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# Benzodiazepine-associated delirium in critically ill adults

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**Take-home message:** Benzodiazepine administration increases the risk for delirium in critically ill adults, although this association is less pronounced than previously reported and seems to be limited to IV infusion use only.

**Electronic supplementary material**
The online version of this article (doi: 10.1007/s00134-015-4063-z) contains supplementary material, which is available to authorized users.

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**Abstract** *Purpose:* The association between benzodiazepine use and delirium risk in the ICU remains unclear. Prior investigations have failed to account for disease severity prior to delirium onset, competing events that may preclude delirium detection, other important delirium risk factors, and an adequate number of patients receiving continuous midazolam. The aim of this study was to address these limitations and evaluate the association between benzodiazepine exposure and ICU delirium occurrence. *Methods:* In a cohort of consecutive critically ill adults, daily mental status was classified as either awake without delirium, delirium, or coma. In a first-order Markov model, multinomial logistic regression analysis was used, which considered five possible outcomes the next day (i.e., awake without delirium, delirium, coma, ICU discharge, and death) and 16 delirium-related covariables, to quantify the association between benzodiazepine use and delirium occurrence the following day. *Results:* Among 1112 patients, 9867 daily transitions occurred. Benzodiazepine administration in an awake patient without delirium was associated with increased risk of delirium the next day [OR 1.04 (per 5 mg of midazolam equivalent administered) 95 % CI 1.02–1.05). When the method of benzodiazepine administration was incorporated in the model, the odds of transitioning to delirium was higher with benzodiazepines given continuously (OR 1.04, 95 % CI 1.03–1.06) compared to benzodiazepines given intermittently (OR 0.97, 95 % CI 0.88–1.05). *Conclusions:* After addressing potential methodological limitations of prior studies, we confirm that benzodiazepine administration increases the risk for delirium in critically ill adults but this association seems to be limited to continuous infusion use only.

**Keywords** Delirium · Benzodiazepine · Midazolam · Risk · Intensive care

## Introduction

Delirium is common during critical illness and is associated with substantial morbidity both during and after the intensive care unit (ICU) admission [1–3]. Medications are an important modifiable risk factor for delirium in the critically ill [4–7]. Benzodiazepines are frequently administered to maintain patient comfort and safety in the ICU [8]. While a number of investigations have found a positive relationship between benzodiazepine use and delirium occurrence in critically ill adults [9–16], other reports have failed to demonstrate such an association [17–23].

When investigating the relationship between benzodiazepine use and delirium in the ICU, it is important to use time-dependent multivariable analysis methods given that disease severity, benzodiazepine administration, and delirium occurrence frequently oscillate over the course of the ICU stay [24]. Prior studies evaluating the association between benzodiazepine use and delirium failed to consider the time-varying nature of disease severity prior to delirium onset [9–23], performed the delirium assessment only once daily [9, 11–16, 18, 19, 22, 23], had a small proportion of patients on midazolam (an agent used far more commonly than lorazepam) [9, 13, 16, 18–23], assumed that delirium cannot be preceded by coma [11, 12, 14–23], failed to consider that benzodiazepines administered by intermittent versus continuous administration strategies may be associated with different delirium risks [9–23], and did not did not consider competing risks for delirium evaluation such as ICU discharge and death [9–23].

In an effort to address each of these limitations and to evaluate the two daily ICU transitions of greatest interest to clinicians when they are considering the risk for delirium occurrence associated with benzodiazepine use, we sought to determine whether the administration of a benzodiazepine is an independent risk factor for the transition from either an awake state without delirium to delirium or from coma to delirium the next day. Secondly, the association between delirium and continuous intravenous (IV) versus intermittent benzodiazepine use was explored as the indications, and therefore the decision-making process on the part of the ICU prescriber could be different between these two administration strategies [25, 26].

