coronary care
97 unit.

98

99 The diagnosis of ACS included ST-elevated MI (STEMI), non–ST-elevated MI
100 (NSTEMI), and unstable angina pectoris (USAP). MI was defined according to the fourth
101 universal MI definitions of the 2018 European Society of Cardiology [12]. Our study
102 included type 1 (spontaneous) MI. Acute MI was classified as either STEMI or NSTEMI
103 according to the presence or absence of ≥ 1 mm of ST-segment elevation in two or more
104 contiguous leads on initial electrocardiography. USAP referred to admitted patients with
105 typical chest pain lasting more than 20 min without increased cardiac markers and ST-
106 segment elevation.

107 The medical history was obtained on the second day of hospitalization. Fasting (>10
108 h) venous blood samples were taken in the first 24 h of MI to measure blood cholesterol
109 levels. Low-density lipoprotein cholesterol (LDL-C) values were calculated using the

110 Friedewald method [13]. For triglyceride levels > 400 mg/dl, “direct LDL-C” measurements
111 were used.

112 Blood pressure was measured before any treatment that can affect blood pressure
113 levels. In this study, a resting systolic blood pressure >140 mm Hg and/or diastolic blood
114 pressure > 90 mm Hg or treatment with antihypertensive medications defined hypertension
115 (HTN). DM was defined as having an established diagnosis of DM or using insulin or oral
116 hypoglycemic drugs. Furthermore, hyperlipidemia (HLD) was defined as having an
117 established diagnosis or treatment with a lipid-lowering agent. A smoker for >1 year
118 consuming at least 1 pack per year was considered as a “current smoker.”

119 Psychosocial stress was determined according to patient declaration. Patients were
120 asked the following questions: “When you think about your situation before this heart attack,
121 do you describe yourself as a stressed person?” If the answer was “yes,” they were also asked
122 if they had a stress risk factor, and if no, it was considered absent. The following questions
123 were asked to people who were not familiar with the concept of stress: “Do you think you
124 have psychosocial stress about economic status, working conditions, family life, or for any
125 other reason?” Those patients who responded positively were considered to have experienced
126 psychosocial stress.

127 Moreover, anthropometric parameters were measured within 48 h of admission. Two
128 trained research nurses measured the weight and height 48 h after admission. Body weight
129 was measured twice, with the patient in light indoor clothing and without shoes; the average
130 value was then recorded. BMI (kg/m^2) was calculated by dividing the body weight by the
131 square of height. BMI was categorized into the following groups: Group 0 (normal weight)
132 for $<25 \text{ kg}/\text{m}^2$; Group 1 (overweight) for $25.1\text{--}30.0 \text{ kg}/\text{m}^2$; Group 2 (obesity) for $30.1\text{--}35.0$
133 kg/m^2 ; Group 3 (severe obesity) for $>35 \text{ kg}/\text{m}^2$ [4]. BMI of $\geq 40 \text{ kg}/\text{m}^2$ or $\geq 35 \text{ kg}/\text{m}^2$ with

134 comorbidities (CAD, DM, HTN, and HLD) defined severe obesity. In this study, all patients
135 had comorbidities such as CAD; therefore, patients with a BMI of ≥ 35 kg/m² belonged to the
136 severe-obesity group.

137 *Statistical Analysis*

138 We present normally distributed continuous variables by arithmetic mean \pm standard
139 deviation, non-normal distributed or ordered variables by median (interquartile range), and
140 categorical variables by frequency and percentage. Normal distribution was analyzed by the
141 Lilliefors-corrected Kolmogorov–Smirnov test. The homogeneity of the variances was
142 determined by Levene’s test. The dependent groups of categorical variables were compared
143 by McNemar’s test. Normally distributed continuous variables with three or more
144 independent groups were evaluated by one-way analysis of variance, while the non-normally
145 distributed variables were examined by the Kruskal–Wallis test. When the *p* values from the
146 Kruskal–Wallis test statistics were statistically significant, the group that differed from the
147 other groups was determined by Dunn’s post-hoc test. Furthermore, the *p* values were
148 corrected for multiple comparisons, and the dependent groups were compared using the
149 Wilcoxon test. The age during the first ACS episode was estimated by multiple linear
150 regression analysis. Multiple linear regression analysis was performed with variables
151 determined as $p < 0.25$ as a result of univariate statistical analysis. Starting from the most
152 significant value, individual values were added to the model, and the final regression model
153 was established. The LDL-C value was categorized into five groups (70, 100, 130, 160, and
154 190 mg/dl) in the estimated age table for patients with severe obesity; in all other analyses,
155 the LDL-C value was used as a continuous variable. All statistical data were analyzed by R
156 version 3.4.4, and $p < 0.05$ was considered to be statistically significant.

157 **Results**

158 Ultimately, we included 1005 patients (194 female) presenting with first ACS. The
 159 mean age was 57.4 ± 12.3 years, while the mean BMI was 27.9 ± 4.6 kg/m². Based on the
 160 BMI, 268 (26.7%) patients had a normal weight, 441 (43.9%) were overweight, 224 (22.3%)
 161 had obesity, and 72 (7.2%) had severe obesity. Table 1 lists the demographic characteristics
 162 of patients according to the BMI categories.

163 **Table 1: Baseline characteristics of the study population**

| | BMI (kg/m ²) Group | | | | p-value |
|----------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------|---------|
| | Normal weight | Overweight | Obesity | Severe obesity | |
| Variable | <25.0 n = 268 (26.7%) | 25.0–24.9 n = 441 (43.9%) | 30.0–34.9 n = 224 (22.3%) | ≥35.0 n = 72 (7.2%) | |
| Female n (%) | 57 (21.3) | 74 (16.8) | 46 (20.5) | 17 (23.5) | 0.315 |
| DM n (%) | 50 (18.7) | 117 (26.5) | 82 (36.6) | 27 (37.5) | <0.001 |
| HLD n (%) | 30 (12.3) | 73 (18.3) | 47 (23.6) | 13 (20.3) | 0.021 |
| Current Smoker n (%) | 157 (58.6) | 263 (59.6) | 114 (50.9) | 44 (61.1) | 0.313 |
| Pack × Years | 37.7 ± 23.5 | 34.6 ± 21.2 | 33.7 ± 24.6 | 31.7 ± 26.0 | |
| Median, (Q1-Q3) | 34.5/ 25.0/ 45.0 | 30.0/ 22.0/ 40.0 | 28.0/ 20.0/ 40.0 | 26.0/ 15.0/ 39.0 | 0.209 |
| FH of CAD n (%) | 118 (44.0) | 214 (48.5) | 101 (45.1) | 39 (54.2) | 0.366 |

