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Association between body mass index and delirium incidence in critically ill patients: a retrospective cohort study based on the MIMIC-IV Database

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ABSTRACT

Objectives Delirium is a form of brain dysfunction with high incidence and is associated with many negative outcomes in the intensive care unit. However, few studies have been large enough to reliably examine the associations between body mass index (BMI) and delirium, especially in critically ill patients. The objective of this study was to investigate the association between BMI and delirium incidence in critically ill patients.

Design A retrospective cohort study.

Setting Data were collected from the Medical Information Mart for Intensive Care-IV V2.0 Database consisting of critically ill participants between 2008 and 2019 at the Beth Israel Deaconess Medical Center in Boston.

Participants A total of 20 193 patients with BMI and delirium records were enrolled in this study and were divided into six groups.

Primary outcome measure Delirium incidence.

Results Generalised linear models and restricted cubic spline analysis were used to estimate the associations between BMI and delirium incidence. A total of 30.81% of the patients (6222 of 20 193) developed delirium in the total cohort. Compared with those in the healthy weight group, the patients in the different groups (underweight, overweight, obesity grade 1, obesity grade 2, obesity grade 3) had different relative risks (RRs): RR=1.10, 95% CI=1.02 to 1.19, p=0.011; RR=0.93, 95% CI=0.88 to 0.97, p=0.003; RR=0.88, 95% CI=0.83 to 0.94, p<0.001; RR=0.94, 95% CI=0.86 to 1.03, p=0.193; RR=1.14, 95% CI=1.03 to 1.25, p=0.010, respectively. For patients with or without adjustment variables, there was an obvious U-shaped relationship between BMI as a continuous variable and delirium incidence.

Conclusion BMI was associated with the incidence of delirium. Our results suggested that a BMI higher or lower than obesity grade 1 rather than the healthy weight in critically ill patients increases the risk of delirium incidence.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study enrolled 20 193 patients, which is a very large sample size for a clinical study of critically ill patients with delirium.
⇒ Generalised linear models, restricted cubic spline and subgroup analyses were used to evaluate the association between body mass index (BMI) and delirium incidence, and BMI was used not only as a categorical variable but also as a continuous variable.
⇒ This was a single-centre retrospective observational study, so it was difficult to avoid selection bias.
⇒ The data selected in the Medical Information Mart for Intensive Care-IV V.2.0 span a long study period; clinical practice is evolving quickly and new management strategies may be implemented during this period.

INTRODUCTION

Delirium is the most common manifestation of brain dysfunction in critically ill patients, with an incidence of 60–80% in mechanically ventilated patients and 20–50% in intensive care unit (ICU) patients with lower severity of illness. The duration of delirium is independently associated with excess death, length of stay (LOS), cost of care and acquired dementia.[1] Based on the Clinical Practice Guidelines, it was proposed that delirium is at the core of the pain, agitation and delirium triangle.[2 3]

13% of people worldwide meet the WHO definition of obesity (body mass index (BMI) ≥30 kg/m²). A substantial body of literature details the impact of obesity on critical illness pathophysiology and management.[4–7] A large epidemiological study recently revealed that BMI had J-shaped associations with overall mortality and the most specific causes of death.[8] In addition, the association between obesity and psychiatric disorders has held the attention of an increasing number of researchers. It has been reported that psychiatric disorders, including depression, anxiety and Alzheimer's disease, are associated with BMI,[9 10] and the mechanisms of these associations have been explored.[11 12] To date, a few studies have begun to pay attention to the

relationship between BMI and delirium incidence in critically ill patients, as delirium is also a form of psychiatric disorder with a high incidence and poor outcomes in critically ill patients. In this retrospective cohort study, we aimed to examine the association between BMI and the incidence of delirium in patients from a large database.

MATERIALS AND METHODS

This was a retrospective cohort study using data extracted from the Medical Information Mart for Intensive Care (MIMIC-IV) V2.0 Database (dataset),[13] which is a large, open, freely available and single-centre database that includes information from more than 50 000 adult patients admitted to the various critical care units at Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) from 2008 to 2019. The personal information included in the database was processed to protect privacy. One author completed the Collaborative Institutional Training Initiative examination (certification number: 36927411) to achieve access to the database for data extraction.

STUDY POPULATION

Patients with recorded information for BMI calculation who were at least 18 years old were included. If there was a repeat admission to the ICU, only the first admission information was used for analysis. The exclusion criteria were as follows: (1) the length of ICU stay was less than 24 hours; (2) the patient's delirium assessment results were missing; (3) the result of delirium assessment was 'UTA' (unable to assess) and (4) the patient's delirium was prior to ICU admission.

DATA EXTRACTION

Data management was performed by using PostgreSQL. Demographic data, vital signs, laboratory values, relevant comorbidities, treatment measures and severity scores within 24 hours were extracted for analysis. The demographic data included age, sex, ethnicity, admission location and insurance type, while the vital signs included mean arterial pressure (MAP), heart rate (HR), respiratory rate, temperature and pulse oxygen saturation (SpO_2). The laboratory values included white blood cell counts (WBCs), haematocrit (HCT), haemoglobin (HGB), platelet counts (PLTs), serum sodium, serum potassium, serum chloride, blood glucose, blood urea nitrogen (BUN), serum creatinine (Scr), partial thromboplastin time (PTT), prothrombin time (PT) and the international normalised ratio (INR). For variable data with multiple measurements, the minimum value within the first 24 hours of SpO_2, HCT and HGB was included for analysis, while the maximum values of the other variables were included in the analysis. Relevant comorbidities, such as congestive heart failure (CHF), chronic pulmonary disease, dementia, cerebrovascular diseases, diabetes, liver diseases and other diseases, were also extracted. Scores reflecting the severity of patient illness, including the Sequential Organ Failure Assessment (SOFA) score,[14] Oxford Acute Severity of Illness Score (OASIS),[15] Acute Physiology Score III (APS III),[16] Simplified Acute Physiology Score II (SAPS II),[17] Glasgow Coma Scale (GCS) and the Systemic Inflammatory Response Syndrome (SIRS),[18] were extracted. Treatment measures including continuous renal replacement therapy (CRRT), invasive mechanical ventilation, vasoactive drugs, cardiotonic drugs, sedation, analgesia, emergency surgery and family communication were also collected. The BMI data, with the BMI defined as the weight (kg)/height (m^2), were extracted from the 'Online Medical Record' table of the MIMIC-IV V.2.0 directly, which was not available in the previous version. Delirium data were extracted from the 'chartevents' table in the 'mimic_icu' module with an item ID of '228332'. The primary outcome was delirium incidence. For normally distributed continuous variables, the missing values were replaced with the mean for the patient group. For skewed distributions related to continuous variables, missing values were replaced with their median. There were no missing dichotomous variables in our study (online supplemental table 1).[19]