## Methods

### Study design and patients

From January 2011 through June 2013, all consecutive adults admitted for at least 24 h to the 32-bed mixed-ICU of the University Medical Center Utrecht were considered for inclusion. A well-established institutional protocol was in place throughout the study period that advocated targeting of sedation to a light level, daily sedation interruption, and assessment of all patients for delirium at least twice daily using the CAM-ICU [27]. Patients with an acute neurological disease or other disorders precluding delirium assessment were excluded. The local institutional review board waived the need for informed consent (IRB #010/056/c and #12/421/c) given the non-interventional nature of the investigation.

### Mental status classification and outcome

For each day in the ICU, the mental status of each patient was assessed by a study investigator using a previously published, validated protocol [28]. In short, patient wakefulness was evaluated every 3 h using the Richmond Agitation and Sedation Scale (RASS) with a RASS $\leq 4$ denoting coma [29]. The presence of delirium during each 24-h period was determined when the patient was maximally awake (e.g., after daily sedation interruption) using a previously validated, five-step algorithm (interobserver agreement 0.94–0.97, sensitivity 0.85, specificity 0.85) [28]. This algorithm also incorporated a review by a study investigator of all CAM-ICU scores documented by the bedside nurse, whether a treatment for delirium had been initiated by the ICU physician, a chart review, and an additional CAM-ICU assessment by the investigator for any patient not yet classified using the prior steps [28]. Given that a single CAM-ICU assessment by the bedside nurse is highly predictive of delirium, patients were classified as delirious at any time in the prior 24 h when one CAM-ICU assessment was positive [30]. The additional steps in the delirium recognition algorithm used for the study were present to minimize the risk of misclassification bias.

The mental status for each patient on a certain day of the ICU admission (day $t$) was then classified as (1) awake without delirium, (2) delirium, or (3) coma. For the outcome the next day (day $t + 1$), ICU discharge and death were added, resulting in five possible outcome categories. While the daily transitions from "awake without delirium" to "delirium" and from "coma" to "delirium" served as the transitions of interest in the analysis, all potential daily mental status transitions were concomitantly modeled (Online Data Supplement Fig. E1).

### Data collection and definitions

Medication data, including dose, route, and time of administration, were retrieved from the electronic patient data management system. All administered benzodiazepines were converted into equivalent doses of midazolam (MDZE) (Online Data Supplement Table E1).

The dose of any benzodiazepine administered via the enteral route was reduced by 50 % given the reduced bioavailability associated with this route of administration in critically ill patients [31].

Demographics, the presence of comorbidities, ICU admission characteristics, and daily physiological measurements and vital signs were prospectively collected by trained physicians. Daily severity of disease was assessed using the modified Sequential Organ Failure Assessment (mSOFA) that excludes the neurological component to avoid adjusting for a component of the primary outcome [32]. A trend imputation for missing covariables was performed because of the availability of longitudinal data prior and following each observation day [33].

### Statistical methods

Within a first-order Markov model, multinomial logistic regression was used. Discharged alive from the ICU [971/9867 (10 %)] and death [144/9867 (1 %)] were combined into one category given that each represented few of the total daily transitions and neither was the outcome of interest [34]. The primary exposure to benzodiazepines was modeled using an interaction term of benzodiazepines per 5 mg MDZE on day $t$ and the mental status on day $t$. In a second model, differentiating between the method of benzodiazepine administration [i.e., intermittent (either oral or IV) or continuous IV infusion], the exposure to benzodiazepines was modeled using two non-mutually exclusive (given that intermittent and continuous administration could both occur on the same day) interaction terms: (1) benzodiazepine per 5 mg MDZE on day $t$ administered intermittently and the mental status on day $t$ and (2) benzodiazepine per 5 mg MDZE on day $t$ administered by continuous infusion and the mental status on day $t$.

