A negative impact of recent weight loss on in-hospital mortality is not modified by overweight and obesity

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SUMMARY

Background: Obesity [Body Mass Index (BMI) > 30 kg/m^2] is a risk factor for disease conditions enhancing hospitalization and mortality risks, but higher BMI was paradoxically reported to reduce mortality in several acute and chronic diseases. Unintentional weight loss (WL) is conversely associated with disease development and may worsen patient outcome, but the impact of weight loss and its interaction with obesity in modulating risk of death in hospitalized patients remain undefined.
Methods: We investigated the ESPEN nutritionDay database of non-critically ill hospitalized patients to assess the impact of self-reported 3-month WL (WL1:2.5–6.6%; WL2: 6.6–12.6%, WL3: >12.6%) and its interaction with BMI in modulating 30-day in-hospital mortality. Multivariate Cox regression was used to estimate hazard ratios (HR), with stable weight (WL0) as reference category.
Results: In 110835 nDay patients, 30-day mortality increased with increasing WL. Male gender, increasing disease severity index PANDORA score (age, nutrient intake, mobility, fluid status, cancer and main patient group) and not having had surgery also predicted 30-day mortality. HR for 30-day mortality remained significantly higher compared to WL0 for WL2 and WL3 after multiple adjustment. Adjusted HR and its increments through increasing weight loss categories were comparable in lean (BMI<25), overweight (BMI 25–30) and obese individuals (BMI>30 kg/m2). Impact of gender, PANDORA score and surgery on 30-day mortality were conversely comparable in the three BMI groups.
Conclusions: These results indicate that self-reported WL could represent a relevant prognostic factor in every hospitalized patient. Overweight and obesity per se have no protective impact against WL-associated mortality.

1. Introduction

Prognostic tools that allow assessment and stratification of patient risk of death provide key information for optimization of patient management and treatment as well as optimal resources utilization in the hospital setting. Nutritional status and its changes are specifically recognized as strong predictors of disease development, progression and outcome [1,2]. In particular, overweight and obesity as defined by body mass index (BMI) higher than 25 or 30 kg/m^2 respectively favour the onset of several disease conditions that commonly result in acute complications, hospitalizations and overall reduced survival [3]. Being overweight or obese has been however paradoxically reported to reduce mortality associated with several acute and chronic diseases [4–11], and increasing BMI was also recently reported to be associated with lower mortality compared to low BMI in a large cohort of hospitalized patients from internal medicine, surgical, geriatric and various specialty departments through various age groups enrolled in the ESPEN nutritionDay survey [2]. Weight changes may however also influence patient outcome; unintentional weight loss associated with

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disease development, worsening and complications has indeed been reported to independently enhance risk of death in ambulatory patients with clinically relevant conditions [12,13], aging [14–18], as well as in the general population [19,20]. The impact of weight loss on risk of death in hospitalized patients and its potential interaction with obesity in modulating patient outcome remains however undefined.

In the current study, the ESPEN nutritionDay database of hospitalized patients was therefore investigated in order to assess the impact of recent weight loss over 3 months prior to hospital admission on 30-day in-hospital mortality; data was available from representative departments including internal medicine, surgery, geriatrics and several specialty wards with exclusion of intensive care units. The potential additional role of obesity and its interaction with self-reported 3-month weight loss in modulating patient outcome were also investigated. Adjustments were performed for co-determinants of patient mortality, including the composite disease severity index and mortality predictor PANDORA score (combining age, food intake, mobility, fluid status, cancer presence and main patient group).