DEFINITION OF DELIRIUM INCIDENCE

Delirium is a sudden change in mental state. It is marked by sudden onset of confusion that may come and go. The confusion may include disorientation, decreased consciousness, trouble focusing or difficulty remembering recent events.[20] In the database, delirium was detected by the Confusion Assessment Method for the ICU which is a validated ICU bedside instrument for routine monitoring of delirium. Patients who scored positive for delirium were defined as having at least one positive delirium screening at any time during the ICU stay, while those who scored negative for delirium were defined as having all negative delirium screening results. Delirium was defined as 'UTA' if all the results of the evaluation were recorded as 'UTA' during the ICU stay. The correlation between delirium and critical illness before admission to the ICU and the diagnostic data for delirium cannot be confirmed, so the patients with delirium prior to ICU admission were excluded, which were defined as those whose primary diagnosis in the diagnostic message was delirium-related diagnosis with its 'seq_num' being '1' in the 'diagnoses_icd' table.

STATISTICAL ANALYSIS

The patients were divided into six groups according to BMI: underweight (BMI <18.5 kg/m^2), healthy weight (18.5≤BMI<25 kg/m^2), overweight (25≤BMI<30 kg/m^2), obesity grade 1 (30≤BMI<35 kg/m^2), obesity grade 2 (35≤BMI<40 kg/m^2) and obesity grade 3 (BMI ≥40 kg/m^2).[21] The healthy weight group was used as the reference group. Non-normally distributed data are presented as the median and IQR, and the Kruskal-Wallis test was

used for comparisons between groups. Categorical variables are presented as numbers (percentages) and were tested by the X^2 test or Fisher's exact test between groups. Generalised linear models (GLMs, either Poisson regression with robust variance estimates or log-binomial regression) were used to estimate the association between the BMI levels and delirium incidence, and Poisson regression with robust variance estimates was used if the log-binomial regression did not converge.[22] The results were presented as relative risks (RRs) with 95% CIs.

Considering the reverse causation, and the clinical implications of variables, the final confounders were evaluated using prior knowledge and descriptive statistics from our cohort through the use of directed acyclic graphs (online supplemental figure 1).[2] The confounders were identified and two minimal sufficient adjustment sets for estimating the direct effect of BMI on delirium were derived: (1) age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, paraplegia, creatinine and BUN; (2) age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, renal disease and paraplegia. Covariates were additionally included in the final models if they were strong predictors of the outcome based on previous studies. For the crude model, log-binomial regression was used and only included BMI categories. Model 1 was adjusted for age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, paraplegia, creatinine and BUN based on the crude model. Model 2 was adjusted for age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, renal disease and paraplegia based on the crude model. Model 3 was additionally adjusted for admission location, sepsis, chronic pulmonary disease, scores of severity (APS III, SOFA, GCS), HR, MAP, respiratory rate, temperature, SpO_2, HCT, serum sodium, blood glucose, LOS in the ICU and treatment measures (family communication, fentanyl, invasive ventilation, propofol, midazolam, dexmedetomidine, emergency surgery) based on model 1 which had a smaller Akaike information criterion value than model 2 (online supplemental table 2). The potential non-linear relationships between BMI and delirium incidence were evaluated based on GLM by restricted cubic spline with knots set at 18.5 kg/m², 25 kg/m², 30 kg/m², 35 kg/m² and 40 kg/m². Subgroup analyses were also conducted to determine the consistency of the association between BMI and delirium incidence in critically ill patients. In addition, the potential presence of collinearity was assessed using the variance inflation factor before multivariable regression analysis, and no collinearity was detected (online supplemental tables 3–5). A two-tailed $p \leq 0.05$ was considered statistically significant, while p values were adjusted for multiple testing using Bonferroni correction and a significance level of $\alpha = 0.05$ was applied. Stata/SE V.16.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Patient and public involvement

Patients from MIMIC-IV V2.0 Database and/or the public were not involved in the design, or conduct, or reporting of this research. The results of the research are disseminated to the general public through presentations and press releases.

RESULTS

Selection and baseline characteristics of participants

According to the inclusion criteria, 34 737 critically ill patients were eligible, and 14 544 patients were excluded according to the exclusion criteria: (1) ICU stay <24 hours (n=10 871); (2) missing delirium assessment result (n=3169); (3) delirium assessment result was 'UTA' (n=447) and (4) delirium was prior to ICU admission (n=57). Finally, 20 193 critically ill patients were enrolled in this study (figure 1). The median (IQR) age was 67 (56–77) years, while 55.88% (11 283 of 20 193) of the patients were male, most of whom were of the white race. The underweight, healthy weight, overweight, obesity grade 1, obesity grade 2 and obesity grade 3 groups were comprised of 1533, 7618, 5989, 2983, 1235 and 835 critically ill patients, respectively, and the incidences of delirium in each group were 35.03% (537 of 1533), 31.75% (2419 of 7618), 29.37% (1759 of 5989) 28.06% (837 of 2983), 29.88% (369 of 1235) and 36.05% (301 of 835), respectively. The obesity grade 1 group had the lowest incidence of delirium among the six groups (online supplemental table 6 lists the characteristics of the patients by BMI group).