A thorough review of the literature was conducted to identify covariables that might influence the presence of delirium, the use of a benzodiazepine or its resulting pharmacodynamic response [4, 15, 35–37]. Only covariables with an absolute prevalence of at least 10 % were eligible for inclusion into the multivariable analysis. In total, eight variables measured at ICU admission and eight time-varying variables measured daily were included in the model (Online Data Supplement Table E2). Three planned sensitivity analyses were performed for the transition from "awake without delirium" to "delirium". First, to account for any benzodiazepine use to treat early symptoms of delirium on the day before it was diagnosed, and the fact that disease severity often increases after delirium onset (i.e., reverse causation), we used benzodiazepine exposure and mSOFA on day $t - 1$ instead of day $t$ to explore the association of benzodiazepine use with delirium on day $t + 1$ [38]. To account for a possible carry-over effect of benzodiazepine therapy beyond the first-order Markov assumption (i.e., that the probability of an observation at day $t + 1$ only depends on the observation at day $t$), in a second sensitivity analysis, we included only the days until delirium, ICU discharge, or death on day $t + 1$ (whichever occurred first). To explore whether the relationship between benzodiazepine exposure and delirium is one that primarily affects older adults, we conducted a third sensitivity analysis between younger (below 65 years) and older (at least 65 years) adults.

SPSS 20 (IBM, New York, USA) and R 3.0.1 (http://www.r-project.org) were used to perform the statistical analysis. All statistical tests were performed against two-sided alternatives and $p$ values less than 0.05 were defined as statistically significant.

## Results

### Patients and observation days

Among 2669 patients admitted to the ICU during the study period, 1112 were included in the analysis (Fig. 1). These patients were mostly male (60 %), had an average age of 60 years (standard deviation (SD) 16), ICU admission Acute Physiology and Chronic Health Evaluation (APACHE) IV score of 74 (SD 28), and a median [interquartile range, IQR] mSOFA of 7 [4–10] (Table 1). While the number of observation days ($n = 9867$) where

