The Association Between Body Mass Index and the Risk of Hospitalization and Mortality due to Infection: A Prospective Cohort Study

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Background. We aim to determine whether obesity increases the risk of various infections using a large prospective population-based cohort.

Methods. A total of 120 864 adults were recruited from the New Taipei City health screening program from 2005 to 2008. Statistics for hospitalization and mortality due to infection were obtained from the National Health Insurance Database and the National Death Registry in Taiwan.

Results. During a mean follow-up period of 7.61 years, there were 438, 7582, 5298, and 1480 first hospitalizations due to infection in the underweight, normal, overweight, and obese groups, respectively. Obesity significantly increases the risk of hospitalization for intra-abdominal infections (adjusted hazard ratio [aHR], 1.19; 95% CI, 1.00–1.40), including diverticulitis, liver abscess, acute cholecystitis and anal and rectal abscess, reproductive and urinary tract infection (aHR, 1.38; 95% CI, 1.26–1.50), skin and soft tissue infection (aHR, 2.46; 95% CI, 2.15–2.81), osteomyelitis (aHR, 1.70; 95% CI, 1.14–2.54), and necrotizing fasciitis (aHR, 3.54; 95% CI,1.87–6.67), and this relationship is dose-dependent. This study shows that there is a U-shaped association between body mass index (BMI) and hospitalization for lower respiratory tract infection, septicemia, and the summation of all infections and that underweight people are at the greatest risk, followed by obese people. There is a clear negative relationship between BMI and infection-related mortality.

Conclusions. The pattern that BMI affects the risk of hospitalization and mortality due to infection varies widely across infection sites. It is necessary to tailor preventive and therapeutic measures against different infections in hosts with different BMIs.

Keywords. body mass index; infection; obese; overweight; underweight.

Obesity has surged rapidly worldwide in recent decades. Obesity increases the risk of type 2 diabetes mellitus, hypertension, obstructive sleep apnea, osteoarthritis, cardiovascular diseases, and certain types of cancers. However, in terms of infections, the role of body mass index (BMI) or obesity is complicated. Large population-based studies demonstrate that both being underweight and obesity are associated with increased mortality [1–3]. Obesity is associated with an altered immune response [4] and chronic inflammation [5], which can lead to

an increased risk of infection. Excessive weight also stresses the respiratory system, increases soft tissue burden, and impairs skin and urinary tract hygiene [6, 7]. Being underweight can be a symptom of malnutrition, which compromises host defense and increases the risk of infection as well.

Studies show that obese people are at a higher risk of cellulitis [8], urinary tract infection [9–11], and respiratory tract infection [10, 12, 13]. However, the association between obesity and other types of infection is unverified [14]. Obesity has been linked to diverticulitis [15–17] and intestinal infection [13], but its relationship with other intra-abdominal infections is unclear. Although obesity is clearly a risk factor for gall stones and gall bladder dysfunction [18, 19], it is unclear whether obesity is a risk factor for acute cholecystitis. The heterogeneity in patient population and study methods in the literature also gave inconclusive results. For instance, a small case–control study found that a higher BMI increases the risk of acute cholecystitis [20], but a large cohort study did not show any association between BMI and intra-abdominal infection, including acute cholesystitis [10]. There is also no clear relationship between

BMI and other rare but severe infections, such as necrotizing fasciitis or osteomyelitis.

This is a prospective cohort study to determine the association between BMI and hospitalization and mortality due to infection. This study involves a large number of enrolled subjects, so it clarifies the association between obesity and rare but severe infections, such as osteomyelitis and necrotizing fasciitis. The subtypes of intra-abdominal infections are also considered, including acute cholecystitis, liver abscess, and perianal abscess, which are rarely studied in the general population. Subjects with preexisting major disease lose weight before adverse outcomes occur, which results in bias of reverse causality [21]. Therefore, this study performs a stratified subgroup analysis for clarification.

METHODS

The design of this study has been described previously [22–25]. A total of 125 865 adults aged 40 years or older participated voluntarily in a community-based health screening service in New Taipei City from 2005 to 2008. Each completed a questionnaire about demographics, educational level, and lifestyle information and underwent a standard physical examination as well as a blood test after overnight fasting and analysis of the first morning voided urine. Participants gave consent and individual identification information was removed, so the participants remained anonymous during the entire study process. The New Taipei City health screening program database was then linked to the National Health Insurance Database and

the National Death Registry using each participant's unique national identification number. In Taiwan, national health insurance is compulsory for all residents, and the system serves 99% of the population. Participants were excluded if (1) there was no baseline measurement of body mass index (BMI) and fasting plasma glucose level; (2) there was incomplete information about cigarette smoking, alcohol consumption, and educational level; and (3) no claims for the individual were present in the National Health Insurance Database. The final study population consisted of 120 864 participants (see Figure 1 for a study flow diagram).

Patient Consent

Written consent was obtained from all patients. The design of the work has been approved by the Research Ethics Committee of the National Taiwan University Hospital.

