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Association between BMI and cause-specific long-term mortality in acute myocardial infarction patients

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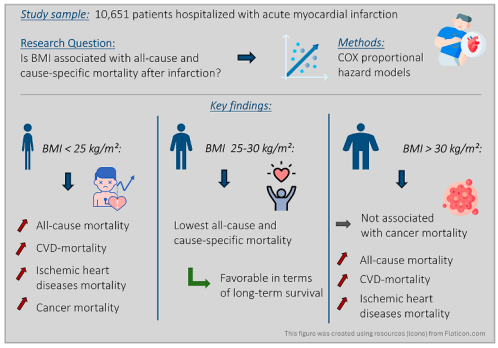
GRAPHICAL ABSTRACT



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ABSTRACT

Aims: To investigate the association between body mass index (BMI) at acute myocardial infarction (AMI) and all-cause as well as cause-specific long-term mortality.
Methods: The analysis was based on 10,651 hospitalized AMI patients (age 25–84 years) recorded by the population-based Myocardial Infarction Registry Augsburg between 2000 and 2017. The median follow-up time was 6.7 years [IQR: 3.5–10.0)]. Cause-specific mortality was obtained by evaluating the death certificates. In multivariable-adjusted COX regression models using cubic splines for the variable BMI, the association between BMI and cause-specific mortality (all-cause, cardiovascular, ischemic heart diseases, cancer) was investigated. Additionally, a subgroup analysis in three age groups was performed for all-cause mortality.
Results: Overall, there was a statistically significant U-shaped association between BMI at AMI and long-term mortality with the lowest hazard ratios (HR) found for BMI values between 25 and 30 kg/m^2. For cancer mortality, higher BMI values > 30 kg/m^2 were not associated with higher mortality. In patients aged <60 years, there was a significant association between BMI values >35 kg/m^2 and increased all-cause mortality; this association was missing in 60 to 84 years old patients. For all groups and for each specific cause of mortality, lower BMI (<25kg/m^2) values were significantly associated with higher mortality.

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Conclusions: Overall, a lower BMI – and also a high BMI in patients younger than 60 years - seem to be a risk factors for increased all-cause mortality after AMI. A BMI in a mid-range between 25 and 30 kg/m^2 is favorable in terms of long-term survival after AMI.

Introduction

Extreme body mass indices (BMI) are known to be a major risk factor for several diseases. Both, very low BMI (e.g. in anorexia or cancer cachexia) and very high values go along with increased risk of mortality [1–3]. In particular, obesity is considered to be an important risk factor for metabolic diseases such as diabetes mellitus and, closely related, a risk factor for several cardiovascular diseases as well [4–6]. However, for patients with coronary artery disease (CAD) or acute myocardial infarction (AMI), previous studies have reported conflicting results regarding the association between high BMI values and long-term mortality: Some researchers found decreased mortality for patients with obesity, often referred to as 'obesity paradox' [7–14]; a phenomenon that has been challenged by the results of several other studies [15, 16]. Therefore, the association between BMI and long-term mortality in AMI survivors remains controversial. The present study aims to contribute to a clearer and deeper understanding of this complex relationship. This requires a large, unselected sample with high quality data, in this case derived from the population-based Myocardial Infarction Registry Augsburg. In addition there is also a lack of knowledge on the association between BMI and cause-specific long-term mortality, like cardiovascular disease (CVD) mortality, ischemic heart disease mortality or cancer mortality in AMI survivors. Finally, the effect of age on the associations between BMI and mortality will be investigated.

Methods

Study population

The study used data from the Myocardial Infarction Registry in Augsburg, Germany. It was originally established in 1984 as part of the World Health Organization's MONICA project (Monitoring Trends and Determinants in Cardiovascular Disease). For almost 40 years, all cases of non-fatal AMI and coronary deaths in the study region (city of Augsburg and the two adjacent counties, approximately 680,000 inhabitants) were registered. Inclusion criteria for patients were: primary residence in the study region and age between 25 and 74 years (until 2008) and 25–84 years (from 2009 to 2017), respectively.

Detailed information on case identification, classification and quality control of the data can be found in a previous publication [17]. All study participants gave written informed consent. Methods of data collection and questionnaires have been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the study was performed in accordance with the Declaration of Helsinki. The study was registered at the German Register of Clinical Studies (DRKS, project number DRKS00029042).

