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Post-operative complications after colorectal cancer surgery increased with higher BMI

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ABSTRACT

INTRODUCTION. Because of conflicting evidence regarding overweight and post-operative complications, this study focused on post-operative complications and death within 30 and 90 days after curatively intended surgery for colorectal cancer and its association with BMI.

METHODS. The study included all patients who had potentially curative surgery for colon or rectum cancer in Denmark from 2014 through 2018. The primary endpoint was post-operative complications within 30 days of surgery and secondary endpoints were 30- and 90-day mortality. All clinically relevant confounders were included in a multivariate analysis.

RESULTS. The cohort included 14,004 patients. In the multivariate logistic regression analysis, adjusting for relevant confounders, we found the odds ratio of having a surgical complication or having both a surgical and medical complication at the same time to be rising with increasing weight class. The multivariate analysis showed the odds ratio for both 30- and 90-day mortality to be higher for underweight patients and for obesity class III patients, but the rest of the patients had no significant differences in relative risk compared with normal-weight patients.

CONCLUSION. Based on our results, the risk of post-operative complications rises with increasing weight, whereas post-operative morbidity is increased only in the underweight and morbidly obese patients.

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TRIAL REGISTRATION. The study was approved by the Danish Data Protection Agency (REG-008-2020).

The incidence of colorectal cancer (CRC) is higher in the developed countries than in the rest of the world, especially in Australia, Europe and North America [1] as is the incidence of obesity. In developed countries, an increasing incidence of obesity is observed and almost half of the European population is overweight or obese [1]. Several earlier studies found that obesity is associated with an increased risk of developing CRC [2]. Evidence is conflicting regarding the association between weight class, measured by BMI, and post-operative complications in CRC patients. In obese patients, a possibly increased comorbidity and technical difficulties during surgery may lead to an increased risk of post-operative complications [3]. In underweight patients, a higher risk of having complications after major surgery [3] is observed, but consensus is greater on the cause of this association, which is thought to be cachectic patients' lack of muscle mass and strength [4].

Surgery for CRC is a major operation and post-operative complications have an important impact on morbidity and mortality. Therefore, it is important to identify those patients who have the highest risk of complications in order to enact possible preventive measures such as nutrition, iron infusions and physical training [5].

Several studies have described the relationship between weight class and post-operative complications.

However, in some studies, the study population has been limited [6], whereas in other studies the weight classes were divided too nonspecifically to indicate differences between overweight and obesity [6]. Furthermore, several studies failed to include smoking habits and alcohol consumption as confounders [7].

The aim of this study was to investigate the association between BMI, post-operative complications and short-term mortality after curatively intended surgery for CRC in a nationwide cohort.

METHODS

This was a nationwide observational study with prospectively collected data. The cohort was extracted from the Danish Colon Cancer Group database, which includes all patients with CRC in Denmark since 2001. The database has recently been validated and has a high completeness and a high data quality [8]. The study included patients who had intended curative surgery for colon or rectal cancer between 2014 and 2018. Patients with endoscopically removed cancers, patients younger than 18 years and patients with metastatic disease were excluded. Patients with a calculated BMI of < 10 or > 60 kg/m^2 were excluded as potentially faulty outliers. The cohort was divided into weight groups as defined by the World Health Organization (WHO): BMI < 18.5 kg/m^2 underweight, BMI 18.5-24.9 kg/m^2 normal weight, BMI 25.0-29.9 kg/m^2 pre-obesity, BMI 30.0-34.9 kg/m^2 obesity class I, BMI 35.0-39.9 kg/m^2 obesity class II and BMI > 39.9 kg/m^2 obesity class III [9]. The BMI recorded represents the patients' weight at the time of their diagnosis.

The primary endpoint was post-operative complications within 30 days of surgery and secondary endpoints were 30- and 90-day mortality. The post-operative complications were categorised into medical (pneumonia, heart failure, kidney failure, thrombosis and embolisms, etc.) and surgical (bleeding, abscess, anastomotic leak, stoma complications, etc.) complications and graded according to the Clavien-Dindo Classification [10].

