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Supplementary appendix

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Clinical Phenotypes of Delirium during Critical Illness:

Epidemiology and Relevance to Long-Term Cognitive Impairment

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Methods Supplement

Study Design and Population

We included adults (≥18 years of age) managed in a medical/surgical ICU with respiratory failure and/or septic or cardiogenic shock unless they met one or more exclusion criteria. We defined respiratory failure and shock as organ dysfunction leading to treatment with any of the following: invasive mechanical ventilation, noninvasive positive pressure ventilation, continuous positive airway pressure, supplemental oxygen via a nonrebreather mask, nasal cannula delivering heated high-flow oxygen, intra-aortic balloon pump, dopamine ≥ 7·5 mcg/kg/min, dobutamine ≥ 5 mcg/kg/min, norepinephrine ≥ 5 mcg/min, phenylephrine ≥ 75 mcg/min, epinephrine at any dose, milrinone at any dose (if used with another vasopressor), or vasopressin ≥ 0·03 units/min (if used with another vasopressor).

Identification of Sepsis

We determined whether sepsis was present or absent on a daily basis according to the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference criteria, which were the most recent criteria available at the time of our study. Specifically, we considered sepsis present on each day that two or more systemic inflammatory response syndrome (SIRS) criteria were present and evidence of known or suspected infection was documented in the medical record. We identified known or suspected infection via a two-step process. First, we used medication administration records to determine whether one or more antibiotics were given on the day in question. Second, at least one of three board-certified critical care medicine faculty (TDG, PPP, or EWE) reviewed the medical record (including physician notes, medication records, microbiologic and other lab results, and imaging) to make the final adjudication regarding presence/absence of sepsis on that day.

Covariates

Covariates included age, Charlson Comorbidity Index, Short IQCODE, years of education, Framingham stroke risk profile, duration of coma, duration of severe sepsis, number of 15-minute intervals of hypoxemia, mean modified SOFA during the ICU stay, and mean 24-hour doses of sedating medications received in the ICU (including benzodiazepines, opiates, propofol, dexmedetomidine, and haloperidol). We used participant or surrogate interview at the time of enrollment to determine years of education and estimate preexisting cognitive function according to the Short IQCODE, a validated questionnaire that asks the respondent to compare the participant's ability to perform a number of tasks shortly before their current illness vs. 10 years prior to that time. We modified the SOFA by eliminating the neurologic component since acute brain dysfunction was accounted for separately in our analyses.

Statistical Analysis

In all regression models, we transformed doses of sedating medications by using their cube root to reduce the influence of extreme outliers and used restricted cubic splines to allow for nonlinear associations when modeling continuous variables (except for dexmedetomidine and haloperidol

doses, since the number of unique doses in this cohort was too small for splines). Because participants with at least one missing outcome value during long-term follow-up are different in small but potentially meaningful ways from participants with complete outcomes data, we used multiple imputation by predictive mean matching to impute missing risk factor and outcome data in regression modeling. We did not impute outcome data for participants who did not participate in follow-up. We used single imputation to account for missing delirium and coma assessments, which were missing in 3% of hospital days.

In all models, we allowed the association between delirium phenotype and cognitive outcomes to be modified by duration of coma via an interaction term; if the P-value for the global test of significance for an interaction term was >0.20, we removed it from the model for parsimony. We assessed for multicollinearity using variance inflation factors and we verified model assumptions graphically and accounted for correlation amongst observations due to multiple study days from a single participant using Huber-White standard errors.