Covariates

Diabetes was defined as a fasting plasma glucose of >126 mg/dL or a prescription of any hypoglycemic agent in the health insurance claims database for >28 days in the previous year before enrollment. Diabetic participants were further stratified using glycemic control (fasting plasma glucose levels <90, 91–130, 131–200, >200 mg/dL). The baseline demographic information (sex, age, level of education) and behavioral risk factors (cigarette smoking and alcohol use) were obtained from the questionnaire at enrollment. BMI was calculated as body weight (in kilograms) divided by the square of body height (in meters). Details of use of systemic steroids for >30 days in the year before
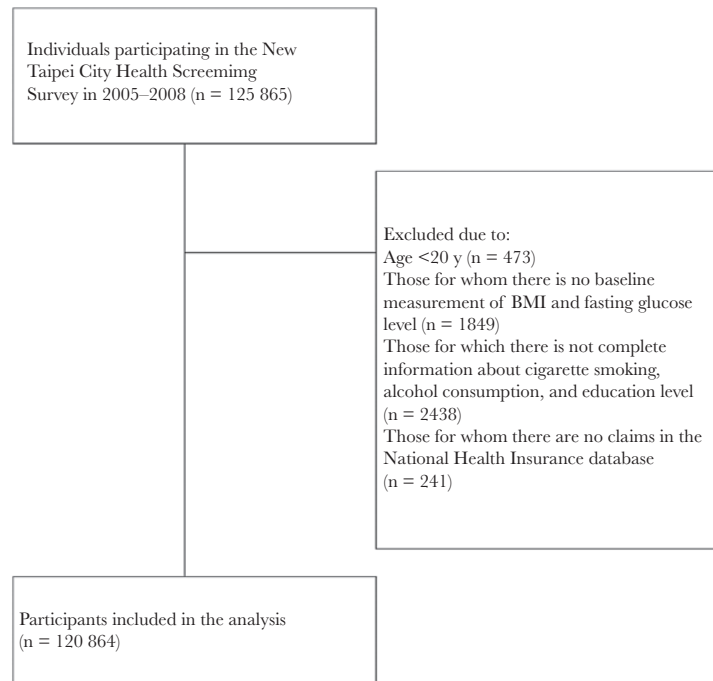

Figure 1. Flowchart for the enrollment of participants into the study.

enrollment and hospitalization <6 months before the index hospitalization due to infection were obtained from the National Health Insurance Database. Inpatient and outpatient files for the 12-month period before the study were used to ascertain patients' history.

Follow-up and Outcome

The primary outcome was the first hospitalization due to infection recorded in the National Health Insurance Database after the beginning of the study. Hospitalization due to infections was further classified according to specific types of infection, including septicemia, lower respiratory tract infection, intraabdominal infection, reproductive and urinary tract infection, skin and soft tissue, osteomyelitis, and necrotizing fasciitis, as defined by the International Classification of Diseases, 9th revision, Clinical Modification (Supplementary Table 1). Codes have been verified for various types of infection in the NHI Claims Database [26]. Patients may have multiple infection sites for this index of hospitalization. The National Death Registry shows the vital status or the date of death, and this information is used to extract infection-related mortality among hospitalization due to infection. Participants were censored upon the first hospitalization due to infection, death, or at the end of 2014, whichever came first. In terms of the specific site of infection, participants who were hospitalized due to 1 specific infection site did not contribute to follow-up person-time for another infection site.

Statistical Analysis

Baseline characteristics for underweight, normal BMI, overweight, and obese participants were compared. A BMI (kg/m^2) <18.5 was defined as underweight, 18.5–24.9 kg/m^2 as normal, 25.0–29.9 as overweight, and >30.0 as obese according to the World Health Organization classification. The rate of hospitalization due to infection and mortality was calculated for different BMI categories and sites of infection. Cox regression modeling was used to determine the adjusted hazard ratios (aHRs) and 95% confidence intervals for hospitalization and mortality due to infection for different BMI categories with a normal BMI as the reference group. Confounders including age category, sex, smoking and alcohol consumption status, low educational level, diabetes category, systemic steroid use <1 year before the study, and hospitalization history for 6 months before index hospitalization due to infection were controlled.

Subgroup Analysis

A subgroup analysis determined whether the risks were modified by diabetes mellitus, age (<50 and ≥50 years), sex, or major systemic disease (including history of hypertension, diabetes, dyslipidemia, myocardial infarction, congestive heart failure, stroke, peripheral artery disease, chronic liver disease, kidney disease, lung disease, autoimmune disease, and cancers). The

inpatient and outpatient claims during the 12-month period before the study were used to determine patients' history of these systemic diseases. Cross-product terms were created and added to the multivariable Cox model, and models with and without cross-product interaction terms were compared using a likelihood ratio test. All analyses used SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 120 864 adults were enrolled from a free community-based health screening service in New Taipei City from 2005 to 2008. The baseline characteristics are summarized in Table 1. Obese people were older and more likely to be male, regular consumers of alcohol, and current smokers. In fact, in those who reported never smoking, only 37.7% were overweight or obese, compared with 44.8% who were ever smokers. They were also more likely to have a low educational level, diabetes mellitus, systemic steroid use, and a history of hospitalization than those with a normal BMI.

