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Original article

Obesity paradox in peripheral artery disease

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SUMMARY

Background & aims: Previous studies have suggested an obesity survival paradox in patients with peripheral artery disease (PAD). We investigated the influence of obesity and underweight on adverse in-hospital outcomes in PAD.

Methods: Patients diagnosed with PAD based on *ICD*-code I70.2 of the German nationwide database were stratified for obesity, underweight and a reference group with normal-weight/over-weight and compared regarding adverse in-hospital outcomes.

Results: Between 01/2005-12/2015, 5,611,484 inpatients (64.8% males) were diagnosed with PAD; of those, 8.9% were coded with obesity and 0.3% with underweight. Obese patients were younger (70 (IQR 63/76) vs. 73 (66/80) years, P < 0.001), more frequently female (36.7% vs. 35.1%, P < 0.001), had less cancer (4.9% vs. 7.9%, P < 0.001) and had less treatment with major amputation (2.6% vs. 3.2%, P < 0.001) compared to the reference group. Overall, 277 876 (5.0%) patients died in-hospital. Obese patients showed lower mortality rate (3.2% vs. 5.1%, P < 0.001) compared to the reference group and reduced risk of in-hospital mortality (OR, 0.617 [95%CI 0.607–0.627], P < 0.001). This "obesity paradox" was demonstrated in obesity classes I (OR, 0.475 [95%CI 0.461–0.490], P < 0.001), II (OR, 0.580 [95%CI 0.557–0.605], P < 0.001), and III (OR, 0.895 [95%CI 0.857–0.934], P < 0.001) and was independent of age, sex and comorbidities. Underweight patients revealed higher in-hospital mortality (6.0% vs. 5.1%, P < 0.001) compared to the reference group (OR, 1.179 [95%CI 1.106–1.257], P < 0.001) and showed higher prevalence of cancer (22.0% vs. 7.9%, P < 0.001).

Conclusions: Coding for obesity is associated with lower in-hospital mortality in PAD patients relative to those with normal-weight/over-weight. This obesity survival paradox was independent of age, gender and comorbidities and observed for all obesity classes.

1. Introduction

Obesity is an important risk factor for cardiovascular disease (CVD) events and mortality in the general population [1–6]. Thus, the American joint guidelines of the American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) of 2011 [7] recommend a weight management with the aim to maintain/achieve a body mass index (BMI) in the normal range between 18.5 and 24.9 kg/m^2 for patients with coronary artery disease (CAD) and other atherosclerotic vascular diseases, including peripheral artery disease (PAD) [7].

Although patients with PAD are affected by significant mortality [8], PAD has received less attention than CAD in the awareness of the general population and physicians; patients with PAD are

Abbreviations: AHA, American Heart Association; ACCF, American College of Cardiology Foundation; aHT, Essential arterial Hypertension; BMI, Body mass index; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; CPR, Cardio-pulmonary resuscitation; CVD, Cardiovascular diseases; CVRF, Cardiovascular risk factors; DRG, Diagnosis related groups; DVT, Deep vein thrombosis; HF, Heart failure; ICD, International Classification of Disease; OPS, Surgery and procedures codes (Operationen- und Prozedurenschlüssel); MI, Myocardial infarction; PAD, Peripheral artery disease; PE, Pulmonary embolism; VTE, Venous thromboembolism.

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frequently managed less intensively than those with CAD, despite an equal or even worse prognosis [9]. The predominant cause of the mortality in PAD patients are life-threatening CVD events, such as myocardial infarction (MI) and stroke [10].

Despite the negative impact of obesity on the development of CVD, including CAD and PAD, numerous studies and meta-analyses in the past decade have highlighted an obesity survival paradox, which is accompanied by a better survival for obese patients with CVD compared to their leaner counterparts [11–14]. The reasons underlying the obesity survival paradox have still not been fully elucidated [10,13,14].

While a few studies demonstrated an obesity paradox for PAD patients for longer follow-up periods and in mid-size cohorts [9,10], other studies could not confirm the existence of such a phenomenon [15]. Additionally, to our knowledge, there are no studies regarding the impact of body composition on in-hospital survival in PAD.

Thus, we aimed to investigate adverse in-hospital outcomes, including in-hospital mortality, in PAD patients relative to underweight and obesity compared to a reference group of PAD patients without coded obesity and underweight.

2. Materials and methods

The nationwide German inpatient sample (diagnosis related groups [DRG] statistic) was used for our analysis. The Federal Statistical Office of Germany (Statistisches Bundesamt) gathers treatment data from all inpatient cases processed according to the DRG system. Diagnoses are coded according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and surgical or interventional procedures with OPS-codes (surgery and procedures codes [Operationen-und Prozedurenschlüssel]).