Demographic, pre-, per- and post-operative data were collected and possible confounding factors were registered, including gender, age, smoking, alcohol consumption, WHO performance status, Charlson Comorbidity Index, tumour location (colon or rectum), acute or planned surgery, type of surgery (minimally invasive surgery or laparotomy) and Union for International Cancer Control Classification. The confounders included were chosen a priori.

Statistics

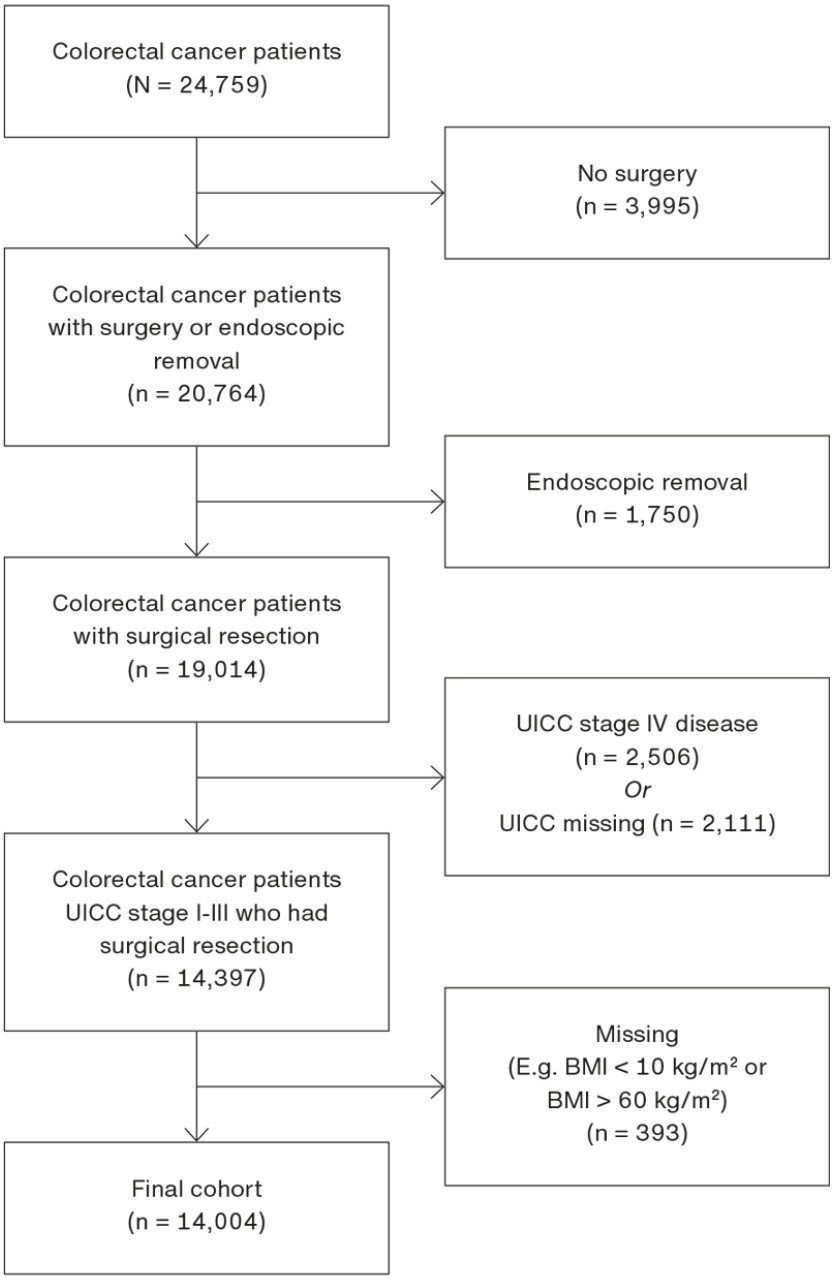
Data were analysed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Cross tables were analysed using the χ^2 test. The associations between weight groups and outcomes, adjusted for the potential confounders, were explored using multiple logistic regression. The significance level used was $p < 0.05$.