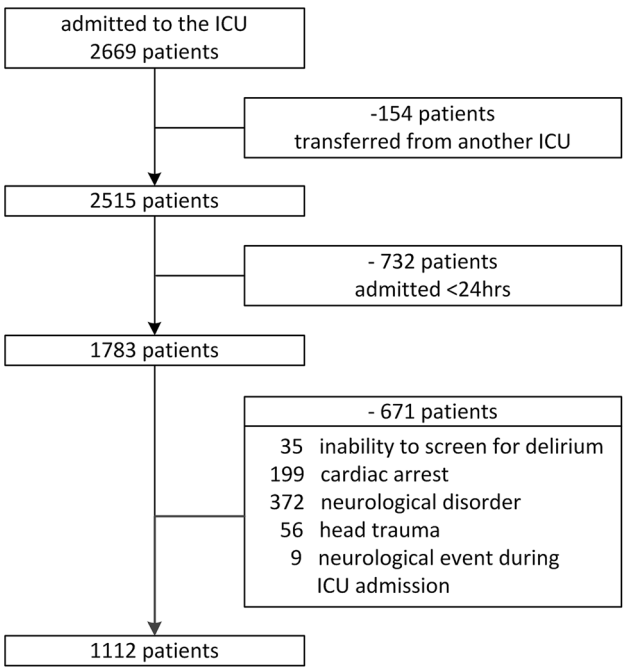


**Fig. 1** Flowchart of patient inclusion. *hrs* hours, *ICU* intensive care unit

**Table 1** Characteristics of study population ($n = 1112$)

| | |
|---|---|
| Age, mean (SD) | 60 (16) |
| Male, *n* (%) | 672 (60) |
| Charlson comorbidity index, median (IQR) | 6 (0–10) |
| Body mass index, mean (SD) | 26 (6) |
| Psychoactive medication, *n* (%) | 212 (19) |
| Smoking, *n* (%) | 90 (8) |
| Alcohol consumption, *n* (%) | 45 (4) |
| Dementia, *n* (%) | 4 (0.4) |
| Hypertension, *n* (%) | 384 (35) |
| Planned admission, *n* (%) | 322 (29) |
| Admission category | |
| Medical, *n* (%) | 493 (44) |
| Surgical, *n* (%) | 544 (49) |
| Trauma, *n* (%) | 75 (7) |
| APACHE IV score, mean (SD) | 74 (28) |
| Length of ICU stay (days), median (IQR) | 5 (2–10) |
| Maximum mSOFA, median (IQR) | 7 (4–10) |
| Mechanical ventilation required, *n* (%) | 1034 (93) |
| Delirium during ICU stay, *n* (%) | 535 (48) |
| Benzodiazepine use during ICU stay, *n* (%) | 814 (73) |
| Days of benzodiazepine use during ICU stay, median (IQR)[a] | 3 (1–6) |

*APACHE* Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *IQR* interquartile range, *mSOFA* modified Sequential Organ Failure Assessment, *SD* standard deviation

[a] Among the 814 patients exposed to a benzodiazepine

no RASS score was documented were very low [$n = 27$ (0.27 %)], the days where a RASS score was recorded six or more times (at least 4 h apart) was very high [$n = 8775$ (89 %)].

Delirium occurred in 538 (48 %) of the 1112 patients and was present on 2672 (27 %) of the 9867 observation days (Table 2). Patients were exposed to a benzodiazepine on 48 % of the observation days with a median daily MDZE dose of 7 (IQR 3–66) mg. On the days a benzodiazepine was administered, midazolam (53 %) and oxazepam (28 %) use were common; lorazepam use was rare (1 %).

### Risk of transitioning to delirium and benzodiazepine administration

Among the 5299 (53.7 %) observation days patients were awake without delirium, 562 (11 %) transitions to delirium occurred the next day. Of the 1896 (19.2 %) observation days patients had coma, a transition to delirium occurred 255 (13 %) times. In the primary analysis, the odds ratio (OR) of the transition from awake without delirium towards delirium was 1.04 (95 % confidence interval (CI) 1.03–1.06) per 5 mg MDZE administered (Table 3).

The method by which benzodiazepines were administered affected the odds of transitioning to delirium. When administered as a continuous IV infusion to an ICU patient who was awake without delirium, the odds for delirium the next day (for every 5 mg MDZE administered) was nearly identical to that for all benzodiazepine exposure days (OR 1.04, 95 % CI 1.03–1.06) (Table 3). Administration of benzodiazepine therapy in patients classified as comatose was not associated with delirium the next day with OR 1.00 (0.99–1.01) (Table 3). The absolute risks of delirium the next day (ranging from 0 to 1) with the daily administration of a continuous infusion of IV midazolam, in patients "awake without delirium" or "coma", along with the mean/median values for all covariables, are presented in Fig. 2 and Online Data Supplement Fig. E2, respectively. Intermittent administration of a benzodiazepine was not associated with delirium the following day (OR 0.97, 95 % CI 0.88–1.05).

Overall, benzodiazepine administration was not associated with an increased risk for a transition to delirium 2 days after the benzodiazepine exposure (OR 1.00, 95 % CI 0.99–1.02) unless the benzodiazepine had been continuously infused (OR 1.02, 95 % 1.00–1.03) (Online Data Supplement Table E3). With the inclusion of only the daily transitions until the first day of delirium, ICU discharge or death (885 patients, 3616 observation days), the findings were similar when compared to the primary analysis with an OR for benzodiazepine administration of 1.03 (95% CI 1.02–1.05), an OR for bolus administration of 1.04 (95% CI 0.92–1.17), and an OR for continuously infused administration of 1.03, (95% CI 1.01–1.05) (Online Data Supplement Table E3). The risk for a transition to delirium was similar between younger and older adults (Online Data Supplement Table E4).

## Discussion

This investigation, by considering the multiple methodological concerns of prior analyses on this topic, provides clinicians with a more accurate estimate of the risk of delirium occurrence in critically ill adults in relation to benzodiazepine use. As little as a daily dose of 5 mg of midazolam administered to a patient who is both coma- and delirium-free will increase the odds that this patient will develop delirium the next day by 4 %.

