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Obesity and pulmonary embolism: The mounting evidence of risk and the mortality paradox☆

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ABSTRACT

Purpose: To determine the prevalence of pulmonary embolism in obese patients according to age, gender and comorbid conditions and explore the relation of obesity to mortality.
Methods: The number of patients discharged from short-stay hospitals throughout the United States from 1998–2008 with pulmonary embolism who were obese or not obese, and in-hospital all-cause mortality were determined from the Nationwide Inpatient Sample.
Results: From 1998–2008, 203,500 of 17,979,200 (1.1%) obese patients were diagnosed with pulmonary embolism compared with 2,034,100 of 346,049,800 (0.6%) non-obese patients [relative risk (RR) = 2.03]. Relative risk for pulmonary embolism was highest among obese patients aged 11–20 years (RR = 5.80) and was higher in obese women (RR = 2.08) than in obese men (RR = 1.74). Mortality was 4.3% in obese patients with pulmonary embolism compared with 9.5% in non-obese patients (RR = 0.45). Obesity had the greatest effect on mortality in older patients and little effect in teenagers and young adults. Among stable patients who did not receive thrombolytic therapy, mortality was 3.8% in obese patients and 8.4% in non-obese patients (RR = 0.45). Among unstable patients, obesity had little effect on mortality.
Conclusions: The prevalence of pulmonary embolism in hospitalized patients was higher in obese patients than in non-obese patients. Mortality in patients with pulmonary embolism was lower in obese patients than in non-obese patients, with the greatest effects in women, older patients and stable patients.

Introduction

There is now considerable evidence that obesity is a risk factor for pulmonary embolism [1–5]. Obesity was suspected to be a risk factor for fatal post-operative pulmonary embolism in 1927 [6]. Over the years, high proportions of patients with venous thromboembolic disease were found to be obese [7,8]. Earlier data (1959 and 1983) showed an increased risk of pulmonary embolism in women, but not in men [2,3]. In 1997, data from the Nurses' Health study among women aged 30–55 years showed a relative risk for pulmonary embolism of 2.9 in women with a body mass index ≥29 kg/m^2 [4]. Subsequently, in 1999, an investigation in middle-aged men showed obesity to be a risk factor for venous thromboembolism [9]. In 2003, the prevalence of deep venous thrombosis was shown to be increased in obese men and obese women [10]. Some, however, found no evidence that obesity was an independent risk factor for venous thromboembolism in men or women [11].

A paradoxical life-sparing effect of obesity has been observed in which the mortality from pulmonary embolism was lower in obese patients than non-obese patients [12]. In the present investigation, we use the database of the Nationwide Inpatient Sample to strengthen and expand the evidence that obesity is a risk factor for pulmonary embolism and further explore the relation of obesity to mortality in pulmonary embolism.

Methods

The number of patients discharged from short-stay hospitals throughout the United States from 1998 through 2008 with pulmonary embolism who were diagnosed with obesity, and the number who were not diagnosed with obesity were determined from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality [13]. The Nationwide Inpatient Sample is designed to approximate a 20% sample of nonfederal, short-term (acute care) hospitals as defined by the American Hospital Association, and is stratified according to geographic region, ownership, location, teaching status, and bed size [13]. From 1998 through 2008 the Nationwide Inpatient Sample contained all discharge data from 984 to 1,056 hospitals located in 22 to 42 states. In 2008 this sample comprised

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Table 1
International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) Codes Used.

Illness or Procedure	ICD-9-CM Codes Used
Pulmonary embolism	415.1, 634.6, 635.6, 636.6, 637.6, 638.6, and 673.2
Obesity*	278.0
Thrombolytic therapy	Procedure code 99.10
Shock	785.5
Ventilator-dependent	V461

* The basis for the diagnosis of obesity was not stated.

approximately 90 percent of all hospital discharges in the United States [13]. Weights are provided to calculate national estimates. The Nationwide Inpatient Sample is drawn from those states participating in the Healthcare Cost and Utilization Project. The Nationwide Inpatient Sample contains uniform inpatient data collected from existing hospital discharge databases maintained by state agencies, hospital associations, and other private data organizations [13].

The International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes were used to identify patients and procedures (Table 1). Unstable was defined as having a discharge code for shock or ventilator-dependence. Patients with a first listed diagnostic code for pulmonary embolism were considered to have a primary diagnosis and we assumed that they were admitted to the hospital because of pulmonary embolism.

Conditions included in the Charlson Comorbidity Index [14] and the ICD-9-CM codes we used to identify these conditions are shown in Table 2. This method of classifying comorbidity provides a simple, readily applicable and valid method of estimating risk of death from comorbid disease [14].

