

Prior exposure to hyperglycaemia attenuates the relationship between glycaemic variability during critical illness and mortality

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Hyperglycaemia develops frequently during critical illness and is a marker of illness severity and associated with increased mortality.¹⁻³ However, the strength of the relationship between acute hyperglycaemia and mortality is diminished or absent in patients with pre-existing diabetes.⁴⁻⁶

Evaluating diabetes as a binary state (present or absent) is a relatively crude approach and risks obscuring important information. A more nuanced approach, using the glycated haemoglobin (HbA_{1c}) level to stratify patients according to pre-existing hyperglycaemia, is intuitively appealing. By incorporating HbA_{1c} and evaluating prior hyperglycaemia, Egi and colleagues identified that the relationship between inpatient glycaemia and mortality varied according to prior hyperglycaemia, such that patients with higher levels of prior hyperglycaemia (HbA_{1c} > 7%) and who were acutely hyperglycaemic (blood glucose [BG] > 10 mmol/L) during their critical illness appeared to be less likely to die, compared with patients with BG concentrations between 6 and 10 mmol/L.⁷ Similar observations have since been reported.⁸⁻¹⁰

To obtain a more refined understanding of the effect of disordered glucose metabolism on outcomes during critical illness, the concept of three distinct but interrelated domains of acute dysglycaemia (hyperglycaemia, hypoglycaemia and glycaemic variability) has also been proposed.⁶ In critically ill patients with previously normal glucose tolerance, each of these domains is associated with increased mortality.⁶ Because prior hyperglycaemia markedly attenuates the association between acute hyperglycaemia and mortality, there is increasing interest in how prior hyperglycaemia may affect the harm associated with hypoglycaemia and glycaemic variability.¹¹

Our primary objective was to evaluate the impact of prior exposure to hyperglycaemia on the association between glycaemic variability and mortality in critically ill patients. Secondary objectives were to describe associations between prior hyperglycaemia and acute hyperglycaemia or hypoglycaemia, hospital mortality and long-term survival.

Methods

Study design

Our retrospective observational study included all patients admitted to the Royal Adelaide Hospital intensive care unit between 1 September 2011 and 30 June 2015, inclusive. The study was approved by the Royal Adelaide Hospital Human

ABSTRACT

Objective: Our primary objective was to determine the impact of prior exposure to hyperglycaemia on the association between glycaemic variability during critical illness and mortality. Our secondary objectives included evaluating the relationships between prior hyperglycaemia and hyperglycaemia or hypoglycaemia during critical illness and mortality.