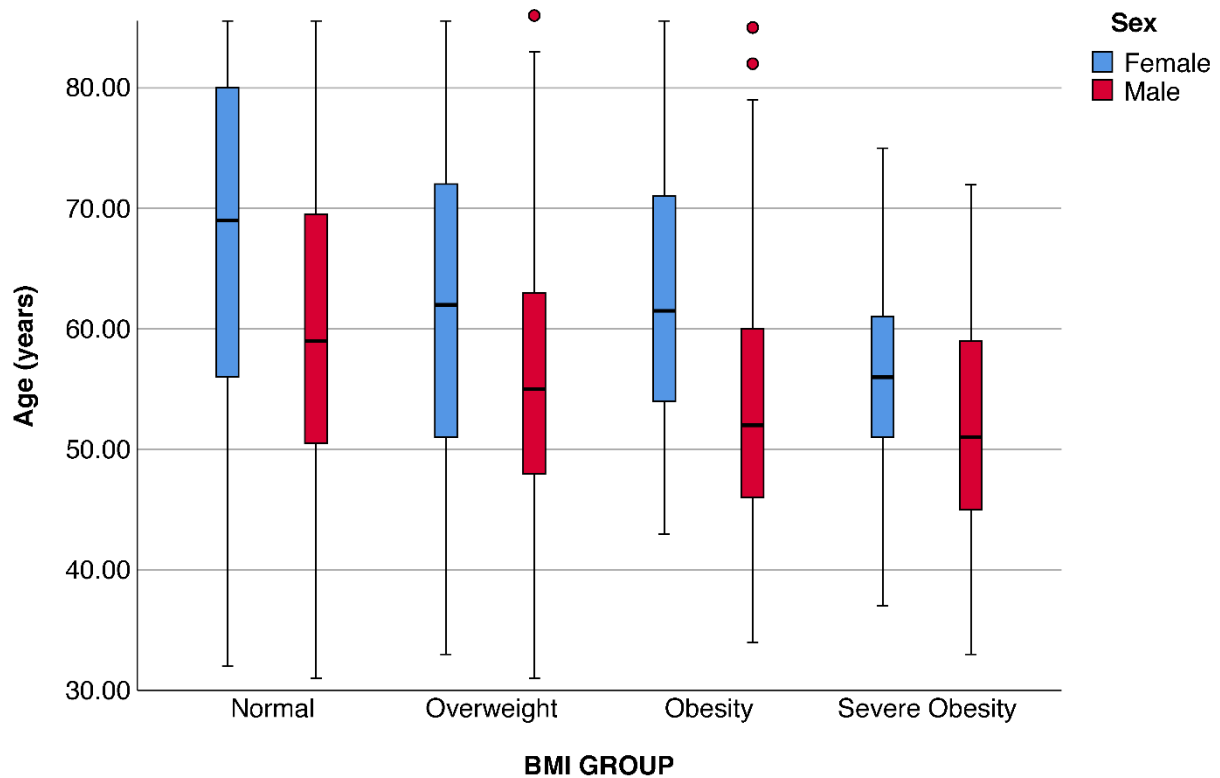
| | | | | | |
|---------------------------|---------------------|---------------------|---------------------|---------------------|------------------|
| Psychosocial stress n (%) | 172 (64.2) | 324 (72.5) | 158 (70.5) | 55 (76.2) | 0.042 |
| HTN n (%) | 86 (32.1) | 176 (39.9) | 110 (49.1) | 39 (54.1) | <0.001 |
| Antihypertensive drug | | | | | |
| Diuretic | 31 (11.6) | 58 (13.2) | 29 (12.9) | 12 (16.7) | 0.717 |
| CCB | 24 (9.0) | 47 (10.7) | 24 (10.7) | 10 (13.9) | 0.663 |
| ARB | 26 (9.7) | 43 (9.8) | 26 (11.6) | 10 (13.2) | 0.655 |
| ACE-I | 14 (5.2) | 42 (9.5) | 17 (7.6) | 8 (11.1) | 0.161 |
| BB | 16 (6.0) | 35 (7.9) | 18 (8.0) | 8 (11.1) | 0.497 |
| Doxazosin | 1 (0.4) | 4 (0.9) | 2 (0.9) | 2 (2.8) | 0.296 |
| Triglyceride (mg/dl) | 128.8 ± 105.6 | 157.1 ± 113.9 | 180.9 ± 148.6 | 190.1 ± 197.7 | |
| (Median, Q1-Q3) | 106.0/ 73.0/ 150.0 | 129.5/ 84.0/ 198.0 | 140.0/ 96.5/ 219.0 | 134.0/ 92.7/ 227.0 | <0.001 |
| LDL-C (mg/dl) | 131.8 ± 36.6 | 129.5 ± 36.6 | 136.9 ± 41.1 | 129.9 ± 41.9 | |
| (Median, Q1-Q3) | 129.0/ 108.0/ 155.0 | 131.0/ 110.5/ 159.5 | 132.0/ 111.0/ 164.8 | 123.5/ 108.0/ 148.5 | 0.207 |
| HDL-C (mg/dl) | 44.2 ± 11.1 | 42.3 ± 9.5 | 41.7 ± 9.3 | 40.3 ± 7.8 | |
| (Median, Q1-Q3) | 42.0/ 37.0/ 42.0 | 42.0 / 36.0/ 49.0 | 41.0/ 35.8/ 47.0 | 41.0/ 35.0/ 43.8 | 0.047 |

| | | | | | |
|--------------------------------|------------------------|------------------------|------------------------|------------------------|------------------|
| Non-HDL-C (mg/dl) | 154.2 ± 41.2 | 166.7 ± 47.9 | 168.7 ± 45.9 | 168.5 ± 57.5 | |
| (Median, Q1- Q3) | 150.5/ 125.8/ 178.0 | 160.0/ 135.3/ 189.0 | 164.0/ 136.0/ 197.0 | 157.8/ 135.0/ 197.0 | 0.001 |
| Age All patients (years) | 61.4 ± 14.2 | 56.8 ± 11.4 | 55.3 ± 10.9 | 52.8 ± 9.9 | <0.001 |
| NSTEMI / USAP (years) | 66.6 ± 13.6 | 58.1 ± 12.4 | 55.7 ± 9.8 | 54.9 ± 9.8 | <0.001 |
| STEMI (years) | 59.4 ± 13.9 | 56.3 ± 11.1 | 55.2 ± 11.3 | 52.3 ± 10.0 | <0.001 |

164 ACE-I: angiotensin converting enzyme-inhibitors, ACS: acute coronary syndrome, ARB:
165 angiotensin receptor blockers, BB: beta blockers, BMI: body mass index, C: cholesterol,
166 CAD: coronary artery disease, CCB: calcium channel blockers, DM: diabetes mellitus, FH:
167 family history, HDL: high-density lipoprotein, HLD: hyperlipidemia, HTN: hypertension,
168 LDL: low-density lipoprotein, NSTEMI: non-ST-elevated myocardial infarction, STEMI:
169 ST-elevated myocardial infarction, USAP: unstable angina pectoris

170

171 BMI had a strong, inverse linear relationship with age during the first ACS. The mean
172 age at first ACS was 61.4 ± 14.2 and 52.8 ± 9.9 years for patients with normal weight (BMI <
173 25 kg/m²) and severe obesity (BMI ≥ 35 kg/m²) (*p* < 0.0001). Figure 1 shows the mean age at
174 first ACS according to BMI categories for both sexes.