Statistical Methods

Mortality was defined as the proportion of deaths among patients with pulmonary embolism. Differences in prevalences of pulmonary embolism in obese and non-obese patients and differences of mortality were assessed by chi-square using Graph Pad Software (San Diego, CA). Relative risk and 95% confidence intervals (CI) were calculated using calculator for confidence intervals of relative risk (www.sign.ac.uk/methodology/risk.xls).

Results

Prevalence of Pulmonary Embolism with Obesity

From 1998 through 2008, 203, 500 of 17,979,200 (1.1%) obese patients were diagnosed with pulmonary embolism compared with 2,034,100 of 346,049,800 (0.6%) who did not have a discharge diagnostic code of obesity (relative risk 2.03, P<0.0001) (Table 3). The relative risk for pulmonary embolism among obese patients was highest among patients aged 11–20 years (relative risk 5.80) (Table 3). The prevalence of pulmonary embolism in obese and non-obese patients according to age is shown in (Fig. 1).

Comorbid conditions listed in the Charlson Index in obese and non-obese patients with pulmonary embolism are shown in Table 2. Obese patients had a lower prevalence of more comorbid conditions than non-obese patients, but chronic obstructive pulmonary disease, diabetes mellitus and diabetes with chronic complications were more prevalent in obese patients.

The prevalence of hospitalized patients diagnosed with obesity increased from 2.9% in 1998 to 7.6% in 2008 (Fig. 2). The proportion of hospitalized patients who had pulmonary embolism increased from 1998–2008 in both obese and non-obese patients. In 1998, 8,000 of 892,300 (0.9%) obese hospitalized patients had pulmonary embolism and in 2008, 36,000 of 2,670,100 (1.3%) obese patients had pulmonary embolism. In 1998, 119,400 of 29,626,000 (0.4%) non-obese hospitalized patients had pulmonary embolism and in 2008, 275,600 of 32,390,400 (0.9%) non-obese patients had pulmonary embolism.

The relative risk for pulmonary embolism in obese patients decreased with increasing age until > aged 70 years (Table 3). The relative risk for pulmonary embolism was higher in obese women (2.08) than in obese men (1.74) (Table 3). The relative risk for pulmonary embolism was somewhat higher in obese black patients than obese white patients (Table 3).

Mortality in Patients with Pulmonary Embolism and Obesity

All-cause in-hospital mortality was lower in obese patients with pulmonary embolism than in non-obese patients, 8,800 of 203,400 (4.3%) compared with 193,600 of 2,031,700 (9.5%) (relative risk 0.45) (P<0.0001) (Table 4). The relative risk for in-hospital death in obese females was 0.43 and in obese males relative risk was 0.50.

Table 2
Comorbid Conditions in Obese and Non-obese Patients with Pulmonary Embolsim.

Condition	ICD-9-CM odes	Obese* 203,530 n(%)	Non-obese 2,034,130 n(%)	P Value
Age (Mean ± SD)		55 ± 16	64 ± 18	< 0.0001
Acute Myocardial infarction	410	4,740 (2.3)	77,210 (3.8)	< 0.0001
Heart failure	428	30,650 (15)	328,760 (16)	< 0.0001
Peripheral vascular disease	440.2, 443.9	3,120 (1.5)	44,020 (2.2)	< 0.0001
Cerebrovascular disease	430-438	4,930 (2.4)	109,290 (5.4)	< 0.0001
Dementia	290	305 (0.1)	16,960 (0.8)	< 0.0001
Chronic obstructive pulmonary disease	490-496	53,570 (26)	484,860 (24)	< 0.0001
Rheumatologic disease	710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.8	1,620 (0.8)	20,440 (1.0)	< 0.0001
Ulcer disease	531-534	2,010 (1.0)	29,690 (1.5)	< 0.0001
Acute or chronic liver disease	570,571	2,670 (1.3)	25,860 (1.3)	NS
Diabetes mellitus	250.0-250.3	57,780 (28)	271,750 (13)	< 0.0001
Hemiplegia and hemiparesis	342.0-342.9	650 (0.3)	13,560 (0.7)	< 0.0001
Paraplegia	344.1	460 (0.2)	6,030 (0.3)	< 0.0001
Moderate or severe renal disease	580-586, 588	15,380 (7.6)	202,290 (10)	< 0.0001
Diabetes with chronic complications	250.4-250.6	5,800 (2.8)	33,330 (1.6)	< 0.0001
Any neoplasms, leukemia, lymphoma	140-195, 200-208	11,730 (5.8)	346,060 (17)	< 0.0001
Metastatic cancer	196-199	5,620 (2.8)	220,890 (11)	< 0.0001
HIV and AIDS	042	170 (0.1)	10,700 (0.5)	< 0.0001

*Patients may have more than one comorbid condition.
ICD-9-CM = International Classification of Diseases, 9th Edition, Clinical Modification.
HIV = human immunodeficiency virus.
AIDS = Acquired immune deficiency syndrome.