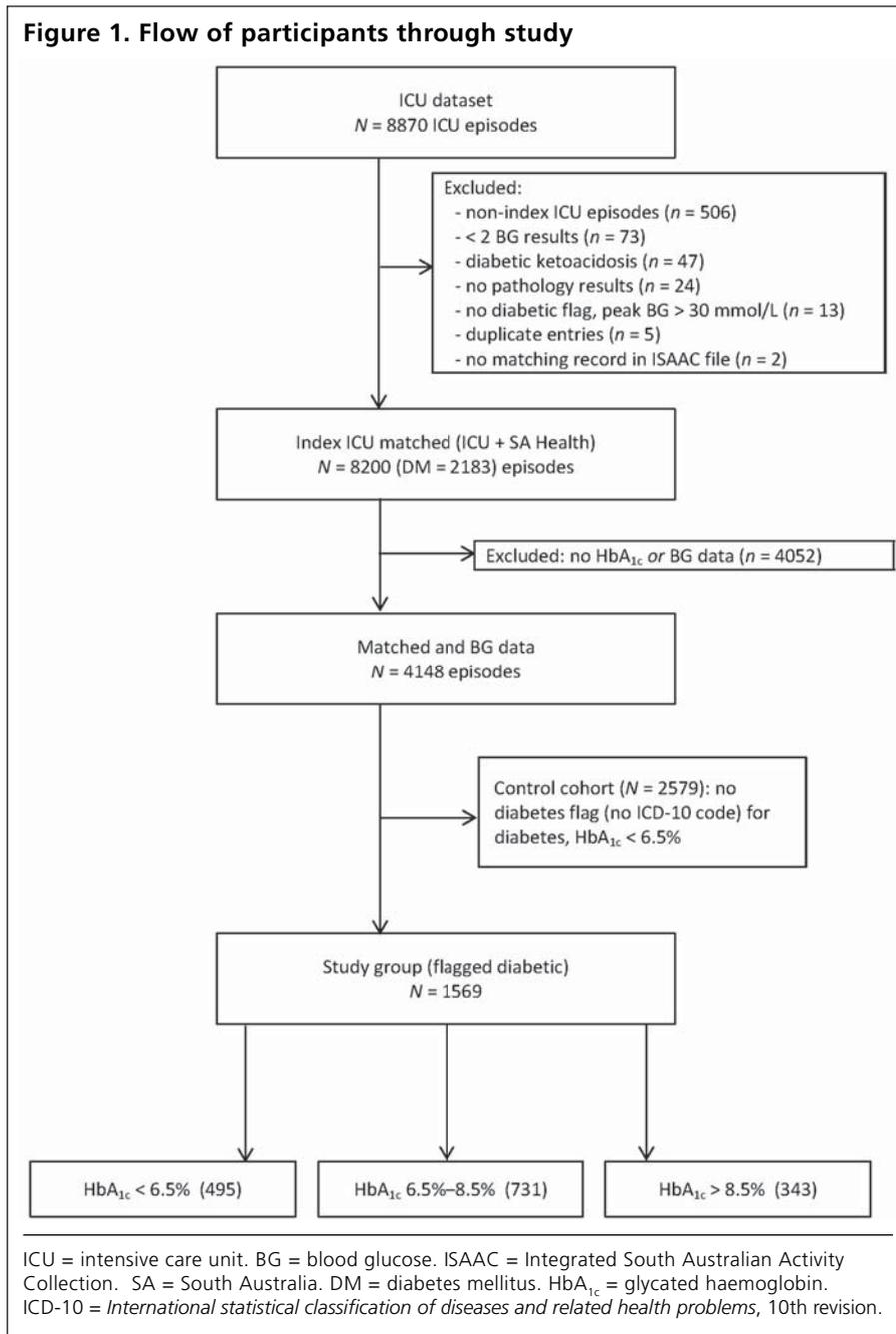
Design and participants: A single-centre, retrospective, observational study in a tertiary intensive care unit. Patients admitted to the ICU between 1 September 2011 and 30 June 2015, with diabetes recorded using ICD-10-AM coding or a glycated haemoglobin (HbA_{1c}) level of $\geq 6.5\%$, were stratified by prior hyperglycaemic level (HbA_{1c} < 6.5%, 6.5%–8.5%, or > 8.5%).

Main outcome measures: Glycaemic variability was assessed as the blood glucose coefficient of variation during the patient's stay in the ICU. Multivariate logistic regression and marginal predictive plots were used to assess the impact of prior hyperglycaemia on the association between glycaemic metrics and mortality.

Results: We studied 1569 patients with diabetes (HbA_{1c} < 6.5%, $n = 495$; HbA_{1c} 6.5%–8.5%, $n = 731$; and HbA_{1c} > 8.5%, $n = 343$). Glycaemic variability was strongly associated with hospital mortality ($P = 0.001$), but this association showed a significant interaction with prior hyperglycaemia ($P = 0.011$), such that for patients with HbA_{1c} > 8.5%, increasing glycaemic variability was not associated with increased mortality. Acute hyperglycaemia was strongly associated with mortality ($P < 0.0001$) and also showed a significant interaction with prior hyperglycaemia ($P = 0.001$), such that for patients with HbA_{1c} > 8.5%, acute hyperglycaemia was not associated with mortality. Hypoglycaemia was also associated with mortality ($P < 0.0001$), but prior exposure to hyperglycaemia had a lesser effect on this relationship.

Conclusion: Prior exposure to hyperglycaemia attenuates the association between glycaemic variability and mortality in critically ill patients with diabetes.

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Figure 1. Flow of participants through study

Research Ethics Committee and the South Australian Department of Health Human Research Ethics Committee, with the need for informed consent waived. During this period, hyperglycaemia was treated with intravenous insulin titrated according to a paper-based algorithm.¹²

Data sources

Demographic and ICU admission data for patients were extracted from the local Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD; www.anzics.com.au/core). All ANZICS-APD data were recorded prospectively by trained data collectors.

This dataset was matched against the Integrated South Australian Activity Collection (ISAAC; www.sahealth.sa.gov.au/isaac) dataset to generate a “known diabetes” flag and mortality data, and against the South Australian electronic data warehouse for HbA_{1c} and BG results.