In addition to the a priori-specified analyses described in the manuscript, we also conducted several post hoc analyses. First, since our definitions of delirium phenotypes were based on clinical judgement rather than preexisting evidence, we repeated our analyses after using alternative definitions of hypoxic delirium and metabolic delirium shown in **table e2**. Second, because certain classes of sedatives may have different effects on cognition than other sedatives, we used separate multiple linear regression models to analyze the associations between the duration of three subtypes of sedative-associated delirium (benzodiazepine-, propofol-, and opioid-associated delirium) and 3- or 12-month RBANS global cognition scores. We did not analyze dexmedetomidine -associated delirium because the drug was used so infrequently in this cohort. Finally, since differential follow-up due to earlier death may confound analyses of long-term cognitive outcomes, we used separate Cox regression models to analyze the association between the duration of each delirium phenotype and 3- or 12-month mortality, adjusting for age, Charlson Comorbidity Index, Short IQCODE, Framingham stroke risk profile, duration of coma, duration of severe sepsis, number of 15-minute intervals of hypoxemia, and mean modified SOFA during the ICU stay.

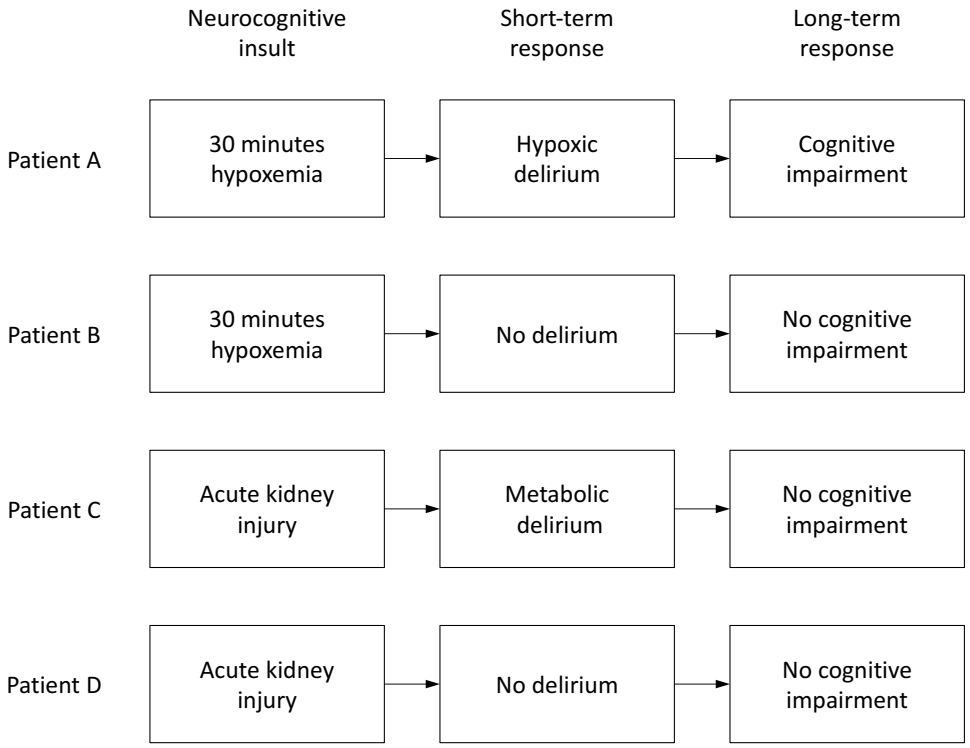

Figure e1: **Conceptual diagram**

This diagram shows theoretical short- and long-term responses to two neurocognitive insults, hypoxemia and acute kidney injury. The scenarios shown here represent two of our a priori hypotheses, namely that hypoxic delirium is associated with long-term cognitive impairment whereas metabolic delirium is not associated with long-term cognitive impairment. Note that patients A and B experienced identical insults but had short-term different responses. By including the insults/risk factors (e.g., duration of hypoxemia and severity of acute kidney injury [captured in the daily SOFA score]) as separate covariates in regression models, we sought to isolate the relationship between a patient's short-term response to an insult (in the form of delirium) and their long-term outcome from the relationship between the insult itself and the long-term outcome.