Analyses were performed on our behalf by the Research Data Center of the Federal Statistical Office and the Statistical Offices of the federal states (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2015, own calculations), in Wiesbaden (Germany) and the aggregated statistics were provided on the basis of SPSS codes (SPSS® software, version 20.0, SPSS Inc., Chicago, Illinois), which were supplied to the Research Data Center. For our analyses, all inpatients diagnosed with PAD (ICD-code I70.2) aged $\geq$18 years between January 2005 and December 2015 were selected. Only for the analysis regarding the impact of obesity on the outcomes in the different age-groups all PAD patients (additionally those <18 years) were included.

The selected PAD patients were stratified for additionally coded obesity (ICD-code E66) and underweight (ICD-code R63.4). PAD patients without coded obesity or underweight were included in the normal-weight/overweight reference group. Patients with obesity were further classified in obesity class I (body mass index [BMI] 30 to <35 kg/m^2, ICD-codes E66.00, E66.10, E66.20, E66.80, E66.90), class II (BMI 35 to <40 kg/m^2, ICD-codes E66.01, E66.11, E66.21, E66.81, E66.91) and class III (BMI >40 kg/m^2, ICD-codes E66.02, E66.12, E66.22, E66.82, E66.92).

Major amputations were defined as amputations above the ankle (OPS-code: 5–864) and minor amputations comprised amputations below the ankle (OPS-code: 5–865). Amputations of the upper extremities and amputations due to reasons other than limb ischaemia, such as venous ulceration, trauma and malignancy, were not included in the analysis [16,17].

2.1. Study endpoints

The primary outcome of this study was death of all-causes during in-hospital stay (in-hospital death). The primary outcome of in-hospital death refers to patient‘s respective hospitalization. The secondary outcomes were cardio-pulmonary resuscitation (CPR, OPS-code 8–77]), and amputation, including minor amputation and major amputation, MI (ICD-code I21), pulmonary embolism (PE, ICD-code I26), deep venous thrombosis or thrombophlebitis (DVT, ICD-code I80) and shock (ICD-code R57).

2.2. Ethical aspects

Since this study did not involve a direct access by the investigators to the data of the individual patients, an approval by an ethics committee and informed consent were not required, in accordance with German law.

2.3. Statistics

Descriptive statistics for relevant baseline comparisons of obese and underweight patients with the reference group (consisting of patients without obesity and underweight), respectively, are represented as median and interquartile range (IQR) or absolute numbers and corresponding percentages. In addition, patients stratified by obesity classes were compared with the reference group. Continuous variables were tested using the Wilcoxon-Mann-Whitney-*U* test and categorical variables with Fisher's exact or chi-square test, as appropriate.

Uni- and multi-variate logistic regression models were computed to investigate the impact of obesity, obesity classes and underweight on the different study outcomes. Results were presented as Odds Ratios (OR) and corresponding 95% confidence intervals (CI). In order to test the independence of the impact of obesity and underweight on the outcomes, we performed multivariate regression models, which were adjusted for age, sex, surgery (OPS-codes 5-01 to 5–99), cancer (ICD-codes C00–C97), CAD (ICD-code I25), heart failure (HF; ICD-code I50), chronic obstructive pulmonary disease (COPD; ICD-code J44), essential arterial hypertension (aHT, ICD-code I10), renal insufficiency (comprised diagnosis of all renal insufficiency stages, ICD-codes N17–N19), diabetes (ICD-codes E10-E14), and atrial fibrillation or flutter (ICD-code I48). We selected an epidemiological approach for the adjustment with age, sex, all mentioned comorbidities and the surgical treatments to test the associations of obesity and underweight with the outcomes for their widespread truly independence since especially from CVD, COPD, renal diseases and cancer, which are well-known potential fatal conditions.

The software SPSS® (version 20.0; SPSS Inc., Chicago, Illinois) was used for computerized analysis. P values of <0.05 (two-sided) were considered to be statistically significant.

3. Results

In total, 5, 611, 827 inpatients aged $\geq$18 years with PAD were treated between 2005 and 2015 in Germany. Of these, 343 patients could not be clearly categorized in one of the three subgroups and were excluded. Therefore, overall 5,611,484 PAD patients (64.8% males) remained in the analysis. Among these, 500,027 (8.9%) were additionally coded with obesity and 16,620 (0.3%) with underweight, whereas 5,094,837 (90.8%) without both (reference) (Figure S1 in the supplements).

