Diabetes and Glucose Dysregulation and Transition to Delirium in ICU Patients

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Objectives: To investigate whether diabetes and glucose dysregulation (hyperglycemia and/or hypoglycemia) are associated with ICU delirium.

Design: Prospective cohort study.

Setting: Thirty-two–bed mixed intensive care in a tertiary care center.

Patients: Critically ill patients admitted to the ICU with transitions of mental status from awake and nondelirious to delirious or remaining awake and nondelirious on the next day. Patients admitted because of a neurologic illness were excluded.

Interventions: None.

Measurements and Main Results: The study population consisted of 2,745 patients with 1,720 transitions from awake and nondelirious to delirious and 11,421 nontransitions remaining awake and nondelirious. Generalized mixed effects models with logit link function were performed to study the association between diabetes mellitus, glucose dysregulation, and delirium, adjusting for potential confounders. Diabetes was not associated with delirium (odds ratio adjusted, 0.93; 95% CI, 0.73–1.18). In all patients, the occurrence of hyperglycemia (odds ratio adjusted, 1.35; 95% CI, 1.15–1.59) and the occurrence of both hyperglycemia and hypoglycemia on the same day (odds ratio adjusted, 1.65; 95% CI, 1.12–2.28) compared with normoglycemia were associated with transition to delirium. Hypoglycemia was not associated with transition to delirium (odds ratio adjusted, 1.86; 95% CI, 0.73–3.71). In patients without diabetes, the occurrence of hyperglycemia (odds ratio adjusted, 1.41; 95% CI, 1.16–1.68) and the occurrence of both hyperglycemia and hypoglycemia on the same day (odds ratio adjusted, 1.87; 95% CI, 1.07–2.89) were associated with transition to delirium. In patients with diabetes, glucose dysregulation was not associated with ICU delirium.

Conclusions: Diabetes mellitus was not associated with the development of ICU delirium. For hypoglycemia, only a nonsignificant odds ratio for ICU delirium could be noted. Hyperglycemia and the occurrence of hyperglycemia and hypoglycemia on the same day were associated with ICU delirium but only in patients without diabetes. Our study supports the institution of measures to prevent glucose dysregulation in nondiabetic ICU patients and contributes to the understanding of the determinants of delirium. (*Crit Care Med* 2018; 46:1444–1449)

Key Words: delirium; diabetes; hyperglycemia; hypoglycemia; intensive care unit patients

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000003285

Delirium is very common in ICU patients with an occurrence rate of more than 50% (1–3). Delirium is associated with serious negative outcomes such as prolonged ICU stay (4), increased healthcare costs (4, 5), and long-term cognitive impairment (6, 7).

Several predisposing and precipitating risk factors contributing to ICU delirium have been reported in previous research with very heterogeneous study designs and strategies to account for potential confounders (8). Gaining more knowledge of risk factors in ICU delirium is of importance to increase our knowledge of the pathophysiology and to identify patients at risk in order to prevent the condition and ultimately improve outcomes.

Diabetes has been linked to cognitive dysfunction, including dementia and Alzheimer disease (9) which may be driven by insulin resistance, altered glucose metabolism, vascular changes, and metabolism of β-amyloid and tau (10). Past studies concerning the association between diabetes and delirium

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were small or retrospective and yielded conflicting results. Hyperglycemia and hypoglycemia have been suggested as precipitating risk factors for ICU delirium, but this was found in studies that were subject to various methodological limitations such as a high risk of selection bias, unclear outcome definitions, retrospective data collection, and conductance in a selected ICU population (8, 11–14).

The interplay between diabetes mellitus and glucose dysregulation has never been investigated in relation to ICU delirium in one study. Based on previously conducted research on diabetes, glucose variability, and mortality in ICU patients (15), our hypothesis is that diabetes may modify the risk of ICU delirium after glucose dysregulation. We expected patients without diabetes who experience glucose dysregulation to be at higher risk of ICU delirium than patients with diabetes. Therefore, this study aims to determine whether diabetes mellitus, hyperglycemia, and hypoglycemia are associated with development of delirium in ICU patients.