Trial registration: The study was approved by the Danish Data Protection Agency (REG-008-2020). As the study was register-based and in agreement with Danish legislation, no approval from an ethics committee was needed, nor was consent from the patients.

RESULTS

This study included 23,424 patients from 2014 to 2018 in Denmark. In total, 9,420 patients were excluded (**Figure 1**). The included 14,004 patients comprised 7,564 (54.0%) men, and the median age was 71 years. Colon cancer accounted for 10,419 (74.4%) cases. A total of 346 (2.5%) patients were underweight and 2,720 (19.4%) were obesity class I-III patients (**Table 1**).

FIGURE 1 Flow chart.



UICC = Union for International Cancer Control.

TABLE 1 Demographic and tumour variables.

	All (N_a = 14,004 (100%))	Underweight: BMI < 18.5 kg/m² (N_u = 349 (2.5%))	Normal weight: BMI 18.5-24.9 kg/m² (N_n = 5,734 (40.9%))	Pre-obese: BMI 25.0-29.9 kg/m² (N_p = 5,201 (37.1%))	Obesity class I: BMI 30.0-34.9 kg/m² (N_1 = 1,970 (14.1%))	Obesity class II: BMI 35.0-39.9 kg/m² (N_2 = 552 (3.9%))	Obesity class III: BMI > 39.9 kg/m² (N_3 = 198 (1.4%))	Missing data
Age, median (interquartile range) yrs	71 (± 13)	74 (± 15)	72 ± (14)	71 (± 13)	70 (± 11)	68.5 (± 10)	67 (± 12)	0
Gender, male, n (%)	7,564 (54.0)	75 (21.5)	2,653 (46.3)	3,303 (63.5)	1,150 (58.4)	297 (53.8)	86 (43.4)	0
Tobacco usage, n (%)								1,336 (7.2)
Never smoker	5,572 (39.2)	128 (36.7)	2,266 (39.5)	2,073 (39.9)	797 (40.5)	213 (38.6)	95 (48.0)	
Former smoker	5,248 (37.5)	78 (22.3)	1,927 (33.6)	2,088 (40.1)	838 (42.5)	241 (43.7)	76 (38.4)	
Smoker	2,270 (16.2)	125 (35.8)	1,123 (19.6)	696 (13.4)	237 (12.0)	68 (12.3)	21 (10.6)	
Alcohol consumption[a], n (%)								691 (4.9)
0 U	2,901 (20.7)	107 (30.7)	1,205 (21.0)	987 (19.0)	407 (20.7)	139 (25.2)	56 (28.3)	
1-14 U	8,716 (62.2)	191 (54.7)	3,626 (63.2)	3,249 (62,5)	1,218 (61.8)	316 (57.2)	116 (58.6)	
15-21 U	1,059 (7.6)	50 (5.7)	367 (6.4)	440 (8.5)	180 (9.1)	41 (7.4)	11 (5.6)	
> 21 U	637 (4.5)	10 (2.9)	218 (3.8)	279 (5.4)	93 (4.7)	29 (5.3)	8 (4.0)	
CCI score, n (%)								0
0	8,433 (60.2)	207 (59.3)	3,550 (61,9)	3,168 (60.9)	1,127 (57.2)	281 (50.9)	100 (50.5)	
1	2,554 (18.2)	79 (22.6)	1,028 (17.9)	906 (17.4)	401 (20.4)	101 (18.3)	39 (19.7)	
2	1,665 (11.9)	27 (7.7)	656 (11.4)	638 (12.3)	227 (11.5)	85 (15.4)	32 (16.2)	
≥ 3	1,352 (9.7)	36 (10.3)	500 (8.7)	489 (9.4)	215 (10.9)	85 (15.4)	27 (13.6)	
WHO performance status, n (%)								503 (3.6)
0	8,975 (64.1)	158 (45.3)	3,732 (65.1)	3,484 (67.0)	1,228 (62.3)	287 (52.0)	86 (43.4)	
1	3,279 (23.4)	104 (29.8)	1,262 (22.0)	1,151 (22.1)	502 (25.5)	187 (33.9)	73 (36.9)	
2	991 (7.1)	48 (13.8)	408 (7.1)	322 (6.2)	143 (7.3)	45 (8.2)	25 (12.6)	
3	217 (1.5)	16 (4.6)	97 (1.7)	60 (1.2)	28 (1.4)	8 (1.4)	8 (4.0)	
4	39 (0.3)	6 (1.7)	15 (0.3)	6 (0.1)	9 (0.5)	2 (0.4)	1 (0.5)	
Tumour location, n (%)								0
Colon	10,419 (74.4)	286 (81.9)	4,260 (74.3)	3,810 (73.3)	1,468 (74.5)	440 (79.7)	155 (78.3)	
Rectum	3,585 (25.6)	63 (18.1)	1,474 (25.7)	1,391 (26.7)	502 (25.5)	112 (20.3)	43 (21.7)	
UICC stage, n (%)								0
I	3,769 (26.9)	65 (18.6)	1,464 (25.5)	1,452 (27,9)	582 (29.5)	157 (28.4)	49 (24.7)	
II	5,303 (37.9)	155 (44.4)	2,270 (39.6)	1,918 (36,9)	681 (34.6)	207 (37.5)	72 (36.4)	
III	4,932 (35.2)	129 (37.0)	2,000 (34.9)	1,831 (35.2)	707 (35.9)	188 (34.1)	77 (38.9)	
Type of surgery, n (%)								0
Open surgery	2,238 (16.0)	87 (24.9)	1,025 (17.9)	729 (14.0)	277 (14.1)	79 (14.3)	41 (20.7)	
Minimally invasive surgery	11,766 (84.0)	262 (75.1)	4,709 (82.1)	4,472 (86.0)	1,693 (85.9)	473 (85.7)	157 (79.3)	
Timing of surgery, n (%)								8 (0.1)
Planned	13,258 (94.7)	303 (86.8)	5,318 (92.7)	5,000 (96.1)	1,904 (96.6)	538 (97.5)	195 (98.5)	
Acute	738 (5.3)	45 (12.9)	414 (7.2)	198 (3.8)	64 (3.2)	14 (2.5)	3 (1.5)	