3.1. Patients’ characteristics

The patients’ characteristics of the 3 groups are shown in Table 1. Briefly summarized, obese PAD patients were younger, more frequently female, had less cancer, but, as expected, more often CVD risk factors (CVRF), such as diabetes and aHT compared to the

Table 1
Patients' characteristics, outcomes and treatments of the 5,611,484 PAD inpatients aged ≥18 years stratified by obesity, underweight and without both.

	PAD patients without additionally coded obesity and without underweight n = 5,094,837 (90.8%)	PAD patients with additionally coded obesity n = 500,027 (8.9%)	P-value[a]	PAD patients with additionally coded underweight n = 16,620 (0.3%)	P-value[b]
Age (median, IQR)	73.0 years (66.0–80.0)	70.0 years (63.0–76.0)	**<0.001**	73.0 years (66.0–80.0)	0.981
Sex (females)	1,787,637 (35.1%)	183,426 (36.7%)	**<0.001**	5486 (33.0%)	**<0.001**
In-hospital stay (days)	8 (4–15)	9 (4–17)	**<0.001**	10 (6–17)	**<0.001**
Comorbidities					
Surgery	3,429,217 (67.3%)	359,007 (71.8%)	**<0.001**	12,602 (75.8%)	**<0.001**
Cancer	403,376 (7.9%)	24,702 (4.9%)	**<0.001**	3657 (22.0%)	**<0.001**
Coronary artery disease	1,900,364 (37.3%)	225,128 (45.0%)	**<0.001**	5905 (35.5%)	**<0.001**
Essential arterial Hypertension	3,028,936 (59.5%)	341,368 (68.3%)	**<0.001**	9013 (54.2%)	**<0.001**
Renal insufficiency	1,593,358 (31.3%)	186,602 (37.3%)	**<0.001**	4798 (28.9%)	**<0.001**
Diabetes	2,164,842 (42.5%)	321,338 (64.3%)	**<0.001**	5706 (34.3%)	**<0.001**
Heart failure	1,130,963 (22.2%)	143,330 (28.7%)	**<0.001**	3296 (19.8%)	**<0.001**
Stroke	131,210 (2.6%)	10,373 (2.1%)	**<0.001**	271 (1.6%)	**<0.001**
Chronic obstructive pulmonary disease	679,245 (13.3%)	78,198 (15.6%)	**<0.001**	3507 (21.1%)	**<0.001**
Outcomes					
All-cause death	260,769 (5.1%)	16,113 (3.2%)	**<0.001**	994 (6.0%)	**<0.001**
Cardio-pulmonary resuscitation	55,148 (1.1%)	6148 (1.2%)	**<0.001**	140 (0.8%)	**0.003**
Amputation	414,738 (8.1%)	41,730 (8.3%)	**<0.001**	434 (2.6%)	**<0.001**
Minor amputation	281,273 (5.5%)	31,699 (6.3%)	**<0.001**	268 (1.6%)	**<0.001**
Major amputation	162,565 (3.2%)	13,205 (2.6%)	**<0.001**	193 (1.2%)	**<0.001**
Myocardial infarction	171,813 (3.4%)	19,337 (3.9%)	**<0.001**	314 (1.9%)	**<0.001**
Deep venous thrombosis	50,009 (1.0%)	5127 (1.0%)	**0.003**	228 (1.4%)	**<0.001**
Pulmonary embolism	22,281 (0.4%)	2510 (0.5%)	**<0.001**	114 (0.7%)	**<0.001**
Shock	63,881 (1.3%)	6611 (1.3%)	**<0.001**	203 (1.2%)	0.708
Treatment					
Transfusion of blood constituents	668,298 (13.1%)	59,449 (11.9%)	**<0.001**	2197 (13.2%)	0.698

P values of <0.05 were considered to be statistically significant.
Definitions:
[a] P-value for differentiation between PAD patients with and without obesity excluding the PAD patients with underweight.
[b] P-value for differentiation between PAD patients with and without underweight excluding the PAD patients with obesity.

reference group. Additionally, CVD, such as CAD and HF, but also renal insufficiency and COPD, were more prevalent in obese patients in comparison to the reference group.

Underweight PAD patients had significantly higher frequencies of cancer and COPD, but lower rates of CVRF and CVD (diabetes mellitus, aHT, CAD and HF) compared to the reference group (Table 1).

Obese as well as underweight PAD patients stayed respectively longer in the hospital than the PAD patients without underweight or obesity.

