Obesity as protective against, rather than a risk factor for, postoperative *Clostridium difficile* infection: A nationwide retrospective analysis of 1,426,807 surgical patients

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BACKGROUND: Recent studies suggest that obesity is a risk factor for *Clostridium difficile* infection, possibly due to disruptions in the intestinal microbiome composition. We hypothesized that body mass index (BMI) is associated with increased incidence of *C. difficile* infection in surgical patients.

METHODS: In this nationwide retrospective cohort study in 680 American College of Surgeons National Surgical Quality Improvement Program participating sites across the United States, the occurrence of *C. difficile* infection within 30 days postoperatively between different BMI groups was compared. All American College of Surgeons National Surgical Quality Improvement Program patients between 2015 and 2016 were classified as underweight, normal-weight, overweight, or obese class I-III if their BMI was less than 18.5, 18.5 to 25, 25 to 30, 30 to 35, 35 to 40 or greater than 40, respectively.

RESULTS: A total of 1,426,807 patients were included; median age was 58 years, 43.4% were male, and 82.9% were white. The postoperative incidence of *C. difficile* infection was 0.42% overall: 1.11%, 0.56%, 0.39%, 0.35%, 0.33% and 0.36% from the lowest to the highest BMI group, respectively ($p < 0.001$ for trend). In univariate then multivariable logistic regression analyses, adjusting for patient demographics (e.g., age, sex), comorbidities (e.g., diabetes, systemic sepsis, immunosuppression), preoperative laboratory values (e.g., albumin, white blood cell count), procedure complexity (work relative unit as a proxy) and procedure characteristics (e.g., emergency, type of surgery [general, vascular, other]), compared with patients with normal BMI, high BMI was inversely and incrementally correlated with the postoperative occurrence of *C. difficile* infection. The underweight were at increased risk (odds ratio, 1.15 [1.00–1.32]) while the class III obese were at the lowest risk (odds ratio, 0.73 [0.65–0.81]).

CONCLUSION: In this nationwide retrospective cohort study, obesity is independently and in a stepwise fashion associated with a decreased risk of postoperative *C. difficile* infection. Further studies are warranted to explore the potential and unexpected association. (*J Trauma Acute Care Surg.* 2019;86: 1001–1009. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic/Epidemiologic, Level IV.

KEY WORDS: Obesity; *Clostridium difficile* infection; ACS NSQIP.

The incidence, severity, and lethality of *Clostridium difficile* infection (CDI) continue to increase among hospitalized patients in developed nations.[1–7] The incidence of CDI in the United States nearly doubled from 4.5 cases to 8.2 per 1000 patients between 2001 and 2010, while its associated mortality increased from 6.6% to 7.2% in the same time period.[5] Patient risk factors (e.g., advanced age, comorbidities, immunosuppression), alterations in the intestinal microbiome (e.g., antibiotic use, surgery, chemotherapy) and exposure to bacterial spores (e.g., by hospitalization) all increase the risk of intestinal CDI.[8]

Among patient risk factors, both obesity and underweight are often found to be risk factors for infections, mortality, and hospitalization.[9–11] In surgical patients specifically, obesity is associated with increased perioperative morbidity as well as infectious complications such as urinary tract infection and surgical site infections.[12,13] It is hypothesized that excess adipose tissue initiates and propagates a series of metabolic changes and hormonal alterations, increases production of inflammatory cytokines (e.g., leptin), leading to a chronic low-grade state of inflammation as well as decreased immune cell function.[14,15] In addition, obesity alters the composition of the intestinal microbiome, resulting in fewer bacteroidetes and potential pathogenic firmicutes, proteobacteria, and actinobacteria.[16,17]

Currently, more than a third of the United States adult population is obese.[18] The United States surgical population reflect these biometric shifts, and the inherent risks of increased nosocomial infections due to an altered immune response. More recently, obesity was suggested as a potential risk factor for both community-acquired and hospital-onset CDI. Three small retrospective studies have suggested that obesity is associated with an increased susceptibility to CDI.[19–21] However, other similar studies have failed to demonstrate a relationship between obesity and CDI.[22,23]

In this study, we sought to test the relationship between body mass index (BMI) and the incidence of postoperative CDI in surgical patients. We hypothesized that both the obese and the underweight surgical patient are most susceptible to postsurgical intestinal CDI.

