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Underweight and obesity are related to higher mortality in patients undergoing coronary angiography: The KARDIO invasive cardiology register study

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Abstract

Background: In patients with some cardiovascular disease conditions, slightly elevated body mass index (BMI) is associated with a lower mortality risk (termed "obesity paradox"). It is uncertain, however, if this obesity paradox exists in patients who have had invasive cardiology procedures. We evaluated the association between BMI and mortality in patients who underwent coronary angiography.

Methods: We utilised the KARDIO registry, which comprised data on demographics, prevalent diseases, risk factors, coronary angiographies, and interventions on 42, 636 patients. BMI was categorised based on WHO cut-offs or transformed using P-splines. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated for all-cause mortality.

Results: During a median follow-up of 4.9 years, 4688 all-cause deaths occurred. BMI was nonlinearly associated with mortality risk: compared to normal weight category (18.5–25 kg/m^2), the age-adjusted HRs (95% CIs) for all-cause mortality were 1.90 (1.49, 2.43), 0.96 (0.92, 1.01), 1.04 (0.99, 1.09), 1.08 (0.96, 1.20), and 1.45 (1.22, 1.72) for underweight (<18.5 kg/m^2), preobesity (25 to <30 kg/m^2), obesity class I (30 to <35 kg/m^2), obesity class II (35 to <40 kg/m^2), and obesity class III (>40 kg/m^2), respectively. The corresponding multivariable adjusted HRs (95% CIs) were 2.00 (1.55, 2.58), 0.92 (0.88, 0.97) 1.01 (0.95, 1.06), 1.10 (0.98, 1.23), and 1.49 (1.26, 1,78), respectively.

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Conclusions: In patients undergoing coronary angiography, underweight and obesity class III are associated with increased mortality risk, and the lowest mortality was observed in the preobesity class. It appears the obesity paradox may be present in patients who undergo invasive coronary procedures.

KEYWORDS
angiography, body mass index, coronary artery disease, hospital register, mortality

1 | INTRODUCTION

Obesity is related to coronary artery disease (CAD) risk factors, such as hypertension, hyperlipidaemia, and diabetes. Patients with obesity have an increased risk of cardiovascular diseases (CVDs) and all-cause mortality, which is partly due to the accumulation of CAD risk factors. Obesity may increase the risk of fatal CVDs due to a more extensive and diffuse form of CAD. Subsequently, obesity increases the risk of other common CAD-related adverse events, including heart failure (HF), atrial fibrillation (AF), and sudden cardiac death (SCD).[1,2] Though a J-shaped relationship between body mass index (BMI; kg/m^2) (a common measure of body weight status) and mortality has generally been reported in the general population,[3] the relationship between the whole spectrum of BMI levels (from very low to very high) and mortality among cardiac patients is still debatable.

Some epidemiological studies suggest that slightly higher BMI levels might be associated with better outcomes—particularly a lowered risk of mortality—in patients with existing HF.[4,5] This phenomenon has led to the concept of "obesity paradox" and has been observed in patients with CVDs such as acute coronary syndromes (ACSs), CAD, and AF.[6-9] Indeed, it has been suggested that mildly overweight patients with ST-elevation myocardial infarction (STEMI) may have less extensive CAD and even better left ventricular systolic function and quality of life, compared to patients with normal weight or more severe obesity.[10] A meta-analysis of over 200,000 patients with acute myocardial infarction (AMI) reported that patients with elevated BMI had a 30%–40% lower mortality risk compared with individuals with normal BMI. Another large observational study with prospectively collected data strengthens the obesity paradox concept in patients with ACS or chronic CAD.[11] The phenomenon of "obesity paradox" may also exist among elderly CAD patients who need invasive interventions such as percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG), with a higher mortality in those patients with a very low BMI.[12]

However, there is very limited evidence on the relationship between BMI and mortality risk in cardiac patients in the contemporary era of invasive cardiology; therefore, a comprehensive evaluation based on current up-to-date data is needed. Previous studies that have included a variety of patients with very low to extremely high BMI levels undergoing invasive coronary angiography with long-term mortality rates beyond 12 months are nonexistent. Using an ongoing real-life multicentre Finnish coronary angiography register, we sought to explore whether the obesity paradox also exists in invasive cardiology practice, by investigating the association between extremes of BMI levels and overall mortality in patients who underwent coronary angiography.

2 | METHODS

2.1 | Study population

This study is based on data obtained from the Finnish KARDIO registry of cardiac patients undergoing invasive diagnostic and interventional procedures. The purpose of the registry is to provide data on evidence-based cardiac care and thereby supporting the improvement in therapies for cardiac diseases, combining data of demographic characteristics, chronic diseases, cardiovascular risk factors, coronary angiographies, and interventions (PCIs and CABGs). The KARDIO registry is updated prospectively by treating physicians and it provides users with online interactive reports monitoring the processes of care and outcomes and allowing direct comparisons over time and with other hospitals. The performing cardiologist reports patient data from each procedure on-line via a web-based form directly from the catheterization laboratory using hospital documents, laboratory measurements, prevalent conditions, interviews, and all details of the invasive operation procedure.