2. Research design and methods

2.1. Study design and population

The nutritionDay is a one-day survey that enables health care institutions around the world to improve knowledge and awareness of malnutrition and to overall enhance the quality of nutritional care in three main settings: hospital wards, intensive care area and nursing homes [2,21]. The survey is implemented through the European Society for Clinical Nutrition and Metabolism (ESPEN) with voluntary participation and registration via an open web based application (www.nutritionday.org). The first edition of nutritionDay dates back 2006 and yearly editions have taken place since; data collected in hospital wards during the 2006–2015 editions were the object of the current investigation. Relevant information included demographic and anthropometric parameters as well as all information relevant to the composite disease severity index and mortality predictor PANDORA score [21–23] including food intake, mobility, fluid status, cancer presence and additional comorbidities and main patient group. Three-month weight change was recorded based on self-reported patient information and classified in the following weight loss (WL) categories: weight-stable (WL0: weight loss < 2.5%) WL1 (2.5–6.6%), WL2 (6.6–12.6%) and WL3 (>12.6%). Patient status at discharge until 30 days after the nutritionDay survey (death, transferred to another hospital, transferred to long-term care, discharged home) was the main outcome prospective parameter. Patients with recorded and registered information on 30-day mortality, BMI and PANDORA score were included in the current analysis (n = 110835).

3. Statistical analysis

Continuous data are given as mean with standard deviation or as median with range or interquartile range (IQR) as appropriate. Multivariate Cox regression was used to estimate hazard ratios (HR) with confidence intervals (CI) for the subgroups. Stable weight (WL0) was used as reference category. The Aalen-Johansen method (population at risk including all non-dying) was used to calculate cumulative event curves for dying in hospital for different self-reported weight-loss groups and in different BMI groups (Lean: BMI<25 kg/m^2; Overweight: 25 < BMI<30 kg/m^2; Obese: BMI >30 kg/m^2). Adjustment was performed with the variables PANDORA score, sex, previous surgery and duration in hospital before nutritionDay. p-value is defined as the probability that, for the used statistical model and under the assumption that the null-hypothesis is true, the statistical results would be equal or more extreme than the actual observed results. In this study $p < 0.05$ was considered significant.

4. Results

4.1. Study cohort

The study cohort was selected from the nDay hospital wards database available at the time of writing. Exclusion criteria were being children or psychiatric patients, missing information on outcome, BMI and PANDORA score. The remaining 110835 patients were included in study analyses (Fig. 1). Cohort demographics and descriptive statistics are reported in Table 1.

4.2. Impact of recent weight loss on patient outcome

In the above describe study cohort, risk of 30-day mortality increased with increasing weight loss (Table 2); male gender, disease severity index and mortality predictor PANDORA score (including age, nutrient intake, mobility, fluid status, cancer and main patient group) and not having had surgery were also associated with higher 30-day mortality (Table 2). The unadjusted cumulative event curve for dying in hospital in the different self-reported short-term weight loss groups is shown in Fig. 2, also demonstrating increments in deaths with increasing weight loss for WL2 and WL3. In multivariate analyses including all factors associated with mortality, the hazard ratio (HR) for 30-day mortality also remained significantly higher compared to weight-stable individuals for WL2 and WL3 patient groups after adjustment for other mortality predictors (Fig. 3).

4.3. Impact of overweight and obesity on weight loss-associated changes in patient outcome

32,826 (29.6%) out of the 110,835 patients were overweight and 21,245 (19.2%) were obese as defined by BMI > 25 or 30 kg/m^2 respectively. The unadjusted cumulative event curve for dying in hospital in the different self-reported short-term weight loss groups subdivided by BMI group is shown in Fig. 4, indicating that deaths were lower in WL2 and WL3 for overweight and obese patient groups. 30-day mortality HR and its relative increments through increasing weight loss categories were however interestingly comparable in lean, overweight and obese individuals after multiple adjustments including other mortality predictors gender, PANDORA score, not having had surgery (Fig. 5). The impact of gender, PANDORA score and surgery on 30-day mortality HR were also comparable in non-obese and overweight or obese individuals (Fig. 6).