Table 3
Prevalence of Pulmonary Embolism in Obese and Non-obese Patients.

	PE/Obese (%)	PE/Not Obese (%)	Relative Risk (95% CI)
Male*	71,700/6,212,300 (1.2)	911,700/137,325,100 (0.7)	1.74 (1.73-1.75)
Female	131,800/11,758,600 (1.1)	1,121,800/208,261,500 (0.5)	2.08 (2.07-2.09)
White	112,500/9,539,800 (1.2)	1,157,400/181,324,100 (0.6)	1.85 (1.84-1.86)
Black	28,400/2,376,700 (1.2)	209,300/34,711,500 (0.6)	1.98 (1.96-2.01)
Age Groups			
1-10	-/56,200 (—)**	1,300/10,361,100 (0.01)	-
11-20	2,200/370,500 (0.6)	18,600/18,179,200 (0.1)	5.80 (5.55-6.07)
21-30	11,000/1,207,500 (0.9)	76,900/40,823,300 (0.2)	4.48 (4.74-4.93)
31-40	24,700/2,203,200 (1.1)	134,300/39,782,300 (0.3)	3.33 (3.29-3.38)
41-50	39,900/3,499,200 (1.1)	223,200/37,922,400 (0.6)	1.95 (1.93-1.97)
51-60	47,800/4,187,100 (1.1)	305,600/41,631,000 (0.7)	1.56 (1.54-1.57)
61-70	41,200/3,485,300 (1.2)	392,200/46,894,400 (0.8)	1.41 (1.40-1.43)
71-80	28,600/2,277,900 (1.3)	495,900/58,386,500 (0.8)	1.48 (1.46-1.50)
> 80	8,200/692,300 (1.2)	386,100/52,165,400 (0.7)	1.60 (1.57-1.64)
Total	**203,500/17,979,200 (1.1)**	**2,034,100/364,049,800 (0.6)**	**2.03 (2.02-2.03)**

PE = pulmonary embolism; CI = confidence interval.
*Gender data missing in some.
** Insufficient data.

The relative risks for mortality were similar in obese black patients and obese white patients.

All-cause in-hospital mortality increased in non-obese patients after aged 30 years and in obese patients after aged 40 years (Table 4, Fig. 3). There was less of an increasing mortality with age in obese adults than non-obese adults.

Mortality, Stable and Unstable Patients

The greater the severity of the pulmonary embolism, the less obesity was associated with a lower mortality. Among patients who were stable and did not receive thrombolytic therapy, in-hospital all-cause mortality was 7500 of 197,200 (3.8%) in obese patients and 165,300 of 1,956,700 (8.4%) in non-obese patients (relative risk 0.45, 95% CI 0.44-0.46) (P<0.0001) (Fig. 4).

Among patients who were stable and received thrombolytic therapy; in-hospital all-cause mortality was 400 of 4000 (10.0%) in obese patients and 3200 of 23,900 (13.4%) in non-obese patients (relative risk 0.75, 95% CI 0.68-0.82) (P<0.0001) (Fig. 4).

Among patients who were unstable, in-hospital all-cause mortality was 1,000 of 2,300 (43.5%) in obese patients and 25,100 of 53,500 (46.9%) in non-obese patients (relative risk 0.93, 95% CI 0.88-0.97) (P = 0.0013) (Fig. 4).

Prevalence with No Comorbidity

The proportion of patients who had a primary (first listed) diagnosis of pulmonary embolism and no associated comorbid condition listed in the Charlson Index was 61,800 of 17,979,200 (0.4%) in obese patients and 557,600 of 346,049,800 (0.2%) in non-obese patients (relative risk 2.13, 95% CI 2.12-2.15) (P<0.0001).

Mortality with No Comorbidity

Among patients with a primary diagnosis of pulmonary embolism who had none of the comorbid conditions listed in the Charlson Index, we assume that deaths were caused by pulmonary embolism. In-hospital mortality attributable to pulmonary embolism among these patients was 800 of 61,800 (1.3%) in obese patients compared with 12,500 of 557,300 (2.2%) in non-obese patients (relative risk 0.58) (P<0.0001) (Table 5, Fig. 5). The relative risk for mortality from pulmonary embolism was lower in obese women than in obese men. The relative risk for mortality was somewhat lower in obese blacks than obese whites.