METHODS

Design, Study Population, and Procedures

Data were collected as part of a prospective observational cohort study conducted in the 32-bed mixed ICU of the University Medical Center Utrecht, the Netherlands (16). Patients were included when they stayed for more than 24 hours at the ICU in the period between January 2011 and July 2016. Patients were excluded in case of admission to the ICU because of a neurologic illness, if delirium assessment was hampered due to deafness or if patients were unable to understand Dutch or English. The local Institutional Review Board (IRB) waived the need for informed consent in this noninterventional investigation (IRB 010/056/c and 12/421/c).

During the study period, the applicable glucose regulation protocol (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D685) was used to maintain target glucose levels between 5.0 and 8.0 mmol/L (90–144 mg/dL), except in those ICU patients with a low risk of prolonged hyperglycemia such as patients who underwent uncomplicated surgery. During insulin infusion, glucose levels were measured repeatedly on fixed time points between 0.5 and 4 hours after the last glucose measurement according to the protocol (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/D685). Glucose levels were measured in blood samples obtained from an arterial catheter using BeckmanCoulter AU5800 (Beckman Coulter, Brea, CA) or if an arterial catheter was absent by finger stick using Precision Xceed Pro (Abbott, Abbott Park, IL). Glucose levels were automatically stored in the electronic patient data management system. Trained research physicians collected the following data at admission and daily thereafter: demographic data, (chronic) comorbidities, medication use, ICU admission characteristics, daily physiologic measurements, and vital signs as well as therapeutic interventions. The Acute Physiology and Chronic Health Evaluation (APACHE) IV score was used to classify admission diagnosis, severity of disease, and infection at ICU admission (17). The extent of chronic comorbidities was assessed with the Charlson Comorbidity Index (CCI) (18). The Sequential Organ Failure Assessment (SOFA) score without the CNS component was used to classify the daily severity of disease (19). The presence of severe sepsis or septic shock was classified using international sepsis definitions at the time of patient inclusion (20).

For this investigation, we selected from the above described cohort all patients who had at least one transition from "awake and nondelirious" at a certain day (day *t*) during ICU admission to either "awake or nondelirious" (reference) or "delirious" at day *t+1* (index transition), as described in more detail below. Patients were excluded for this investigation when the status of diabetes at hospital admission was missing.

Determinants

The determinants of interest were diabetes and glucose dysregulation (hyperglycemia and/or hypoglycemia). The presence of diabetes mellitus at ICU admission was defined as present in the medical record (diagnosis or treatment) or use of insulin and/or oral antidiabetic drugs before hospital admission. Glucose dysregulation on day *t* was explored in four categories. Hyperglycemia was defined to be present if at least one blood glucose level was measured greater than 8.0 mmol/L on that day (day *t*), and hypoglycemia was defined as at least one measured glucose level less than 3.5 mmol/L on day "t." When both were present on day *t*, the exposure was categorized as both hyperglycemia and hypoglycemia. Day *t* was marked with "normoglycemia" when none of the determined blood glucose levels met the criteria for hyperglycemia or hypoglycemia.

Outcome

The mental status on each ICU day was evaluated by the research team using a previously validated algorithm (interobserver agreement, 0.94–0.97; sensitivity, 0.75; and specificity, 0.85) and classified for every day in the ICU as either "awake and nondelirious," "delirious," or "comatose" (16). The multistep algorithm to determine delirium incorporates a review of all Confusion Assessment Method for the ICU (CAM-ICU) (21) assessments conducted by bedside nurses, whether treatment with haloperidol or quetiapine was initiated for delirium, and meticulous chart review for the presence of documented terms clinically associated with delirium, as well as CAM-ICU assessments by researchers. Patients' wakefulness was evaluated every 4 hours with the Richmond Agitation and Sedation Scale (RASS). A RASS of less than or equal to –4 was denoted as coma.

Data Analysis

Patient characteristics were reported as frequencies with percentages and as means with SD in case of normally distributed continuous data. In case of a skewed distribution of continuous variables, medians with interquartile ranges were presented. Characteristics of patients with and without delirium were compared with the Student independent sample *t* test or the Mann-Whitney *U* test as appropriate in case of continuous

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data or with the chi-square test in the case of nominal data. The proportion of transition to delirium was graphically plotted against age.