METHODS

Design and Setting

This is a nationwide population-based cohort study, using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database that contains information on surgical patients from up to 680 participating sites across the United States. The study was approved and granted "exempted" status by our institutional review board.

Patients

All surgical cases from the ACS-NSQIP 2015 to 2016 database with available information on age, sex, BMI, CDI status, and surgical specialty were included. The data on postoperative CDI were not routinely collected by ACS-NSQIP prior to the third quarter of 2015.

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Main Outcome Measure

The main study outcome was the incidence of postoperative intestinal CDI. In order for subjects to be categorized as having postoperative CDI by the ACS-NSQIP surgical clinical reviewers, patients had to meet the follow criteria: (1) no active CDI at the time of principal operative procedure, and (2) at least one of the following documentations in the medical record: a positive *C. difficile* laboratory up to 30 days postoperatively, or the patient is receiving current treatment for *C. difficile* (Supplemental Digital Content, Appendix 1, http://links.lww.com/TA/B312).[24]

Body Mass Index

Body mass index is defined as weight in kilograms divided by the square of the height in meter. In our study, BMI was calculated and patients were divided into the following groups: underweight (<18.5 kg/m^2), normal weight (≥18.5 to <25 kg/m^2), overweight (≥25 to <30 kg/m^2), obese class I (≥30 to <35 kg/m^2), obese class II (≥35 to <40 kg/m^2), obese class III (>40 kg/m^2) (Supplemental Digital Content, Appendix 1, http://links.lww.com/TA/B312).[25]

Variables

Appendix 1 (Supplemental Digital Content, http://links.lww.com/TA/B312) contains a description of all variables used in our study. ethnicity was recorded as white, black, Hispanic, Asian/Pacific Islander and Other. Perioperative variables included but were not limited to dyspnea (none, at moderate exertion, at rest), chronic obstructive pulmonary disorder (COPD), ventilator dependence, ascites, congestive heart failure, hypertension, acute renal failure requiring dialysis, disseminated cancer, open wound (with or without infection), steroid use for chronic condition, >10% weight loss in the past 6 months, bleeding disorder, transfusion, systemic sepsis, functional health status (independent, partially dependent, totally dependent), as well as wound classification. Preoperative laboratory values included but were sodium, blood urea nitrogen, creatinine, albumin, bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, white blood cells (WBC), hematocrit, platelets, partial thromboplastin time, international normalized ratio (INR), and prothrombin time. Procedure-related characteristics were surgical specialty, work relative value unit (used as a proxy for procedural complexity[26,27]), operation time, days from admission to surgery, and whether the case was emergent or not. The American Society of Anesthesiologists (ASA) classification and type of anesthesia were included as well.

Missing Variables

Missing categorical variables were grouped separately in the analyses: the 14.5% missing ethnicities were categorized as "unknown/other" and 0.26% missing ASA classifications as "none assigned." Missing data of comorbidities (≤0.001%) was coded as if they were not present (no comorbidity). Missing operation time (≤0.001%) was imputed using linear regression analyses with age, sex, and surgical specialty as predictors. Missing laboratory values (15.7% to 99.8%) were assumed to be within normal range and classified as such.[28]

Statistical Analyses

All analyses were performed in Stata 15.1 (StatCorp LP, College Station, TX). Categorical variables were expressed as frequencies and percentages and compared using χ^2 test. Continuous variables were expressed as median (interquartile range [IQR]) and compared using Wilcoxon rank-sum test. Two-sided p value less than 0.05 was considered statistically significant. Odds ratios (OR) of incidence of CDI were calculated using a multivariable logistic regression, adjusted for all the patient demographics, comorbidities, preoperative laboratory values and procedure type, complexity, and characteristics that had p values of 0.20 or less in the initial univariate analysis.