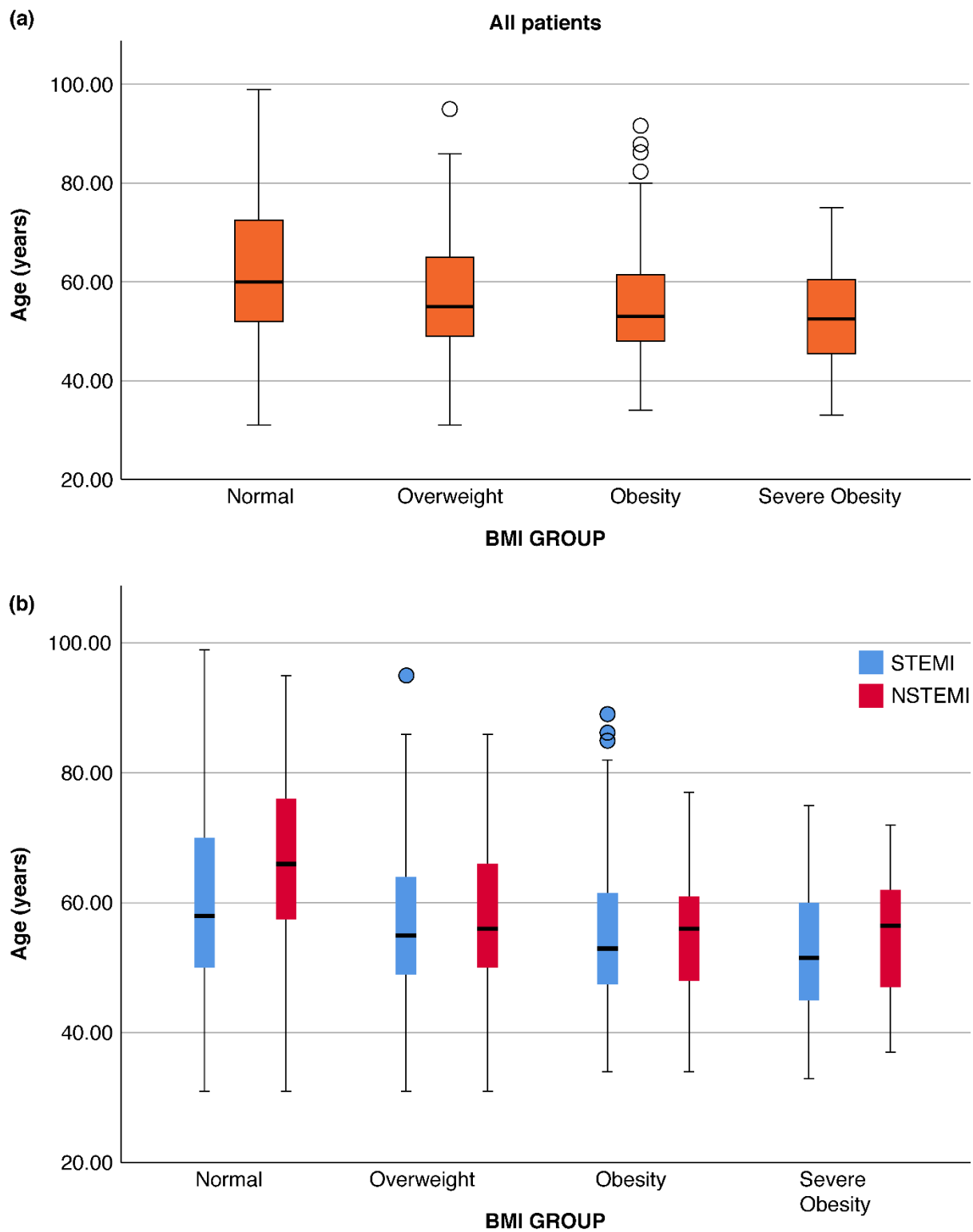


175

176 **Figure 1: Comparison of the mean age of first acute coronary syndrome by body mass**
 177 **index (BMI) groups for both sexes.**

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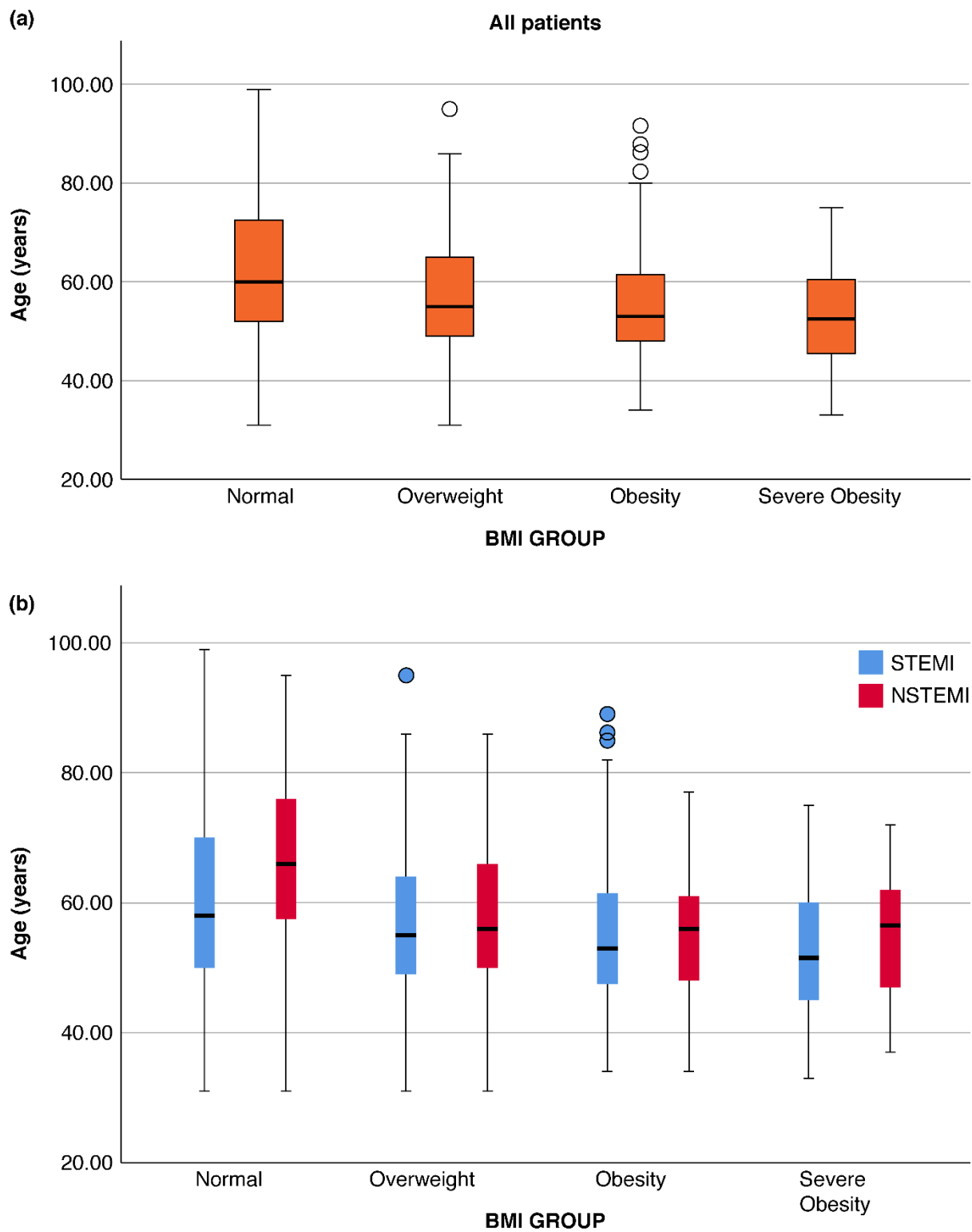
179 When patients were divided into STEMI and NSTEMI/USAP groups, a similar
 180 relationship was found between the age at first ACS and the obesity grade. In both groups,
 181 the obesity group had a lower age at first ACS than the normal-weight group (Figure 2). The
 182 severe-obesity group was likely to have the first episode of NSTEMI and STEMI 11.7 and
 183 7.1 years earlier than the normal-weight group, respectively ($p < .001$).



184

185 **Figure 2: Comparison of the mean age of first acute coronary syndrome by body mass**
 186 **index (BMI) groups (a) for all patients (b) for ST-elevated myocardial infarction**
 187 **(STEMI) and non-ST-elevated myocardial infarction/ unstable angina pectoris**
 188 **(NSTEMI/USAP) patients separately.**

189 The factors affecting the age of patients at first ACS were identified using the multiple
190 linear regression model. Sex, obesity grade, smoking status, DM, psychosocial stress, and
191 LDL-C values were independent variables (Table 2). An interaction was found between
192 “smoking and sex” and “smoking and DM;” therefore, these interaction terms were added to
193 the model ($p = .001$; $<.001$). According to the regression model, the differences in the age at
194 first ACS between the normal-weight group and the overweight, grade-I obesity, and severe-
195 obesity groups were -3.4 , -5.6 , and -7.1 years, respectively ($p <.001$); other variables were
196 constant (Figure 3). In addition, the estimated average age during the first ACS episode (with
197 upper and lower limits for 95% confidence interval) was established for the severe-obesity
198 group (Table 2, Supplementary Table 1). The upper-left corner of the table presents all the
199 risks present in patients, while the lower-right corner is the age calculated for patients with
200 the lowest risk. In the presence of all risk factors, the expected age at first ACS for patients
201 with a LDL-C level of 190 mg/dl was 48 years. At this risk level, the expected age was the
202 same for both sexes. In patients without risk factors and with a LDL-C value of 70 mg/dl, the
203 mean age at first ACS was 73 for females and 66 for males. In this table, modifiable risk
204 factors include LDL-C, height, smoking, and psychosocial stress. The average age at first
205 ACS of the severe-obesity group without these risk factors was similar to the normal-weight
206 group. A high obesity grade was associated with increased triglyceride values and decreased
207 high-density lipoprotein cholesterol values ($p <0.001$). In addition, high-density lipoprotein
208 cholesterol values were inversely related to obesity grade ($p <0.001$). However, the mean
209 LDL-C values were not significantly different between the groups (Supplementary Figure 2).