Analysis of the baseline data between the delirium-positive and delirium-negative groups

The patients were divided into a delirium-positive group and a delirium-negative group according to whether delirium occurred. The overall incidence of delirium in this study was 30.81% (6222 of 20 193). Analysis of the baseline data indicated that BMI was significantly different between the delirium-positive and delirium-negative groups ($p<0.001$). Other variables, including age, ethnicity, insurance type, admission location, temperature, HR, MAP, respiratory rate, SpO_2, WBCs, HCT, HGB, PLTs, PT, INR, PTT, BUN, Scr, serum sodium, serum potassium, blood glucose, CHF, cerebrovascular disease, dementia, chronic pulmonary disease, paraplegia, renal disease, liver disease, diabetes, sepsis, SIRS, SOFA, APS III, SAPS II, OASIS, vasoactive drugs, cardiotonic drugs, propofol, midazolam, dexmedetomidine, fentanyl, CRRT, invasive mechanical ventilation, family communication, ICU mortality and LOS in the ICU, were also significantly different between the delirium-positive and delirium-negative groups ($p \leq 0.05$, online supplemental table 7).

Association between BMI and delirium incidence

GLMs were used to evaluate the associations between BMI and delirium incidence. A crude model of log-binomial regression showed that the underweight and obesity grade 3 groups were associated with an increased risk of delirium incidence (RR=1.10, 95% CI=1.02 to 1.19, p=0.011; RR=1.14, 95% CI=1.03 to 1.25, p=0.010, respectively);

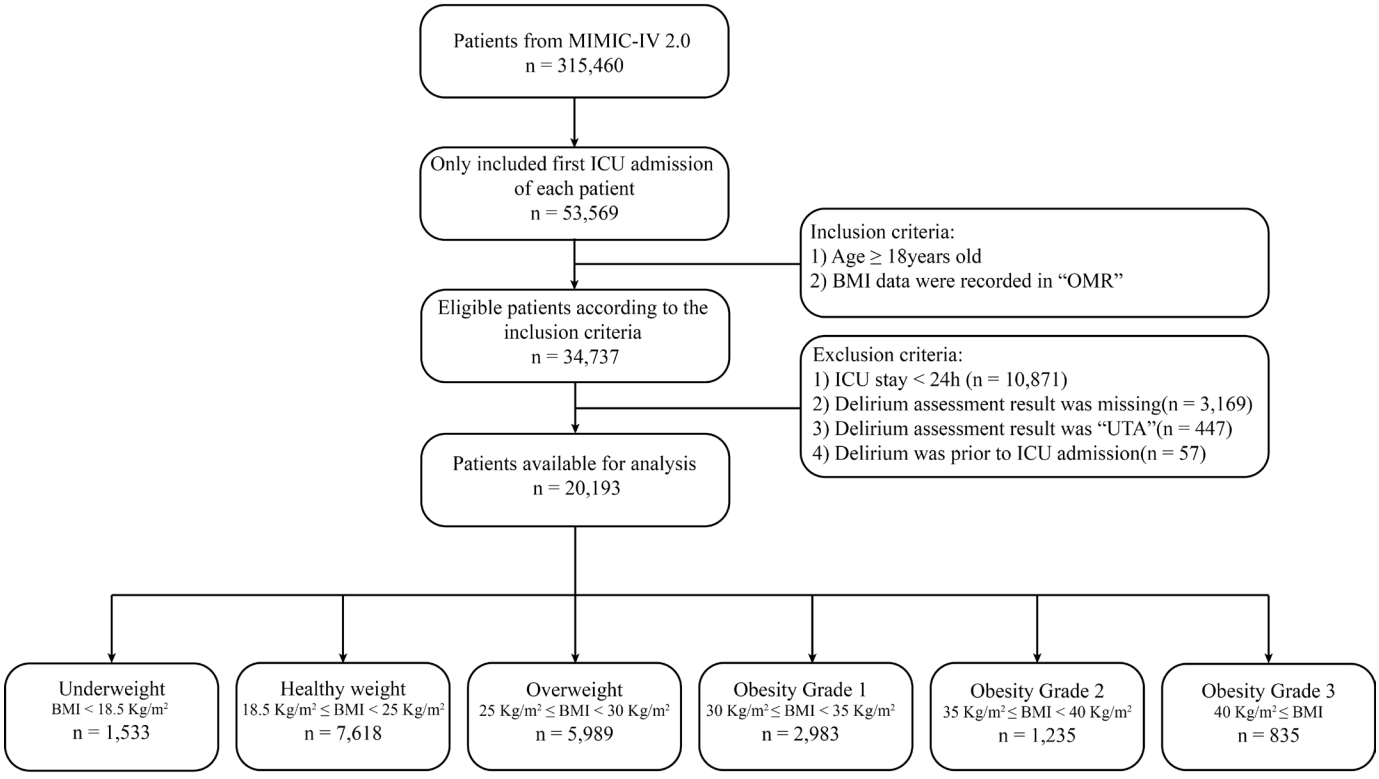

Figure 1 Flow chart of the participant selection. BMI, body mass index; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care-IV; OMR, Online Medical Record; UTA, unable to assess.

however, the overweight and obesity grade 1 groups were associated with a decreased risk of delirium incidence (RR=0.93, 95% CI=0.88 to 0.97, p=0.003; RR=0.88, 95% CI=0.83 to 0.94, p<0.001, respectively). The obesity grade 2 group also had a trend toward a decreased risk of delirium incidence compared with that of the healthy weight group, but the difference was not significant (RR=0.94, 95% CI=0.86 to 1.03, p=0.193). Poisson regression with robust variance estimate was used to perform a multivariate analysis and the results indicated that the critically ill patients in the obesity grade 1 group were prone to have a lower risk of delirium incidence. However, the patients in the underweight and obesity grade 3 groups were prone to suffer a higher risk of delirium incidence, even after adjustment for confounders and covariates (table 1 and figure 2) (further details can be found in online supplemental tables 3–5 and 8).

Analyses of the detailed relationships between BMI and delirium incidence

Restricted cubic splines with five knots were used to visualise the relationship between BMI as a continuous variable and delirium incidence, which showed a U-shaped association. For the crude mode, the risk of delirium incidence decreased until approximately 30.5 kg/m² and then started to increase afterward (p for non-linearity<0.001). However, for model 1 and model 2, the inflection point of BMI for the risk of delirium incidence was approximately 30.4 kg/m² (p for non-linearity<0.001); in model 3, the shape of the curve was still U-shaped, and BMI for the lowest risk of delirium incidence was approximately 31.2 kg/m² (p for non-linearity=0.005). According to the models, the inflection points of BMI for delirium incidence all fell within the range of obesity grade 1 (figure 3).