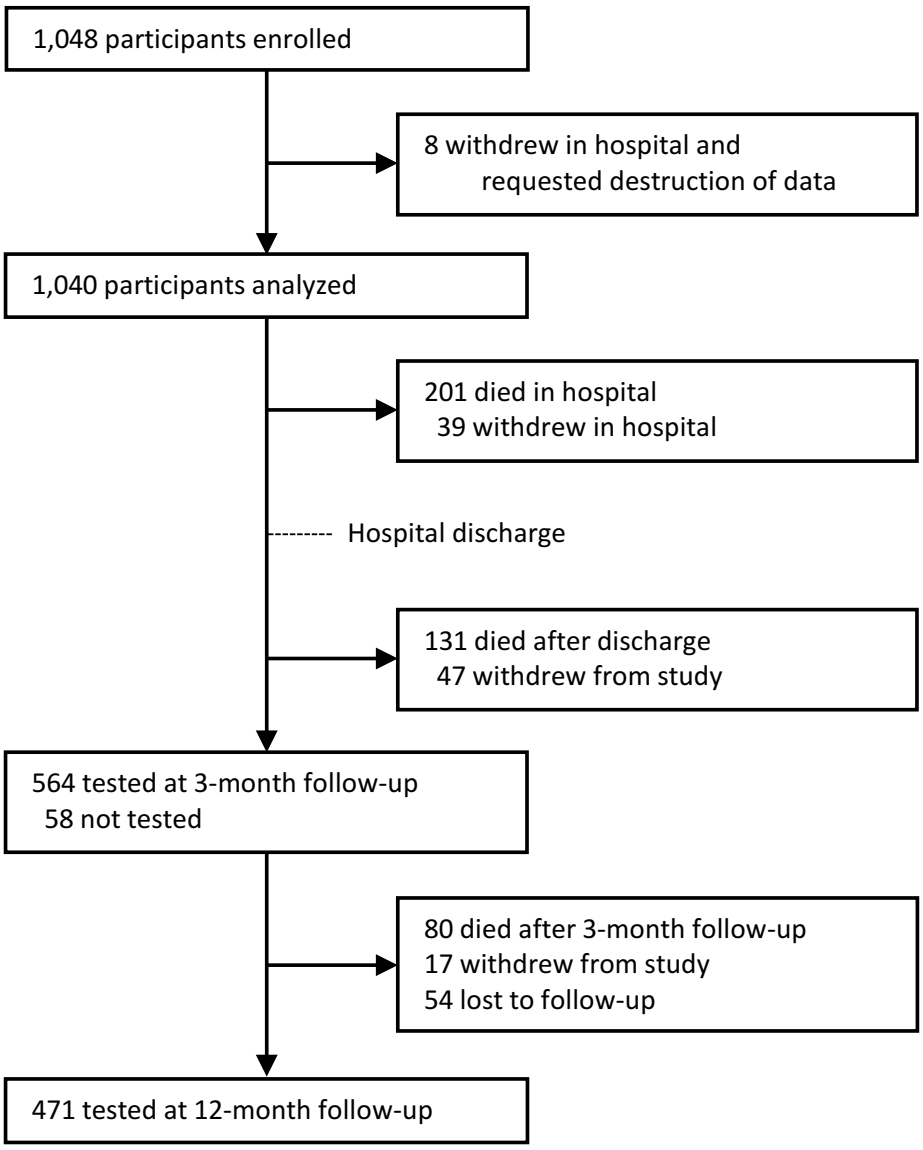

Figure e2: **Participant enrolment and follow up**

Table e1: **Approach to participants with multiple delirium phenotypes**

	Study day													
Delirium	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Any	**													
Hypoxic														
Septic														
Sedative-associated														
Metabolic														
Unclassified														

**Coma precludes assessment for delirium on this study day

For the hypothetical participant shown here, the model analyzing hypoxic delirium would include 2 days for hypoxic delirium, the model analyzing septic delirium would include 5 days for septic delirium, the model analyzing sedative-associated delirium would include 4 days for sedative-associated delirium, and the model analyzing unclassified delirium would include 1 day for unclassified delirium.