210

211 **Figure 3: Comparison of the mean age of first acute coronary syndrome between the**
 212 **normal weight group and overweight, obesity, and severe-obesity groups.**

213 BMI: body mass index, NSTEMI: non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction. USAP:
 214 unstable angina pectoris

215 **Table 2: Effect of risk factors on the age of first acute coronary syndrome**

| | B | p-value |
|---|--------|---------|
| Gender | -6.59 | <0.001 |
| Smoking | -15.11 | <0.001 |
| Diabetes mellitus | -4.63 | 0.001 |
| Psychosocial stress | -5.19 | <0.001 |
| Low-density lipoprotein cholesterol | -0.031 | <0.001 |
| Overweight–Normal body mass index | -3.54 | <0.001 |
| Grade I obesity–Normal body mass index | -5.68 | <0.001 |
| Severe obesity–Normal body mass index | -7.34 | <0.001 |
| Interaction term: Diabetes mellitus and Smoking | 6.23 | <0.001 |
| Interaction term: Gender and Smoking | 6.80 | 0.001 |

216 Linear regression model: dependent variable is age; $R^2 = 0.251$, $p < 0.001$

217 **Supplementary Table 1: Estimated age at the first episode of acute coronary syndrome (ACS) in patients with severe obesity**

218

| | | FEMALE | | | | | | | |
|-------------|---------|------------------|-------------|------------------|-------------|------------------|-------------|------------------|-------------|
| | | Current Smoker | | | | Non-smoker | | | |
| | | Family History + | | Family History – | | Family History + | | Family History – | |
| | | Pss + | Pss– | Pss + | Pss– | Pss + | Pss– | Pss + | Pss – |
| LDL-C | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a |
| | (mg/dl) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) |
| | years | years | years | years | years | years | years | years | years |
| 190 | 48 | 53 | 50 | 55 | 57 | 62 | 59 | 65 | |
| | (44–52) | (49–57) | (47–54) | (51–59) | (53–60) | (58–66) | (56–63) | (61–68) | |
| 160 | 49 | 54 | 51 | 56 | 58 | 63 | 60 | 65 | |
| | (45–52) | (50–58) | (47–55) | (52–60) | (54–61) | (59–66) | (57–64) | (62–69) | |
| DM + 130 | 50 | 55 | 52 | 57 | 59 | 64 | 61 | 66 | |
| | (46–53) | (51–59) | (48–56) | (53–61) | (55–62) | (60–67) | (58–65) | (63–70) | |
| 100 | 50 | 56 | 53 | 58 | 59 | 65 | 62 | 67 | |

| | | | | | | | | | |
|------|-----|---------|---------|---------|---------|---------|---------|---------|---------|
| | | (47–54) | (52–59) | (49–57) | (54–62) | (56–63) | (61–68) | (59–65) | (64–71) |
| | 70 | 51 | 56 | 54 | 59 | 60 | 65 | 63 | 68 |
| | | (47–55) | (52–60) | (50–58) | (55–63) | (57–64) | (62–69) | (59–66) | (64–72) |
| | 190 | 46 | 51 | 49 | 54 | 61 | 67 | 64 | 69 |
| | | (43–50) | (48–55) | (45–52) | (50–58) | (58–65) | (63–70) | (60–68) | (65–73) |
| | 160 | 47 | 52 | 50 | 55 | 62 | 67 | 65 | 70 |
| | | (44–51) | (49–56) | (46–53) | (51–59) | (59–66) | (64–71) | (61–68) | (66–74) |
| | 130 | 48 | 53 | 51 | 56 | 63 | 68 | 66 | 71 |
| | | (45–51) | (50–57) | (47–54) | (52–59) | (60–67) | (65–72) | (62–69) | (67–74) |
| DM – | 100 | 49 | 54 | 52 | 57 | 64 | 69 | 67 | 72 |
| | | (45–52) | (50–58) | (48–55) | (53–60) | (61–67) | (66–73) | (63–70) | (68–75) |
| | 70 | 50 | 55 | 52 | 58 | 65 | 70 | 67 | 73 |
| | | (46–53) | (51–59) | (49–56) | (54–61) | (61–68) | (66–74) | (64–71) | (69–76) |

219

220

| | | Current Smoker | | | | Non-smoker | | | |
|---------|-----|------------------|-------------|------------------|-------------|------------------|-------------|------------------|-------------|
| | | Family History + | | Family History - | | Family History + | | Family History - | |
| LDL-C | | Pss + | Pss- | Pss + | Pss - | Pss + | Pss- | Pss + | Pss - |
| (mg/dl) | | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a | e.a.a |
| | | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) | (l.-u. lim) |
| | | years | years | years | years | years | years | years | years |
| | 190 | 48 | 53 | 50 | 56 | 50 | 55 | 53 | 58 |
| | | (45-51) | (50-56) | (47-54) | (52-59) | (46-54) | (51-59) | (49-56) | 54-61 |
| DM + | 160 | 49 | 54 | 51 | 56 | 51 | 56 | 53 | 59 |
| | | (46-52) | (51-57) | (48-54) | (53-60) | (47-54) | (52-60) | (50-57) | (55-62) |
| | 130 | 50 | 55 | 52 | 57 | 52 | 57 | 54 | 59 |
| | | 47-53 | (52-58) | (49-55) | (54-60) | (48-55) | (53-60) | (51-58) | (56-63) |
| | 100 | 50 | 56 | 53 | 58 | 53 | 58 | 55 | 60 |
| | | (48-53) | (52-59) | (50-56) | (55-61) | (49-56) | (54-61) | (52-59) | (57-64) |
| | 70 | 51 | 56 | 54 | 59 | 54 | 59 | 56 | 61 |

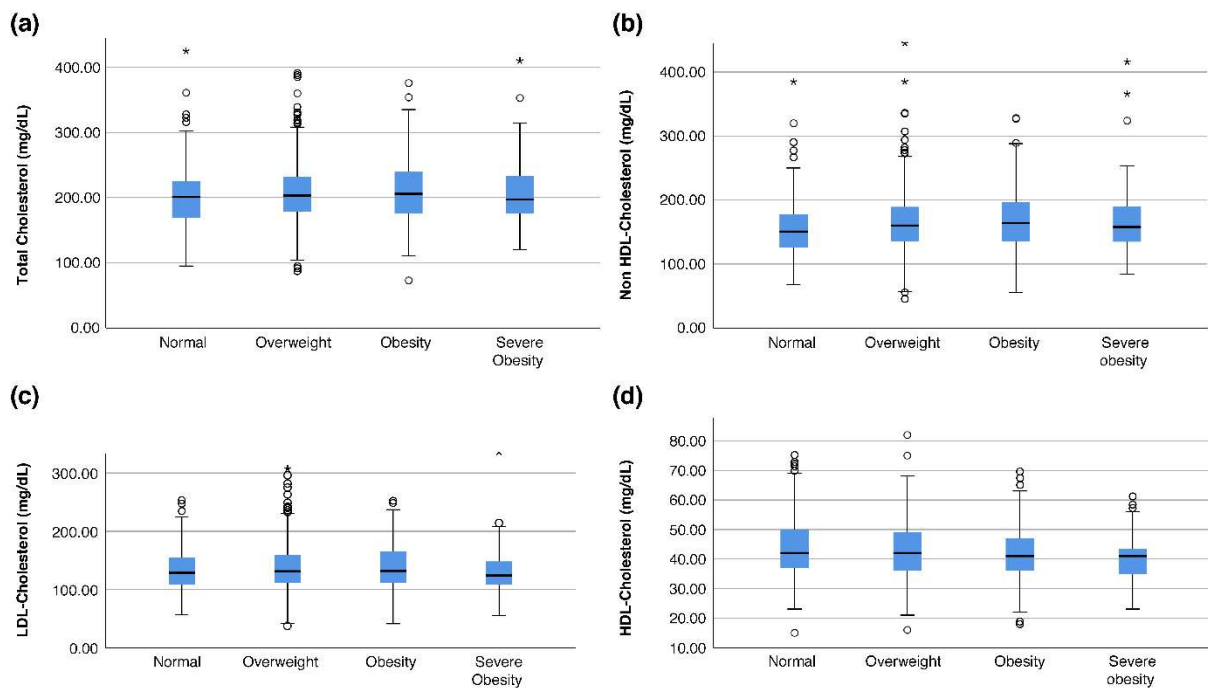
| | | | | | | | | |
|------|---------|---------|---------|---------|---------|---------|---------|---------|
| | (48–54) | (53–60) | (51–57) | (56–62) | (50–57) | (55–62) | (52–60) | (58–65) |
| 190 | 46 | 52 | 49 | 54 | 55 | 60 | 57 | 62 |
| | (44–49) | (49–55) | (46–52) | (51–57) | (51–58) | (56–58) | (54–61) | (59–66) |
| 160 | 47 | 52 | 50 | 55 | 56 | 61 | 58 | 63 |
| DM – | (45–50) | (50–55) | (47–53) | (52–58) | (52–59) | (57–54) | (55–61) | (60–67) |
| 130 | 48 | 53 | 51 | 56 | 56 | 62 | 59 | 64 |
| | (46–51) | (50–56) | (48–53) | (53–59) | (53–60) | (58–65) | (56–62) | (61–67) |
| 100 | 49 | 54 | 52 | 57 | 57 | 62 | 60 | 65 |
| | (46–52) | (51–57) | (49–57) | (54–60) | (54–61) | (59–66) | (57–63) | (62–68) |
| 70 | 50 | 55 | 52 | 58 | 58 | 63 | 61 | 66 |
| | (47–53) | (52–58) | (50–55) | (55–61) | (55–62) | (60–67) | (57–64) | (62–69) |