Subgroup analyses between BMI and delirium incidence

Subgroup analyses were conducted to determine the consistency of the association between BMI and delirium incidence in critically ill patients, which were stratified by age (age ≤65 years and age >65 years), sex (online supplemental figure 2), congestive heart disease, dementia, cerebrovascular disease, chronic pulmonary disease, paraplegia (online supplemental figure 3), sepsis, SOFA (SOFA score ≤4 and SOFA score >4), GCS (GCS score ≤8 and GCS score >8) (online supplemental figure 4) and treatment measures (invasive ventilation, midazolam, emergency surgery) (online supplemental figure 5). The results are shown in table 2. Most of the variables analysed in the subgroup analyses showed the same trend of association between BMI and delirium incidence. There was a significant interaction effect between BMI and sepsis for delirium incidence (p for interaction effect=0.007). Patients without sepsis in the obesity grade 1 group had a significantly lower risk of delirium (RR=0.84, 95% CI=0.73 to 0.97, p<0.05) than did those in the healthy weight group. For the critically ill patients with sepsis, we observed that the group with the lowest incidence of delirium was still the obesity grade 1 group, although there was no significant difference (RR=0.94, 95% CI=0.88 to 1.00, p>0.05).

Table 1 Associations between BMI and delirium incidence

BMI levels	Crude model		Model 1		Model 2		Model 3	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Underweight	1.10 (1.02 to 1.19)	0.011	1.09 (0.99 to 1.20)	0.060	1.10 (1.01 to 1.21)	0.039	1.01 (0.94 to 1.08)	0.838
Healthy weight	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Overweight	0.93 (0.88 to 0.97)	0.003	0.93 (0.88 to 0.99)	0.031	0.93 (0.87 to 0.99)	0.019	0.95 (0.90 to 0.99)	0.021
Obesity grade 1	0.88 (0.83 to 0.94)	<0.001	0.89 (0.82 to 0.96)	0.003	0.89 (0.82 to 0.97)	0.005	0.90 (0.85 to 0.96)	0.001
Obesity grade 2	0.94 (0.86 to 1.03)	0.193	0.97 (0.86 to 1.08)	0.539	0.97 (0.87 to 1.08)	0.577	0.95 (0.88 to 1.03)	0.254
Obesity grade 3	1.14 (1.03 to 1.25)	0.010	1.17 (1.04 to 1.32)	0.011	1.18 (1.05 to 1.33)	0.007	1.01 (0.93 to 1.11)	0.752

Models were derived from generalised linear model (log-binomial or Poisson regression with robust variance estimate). Model 1 was adjusted for age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, paraplegia, creatinine and BUN based on the crude model. Model 2 was adjusted for age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, renal disease and paraplegia based on the crude model. Model 3 was additionally adjusted for admission location, sepsis, chronic pulmonary disease, scores of severity (APS III, SOFA, GCS), HR, MAP, respiratory rate, temperature, SpO_2, HCT, serum sodium, blood glucose, length of stay in ICU and treatment measures (family communication, fentanyl, invasive ventilation, propofol, midazolam, dexmedetomidine, emergency surgery) based on model 1.
APS III, Acute Physiology Score III; BMI, body mass index; BUN, blood urea nitrogen; CHF, congestive heart failure; GCS, Glasgow Coma Scale; HCT, haematocrit; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; RR, relative risk; SOFA, Sequential Organ Failure Assessment; SpO_2, pulse oxygen saturation.

Restricted cubic splines showed that the inflection point of BMI for delirium incidence in patients without sepsis was 34.7 kg/m^2 (p for non-linearity=0.009), while in patients with sepsis, the inflection point was 30.6 kg/m^2 (p for non-linearity=0.334) (figure 4A,B).

DISCUSSION

In this study, we estimated GLM with log-binomial or Poisson regression with robust variance to assess the association between BMI and delirium incidence. The results suggested that the patients in the obesity grade 1 group had the lowest incidence of delirium, while the healthy weight group did not. Restricted cubic splines were used to explore the detailed relationship between BMI as a continuous variable and delirium incidence, which showed a nadir of the U-shaped association of BMI with delirium incidence at a BMI between 30 kg/m^2 and 35 kg/m^2. The subgroup analyses for most factors also showed that the patients with the lowest delirium incidence were located in the obesity grade 1 group.

Delirium, a major complication of critical illness that occurs in response to numerous pathophysiological insults, is associated with short-term and long-term adverse outcomes.[23–28] The incidence of delirium in critically ill patients is high, and the delirium prevalence was reported to be 48% in a large, 21-centre, prospective study that included only mechanically ventilated and shock patients, a population that for >15 years had consistently shown delirium rates of approximately 75% using the same methodology.[29] However, the incidence of ICU delirium reported in the previous literature varies greatly because of the population studied. According to epidemiological studies, the incidence of postoperative delirium is approximately 45–50%.[30 31] Another study reported that the incidence of postoperative delirium after intracranial surgery was 19%, ranging from 12% to 26% caused by variation in clinical features and delirium assessment methods,[32] and a systematic review of the incidence of delirium in critically ill patients receiving extracorporeal membrane oxygenation treatment revealed a pooled prevalence rate of 40.79%.[33] In our study, the incidence of delirium was 30.81%, which we considered that our study was not limited by the type of disease, or specific treatments, so the reported incidence of delirium was not consistent with the above literature which could also be explained. Two systematic reviews of critically ill patients with no defined disease type or treatment measures reported that the incidence of delirium was 31.8% and 31%,[34 35] respectively. These findings were consistent with ours. The mechanism of delirium is unclear and is most likely a result of multiple pathways that are affected during critical illness that alter normal cognition. Numerous pathological mechanisms have been proposed, ranging from genetic defects to worsening brain inflammation and poor cerebral blood flow or decreased oxygen supply and neurotransmitter imbalance.[36 37] There are currently two categories of