The number of cases and the crude incidence of hospitalization due to infection for participants who were underweight, normal weight, overweight, and obese are summarized in Table 2. The crude and adjusted HRs for hospitalization and mortality due to infection for underweight, overweight, and obese people are compared with those of people with a normal BMI in Table 3 and in Figure 2 according to infection sites. During an average follow-up period of 7.61 years, there were 1919 admissions due to intra-abdominal infection, 6007 due to reproductive and urinary tract infection, 1933 due to skin and soft tissue infection, 269 for osteomyelitis, and 59 for necrotizing fasciitis. Obesity increases the risk of hospitalization due to the above infections in a dose-dependent manner (intra-abdominal infection aHR, 1.19; 95% CI, 1.00–1.40; reproductive and urinary tract infection aHR, 1.38; 95% CI, 1.26–1.50; skin and soft tissue infection aHR, 2.46; 95% CI, 2.15–2.81; osteomyelitis aHR, 1.70; 95% CI, 1.14–2.54; necrotizing fasciitis aHR, 3.54; 95% CI, 1.87–6.67). The risk associated with obesity is greatest for skin and soft tissue infection, osteomyelitis, and necrotizing fasciitis.

The relationship between BMI and specific intra-abdominal infection was studied. The crude HRs and aHRs are listed in Table 3 and Figure 3. Obese people had a dose-dependent increased risk of hospitalization due to diverticulitis, anal and rectal abscess, liver abscess, and acute cholecystitis, but not due to appendicitis or peritonitis.

There was a U-shaped association between BMI and the risk of hospitalization due to lower respiratory tract infection, septicemia, and for all hospitalization due to infection (Figure 2). The underweight group had the greatest risk of hospitalization due to lower respiratory tract infection (aHR, 2.22; 95 % CI, 1.92–2.56) and septicemia (aHR, 1.55; 95% CI, 1.23–1.94). In

Table 1. Baseline Characteristics for Study Participants (n = 120 864)

Variable	BMI				P Value Under-weight vs Normal	P Value Over-weight vs Normal	P Value Obese vs Normal
	Underweight	Normal	Overweight	Obese			
No.	3406	70 098	39 093	8267			
Male, %	22.52	31.58	44.48	35.76	**<.001**	**<.001**	**<.001**
Age, mean (SD), y	47.68 (14.38)	50.84 (11.88)	53.82 (11.53)	53.17 (11.73)	**<.001**	**<.001**	**<.001**
20–40	39.05	20.16	12.26	15.05			
41–50	26.10	32.79	28.40	27.35			
51–60	15.80	26.94	31.88	30.93			
61–70	9.45	13.07	18.69	18.63			
71–100	9.60	7.04	8.76	8.04			
Cigarette smoking, %					**<.001**	**<.001**	**<.001**
Never	81.03	80.43	75.05	77.25			
Ever	18.96	19.57	24.95	22.75			
Alcohol consumption, %					**<.001**	**<.001**	**<.001**
Never	68.35	60.97	58.71	62.39			
Ever	31.65	39.04	41.3	37.61			
Educational level, %					**<.001**	**<.001**	**<.001**
Illiterate	5.40	6.28	9.89	12.27			
Literate but did not attend elementary school	1.35	1.76	2.61	2.90			
Elementary school	14.56	22.28	29.15	31.75			
Junior high school	12.77	16.15	16.51	16.52			
High school	33.18	30.58	24.89	23.35			
College	30.45	20.95	15.43	12.29			
Graduate school	2.29	1.99	1.52	0.92			
Systemic steroid use >30 d before entry into the study, %	1.32	1.12	1.46	2.00	.29	**<.001**	**<.001**
History of hospitalization 6 mo before entry into the study, %	3.02	2.64	3.02	4.02	.18	**<.001**	**<.001**
History of hospitalization 6 mo before index hospitalization due to infection, %	2.20	2.28	2.87	3.60	.75	**<.001**	**<.001**
Diabetes control, %					**<.001**	**<.001**	**<.001**
Fasting glucose <90	0.18	0.16	0.20	0.34			
Fasting glucose 91–130	0.65	1.43	2.98	4.81			
Fasting glucose 131–200	1.50	3.06	6.64	11.49			
Fasting glucose >200	0.65	1.38	2.39	3.41			

Abbreviation: BMI, body mass index.

Table 2. Duration of Follow-up, Number of Incident Cases, and Crude Incidence of Hospitalization and Mortality due to Infection (n = 120 866)