222 DM: Diabetes mellitus, e.a.a: expected average age, LDL-C: Low-density lipoprotein cholesterol, l.-u. lim: Lower and upper limits for 95%

223 Confidence interval, Pss: Psychosocial stress.

224 This chart shows the age of first ACS calculated for cardiovascular risks in patients with
 225 severe obesity. The upper-left corner of the table represents the presence of all risk factors in
 226 patients with severe obesity, while the lower-right corner is the case where no risk factors are
 227 present. The first estimated ACS age is 48 years for a patient with severe obesity, family
 228 history of diabetes mellitus (DM), expressed psychosocial stress, and a LDL-C value of 190
 229 mg/dl. In females and males with severe obesity and LDL-C values of 70 mg/dl with no risk
 230 factors, the expected age of ACS is 73 and 66 years, respectively. Smoking - sex and
 231 smoking - DM interaction terms were included in the regression model; therefore, the
 232 estimated age of first ACS was lower in both male and female patients with diabetes who
 233 smoked than those who did not smoke. These differences are not statistically significant.

234



235

236 **Supplementary Figure 2: Comparison of cholesterol values according to the body mass**
 237 **index groups**

238 BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density
239 lipoprotein cholesterol, TG: triglyceride, Total-C: total cholesterol

240

241 **Discussion**

242 The current study shows that obesity is an independent risk factor for premature ACS.
243 As obesity aggravated, patient's age at first ACS decreased in both sexes. When STEMI and
244 NSTEMI/USAP diagnoses are examined separately, an inverse correlation was found
245 between obesity and the age of first ACS episode. However, females with severe obesity with
246 the least number of risk factors experienced the first ACS episode 27 years later than those
247 with the highest number of risk factors. In males, the age difference was 20 years. Although
248 the body weight remained the same, elimination of modifiable risk factors may significantly
249 delay the age of the first ACS episode. Therefore, controlling the CV risk factors should be as
250 important as controlling the body weight in patients with obesity.

251 The effect of obesity on the age of patients at first ACS has been seldom studied.
252 Some studies focused on the effect of obesity on STEMI, while others focused on the effect
253 of obesity on the age of patients during NSTEMI; overall, obesity was associated with ACS
254 at an earlier age in both STEMI and NSTEMI groups. However, the effect of obesity on ACS
255 age was different in these studies. Suwaidi et al. showed that patients with obesity are likely
256 to have acute MI onset 8.2 years earlier than those with normal weight after adjustment for
257 sex, smoking status, prodromal angina, Killip class, acute MI history, DM, and HLD [11].
258 Wienbergen et al. found that patients with obesity experiencing first STEMI were 3 years
259 younger than those with normal weight with first STEMI [14]. In the current study, the
260 corrected age difference between the severe-obesity and normal-weight groups with acute MI
261 was -5.6 years. All these studies emphasize that patients with obesity experience an acute MI

262 at an earlier age. Madala et al. showed that patients with severe obesity (BMI > 40 kg/m²)
263 and grade II obesity (BMI 35–40kg/m²) experienced their first MI approximately 12 and 9
264 years earlier than those with normal weight, respectively [10]. The current study showed that
265 grade II and grade III obesity were classified as severe obesity and that the age difference
266 between the severe-obesity (BMI > 35 kg/m²) and normal-weight (BMI < 25 kg/m²) groups
267 with NSTEMI/USAP was –10.1 years. Additionally, the average age of patients with normal
268 weight experiencing ACS is younger than the average age determined in other studies.
269 However, the ACS age of the normal-weight group in our study is close to that of the severe-
270 obesity group in other similar studies [10, 11, 14]. This finding may be related to the idea that
271 these studies were conducted in different societies. Although our data inadequately represent
272 the Turkish community, our study revealed that the age at first ACS episode in our country is
273 lower and that the mean age of ACS varies between countries. In the recently published
274 multicenter TURKMI study, the MI age range is, in fact, close to the MI age range in our
275 study [15]. Similar to our study, the TURKMI study demonstrated that patients with MI in
276 Turkey were younger than those in developed countries.

277 The present study showed that BMI, male sex, smoking, DM, family history,
278 psychosocial stress, and LDL-C levels were independent variables that affect the age of first
279 ACS episode. Sex, DM, HLD, HTN, family history, and smoking are the traditional risk
280 factors for coronary artery disease. Modification of DM, HLD, HTN, and smoking risk
281 factors is crucial for preventing CV events [16]. Smoking, family history of premature CHD,
282 and male sex among young patients with MI were more prevalent than those among their
283 older counterparts [17].

284 According to our analysis, HTN was not related to premature ACS, probably because
285 of the prevalence of HTN that changes with age. HTN was prevalent by 19% in patients aged
286 <45 years and by 58% in patients aged >75 years in our study population. Similarly, in Gulf

287 RACE and Gulf RACE-2, HTN is less prevalent in younger individuals with ACS than in
288 older individuals with ACS. Furthermore, GISSI-2 showed that the risk of MI (0.45 [0.40–
289 0.50]) is lower in younger (<50 years) than in older (50–70 years) individuals with HTN [18].

290 In the last few decades, the incidence of obesity and DM has increased at younger
291 ages. This situation could lead them to premature ACS [2]. In addition to these traditional
292 risk factors, nontraditional risk factors (e.g., human immunodeficiency virus, inflammatory
293 diseases, recreational drug use, and psychosocial stress) are associated with premature
294 atherosclerotic events [19]. Chronic stress is associated with a considerable risk for CHD
295 incidence, supporting the notion that stress is a causal CHD risk factor. Furthermore, studies
296 involving survivors of ACS suggested that acute emotional stress can trigger ACS [20, 21].

297 The findings support the hypothesis that obesity is independently linked with the
298 premature occurrence of ACS. Adipose tissue is not only involved in energy storage but also
299 acts as an endocrine organ that secretes various bioactive substances. Irregular expression of
300 these factors caused by excessive fat and adipocyte dysfunction is associated with the
301 pathogenesis of various disease processes through altered immune responses [22-24]. Obesity
302 is a chronic, low-grade inflammatory condition that contributes to the development of
303 obesity-related disorders, particularly because of metabolic dysfunction [25, 26].