The fact that the risk we report is less strong than previously reported by Pandharipande et al. is primarily a reflection of the trend over the past decade to reduce benzodiazepine dosing in an effort to promote patient wakefulness [4, 9]. The administration of benzodiazepines in patients who are comatose was not associated with an increased risk of delirium the next day. Given an increased risk for delirium with continuous benzodiazepine use clinicians should employ strategies known to reduce the daily amount of benzodiazepine administered and convert patients when possible to an intermittent administration regimen [4, 25, 26]. In a patient deemed to

**Table 2** Characteristics of individual ICU days ($n = 9867$) by mental status category

| Characteristic on day $t$ | All ICU patient days ($n = 9867$) | Mental status day $t$ | | |
|---|---|---|---|---|
| | | Awake without delirium ($n = 5299$) | Delirium ($n = 2672$) | Coma ($n = 1896$) |
| Characteristics of benzodiazepine use | | | | |
| Use of any benzodiazepine, *n* (%) | 4716 (48) | 2253 (43) | 1241 (46) | 1222 (64) |
| Dose (if any) in mg, median (IQR)[a] | 6.9 (2.5–65.9) | 3.8 (1.9–8.3) | 6.4 (3.0–29.9) | 125.0 (33.3–254.8) |
| Use of midazolam, *n* (%)[b] | 2513 (53) | 646 (29) | 687 (55) | 1180 (97) |
| Other benzozodiazepine, *n* (%)[b] | 2574 (55) | 1772 (79) | 710 (57) | 92 (8) |
| Use of oxazepam, *n* (%)[b] | 1323 (28) | 857 (38) | 395 (32) | 71 (6) |
| Use of lorazepam, *n* (%)[b] | 55 (1) | 37 (2) | 14 (1) | 4 (0.3) |
| Use of an intermittent benzodiazepine, *n* (%) | 4009 (41) | 2122 (40) | 1129 (42) | 758 (40) |
| Dose (if any) in mg, median (IQR)[a] | 4.1 (1.9–8.3) | 3.5 (1.9–6.6) | 5.0 (2.0–9.9) | 7.5 (4.6–14.0) |
| Use of a continuous IV benzodiazepine, *n* (%) | 1904 (19) | 366 (7) | 443 (17) | 1095 (58) |
| Dose (if any) in mg, median (IQR)[a] | 99.0 (29.4–212.0) | 50.0 (16.2–111.7) | 50.2 (17.8–120.0) | 142.7 (60.0–268.5) |
| Characteristics of covariables | | | | |
| mSOFA, median (IQR) | 5 (3–7) | 3 (2–6) | 5 (3–8) | 8 (6–11) |
| Metabolic acidosis, *n* (%) | 1354 (14) | 522 (10) | 290 (11) | 542 (29) |
| Severe sepsis or septic shock, *n* (%) | 2458 (25) | 674 (13) | 822 (31) | 962 (51) |
| Use of mechanical ventilation, *n* (%) | 7706 (78) | 3738 (71) | 2162 (81) | 1806 (95) |
| Use of propofol, *n* (%) | 1312 (13) | 518 (10) | 367 (14) | 427 (23) |
| Use of an opioid(s), *n* (%) | 4686 (47) | 2048 (39) | 1296 (49) | 1342 (71) |
| Use of an alpha-2-agonist, *n* (%) | 1072 (11) | 359 (7) | 521 (19) | 192 (10) |

*ICU* intensive care unit, *IQR* interquartile range, *mg* milligrams, *mSOFA* modified Sequential Organ Failure Assessment (without central nervous component)

[a] In midazolam equivalents

[b] Use of benzodiazepine on day $t$ is not mutually exclusive; percentages do not add up to 100 %