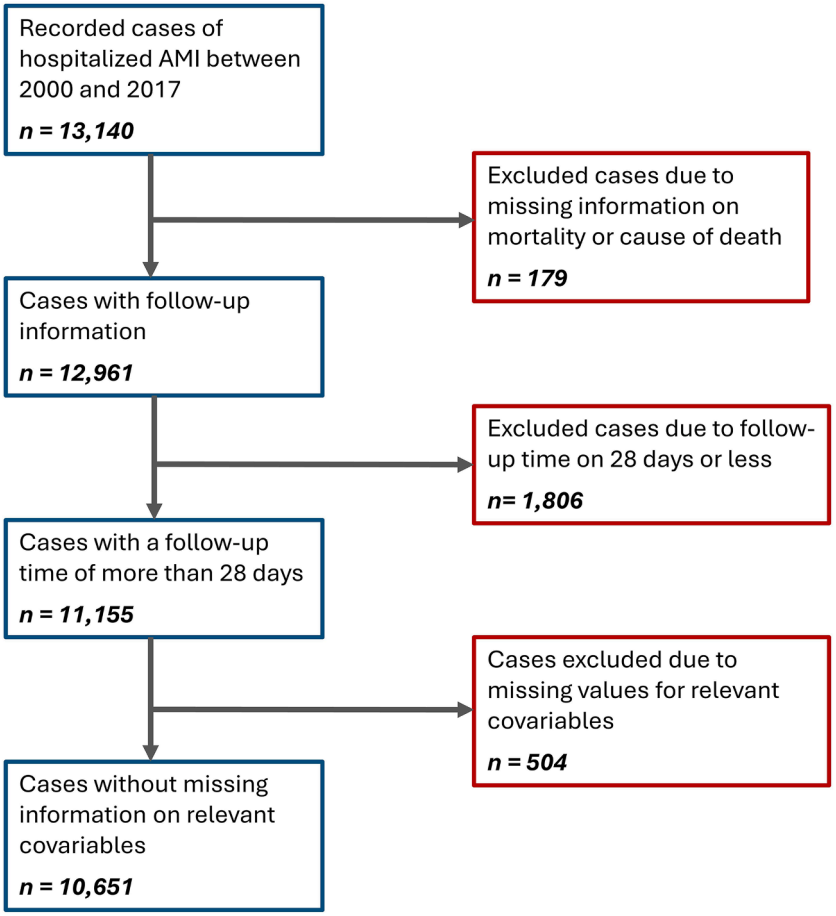

Fig. 1. Flow-chart displaying all inclusions and exclusions and how the final sample size was achieved.

Sample size

For this analysis, we initially considered all patients with hospitalized AMI recorded by the Augsburg Myocardial Infarction Registry between 2000 and 2017 (n = 13,140). Cases with missing follow-up information (n = 179) were excluded. To focus on long-term-mortality, we further excluded all patients with a follow-up time of 28 days or less (n = 1806). Finally, 504 cases with missing values on BMI, diabetes, hypertension, PCI (yes/no) and bypass therapy (yes/no) were excluded; leaving 10,651 for the final analysis, see Fig. 1.

Data collection

During their hospital stay, patients were interviewed by trained study nurses using a standardized questionnaire. In addition, the patients' medical charts were reviewed in detail to confirm the information obtained during the interview and to collect additional data. By this procedure, a wide range of demographic data, data on cardiovascular risk factors, medical history, comorbidities, laboratory values, diagnostics, treatment and medication was collected for each patient.

In particular, information on body weight and height was obtained from the patients' medical files. The variable BMI was calculated as weight in kg divided by the square of height in meters. Renal function according to the estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.

Outcome

The outcomes of this study were all-cause and cause-specific long-term mortality. Mortality was ascertained by regularly checking the vital status of all registered AMI patients in cooperation with the regional population registries. Death certificates were obtained from local health departments. In addition, a standardized questionnaire was sent out to the former general practitioner and/or coroner for each deceased patient. The questionnaire included, among other topics, questions about pre-existing comorbidities and diseases, circumstances of the acute event (e.g., resuscitation) and specific medications. The main cause of death, encoded by the ICD-10 classification [18,19], was determined on the basis of the death certificate. CVD deaths included all deaths encoded by I00 to I99, ischemic heart disease deaths were coded I20 to I25 and finally, cancer deaths included the ICD-10 codes C00 to D48.

Statistical analysis

For categorical variables, the results were presented as absolute frequencies with percentages and the Chi-square test was used to test for differences between groups. For normally-distributed continuous variables, the results were presented as means with standard deviations and we used Student's t-tests to test for differences. For non-normally distributed continuous variables the results were presented as medians with inter-quartiles ranges and nonparametric tests were applied.

As there was no follow-up information on BMI over time, we limited the observation period to 10 years after AMI; patients with longer observation periods were censored after 10 years. To focus on long-term mortality, all patients with an observational time of 28 days and less (the common definition of short-term mortality in the Augsburg Myocardial Infarction Registry is death within 28 days after AMI) were excluded from the analysis.

COX regression analyses

Multivariable adjusted COX proportional hazard regression models were used to analyze the association between BMI and all-cause and cause-specific long-term mortality (CVD mortality, ischemic heart disease (IHD) mortality and cancer mortality). The association between BMI and mortality was modeled using restricted cubic splines (RCS) with 4 degrees of freedom, which allows to capture a potential non-linear association; with a reference BMI of 27.5 kg/m^2. The models were adjusted for the continuous variable age (in years) and the categorical variables sex (male/female), diabetes (yes, no), hypertension (yes, no), hyperlipidemia (yes/no), smoking (current smoker, ex-smoker, never smoker, smoking status unknown), renal function according to eGFR ($\geq$ 60ml/min, 30–59ml/min, $<$ 30ml/min, unknown), left ventricular ejection fraction (EF) ($\leq$30 %, $>$30 %, unknown), type of infarction (STEMI, NSTEMI, other/unknown), family history of CVD (parental history of myocardial infarction or stroke [yes/no/no information]), time period of infarction (years 2000–2005, years 2006–2011, years 20,012–2017), severe infection (CRP at hospital admission $>$ 10 mg/dl [yes/no/no information]), percutaneous coronary intervention (PCI) (yes, no) and bypass therapy (yes, no).