The data is collected from seven Finnish cardiology centres from Western, Central, and Northern Finland. Together, these seven centres provide specialized health care for a catchment area of approximately two million inhabitants. Between January 1, 2012 and December 30, 2018, a total of 82,911 patients (over 17 years) underwent cardiac catheterization, and the original KARDIO database comprised 149,028 procedures among these included patients. The registry includes patients who underwent a diagnostic coronary angiography for diagnostic purposes or to establish disease severity in known CAD. A considerable proportion of the patients had ACS (ST-segment elevation myocardial infarction [STEMI], non-STE-ACS [NSTEMI], or unstable angina pectoris [UAP]). Those who underwent revascularization (catheter-based or surgical) and those treated conservatively were included. Patients who were referred to cardiac catheterization for valvular heart disease as the primary reason were excluded, leaving 79,738 subjects into the analyses (Supporting

Information: Figure S1). Missing data for one or more main variables occurred in 48,727 patients who were included in the registry. High workload of the performing cardiologist is recognized as a potential reason for the incomplete data entry. Data are therefore assumed to be missing at random (MAR). According to the Finnish national and ethical regulations on the use of hospital quality registry data for research and development purposes, written informed consent from patients is not mandatory for registration of data. Standards of care for coronary intervention procedures and related management were adopted at the discretion of the treating physicians. The National Board of Health and Welfare of Finland approved the registry and the linkage of data with the national death registry. Linkage was performed using the personal identification code (PIN), which is possessed by all Finnish citizens and permanent residents.

2.2 | Clinical data collection

The registry comprises data on baseline characteristics, ECG changes, biochemical markers, coronary angiography findings, medical and invasive therapy. Standards of care for interventional coronary procedures and related management were adopted at the discretion of the treating physicians. The accurate collection of data was the responsibility of the treating physicians and participating investigators. Data collected before coronary angiography includes age, sex, smoking status, hypertension, diabetes, dyslipidaemia, New York Heart Association (NYHA) functional classification, angina pectoris symptoms, kidney function, medication, symptoms, and electrocardiogram changes at entry and at specified time points (for STEMI patients), previous MI, coronary revascularization, heart failure, stroke.

BMI was computed as weight in kilograms divided by the square of height in meters. Hypertension at rest was defined as hypertension confirmed by the current use of antihypertensive medication and/or SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg. Diabetes was defined as a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment. Dyslipidaemia was defined as the current use of lipid-lowering medication (or plasma low-density cholesterol level of over 3.0 mmol/L). Smoking was classified as nonsmoker or current smoker. A patient was described as a current smoker if he or she had ever smoked regularly and had smoked cigarettes, cigars, or pipes within 1 month before the hospital admission. A family history of CAD was defined as positive when at least one first-degree relative had been diagnosed with MI or CAD requiring revascularization before the age of 65 years for women and 55 years for men. Hospitalization-related variables, including final diagnosis, therapy-related complications, and other intervention-related outcomes, were recorded.

2.3 | All-cause mortality events

In addition to collected phenotypic data, KARDIO-registry is also directly linked to the National Death Registry providing continuously updated information on overall mortality of all treated patients. The primary endpoint in this study was all cause-mortality. The study design ensured that a first clinical evaluation was made at hospital discharge (a baseline visit) and follow-up was carried out by linkage to the National Death Registry using a PIN. Follow-up data were available by merging data from the mandatory Finnish Cause of Death Register with the KARDIO register data: merging was performed at the National Board of Health and Welfare in Finland based on the PIN. There was no loss-to follow-up.

2.4 | Statistical analysis

Continuous variables are expressed as mean (standard deviation, SD) or median (interquartile range, IQR) and categorical data were presented as frequencies (percentages). Descriptive statistics were used to summarize the baseline characteristics overall and by BMI categories. We used the BMI categories established by the World Health Organization (WHO): underweight (15 to <18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2; pre-obesity), moderately obese (30 to <35 kg/m^2; obesity I class), severely obese (35 to <40 kg/m^2; obesity II class) and very severely obese (40 to <60 kg/m^2; obesity III class).

To handle the missing data properly under the MAR assumption, we used areg impute function from Hmisc R package for multiple imputation ($m = 20$ rounds).[13,14] This uses predictive mean matching (PMM) based on canonical-correlation analysis (CCA).[15] The imputation model may include nonlinear associations (restricted cubic splines). The model uncertainty is handled by taking a bootstrap sample from the original data at every imputation round. In addition to variables in the actual analyses, some other variables derived from visits and follow-up time were used to improve the imputations (Supporting Information: Spreadsheet S1).