**Table 3** Multinomial model on transitions of daily mental status conditional on benzodiazepine exposure

| Mental status | | Exposure | Adjusted odds ratio[a,b,c] | $p$ value |
|---|---|---|---|---|
| Day $t$ | Day $t + 1$ | | | |
| Awake without delirium | Awake without delirium | No | Reference | |
| Awake without delirium | Delirium | Yes[d] | 1.04 (1.02–1.05) | <0.001 |
| Awake without delirium | Delirium | Bolus[e] | 0.97 (0.88–1.05) | 0.44 |
| Awake without delirium | Delirium | Continuous[e] | 1.04 (1.03–1.06) | <0.001 |
| Coma | Delirium | Yes[d] | 1.00 (0.99–1.01) | 0.90 |
| Coma | Delirium | Bolus[e] | 1.07 (0.95–1.20) | 0.27 |
| Coma | Delirium | Continuous[e] | 1.00 (0.99–1.01) | 0.56 |

[a] Per 5 mg midazolam equivalents

[b] Adjusted for time-fixed covariables: admission category (medical, surgical, trauma), age, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, body mass index, Charlson comorbidity index, hypertension, elective admission (vs. emergency admission), use of a psychoactive medication(s) prior to hospital admission

[c] Adjusted for time-varying covariables on day $t$: day of ICU admission, metabolic acidosis, modified Sequential Organ Failure Assessment score (without neurological component), presence of severe sepsis or septic shock, use of mechanical ventilation, use of an alpha-2-agonist, use of an opioid, use of propofol

[d] Model 1 with interaction between mental status on day $t$ and benzodiazepine administration per 5 mg midazolam equivalent

[e] Model 2 with interaction term between mental status on day $t$ and benzodiazepine administration per 5 mg midazolam equivalent administered as (1) boluses and (2) continuous infusion

require continuous sedation, clinicians should consider non-benzodiazepine sedatives not strongly associated with delirium (e.g., dexmedetomidine, propofol) [39–42]. Even intermittent benzodiazepine therapy is not without risk and is associated with a greater duration of mechanical ventilation than with propofol [43].

There are unique and novel aspects of our analysis. The size of our cohort is the largest evaluated to date (1112 critically ill adults were evaluated over 9786 ICU days), a large proportion of patients were exposed to midazolam (the most commonly used benzodiazepine in the ICU), the daily mental status of each patient was classified using a validated delirium assessment protocol that evaluated all patients at least twice daily, benzodiazepine exposure was dichotomized between intermittent only and continuous IV