Proportional hazard assumptions were checked graphically by inspecting the Kaplan-Meier survival curves and log(-log(survival)) plots; for the continuous variables BMI and age the survival curves stratified for the corresponding quartiles were examined.

In a subgroup analysis, we calculated COX regression models stratified for three age groups: $<$ 60 years, between 60 and 74 years, and $\geq$ 75 years.

Furthermore, we calculated all models using quartiles instead of splines for the variable BMI (displayed in the supplementary material). We also performed a sensitivity analysis by calculating a COX model for the outcome 'cancer mortality' and including only cases with a follow-up time of two years and more (also excluding deaths within the first 2 years). Finally, we tested for an interaction between smoking and BMI, as suggested by a previous publication and calculated all COX regression models separately for smokers, ex-smokers and never smokers.

All statistical analyses were carried out with the R program version 4.3.2. A p value of $<$ 0.05 was considered as statistically significant.

Results

Baseline characteristics of the study sample were displayed in table 1. The mean age was 63.7 (11.1) years and 73.3 % of all patients were male. During the observation period of up to ten years, 2,770 deaths were recorded among the 10,651 AMI patients. In total, 1,435 (51.8 %) deaths were attributed to CVD, 1,042 (37.6 %) to ischemic heart disease and 577 (20.8 %) to cancer. Elderly patients $\geq$75 years were less likely to die from cancer and had more comorbidities (diabetes, hypertension, impaired renal function) compared to AMI patients $<$ 75 years. The percentage of current smokers decreased from 58.0 % among patients $<$ 60 years to only 7.0 % in the group $\geq$ 75 years. PCI was performed in 70.5 % of all cases, with the highest frequency in the age group $<$ 60 years and the lowest frequency among the elderly, aged $\geq$ 75 years.

All-cause and cause-specific mortality - total sample

There was a U-shaped association between BMI and long-term all-cause mortality in the total sample (Fig. 2A). Compared to the reference BMI value of 27.5 kg/m^2, patients with a BMI of 20 kg/m^2 had a strongly increased risk of mortality (HR 1.91 [1.70,2.14]); patients with BMI values of 25 and 30 kg/m^2 had HRs of 1.03 [0.99,1.14] and 1.08 [1.03,1.14] respectively. Obese patients again had an increased risk of mortality with HRs of 1.23 [1.13,1.34] and 1.38 [1.17,1.63] for patients with BMI of 35 and 40 kg/m^2, respectively. Table S1 shows HR values and 95 %CI for specific BMI values and for each outcome). The U-shaped relation for all-cause mortality was confirmed by the COX model using BMI quartiles: the first and the fourth quartiles had significantly higher HR values compared to the second quartile (reference group) (supplementary table S2).

A similar result was obtained for CVD mortality (Fig. 2B). For ischemic heart diseases, there also appeared to be a U-shaped association as well (Fig. 2C), but the results were no longer significant for high BMI values. The situation was different for cancer mortality: low BMI

Table 1
Baseline characteristics of patients with and without diabetes. Categorical data presented as total numbers (%). Numeric data is presented as mean (SD) or median (IQR).