Cox proportional hazard modelling was used to explore the relationship of categorical BMI (normal weight as the reference level) and risk of all-cause mortality with three different adjustment models: adjusted for age (Model 1); Model 1 plus smoking status, diabetes, hypertension, family history of CAD, sex and age-sex-interaction (Model 2); and Model 2 plus angiographic findings (Model 3). To explore the shape of the relationship between BMI and all-cause mortality, we performed spline-transformation for BMI adjusting for covariates as in Model 3; BMI of 23 kg/m^2 was set as the normal-weight reference level because it is approximately the mean (23.0 kg/m^2) and the median (23.4) of BMI. Complexity of the P-spline curve was controlled visually and degree of freedom was set to 3.[16] Scaled Schoenfeld residuals were used to investigate proportional hazards assumption in complete cases analysis and to decide whether adjusting (categorical) variables should be treated as covariates or stratifying variables.[17] All models were stratified by the hospital the patient visited. Also, residuals showed that diabetes, dyslipidaemia, and angiographic finding possibly violated the proportionality assumption, so they were used as stratifying variables. Then Rubin's rules were applied to get the pooled hazard ratios (HRs) and

corresponding 95% confidence intervals (CIs).[14] Subgroup analyses were performed using the following characteristics: sex, operation urgency, family history of CAD, kidney failure, and follow-up time (truncating to 1 year and focusing on first-year survivors). The following sensitivity analyses were applied: imputing with only one interaction term (age-sex), using BMI calculated from PMM imputed weight and height instead of PMM-imputed BMI, turning all stratifying variables into covariates and removing patients from two smallest hospitals. We also conducted the analyses using complete cases only, without any missing variable in the analyses. The Kaplan–Meier method was used to show survival curves for BMI categories. All analyses and graphics were carried out using R software[18] and the following R packages: Hmisc (imputation), mice (pooling),[13] survival (Cox models),[17] ggplot2 (graphics),[19] and survminer (graphics).[20]

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics overall and according to the different BMI categories are shown in Table 1. The majority of patients were male (60.4%) and overall mean (standard deviation, SD) age was 65.3 (10.8) years. The overall median (interquantile range, IQR) for BMI was 27.4 (24.8–30.8) kg/m^2. Patients with obesity were more likely to be younger and they had a higher level of common CVD factors such as dyslipidaemia, hypertension, and diabetes compared to underweight patients and those with normal BMI. Obese patients had more prevalent CAD at baseline compared to underweight patients. Underweight patients were more often females and smokers. Left ventricular ejection fraction (EF) was the lowest among underweight and very severely obese patients (Table 1). Patients with very severe obesity had less 1- to 3-vessel CAD compared to normal-weight and overweight patients. Left main CAD was most common among lean patients. Invasive interventions such as PCI and CABG were performed more commonly for normal-weight than obese patients (Table 1). Supporting Information: Table S1 involves statistics based on whether BMI is available or missing, providing data on clinical characteristics in these two categories.

3.2 | Follow-up

During a median (IQR) follow-up of 5.5 (2.5–8.6) years (445,641 person-years at risk), a total of 11,896 all-cause-deaths were recorded. The P-spline curve showed a nonlinear U-shaped relationship between BMI and all-cause mortality risk (Figure 1); the curve based on the complete case analysis was steeper. Patients in the underweight category were at substantially increased risk of death compared to the other BMI categories. Compared to the normal weight category, the age-adjusted HRs (95% CIs) for all-cause mortality were 1.90 (1.49, 2.43), 0.96 (0.92, 1.01), 1.04 (0.99, 1.09), 1.08 (0.96, 1.20), 1.45 (1.22, 1.72) for underweight, preobesity, obesity class I, obesity class II and obesity class III, respectively. The HRs (95% CIs) were minimally amplified to 2.00 (1.55, 2.58), 0.92 (0.88, 0.97), 1.01 (0.95, 1.06), 1.10 (0.98, 1.23), and 1.49 (1.26, 1.78) upon further adjustment for smoking status, diabetes, hypertension, and family history of CAD and angiographic findings.

3.3 | Subgroup and sensitivity analyses

In subgroup analyses, the associations did not vary importantly by sex, family history of CAD, and follow-up time. On the other hand, when subjects with elective and urgent procedures were analysed separately, the HR (95% CI) for mortality in underweight patients was extreme when the procedure was elective 3.09 (2.13, 4.48) and lower when procedure was urgent 1.50 (1.06, 2.14). Kidney failure did not seem to modify the association between BMI and all-cause mortality risk (Supporting Information: Figure S2).

Changing stratifying variables into covariates produced almost identical results, suggesting no major violation of the proportional hazards assumptions. Using BMI calculated from PMM-imputed weight and height instead of PMM-imputed BMI gave a slightly higher HR for underweight (2.11 [1.66, 2.69]) but the rest of the estimates remained nearly unchanged. Limiting interactions into age-sex-interaction in the imputation phase diminished the HRs only marginally (1.86 [1.43, 2.42] in underweight) whereas focusing on the biggest hospitals amplified the effects to some extent (HR 2.07 [1.59, 2.70] in underweight). In general, the results seem to be robust for changes in the analysis settings.