CCI = Charlson Comorbidity Index; UICC = Union for International Cancer Control.
a) 1 U = 12 g of alcohol.

Demographic variables and tumour characteristics are listed in Table 1. The proportion of smokers declined with increasing BMI; thus, 35.8% of the underweight patients were current smokers compared with only 10.6% of the patients in obesity class III. The pre-obese and obesity class I and II had a higher percentage of patients drinking > 14 units of alcohol/week.

Eighty-four percent of all patients were operated upon with minimally invasive techniques, predominantly laparoscopic surgery.

Overall, complications after surgery increased with increasing BMI (odds ratio (OR) = 1.12 (95% confidence interval (CI): 1.02-1.23) for pre-obese rising to OR = 1.68 (95% CI: 1.22-2.32) for obesity class III). This was also the case for surgical complications alone, such as wound infection, bleeding or anastomotic leak (OR = 1.14 (95% CI: 1.02-1.28) to OR = 1.82 (95% CI: 1.25-2.66)). Medical complications alone, such as pneumonia, heart disease or kidney failure, were not increased among pre-obese patients (OR = 1.03 (95% CI 0.87-1.22) but rose to OR 1.96 (95% CI: 1.11-3.47) in obesity class III patients. Underweight patients had no more complications than patients of normal weight (**Table 2**). In a subgroup analysis of colon versus rectum patients, no obvious difference in overall complications was found. OR was 1.30 (95% Cl: 1.12-1.95), 1.55 (95% Cl: 1.22-1.95) and 1.76 (95% Cl: 1.23-2.56) for obese I through III in the colon group. In the rectum group, the figures were 1.64 (95% Cl: 1.32-2.04) and 2.0 (95% Cl: 1.36-3.03) for obese grade I and II patients, respectively, whereas the OR for obese patients of grade III did not reach significance.