5. Discussion

The current study demonstrated in the 2006–2016 ESPEN nutritionDay cohort of hospitalized patients that 1) stepwise increments in self-reported recent weight loss enhance 30-day mortality independently of major confounding factors; 2) after adjustment for co-predictors of mortality representing major potential confounding factors, weight loss similarly enhances mortality in lean, overweight and obese individuals; BMI category also does not influence the impact of additional variables modulating mortality. The current results therefore demonstrate that self-reported recent weight loss is an independent predictor of 30-day mortality; overweight and obesity per se conversely have no

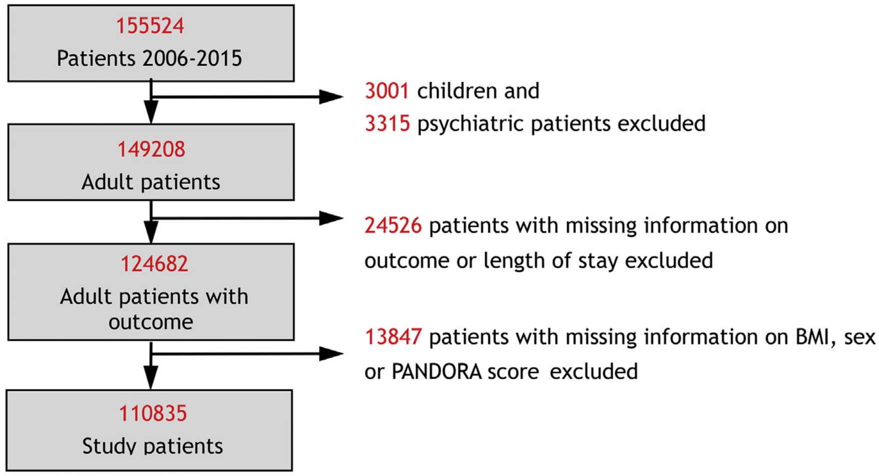

Fig. 1. Flow chart describing selection of study subjects.

Table 1
Cohort demographics and study parameters. Data are presented as percentage (%), mean with standard deviation (SD) or as median with interquartile range (IQR) as appropriate.

Variable	Level	n	%/mean (SD)/median (IQR)
BMI		110,835	25.7 (SD 6.02)
Age		110,835	67 (IQR 53–79)
Gender	Male	55,113	49.7%
	Female	55,722	50.3%
Surgery	No	72,855	65.7%
	Before today	28,918	26.1%
	Today	9062	8.2%
PANDORA score	per 10 points	110,835	26 (IQR 19–34)
Weight loss	Gained	9365	8.4%
	Stable	42,429	38.3%
	2.5–6.6%	15,573	14%
	6.6–12.6%	14,999	13.5%
	>12.6%	15,400	13.9%
	Missing	13,069	11.8%
Specialty	Internal	49,840	45%
	Surgery	29,669	26.8%
	Geriatrics	9878	8.9%
	ENT	3667	3.3%
	Neurology	2777	2.5%
	Gynecology	1782	1.6%
	Others	13,222	11.9%
Duration before ND		110,835	6 (IQR 3–14)

protective impact against weight loss-associated mortality in hospitalized patients.

Loss of body weight is commonly caused by several acute and chronic disease conditions [1] through loss of appetite, physical inactivity and skeletal muscle as well as adipose tissue catabolic changes [1,24–27]. A negative impact of weight loss on survival has been reported in general population studies with long-term follow-up [19,20] and this observation may reflect at least in part the negative impact of known or unknown underlying disease [28]. Self-reported weight loss in the current large nDay cohort indeed likely reflected at least in part development or worsening of heterogeneous disease conditions that lead to hospitalization. It should also be pointed out that weight loss and ensuing malnutrition [29] may further independently worsen prognosis [30] through impaired immune function, infectious complications and frailty development [31–35]. The association between weight loss and mortality was accordingly less pronounced for the lowest weight loss category in unadjusted analyses and after adjusting for disease-associated clinical and anthropometric or demographic variables such as those included in the PANDORA score [21]. Consistent with this view, more pronounced weight loss conversely retained an independent impact on mortality after multiple adjustments. While strongly underlining the important role of

Table 2
Variables with significant impact on Hazard Ratio (HR) for 30-day mortality. Univariate and multivariate analyses (COX regression) results are presented as Hazard Ratio (HR) ± Confidence Interval (CI).