4 | DISCUSSION

4.1 | Main findings

This study showed that very severely obese and underweight patients who underwent invasive coronary angiography had an increased risk of all-cause death compared to normal-weight patients. Our contemporary register data also showed that normal and overweight patients had the lowest risk of overall death, which suggest that the obesity paradox exists also in patients undergoing an invasive coronary procedure. The results show a bimodal mortality pattern across the whole spectrum of BMI categories. The associations remained robust in subgroup and sensitivity analyses. High BMI levels were associated with common cardiac comorbidities such as diabetes mellitus, hypertension, and dyslipidaemia.

4.2 | Previous studies

Previous studies have suggested that overweight or obese patients with CAD may have lower morbidity and mortality than their leaner counterparts.[8,21,22] After coronary revascularization procedures, such

TABLE 1 Baseline characteristics by body mass index categories

Variable	Underweight (BMI 15–18.5 kg/m^2)	Normal (BMI 18.5–25 kg/m^2)	Overweight (BMI 25–30 kg/m^2)	Moderately obese (BMI 30–35 kg/m^2)	Severely obese (BMI 35–40 kg/m^2)	Very severely obese (BMI over 40 kg/m^2)	Total	Missing
Patient, *N*	254 (0.6%)	11,404 (26.7%)	18,323 (43.0%)	8934 (21.0%)	2704 (6.3%)	1017 (2.4%)	42,636	-
Age, years	66.7 (11.2)	66.5 (11.1)	65.4 (10.7)	64.5 (10.5)	63.1 (10.5)	61.9 (9.9)	65.3 (10.8)	0
Body mass index (kg/m^2)	17.5 (17.2–18.1)	23.4 (22.1–24.2)	27.3 (26.2–28.4)	31.8 (30.8–33.1)	36.7 (35.7–38.0)	42.6 (41.0–45.0)	27.4 (24.8–30.8)	0
Ejection fraction (%)	55.0 (50.0–60.0)	60.0 (52.0–68.0)	60.0 (55.0–67.0)	60.0 (53.0–65.0)	60.0 (50.0–65.0)	56.5 (50.0–62.0)	60.0 (53.0–67.0)	35,561
Sex								0
Female	158 (62.2%)	4863 (42.6%)	6403 (34.9%)	3666 (41.0%)	1261 (46.6%)	433 (52.4%)	16,884 (39.6%)	
Male	96 (37.8%)	6541 (57.4%)	11,920 (65.1%)	5268 (59.0%)	1443 (53.4%)	484 (47.6%)	25,752 (60.4%)	
Hypertension								1250
No	157 (65.4%)	6398 (58.2%)	8763 (49.3%)	3369 (38.8%)	831 (32.9%)	266 (31.5%)	19,811 (47.9%)	
Yes	83 (34.6%)	4600 (41.8%)	8995 (50.7%)	5317 (61.2%)	1809 (67.1%)	728 (68.5%)	21,575 (52.1%)	
Heart failure								728
No	232 (92.4%)	10,840 (96.8%)	17,508 (97.2%)	8434 (96.0%)	2509 (94.1%)	904 (91.1%)	40,427 (96.5%)	
Yes	19 (7.6%)	361 (3.2%)	507 (2.8%)	348 (4.0%)	158 (5.9%)	88 (8.9%)	1,481 (3.5%)	
Kidney failure								656
No	238 (94.4%)	10,734 (95.7%)	17,306 (95.9%)	8394 (95.5%)	2536 (94.9%)	928 (93.0%)	40,136 (95.6%)	
Yes	14 (5.6%)	488 (4.3%)	735 (4.1%)	400 (4.5%)	137 (5.1%)	70 (7.0%)	1844 (4.4%)	
Anticoagulation								3803
No	204 (89.1%)	9412 (90.6%)	15,078 (90.2%)	7122 (87.6%)	2115 (86.2%)	762 (83.5%)	34,693 (89.3%)	
Yes	25 (10.9%)	979 (9.4%)	1640 (9.8%)	1005 (12.4%)	340 (13.8%)	151 (16.5%)	4140 (10.7%)	
ASO								27,899
No	84 (90.3%)	3624 (94.6%)	5954 (94.9%)	3007 (95.1%)	925 (95.8%)	401 (96.9%)	13,995 (95.0%)	
Yes	9 (9.7%)	205 (5.4%)	319 (5.1%)	155 (4.9%)	41 (4.2%)	13 (3.1%)	742 (5.0%)	
NYHA class								10,423
I	6 (4.3%)	624 (10.2%)	898 (8.9%)	368 (7.3%)	110 (6.8%)	25 (3.9%)	2031 (8.6%)	
II	30 (21.4%)	1599 (26.2%)	2666 (26.6%)	1308 (26.0%)	398 (24.6%)	164 (25.7%)	6165 (26.2%)	
III	45 (32.1%)	2267 (37.2%)	3745 (37.3%)	1967 (39.0%)	631 (38.9%)	242 (38.0%)	8897 (37.7%)	
IV	59 (42.1%)	1609 (26.4%)	2726 (27.2%)	1395 (27.7%)	482 (29.7%)	206 (32.3%)	6477 (27.5%)	
Coronary artery dominant								5427
Balanced	56 (26.2%)	2645 (26.9%)	4348 (27.1%)	2202 (27.9%)	606 (25.6%)	257 (29.2%)	10,114 (27.2%)	
Right	102 (47.7%)	4378 (44.6%)	7149 (44.6%)	3543 (45.0%)	1078 (45.6%)	418 (47.5%)	16,668 (44.8%)	
Left	56 (26.2%)	2803 (28.5%)	4549 (28.3%)	2134 (27.1%)	680 (28.8%)	205 (23.3%)	10,427 (28.0%)	
Family history of CAD								3470
No	149 (63.7%)	5963 (56.9%)	9309 (55.1%)	4525 (55.2%)	1360 (55.0%)	497 (54.9%)	21,803 (55.7%)	
Yes	85 (36.3%)	4516 (43.1%)	7575 (44.9%)	3667 (44.8%)	1111 (45.0%)	409 (45.1%)	17,363 (44.3%)	
Smoking status								2023
Never	181 (73.9%)	9074 (83.3%)	14,160 (81.1%)	6724 (79.2%)	2002 (78.2%)	718 (75.6%)	32,859 (80.9%)	
Former	14 (5.7%)	579 (5.3%)	1210 (6.9%)	660 (7.8%)	215 (8.4%)	111 (11.7%)	2789 (6.9%)	
Current	50 (20.4%)	1242 (11.4%)	2099 (12.0%)	1110 (13.1%)	343 (13.4%)	121 (12.7%)	4965 (12.2%)	