3.2. Outcomes

Overall, 277,876 (5.0%) inpatients died in-hospital. In total, 191,464 (3.4%) developed a MI, 55,364 (0.9%) a DVT, 24,905 (0.4%) a PE, 70,695 (1.3%) a shock, 61,436 (1.1%) had to undergo CPR and 456,902 (8.1%) an amputation surgery (minor amputation: 313,240 [5.6%]; major amputation: 175,963 [3.1%]).

The all-cause in-hospital mortality was significantly lower in obese PAD patients compared to the reference group (3.2% vs. 5.1%, $P < 0.001$) and lower in the reference group in comparison to the underweight patients (5.1% vs. 6.0%, $P < 0.001$) (Table 1). The univariate logistic regression analyses showed consistently a significant association between obesity and a reduced risk for in-hospital mortality (OR 0.617 [0.607–0.627], $P < 0.001$) in the univariate logistic regression model, which remained stable after adjustment for age, sex and comorbidities (Table 2). In contrast, underweight was associated with an increased risk for in-hospital mortality (OR 1.179 [1.106–1.257], $P < 0.001$) proving its independence in the multivariate regression model.

In-hospital mortality was significantly lower in all obesity classes, but lowest in obesity class I with 2.5%, followed by class II (3.0%) and class III (4.6%) compared to the reference group (5.1%) (Table S1 in the supplements). Figure 1 shows a typical U-shaped character for the mortality–rate curve of the PAD patients stratified for obesity classes, underweight and the reference group. Logistic regression analyses emphazise a significant association between all obesity classes and decreased risk to die during the in-hospital stay independently of age, sex and comorbidities compared to the reference group (Table 3).

The risk for in-hospital mortality was reduced in all age-groups ≥40 years, with an increasing mortality reduction with inclining age (Table S2 in the supplements). Figure 1A highlights that cancer has a very important impact on the in-hospital mortality especially in the underweight PAD patients, recognizable in the divergent curve shapes of the curves for PAD patients with and without cancer in the underweight weight class. The impact of HF on the in-hospital mortality is extensively high in the normal-/overweight and the underweight weight class (Fig. 1B). The mortality curves for PAD patients with and without COPD run widely parallel with higher mortality rates in PAD patients with additional COPD (Fig. 1C).

Obese PAD patients had slightly higher rates of MI (3.9% vs. 3.4%, $P < 0.001$) as well as venous thromboembolic (VTE) events and had to undergo more often amputation surgery (8.3% vs. 8.1%, $P < 0.001$), including higher relative number of minor amputations (6.3% vs. 5.5%, $P < 0.001$), whereas the major amputation rates were lower in obese patients (2.6% vs. 3.2%, $P < 0.001$) (Table 1). The univariate logistic regression model showed a significant association between obesity and lower risk regarding major amputation

Table 2
Impact of obesity and underweight on risk stratification markers, outcomes and treatment in PAD patients aged ≥18 years.

	Impact of obesity				Impact of underweight			
	Univariate regression model		Multi-variate regression model		Univariate regression model		Multi-variate regression model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Outcomes								
All-cause death	0.617 (0.607–0.627)	**<0.001**	0.642 (0.632–0.653)	**<0.001**	1.179 (1.106–1.257)	**<0.001**	1.091 (1.022–1.166)	**0.009**
Cardio-pulmonary resuscitation	1.138 (1.108–1.168)	**<0.001**	0.911 (0.886–0.936)	**<0.001**	0.776 (0.657–0.917)	**0.003**	0.779 (0.659–0.921)	**0.004**
Amputation	1.028 (1.017–1.038)	**<0.001**	0.856 (0.847–0.866)	**<0.001**	0.303 (0.275–0.333)	**<0.001**	0.301 (0.273–0.332)	**<0.001**
Minor amputation	1.158 (1.145–1.172)	**<0.001**	0.921 (0.910–0.933)	**<0.001**	0.280 (0.249–0.316)	**<0.001**	0.291 (0.258–0.329)	**<0.001**
Major amputation	0.823 (0.808–0.838)	**<0.001**	0.765 (0.751–0.779)	**<0.001**	0.356 (0.309–0.411)	**<0.001**	0.351 (0.304–0.405)	**<0.001**
Myocardial infarction	1.153 (1.135–1.170)	**<0.001**	0.915 (0.901–0.930)	**<0.001**	0.552 (0.493–0.617)	**<0.001**	0.587 (0.524–0.658)	**<0.001**
Deep venous thrombosis	1.045 (1.015–1.076)	**0.003**	1.183 (1.148–1.218)	**<0.001**	1.403 (1.231–1.600)	**<0.001**	1.277 (1.120–1.456)	**<0.001**
Pulmonary embolism	1.149 (1.102–1.197)	**<0.001**	1.239 (1.188–1.293)	**<0.001**	1.572 (1.307–1.891)	**<0.001**	1.342 (1.115–1.614)	**0.002**
Shock	1.055 (1.029–1.082)	**<0.001**	0.874 (0.851–0.897)	**<0.001**	0.974 (0.848–1.119)	0.708	0.942 (0.819–1.083)	0.402

P values of <0.05 were considered to be statistically significant.