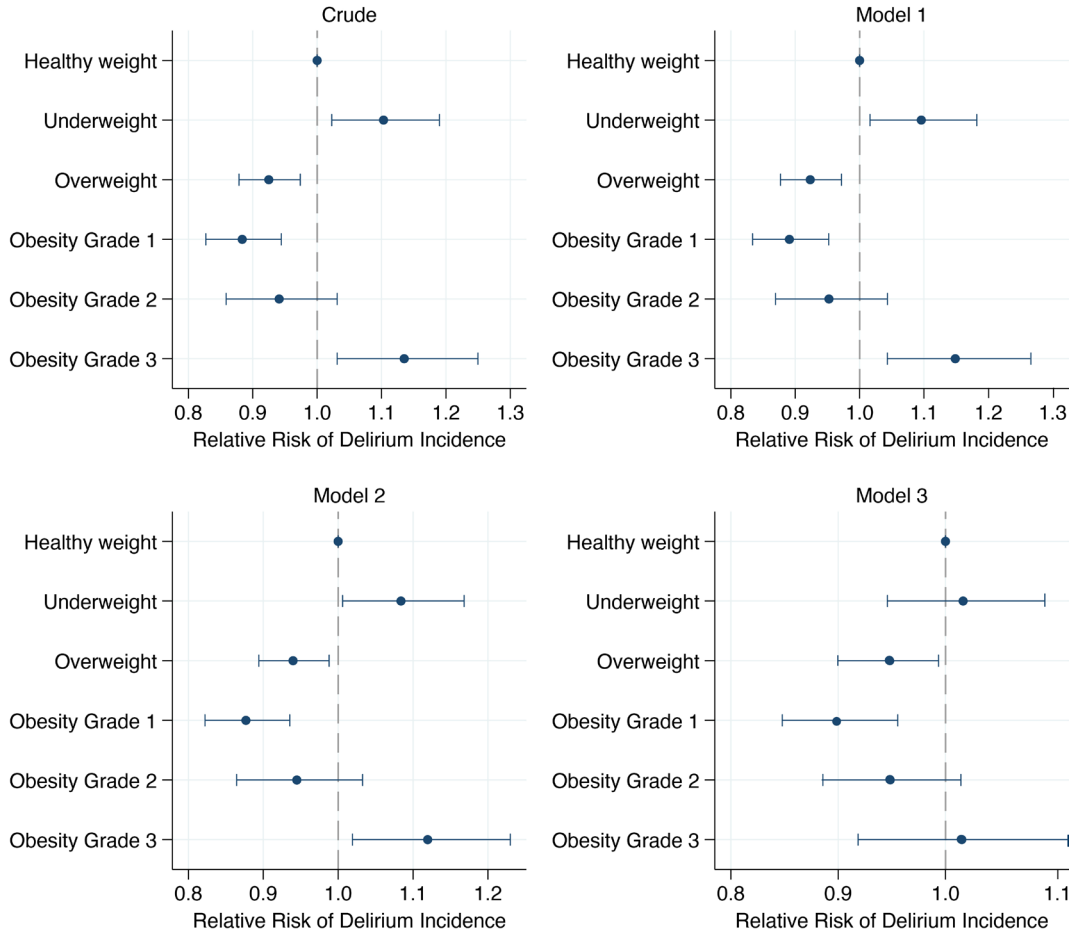

Figure 2 Association between BMI and delirium incidence in critically ill patients. The association between BMI levels and delirium incidence in critically ill patients was based on generalised linear models. For the crude model, log-binomial regression was used and only included BMI categories. Model 1 was adjusted for age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, paraplegia, creatinine and BUN based on the crude model. Model 2 was adjusted for age, sex, ethnicity, CHF, dementia, cerebrovascular disease, liver disease, renal disease and paraplegia based on the crude model. Model 3 was additionally adjusted for admission location, sepsis, chronic pulmonary disease, scores of severity (APS III, SOFA, GCS), HR, MAP, RR, temperature, SpO_2, HCT, serum sodium, blood glucose, length of stay in ICU and treatment measures (family communication, fentanyl, invasive ventilation, propofol, midazolam, dexmedetomidine, emergency surgery) based on model 1. The dashed vertical lines represent the null value (relative risk=1). APS III, Acute Physiology Score III; BMI, body mass index, BUN, blood urea nitrogen; CHF, congestive heart failure; GCS, Glasgow Coma Scale; HCT, haematocrit; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; SpO_2, pulse oxygen saturation.

risk factors for delirium in critically ill patients: 'modifiable'—benzodiazepine use and blood transfusions, and 'non-modifiable'—greater age, dementia, prior coma, pre-ICU emergency surgery or trauma, and increasing Acute Physiology and Chronic Health Evaluation and American Society of Anesthesiologists scores. For all the other potential delirium-associated risk factors, including BMI, the evidence currently remains inconclusive.[2]

A large epidemiological study recently showed that BMI had J-shaped associations with overall mortality and the most specific causes of death,[8] and some recent studies have shown that overweight and moderate obesity were associated with lower mortality compared with a normal BMI.[38–41] Recently, researchers have begun to pay attention to the correlation between body weight and delirium occurrence. A recent study showed that low body weight was an independent risk factor for the occurrence of delirium and obese or overweight status was not associated with delirium.[42] However, in this study, the patients were categorised according to the WHO and Asia-Pacific guidelines: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2) and obese (>25 kg/m^2) and were not further classified according to the severity of obesity. Interestingly, another study showed that a higher BMI mediated the protective effects of BMI on postoperative delirium patients (OR=0.900, 95% CI=0.823 to 0.985, p=0.022). However, this study excluded low weight patients and included only a few obese patients, which could skew the results.[43] Critically ill patients can have excessively high or low body weight. However, information on patients with low body weight is very scarce and has been mostly drawn