Table e2: **Alternative definitions for delirium phenotypes***

Phenotype	Original definitions	Alternative definitions
Hypoxic delirium	SaO_2 < 90% in ≥2 15-min intervals or MAP < 65 mmHg in ≥2 15-min intervals or Lactate > 4·4 mmol/L	SaO_2 < 90% in ≥4 15-min intervals or MAP < 65 mmHg in ≥4 15-min intervals or Lactate > 4·4 mmol/L
Metabolic delirium	BUN > 50 mg/dL or Glucose < 45 mg/dL or INR > 2·5 *and* [AST or ALT] >200 U/L or Sodium < 120 mEq/L or Sodium > 160 mEq/L	BUN > 80 mg/dL or Glucose < 45 mg/dL or INR > 2·5 *and* [AST or ALT] >200 U/L or Sodium < 120 mEq/L or Sodium > 160 mEq/L

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; INR, international normalized ratio

*Every study day that a participant was delirious according to the Confusion Assessment Method for the ICU (CAM-ICU), delirium phenotypes were determined according to the criteria listed above.

Table e3: **Associations between delirium phenotypes and long-term RBANS global cognition scores***

Delirium phenotype	Comparison	RBANS global cognition at 3 months Estimate (95% CI)	RBANS global cognition at 12 months Estimate (95% CI)
Hypoxic	1 vs 0 days	-1·72 (-3·30 to -0·15)	-1·98 (-3·65 to -0·31)
	2 vs 0 days	-3·01 (-5·64 to -0·37)	-3·23 (-6·03 to -0·44)
	3 vs 0 days	-3·85 (-7·07 to -0·64)	-3·76 (-7·16 to -0·37)
	4 vs 0 days	-4·38 (-7·87 to -0·90)	-3·75 (-7·42 to -0·07)
	5 vs 0 days	-4·71 (-8·33 to -1·10)	-3·37 (-7·18 to 0·45)
	6 vs 0 days	-4·96 (-8·72 to -1·20)	-2·80 (-6·78 to 1·18)
	7 vs 0 days	-5·20 (-9·19 to -1·21)	-2·21 (-6·48 to 2·06)
	8 vs 0 days	-5·44 (-9·73 to -1·14)	-1·62 (-6·29 to 3·05)
	9 vs 0 days	-5·68 (-10·33 to -1·02)	-1·03 (-6·18 to 4·13)
	10 vs 0 days	-5·92 (-10·98 to -0·85)	-0·43 (-6·14 to 5·27)
Septic	1 vs 0 days	-1·11 (-2·78 to 0·56)	-3·24 (-6·70 to 0·21)
	2 vs 0 days	-2·00 (-4·80 to 0·80)	-3·80 (-7·02 to -0·57)
	3 vs 0 days	-2·65 (-6·05 to 0·75)	-3·67 (-7·13 to -0·22)
	4 vs 0 days	-3·12 (-6·79 to 0·56)	-3·55 (-7·38 to 0·28)
	5 vs 0 days	-3·45 (-7·28 to 0·39)	-3·42 (-7·38 to 0·53)
	6 vs 0 days	-3·68 (-7·76 to 0·40)	-3·30 (-7·28 to 0·69)
	7 vs 0 days	-3·87 (-8·42 to 0·68)	-3·17 (-7·26 to 0·92)
	8 vs 0 days	-4·05 (-9·28 to 1·18)	-3·04 (-7·34 to 1·25)
	9 vs 0 days	-4·23 (-10·28 to 1·83)	-2·92 (-7·50 to 1·66)
	10 vs 0 days	-4·41 (-11·38 to 2·57)	-2·79 (-7·73 to 2·14)
Sedative-associated	1 vs 0 days	-3·14 (-4·62 to -1·66)	-2·07 (-3·90 to -0·25)
	2 vs 0 days	-5·31 (-7·84 to -2·79)	-3·42 (-6·49 to -0·34)
	3 vs 0 days	-6·52 (-9·66 to -3·37)	-4·03 (-7·80 to -0·26)
	4 vs 0 days	-7·00 (-10·47 to -3·52)	-4·10 (-8·22 to 0·03)
	5 vs 0 days	-6·99 (-10·65 to -3·33)	-3·80 (-8·12 to 0·53)
	6 vs 0 days	-6·75 (-10·57 to -2·93)	-3·32 (-7·87 to 1·24)
	7 vs 0 days	-6·46 (-10·49 to -2·43)	-2·81 (-7·70 to 2·09)
	8 vs 0 days	-6·18 (-10·48 to -1·88)	-2·29 (-7·64 to 3·05)
	9 vs 0 days	-5·89 (-10·51 to -1·28)	-1·78 (-7·66 to 4·10)
	10 vs 0 days	-5·61 (-10·58 to -0·63)	-1·27 (-7·75 to 5·21)
Metabolic	1 vs 0 days	0·05 (-0·51 to 0·60)	0·48 (-0·04 to 1·00)
	2 vs 0 days	0·10 (-1·01 to 1·20)	0·96 (-0·08 to 2·00)
	3 vs 0 days	0·15 (-1·52 to 1·81)	1·44 (-0·12 to 3·01)
	4 vs 0 days	0·19 (-2·02 to 2·41)	1·92 (-0·16 to 4·01)
	5 vs 0 days	0·24 (-2·53 to 3·01)	2·41 (-0·20 to 5·01)
	6 vs 0 days	0·29 (-3·03 to 3·61)	2·89 (-0·24 to 6·01)
	7 vs 0 days	0·34 (-3·54 to 4·21)	3·37 (-0·28 to 7·02)
	8 vs 0 days	0·39 (-4·04 to 4·82)	3·85 (-0·32 to 8·02)