To further account for the relationship between BMI and CDI in sensitivity analyses, we repeated the analysis excluding

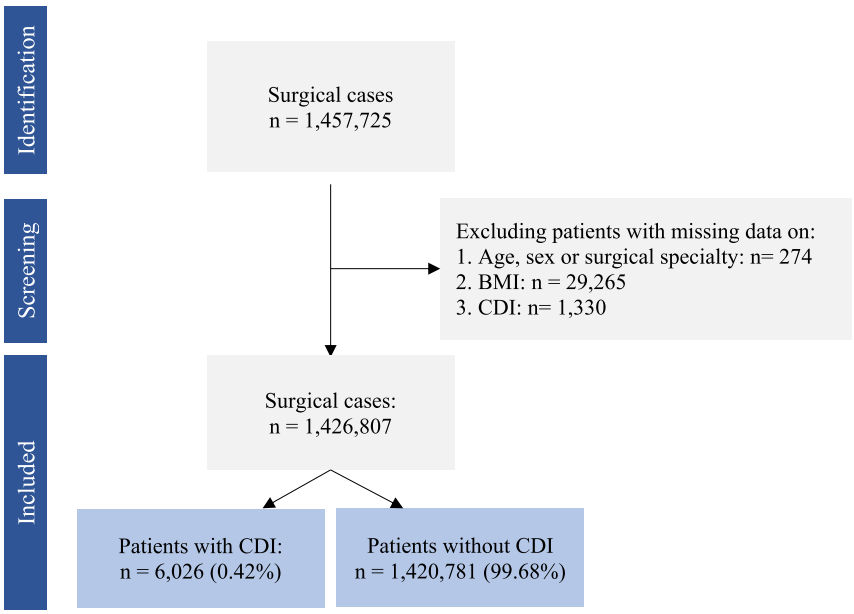

Figure 1. Included cases from the ACS-NSQIP database.

TABLE 1. Characteristics of the 1,426,807 Surgical Cases by Occurrence of CDI

CDI	No	Yes	All	*p* value
n (%)	1,449,827 (99.68)	6,225 (0.48)	1,456,807 (100)	
Patient demographics				
Age, median (IQR), y	58 (45–69)	66 (55–76)	58 (45–69)	<0.001
Men, %	43.4	46.1	43.4	<0.001
BMI, median (IQR), kg/m^2	29.0 (25.0–34.1)	27.4 (23.4–32.6)	29.0 (25.0–34.1)	<0.001
Smoker, %	17.6	20.5	17.7	<0.001
Ethnicity, %				0.075
White	82.9	83.5	82.9	
Black	11.7	11.7	11.7	
Asian or Pacific Islander	3.5	2.9	3.5	
Hispanic	2.0	1.9	2.0	
Preoperative comorbidities				
Diabetes, %				<0.001
No diabetes	84.3	78.7	84.3	
Insulin therapy	5.8	12.3	5.8	
Noninsulin therapy	9.9	9.0	9.9	
Dyspnea, %				<0.001
No dyspnea	94.5	90.6	94.5	
Moderate exertion	5.1	8.2	5.1	
At rest	0.4	1.2	0.4	
COPD, %	4.4	10.0	4.4	<0.001
Ventilator dependent, %	0.3	2.2	0.3	<0.001
Ascites, %	0.3	1.8	0.3	<0.001
Congestive heart failure, %	0.9	3.4	0.9	<0.001
Hypertension, %	44.9	59.7	45.0	<0.001
Acute renal failure, %	0.3	2.2	0.4	<0.001
Currently on dialysis, %	1.3	5.1	1.3	<0.001
Disseminated cancer, %	2.2	6.4	2.3	<0.001
Open wound (with or without infection), %	2.8	11.3	2.9	<0.001
Steroid use for chronic condition, %	3.6	8.2	3.6	<0.001
>10% weight loss in the past 6 mo, %	1.2	5.5	1.2	<0.001
Bleeding disorder, %	4.0	11.9	4.1	<0.001
Transfusion, %	0.8	4.4	0.8	<0.001
Systemic sepsis, %	5.2	20.6	5.2	<0.001
Functional health status, %				<0.001
Independent	97.5	89.7	97.5	
Partially dependent	2.1	8.1	2.1	
Totally dependent	0.4	2.2	0.4	
ASA classification, %				<0.001
Normal healthy	8.6	2.1	8.6	
Mild systemic disease	45.0	21.4	44.9	
Severe systemic disease	40.5	54.7	40.5	
Severe systemic disease, threat	5.8	20.7	5.8	
Moribund	0.2	1.1	0.2	
Wound classification, %				<0.001
Clean	57.2	28.3	56.1	
Clean/contaminated	32.1	43.3	32.1	
Contaminated	6.0	12.1	6.0	
Dirty/infected	4.8	16.4	4.9	
Preoperative laboratory values				
Sodium, median (IQR), mEq/L	139 (137–141)	139 (136–141)	139 (137–141)	<0.001
BUN, median (IQR), mg/dL	15 (11–19)	16 (12–24)	15 (11–19)	<0.001
Creatinine, median (IQR), mg/dL	0.85 (0.70–1.02)	0.90 (0.72–1.23)	0.85 (0.70–1.02)	<0.001
Albumin, median (IQR), g/dL	4.0 (3.6–4.3)	3.5 (2.9–4.0)	4.0 (3.6–4.3)	<0.001