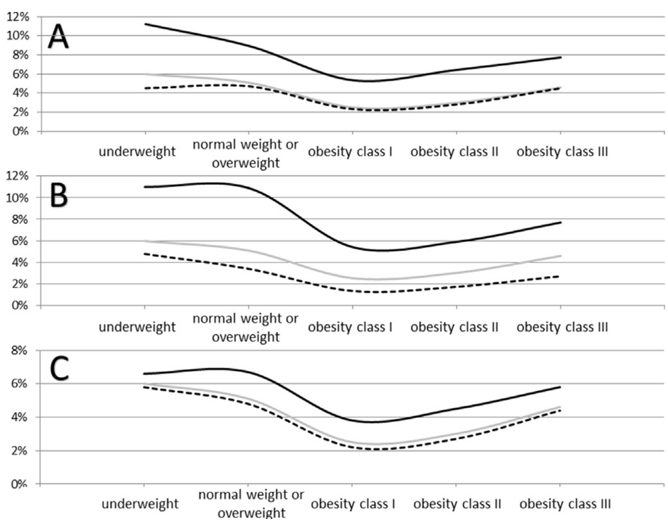

Fig. 1. Mortality rates in PAD patients aged ≥18 years stratified for underweight, normal weights/overweight and the obesity classes I–III. **A:** All PAD patients (grey line), PAD patients with cancer (black solid line), and PAD patients without cancer (black dashed line). **B:** All PAD patients (grey line), PAD patients with heart failure (black solid line), and PAD patients without heart failure (black dashed line). **C:** All PAD patients (grey line), PAD patients with chronic obstructive pulmonary disease (black solid line), and PAD patients without chronic obstructive pulmonary disease (black dashed line).

surgeries (OR 0.823 [0.808–0.838], P < 0.001) (Table 2), which remained stable after multi-variate adjustment.

In contrast, underweight PAD patients had significantly lower rates of MI (1.9% vs. 3.4%, P < 0.001), but higher event rates of DVT (1.4% vs. 1.0%, P < 0.001) and PE (0.7% vs. 0.4%, P < 0.001) in comparison to the reference group (Table 1). The frequency of an amputation surgery was significant less prevalent in underweight patients compared to the reference group (2.6% vs. 8.1%, P < 0.001). Consequently, also the rates of minor (1.6% vs. 5.5%, P < 0.001) as well as major amputations (1.2% vs. 3.2%, P < 0.001) were significantly lower in comparison to the reference group.

The logistic regression models also revealed a decreased risk for amputation surgery, CPR and MI, but an increased risk for DVT and PE compared to the reference group (Table 2).

4. Discussion

With the present study we analyzed the in-hospital mortality and other adverse in-hospital outcomes in patients with PAD relative to underweight and obesity in the large nationwide inpatient sample of Germany. The key findings of our study comprise the following aspects: I) Our study results demonstrate an obesity survival paradox in PAD patients independent of age, gender and comorbidities. II) Lower case-fatality rates were observed for all obesity classes in comparison to the normal-/over-weighted reference group. III) Underweight PAD patients had the highest in-hospital mortality rate mainly driven by the comorbidity of cancer. IV) Underweight PAD patients and those with obesity showed lower frequencies for major amputations than the normal-/over-weighted reference group.

The most important finding of our study is that our data demonstrate an obesity survival paradox in PAD patients, emphasizing lower in-hospital mortality in obese patients independent of age, gender and comorbidities. Lower case-fatality rate of obese patients was observed for all obesity classes in comparison to the normal-/over-weighted reference. These findings are consistent with findings in other CVD, including CAD and, especially HF, but also atrial fibrillation, all also showing obesity survival paradoxes [12–14].

PAD is estimated to affect approximately 15% of the US population with a sharp increase with incline of age [16,18,19]. PAD is associated to CVRF and CVD as well as their complications [18,20,21] and is accompanied by significant mortality [8,9]. Beside this, PAD leads to reduced quality of life [22] and significant functional limitations in daily life [18,23].