	Total sample (n = 10,651)	Age groups			p-value
		< 60 yearsy (n = 3604)	60–74 years (n = 5369)	≥75 years (n = 1678)	
Sex (male)	7809 (73.3)	2961 (82.2)	3846 (71.6)	1002 (59.7)	<0.001
Age (mean, sd)	63.7 (11.1)	50.9 (6.2)	67.5 (4.3)	78.9 (2.8)	<0.001
BMI in kg/m^2 (median, IQR)	27.1 (24.5–30.1)	27.5 (24.9 - 30.5)	27.1 (24.5 - 30.1)	26.3 (24.0 - 29.3)	<0.001
Time period of infarction					<0.001
2000–2005	3231 (30.3)	1281 (35.5)	1950 (36.3)	0 (0.0)	
2006–2011	3472 (32.6)	1183 (32.8)	1779 (33.1)	510 (30.4)	
2012–2017	3948 (37.1)	1140 (31.6)	1640 (30.5)	1168 (69.6)	
Mortality					
Total number of deaths* (% of all cases)	2770 (26.0)	376 (10.4)	1627 (30.3)	767 (45.7)	<0.001
CVD deaths* (% of all deaths)	1435 (51.8)	196 (52.1)	829 (51.0)	410 (53.5)	0.515
Ischemic heart disease deaths* (% of all deaths)	1042 (37.6)	155 (41.2)	619 (38.0)	268 (34.9)	0.103
Cancer deaths* (% of all deaths)	591 (21.3)	106 (28.2)	369 (22.7)	116 (15.1)	<0.001
Comorbidities and clinical characteristics					
Diabetes mellitus	3367 (31.6)	809 (22.4)	1893 (35.3)	665 (39.6)	<0.001
Hypertension	8309 (78.0)	2384 (66.1)	4417 (82.3)	1508 (89.9)	<0.001
Hyperlipidemia	6753 (63.4)	2318 (64.3)	3515 (65.5)	920 (54.8)	<0.001
Smoking status					<0.001
Current smoker	3400 (31.9)	2090 (58.0)	1193 (22.2)	117 (7.0)	
Ex-smoker	3370 (31.6)	815 (22.6)	1953 (36.4)	602 (35.9)	
Never smoker	3265 (30.7)	606 (16.8)	1836 (34.2)	823 (49.0)	
Smoking status unknown	616 (5.8)	93 (2.6)	387 (7.2)	136 (8.1)	
Family history of CVD (myocardial infarction or stroke)					<0.001
Yes	2776 (26.1)	1192 (33.1)	1343 (25.0)	241 (14.4)	
No	3570 (33.5)	1120 (31.1)	1962 (36.5)	488 (29.1)	
Insufficient information	4305 (40.4)	1292 (35.8)	2064 (38.4)	4305 (40.4)	
Type of infarction					<0.001
- STEMI	3849 (36.1)	1620 (45.0)	1802 (33.6)	427 (25.4)	
- NSTEMI	5637 (52.9)	1767 (49.0)	2958 (55.1)	912 (54.4)	
- other/unknown	1165 (10.9)	217 (6.0)	609 (11.3)	339 (20.2)	
Renal function					<0.001
- GFR ≥ 60ml/min	5530 (51.9)	2271 (63.0)	2542 (47.3)	717 (42.7)	
- GFR 30–59ml/min	1930 (18.1)	186 (5.2)	987 (18.4)	757 (45.1)	
- GFR < 30ml/min	395 (3.7)	38 (1.1)	183 (3.4)	174 (10.4)	
- GFR unknown	2796 (26.3)	1109 (30.8)	1657 (30.9)	30 (1.8)	
Severe infection (CRP at hospital admission)					<0.001
CRP > 10mg/dl	433 (4.1)	88 (2.4)	231 (4.3)	114 (6.8)	
CRP ≤ 10mg/dl	9452 (88.7)	3277 (90.9)	4737 (88.2)	1438 (85.7)	
No information	766 (7.2)	239 (6.6)	401 (7.5)	126 (7.5)	
Therapy					
PCI	7505 (70.5)	2860 (79.4)	3545 (66.0)	1100 (65.6)	<0.001
Bypass therapy	1599 (15.0)	401 (11.1)	963 (17.9)	235 (14.0)	<0.001
Medication at discharge					
Statins					<0.001
Yes	9354 (87.8)	3294 (91.4)	4673 (87.0)	1387 (82.7)	
No	1028 (9.7)	270 (7.5)	597 (11.1)	161 (9.6)	
No information	269 (2.5)	40 (1.1)	99 (1.8)	130 (7.7)	
Number of antihypertensive medications (antiduretics, beta blockers, calcium antagonists, ace inhibitors, angiotensin 2 receptor blockers)					<0.001
3 or more antihypertensive drugs	4995 (46.9)	1248 (34.6)	2771 (51.6)	976 (58.2)	
2 antihypertensive drugs	4233 (39.7)	1820 (50.5)	1953 (36.4)	460 (27.4)	
1 antihypertensive drug	1069 (10.0)	461 (12.8)	506 (9.4)	102 (6.1)	
Insufficient information	354 (3.3)	75 (2.1)	139 (2.6)	140 (8.3)	
Antiplatelet medication (including aspirin)					<0.001
Yes	10,105 (94.9)	3483 (96.6)	5106 (95.1)	1516 (90.3)	
No	279 (2.6)	81 (2.2)	166 (3.1)	32 (1.9)	
No information	267 (2.5)	40 (1.1)	97 (1.8)	130 (7.7)	
antidiabetic medication					<0.001
Insulin and oral antidiabetic drugs	412 (3.9)	97 (2.7)	223 (4.2)	92 (5.5)	
Only insulin	671 (6.3)	153 (4.2)	405 (7.5)	113 (6.7)	
Only oral antidiabetic drugs	1141 (10.7)	254 (7.0)	643 (12.0)	244 (14.5)	
No antidiabetic medication/insulin	8154 (76.6)	3059 (84.9)	3997 (74.4)	1098 (65.4)	
No Information	273 (2.6)	41 (1.1)	101 (1.9)	131 (7.8)	

* All deaths occurring in the time period between 28 days until 10 years after AMI.