Continued next page

TABLE 1. *(Continued)*

CDI	No	Yes	All	*p* value
Bilirubin, median (IQR), mg/dL	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.5 (0.4–0.7)	<0.01
SGOT, median (IQR), mU/mL	21 (17–28)	22 (17–31)	21 (17–28)	<0.001
Alkaline phosphatase, median (IQR), U/L	76 (62–96)	83 (65–111)	76 (62–96)	<0.001
WBC, median (IQR), K/μL	7.3 (5.9–9.3)	8.3 (6.2–11.4)	7.3 (5.9–9.3)	<0.001
Hematocrit, %	40.3 (37.0–43.2)	36.9 (31.9–41.0)	40.2 (37.0–43.2)	<0.001
Platelets, median (IQR), K/μL	240 (197–289)	239 (186–306)	240 (197–289)	0.959*
PTT, median (IQR), s	29.4 (27.0–32.5)	30.0 (27.0–34.0)	29.4 (27.0–32.5)	<0.001
INR, median (IQR)	1.0 (1.0–1.1)	1.1 (1.0–1.2)	1.0 (1.0–1.1)	<0.001
PT, median (IQR), s	11.5 (10.5–13.2)	11.9 (10.7–13.3)	11.5 (10.5–13.2)	0.499*
Procedure-related characteristics				
Work RVU, median (IQR)	15.4 (10.1–20.7)	20.8 (14.5–26.8)	15.4 (10.1–20.7)	<0.001
Operation time, median (IQR), min	84 (50–138)	123 (69–212)	84 (50–139)	<0.001
Time from admission to procedure, median (IQR), d	0 (0–0)	0 (0–1)	0 (0–0)	<0.001
Emergency, %	8.1	20.3	8.1	<0.001
Type of anesthesia, %				<0.001
General anesthesia	88.9	93.7	89.0	
Monitored anesthesia care	4.7	2.6	4.7	
Regional/local/epidural/spinal	6.2	3.6	6.2	
Other/none	0.1	0.1	0.1	
Surgical specialty, %				<0.001
General surgery	44.8	64.0	44.9	
Orthopedics	23.3	11.2	23.2	
Gynecology	7.8	3.0	7.7	
Vascular surgery	5.8	9.3	5.8	
Urology	5.8	5.4	5.8	
Neurosurgery	5.3	3.2	5.3	
Plastic surgery	2.9	0.9	2.9	
Otolaryngology	2.9	1.0	2.8	
Thoracic surgery	1.1	1.2	1.1	
Cardiac surgery	0.4	0.7	0.4	