It is well established that atherosclerosis is the common root of both CAD and PAD and is associated with typical CVRF [18,19]. Although obesity is a major risk factor for CVD in general [1–6,24], the impact of obesity on the development of PAD remains controversial. While some studies revealed an association between obesity and increased PAD frequency [25–27], other studies reported a lower PAD prevalence with increased BMI [18,28,29] or observed no associations of BMI with incident clinical PAD events [18,19] or the presence of PAD was not independently associated with obesity or BMI [30,31].

Despite this negative impact of obesity on the development of CVD, several studies in the past decade have highlighted an obesity survival paradox, which is accompanied by a better survival for obese patients with acute and chronic CVD compared to their leaner counterparts [11–14,32–38].

While a few studies have reported an obesity paradox for PAD patients in longer follow-up periods and in mid-size cohorts [9,10] and other studies could not confirm the existence of such a phenomenon [15], our study is the first to our knowledge to demonstrated in a large nationwide cohort study an obesity survival paradox for the short-term in-hospital survival.

Table 3
Impact of the different obesity classes on outcomes and treatment in PAD patients aged ≥18 years.

Parameters	Obesity class I (n = 169,916; 57.4% of the subclassified obese patients)				Obesity class II (n = 77,691; 26.2% of the subclassified obese patients)				Obesity class III (n = 48,466; 16.4% of the subclassified obese patients)			
	Univariate regression model		Multi-variate regression model		Univariate regression model		Multi-variate regression model		Univariate regression model		Multi-variate regression model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Outcomes												
All-cause death	0.475 (0.461 −0.490)	**<0.001**	0.470 (0.455 −0.485)	**<0.001**	0.580 (0.557 −0.605)	**<0.001**	0.564 (0.541 −0.588)	**<0.001**	0.895 (0.857 −0.934)	**<0.001**	0.844 (0.807 −0.882)	**<0.001**
Cardio-pulmonary resuscitation	0.957 (0.912 −1.004)	0.070	0.747 (0.712 −0.783)	**<0.001**	1.197 (1.124 −1.274)	**<0.001**	0.883 (0.829 −0.941)	**<0.001**	1.632 (1.524 −1.747)	**<0.001**	1.113 (1.038 −1.193)	**0.002**
Amputation	0.924 (0.908 −0.941)	**<0.001**	0.757 (0.743 −0.771)	**<0.001**	1.089 (1.062 −1.116)	**<0.001**	0.855 (0.833 −0.878)	**<0.001**	1.202 (1.166 −1.239)	**<0.001**	0.947 (0.918 −0.978)	**0.001**
Minor amputation	1.118 (1.096 −1.141)	**<0.001**	0.879 (0.861 −0.898)	**<0.001**	1.290 (1.254 −1.326)	**<0.001**	0.961 (0.934 −0.989)	**0.007**	1.335 (1.290 −1.382)	**<0.001**	0.991 (0.956 −1.027)	0.622
Major amputation	0.587 (0.567 −0.608)	**<0.001**	0.536 (0.518 −0.556)	**<0.001**	0.738 (0.705 −0.773)	**<0.001**	0.657 (0.626 −0.688)	**<0.001**	0.949 (0.901 −1.000)	**0.049**	0.846 (0.802 −0.892)	**<0.001**
Myocardial infarction	1.113 (1.085 −1.142)	**<0.001**	0.844 (0.822 −0.866)	**<0.001**	0.964 (0.926 −1.003)	0.068	0.749 (0.719 −0.780)	**<0.001**	0.913 (0.867 −0.961)	**0.001**	0.743 (0705 −0.784)	**<0.001**
Deep venous thrombosis	0.939 (0.893 −0.987)	**0.014**	1.069 (1.016 −1.125)	**0.010**	1.090 (1.018 −1.168)	**0.014**	1.233 (1.150 −1.321)	**<0.001**	1.170 (1.075 −1.272)	**<0.001**	1.280 (1.176 −1.393)	**<0.001**
Pulmonary embolism	0.957 (0.889 −1.031)	0.252	1.033 (0.958 −1.113)	0.398	1.162 (1.052 −1.284)	**0.003**	1.220 (1.104 −1.348)	**<0.001**	1.622 (1.458 −1.805)	**<0.001**	1.597 (1.433 −1.779)	**<0.001**
Shock	0.993 (0.951 −1.038)	0.760	0.805 (0.770 −0.841)	**<0.001**	1.135 (1.069 −1.205)	**<0.001**	0.863 (0.812 −0.917)	**<0.001**	1.701 (1.598 −1.810)	**<0.001**	1.169 (1.097 −1.246)	**<0.001**

P values of <0.05 were considered to be statistically significant.
Overall, 40.8% of the obese patients, coded with the ICD-code E66, were not subclassified in one of the obesity classes due to a missing further coding and therefore these patients were not included in this subclass analysis.