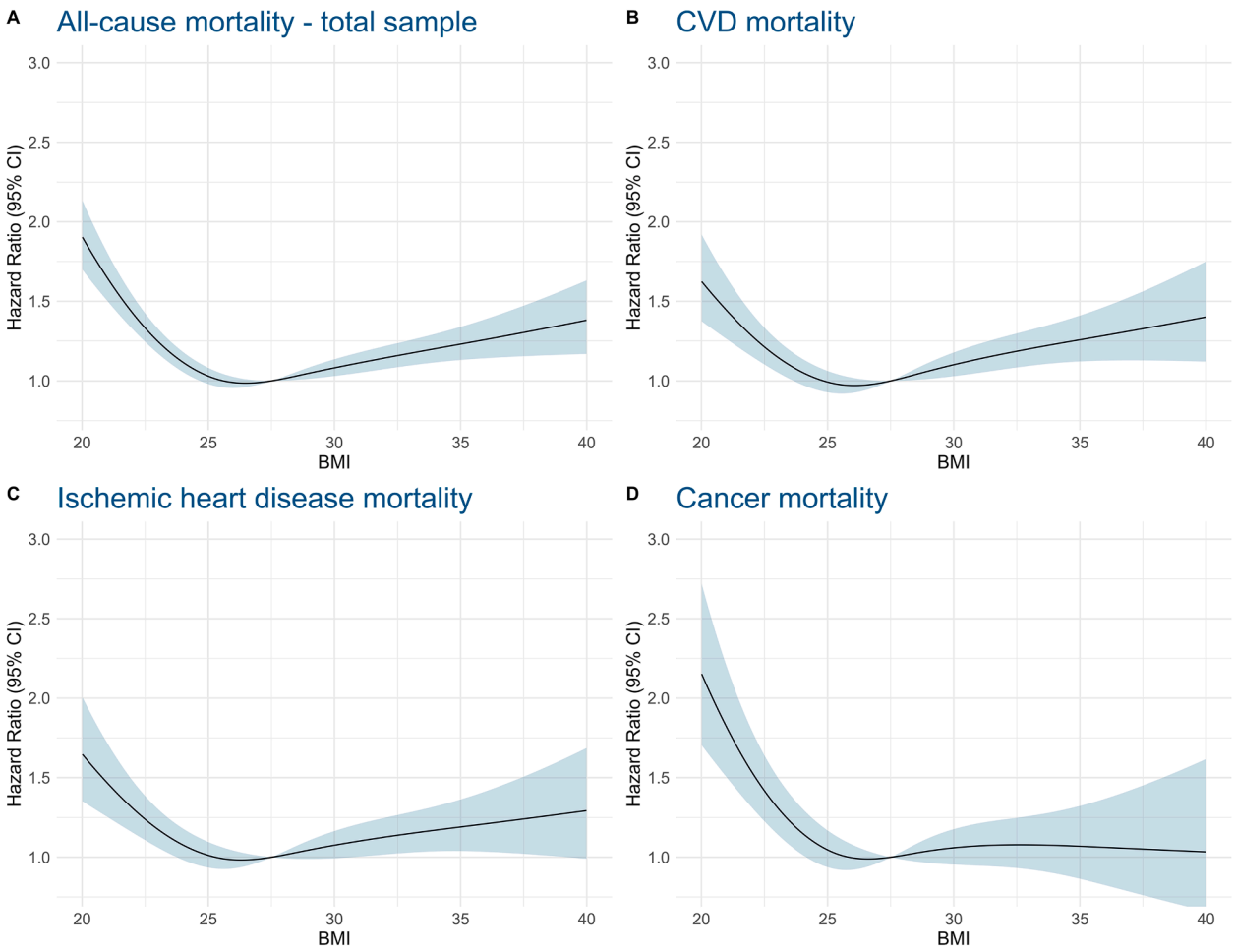

Fig. 2. Association between BMI and all-cause and cause specific mortality in the total sample. The COX regression models were adjusted for age, sex, time period of infarction, diabetes, hypertension, hyperlipidemia, smoking status, eGFR, left-ventricular EF, type of infarction, family history of CVD, time period of infarction, severe infection, PCI and bypass therapy.

values were still strongly associated with higher mortality, but we didn't observe a higher risk of cancer mortality in patients with high BMI values (Fig. 2D).

All-cause mortality in different age groups

In the age group < 60 years, there was a pronounced U-shaped association between BMI and all-cause mortality (Fig. 3A). However, in the regression model using BMI quartiles, only the first, but not the fourth BMI quartile was significantly associated with mortality compared to the second quartile (reference), see table S2. In the age group 60–74 years there was also a U-shaped association (Fig. 3B) and significantly higher mortality for patients in the first and fourth quartile, see table S2. In the elderly group ≥ 75 years, higher BMI levels were not associated with increased mortality (Fig. 3C and table S2). Hence, low BMI levels were significantly associated with an elevated risk of dying for all age groups, (Fig. 3), but only for AMI patients < 75 years high BMI values were also significantly associated with increased mortality.

Sensitivity analyses and stratified COX models

Fig. 4 displays the all-cause survival curves for 4 different BMI groups (BMI<25kg/m^2 [no overweight/obesity], BMI 25–29.9 kg/m^2 [overweight], BMI 30–34.9 kg/m^2 [obesity class I], BMI ≥35 kg/m^2 [obesity class II/III]). It shows that patients with a BMI < 25 kg/m^2 have the highest mortality risk of all groups in the first years after AMI. In patients with obesity class II/III, the mortality increases after about 4 years, leading to a convergence of the survival curves. The phenomenon wasnt observed for the overweight and obesity class I curve, as they remained having a lower mortality than the group BMI <25kg/m^2 over the whole follow-up period of 10 years.

In a further analysis, we excluded all cases with an observational time of less than two years, which had only minor impact on the association between BMI and cancer mortality, see table S2 and figure S1 (supplementary material). Furthermore, testing for a significant interaction between smoking and BMI by adding an interaction term revealed no or very limited interaction between the two variables. A stratified analysis for smokers, ex-smokers and never smokers showed similar associations between BMI and cause-specific mortality for the three groups, see figures S2-S7 (supplementary material). Only the association between high BMI values and cancer mortality differed between the three smoking groups: while no significant associations were found in ex-smokers and never smokers, high BMI values went along with a higher mortality in current smokers.

Discussion

In this study, there was an overall U-shaped association between BMI and all-cause and cause-specific long-term mortality after AMI. However, in the older age group (≥75 years) and for cancer mortality, high BMI was not associated with higher risk of premature mortality.