Outcome	Underweight	Normal	Overweight	Obesity
		BMI Category		
No.	3406	70 098	39 093	8267
Duration of follow-up				
Total person-days	9 240 449	196 105 720	108 177 323	22 328 385
Median (IQR), d	2967 (946)	3000 (919)	2868 (931)	2819 (930)
Hospitalization due to infection				
All infections				
No. of cases	438	7582	5298	1480
Crude incidence rate	17.31 (15.77~19.01)	14.12 (13.81~14.44)	17.89 (17.41~18.38)	24.21 (23.01~25.48)
Intra-abdominal				
No. of cases	42	1019	698	160
Crude incidence rate	1.66 (1.23~2.25)	1.90 (1.78~2.02)	2.36 (2.19~2.54)	2.62 (2.24~3.06)
Appendicitis				
No. of cases	19	524	267	53
Crude incidence rate	0.75 (0.48~1.18)	0.98 (0.90~1.06)	0.90 (0.80~1.02)	0.87 (0.66~1.13)
Diverticulitis				
No. of cases	5	155	114	3
Crude incidence rate	0.20 (0.08~0.47)	0.29 (0.25~0.34)	0.38 (0.32~0.46)	0.49 (0.34~0.70)
Abscess of anal and rectal regions				
No. of cases	*	26	50	11
Crude incidence rate	*	0.05 (0.03~0.07)	0.17 (0.13~0.22)	0.18 (0.10~0.32)
Peritonitis				
No. of cases	14	221	156	32
Crude incidence rate	0.55 (0.33~0.93)	0.41 (0.36~0.47)	0.53 (0.45~0.62)	0.52 (0.37~0.74)
Abscess of liver				
No. of cases	3	67	80	18
Crude incidence rate	0.12 (0.04~0.37)	0.12 (0.10~0.16)	0.27 (0.22~0.34)	0.29 (0.19~0.47)
Acute cholecystitis				
No. of cases	3	64	60	23
Crude incidence rate	0.12 (0.04~0.37)	0.12 (0.09~0.15)	0.20 (0.16~0.26)	0.38 (0.25~0.57)
Reproductive and urinary tract				
No. of cases	151	3080	2161	615
Crude incidence rate	5.97 (5.09~7.00)	5.74 (5.54~5.94)	7.30 (7.00~7.61)	10.06 (9.30~10.89)
Reproductive tract (601, 604, 614, 615, 616)				
No. of cases	40	700	356	78
Crude incidence rate	1.58 (1.16~2.16)	1.30 (1.21~1.40)	1.20 (1.08~1.33)	1.28 (1.02~1.59)
Urinary tract (590, 599.0)				
No. of cases	113	2432	1850	541
Crude incidence rate	4.47 (3.71~5.37)	4.53 (4.35~4.71)	6.25 (5.97~6.54)	8.85 (8.13~9.63)
Skin and soft tissue				
No. of cases	37	843	747	306
Crude incidence rate	1.46 (1.06~2.02)	1.57 (1.47~1.68)	2.52 (2.35~2.71)	5.01 (4.48~5.60)
Osteomyelitis				
No. of cases	4	123	111	31
Crude incidence rate	0.16 (0.06~0.42)	0.23 (0.19~0.27)	0.37 (0.31~0.45)	0.51 (0.36~0.72)
Necrotizing fasciitis				
No. of cases	0	27	16	16
Crude incidence rate	NA	0.05 (0.03~0.07)	0.05 (0.03~0.09)	0.26 (0.16~0.43)
Lower respiratory tract				
No. of cases	208	2274	1400	325
Crude incidence rate	8.22 (7.18~9.42)	4.24 (4.06~4.41)	4.73 (4.49~4.98)	5.32 (4.77~5.93)
Septicemia				
No. of cases	80	1336	1045	282
Crude incidence rate	3.16 (2.54~3.94)	2.49 (2.36~2.63)	3.53 (3.32~3.75)	4.61 (4.10~5.18)
Infection-related mortality				
No. of cases	32	247	143	22
Crude mortality rate	1.20 (0.85~1.70)	0.44 (0.39~0.50)	0.46 (0.39~0.54)	0.33 (0.22~0.50)

Crude incidence rate: per 1000 person-years.
Abbreviation: BMI, body mass index.

Table 3. Crude and Adjusted Hazard Ratios for Hospitalization due to Infection and Mortality According to BMI Category (n = 120 864)