304 Additionally, patients with a high BMI are associated with impaired microvascular coronary
305 endothelial dependent function [27]. Considering these physiopathological mechanisms,
306 obesity results in wide-ranging diseases that reduce life expectancy, such as insulin
307 resistance, type 2 DM, atherosclerosis, and ischemic heart disease, further leading to great
308 economic and social consequences [28, 29]. Previous meta-analysis showed that if the
309 normal-weight limit exceeds, the mortality rate increases linearly with BMI [30]. In the upper
310 BMI range (25–50 kg/m²), each 5 kg/m² higher BMI is associated with approximately 40%
311 higher mortality in ischemic heart disease. Ischemic CAD is associated with lower life

312 expectancy [1, 31, 32]. Therefore, initiating CV preventive treatment in patients with obesity
313 at an earlier age is important. However, the risk algorithms used by current guidelines do not
314 consider obesity or BMI increase as an independent risk factor [33]. In preventive treatment
315 recommendations, considering the relationship between obesity and ACS at an earlier age
316 may be beneficial.

317 Some people with obesity are protected from many of the adverse metabolic effects of
318 excess body fat tissue, indicating a “metabolically healthy” state. Unfortunately, MHO has no
319 any universally accepted description. Most investigators define MHO as having either 0, 1, or
320 2 metabolic syndrome components [34]. The risk of CV events does not increase significantly
321 in people identified as MHO [35, 36]. The main risk increase is in MUO. The risk of CV
322 events in MONW individuals is higher than in MHO. The current study was not designed to
323 examine MHO, MUO, and MONW groups separately; however, the effect of CV risk factors
324 was investigated. The presence of CV risk factors in people with severe obesity makes the
325 age of ACS noticeably younger, consistent with the findings of increased CV risk in
326 individuals with MUO. Additionally, in line with the MHO concept, CV events can be
327 delayed in patients without risk factors. However, the kind of approach that should be used in
328 patients with obesity remains unclear. Is weight loss an absolute goal in patients with
329 obesity? According to a recent article regarding patients with pre-DM or type 2 DM
330 presenting with obesity, weight loss was related to higher all-cause and CV mortality
331 compared with the lack of weight loss; such relationship was not observed in weight gain
332 [37]. In preventing or delaying CV events, the same approach given to all people with obesity
333 may be incorrect and the main goal should not be to lose weight. A recent study showed that
334 weight loss was an independent risk factor for higher mortality than no weight loss in
335 prediabetes or type 2 DM patient with obesity [37]. Detecting whether CV risk factors are
336 present and eliminating the modifiable ones may benefit patients with severe obesity.

337 There are some limitations to the study. One limitation of our study is the single-
 338 center design; however, the characteristics of the patient group are compatible with the
 339 multicenter TURKMI study [15]. The study was conducted in the center with the highest
 340 ACS patient burden in Antalya. Antalya is one of the cities in Turkey with the highest
 341 number of immigrants. When the data were analyzed according to the immigration status of
 342 the patients, it was observed that half of the participating patients were migrants from other
 343 provinces, and 501 patients had emigrated from Turkey's 12 different geographical regions
 344 (Supplementary Table 2). Although our study was not planned as a multicenter study,
 345 patients from all geographical regions were included in the study.

346 **Supplementary Table 2: Distribution of migrated patients by regions of Turkey**

| | n | % |
|------------------------------------|-----|-------|
| Istanbul Region (TR1) | 16 | 3.2 |
| West Marmara Region (TR2) | 25 | 5.0 |
| East Marmara Region (TR4) | 9 | 1.8 |
| Aegean Region (TR3) (| 67 | 13.4 |
| West Anatolia Region (TR5) | 51 | 10.2 |
| Mediterranean Region (TR6) | 102 | 20.4 |
| Central Anatolia Region (TR7) | 48 | 9.6 |
| West Black Sea Region (TR8) | 41 | 8.2 |
| East Black Sea Region (TR9) | 26 | 5.2 |
| Northeast Anatolia Region (TRA) | 28 | 5.6 |
| Central East Anatolia Region (TRB) | 35 | 7.0 |
| Southeast Anatolia Region (TRC) | 53 | 10.6 |
| Total immigration patients | 501 | 100.0 |

347

348 Furthermore, the number of patients in the severe-obesity group is relatively low;
349 more studies involving this group of patients are needed. In addition, results should be tested
350 with prospective cohort studies in patients with obesity. Nonetheless, the current study
351 provides data for risk factors to be studied in prospective cohort studies.

352 Another limitation of our study is that we did not use specific questionnaires to define
353 psychosocial stress; thus, we could not make a more detailed psychological evaluation.
354 Furthermore, ACS may have possibly affected patients' answers. The tests to be used in
355 stress assessments would affect the current ACS and coronary intensive care admission
356 period. For this reason, instead of providing questions that would emphasize on the patient's
357 current feelings, we provided questions that would emphasize on whether the patients had a
358 stressful character or life. To mitigate this disadvantage, we asked such questions when
359 patient's condition was stable. We also emphasized to give an answer considering the
360 situation before the event. Despite all these interventions, the reliability of psychosocial stress
361 factor assessment during ACS is still controversial. Findings need to be evaluated in
362 prospective cohort studies. However, excluding psychosocial stress status in the analysis may
363 also create a scientific deficiency.

364 In addition, the fact that the study covers a period of 5 years may cause limitations in
365 terms of standardization of laboratory results. In the laboratory reviews included in the study
366 within this time period, the kit or calculation methods remained the same.

367 An important difference between our study and other similar studies was that we
368 included patients with culprit lesions in CAG, and excluded those without CAG. Moreover,
369 patients diagnosed with Type 1 MI were included in the study, and other types of AMI were
370 excluded. Thus, a more specific patient group was formed to calculate the age of the first
371 ACS due to atherosclerotic plaque rupture. In addition, patients using drugs, such as statin

372 and antiplatelet that affect the first ACS age, were excluded from the study. Hence, confusing
373 factors were removed before calculating the first ACS age.

374 **Conclusions**

375 Patients with severe obesity experienced their first ACS episode 7 years earlier than
376 those with normal weight. However, the absence of CV risk factors in people with obesity
377 eliminated the potential negative effect of obesity on the ACS age. For the prevention of
378 premature ACS in individuals with obesity, the necessity of additional prevention strategy at
379 an early age should be investigated through prospective cohort studies.

380 **List of abbreviations**

381 ACE-I: angiotensin converting enzyme-inhibitors

382 ACS: acute coronary syndrome

383 ARB: angiotensin receptor blockers

384 BB: beta blockers

385 BMI: body mass index

386 CV: cardiovascular

387 CVD: cardiovascular disease

388 HLD: hyperlipidemia

389 HTN: hypertension

390 LDL-C: low-density lipoprotein cholesterol

391 MHO: metabolically healthy obese

392 MI: myocardial infarction

393 MONW: metabolically obese but has a normal weight

394 MUO: metabolically unhealthy obese

395 NSTEMI: non–ST-elevated myocardial infarction

396 STEMI: ST-elevated myocardial infarction

397 USAP: unstable angina pectoris

398 **Ethics approval and consent to participate:** This was approved by the ethics committee of
399 Antalya Training and Research Hospital, University of Health Sciences (2014-097). Written
400 informed consent was obtained from all participants.

401 **Consent for publication:**

402 **Availability of data and materials:** The datasets generated during and/or analyzed during
403 the current study are available from the corresponding author on reasonable request.

404

405 **Competing interests:** The authors have no conflicts of interest to declare.