Discussion

The prevalence of pulmonary embolism in hospitalized patients throughout the United States from 1998–2008 was higher in obese patients than non-obese patients. The prevalence of pulmonary embolism was higher in hospitalized obese women than obese men. The relative risk for pulmonary embolism, comparing obese to non-obese patients, was highest in teenagers and young adults, and the relative risk decreased until > aged 70 years. This may reflect the fact that older patients have more associated comorbid conditions,

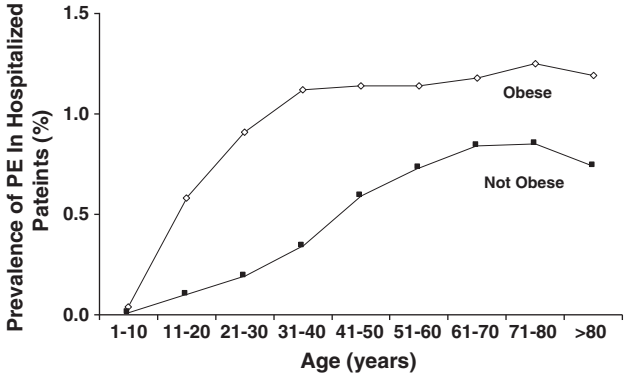

Fig. 1. Prevalence of pulmonary embolism (PE) according to age in hospitalized obese and non-obese patients.

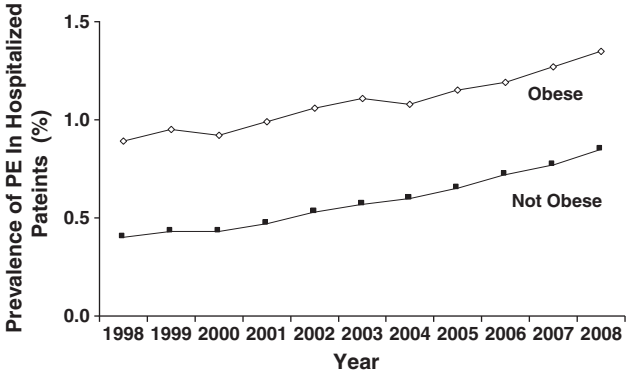

Fig. 2. Prevalence of pulmonary embolism (PE) from 1998 through 2008 in hospitalized obese and non-obese patients.

Table 4
All-cause In-Hospital Mortality With Pulmonary Embolism. In Obese and Non-obese Patients.

	Died/PE Obese (%)	Died/PE Not Obese (%)	Relative Risk (95% CI)
Male*	3,500/71,600 (4.9)	89,300/910,700 (9.8)	0.50 (0.48-0.52)
Female	5,300/131,700 (4.0)	104,200/1,120,400 (9.3)	0.43 (0.42-0.44)
White	5,000/107,400 (4.7)	111,300/1,155,700 (9.6)	0.46 (0.45-0.47)
Black	1,400/28,400 (4.9)	21,400/209,000 (10.2)	0.48 (0.46-0.51)
Age Groups			
1-10	-**	110/1,300 (8.5)	-
11-20	70/2,200 (3.2)	600/18,000 (3.2)	0.99 (0.77-1.26)
21-30	320/11,000 (2.9)	2,300/76,900 (3.0)	0.97 (0.87-1.09)
31-40	800/24,700 (3.2)	5,500/134,300 (4.1)	0.79 (0.74-0.85)
41-50	1,700/39,900 (4.3)	12,600/223,000 (5.7)	0.75 (0.72-0.79)
51-60	2,000/47,700 (4.2)	24,400/305,400 (8.0)	0.52 (0.50-0.55)
61-70	1,900/41,200 (4.6)	37,800/391,800 (9.7)	0.48 (0.46-0.50)
71-80	1,500/28,500 (5.3)	55,700/495,100 (11.2)	0.47 (0.45-0.49)
> 80	600/8,200 (7.3)	54,500/385,300 (14.1)	0.52 (0.48-0.56)
Total	**8,800/203,400 (4.3)**	**193,600/2,031,700 (9.5)**	**0.45 (0.44-0.46)**

PE = pulmonary embolism; CI = confidence interval.
*Gender data missing in some.
** Insufficient data.

so the impact of obesity as a risk factor diminishes with age. The prevalence of pulmonary embolism in obese patients was higher than in non-obese patients even among those with a primary diagnosis of pulmonary embolism and none of the associated comorbid conditions listed in the Charlson Comorbidity Index. This indicates that the increased prevalence of pulmonary embolism in obese patients is not necessarily a reflection of associated comorbid conditions.