TABLE 2 Complications. In all adjusted values, multivariate logistic regression analysis has been done and adjusted for the confounders gender, age, smoking, alcohol consumption, WHO performance status, Charlson Comorbidity Index, tumour location (colon or rectum), acute or planned surgery, type of surgery (minimally invasive surgery or laparotomy) and Union for International Cancer Control classification.

				Obesity		
	Underweight: BMI < 18.5 kg/m²	Normal weight[a]: BMI 18.5-24.9 kg/m²	Pre-obese: BMI 25.0-29.9 kg/m²	class I: BMI 30.0-34.9 kg/m²	class II: BMI 35.0-39.9 kg/m²	class III: BMI > 39.9 kg/m²
Complications after surgery						
OR (95% CI), all kinds [p value]:						
Unadjusted	1.38 (1.08-1.76) [0.01]	1	1.06 (0.96-1.16) [0.24]	1.30 (1.16-1.47) [< 0.001]	1.52 (1.25-1.85) [< 0.001]	1.62 (1.19-2.20) [0.002]
Adjusted	1.19 (0.92-1.54) [0.18]	1	1.12 (1.02-1.23) [0.022]	1.40 (1.24-1.58) [< 0.01]	1.66 (1.36-2.03) [< 0.01]	1.68 (1.22-2.32) [< 0.01]
Surgical complications after surgery						
OR (95% CI) [p value]:						
Unadjusted	1.03 (0.73-1.46) [0.849]	1	1.13 (1.01-1.27) [0.03]	1.47 (1.27-1.70) [< 0.01]	1.64 (1.29-2.08) [< 0.001]	1.86 (1.29-2.70) [< 0.001]
Adjusted	1.02 (0.72-1.46) [0.90]	1	1.14 (1.02-1.28) [0.026]	1.48(1.27-1.72) [< 0.01]	1.69 (1.32-2.16) [< 0.01]	1.82 (1.25-2.66) [< 0.01]
Medical complications after surgery						
OR (95% CI) [p value]:						
Unadjusted	1.96 (1.38-2.79) [< 0.001]	1	0.87 (0.74-1.03) [0.10]	1.01 (0.82-1.26) [0.92]	1.15 (0.80-1.64) [0.45]	1.36 (0.79-2.34) [0.27]
Adjusted	1.41 (0.96-2.07) [0.079]	1	1.03 (0.87-1.22) [0.75]	1.25 (0.99-1.56) [0.058]	1.49 (1.02-2.16) [0.038]	1.96 (1.11-3.47) [0.020]
30-day mortality						
OR (95% CI) [p value]:						
Unadjusted	2.97 (1.78-4.96) [< 0.001]	1	0.72 (0.53-0.99) [0.04]	0.87 (0.58-1.31) [0.51]	0.91 (0.46-1.80) [0.78]	2.61 (1.30-5.22) [0.07]
Adjusted	1.87 (1.07-3.25) [0.027]	1	0.93 (0.67-1.28) [0.64]	1.23 (0.80-1.88) [0.34]	1.50 (0.73-3.05) [0.27]	4.14 (1.90-8.99) [< 0.01]
90-day mortality						
OR (95% CI) [p value]:						
Unadjusted	3.54 (2.42-5.18) [< 0.001]	1	0.65 (0.51-0.84) [< 0.001]	0.84 (0.62-1.16) [0.29]	0.77 (0.43-1.36) [0.36]	1.69 (0.88-3.25) [0.12]
Adjusted	2.24 (1.46-3.42) [< 0.01]	1	0.82 (0.64-1.07) [0.14]	1.13 (0.80-1.58) [0.50]	1.15 (0.64-2.09) [0.64]	2.27 (1.10-4.70) [0.027]

CI = confidence interval; OR = odds ratio.
a) Normal weight was the reference.