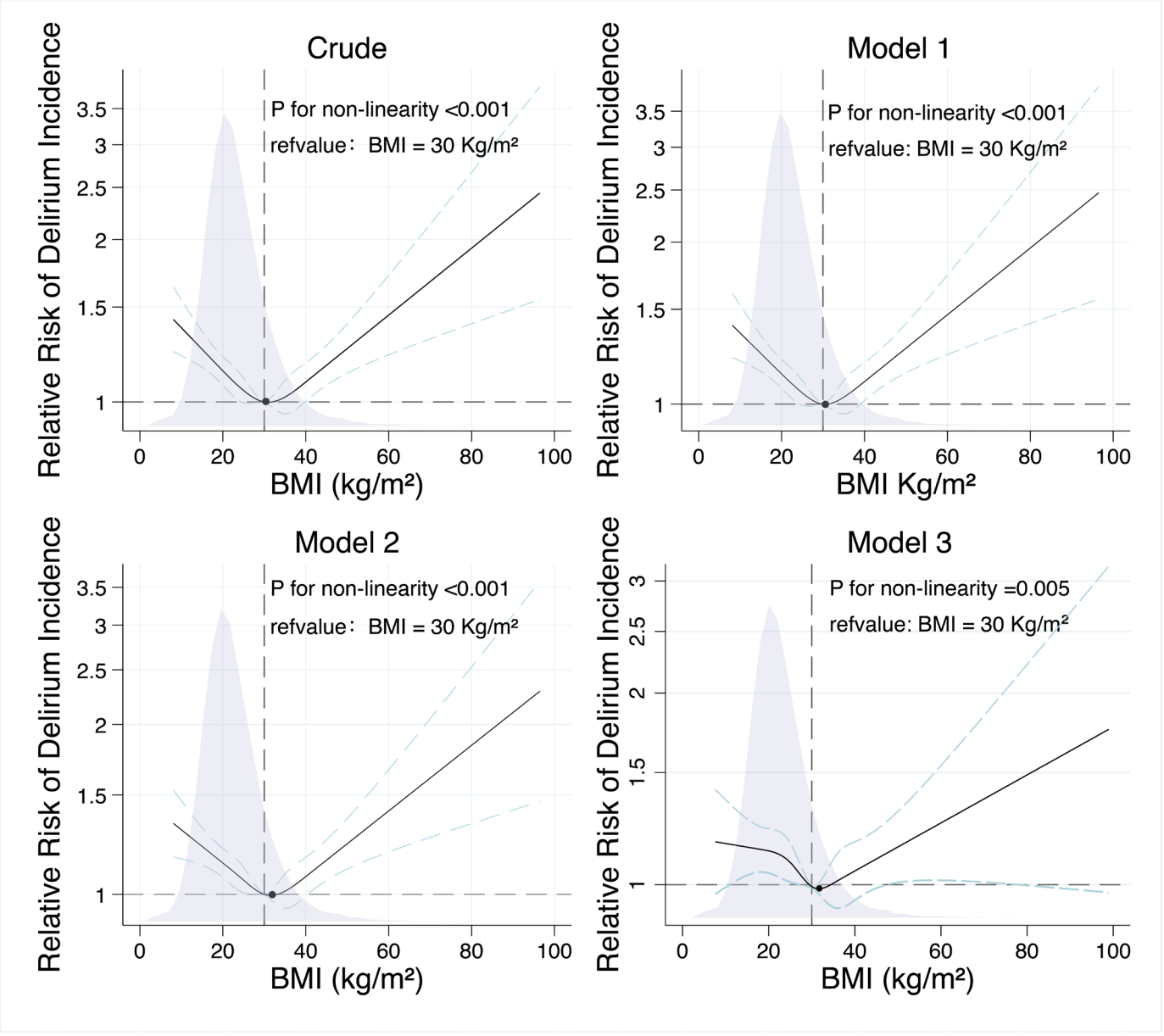

Figure 3 Detailed relationship between BMI and delirium incidence. Association between BMI as a continuous variable and delirium incidence in critically ill patients using restricted cubic splines based on GLM. The dashed vertical lines represent the reference value of 30 kg/m². The dashed horizontal lines represent the null value (RR=1). The black dots were used to represent the inflection point at which the RR of BMI for delirium incidence was lowest (crude model: 30.5 kg/m^2, model 1: 30.4 kg/m^2, model 2: 30.4 kg/m^2, model 3: 31.2 kg/m^2). BMI, body mass index; GLM, generalised linear model; RR, relative risk.

from paediatric patients. Our results showed that underweight and obesity grade 3 groups increased the risk of delirium incidence, while the overweight and obesity grade 1 groups had a decreased risk compared with the healthy weight group. After adjustment for demographic features, vital signs, laboratory examinations, comorbidities, treatment measures and severity scores, the results of the three additional models suggested that the patients in the obesity grade 1 group also had the lowest risk of delirium incidence among the critically ill patients. Restricted cubic splines with five knots were used to visualise the relationship between BMI as a continuous variable and delirium incidence, which showed a U-shaped association. The inflection point fell within the range of obesity grade 1 in all the models, and above or below this point, the incidence of delirium increased.

Sepsis-associated delirium (SAD) is a highly relevant clinical problem: depending on the study, 30–70% of in-hospital patients with sepsis and SIRS develop SAD.[44] Similar to those incidences reported in previous studies, our data showed that the delirium incidence of patients with sepsis was 42.07% (4631 of 11 007). In the subgroup analysis, there was a significant interaction between BMI and sepsis, and restricted cubic splines showed the relationship between BMI and delirium incidence no longer fit the non-linear relationship; however, the lowest