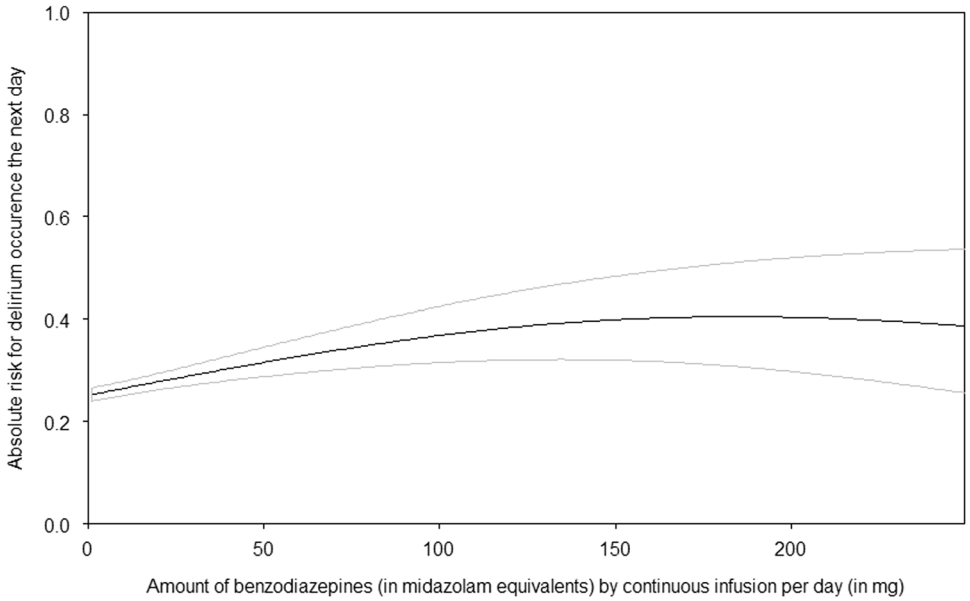


**Fig. 2** Continuous infusion of benzodiazepines and the risk for delirium the next day. Among patients awake and without delirium with mean/median values for all other covariables, the absolute risk is plotted for delirium occurring the next day (*y-axis*) conditional on continuously infused IV benzodiazepine (*x-axis*). The 95 % confidence interval is plotted in *gray*

administration strategies, the time-varying nature of both disease severity and delirium were considered, all possible competing events for delirium (i.e., coma, ICU discharge, and death) were incorporated, and 16 different delirium covariables (eight of which were time-dependent) were included in the model. Moreover, using sensitivity analyses, we carefully investigated the role of factors that could have affected the risk of delirium other than the use of benzodiazepines. Neither reverse causation nor a benzodiazepine carry-over effect was found to influence delirium risk. It should be noted, however, that ruling out either of these effects completely would require far more frequent mental status evaluations on an around-the-clock basis.

Our analysis has several potential limitations. Results from a single-center analysis may not be generalizable to centers having patients with differing underlying risk factors for delirium (e.g., severity of illness) or where the use of strategies to reduce delirium (e.g., early mobilization) differ [4, 44]. That said, the case-mix of patients and sedative use patterns in our cohort are similar to that of other studies in this field [45, 46]. Unlike other published analyses, the proportion of benzodiazepine use accounted for by midazolam was high [9, 13, 18–23]. When replicating our primary analysis on only midazolam exposure (instead of all benzodiazepine exposure) our results were nearly identical to our primary results: (OR 1.04, 95 % CI 1.03–1.05) for all benzodiazepine use. Within the first-order Markov model, correlations within patient observations were ignored and thus the probability of a daily transition was assumed to be independent of the patient history beyond the prior day (Markov assumption). With many patients administered continuous benzodiazepine therapy also receiving intermittent therapy on the same day, the risks for a daily transition to delirium reported for each administration method are mutually exclusive and thus the odds reported cannot be compared.

While a recently published systematic review of the published literature was used to generate many of the covariables included in the multivariable analyses, it is possible, as in any observational study, that other unmeasured covariables could have influenced the results reported [35]. Some of the factors with the potential to affect the pharmacodynamic properties of midazolam (e.g., acute renal failure) were not included [31]. The low number of patients in our cohort with a history of chronic alcohol use or dementia (both proven risk factors for ICU delirium) did not allow us to include these variables in our model. Assuming patients with chronic alcohol use might be administered a higher daily benzodiazepine dose, the inclusion of this variable in our model could have altered the degree of risk reported but not the direction of association described given that the daily dose of benzodiazepine administered was also considered. A marker of acute systematic inflammation (e.g., C reactive protein) was not able to be included in our model despite the correlation between acute inflammation and delirium [2, 4, 16]. Although mental status classification over the 24-h period minimized the risk for misclassification, and patients were routinely evaluated for delirium when maximally awake, some of the delirium detected in the cohort may have been rapidly reversible and potentially not clinically relevant [47]. While it is possible that patients with delirium may have been missed during the CAM-ICU assessment, the use of a validated delirium recognition algorithm that advocated frequent CAM-ICU assessment and incorporated additional criteria to define delirium makes this unlikely [28, 30].

In conclusion, after addressing a number of potential methodological limitations from previously published investigations in this area, our paper confirms that benzodiazepine administration, especially via continuous infusion, in patients awake and without delirium increases the risk for delirium in critically ill adults and should therefore be used with caution.

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**Compliance with ethical standards**

**Conflicts of interest** None of the authors have potential conflicts of interest regarding this manuscript.

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