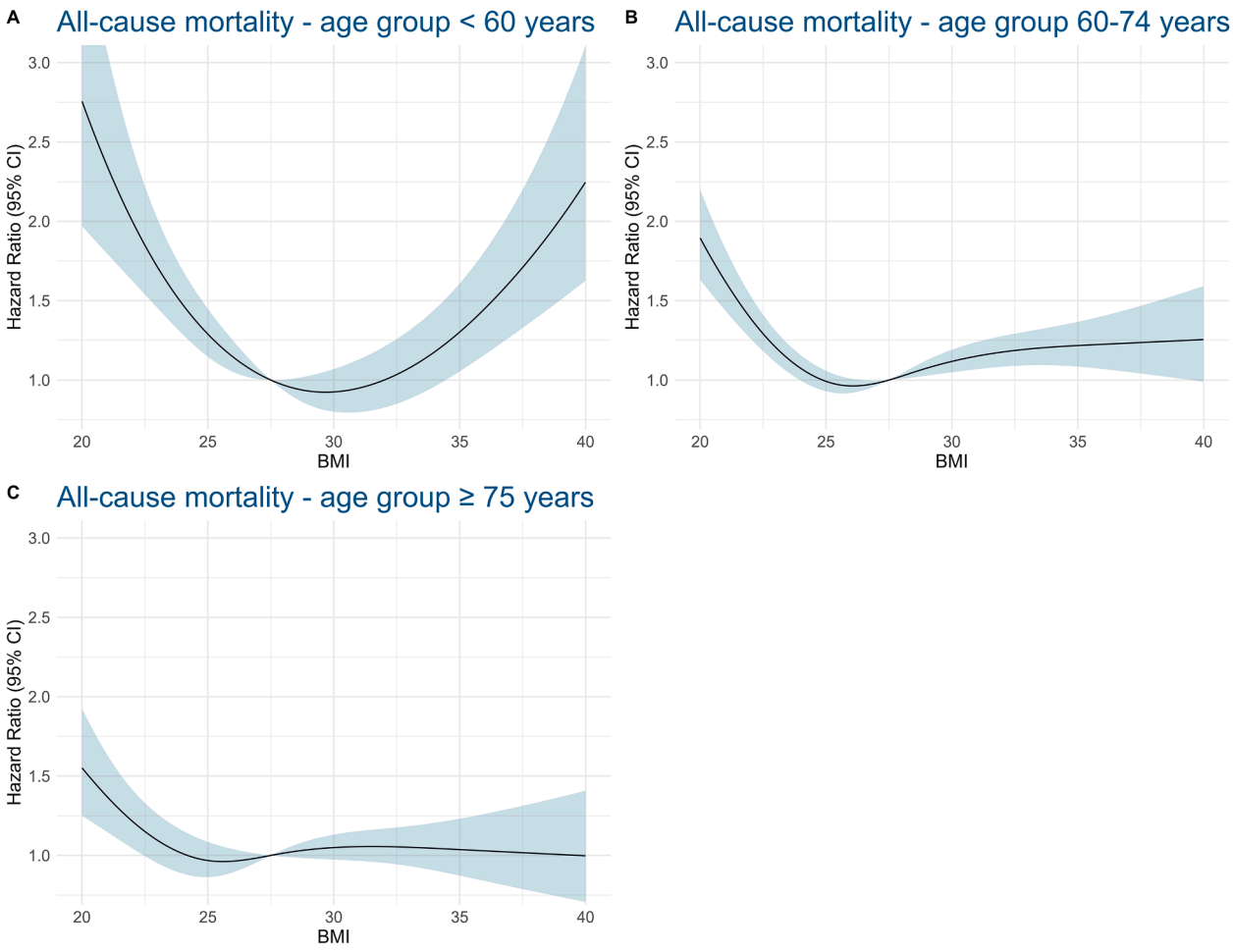

Fig. 3. Association between BMI and all-cause mortality in different age groups. The COX regression models were adjusted for age, sex, time period of infarction, diabetes, hypertension, hyperlipidemia, smoking status, eGFR, left-ventricular EF, type of infarction, family history of CVD, time period of infarction, severe infection, PCI and bypass therapy.

High BMI values and long-term mortality

Several previous studies have examined the relationship between (high) BMI and long-term mortality after myocardial infarction, and thereby reporting conflicting results. Some studies and meta-analyses suggested a survival benefit for patients with higher BMI in coronary artery disease (CAD), acute coronary syndrome and AMI [7–14]; a phenomenon often referred to as 'obesity paradox'. This phenomenon was only partially confirmed by the present study, as we found the lowest mortality in patients with BMI values between 25 and 30 kg/m^2, which is categorized as 'pre-obesity' or 'overweight' by the WHO classification [20]. For BMI $\geq$ 30 kg/m^2, which is classified as obesity, mortality started to increase. These observations are supported by a recent study from Sweden that analyzed more than 25,000 STEMI patients and found the lowest 1-year all-cause mortality for the overweight group (BMI 25.0–29.9 kg/m^2) [21].

There are previous studies and meta-analyses that question this 'obesity paradox' in CAD and AMI patients [15,16]. One example is a recent study by Al-Shaar et al. [16] that found higher mortality in patients with higher BMI for all-cause and CVD mortality, which is in line with our results.

The 'obesity paradox' would somehow contradict the concept of overweight and obesity being a strong risk factor for the development of cardiovascular diseases. Our results suggest that a BMI $\geq$ 30 kg/m^2 is also a risk factor for increased mortality in AMI patients and in this sense is consistent with the concept of obesity being a cardiovascular risk factor not only in primary (and secondary), but also in tertiary prevention.