Table 2 Subgroup analyses of the association between BMI and delirium incidence

Variables, n	No of events*	Healthy weight 18.5≤BMI<25 kg/m² Reference group	Underweight BMI <18.5 kg/m² RR (95% CI)	Overweight 25≤BMI<30 kg/m² RR (95% CI)	Obesity grade 1 30≤BMI<35 kg/m² RR (95% CI)	Obesity grade 2 35≤BMI<40 kg/m² RR (95% CI)	Obesity grade 3 BMI ≥40 kg/m² RR (95% CI)	P for interaction value
Age, years								0.993
≤65, 9536	2679	1	1.01 (0.90 to 1.13)	0.96 (0.90 to 1.04)	0.93 (0.85 to 1.01)	0.93 (0.83 to 1.05)	1.03 (0.91 to 1.15)	
>65, 10657	3543	1	1.01 (0.92 to 1.11)	0.94 (0.89 to 1.00)	0.90 (0.83 to 0.98)*	1.00 (0.90 to 1.12)	1.06 (0.93 to 1.21)	
Gender								0.773
Male, 11283	3416	1	1.03 (0.92 to 1.14)	0.94 (0.89 to 1.00)	0.87 (0.81 to 0.95)**	0.94 (0.83 to 1.05)	1.01 (0.88 to 1.15)	
Female, 8910	2806	1	0.99 (0.90 to 1.09)	0.95 (0.88 to 1.02)	0.93 (0.85 to 1.02)	0.97 (0.86 to 1.08)	1.02 (0.91 to 1.14)	
CHF								0.463
Yes, 4838	1613	1	0.98 (0.84 to 1.14)	0.99 (0.91 to 1.09)	0.98 (0.87 to 1.09)	1.08 (0.94 to 1.24)	1.06 (0.91 to 1.24)	
No, 15355	4609	1	1.03 (0.95 to 1.11)	0.94 (0.89 to 0.99)*	0.88 (0.82 to 0.95)**	0.91 (0.83 to 1.01)	1.01 (0.91 to 1.12)	
Dementia								0.463
Yes, 596	383	1	1.10 (0.92 to 1.31)	1.11 (0.96 to 1.27)	0.98 (0.82 to 1.18)	1.32 (1.01 to 1.74)*	1.16 (0.70 to 1.95)	
No, 19597	5839	1	1.00 (0.93 to 1.08)	0.94 (0.90 to 0.99)*	0.91 (0.85 to 0.96)**	0.94 (0.87 to 1.02)	1.01 (0.92 to 1.10)	
Cerebrovascular disease								0.099
Yes, 2404	945	1	1.09 (0.91 to 1.30)	1.06 (0.96 to 1.19)	0.99 (0.86 to 1.15)	0.97 (0.79 to .21)	0.93 (0.71 to 1.22)	
No, 17789	5277	1	0.99 (0.92 to 1.07)	0.92 (0.88 to 0.97)**	0.89 (0.83 to 0.95)***	0.95 (0.87 to 1.03)	1.02 (0.93 to 1.12)	
Paraplegia								0.655
Yes, 617	304	1	0.93 (0.64 to 1.34)	0.98 (0.82 to 1.17)	0.99 (0.79 to 1.24)	0.99 (0.73 to 1.35)	0.96 (0.64 to 1.43)	
No, 19576	5918	1	1.01 (0.94 to 1.08)	0.94 (0.90 to 0.99)*	0.90 (0.84 to 0.95)**	0.96 (0.88 to 1.04)	1.02 (0.93 to 1.11)	
Chronic pulmonary disease								0.069
Yes, 4598	1531	1	1.05 (0.92 to 1.18)	0.91 (0.83 to 1.01)	1.00 (0.89 to 1.12)	1.04 (0.90 to 1.19)	1.03 (0.88 to 1.21)	
No, 15595	4691	1	0.99 (0.91 to 1.08)	0.95 (0.91 to 1.01)	0.87 (0.81 to 0.93)***	0.92 (0.83 to 1.01)	1.01 (0.91 to 1.12)	
Sepsis								0.007

Continued

Table 2 Continued

Variables, n	No of events*	Healthy weight 18.5≤BMI<25 kg/m² Reference group	Underweight BMI <18.5 kg/m² RR (95% CI)	Overweight 25≤BMI<30 kg/m² RR (95% CI)	Obesity grade 1 30≤BMI<35 kg/m² RR (95% CI)	Obesity grade 2 35≤BMI<40 kg/m² RR (95% CI)	Obesity grade 3 BMI ≥40 kg/m² RR (95% CI)	P for interaction value
Yes, 11 007	4631	1	0.97 (0.90 to 1.05)	0.97 (0.92 to 1.01)	0.94 (0.88 to 1.00)	1.01 (0.93 to 1.10)	1.04 (0.95 to 1.14)	
No, 9186	1591	1	1.13 (0.96 to 1.34)	0.94 (0.85 to 1.05)	0.84 (0.73 to 0.97)**	0.81 (0.66 to 1.00)*	0.99 (0.79 to 1.24)	
SOFA score								0.118
≤4, 11 116	2197	1	1.10 (0.97 to 1.25)	0.96 (0.88 to 1.05)	0.94 (0.84 to 1.05)	1.00 (0.86 to 1.16)	1.13 (0.95 to 1.35)	
>4, 9077	4025	1	0.96 (0.88 to 1.04)	0.95 (0.91 to 1.01)	0.88 (0.82 to 0.94)***	0.94 (0.86 to 1.03)	0.99 (0.90 to 1.09)	
Invasive ventilation								0.291
Yes, 6333	2843	1	0.93 (0.85 to 1.03)	0.92 (0.86 to 0.98)	0.90 (0.83 to 0.97)	0.98 (0.88 to 1.09)	1.03 (0.93 to 1.15)	
No, 13 860	3379	1	1.05 (0.95 to 1.16)	0.97 (0.91 to 1.04)	0.92 (0.84 to 1.00)	0.94 (0.83 to 1.06)	1.03 (0.90 to 1.19)	
Emergency surgery								0.114
Yes, 15 113	4618	1	0.97 (0.89 to 1.05)	0.94 (0.89 to 0.99)*	0.88 (0.82 to 0.94)***	0.93 (0.85 to 1.02)	1.04 (0.94 to 1.14)	
No, 5080	1604	1	1.11 (0.98 to 1.26)	0.98 (0.89 to 1.07)	0.98 (0.87 to 1.10)	1.02 (0.87 to 1.20)	0.93 (0.76 to 1.13)	
GCS								0.345
GCS >8, 19 064	5982	1	1.02 (0.95 to 1.10)	0.97 (0.93 to 1.02)	0.93 (0.87 to 0.98)**	0.97 (0.89 to 1.06)	1.02 (0.94 to 1.12)	
GCS ≤8, 589	240	1	0.83 (0.59 to 1.16)	0.93 (0.74 to 1.17)	0.98 (0.76 to 1.26)	1.29 (0.94 to 1.77)	1.16 (0.68 to 1.99)	
Midazolam								0.068
Yes, 3407	1901	1	1.02 (0.93 to 1.13)	1.00 (0.93 to 1.07)	1.02 (0.94 to 1.12)	1.07 (0.95 to 1.20)	1.02 (0.90 to 1.14)	
No, 16 723	4321	1	1.01 (0.92 to 1.11)	0.94 (0.89 to 1.00)*	0.88 (0.82 to 0.95)**	0.93 (0.84 to 1.03)	1.02 (0.91 to 1.15)	