While our study results showed an univariate OR of 0.62 for the in-hospital morality rate, Galal et al. [10] reported an univariate HR of 0.95-fold for each BMI unit regarding the risk to die during a median follow-up period of 4.37 years [10] and Golledge et al. [9] a relative risk of 0.59 for mortality during a median follow-up of 1.4 years [9]. Although these study results are only somewhat comparable with our results, nevertheless all studies demonstrated a survival paradox in PAD patients. We identified a typical U-shaped BMI-mortality curve with lowest mortality in the obesity class I and increased mortality at its extremes obesity and underweight (Fig. 1), highlighting that the accepted "normal" and overweight-BMI range between 18.5 and 30 kg/m^2 was not associated with the best outcome [11,32,33]. Interestingly, all obesity classes had lower mortality rates than the normal-/overweight reference. Although underweight PAD patients were less likely to undergo CPR and had lower coding for MI, the case-fatality rate was higher than in the normal-/overweight reference. It is well known that underweight correlates with poorer prognosis in several acute diseases, and this frailty is associated with comorbidities, such as cancer, COPD and sarcopenia [10,11,32,34].

Moreover, our results showed a higher risk for amputation, CPR, MI and shock in obese patients in the univariate regression model, but a lower risk for these interventions/comorbidities/conditions after adjustment of the multivariate regression model for sex, age, surgery and important comorbidities. This finding might indicate for an important impact of the adjusted variables on the mentioned interventions/comorbidities/conditions, veiling the true impact of obesity on these interventions/comorbidities/conditions in the univariate regressions, but revealing its true associations after the provided adjustment.

The underlying reasons for the obesity paradox have still not been fully elucidated [10]. It was hypothesized that the following reasons may explain the obesity paradox phenomenon in part or in whole:

First, obese patients are younger at the onset of the CVD, present earlier at medical centers, and may be more aggressively treated [13,33,35–39]. Thus, the CVD may be diagnosed in obese patients at an earlier stage due to more symptomatic status compared to the patients with leaner body mass [10]. Our study results confirmed this assumption, in accordance with some [40], but in contrast to others [41], that obese PAD patients were younger than normal-/overweight patients as well as underweight patients. Epidemiologically, increasing age is accompanied by an accumulation of relevant comorbidities [42,43] resulting in an unfavourable outcome [44].

Second, comorbidities might be causative for the obesity paradox phenomenon, maybe in connection with the accumulation of relevant comorbidities due to increased age [42–44]. Underweight status has also been associated with overt or occult malignancy and COPD [10]. In the underweight patients of our study, cancer, as well as COPD, were both more commonly detected with frequencies >20%. Cigarette smoking is an important risk factor for both PAD [21,27,30,45] and overall mortality accompanied by the five major causes of death (lung cancer, COPD, CAD/MI, other heart disease, and stroke) [46]. Studies have shown a lower BMI in smokers [47–49] and COPD patients [47,50]. COPD, as well as cancer, being important mortality predictors, were more frequently observed in the underweight patients [46,51]. Galal et al. reported that the higher prevalence of COPD in PAD patients with underweight might explain in part the higher mortality rate in this weight class [10]. In addition, higher frequency of cancer as an established risk factor for VTE events in PAD patients with underweight was connected with a higher rate of DVT and, especially, PE events [42]. However, the results of our multivariate logistic regression models revealed that the survival benefit due to obesity was independent of age, gender and comorbidities, including cancer and COPD, but remarkably, underweight PAD patients revealed a significantly decreased survival due to cancer.

Third, the hypothesis was generated that the majority of older individuals in Western populations without cancer and chronic diseases are obese and being of normal-weight while suffering an acute CVD is uncommon and may reflect (presence of unmeasured) serious comorbid conditions [33,52,53]. Therefore, life-saving benefits that have been attributed to overweight/obesity in patients with CVD may be caused by (undiagnosed) comorbidities [33,37,52,53]. This hypothesis is partly supported by a lower prevalence of cancer in the obese patients in comparison to the reference group of our study, but seems unlikely when also evaluating other chronic diseases, such as renal insufficiency, CAD, HF and COPD, which are all more prevalent in the obese patients. In this context, our logistic multi-variate regression analyses demonstrated the independence of the obesity survival paradox from age, gender and comorbidities. Therefore, these hypotheses that suggest that age and comorbidities cause the obesity paradox phenomenon are unlikely.