		Underweight	Normal	Overweight	Obesity
All infections (n = 14 798)					
	Crude HR	1.23 (1.12~1.35)[**]	1	1.27 (1.22~1.31)[**]	1.72 (1.63~1.82)[**]
	aHR	1.35 (1.23~1.49)[**]	1	1.05 (1.02~1.09)[*]	1.35 (1.28~1.43)[**]
Intra-abdominal infection (n = 1919)					
All (n = 1919)	Crude HR	0.88 (0.64~1.19)	1	1.24 (1.13~1.37)[**]	1.38 (1.17~1.63)[**]
	aHR	0.96 (0.70~1.30)	1	1.09 (0.99~1.20)	1.19 (1.00~1.40)[*]
Appendicitis (n = 863)	Crude HR	0.77 (0.49~1.21)	1	0.92 (0.80~1.07)	0.89 (0.67~1.18)
	aHR	0.77 (0.49~1.22)	1	0.90 (0.78~1.05)	0.87 (0.65~1.16)
Peritonitis (n = 87)	Crude HR	1.35 (0.79~2.32)	1	1.28 (1.04~1.57)[*]	1.28 (0.88~1.85)
	aHR	1.66 (0.96~2.86)	1	1.02 (0.83~1.26)	1.00 (0.69~1.45)
Diverticulitis (n = 304)	Crude HR	0.68 (0.28~1.67)	1	1.33 (1.05~1.70)[*]	1.70 (1.15~2.51)[*]
	aHR	0.73 (0.30~1.78)	1	1.20 (0.94~1.54)	1.50 (1.01~2.24)[*]
Anal and rectal abscess (n = 87)	Crude HR	0.82 (0.11~6.01)	1	3.48 (2.17~5.59)[**]	3.71 (1.83~7.50)[**]
	aHR	1.03 (0.14~7.66)	1	2.61 (1.62~4.21)[**]	2.98 (1.46~6.09)[*]
Liver abscess (n = 168)	Crude HR	0.95 (0.30~3.02)	1	2.17 (1.57~3.00)[**]	2.37 (1.41~3.99)[*]
	aHR	1.18 (0.37~3.77)	1	1.62 (1.17~2.26)[*]	1.66 (0.98~2.81)
Acute cholecystitis (n = 150)	Crude HR	1.00 (0.31~3.17)	1	1.70 (1.20~2.42)[*]	3.16 (1.96~5.09)[**]
	aHR	1.25 (0.39~3.99)	1	1.32 (0.93~1.89)	2.46 (1.52~4.00)[**]
Reproductive and urinary tract infection (n = 6007)					
	Crude HR	1.04 (0.89~1.23)	1	1.27 (1.20~1.34)[**]	1.76 (1.61~1.92)[**]
	aHR	1.07 (0.91~1.26)	1	1.14 (1.08~1.21)[**]	1.38 (1.26~1.50)[**]
Skin and soft tissue (n = 1923)					
	Crude HR	0.93 (0.67~1.30)	1	1.61 (1.46~1.77)[**]	3.19 (2.80~3.64)[**]
	aHR	1.06 (0.76~1.48)	1	1.29 (1.17~1.43)[**]	2.46 (2.15~2.81)[**]
Osteomyelitis (n = 269)					
	Crude HR	0.69 (0.26~1.87)	1	1.63 (1.26~2.11)[**]	2.21 (1.49~3.28)[**]
	aHR	0.80 (0.30~2.18)	1	1.28 (0.99~1.66)	1.70 (1.14~2.54)[*]
Necrotizing fasciitis (n = 59)					
	Crude HR	NA	1	1.07 (0.58~1.99)	5.20 (2.80~9.64)[**]
	aHR	NA	1	0.76 (0.41~1.42)	3.54 (1.87~6.67)[**]
Lower respiratory tract (n = 4207)					
	Crude HR	1.95 (1.69~2.24)[**]	1	1.12 (1.05~1.19)[*]	1.26 (1.12~1.42)[**]
	aHR	2.22 (1.92~2.56)[**]	1	0.86 (0.80~0.92)[**]	0.99 (0.88~1.12)
Septicemia (n = 2733)					
	Crude HR	1.28 (1.02~1.60)[*]	1	1.42 (1.31~1.54)[**]	1.86 (1.64~2.12)[**]
	aHR	1.55 (1.23~1.94)[**]	1	1.09 (1.00~1.18)[*]	1.36 (1.20~1.55)[**]
Infection-related mortality (n = 444)					
	Crude HR	2.76 (1.91~3.99)[**]	1	1.04 (0.84~1.27)	0.75 (0.49~1.16)
	aHR	2.86 (1.97~4.15)[**]	1	0.78 (0.63~0.96)[*]	0.62 (0.40~0.96)[*]

Adjusted for age category, sex, smoking, alcohol consumption, educational level, diabetes (fasting glucose <90, 91–130, 131–200, >200), use of systemic steroids >30 days before entry into the study, and history of hospitalization for 6 months before hospitalization due to infection.

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; HR, hazard ratio.

*P < .05; **P < .001.

terms of the risk for all hospitalization due to infection, the aHR was 1.35 (95%, 1.23–1.49) for the underweight group and 1.35 (95% CI, 1.28–1.43) for obese patients, compared with the figure for a normal BMI (Figure 2).

BMI was inversely related to mortality due to infection. The highest aHR value was observed in the underweight subjects (aHR, 2.86, 95% CI, 1.97–4.15). Compared with those with a normal BMI, overweight and obese people were protected from mortality due to infection, with aHRs of 0.78 (95% CI, 0.63~0.96) and 0.62 (95% CI, 0.40~0.96), respectively. It is possible that some of the underweight people actually suffered from