* Not included in multivariable logistic regression analysis for incidence of CDI.
BUN, blood urea nitrogen; SGOT, serum glutamic oxaloacetic transaminase; PTT, partial thromboplastin time; PT, prothrombin time; RVU, work relative value unit.

bariatric surgery patients that typically have shorter length of stay and likely lower risk of postoperative CDI. As a second sensitivity analysis, we performed a competing risk multivariable proportional hazards model for the risk for CDI within 30 postsurgical days, corrected for the competing risk of dying within 30 postsurgical days.[29] Death is a competing risk or competing event of CDI, as mortality among patients alter the probability of CDI from occurring and patients with longer postoperative survival have an increased for developing CDI. The multivariable proportional hazards method, based on the method of Finn et al., accounts for the time-varying confounder mortality as a competing risk for the risk of having CDI.[30] A new variable "days to death or CDI" will be calculated as days from admission to postoperative CDI, or as days from admission to death if the patient did not have CDI, but death occurred. Patients without CDI or patients that survive will be set at 30 days. The *stcrreg* package in Stata fits the competing risks regression model, according to the subdistribution hazard method.[30] The failure event will be set at CDI, and the competing event at death. The model will again be adjusted for the same aforementioned covariables.

RESULTS

A total of 1,426,807 patients were included (Fig. 1). The median age was 58 years (IQR, 45–69); 43.4% were male and 82.9% were white (Table 1). The overall incidence of postoperative CDI was 0.42%. Of the patients with postoperative CDI, 56.42% (n = 2,400) were diagnosed before hospital discharge and 43.58% (n = 2,626) were diagnosed after hospital discharge. Per BMI group, the incidence of CDI was 1.11% in the underweight, 0.56% in the normal weight, 0.39% in the overweight, 0.35% in the class I obese, 0.33% in the class II obese and 0.36% in the class III obese patients (*p* value for the trend from lowest to highest BMI group <0.001) (Table 1).

The multivariable logistic regression adjusting for patient demographics (e.g., age, sex), comorbidities (e.g., diabetes, immunosuppression), preoperative laboratory values (e.g., albumin, WBC count), procedure complexity (work relative unit as proxy), and procedure characteristics (e.g., emergency, type [general, vascular, other]) is displayed in Table 2. In summary, the higher the BMI, the lower the risk of postoperative CDI was. Specifically, compared to normal weight, the adjusted OR of CDI was 1.15