Generalized mixed effects models with logit link function were performed to investigate the association between diabetes or glucose dysregulation with delirium. Patients were able to have more than one transition to delirium. Nontransitions remaining awake and nondelirious were collected from patients without delirium and from patients with delirium before delirium and after delirium resolved. The following potential confounders were tested based on a systematic review (8): age, gender, admission type, planned admission, confirmed infection, APACHE IV score, CCI as well as the following time-dependent variables: SOFA score, support of mechanical ventilation, presence of severe sepsis, or septic shock. The effects of the following variables were not investigated as potential confounder, because they were presumed to be on the causal pathway of exposure and outcome, and did therefore not meet the criteria for a potential confounder (22): insulin use, corticosteroid use, and the frequency of blood glucose measurement. Confounders were selected based on p values (< 0.05) and effect sizes in deregression model. Covariates were included in the final regression model as fixed effects, when possible as time-dependent covariate and patient (participant number) as random effect. Ninety-five percent bootstrap percentile CIs or confidence bands (CBs) were expressed. Two-stage bootstrap resampling procedure with "patient" as cluster variable was used for obtaining CIs or plot CBs from 1,000 replications. The effects were expressed as odds ratio (OR) with 95% CIs. All statistical analyses were carried out with R version 3.2.3 with package "lme4" (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 3,809 patients were admitted to the ICU, with a total of 33,302 observation days. After exclusion (**Fig. 1**), a total of 2,745 patients were included in the present investigation with 1,720 transitions from awake and nondelirious to delirious and 11,421 nontransitions remaining awake and nondelirious.

Patient characteristics of the included 2,745 patients are presented in **Table 1**. Of those, 1,127 patients (41.1%) had a delirium at any time during ICU stay. Patients with a delirium during ICU stay were on average older, were more often male than female, and had a longer ICU stay. Furthermore, delirious patients were compared with nondelirious patients, more frequently acutely admitted to the ICU and admitted by medical rather than surgical disciplines, had higher APACHE IV and CCI scores, and had more often an infection in the first 24 hours of ICU stay.