chronic wasting conditions, leading to a greater risk of infection or mortality. To take into account the potential reverse causation between underlying illness and extreme BMI, stratified analyses were used to determine the presence or absence of major systemic diseases. The results are shown in Supplementary Tables 2A and 2B. The incidence of hospitalization due to infection was similar in the presence or absence of major systemic diseases. However, the protective effect of obesity against mortality was diminished in those without systemic disease (Supplementary Table 2B). An underweight condition in elderly people could be a sign of sarcopenia, and some types of infection, such as urinary
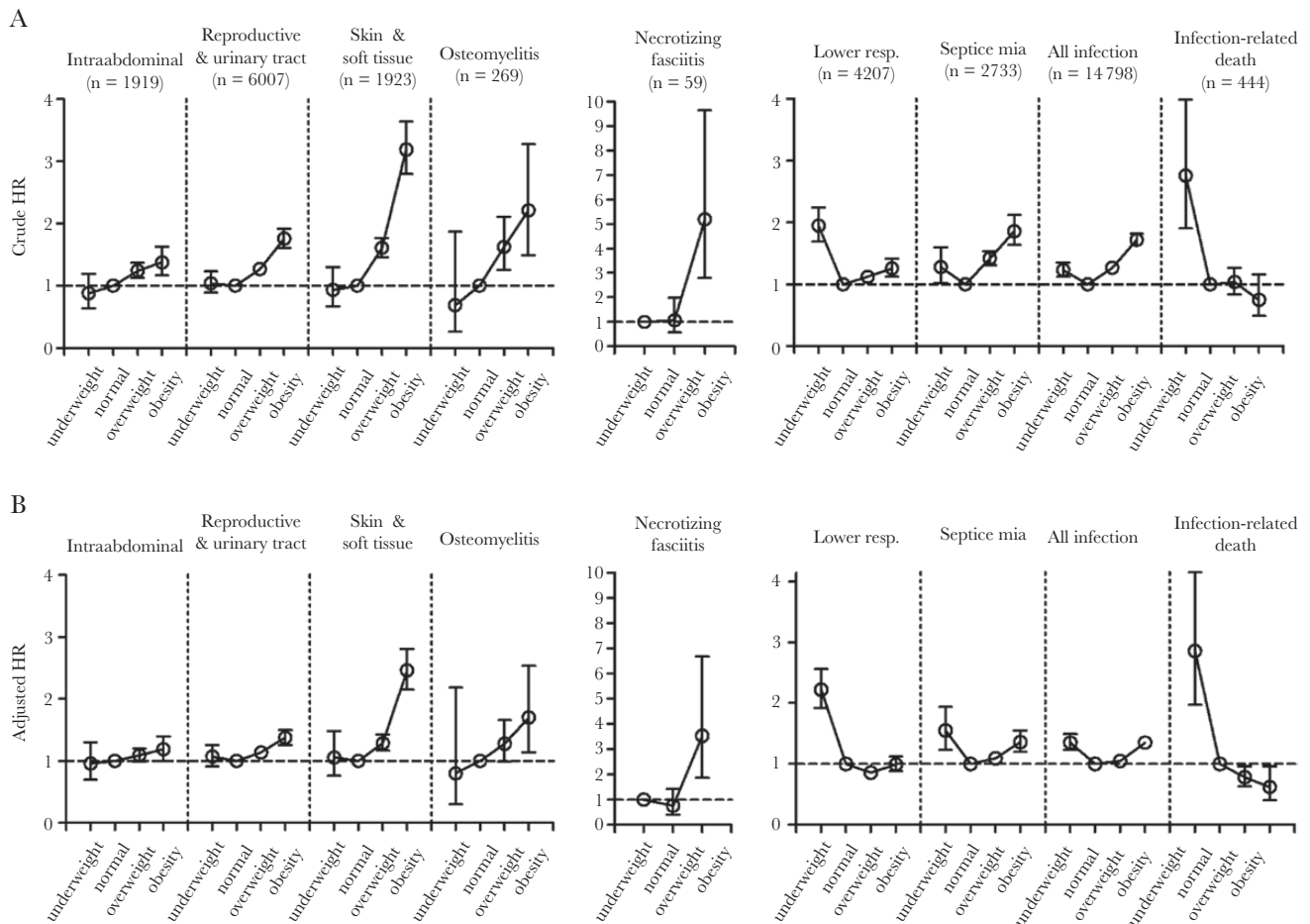
Figure 2. A, Crude and (B) adjusted hazard ratios[a] for risk of hospitalization due to infection and mortality for different BMI categories compared with those with a normal BMI (n **=** 120 864). [a]Adjusted for age category, sex, smoking, alcohol consumption, educational level, diabetes (fasting glucose <90, 91–130, 131–200, >200), use of systemic steroids >30 days before entry into the study, and history of hospitalization for 6 months before hospitalization due to infection. Abbreviations: BMI, body mass index; HR, hazard ratio.

tract infection, are affected by sex. Hence we performed age- and sex-stratified analysis (Supplementary Tables 3 and 4); the results were similar for each stratum. The results for people with and without diabetes were also similar. However, in the diabetic group, the risks associated with obesity were attenuated for all types of infection, and obesity had a greater protection against infection-related mortality (Supplementary Table 5A). We also performed subgroup analysis according to smoking status; the results are presented in Supplementary Table 6A and B. In the underweight group, the risks of all infections, lower respiratory infection, septicemia, and infection-related mortality were all higher than in normal weight subjects, ever and nonsmokers alike. For overweight subjects, nonsmokers had higher risks for all infections, reproductive and urinary tract infection, and septicemia, while overweight ever smokers were protected from infection-related mortality. In the obese group, the risks of all infections, skin and soft tissue infection, and necrotizing fasciitis were higher than in normal weight subjects or ever and nonsmokers alike, but obese nonsmokers had higher risks for

reproductive and urinary tract infection and septicemia. As mentioned above and in Table 1, ever smokers were more likely to be overweight or obese. Therefore, residual confounding was likely in the subgroup analysis considering smoking status, especially in the overweight and obese population.