Subgroup analyses based on model 3.
*P<0.05; **p<0.01; ***p<0.001.
*The number of patients with delirium.
BMI, body mass index; CHF, congestive heart failure; GCS, Glasgow Coma Scale; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

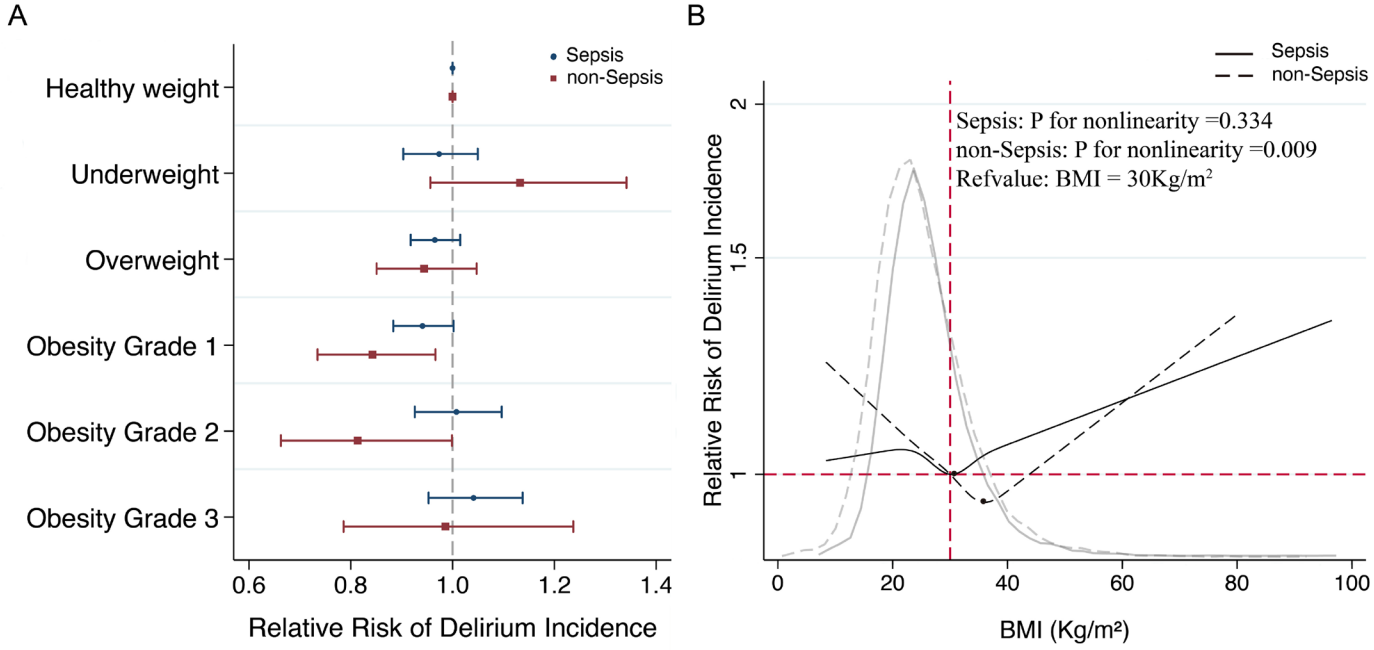

Figure 4 Subgroup analyses of the association between BMI and delirium incidence stratified by sepsis. The subgroup analyses based on model 3. (A) Association between BMI levels and delirium incidence in critically ill patients stratified by sepsis based on generalised linear models (GLMs). The dashed vertical lines represent the null value (RR=1). (B) The detailed relationship between BMI as a continuous variable and delirium incidence stratified by sepsis using restricted cubic splines based on GLM. The dashed vertical lines represent the reference value of 30 kg/m². The dashed horizontal lines represent the null value (RR=1). The black dots were used to represent the inflection point at which the RR of BMI for delirium incidence was lowest (non-sepsis: 34.7 kg/m^2, sepsis: 30.6 kg/m^2). BMI, body mass index; RR, relative risk.

incidence of delirium in patients with or without sepsis still fell in the range of obesity grade 1. The subgroup analysis in our study was a post hoc analysis, and the sample size of some subgroups was small. Therefore, the conclusions from the subgroup analyses still need to be confirmed.

To date, no single pharmacological agent can prevent brain dysfunction in the form of delirium. It is necessary to actively monitor for delirium and pay attention to the details that may put patients at risk of delirium.[2 45] Therefore, it is extremely important to study and recognise various risk factors for delirium to promote early identification and prevention, which is also the original intention and the clinical significance of this study. For these reasons, we conducted this study to investigate the association between BMI and delirium incidence in critically ill patients. We used real-world data containing a large and diverse population. In addition, GLMs (either Poisson regression or log-binomial regression), restricted cubic splines and subgroup analyses were used to evaluate the association between BMI and delirium incidence, and BMI was used not only as a categorical variable but also as a continuous variable.

Our study also has a few limitations. First, this was a single-centre retrospective observational study, so it was difficult to avoid selection bias. Second, although we adjusted for certain factors, our results may have been influenced by other unknown factors. Third, the data selected in this database span a long study period; clinical practice is evolving quickly and new management strategies may be implemented during this period. Fourth, due to the limitations of the database, the MIMIC-IV does not record all variables and variables with missing data are common, and we lack some indicators, such as a history of smoking and drinking. In addition, there are few reports on delirium and BMI in the past; therefore, prospective studies are needed to verify these results.

CONCLUSION

BMI was associated with delirium incidence. Our results suggested that a higher and lower BMI than obesity grade 1 not healthy weight in critically ill patients would increase the risk of delirium, and restricted cubic splines showed a U-shaped association between BMI as a continuous variable and delirium incidence with an inflection point located in the obesity grade 1. BMI could be a predictor for delirium incidence. However, studies involving mechanisms and further prospective studies with multicentre larger sample sizes are needed to confirm our findings.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, Massachusetts) and Beth Israel Deaconess Medical Center (Boston, Massachusetts), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

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