(Continues)

TABLE 1 (Continued)

Variable	Underweight (BMI 15–18.5 kg/m^2)	Normal (BMI 18.5–25 kg/m^2)	Overweight (BMI 25–30 kg/m^2)	Moderately obese (BMI 30–35 kg/m^2)	Severely obese (BMI 35–40 kg/m^2)	Very severely obese (BMI over 40 kg/m^2)	Total	Missing
Dyslipidemia								1937
No	95 (40.1%)	3117 (28.8%)	4180 (23.8%)	1895 (22.1%)	574 (22.3%)	194 (20.1%)	10,055 (24.7%)	
Yes	142 (59.9%)	7710 (71.2%)	13,352 (76.2%)	6668 (77.9%)	2002 (77.7%)	770 (79.9%)	30,644 (75.3%)	
Diabetes								1476
No	196 (81.7%)	8614 (78.4%)	12,921 (73.1%)	5358 (62.0%)	1353 (51.7%)	438 (44.3%)	28,880 (70.2%)	
Yes	44 (18.3%)	2370 (21.6%)	4762 (26.8%)	3288 (38.0%)	1265 (48.3%)	551 (55.7%)	12,280 (29.8%)	
Prior stroke								25,442
No	96 (91.4%)	4199 (95.0%)	6945 (94.5%)	3546 (95.0%)	1067 (94.8%)	435 (93.3%)	16,288 (94.7%)	
Yes	9 (8.6%)	220 (5.0%)	403 (5.5%)	185 (5.0%)	58 (5.2%)	31 (6.7%)	906 (5.3%)	
Prior MI								751
No	86 (34.4%)	3626 (32.4%)	5846 (32.5%)	2970 (33.9%)	903 (33.8%)	391 (39.4%)	13,822 (33.0%)	
Yes	164 (65.6%)	7572 (67.6%)	12,156 (67.5%)	5803 (66.1%)	1767 (66.2%)	601 (60.6%)	28,063 (67.0%)	
Prior PCI								467
No	235 (92.9%)	10,337 (91.8%)	16,418 (90.5%)	7987 (90.4%)	2442 (91.0%)	913 (91.0%)	38,332 (90.9%)	
Yes	18 (7.1%)	925 (8.2%)	1714 (9.5%)	848 (9.6%)	242 (9.0%)	90 (9.0%)	3837 (9.1%)	
Urgency								4731
Elective	105 (47.7%)	5732 (56.6%)	9581 (58.5%)	4711 (59.7%)	1477 (61.7%)	547 (60.9%)	22,153 (58.4%)	
Urgent	115 (52.3%)	4398 (43.4%)	6788 (41.5%)	3183 (40.3%)	917 (38.3%)	351 (39.1%)	15,752 (41.6%)	
Angiographic findings								2563
<50%	93 (39.9%)	4140 (38.9%)	5975 (34.6%)	3194 (37.9%)	1043 (40.9%)	438 (46.2%)	14,883 (37.1%)	
1–3-VD	125 (53.6%)	6035 (56.7%)	10,495 (60.8%)	4884 (57.9%)	1412 (55.3%)	475 (50.1%)	23,426 (58.5%)	
Left main stenosis	14 (6.0%)	434 (4.1%)	714 (4.1%)	318 (3.8%)	87 (3.4%)	28 (3.0%)	1595 (4.0%)	
Other	1 (0.4%)	44 (0.4%)	69 (0.4%)	37 (0.4%)	11 (0.4%)	7 (0.7%)	169 (0.4%)	
Treatment decision								1044
No treatment for CAD	31 (12.4%)	1066 (9.6%)	1549 (8.7%)	839 (9.6%)	276 (10.4%)	127 (12.9%)	3888 (9.3%)	
Medical treatment	117 (46.8%)	4658 (41.9%)	6890 (38.6%)	3595 (41.3%)	1139 (43.0%)	439 (44.6%)	16,838 (40.5%)	
PCI	86 (34.4%)	4243 (38.1%)	7439 (41.6%)	3363 (38.6%)	976 (36.9%)	345 (35.1%)	16,452 (39.6%)	
CABG	14 (5.6%)	927 (8.3%)	1720 (9.6%)	816 (9.4%)	221 (8.3%)	64 (6.5%)	3,762 (9.0%)	
Aortic valve surgery	0 (0.0%)	6 (0.1%)	8 (0.0%)	3 (0.0%)	1 (0.0%)	0 (0.0%)	18 (0.0%)	
Mitral valve surgery	2 (0.8%)	210 (1.9%)	245 (1.4%)	92 (1.1%)	30 (1.1%)	8 (0.8%)	587 (1.4%)	
CAD (PCI/CABG) + valve	0 (0.0%)	8 (0.1%)	5 (0.0%)	3 (0.0%)	2 (0.1%)	0 (0.0%)	18 (0.0%)	
Other surgery	0 (0.0%)	7 (0.1%)	14 (0.1%)	2 (0.0%)	3 (0.1%)	0 (0.0%)	26 (0.1%)	
Hybrid operation	0 (0.0%)	0 (0.0%)	2 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.0%)	