The all-cause in-hospital mortality in patients with pulmonary embolism was lower in obese patients than in non-obese patients. This confirms the previously observed paradoxical effect of a lower mortality in obese patients [12]. Although obese patients had a lower prevalence of most comorbid conditions listed in the Charlson Index, this does not seem to explain their lower mortality because obese patients with none of the comorbid conditions listed in the Charlson Index also had a lower mortality than non-obese patients.

We showed that obesity in women had a greater effect on mortality than obesity in men. Obesity had little or no effect on lowering mortality in children or young adults (aged 21–30). Obesity was associated with a lower mortality with increasing age until > aged 80 years. Obesity had the greatest effect in lowering mortality in stable patients and had little effect on mortality in unstable patients.

Among patients with a primary diagnosis of pulmonary embolism and none of the comorbid conditions listed in the Charlson Index, mortality presumably due to pulmonary embolism was approximately 40% lower in obese patients than non-obese patients.

Data from the National Hospital Discharge Survey from 1979–1999 among 12,015,000 hospitalized patients with obesity showed pulmonary embolism in 0.76% compared with 0.34% among 691,000,000 patients who were not obese (relative risk = 2.21) [1]. The relative risk of deep venous thrombosis, comparing obese with non-obese patients, was 2.50 [1].

The relative risk for pulmonary embolism base on Data from the National Hospital Discharge Survey was higher in elderly obese women than in elderly obese men [1]. Data were sufficient for comparison of the relative risk of pulmonary embolism only among men and women aged 60–79 years. Obese women, had a greater relative risk for deep venous thrombosis than obese men, relative risk 2.75 in women compared with 2.02 in men [1].

Data from the National Hospital Discharge Survey showed that obesity had the greatest impact on the prevalence of pulmonary embolism in patients aged < 40 years, in whom the relative risk for pulmonary embolism in obese patients was 5.19 [1]. In older patients the relative risk ranged from 1.94 to 3.15. The relative risk for deep venous thrombosis in patients aged < 40 years was 5.20 and in older patients the relative risk ranged from 1.67 to 2.16.

The Nurses Health Study in 2009 showed that the prevalence of pulmonary embolism in women was linearly related to the body mass index [5]. The relative risk for pulmonary embolism that we calculated from their data, comparing those with a body mass index ≥ 30 kg/m^2 to those with a lower body mass index was 2.48. The Copenhagen City Heart Study in 2010 showed that the hazard ratio for venous thromboembolism increased with body mass index in both men and women [15].

In the Computerized Registry of Patients with Venous Thromboembolism (Registro Informatizado de la Enfermedad Tromboembólica) (RIETE), among 10,114 patients with acute venous thromboembolism, 3-month all-cause mortality was reported according to body mass indexes of <18.5 kg/m^2, 18.5-24.9 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2

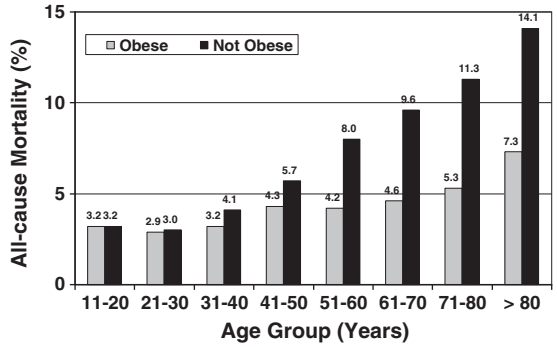

Fig. 3. All-cause mortality according to age in hospitalized obese and non-obese patients with pulmonary embolism (PE).

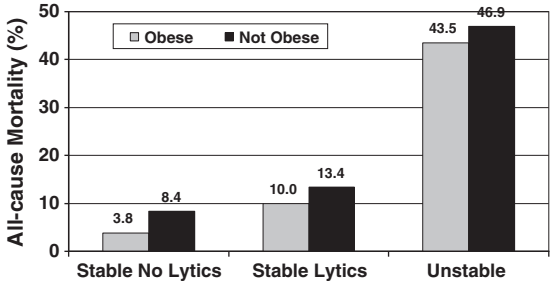

Fig. 4. Mortality among obese and non-obese patients with pulmonary embolism according to whether they were stable and did not receive thrombolytic therapy (lytics), stable and received thrombolytic therapy, or unstable. Relative risks were 0.45, 0.75 and 0.93 respectively.

Table 5
Mortality Attributable to Pulmonary Embolism In Patients With Primary Pulmonary Embolism and No Comorbidity By Charlson Index In Obese and Non-obese Patients.