Variable	Level	30-day mortality			
		Univariate analysis		Multivariate analysis	
		HR + CI	p	HR + CI	p
gender	Female	reference		reference	
	Male	1.18 (1.1,1.26)	0.000004	1.32 (1.23,1.41)	<0.000001
surgery	No	reference		reference	
	Before today	0.43 (0.38,0.48)	<0.000001	0.57 (0.51,0.64)	<0.000001
	Today	1.01 (0.85,1.19)	0.936769	0.99 (0.84,1.16)	0.872383
Pandora score	Per 10 points	2.3 (2.23,2.37)	<0.000001	2.14 (2.07,2.22)	<0.000001
Weight loss	Gained	0.88 (0.71,1.08)	0.222255	0.97 (0.79,1.18)	0.740384
	Stable	reference		reference	
	2.5–6.6%	1.28 (1.13,1.46)	0.000148	1.08 (0.95,1.22)	0.266082
	6.6–12.6%	1.99 (1.78,2.24)	<0.000001	1.46 (1.3,1.64)	<0.000001
	>12.6%	2.87 (2.58,3.2)	<0.000001	1.65 (1.47,1.84)	<0.000001
	Missing	3.19 (2.83,3.58)	<0.000001	2.14 (1.89,2.42)	<0.000001
Duration before nDay	Per week	0.98 (0.97,0.99)	0.002165	0.97 (0.96,0.98)	0.000013

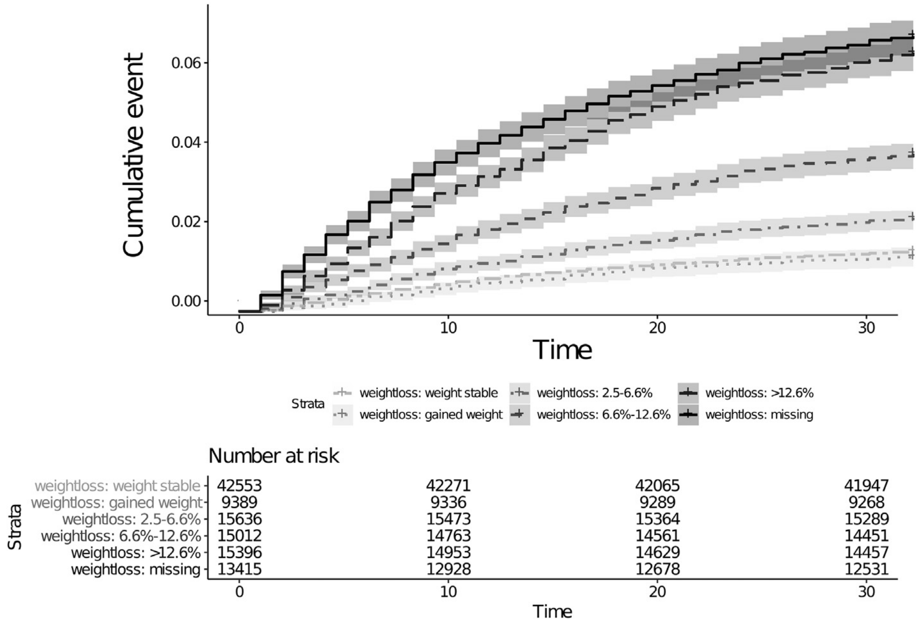

Fig. 2. Unadjusted cumulative event curve for dying in hospital in different self-reported short-term weight loss groups. Curve is based on the Aalen-Johansen method. Population at risk includes all non-dying.