Low BMI values and long-term mortality

Previous publications have reported, that lower BMI $<$ 25 kg/m^2 is associated with an increased long-term mortality in CAD and AMI patients [7,8,11,12,21,22], which is consistent with the results of the present study. However, there are studies reporting conflicting results [16]. For example, in the above mentioned study by Al-Shaar et al., lower BMI was only non-significantly associated with a slightly increased mortality [16]. They speculated, that this might be an artefact caused by unintentional weight loss due to pre-existing disease (reverse causation). In particular, patients with preexisting cancer might drive this potential reverse causation, which potentially could also apply to the present study. However, our results were very clear in this respect: we observed a higher mortality for lower BMI not only for all-cause and cancer mortality, but also for CVD mortality and IHD mortality. Moreover, we performed a sensitivity analysis for cancer mortality by excluding all patients with less than 2 years of follow-up, therefore excluding patients with pre-existing, severe and advanced underlying diseases such as cancer. Nevertheless, BMI values $<$ 25 kg/m^2 were strongly associated with higher mortality. Therefore, the associations between lower BMI and higher mortality reported in this study are considered valid and important findings.

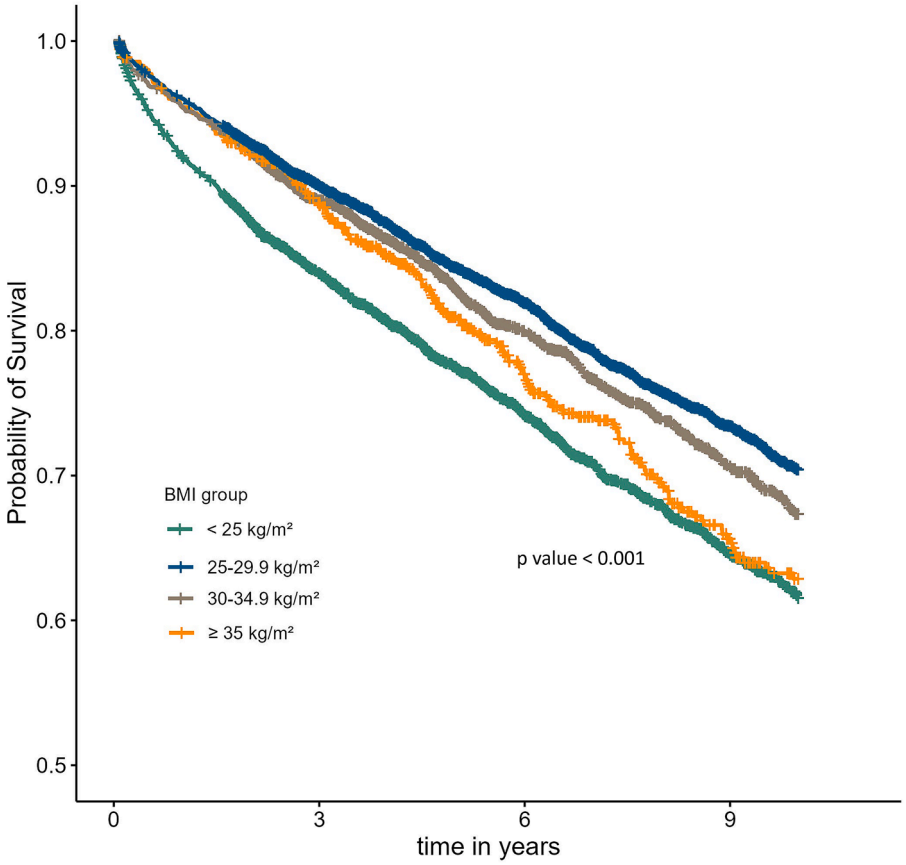

Fig. 4. Kaplan-Meier survival curves for 4 different BMI groups: BMI<25kg/m^2, BMI 25–29.9 kg/m^2 [overweight], BMI 30–34.9 kg/m^2 [obesity class I], BMI ≥35 kg/m^2 [obesity class II/III]. While patients with BMI < 25 kg/m^2 had the highest mortality in the first years after AMI, the mortality of patients with obesity class II/III increased after about 4 years. Patients with overweight and obesity class I remained having a lower mortality than the group BMI <25 kg/m^2 over the whole follow-up period of 10 years.

All-cause mortality and age groups

While there was a pronounced U-shaped association between BMI and all-cause mortality in AMI patients younger than 60 years, there was no association between higher BMI values and mortality in the elderly group. We can only speculate about the reason for this observation: Younger AMI patients have a longer life expectancy after their infarction compared to older patients. Previous studies have reported that a longer duration of obesity is associated with an increased risk of developing secondary diseases such as diabetes mellitus [23,24] or CVD [25]. For that reason, obesity might reveal more distinct impacts on health in younger patients, who live long enough to develop secondary conditions and are more likely to be affected by life-threatening complications. Older patients in their seventies and eighties on the other hand often struggle to maintain their weight: Many older patients are affected by sarcopenia, which may have an impact on physical functions, including the immune response to infections [26]. Therefore, in old age, a higher BMI likely represents higher muscle mass and energy reserves and consequently less frailty. This may offset the effect of obesity-related complications like diabetes and CVD, resulting in comparable mortality in obese AMI patients compared to individuals with a BMI < 30 kg/m^2.