TABLE 1 (Continued)

Variable	Underweight (BMI 15–18.5 kg/m^2)	Normal (BMI 18.5–25 kg/m^2)	Overweight (BMI 25–30 kg/m^2)	Moderately obese (BMI 30–35 kg/m^2)	Severely obese (BMI 35–40 kg/m^2)	Very severely obese (BMI over 40 kg/m^2)	Total	Missing
Outcomes								
All cause death								0
No	188 (74.0%)	9955 (87.3%)	16,504 (90.1%)	8022 (89.8%)	2393 (88.5%)	886 (87.1%)	37,948 (89.0%)	
Yes	66 (26.0%)	1449 (12.7%)	1819 (9.9%)	912 (10.2%)	311 (11.5%)	131 (12.9%)	4688 (11.0%)	

Note: Data are *n* (%), median (IQR) or mean (SD).

Abbreviations: ASO, arteriosclerosis obliterans; CABG, coronary artery by-pass grafting; CAD, coronary artery disease; MI, myocardial infarction; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; VD, vessels disease.

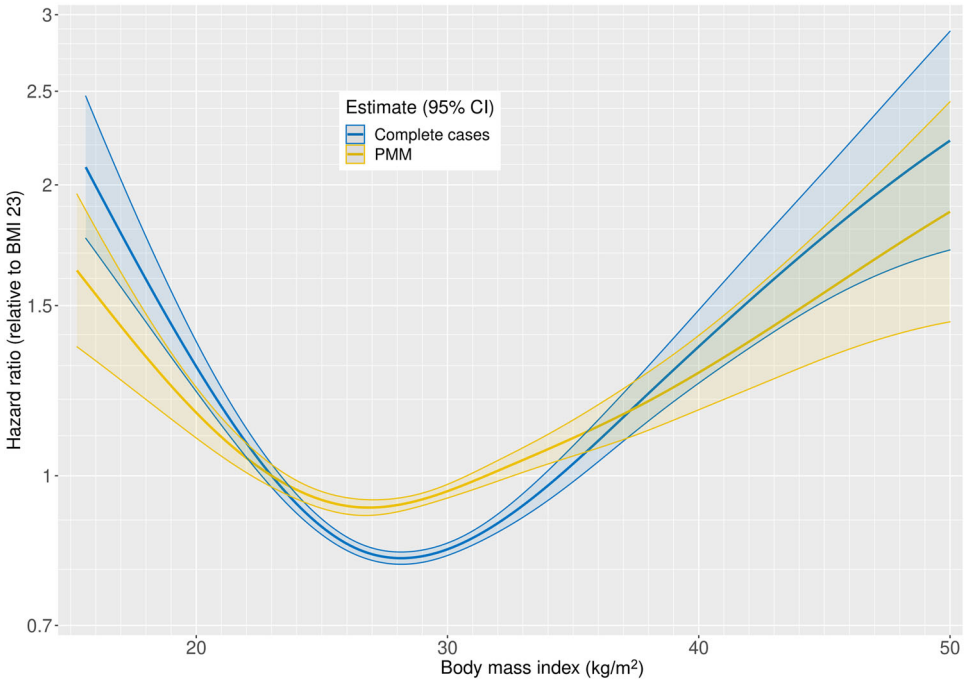

FIGURE 1 Relationship between body mass index and all-cause mortality. Association between body mass index and mortality in complete cases analysis (CC) and analysis based on PMM-imputed data sets.