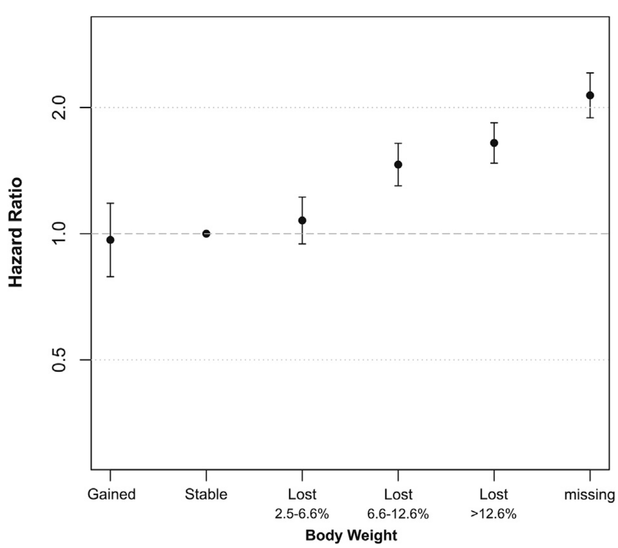

Fig. 3. Self-reported short-term weight loss enhances 30-day mortality. Results are adjusted for confounders associated with mortality (gender, PANDORA score, not having surgery) by COX regression modelling.

nutritional status in defining patient outcome in the context of hospitalization, the current results across different hospital and specialty settings specifically indicate that seeking information on recent weight loss may provide a potentially important tool to predict outcome and stratify risk of death in non-critically ill patients.

Determining whether being overweight or obese influences the association between recent weight loss and in-hospital mortality was the second major goal of the current investigation of the nDay database. Overweight and obesity have emerged in recent years as potential protective prognostic factors, particularly in the intensive care setting for acute cardiac, neurological and infectious events [1,5,9–11]. A positive impact of increasing BMI on survival was also recently reported in the nDay non-critically ill patient database [2] and these results indicate a potential protective role of higher energy stores also in a mixed non-ICU medical and surgical hospital patient population, indeed representing the large majority of hospitalizations worldwide [36]. In the current nutritionDay cohort, lower deaths occurred with increasing BMI throughout different weight loss categories in unadjusted analyses; overweight and obesity however failed to modulate risk of death in the presence of short-term weight loss after adjustment for major confounders and mortality enhancers. These combined results most importantly support two relevant conclusions: 1) higher deaths and more negative outcome in unadjusted analyses in lower BMI individuals reflect higher prevalence of additional mortality risk factors; it is particularly likely that a negative nutritional impact of pre-existing disease conditions was most pronounced and causally contributed to low BMI; 2) the negative impact of weight loss on 30-day mortality is at least in part independent of pre-existing nutritional conditions with no protective effect of overweight and obesity per se. Lack of independent protective roles of overweight and obesity per se in modulating patient outcome could be mediated by the clinical impact of weight loss-associated underlying disease severity as well as negative energy balance and malnutrition per se [29]. These observations and conclusions are notably indirectly supported by previous studies showing that obesity-associated reductions in risk of death were attenuated in the presence of malnutrition diagnosis according to a multidimensional evaluation based on both clinical judgement by a registered dietician and a combination of objective factors [37]. Also interestingly, overweight and obesity failed to modulate the negative impact of additional risk enhancers such as gender, lack of surgical treatment and the multifactorial disease severity index PANDORA score [21]; these findings are further consistent with the concept that any obesity-induced protection from unfavourable outcome may be offset by heterogeneous disease characteristics with negative diagnostic impact in non-critically ill hospitalized patients.

The current study investigated a large international cohort [2,21–23] that allowed robust statistical analyses and adjustments. Some potential weaknesses also need to be pointed out. First, weight loss was self-reported; such potential source of error is