	9 vs 0 days	0·44 (-4·55 to 5·42)	4·33 (-0·36 to 9·02)
	10 vs 0 days	0·49 (-5·05 to 6·02)	4·81 (-0·40 to 10·02)
Unclassified	1 vs 0 days	-1·57 (-2·31 to -0·84)	-1·57 (-2·39 to -0·75)
	2 vs 0 days	-3·15 (-4·62 to -1·67)	-3·14 (-4·77 to -1·50)
	3 vs 0 days	-4·72 (-6·93 to -2·51)	-4·70 (-7·16 to -2·25)
	4 vs 0 days	-6·29 (-9·24 to -3·34)	-6·27 (-9·55 to -3·00)
	5 vs 0 days	-7·86 (-11·55 to -4·18)	-7·84 (-11·93 to -3·74)
	6 vs 0 days	-9·44 (-13·86 to -5·01)	-9·41 (-14·32 to -4·49)
	7 vs 0 days	-11·01 (-16·17 to -5·85)	-10·97 (-16·71 to -5·24)
	8 vs 0 days	-12·58 (-18·48 to -6·68)	-12·54 (-19·09 to -5·99)
	9 vs 0 days	-14·16 (-20·79 to -7·52)	-14·11 (-21·48 to -6·74)
	10 vs 0 days	-15·73 (-23·10 to -8·35)	-15·68 (-23·87 to -7·49)

Abbreviations: CI, confidence interval; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status

*The point estimates indicate the change in RBANS global cognition score associated with the specified increase in the number of days of the delirium phenotype according to a multiple linear regression that adjusted for potential confounders; because delirium phenotypes were allowed to have a nonlinear association with RBANS global cognition to the magnitude of association depends on the comparison chosen. Because unclassified delirium was rare (with more than 75% of participants having 0 days of unclassified delirium), we compared the minimum and the maximum. As an illustrative example to an increase from 0 days to 3 days of sedative-associated delirium (with all other covariates held constant at their median or mode) was associated with a 6·87-point decline in RBANS global cognition scores at 3-month follow-up.