as PCI or CABG, the risk of total and CVD mortality and MI rate was highest among underweight patients as defined by low BMI. Indeed, the overall mortality rate was lowest among slightly overweight patients.[21] Some explanations have been proposed for the observed "obesity paradox" in cardiac patients. For example, younger cardiac patients may have less extensive and non-diffuse form of CAD, which is easier to treat invasively than more advanced disease; which could be one of the main factors contributing to this phenomenon. It is likely that exposure time to common atherosclerotic risk factors on the development of CVDs is shorter in younger patients. Second, younger patients with CVDs may have a stronger physiological reserve to correct abnormal conditions; younger patients who present earlier tend to have effective pharmacological treatment from an early age. Our current study also confirmed that patients with a high BMI were slightly younger than those with a low BMI, while obese patients had a higher prevalence of cardiovascular risk factors. Central obesity is associated with insulin resistance and an atherogenic lipoprotein profile, and is independently related to CVD mortality in patients with CAD.[22,23]

4.3 | Mechanisms and explanations

Major bleeding complications are somewhat lower in overweight and moderately obese patients.[21] Excess dosing of anticoagulant and antiplatelet drugs may cause more harm in very lean, aged patients, whereas bleeding is less likely to occur in overweight and obese patients[24]; bleeding is associated with higher short-and long-term mortality rates, which may explain our results to some extent. Low BMI reflects lean body mass, which is associated with poorer

cardiorespiratory and muscular fitness, both of which are related to adverse clinical outcomes.[6,7] Very low body mass may be a marker of other underlying diseases, explaining the higher mortality risk in these patients. However, the associations were consistent in subgroup analysis by follow-up time (≤1 vs. >1 year), which suggest that underlying diseases, such as cancer among very lean patients, do not totally explain the observed associations. The obesity paradox, or the "BMI paradox," has also been observed in patient with other chronic disease conditions such as congestive heart failure, chronic kidney disease on haemodialysis, malignancies, and peripheral artery disease, respiratory conditions, infections, as well as osteoarthritis.[7,8,25] Normal weight and mildly obese patients may be an optimal group for all kind of treatments, including antihypertensive and lipid-lowering therapies. Among patients with suspected CAD referred for coronary computed tomographic angiography, patients with higher BMI had greater prevalence, extent, and severity of CAD that was not totally explained by the presence of traditional risk factors.[26]

The increased mortality risk was observed in patients with very severe obesity. Mild-to-moderately overweight patients may be less likely to present with serious acute coronary events leading to fatal outcomes, including cardiac arrest. There is also some evidence that a small amount of adipose tissue might provide some cardioprotective effects by producing hormones such as leptin and adiponectin,[27] which is a molecule that protects cardiac muscle from ischemia/reperfusion injury by inhibition of iNOS and nicotinamide adenine dinucleotide phosphate-oxidase protein expression.[27,28] The body weight loss associated decrease in endocannabinoid (EC) plasma levels of anandamide (AEA) and increases in adiponectin plasma levels were associated with the normalization of coronary circulatory function after weight loss, signifying that the imbalance between ECs and adipocytokines may be seen as an important determinant of coronary circulatory function in obesity. Increased AEA and 2-arachidonoylglycerol, which are predominantly produced and released from the adipose tissue in obese individuals, are associated with coronary circulatory dysfunction.[29] Overweight may also be protective against malnutrition following a major cardiac event or invasive procedure in advanced CAD and heart failure.[30] These factors may at least partly explain the protective effects of overweight among cardiac patients.[31,32] However, we have no data on factors such as the details in body composition, including decrease in muscle mass that occurs with aging as well as underlying chronic diseases that may have led to involuntary weight loss.

Previous studies have found that both unfit and inactive patients have significantly higher risk of death compared to fit and active subjects regardless of BMI levels.[33-35] Habitual physical inactivity is a significant contributor to the increased mortality risk in obese individuals since sedentary lifestyle is more prevalent in obese than leaner people. Higher cardiorespiratory fitness is associated with improved mortality events across all BMI categories, and the prognostic benefits of overweight/obesity disappear among most fit patients but persists in those with low fitness.[35] A complex interplay between fitness and fatness contribute to an individual's CVD and mortality risk profile. Regular physical activity can substantially influence the body fat and its distribution on the body. Physical activity markedly reduces the volume of visceral adipose tissues at varying degrees depending on the amount and intensity of exercise training.[36] High levels of fitness largely offset the adverse effects of excess adiposity, which is also referred as the "fat and fit" phenomenon.[34,37] Exercise training and increased physical activity, with the goal of maintaining or improving cardiorespiratory fitness, are efficient strategies for primary and secondary prevention of CVDs across BMI levels.[36,37]

4.4 | Strength and limitations

A major strength of the KARDIO register study is its ongoing observational prospective nature which provides real-world contemporary data on invasive cardiology interventions and outcomes in Finland. All included hospitals contributed data to the register; these hospitals are sole providers of invasive cardiology treatment in a centralized public health care system. Other strengths include the large sample with adequate numbers of normal weight, overweight, and obese patients across the whole BMI spectrum; its representativeness of invasive cardiology patients; the comprehensive panel of clinical characteristics, comorbidities, and lifestyle characteristics which enabled adequate adjustment for potential confounders. Adequate handling of missing data via multiple imputation increases accuracy and reliability of conclusions; more representative data among patients have been included and especially the missing data pattern can be taken into account when data are MAR. The representativeness of the registry-based cohort was also strengthened by the inclusion of consecutive patients with varying indications for coronary angiography, derived from the general population at centres with different levels of care, representing nearly half of the hospitals, which provide invasive coronary angiography in Finland.