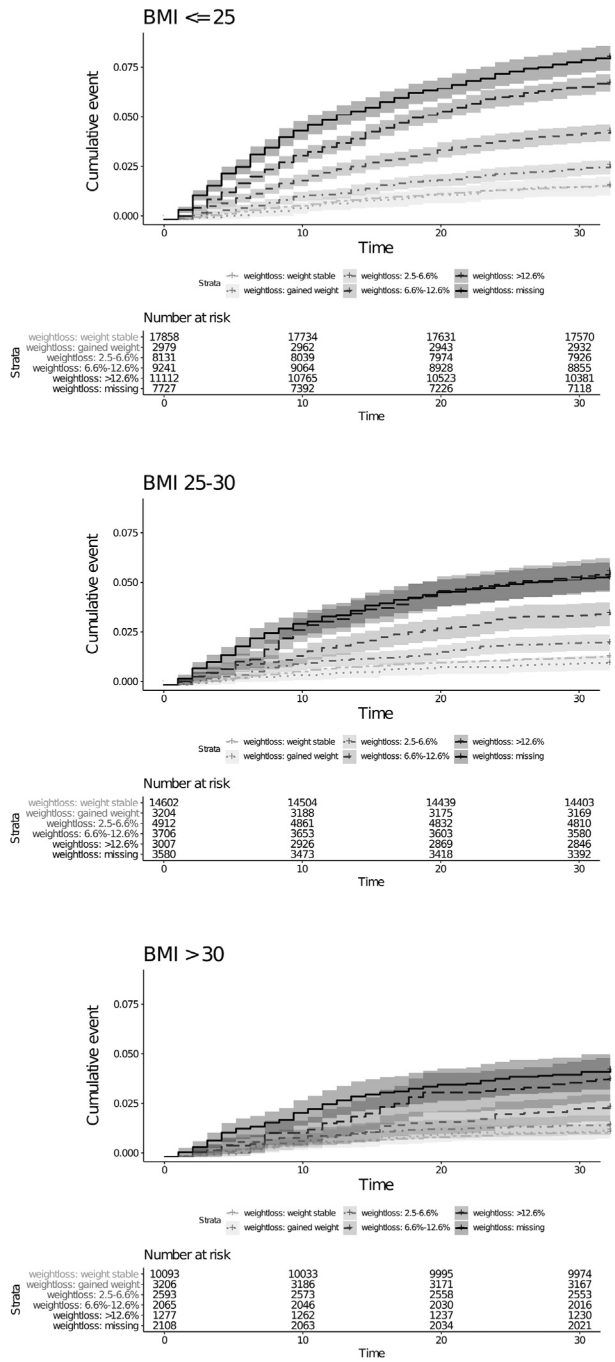

Fig. 4. Unadjusted cumulative event curves for dying in hospital for the different BMI groups. Curve are based on the Aalen-Johansen method. Population at risk includes all non-dying.

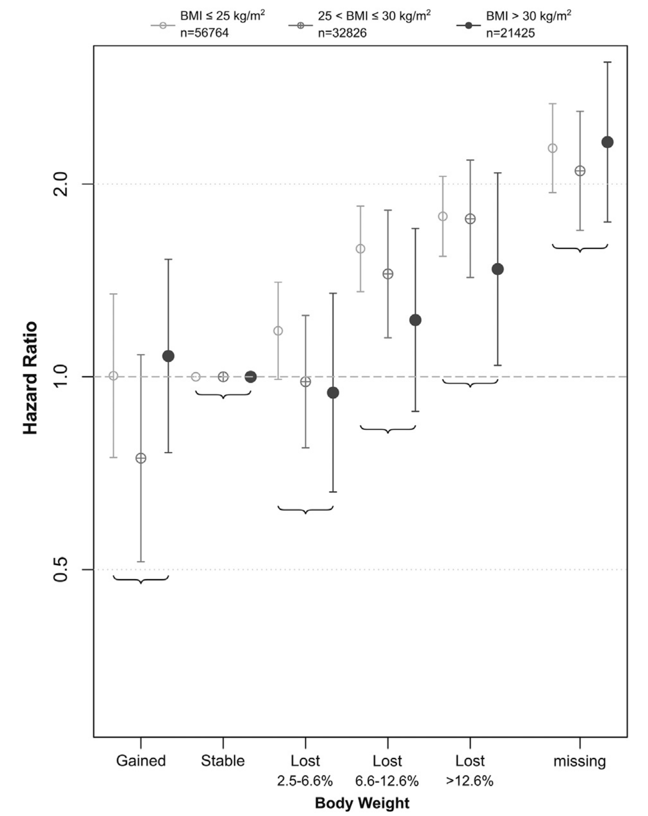

Fig. 5. Overweight and obesity do not modulate the negative impact of weight loss on 30-day mortality. Results are adjusted for confounders associated with mortality (gender, PANDORA score, not having surgery) by COX regression modelling.