DISCUSSION

This large prospective cohort study with a long-term follow-up period of 7 years shows that obesity increases the risk of hospitalization due to intra-abdominal infection, reproductive and urinary tract infection, skin and soft tissue infection, osteomyelitis, and necrotizing fasciitis. The greatest increase in risk associated with obesity was observed for skin and soft tissue infection, osteomyelitis, and necrotizing fasciitis. Obesity also increased the risk of diverticulitis, anal and rectal abscess, liver abscess, and acute cholecystitis, but not of appendicitis or peritonitis. There was a reverse U-shaped relationship between BMI and hospitalization due to lower respiratory tract
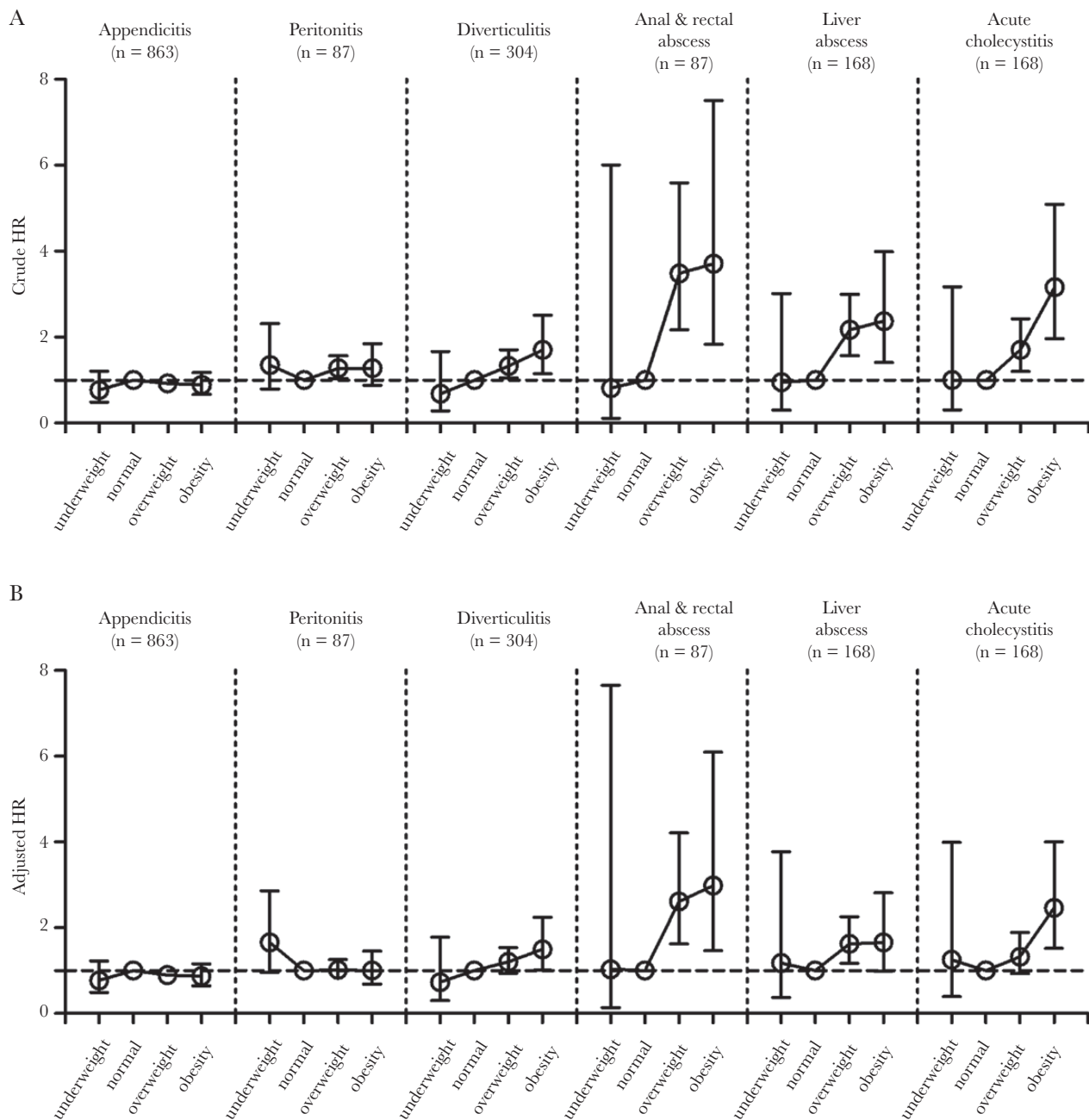
Figure 3. A, Crude and (B) adjusted hazard ratios[a] for risk of intra-abdominal infection for different BMI categories, compared with those for a normal BMI (n = 1659). [a]Adjusted for age category, sex, smoking, alcohol consumption, educational level, diabetes (fasting glucose <90, 91–130, 131–200, >200), use of systemic steroids >30 days before entry into the study, and history of hospitalization for 6 months before hospitalization due to infection. Abbreviations: BMI, body mass index; HR, hazard ratio.

infection, septicemia, and for all hospitalization due to infection. BMI was negatively associated with infection-related mortality.

There are 2 large cohort studies exploring the relationship between BMI and a range of infections [10, 13]. A study by Harpsoe et al. that involved 91 765 Danish women of childbearing age showed that the risk of gastrointestinal infection is only increased for underweight people (BMI < 18.5; adjHR, 1.48; 95% CI, 1.11–1.96) and not for obese people. However, this study did not collect data for male or elderly people and did not consider hepato-biliary infections. The other was a study from the Danish Blood Donor Cohort also showing that BMI is not related to gastrointestinal infections or acute cholecystitis, but this study involved few underweight patients because of regulations for blood donation. The difference in the subject characteristics of these studies partially explains the difference between their results. Intra-abdominal infections other than gastrointestinal infections also require further study.