TABLE 2. Adjusted Significant OR for the Occurrence of CDI

CDI	OR	95% CI	*p*
BMI			
Underweight	1.15	1.00–1.32	<0.05
Normal weight	Reference		
Overweight	0.86	0.81–0.92	<0.001
Obese class I	0.81	0.74–0.87	<0.001
Obese class II	0.76	0.68–0.84	<0.001
Obese class III	0.73	0.66–0.81	<0.001
Patient demographics			
Age, y			
18–19	Reference		
70–79	1.80	1.17–2.77	<0.01
80–89	1.86	1.20–2.87	<0.01
>90	2.27	1.44–3.58	<0.001
Male sex	0.85	0.81–0.90	<0.001
Smoking	1.11	1.03–1.18	<0.01
Ethnicity			
White	Reference		
Black	0.83	0.76–0.91	<0.001
Asian/Pacific Islander	0.85	0.72–1.00	<0.05
Preoperative comorbidities			
Diabetes			
No diabetes	Reference		
—			
Noninsulin therapy	0.72	0.66–0.79	<0.001
COPD	1.16	1.06–1.28	<0.01
Ascites	1.33	1.08–1.62	<0.01
Hypertension	1.09	1.02–1.16	<0.01
Currently on dialysis	1.21	1.05–1.39	<0.01
Open wound (with or without infection)	1.58	1.44–1.75	<0.001
Steroid use for chronic condition	1.25	1.13–1.37	<0.001
>10% weight loss	1.17	1.03–1.31	<0.05
Bleeding disorder	1.28	1.17–1.39	<0.001
Systemic sepsis	1.37	1.26–1.50	<0.001
Functional health status			
Independent	Reference		
Partially dependent	1.41	1.28–1.57	<0.001
Totally dependent	1.39	1.16–1.67	<0.001
ASA classification			
Normal healthy	Reference		
Severe systemic disease	1.82	1.50–2.22	<0.001
Severe systemic disease, threat	2.25	1.83–2.77	<0.001
Moribund	1.61	1.15–2.26	<0.01
Wound classification			
Clean	Reference		
Clean/contaminated	2.60	2.38–2.83	<0.001
Contaminated	2.73	2.45–3.04	<0.001
Dirty/infected	2.41	2.16–2.68	<0.001
Preoperative laboratory values			
Sodium			
Normal	Reference		
Low	1.17	1.08–1.26	<0.001
High BUN	0.93	0.87–1.00	<0.05
High creatinine	1.43	1.30–1.57	<0.001
Low albumin	1.48	1.37–1.59	<0.001
High alkaline phosphatase	1.16	1.08–1.24	<0.001
WBC			
Normal	Reference		
High	1.28	1.19–1.38	<0.001
Low hematocrit	1.39	1.31–1.48	<0.001
High INR	1.19	1.12–1.27	<0.001
Procedure-related characteristics			
Work RVU			
0.00 to <9.45	Reference		
≥ 13.18 to <17.61	1.64	1.45–1.85	<0.001
≥ 17.60 to <21.87	1.64	1.46–1.85	<0.001
≥ 21.87 to 93.0	1.96	1.75–2.20	<0.001
Operation time, min			
>0 to ≤43	Reference		
>70 to ≤101	1.16	1.04–1.29	<0.05
>101 to ≤157	1.34	1.21–1.49	<0.001
>157 to ≤1440	2.03	1.82–2.26	<0.001
Emergency	1.29	1.19–1.39	<0.001
Surgical specialty			
General surgery	Reference		
Orthopedics	0.75	0.68–0.84	<0.001
Gynecology	0.35	0.30–0.41	<0.001
Urology	0.61	0.54–0.69	<0.001
Neurosurgery	0.72	0.61–0.85	<0.001
Plastic surgery	0.55	0.42–0.71	<0.001
Otolaryngology	0.55	0.43–0.71	<0.001
Thoracic surgery	0.45	0.35–0.57	<0.001

(95% confidence interval [CI], 1.00–1.32; $p < 0.05$) in the underweight patients, 0.86 (95% CI, 0.81–0.92; $p < 0.001$) in the overweight patients, 0.80 (95% CI, 0.74–0.87; $p < 0.001$) in the class I obese patients, 0.76 (95% CI, 0.68–0.84; $p < 0.001$) in the class II obese patients, and 0.73 (95% CI, 0.65–0.81; $p < 0.001$) in the class III obese patients (Fig. 2).

Other Predictors of Postoperative CDI in the Adjusted Multivariable Analysis

Patient Characteristics and Comorbidities

In multivariable analyses, the other variables that were associated with significantly higher risk for CDI were all age groups older than 70 years compared with the youngest age group, female sex, smoking, more than 10% weight loss in the past 6 months, COPD, ascites, hypertension, dialysis, steroid use, sepsis, open wounds, functional dependency, higher ASA classification, contaminated/dirty/infected wounds and bleeding disorders.

Preoperative Laboratory Values

Compared with normal preoperative laboratory values, hyponatremia, hypoalbuminemia, leukocytosis, anemia and elevated creatinine, alkaline phosphatase, or INR were associated with an increased risk of postoperative CDI.

Procedure Characteristics

Emergency surgery was a risk factor for CDI. The more complex the procedure, the higher the risk of CDI compared to

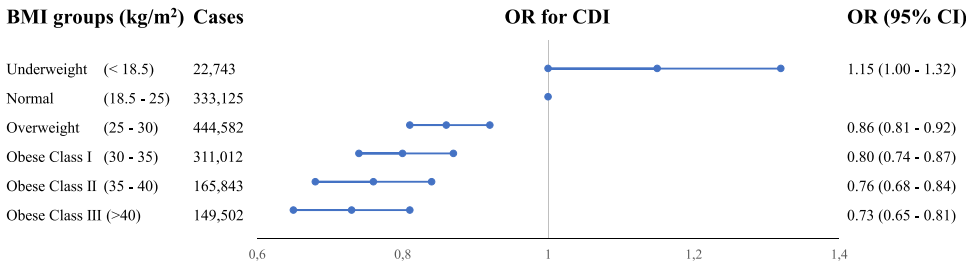

Figure 2. Multivariable adjusted logistic regression demonstrating the risk of CDI across BMI groups.