Several limitations have to be taken into consideration. First, this is a nonrandomized observational study that provides evidence on the association between BMI and mortality and thus causality cannot be claimed and will need to be proved. Second, we evaluated all-cause mortality rather than cardiovascular mortality because cause-specific death data were not available. Third, we cannot rule out the possibility of residual confounding due to possible unmeasured confounding factors. Fourth, we did not capture measurements of body composition or body fat distribution, such as waist circumference (central obesity) and fat percentage, which have been suggested to be more closely related to adiposity-related outcomes. Although BMI is the most commonly used measure of obesity, it cannot distinguish between adipose and lean body mass tissue or central and peripheral adiposity. Fifth, we were unable to control for the role of unintentional weight loss and medication use during the follow-up. Previous studies suggest that fat-free mass could serve as a better physiological scaling factor than BMI, which cannot separate body composition, including both fat and fat-free mass.[38] Indeed, scales, such as the ratio of body mass and height for BMI, commonly used in

clinical practice may underestimate the physiological rationale for using BMI as a scaling factor and a marker of CVD risk. On the other hand, the use of BMI is still endorsed by the WHO to classify obesity worldwide, given its simple and easily quantifiable nature. Other limitations include the use of single baseline measurements of BMI and other time-dependent cofactors such as medication changes. We did not have data on the use of guideline-recommended longer-term secondary prevention therapy, which might also have explained some of the differences in mortality among BMI groups; data on secondary prevention during the follow-up were not collected. However, the internal consistency of results and the overall consistency of our observations with earlier studies suggest that our findings reflect the current clinical scenario. We did not have data on other characteristics, such as physical activity, socioeconomic status, or cardiorespiratory fitness, and thus we cannot exclude the possibility that residual confounding from unmeasured causal factors unevenly distributed between BMI groups may have influenced our results. However, our main analysis included age and smoking status, which are important factors that could lead to involuntary weight loss. There is documented evidence of an interplay between fitness, obesity, and mortality, but this could not be investigated because of the lack of fitness data. We had no data on detailed assessments for contrast agent use and laboratory values, including kidney function markers, after angiography and/or PCI. Patients with valvular heart diseases were excluded from the BMI and mortality analyses as the etiology of these conditions are likely other than metabolic abnormalities in CAD due to obesity and excessive body fatness. Also, we did not have data on recent weight loss before inclusion; very lean patients may have underlying chronic conditions such as cancer and pulmonary disease.[39] In our large study subsidiary analyses, the extent of significant CAD did not significantly alter our results, but left ventricular EF could not be included in the multivariable models due to the high amount of missing data in the registry.

5 | CONCLUSIONS

According to data from an ongoing multicentre cardiology Finnish registry study comprising patients undergoing coronary angiography, underweight and obesity class III are related to increased mortality risk, whereas preobesity and obesity class I are associated with decreased mortality risk. Our results support the concept of the obesity paradox among patients undergoing invasive coronary angiography.

AUTHOR CONTRIBUTIONS

Jari A. Laukkanen: Conceptualization, Methodology, Writing–original draft, Writing–review and editing, Visualization. **Setor K. Kunutsor**: Conceptualization, Methodology, Writing–original draft, Formal Writing–review and editing, Visualization, Formal analysis. **Jussi Hernesniemi**: Conceptualization, Methodology, Formal Writing–review and editing. **Jaakko Immonen**: Methodology, Formal Writing–review and editing, Visualization, Formal analysis. **Markku Eskola**: Conceptualization, Methodology, Formal Writing–review and editing. **Francesco Zaccardi**: Methodology, Formal Writing–review and editing, Formal analysis. **Matti Niemelä**: Conceptualization, Methodology, Formal Writing–review and editing. **Timo Mäkikallio**: Conceptualization, Methodology, Formal Writing–review and editing. **Magnus Hagnäs**: Formal Writing–review and editing. **Jarkko Piuhola**: Formal Writing–review and editing. **Jukka Juvonen**: Formal Writing–review and editing. **Jussi Sia**: Formal Writing–review and editing. **Juha Rummukainen**: Formal Writing–review and editing. **Kari Kervinen**: Conceptualization, Formal Writing–review and editing. **Juha Karvanen**: Methodology, Formal Writing–review and editing. **Kjell Nikus**: Conceptualization, Methodology, Formal Writing–review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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