Table e4: **Associations between delirium phenotypes and individual domains of long-term cognition***

Delirium phenotype	Comparison	Outcome	Difference at 3 months Estimate (95% CI)	Difference at 12 months Estimate (95% CI)
Hypoxic	3 vs 0 days	RBANS global cognition	-4·08 (-7·21 to -0·95)	-3·60 (-6·96 to -0·24)
	3 vs 0 days	RBANS immediate memory	-2·94 (-5·54 to -0·34)	-2·69 (-7·26 to 1·88)
	3 vs 0 days	RBANS delayed memory	-5·04 (-9·16 to -0·92)	-2·50 (-7·05 to 2·06)
	3 vs 0 days	RBANS attention	-3·84 (-8·38 to 0·70)	-5·79 (-10·53 to -1·05)
	3 vs 0 days	Trails B	-3·15 (-6·73 to 0·43)	-4·68 (-8·32 to -1·03)
	3 vs 0 days	MMSE	-7·17 (-12·05 to -2·29)	-3·84 (-6·90 to -0·78)
Septic	3 vs 0 days	RBANS global cognition	-2·65 (-6·05 to 0·75)	-3·67 (-7·13 to -0·22)
	3 vs 0 days	RBANS immediate memory	-2·25 (-4·50 to 0·00)	-2·69 (-7·33 to 1·94)
	3 vs 0 days	RBANS delayed memory	-3·77 (-7·60 to 0·05)	-4·30 (-8·77 to 0·16)
	3 vs 0 days	RBANS attention	-2·81 (-4·87 to -0·74)	-1·15 (-3·04 to 0·74)
	3 vs 0 days	Trails B	-1·17 (-4·52 to 2·19)	-2·26 (-3·90 to -0·61)
	3 vs 0 days	MMSE	-1·96 (-7·48 to 3·57)	-4·50 (-6·90 to -2·11)
Sedative-associated	3 vs 0 days	RBANS global cognition	-6·52 (-9·66 to -3·37)	-4·03 (-7·80 to -0·26)
	3 vs 0 days	RBANS immediate memory	-1·99 (-4·50 to 0·51)	-3·23 (-8·19 to 1·74)
	3 vs 0 days	RBANS delayed memory	-8·97 (-13·14 to -4·81)	-5·07 (-9·87 to -0·27)
	3 vs 0 days	RBANS attention	-1·30 (-3·08 to 0·47)	-0·54 (-2·76 to 1·69)
	3 vs 0 days	Trails B	-2·55 (-6·81 to 1·72)	-0·55 (-1·99 to 0·90)
	3 vs 0 days	MMSE	-7·78 (-12·89 to -2·67)	-1·74 (-4·21 to 0·72)
Metabolic	1 vs 0 days	RBANS global cognition	0·05 (-0·51 to 0·60)	0·48 (-0·04 to 1·00)
	1 vs 0 days	RBANS immediate memory	-0·07 (-0·91 to 0·76)	0·13 (-0·59 to 0·85)
	1 vs 0 days	RBANS delayed memory	0·05 (-0·71 to 0·80)	0·43 (-0·33 to 1·20)
	1 vs 0 days	RBANS attention	-0·36 (-1·03 to 0·30)	0·40 (-1·03 to 1·83)
	1 vs 0 days	Trails B	-0·50 (-1·06 to 0·06)	-0·14 (-0·67 to 0·38)
	1 vs 0 days	MMSE	-0·50 (-1·23 to 0·22)	-0·59 (-1·37 to 0·18)
Unclassified	16 vs 0 days	RBANS global cognition	-25·17 (-36·97 to -13·37)	-25·08 (-38·19 to -11·98)
	16 vs 0 days	RBANS immediate memory	-31·08 (-47·88 to -14·28)	-34·28 (-51·22 to -17·34)
	16 vs 0 days	RBANS delayed memory	-30·80 (-46·08 to -15·52)	-40·49 (-58·69 to -22·30)
	16 vs 0 days	RBANS attention	-21·77 (-38·24 to -5·29)	-6·81 (-25·67 to 12·06)
	16 vs 0 days	Trails B	-17·38 (-27·98 to -6·79)	-17·84 (-27·07 to -8·61)
	16 vs 0 days	MMSE	-28·03 (-49·53 to -6·53)	-25·77 (-51·48 to -0·05)