Only the underweight and obese class III patients had a significantly higher OR for both 30-day mortality (OR = 1.87 (95% CI: 1.07-3.25) and OR = 4.14 (95% CI: 1.90-8.99), respectively) and 90-day mortality (OR = 2.24 (95% CI: 1.46-3.42) and OR = 2.27 (95% CI: 1.10-4.70), respectively). No significant difference in 30- or 90-day mortality was found in the pre-obese or among obese patients of class I and II (Table 2). In the subgroup analysis, a significantly increased 30-day mortality was found in the underweight patients (OR = 5.16 (95% Cl: 1.70-15.6)) and among obese III (OR = 13.6 (95% Cl: 3.24-57.2)) for rectum patients, whereas for colon patients no significantly increased mortality was found.

Subgroup analyses of the surgical and medical complications regarding minor complications (Clavien-Dindo class I + II) and major complications (Clavien-Dindo class ≥ III) showed a larger share of medical complications in the underweight and morbidly-obese patient groups to be severe complications, such as respiratory failure or kidney failure, requiring intensive care admission (**Table 3**).

TABLE 3 Sub-analysis of complications.

				Obesity		
	Underweight: BMI < 18.5 kg/m²	Normal weight[a]: BMI 18.5-24.9 kg/m²	Pre-obese: BMI 25.0-29.9 kg/m²	class I: BMI 30.0-34.9 kg/m²	class II: BMI 35.0-39.9 kg/m²	class III: BMI > 39.9 kg/m²
Surgical complications, n (%)						
No	254 (87.0)	4,497 (87.1)	4,034 (85.7)	1,451 (82.1)	390 (80.6)	137 (78.3)
Minor[a]	7 (2.4)	188 (3.6)	213 (4.5)	102 (5.8)	32 (6.6)	11 (6.3)
Major[b]	31 (10.6)	480 (9.3)	462 (9.8)	214 (12.1)	62 (12.8)	27 (15.4)
Medical complications, n (%)						
Medical complications, n (%)	255 (87.0)	4,502 (92.7)	4,033 (93.5)	1,452 (92.7)	389 (91.5)	137 (90.1)
No	255 (87.0)	4,502 (92.7)	4,033 (93.5)	1,452 (92.7)	389 (91.5)	137 (90.1)
Minor[a]	23 (7.8)	242 (5.0)	196 (4.5)	79 (5.0)	26 (6.1)	9 (5.9)
Major[b]	15 (5.1)	113 (2.3)	83 (1.9)	36 (2.3)	10 (2.4)	6 (3.9)
Both surgical and medical complications, n (%)						
No	254 (94.1)	4,496 (95.6)	4,030 (95.1)	1,453 (94.7)	389 (92.4)	137 (94.5)
Minor[a]	1 (0.4)	31 (0.7)	34 (0.8)	12 (0.8)	3 (0.7)	2 (1.4)
Major[b]	15 (5.6)	175 (3.7)	174 (4.1)	69 (4.5)	29 (6.9)	6 (4.1)

a) Clavien-Dindo class < 3.
b) Clavien-Dindo class ≥ 3.

DISCUSSION

In this study, we found an increased risk of surgical complications after surgery for CRC if the patient was overweight, and the OR rose with increasing weight. A large retrospective study of more than 200,000 patients also found that overweight, obese and morbidly obese patients operated on for CRC were more likely to have deep incisional surgical site infections, superficial surgical site infections and wound disruption than normal-weight patients. They also found that increased BMI was associated with longer operating time [3]. The association between obesity and a higher risk of surgical site infections may be related to low oxygen tension in the adipose tissue, weaker connective tissue and a greater wound area. As mentioned above, obesity may also lead to technical difficulties, longer operating times, higher conversion rates and contamination [11].

The OR of serious complications was also increased in the obese population, which corresponds with the findings of similar studies [11]. This may possibly be caused by comorbidities such as cardiac disease, diabetes and a weaker immune response in obese patients [11].