406

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408

409 **Authors' contributions:**

410 **(1) Study conception and design: DD. (2) Data processing and preliminary analyses:**

411 **DD. (3) Literature searches and reviewing: DD, DED. (4) Data analysis: DD. (5)**

412 **Manuscript writing: DD, DED. (6) Editing and reviewing: all authors. All authors read**

413 **and approved the final manuscript**

414

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417

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422

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518

Figures

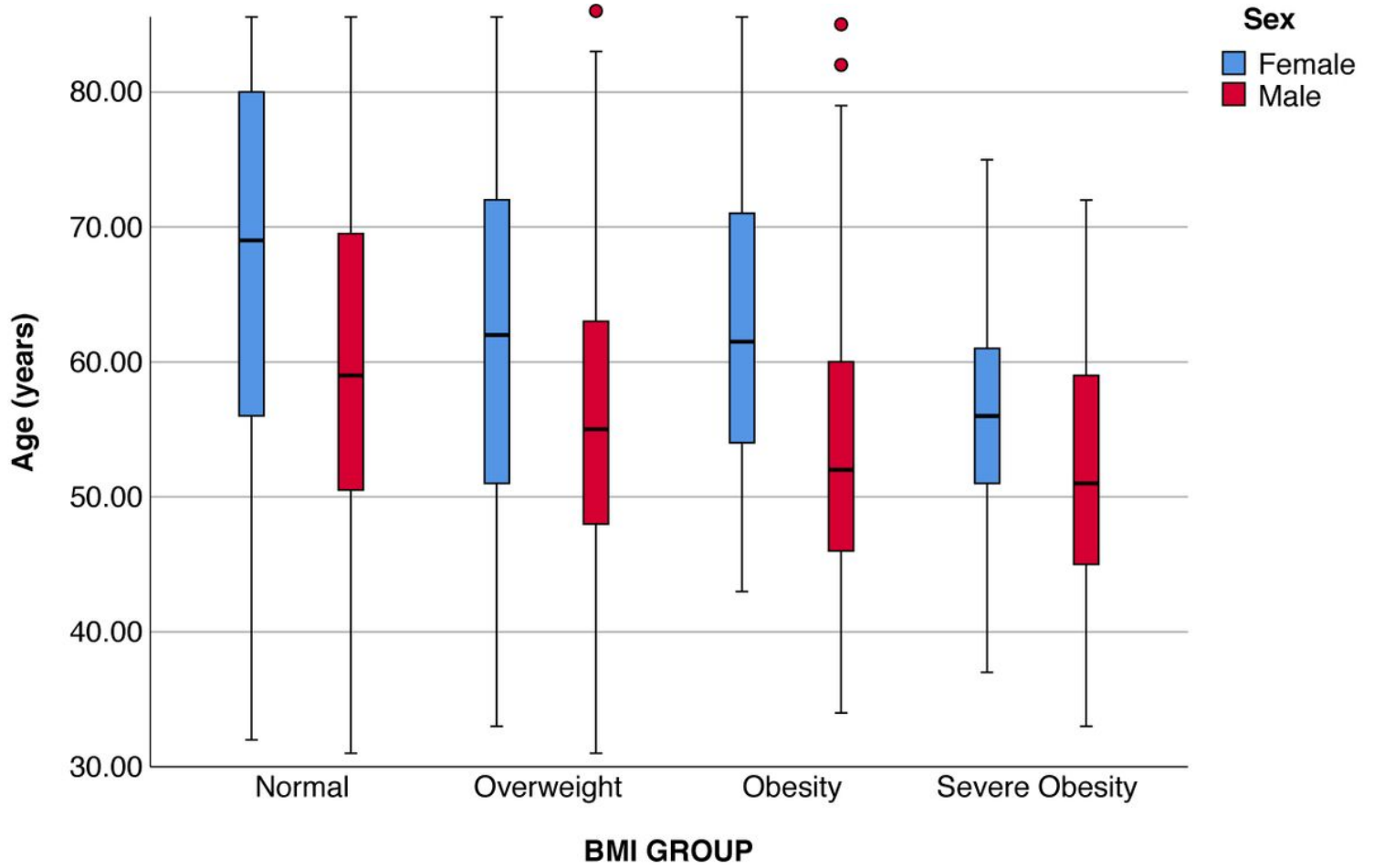


Figure 1

Comparison of the mean age of first acute coronary syndrome by body mass index groups for both sexes. BMI: body mass index

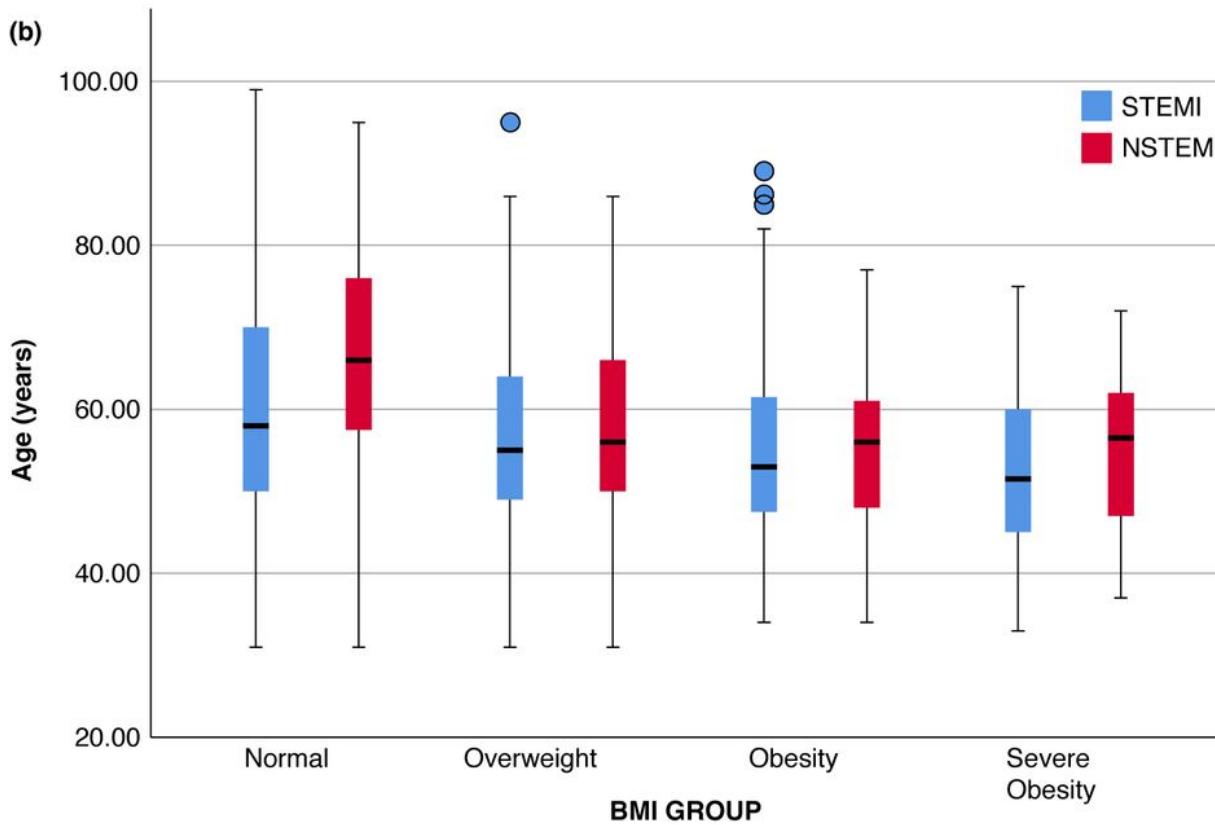
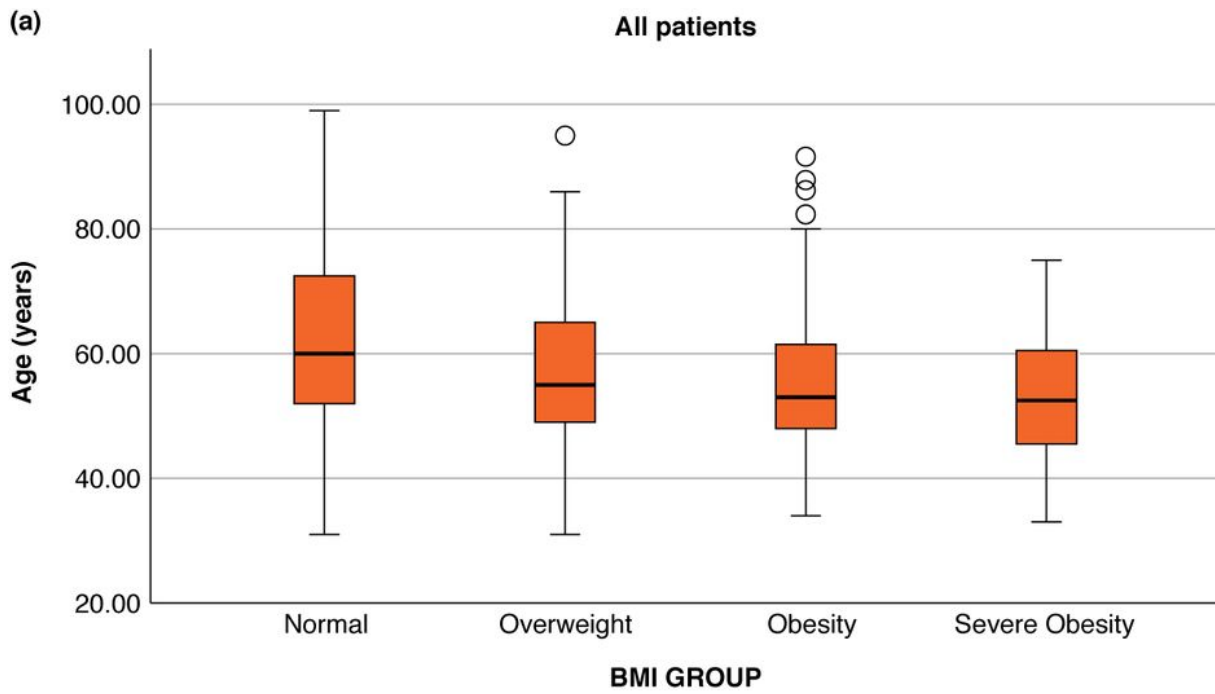