Abbreviations: CI, confidence interval; MMSE, Mini–Mental State Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status

*Each point estimate indicates the change in the specified outcome that was associated with the specified increase in the number of days of the delirium phenotype according to a multiple linear regression model that adjusted for potential confounders; because delirium phenotypes were allowed to have a nonlinear association with RBANS global cognition, the magnitude of association depends on the comparison chosen. For all delirium subtypes except unclassified delirium, we generated point estimates (and confidence intervals) by comparing the 75th to the 25th percentile values of the exposure variable. Because unclassified delirium was rare (with more than 75% of patients having 0 days of unclassified delirium), we compared the minimum and the maximum. As an illustrative example, an increase from 0 days to 3 days of sedative-associated delirium (with all other covariates held constant at their median or mode) was associated with a 6·87-point decline in RBANS global cognition scores at 3-month follow-up.

Table e5: **Associations between delirium phenotypes and long-term cognition using alternative thresholds to define hypoxic delirium and metabolic delirium***

Delirium phenotype	Comparison	RBANS global cognition at 3 months Estimate (95% CI)	RBANS global cognition at 12 months Estimate (95% CI)
Hypoxic delirium			
Original definition	3 vs 0 days	-3·85 (-7·07, -0·64)	-3·76 (-7·16, -0·37)
Alternative definition	3 vs 0 days	-3·34 (-6·54, -0·13)	-1·63 (-5·36, 2·09)
Metabolic delirium			
Original definition	3 vs 0 days	0·15 (-1·52, 1·81)	1·44 (-0·12, 3·01)
Alternative definition	3 vs 0 days	0·43 (-4·14, 5·01)	2·78 (-3·19, 8·75)

Abbreviations: CI, confidence interval; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status

*The point estimates indicate the change in RBANS global cognition score associated with the specified increase in the number of days of the delirium phenotype according to a multiple linear regression model that adjusted for potential confounders; because delirium phenotypes were allowed to have a nonlinear association with RBANS global cognition, the magnitude of association depends on the comparison chosen. For all delirium phenotypes, we generated point estimates by comparing 3 vs 0 days of the exposure variable, chosen because these values represent the 75th to the 25th percentile values of multiple delirium phenotypes (including hypoxic delirium). As an illustrative example, an increase from 0 days to 3 days of hypoxic delirium defined using the original thresholds (with all other covariates held constant at their median or mode) was associated with a 3·85-point decline in RBANS global cognition scores at 3-month follow-up, and an increase from 0 days to 3 days of hypoxic delirium defined using the alternative thresholds was associated with a 3·34-point decline in RBANS global cognition scores at 3-month follow-up.

Table e6: **Associations between sedative-associated delirium and long-term cognition according to class of sedating medication***

Delirium phenotype	Comparison	RBANS global cognition at 3 months Estimate (95% CI)	RBANS global cognition at 12 months Estimate (95% CI)
Any sedative	3 vs 0 days	-6·52 (-9·66 to -3·37)	-4·03 (-7·80 to -0·26)
Benzodiazepine	3 vs 0 days	-3·87 (-7·85 to 0·11)	-2·22 (-6·93 to 2·48)
Opioid	3 vs 0 days	-5·10 (-8·44 to -1·76)	-1·27 (-5·13 to 2·59)
Propofol	3 vs 0 days	-4·83 (-8·40 to -1·26)	-1·75 (-5·83 to 2·32)