	Died/1^{O} PE No Comorbidity Obese (%)	Died/1^{O} PE No Comorbidity Not Obese (%)	Relative Risk (95% CI)
Male*	350/21,200 (1.7)	4,800/243,400 (2.0)	0.84 (0.75-0.93)
Female	490/40,600 (1.2)	7,700/313,400 (2.5)	0.49 (0.45-0.54)
White	490/33,700 (1.5)	7,300/323,800 (2.2)	0.64 (0.59-0.71)
Black	110/7,700 (1.4)	1,200/48,900 (2.5)	0.58 (0.48-0.71)
Age Groups			
1-10	-	-/120 (−)**	-
11-20	-/1,200 (−)**	50/7,600 (0.7)	-
21-30	50/5,600 (0.9)	190/38,300 (0.5)	1.80 (1.32-2.45)
31-40	100/10,400 (1.0)	460/62,100 (0.7)	1.29 (1.04-1.59)
41-50	210/14,100 (1.5)	900/86,500 (1.0)	1.43 (1.23-1.66)
51-60	190/13,300 (1.4)	1,400/87,700 (1.6)	0.89 (0.77-1.04)
61-70	160/9,500 (1.7)	2,000/93,100 (2.2)	0.78 (0.67-0.92)
71-80	70/6,100 (1.1)	3,400/105,000 (3.2)	0.35 (0.28-0.44)
> 80	50/1,600 (3.1)	4,000/76,900 (5.2)	0.60 (0.46-0.79)
Total	**800/142,900 (1.3)**	**12,500/557,300 (2.2)**	**0.58 (0.54-0.62)**

1^{O} PE = Primary diagnosis of pulmonary embolism; CI = confidence interval.
*Gender data missing in some.
** Insufficient data.

[12]. Mortality decreased with increasing body mass indexes. All-cause mortalities were 28%, 12%, 6.2% and 4.2% respectively. Our results were comparable, showing a 9.5% in-hospital all-cause mortality in non-obese patients and 4.3% mortality in obese patients. In the RIETE registry, 3-month death rates from pulmonary embolism were 2.0%, 2.1%, 1.2% and 0.8% respectively. We showed in-hospital death presumably from pulmonary embolism (patients with a primary diagnosis and none of the comorbid conditions listed in the Charlson index) in 2.2% of non-obese patients and 1.3% of obese patients.

As with pulmonary embolism, excess body weight also paradoxically was associated with a decreased mortality in patients with stable heart failure [16], known or suspected coronary heart disease [17,18] and unstable angina or non-ST segment elevation myocardial infarction [19]. Some showed a higher mortality in men with coronary heart disease at both extremes of body mass index (lean and obese) [20].

Various abnormalities of hemostasis may contribute to the increased prevalence of pulmonary embolism in obese patients. Increased plasminogen activator inhibitor-1 (PAI-1) has been reported in obese patients [21,22] and correlated with body mass index [23,24]. Coagulation abnormalities in obese patients include increased platelet activation [25], elevated levels of plasma fibrinogen, factor VII and factor VIII and von Willibrand factor [26]. Fibrinogen and factor VIIc correlated with body mass index [24]. Also circulating procoagulant microparticles have been observed in obese patients [27].

Activity of the endocannabinoid system has been proposed as a possible mechanism for the reduced mortality in obese patients with pulmonary embolism [12]. Increased endocannabinoid levels have been reported in obese patients [28,29]. Blood levels of the endogenous endocannabinoid 2-arachidonoyl glycerol were elevated in obese patients and correlated with body mass index [29]. Plasma levels of the endocannabinoid anandamide, however, did not differ between obese and lean patients [29]. Gene expression in adipose tissue of obese patients for the cannabinoid type 1 receptor and the principal degrading enzyme, fatty acid amide hydrolase was decreased in obese men and women compared to lean patients [29]. Others showed higher levels of circulating arachidonoyl glycerol in obese women compared to lean women and decreased gene expression in adipose tissue of obese patients for cannabinoid type 1 receptor and fatty acid amide hydrolase [28]. In this investigation, circulating levels of anandamide were also elevated in obese women [28]. Men were not studied [28]. Endocannabinoids in rats and mice have been shown to have effects that could be potentially beneficial in patients with pulmonary embolism. These relate to decreased ventricular arrhythmias [30,31], coronary vasodilation [32], protection against the deleterious effects of ischemia [33], inhibition of cardiac myocyte death and fibroblast death [34] and an anti-inflammatory effect [35].