Figure 2

Comparison of the mean age of first acute coronary syndrome by body mass index groups A) for all patients B) for STEMI and NSTEMI/USAP patients separately BMI: body mass index, NSTEMI: non-ST-elevated myocardial infarction, STEMI: ST-elevated myocardial infarction. USAP: unstable angina pectoris

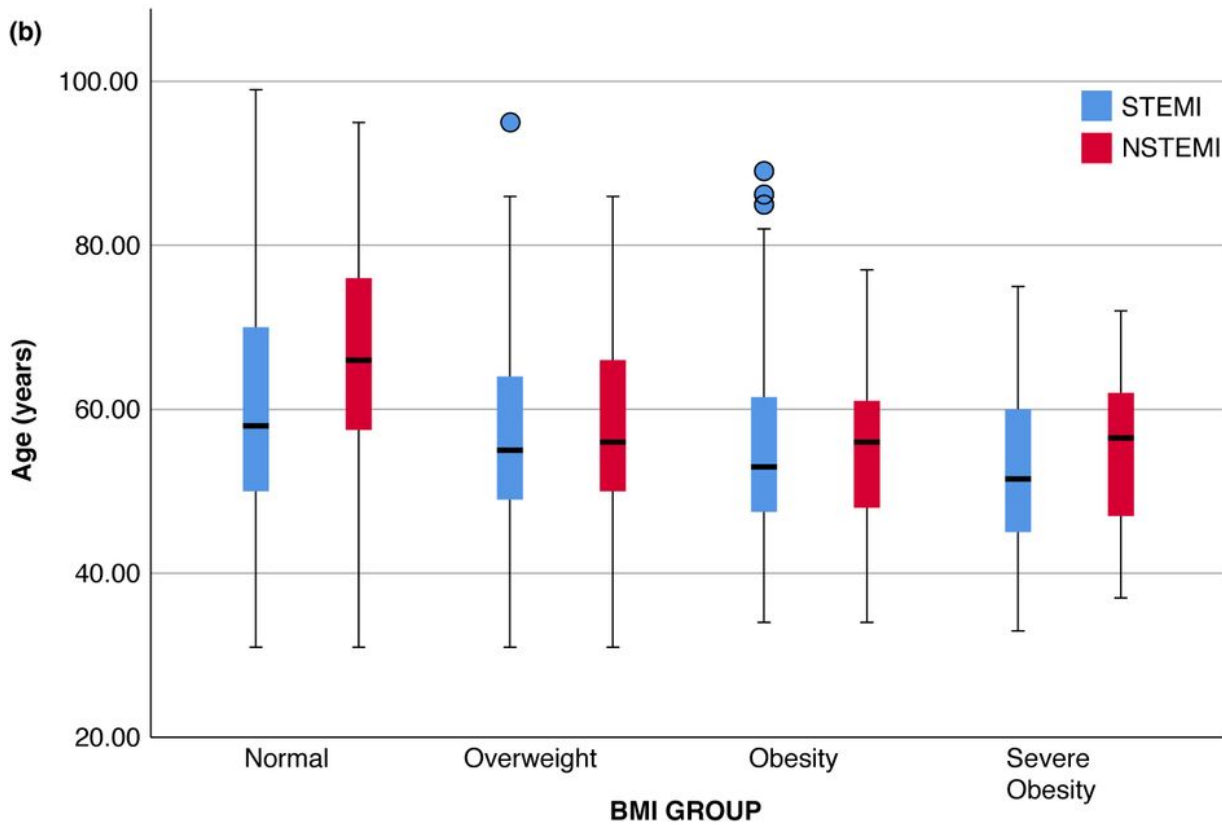
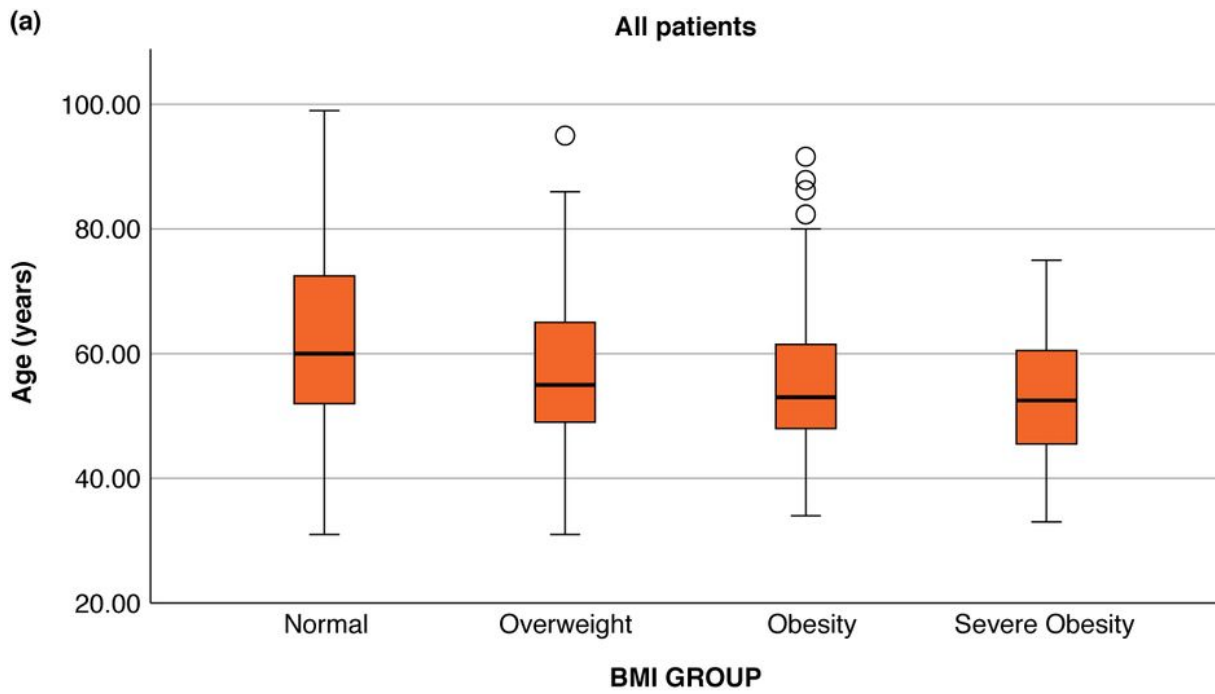


Figure 3

Comparison of the mean age of first acute coronary syndrome between the normal weight group and overweight, obesity, and severe-obesity groups BMI: body mass index, NSTEMI: non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction. USAP: unstable angina pectoris

Supplementary Files

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