Abbreviations: CI, confidence interval; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status

*The point estimates indicate the change in RBANS global cognition score associated with the specified increase in the number of days of the delirium phenotype according to a multiple linear regression that adjusted for potential confounders; because delirium phenotypes were allowed to have a nonlinear association with RBANS global cognition, the magnitude of association depends on the comparison chosen. For all associations shown here, we generated point estimates by comparing 3 vs 0 days of the exposure variable, chosen because these values represent the 75th to the 25th percentile values of sedative-associated delirium (defined as delirium on the same day as receipt of any of the sedating medications studied). As an illustrative example, an increase from 0 days to 3 days of propofol-associated delirium (with all other covariates held constant at their median or mode) was associated with a 4·83-point decline in RBANS global cognition scores at 3-month follow-up.

Table e7: **Sedatives received during days of sedative-associated delirium**

Sedative(s) received	n/total (%)*
Any sedative	2,634/2,634 (100%)
Any benzodiazepine	1,307/2,634 (50%)
Benzodiazepine(s) + opioid(s)	833/2,634 (32%)
Benzodiazepine(s) alone	243/2,634 (9%)
Benzodiazepine(s) + propofol + opioid(s)	112/2,634 (4%)
Other combinations with benzodiazepine (s)	119/2,634 (5%)
Any opioid	2,116/2,634 (80%)
Benzodiazepine(s) + opioid(s)	833/2,634 (32%)
Opioid(s) alone	730/2,634 (28%)
Propofol + opioid(s)	302/2,634 (11%)
Other combinations with opioid(s)	251/2,634 (10%)
Any propofol	672/2,634 (26%)
Propofol + opioid(s)	302/2,634 (11%)
Propofol alone	205/2,634 (8%)
Benzodiazepine(s) + propofol + opioid(s)	112/2,634 (4%)
Other combinations with propofol	53/2,634 (2%)
Any dexmedetomidine	183/2,634 (7%)
Benzodiazepine(s) + opioid(s) + dexmedetomidine	67/2,634 (3%)
Opioid(s) + dexmedetomidine	46/2,634 (2%)
Dexmedetomidine alone	32/2,634 (1%)
Other combinations with dexmedetomidine	38/2,634 (1%)

*Percentages do not sum to 100% since some combinations are listed more than once.

Table e8: **Associations between delirium phenotypes and long-term mortality***

Delirium phenotype	Comparison	3-month mortality HR (95% CI)	12-month mortality HR (95% CI)
Hypoxic	3 vs 0 days	0·94 (0·66 to 1·35)	1·00 (0·74 to 1·36)
Septic	4 vs 0 days	1·19 (0·70 to 2·04)	1·13 (0·72 to 1·76)
Sedative-associated	4 vs 0 days	0·94 (0·64 to 1·38)	0·91 (0·65 to 1·26)
Metabolic	1 vs 0 days	1·03 (0·97 to 1·10)	1·02 (0·98 to 1·07)
Unclassified	16 vs 0 days	3·39 (0·70 to 16·46)	0·96 (0·34 to 2·70)

Abbreviations: CI, confidence interval; HR, hazard ratio

*The hazard ratios indicate the change in hazard of death associated with the specified increase in the number of days of the delirium phenotype according to a Cox regression model that adjusted for age, Charlson Comorbidity Index, Short IQCODE, Framingham stroke risk profile, duration of coma, duration of severe sepsis, number of 15-minute intervals of hypoxemia, and mean modified SOFA during the ICU stay; because delirium phenotypes were allowed to have a nonlinear association with RBANS global cognition, the magnitude of association depends on the comparison chosen. For all delirium subtypes except unclassified delirium, we generated hazard ratios (and confidence intervals) by comparing the 75th to the 25th percentile values of the exposure variable. Because unclassified delirium was rare (with more than 75% of patients having 0 days of unclassified delirium), we compared the minimum and the maximum.