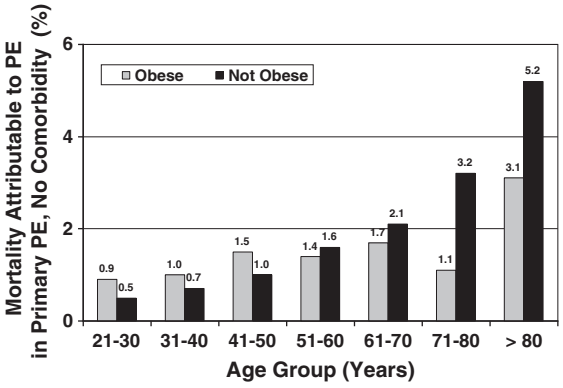

Fig. 5. Mortality attributable to pulmonary embolism (PE) according to age in obese and non-obese patients with primary diagnosis of pulmonary embolism and no comorbidity listed in Charlson Index.

Strengths of this investigation are the large number of patients included in the database. This permitted stratification of results according to age, race and gender. It also permitted an analysis of trends over time.

Weaknesses relate to the imperfection of discharge codes. The criteria for obesity are not defined in the discharge code. It is likely that all patients diagnosed with obesity in the Nationwide Inpatient Sample database were in fact obese, irrespective of the criteria used. However, some obese patients may not have had a listed discharge diagnosis of obesity, and they would have been included in the non-obese group. This would have tended to reduce the apparent relative risk of pulmonary embolism in obese patients. Irrespective, we focus on relative values, not absolute values. The relative risk for pulmonary embolism that we observed in women was similar to the relative risk reported in women in the Nurses Health Study [4,5]. Regarding mortality in obese patients, some of our results were strikingly similar to results reported from the RIETE registry [12], and all were in a comparable range. All-cause 3-month mortality in patients with a body mass index >30 kg/m^2 in the RIETE registry was 4.2%. We observed an all-cause in-hospital mortality of 4.3% in obese patients. The 3-month mortality from pulmonary embolism in patients in the RIETE registry with a body mass index ≤24.9 kg/m^2 was 2.0%-2.1%. We observed 2.2% in-hospital mortality from pulmonary embolism in non-obese patients. These results support the robustness of our data.

The prevalence of patients hospitalized with obesity increased from 1998 to 2008. Whether this represents greater attention to

coding for obesity at discharge or a higher prevalence of obesity among hospitalized patients is uncertain.

In conclusion, the prevalence of pulmonary embolism in hospitalized patients was higher in obese patients than in non-obese patients. The relative risk of pulmonary embolism was higher in obese women than obese men and higher in teenagers and young adults than older patients. The all-cause in-hospital mortality in patients with pulmonary embolism was lower in obese patients than in non-obese patients. The effect of obesity on mortality was greater in obese women than obese men. There was little effect of obesity on mortality in children or young adults and a greater effect in older patients. The effect of obesity on mortality was greatest in stable patients with little effect on mortality in unstable patients.

Conflict of interest statement

None of the authors have any financial or other potential conflicts of interest relative to the data in this manuscript.