the lowest complexity group. The longer the time of the surgical procedure, the higher the risk of CDI, compared to the shortest group. Compared with general surgery, all surgical specialties had a lower risk for CDI, except for cardiac and vascular surgery, which were not significantly different from general surgery.

Sensitivity Analysis

To ensure our findings are not driven by bariatric surgery patients that typically have shorter length of stay and likely lower risk of postoperative CDI, we performed the same multivariable models excluding all bariatric patients (n = 44,764). The same exact results were found as those presented in Figure 2.

The overall mortality within 30 days postoperatively was 1.09%. Per BMI group, mortality was 4.65% in the underweight, 1.68% in the normal weight, 0.95% in the overweight, 0.79% in the class I obese, 0.69% in the class II obese and 0.75% in the class III obese patients (p value for the trend from lowest to highest BMI group <0.001). The risk for CDI within 30 postsurgical days across the different BMI groups was examined using a competing risk multivariable proportional hazards model to account for a potential survival bias of patients that survive longer postoperatively. This model accounted for the time-varying confounder mortality, which is a competing risk for the risk of having CDI.[30] A total 1,405,635 cases were analyzed; 6,026 cases had CDI and 12,877 cases died. The model was adjusted for the same aforementioned covariables. Again, the results were similar. When compared to normal weight patients, the adjusted sub-distribution hazard ratio of CDI was 1.15 (95% CI, 1.00–1.32; $p < 0.05$) in underweight patients, 0.86 (95% CI, 0.81–0.92; $p < 0.001$) in overweight patients, 0.80 (95% CI, 0.74–0.87; $p < 0.001$) in obese class I patients, 0.76 (95% CI, 0.68–0.84; $p < 0.001$) in obese class II patients, and 0.73 (95% CI, 0.65–0.81; $p < 0.001$) in obese class III patients.

DISCUSSION

In this nationwide population-based cohort study, we tested the hypothesis that BMI was a risk factor for postoperative CDI among surgical patients in a nationwide cohort in the United States. Contrary to earlier small reports, and after adjustment for confounders, we surprisingly found an inverse and independent relationship between BMI and CDI in the surgical patient: the more obese the patient, the lower the risk for CDI compared to normal weight. Being underweight was associated with an increased risk for CDI, while the morbidly obese were at the lowest risk for CDI. To the best of our knowledge, this is the largest study exploring the relationship between BMI and CDI in surgical patients.

Our study reflects nationwide estimates of the risk of postsurgical intestinal CDI in the United States and stands with its findings regarding the risk of CDI in the obese to recently published small retrospective studies. In a case control study of 178 adult hospitalized patients by Bishara et al.,[19] obesity was found to associate with the risk of CDI, as diagnosed by laboratory tests and clinical symptoms. In another study by Leung et al.[20] in 132 patients with laboratory proven CDI, obese patients were 1.7 times more likely to have severe CDI compared to overweight patients. In addition, the same study suggested that community-acquired CDI patients were more likely to be obese when compared to patients with CDI patients that were exposed to health care facilities 4 weeks prior to diagnosis.[20] A third retrospective case-control study by Mulki et al.[21] demonstrated that obesity was as an independent risk factor for both severe community-acquired and hospital-onset laboratory-proven CDI in 196 hospitalized patients. Other studies have failed to substantiate the relationship. For example, no relationship between obesity and hospital- or community-acquired CDI was found in 202 pediatric solid organ transplant patients, or in a case-control study of 378 adult patients admitted to one tertiary acute care medical facility.[22,23] Our study that included more than 1.5 million patients suggests the exact opposite: when controlling for confounders and other risk factors of CDI, such as advanced age, comorbidities, decreased immunity or disruption in the intestinal microbiome (e.g., sepsis, surgery or chemotherapy), obesity appears to be a protective factor against the occurrence of CDI.[8]