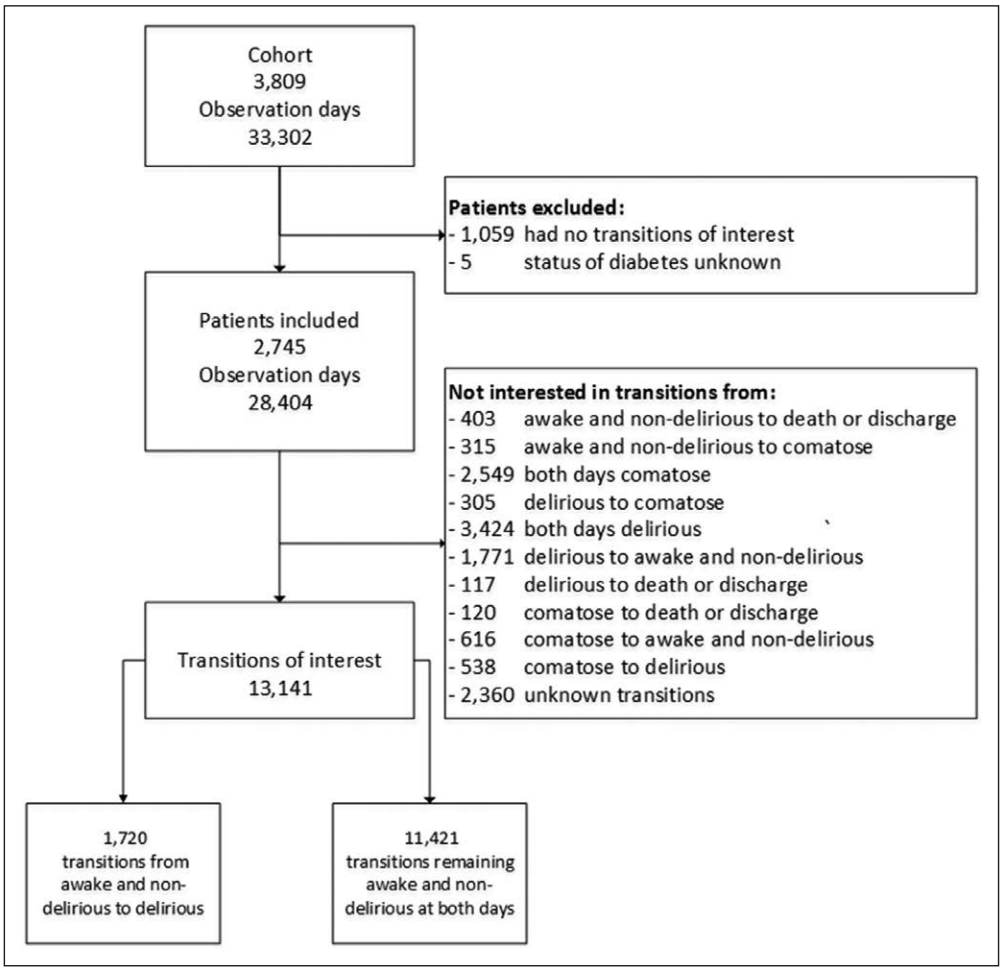

Figure 1. Flow chart of the study inclusion.

Of the cohort, 543 patients (19.8%) had a diagnosis of diabetes at hospital admission of whom 225 (41.4%) had a delirium during ICU stay. Of the 2,202 patients without diabetes, 902 patients (41.0%) experienced delirium during ICU stay.

Figure 2 shows the probability of transition to delirium with age for patients with and without diabetes. Visually plotted, diabetes seems to be associated with a higher probability of transition to delirium in older patients. Patients who had a transition from awake and nondelirious on day t to delirious on day "t+1" had a similar mean glucose level on day t as patients who remained awake and nondelirious (7.46 mmol/L SD 1.27, respectively, 7.41 mmol/L SD 1.48; OR, 1.04; 95% CI, 0.99–1.09, not presented in Table 1).

In total, 65,727 glucose values were determined on

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TABLE 1. Characteristics of the Study Population

Characteristics	All Patients ($n = 2,745$)	Patients With Delirium ($n = 1,127$)	Patients Without Delirium ($n = 1,618$)	p
Age, yr, mean (SD)	60.3 (15.8)	62.5 (14.8)	58.8 (16.3)	< 0.001[b]
Age ≥ 65 yr, *n* (%)	1,198 (43.6)	537 (47.6)	661 (40.9)	< 0.001[c]
Male gender, *n* (%)	1,732 (63.1)	740 (65.7)	992 (61.3)	0.020[c]
Diagnose[a], *n* (%)				< 0.001[c]
Medical	1,120 (40.8)	530 (47.0)	590 (36.5)	
Surgery elective	1,007 (36.7)	300 (26.6)	707 (43.7)	
Surgery emergency	606 (22.1)	295 (26.2)	311 (19.2)	
Planned admission[a], *n* (%)	977 (35.6)	274 (24.3)	703 (43.4)	< 0.001[c]
Confirmed infection[a], *n* (%)	819 (29.8)	553 (40.2)	366 (22.6)	< 0.001[c]
Acute Physiology and Chronic Health Evaluation IV score[a], mean (SD)	59.9 (25.5)	72.2 (26.6)	51.4 (20.7)	< 0.001[b]
Charlson Comorbidity Index[b], mean (SD)	7.2 (6.7)	7.9 (6.8)	6.5 (4.9)	< 0.001[b]
Length of stay on ICU, d, median (interquartile range)	4 (2–10)	10 (5–20)	3 (2–5)	< 0.001[d]

[a]At ICU admission. Missing values for diagnose: 12 for all patients, 2 for patients with ever delirium, and 10 for patients without delirium.
[b]At hospital admission.
[c]Student independent sample *t* test.
[d]χ^2 test.
[e]Mann-Whitney *U* test.

day *t*. As presented in **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/CCM/D686), on the whole study population, hyperglycemia was associated with transition to delirium (OR adjusted, 1.35; 95 CI, 1.15–1.59), whereas a nonsignificant OR was observed for hypoglycemia (OR adjusted, 1.86; 95% CI, 0.73–3.71). In addition, the occurrence of both hyperglycemia and hypoglycemia on day *t* was associated with delirium on day *t+1* (OR adjusted, 1.65; 95% CI, 1.12–2.28).

Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/CCM/D687) presents the association between glucose dysregulation and transition to delirium stratified for diabetes. In patients without diabetes, hyperglycemia (OR adjusted, 1.41; 95% CI, 1.16–1.68) and both hyperglycemia and hypoglycemia on the same day (OR adjusted, 1.87; 95% CI, 1.07–2.89) were associated with transition to delirium. In patients with diabetes, glucose dysregulation was not associated with transition to delirium.

Supplemental Table 4 (Supplemental Digital Content 4, http://links.lww.com/CCM/D688) shows a sensitivity analysis of the number of transitions to delirium in relation to minimum and maximum glucose levels on day *t*.

DISCUSSION

In summary, we found that diabetes mellitus was not associated with the development of ICU delirium. For hypoglycemia, only a nonsignificant OR for ICU delirium could be noted. In patients without diabetes, hyperglycemia (OR adjusted, 1.41; 95% CI, 1.16–1.68) and both hyperglycemia and hypoglycemia on the same day (OR adjusted, 1.87; 95% CI, 1.07–2.89) were associated with transition to delirium. In patients with diabetes, glucose dysregulation was not associated with transition to delirium.

To our knowledge, our study is the first exploring the association between diabetes, glucose dysregulation, and their interplay in relation with delirium. Literature concerning the association between diabetes and delirium in ICU patients shows conflicting results. Our results are in concordance with three investigations (n = 112–196 patients) on ICU patients that did not report an association between diabetes and delirium (11, 23, 24). An investigation with mixed ICU patients (n = 67,333) reported that diabetes was not associated with acute brain failure (25). This study may have subject to residual confounding, did not provide a definition for diabetes, and did not report on delirium. However, further comparison is difficult, since the authors did not report the definitions of diabetes and diabetes with complications. In contrast, in cardiac surgery patients, diabetes was associated with an OR of 1.38–1.96 on delirium (26, 27), and a positive association was reported in ICU patients from India (14), although extrapolation of these findings to the western population may be difficult. The differences in study population and methodology may explain these different results.

Few studies have investigated the association between glucose dysregulation and delirium, although with methodological limitations. In patients undergoing noncardiac thoracic surgery, abnormal glucose levels (glucose levels below 3.4 mmol/L or above 16.5 mmol/L) have been linked to

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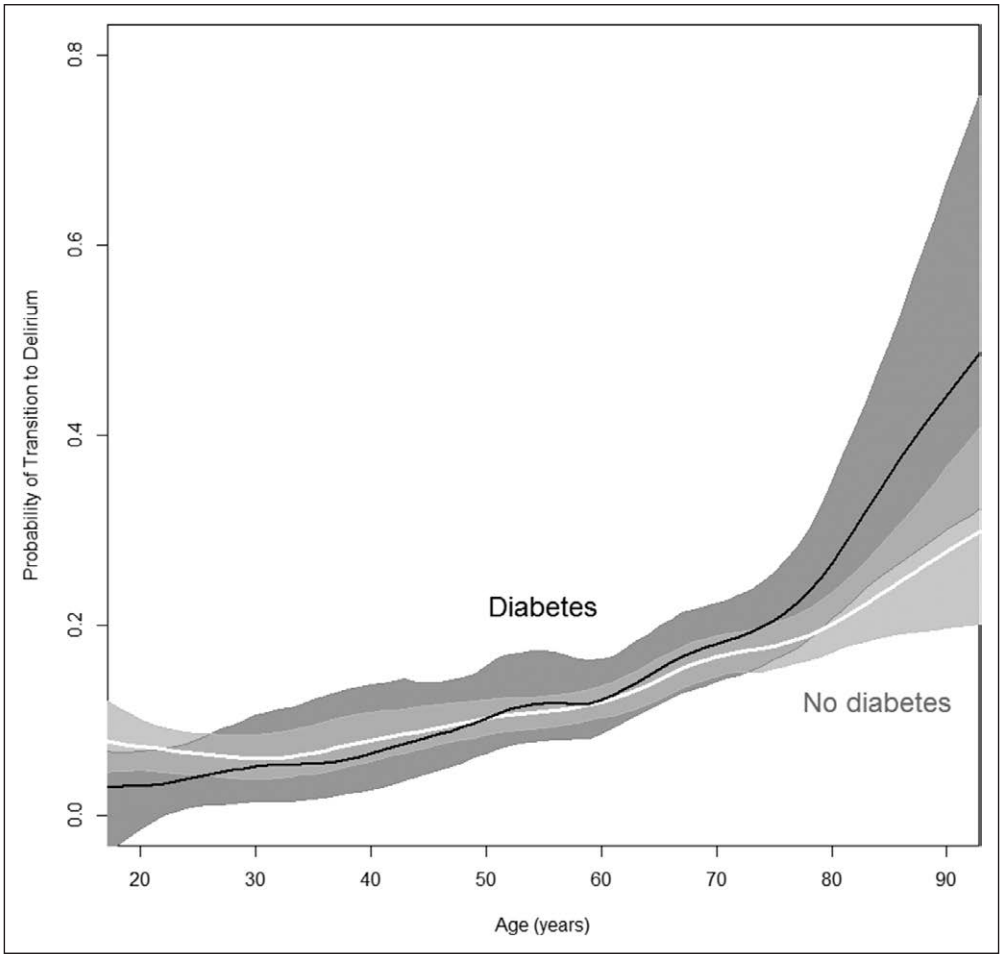