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References

[1] Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med 2005;118:978–80.
[2] Goldhaber SZ, Savage DD, Garrison RJ, Castelli WP, Kannel WB, McNamara PM, et al. Risk factors for pulmonary embolism. The Framingham Study. Am J Med 1983;74:1023–8.
[3] Coon WW, Coller FA. Some epidemiologic considerations of thromboembolism. Surg Gynecol Obstet 1959;109:487–501.
[4] Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA 1997;277:642–5.
[5] Kabrhel C, Varraso R, Goldhaber SZ, Rimm EB, Camargo CA. Prospective study of BMI and the risk of pulmonary embolism in women. Obesity (Silver Spring) 2009;17:2040–6.
[6] Snell AM. The relation of obesity to fatal postoperative pulmonary embolism. Arch Surg 1927;15:237–44.
[7] Anderson Jr FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151:933–8.
[8] Anderson Jr FA, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. Arch Intern Med 1992;152:1660–4.
[9] Hansson PO, Eriksson H, Welin L, Svardsudd K, Wilhelmsen L. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". Arch Intern Med 1999;159:1886–90.
[10] Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost 2003;89:493–8.
[11] Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM, et al. The epidemiology of venous thromboembolism in the community. Thromb Haemost 2001;86:452–63.
[12] Barba R, Zapatero A, Losa JE, Valdés V, Todolí JA, Di Micco P, et al. Riete Investigators. Body mass index and mortality in patients with acute venous thromembolism: Findings from the RIETE registry. J Thromb Haemost 2008;6:595–600.
[13] HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; 1998–2008www.hcup-us.ahrq.gov/nisoverview.jsp.
[14] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[15] Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation 2010;121:1896–903.
[16] Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med 2005;165:55–61.
[17] Kang X, Shaw LJ, Hayes SW, Hachamovitch R, Abidov A, Cohen I, et al. Impact of body mass index on cardiac mortality in patients with known or suspected coronary artery disease undergoing myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 2006;47:1418–26.
[18] Galal W, van Domburg RT, Feringa HH, Schouten O, Elhendy A, Bax JJ, et al. Relation of body mass index to outcome in patients with known or suspected coronary artery disease. Am J Cardiol 2007;99:1485–90.
[19] Buettner HJ, Mueller C, Gick M, Ferenc M, Allgeier J, Comberg T, et al. The impact of obesity on mortality in UA/non-ST-segment elevation myocardial infarction. Eur Heart J 2007;28:1694–701.
[20] Benderly M, Boyko V, Goldbourt U. Relation of body mass index to mortality among men with coronary heart disease. Am J Cardiol 2010;106:297–304.
[21] Pannaciulli N, De Mitrio V, Marino R, Giorgino R, De Pergola G. Effect of glucose tolerance status on PAI-1 plasma levels in overweight and obese subjects. Obes Res 2002;10:717–25.
[22] Juhan-Vague I, Alessi MC, Mavri A, et al. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J Thromb Haemost 2003;1:1575–9.
[23] Margaglione M, Cappuci G, d'Addedda M, Colaizzo D, Giuliani N, Vecchione G, et al. PAI-1 plasma levels in a general population without clinical evidence of atherosclerosis: relation to environmental and genetic determinants. Arterioscler Thromb Vasc Biol 1998;18:562–7.
[24] Bara L, Nicaud V, Tiret L, Cambien F, Samama MM. Expression of a paternal history of premature myocardial infarction on fibrinogen, factor VIIC and PAI-1 in European offspring–the EARS study. European Atherosclerosis Research Study Group. Thromb Haemost 1994;71:434–40.
[25] Basili S, Pacini G, Guagnano MT, Manigrasso MR, Santilli F, Pettinella C, et al. Insulin resistance as a determinant of platelet activation in obese women. J Am Coll Cardiol 2006;48:2531–8.
[26] Mertens I, Van Gaal LF. Obesity, haemostasis and the fibrinolytic system. Obes Rev 2002;3:85–101.
[27] Goichot B, Grunebaum L, Desprez D, Vinzio S, Meyer L, Schlienger JL, et al. Circulating procoagulant microparticles in obesity. Diabetes Metab 2006;32:82–5.
[28] Engeli S, Böhnke J, Feldpausch M, Gorzelniak K, Janke J, Bátkai S, et al. Activation of the peripheral endocannabinoid system in human obesity. Diabetes 2005;54:2838–43.
[29] Blüher M, Engeli S, Klöting N, Berndt J, Fasshauer M, Bátkai S, et al. Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. Diabetes 2006;55:3053–60.
[30] Krylatov AV, Ugdyzhekova DS, Bernatskaya NA, Maslov LN, Mekhoulam R, Pertwee RG, et al. Activation of Type II Cannabinoid Receptors Improves Myocardial Tolerance to Arrhythmogenic Effects of Coronary Occlusion and Reperfusion. Bull Exp Biol Med 2001;131:523–5.
[31] Ugdyzhekova DS, Bernatskaya NA, Stefano JB, Graier VF, Tam SW, Mekhoulam R. Endogenous Cannabinoid Anandamide Increases Heart Resistance to Arrhythmogenic Effects of Epinephrine: Role of CB1 and CB2 Receptors. Bull Exp Biol Med Pharmacol Toxicol 2010;3:251–3.
[32] Ford WR, Honan SA, White R, Hiley CR. Evidence of a noverl site mediating anatamide-induced negative inotropic and coronary vasodilator responses in rat isolated hearts. Br J Pharmacol 2002;135:1191–8.
[33] Lépicier P, Bouchard JF, Lagneux C, Lamontagne D. Endocannabinoids protect the rat isolated heart against ischaemia. Br J Pharmacol 2003;139:805–15.
[34] Defer N, Wan J, Souktani R, Escoubet B, Perier M, Caramelle P, et al. The cannabinoid receptor type 2 promotes cardiac myocyte and fibriblast survival and protects against ischemia/reperfusion-induced cardiomyopathy. FASEB J 2009;23:2120–30.
[35] Conti S, Costa B, Colleoni M, Parolaro D, Giagnoni G. Antiinflammatory action of endocannabinoid palmitoylethanoamide and the synthetic cannabinoid nabilone in a model of acute inflammation in the rat. Br J Pharmacol 2002;135:181–7.