In accordance with several reviews, our study showed that obese patients also seemed to have a higher risk of medical complications such as pulmonary, cardiovascular and thromboembolic events, after colorectal surgery than normal-weight patients [11, 12]. This finding is thought to be associated with the obese patients' increased risk of preoperative comorbidities such as metabolic syndrome, heart failure, arrhythmias and coronary heart disease. Furthermore, a low amount of exercise is often seen in obese patients and is associated with increased risk of pulmonary, cardiovascular and thromboembolic complications. Lastly, the dose of antibiotics, anticoagulants and fluids is often a standard dose based on a normal-weight patient. Therefore, the obese patient with a larger volume and higher percentage of body fat may possibly receive a dose of medicine that is lower than optimal.

This study underpins the finding of previous studies that underweight patients are at greater risk of death within 30 and 90 days after surgery [3]. This finding is probably related to malnutrition, sarcopenia and cachexia, which result in poorer wound healing, and difficulties with both mobilisation and resumption of oral food intake [13]. Also, a larger proportion of the underweight patients were smokers/former smokers and therefore their risk of ventilator dependency was significantly higher [3]. This weight group probably also includes more patients with disease-related weight loss, all though not disseminated, and thereby poorer nutritional status. Weight loss and cachexia are also associated with poorer performance status [14], which may be the reason for the prolonged length of stay observed in this weight group [3]. Weight loss prior to chemotherapy in cancer patients has been

shown to cause a poorer median survival, which may also be the case for underweight patients [14]. It is surprising that underweight patients do not have a higher risk of complications but do have a higher risk of dying after surgery than normal-weight patients. This may be because underweight patients are less resistant than the other weight groups.

In our study, BMI was used to measure overweight and obesity. Using BMI as a measure of obesity is easy and inexpensive and BMI is known to be associated with metabolic disease. However, BMI has its limitations as the measurement method does not describe the distribution of fat relative to muscle or of subcutaneous fat relative to visceral fat. It was suggested that waist circumference is better correlated with the risk of developing metabolic disorders or cardiovascular disease than BMI [15]. Several studies have suggested that diagnostic imaging methods are more reliable at providing an accurate picture of the patient's fat and muscle distribution and thereby a more reliable risk profile before surgery [16]. CT is a relevant measurement method in CRC as most patients have had a staging CT done before surgery. The CT can be used to assess the total area and radiodensity of skeletal muscle and visceral adipose tissue. However, results are inconsistent. Some studies have found that visceral obesity or myopenic obesity lead to higher morbidity after elective colorectal surgery [17], whereas other studies reported no link between body composition profiles and major complications [16].

This study has limitations. The data were collected prospectively but reviewed retrospectively, and it was a large register-based observational study. Despite many clinically relevant variables, a risk remains of unmeasured confounding. Furthermore, a different focus on pre- and post-operative optimization may have existed in the different weight groups. Thus, it seems likely that a surgeon would be more attentive to preoperative poor lung function, impaired cardiac function and post-operative rehabilitation in obese patients than in normal-weight patients.

This was a nationwide study and current legislation at the time required that cancer patients were operated on within 14 days. Therefore, the BMI measured at the time of diagnosis was expected to be approximately the same at the time of surgery. Thus, no standard prehabilitation had been introduced at the time.

The risk of post-operative complications rises with increasing weight after CRC surgery. Surprisingly, mortality does not show the same association with weight class. Underweight patients did not have a higher risk of complications, but their risk of death after surgery was higher than that of normal-weight patients. In contrast, patients with BMI 25-39.9 kg/m^2 had a higher risk of complications after surgery, but their risk of death within 30 and 90 days of surgery was not higher than that of normal-weight patients. Only the patients with BMI > 39.9 kg/m^2 had a higher odds ratio of both post-operative complications and death after surgery.

In the future, we need to focus even more on optimising the underweight and obese patients both pre- and post-operatively. In cancer surgery, no time exists to wait for a weight loss in obese patients or for weight gain in the underweight patients, but they may possibly benefit from exercise, lung physiotherapy and nutritional advice both before and after surgery. Comprehensive nutritional therapy has been shown to improve patient outcome in elective surgery settings [18, 19]. More attention to customised medicine doses for underweight and obese patients may possibly also improve their outcome.

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