Fourth, obesity as a nutritional reserve is particularly important in older patients with frailty when comorbidities and lower homeostatic reserves coexist frequently [37]. In accordance with this hypothesis, our study results demonstrated, that the obesity paradox in PAD patients is limited to older PAD patients aged at least 40 years (and older), but not in younger patients. Also one study of MI patients [37] and another of PE patients [40] indicated an age-dependency of the obesity paradox in these patients.

Fifth, another possible explanation is that obesity may protect against malnutrition and energy wastage during the acute CVD event. This concept suggests that obesity triggers alterations with respect to neuroendocrine status that may subsequently impact modulation of pathologic cardiovascular remodeling [13,33,35,37]. Previous studies have suggested that underweight patients have a higher metabolic rate, a lower antioxidant capacity in skeletal muscles, and an increased systemic inflammatory response, which might contribute to weight-loss, sarcopenia and morbidity. Higher BMI and obesity may protect patients against inflammatory cytokines by an enhanced production of “buffering” lipoproteins [10].

Sixth, studies described that patients with overweight/obesity, who suffer from an acute CVD, such as MI, had higher rates of aggressive treatments, including revascularization therapies, and were more likely to receive guideline-based treatments in comparison to their leaner counterparts [33,37].

Finally, although our study results of the nationwide sample of Germany confirm the presence of an obesity paradox in PAD patients in accordance with a large number of studies [33,37,52–55], some recent study authors suggested that the obesity paradox may be explained in whole or in part by residual confounding [37,38,52,53,55] and it was argued that BMI may not adequately reflect adiposity [32,36,54–56]. Of course, BMI is not able to discriminate between an excess in body fat and increased lean body mass [32,54,55] and BMI might not the perfect tool to discriminate between normal weight and overweight or obesity, but studies using body fat measurements or abdominal circumferences confirmed the presence of an obesity paradox [57]. Therefore, BMI as a measuring instrument is surely not the problem and the explanation of the obesity paradox, but other additional body composition measures, such as measures of central obesity and cardiorespiratory fitness, may provide important additional information to assess the mortality risk in CVD [13,53,56,58–61]. In this context studies have shown that obesity is associated with functional decline in persons with PAD [62] resulting in lower fitness levels, and the prognostic benefits of obesity seem to be especially important in unfit CVD patients [60].

Remarkably, our results emphasize that obese PAD patients had higher rates of VTE complications. Additionally, the risk of amputation depends not only on the severity of ischemia, but also on the presence of diabetes, wounds and infections. Diabetes and PAD cause 54% of the nontraumatic amputations. Although diabetes mellitus and PAD are two separate diseases, all patients with diabetes develop some level of PAD over time [63]. Early recognition of tissue loss and especially referral to a vascular specialist is mandatory to improve the limb salvage [64]. While amputations overall in our study were more prevalent in obese PAD patients, major amputation rate was lower in obese patients compared to the normal-weight/overweight reference group, although the prevalence of diabetes was significantly higher in obese patients. Multivariate regression models showed a lower risk for minor and major amputations in obese patients independently of comorbidities, including diabetes. This might be explained by two aspects, which have to be considered in this context: Correlation between obesity and deficient wound healing has long been established [65], once again confirmed by significant lower amputation rates in underweight PAD patients. In addition, obese PAD patients may present earlier at medical centers, and are more aggressively treated [13,33,35–39].

4.1. Limitations

It is well known that obesity is an increasing problem worldwide [1,66]. The proportion of adults with obesity was estimated to be 21.9% in men and 22.5% in women in Germany [66]. Therefore, a rate of 8.9% of obese PAD patients in our study suggests a possible under-reporting and under-coding of obesity in the nationwide sample, whereby the rates in the nationwide sample of the United States of America were comparable [40]. As, this is a nationwide inpatient sample, we have to be aware that a systematic assessment of hight and weight has not to be expected. Additionally, we were not able to evaluate the impact of tobacco itself, although we did adjust for COPD, which may be a stronger influence on survival than tobacco itself [67–69].

One further key limitation regarding our analysis is the missing data regarding the causes of death of the patients and that we can only report coprevalences. We were not able to adjust the multivariate models for patients' socioeconomic status since these data are not available in the data set of the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis).

5. Conclusions

Obesity is associated with lower in-hospital mortality in PAD patients relative to those with normal-weight/over-weight. This obesity survival paradox was independent of age, sex and comorbidities and was observed for all obesity classes. Therefore, greater concern should be directed to the thinner patients with PAD who are particularly at increased risk of mortality.

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Disclosures

The authors declare that there is no conflict of interest to disclose.

Conflicts of interest

The authors report no conflicts of interest.

Author contributions

This is an original work, and all authors meet the criteria for authorship, including acceptance of responsibility for the scientific content of this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.09.031.

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