however common during collection of patient history in routine clinical practice and it did not prevent identification of clinically relevant associations. Second, weight loss information was not available in a fraction of participating individuals; this was mostly likely due to lack of patient collaboration reflecting more severe acute conditions or chronic deterioration. Consistent with poorer clinical status, patients with missing weight loss information had highest mortality in all analyses. Third, some potentially relevant confounding factors with potential independent impact on weight loss and negative outcome were not collected in the patient questionnaires and database, with particular regard to smoking status and presence of depression. There is however no indicator that their prevalence should differ between different BMI groups, and their impact is therefore not likely to have affected our major conclusions that overweight and obesity do not affect the negative impact of weight loss on outcome. Future studies could however more directly address this issue. Finally, it should be pointed out that the obese phenotype was not characterized for body composition and fat distribution. Sarcopenic obesity with pronounced loss of skeletal muscle mass [38] and abdominal visceral fat accumulation [39–42] indeed have a negative clinical impact and may challenge the validity of the obesity paradox [1,38]. While the large nDay database clearly indicates lack of interaction between higher body mass and weight loss in determining risk of death, future studies should investigate the potential additional mortality burden in sarcopenic obese or predominantly viscerally obese individuals.

In conclusion, this study identified short-term (3-month) self-reported weight loss as a simple reliable parameter to predict in-hospital mortality in the large nutritionDay database of international medical and surgical specialty wards. This association was independent of major clinical and demographic confounders, particularly for more severe weight loss categories above 6.6%. Overweight and obesity per se did not modify the negative impact of weight loss on patient outcome after adjustments for available clinical and demographic confounders. The current results strongly support recording of self-reported weight-loss as a relevant prognostic factor for survival in all non-critically ill hospitalized patients. In addition, they do not support any protective impact of overweight and obesity per se on in-hospital mortality in the presence of negative energy balance, which instead appears to be the major nutritional determinant of patient outcome.

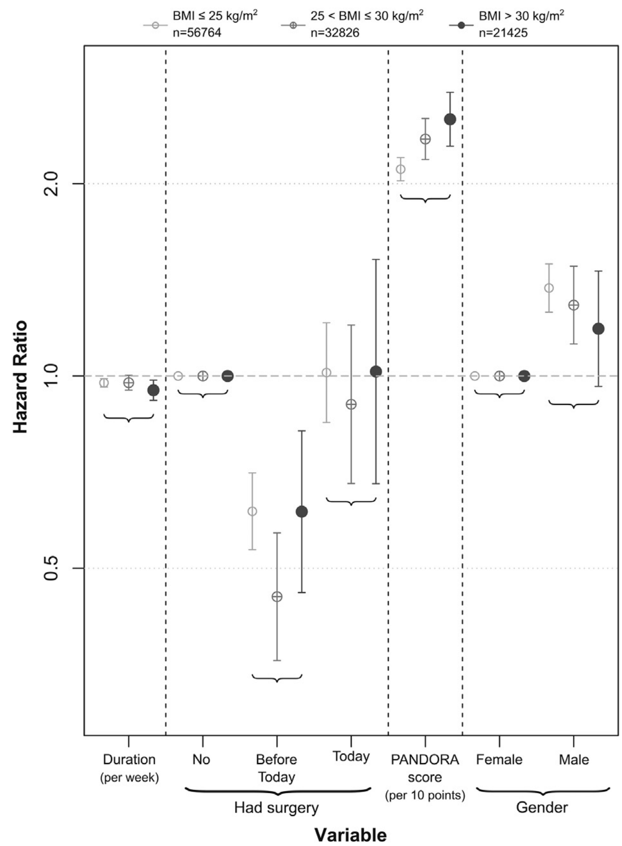

Fig. 6. Overweight and obesity do not modulate the negative impact of gender, not having surgery and PANDORA score on 30-day mortality. Analysis was performed by COX regression modelling.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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