Generally, being underweight results in worse outcomes than being normal weight, as underweight patients have more risk of infectious complications, such as surgical site and respiratory infections.[10] Being underweight is a known risk factor for community-acquired and influenza-related pneumonia in industrialized countries.[31] Throughout literature there is a paucity of information regarding the relationship between being underweight and the risk of intestinal CDI. It is unclear whether underweight patients also recover less from CDI than overweight patients, as one study reports that obese patient with CDI have higher mortality risks than normal weight, while another states that underweight patients with CDI have a higher risk of mortality compared to overweight and obese patients.[32,33]

The exact mechanisms for the relationship between BMI and CDI in our study are uncertain. Our findings could be partially explained by an underdosing of perioperative antibiotics in the obese patients,[34] and as such less risk of CDI. Increased CDI has been noted in patients with altered microbiome caused by antibiotics or proton pump inhibitors use.[35] Also, obesity modifies the microbiome especially when compared with normal

weight individuals.[16,17,36] Increased body fat and obesity-related metabolic disorders are associated with having fewer microbial genes in the colon.[36] Causal relations that a certain microbiome promotes obesity between microbiome and weight regulation have also been suggested. Animal studies have shown that mice receiving gut microbes from obese humans gain more weight than mice receiving gut microbes from a lean human donor.[37] The mechanism of how *C. difficile* can colonize the intestinal microbiome in certain microbiomes remains unclear.

Another interesting finding was that surgical patients with diabetes mellitus receiving noninsulin therapy had a significantly less risk of CDI compared with nondiabetics. The risk of surgical patients with diabetes receiving insulin therapy was similar to nondiabetics. While the mechanism remains unclear, it could be related to the most commonly used oral hypoglycemic metformin. Metformin is believed to influence the function and alter the gut microbiome.[38–40] Metformin also has anti-inflammatory effects.[41,42] It has been shown to reduce intestinal inflammation and acute diverticulitis.[38,39] Recently, Eliakim-Raz et al.[43] have suggested a protective effect of metformin therapy in diabetic patients against CDI. These pathways are poorly understood and future research is needed to examine the relationship between intestinal CDI, BMI, and other factors affecting the microbiome.

Our study has a number of limitations. First, despite our meticulous attempt at controlling for all existing patient and procedure related factors, there likely exist confounders not recorded with the ACS-NSQIP database. These include the duration and type of antibiotic used, the use of proton pomp inhibitors, the use of tube feedings, exposure to health care facilities prior to admission, the geographic locations of the participating center, and whether any unusual outbreaks of CDI impacted our results. However, there is no apparent nonrandom relationship between BMI and any of these confounders that we are aware of. Lastly, the association we found, does not prove causality.

CONCLUSION

Our data suggest that obesity is independently and in a stepwise fashion associated with a decreased risk of postoperative CDI. Further studies are warranted to explore the potential association and mitigate that risk.

AUTHORSHIP

K.M., A.T.N., A.I.E., N.K., J.M.L., M.K., K.R.H., N.K., A.E.M., N.S., D.R.K., G. C.V., and H.M.A.K. contributed to the conception and design of the research. K.M., A.T.N., and J.M.L. contributed to the acquisition of data. K.M., A.T.N., A.I.E., J.M.L., M.K., K.R.H., and N.K., and H.M.A.K. contributed to the data analysis. K.M., A.T.N., A.I.E., N.K., J.M.L., M.K., K.R.H., N.K., A.E.M., N.S., D.R.K., G.C.V., and H.M.A.K. contributed to the data interpretation. K.M. drafted the article. All authors critically revised the article, read and approved the final article, and agree to be fully accountable for ensuring the integrity and accuracy of the work. Each of the individual authors has sufficiently participated in this study to be listed as author.

DISCLOSURE

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