Figure 2. The proportion of transition to delirium the next day is plotted against increasing age for transitions in patients with and without diabetes. *Black line* is plotted for patients with diabetes, and the *white line* for patients without diabetes. The 95% confidence bands are plotted in *dark gray* for patients with diabetes and in *light gray* for patients without diabetes.

postoperative psychiatric disorders including delirium (12). Comparison with our study is difficult because their study was conducted in non-ICU patients, their outcome had a broader definition than delirium, and their threshold for hyperglycemia was higher. Our results are in concordance with a previous study with 196 ICU patients of whom 91.8% was nondiabetic (11). This study reported an association between higher glucose levels and the occurrence of hyperactive delirium; however, the timing of both glucose and delirium was unclear. Our finding of the positive association between hyperglycemia and delirium and the lack of an association between glucose concentration and delirium suggest that patients with diabetes tolerate a higher range of glucose levels better compared with patients without diabetes with regard to delirium. This finding has been previously reported with regard to the risk of mortality at the ICU (15).

This investigation presents new insights on the etiology of delirium, especially in patients without diabetes, glucose dysregulation was associated with delirium. Our study was conducted in by far the largest investigation on determinants of delirium in the world. We carefully investigated potential risk factors for delirium that influence the association between diabetes and glucose dysregulation and their interplay in relation with delirium, including time-dependent covariates. As we used models on daily transitions, we also accounted for fluctuations of delirium status over time. Our analysis was less prone to fluctuating numbers of glucose measurements because hyper- and hypoglycemia were marked on a daily base per protocol (yes/no). Another strength was the high completeness of the data: 91.7% of the daily transitions were adequately recorded in the database.

Our study has some limitations. It was performed as monocenter study in a tertiary care center which may limit the generalizability of our results. In this observational study, we cannot prove that the observed association between hyperglycemia and delirium was causal. Another limitation is the possibility that peaks and nadirs in blood glucose levels could have been missed because glucose levels were not measured continuously. In addition, unmeasured confounding may have occurred as there could have been unmeasured confounding covariates. An important question remaining is how readily reversible the delirious state is with normalization of blood glucose levels and which role insulin plays in this setting.

It has been suggested that metabolic disorders, including impaired glucose oxidation, cause disturbances in neuronal networks in the brain that may lead to delirium (13, 28). Glucose dysregulation may be more harmful compared with chronic high glucose level with regard to development of delirium because we did not find an association between mean glucose level and delirium. Our results suggest that ICU clinicians should prevent glucose dysregulation in ICU patients. Of these, especially patients without diabetes seem to be at risk of delirium.

CONCLUSIONS

In this large ICU study, diabetes mellitus was not associated with the development of ICU delirium. For hypoglycemia, only a nonsignificant OR for ICU delirium could be noted. Hyperglycemia and the occurrence of hyperglycemia and hypoglycemia on the same day were associated with ICU delirium but only in patients without diabetes. Our study supports

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the institution of measures to prevent glucose dysregulation in nondiabetic ICU patients and contributes to the understanding of the determinants of delirium.

ACKNOWLEDGMENTS

We are grateful to L.E.M. Davies, epidemiologist, for her assistance in data preparation.

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