One unique finding of this study is the dose-dependent relationship between BMI and the subtypes of intra-abdominal infections: hepato-biliary infection and peri-anal and rectal abscess. Obesity has been identified as a risk factor for gall bladder stones and gall bladder dysfunction or pathology [18, 19, 27–29], but no direct link between obesity and acute cholecystitis has been established. Cha et al. compared 171 pairs of age- and sex-matched cholecystectomy patients with symptomatic and asymptomatic gall bladder stones and showed that a higher BMI was associated with a greater risk of symptomatic gall bladder stones [20]. Our study is not limited to postcholecystectomy patients or those with gall bladder stones and is rigorously controlled for diabetes and blood sugar level, but it also shows a dose-dependent increased risk of acute cholecystitis. It has also been shown that overweight patients have a greater risk of liver abscess. Obesity and diabetes often occur together, and the latter is a known risk factor for liver abscess [30], but there is an increased risk even after the results are adjusted for diabetes status and blood sugar level. The results of this study show that obesity is a significant risk factor for hepato-biliary infections. Obesity alters gut and perineal microbiota [4, 31–35] and the immune capability and lymphatic system in visceral fat [36]. These pathophysiological changes may explain the increased risk of intra-abdominal infection and peri-anal and rectal abscess for overweight and obese patients.

Similar to previous studies, this study shows that obesity is strongly associated with hospitalization due to skin and soft tissue infection [1, 12, 25–28]. However, few studies have measured hospitalization due to necrotizing fasciitis, and those that have are limited to case series that did not feature control subjects [37, 38]. The diagnosis of necrotizing fasciitis is often delayed, but the consequence of this severe and life-threatening condition is significant; this study shows that primary care professionals should be more alert to this diagnosis, especially for patients with a large BMI.

Few studies have examined the relationship between BMI and osteomyelitis. Osteomyelitis usually results from *Staphylococcus* infection, and obese individuals are known to have low serum *Staphylococcus* IgG antibody titer [39, 40]. Obese mice that are fed a high-fat diet show a defective humoral immune response against *Staphylococcus aureus* and are more prone to severe bone implant infections than lean mice [39]. The mechanism by which obesity increases the risk of necrotizing fasciitis and osteomyelitis in humans is worthy of further study.

Similar to other studies, this study shows that BMI is positively correlated with risk of urinary tract infection [9–11]. There is a J-shaped or U-shaped correlation between BMI and the risk of septicemia and lower respiratory tract infection [13, 41–49] and the summation of all infections [13, 50]. Most importantly, this study shows that BMI is negatively correlated with infection-related mortality. Several hospital-based large prospective studies [43, 51–56] and meta-analyses [57] have

also identified this correlation. It is possible that the increased number of infection types for the underweight group, such as lower respiratory tract infection and septicemia, are more life-threatening, resulting in a negative correlation between BMI and infection-related mortality. Our subgroup analysis also shows that the risk of mortality due to infection is high in those with major systemic diseases, older people (>50 y/o), and those with diabetes mellitus. In those without major systemic diseases, the protective effect of obesity against mortality due to infection disappears. Weight loss in people with chronic disease or the elderly results mostly from muscle wasting or sacropenia, which in turns leads to immune senescence and poor outcomes for infections [58–60]. In Taiwan, the national insurance system only provides free preventive measures such as flu vaccination for elderly and obese people, so underweight people are unprotected. The results of this study show that tailoring this strategy to individual BMI values would save lives and improve the quality of health care.

The strength of this study is its large community-based cohort with a wide range of infections, so the relationship between BMI and rare infections, such as necrotizing fasciitis and osteomyelitis, is verified. Stratified subgroup analyses show that obesity by itself increases the risk of infection even for people who do not have diabetes. The long follow-up and prospective nature also make this study more reliable than studies with other designs such as case–control or retrospective studies. However, the study also has some limitations. A self-reported baseline BMI was used, and dynamic changes in body weight or other parameters over time were not collected. Various covariates were adjusted, but residual confounding factors such as exercise, physical activity, and detailed socioeconomic status must also be considered. There are methods to reduce confounding, such as genome-wide association studies with Mendelian randomization. Although we do not have genetic background information in our database, 2 Mendelian randomization studies have shown findings similar to ours [61, 62]. Body composition and nutritional status were not measured, so wasting subjects in the underweight group were not identified; this may be particularly significant for the elderly group. The healthy volunteer effect may also exist, as the age and gender distribution was slightly different from that of the Taiwanese general population. This study also considered only the first hospitalization; milder infections such as cellulitis and urinary tract infection are treated at outpatient clinics, so the final outcome may be underestimated. We might also have missed occult infection if accompanied by another primary diagnosis at the time of admission, such as pneumonia causing a fall or fracture.

This study determined that obesity increases the risk of hospitalization due to various infections, especially skin and soft tissue infection, osteomyelitis, and necrotizing fasciitis. Obesity also increases the risk of genitourinary infection and intra-abdominal infection, including diverticulitis, liver abscess,

acute cholecystitis, and anal and rectal abscess, but not appendicitis or peritonitis. There was a U-shaped association between BMI, lower respiratory tract infection, all infections, and sepsis. This population-based study shows that BMI and infection-related mortality are inversely correlated. The results of this study have important clinical implications for risk stratification and the prediction of outcomes for patients and show that there is a possibility of novel mechanisms linking BMI to the susceptibility of hosts to different infections.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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