These considerations are consistent with Fig. 4, which shows that patients with class II/III obesity have a lower mortality compared to normal-weight patients in the first years after AMI, but the Kaplan-Meier curves of the two groups converge after several years. Patients with severe obesity may initially benefit from extra muscle and higher energy reserves, an advantage that may be reversed after several years due to a more severe deterioration of the CAD and atherosclerotic processes. This hypothesis would be in line with the results of a meta-analysis by Wang et al. [7], who suggested that the long-term benefit of class II/II obesity disappeared after 5 years in CAD patients.

Mortality and smoking

Many prior studies indicated effects of residual confounding by smoking and/or an interaction between BMI and smoking in mortality analyses [3,16,27–29]. This is not much surprising, as smoking suppresses appetite, which can lead to a substantial weight loss [30]. At the same time, smoking causes premature mortality since cigarette smoke contains a variety of carcinogenic compounds [31] and is involved in the pathophysiology of arterosclerosis [32,33]. To account for this, we adjusted all models for the patients' smoking status. Moreover, we performed subgroup analyses stratified for smokers, ex-smokers and never smokers. This had moderate impact on the observed associations, and the overall shape of the associations was quite similar in all three subgroups. An exception from this was the association between higher BMI values and significantly increased cancer mortality in current smokers, which was absent in ex-smokers and never smokers. Smoking may be an important factor or confounder regarding the association between BMI and long-term all-cause, CVD, and IHD mortality, but the associations described in this study appear to be applicable mainly independent of the smoking status.

Clinical implications

Obesity is considered a major cardiovascular risk factor, and people are often advised to reduce their weight to the normal range. The obesity

paradox questions whether this advice should be given to patients after AMI. Weight loss often goes along with a reduction in muscle mass, increasing the risk of sarcopenia and frailty, especially in the elderly. A previous study analyzed how intentional vs. unintentional weight loss affected the overall mortality after AMI. It was found that substantial weight loss was associated with higher mortality, but an increase in mortality was only seen among patients with unintentional weight loss (neither improving physical activity nor diet) [16]. In view of the fact that we found the lowest overall mortality for BMI in the range between 25 and 30 kg/m^2 (slightly dependent on the age group), an intentional weight loss for obese AMI patients might be recommendable until they reach BMI values of around 30 kg/m^2. Recommendations for a further reduction to the normal range (20–25 kg/m^2) are questioned by the results of the present study. This in particular applies to older patients, in whom we didn't find an increased mortality in obese individuals and who are at greater risk of sarcopenia and frailty. Physicians should be very cautious about suggesting weight reduction in these patients.

Strengths and limitations

The present study used data from the population-based Myocardial Infarction Registry Augsburg with complete enrollment, which minimizes selection bias and ensures highest data quality. The number of included AMI cases is high and the follow-up of patients is long with a median observation period of 6.7 years. The wide range of information on comorbidities, treatment, etc. allowed the calculation of fully-adjusted COX regression models. A particular strength of this study is the information on the main cause of death allowing separate analyses for cause-specific mortality.

There are also some limitations to mention. First, information on BMI was only available at the time of infarction, and there was no follow-up information on BMI, which may have changed considerably over the course of up to ten years. In fact, body-weight fluctuations are quite common [34] and go along with increased mortality in CAD and AMI patients [34,35]. Additionally, measures of body composition such as percentage of body fat or body fat distribution might provide important additional information for the analysis of obesity/body composition and mortality [36,37]. Furthermore, over the course of 17 years, which is the time frame for patient recruitment for this analysis, diagnostics, acute treatment and prevention of coronary artery diseases and AMI have changed significantly (PCI treatment, troponin diagnostics, medication, etc.), which may have affected the observed associations as well. The vast majority of patients included in this analysis can be described as Caucasians, yet no explicit data on ethnicity was recorded, so our results may not be generalized to other ethnic groups. Finally, there may be relevant variables that were not available for this analysis (e.g., information on alcohol or drug use, the presence of a metabolic syndrome or lipid parameters) and we may have not considered all important confounders. We also cannot exclude reverse causation, which refers to the phenomenon that (unintentional) weight loss caused by severe concomitant diseases might have affected the results. Severe illnesses like cancer and other diseases often cause weight loss and sarcopenia, which leads to higher frailty and increases overall mortality. Yet, the underlying illness and poor health are the cause of weight loss and low BMI, and not necessarily low BMI being a risk factor for poor health and higher mortality

Conclusion

There was a general U-shaped association between BMI and long-term all-cause mortality in AMI patients. This association was most dominant in AMI patients < 60 years; in the elderly group high BMI was not associated with increased all-cause mortality. For cancer mortality, only BMI values < 25 kg/m^2 were associated with an increased mortality risk; individuals with obesity (BMI ≥ 30kg/m^2) were not more likely to die from cancer. It can be concluded that patients with a mid-range BMI between 25 and 30 kg/m^2 have the most favorable outcome after AMI; in particular very low BMI values are associated with higher mortality.

CRediT authorship contribution statement

Timo Schmitz: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Dennis Freuer:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Philip Raake:** Writing – review & editing, Resources, Investigation. **Jakob Linseisen:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Christa Meisinger:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

Data collection of the MONICA/KORA MI registry has been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the study was performed in accordance with the Declaration of Helsinki. All study participants have given written informed consent.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to data protection aspects but are available in an anonymized form from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100899.

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