Cohort definitions

Patients with diabetes were defined as those with an ICD-10-AM code for any diabetic chapter (E10–E14) on the current or any previous hospital episode, those with prior insulin use, or those with an HbA_{1c} level of $\geq 6.5\%$ (48 mmol/mol) within the 3 months before or within the ICU admission. Patients with diabetes were stratified according to HbA_{1c} level, forming the primary study subgroups: HbA_{1c} < 6.5%, HbA_{1c} 6.5%–8.5% (48–69 mmol/mol) and HbA_{1c} > 8.5%. These thresholds were selected according to international guidelines and previous studies.^{13–15} Data from patients without diabetes admitted during this period were analysed as a reference cohort (Figure 1).

Patients were excluded if they had an Acute Physiology and Chronic Health Evaluation (APACHE) III admission diagnosis of diabetic ketoacidosis (n = 47)^{16,17} or if fewer than two BG concentrations were recorded throughout their ICU admission (n = 73). To reduce the risk of bias from incorrect data transcription, data were excluded from patients if they did not generate a known diabetes flag but their peak BG concentration was

> 30 mmol/L (n = 13).

Pathology variables

BG measurements were performed either with point-of-care blood-gas analysis (ABL800 Flex, Radiometer)¹⁸ or as part of a laboratory biochemical profile (using SA Pathology). HbA_{1c} level tests were performed by SA Pathology.

Glycaemic and outcome metrics

Glycaemic variability was analysed as the coefficient of variation (SD/mean $\times 100\%$).^{16,19–21} The peak and minimum BG concentrations were the maximum and minimum

Table 1. Demographic data, by study group and prior hyperglycaemia category

Demographic variable	Control	Diabetes	Prior hyperglycaemia category			P*
			HbA _{1c} < 6.5%	HbA _{1c} 6.5%–8.5%	HbA _{1c} > 8.5%	
Separations, <i>n</i> (% of total)	2579 (62%)	1569 (38%)	495 (31.5%)	731 (46.6%)	343 (21.9%)	
Male, <i>n</i> (% of group)	1666 (65%)	1019 (65%)	318 (64.2%)	488 (66.8%)	213 (62.1%)	0.31
Median age, years (IQR)	59 (44–70)	66 (57–74)	68 (59–76)	67 (58–75)	61 (51–69)	< 0.001
Median APACHE III score (IQR)	49 (36–67)	58 (45–76)	61 (49–78)	58 (45–76)	55 (42–72)	0.001
Median length of stay, days (IQR)						
ICU	2.4 (1.1–5.0)	2.7 (1.4–5.0)	2.7 (1.5–5.0)	2.7 (1.4–4.9)	2.7 (1.2–5.0)	0.99
Hospital	10.8 (6–21)	12.2 (7–21)	12.3 (7.9–22.8)	12.1 (7.2–20.6)	13.1 (7.7–20.9)	0.21
Prior insulin use, <i>n</i> (% of group)	–	203 (12.9%)	26 (5.3%)	94 (12.9%)	83 (24.2%)	< 0.001
APACHE IIIj medical diagnostic group, <i>n</i> (% of group)						
All medical	1235 (47.9%)	725 (46.2%)	227 (45.9%)	339 (46.4%)	159 (46.4%)	0.98
Cardiovascular	158 (6.1%)	169 (10.8%)	49 (9.9%)	80 (10.9%)	40 (11.7%)	0.71
Respiratory	266 (10.3%)	190 (12.1%)	58 (11.7%)	93 (12.7%)	39 (11.4%)	0.78
Gastrointestinal	57 (2.2%)	45 (2.9%)	20 (4.0%)	19 (2.6%)	6 (1.8%)	0.12
Neurological, stroke	233 (9.0%)	72 (4.6%)	17 (3.4%)	36 (4.9%)	19 (5.5%)	0.30
Sepsis	102 (3.9%)	127 (8.1%)	44 (8.9%)	60 (8.2%)	23 (6.7%)	0.52
Trauma	259 (10.0%)	39 (2.5%)	10 (2.0%)	18 (2.5%)	11 (3.2%)	0.55
Metabolic	114 (4.4%)	37 (2.4%)	9 (1.8%)	13 (1.8%)	15 (4.4%)	0.02
Haematological	21 (0.8%)	13 (0.8%)	7 (1.4%)	5 (0.7%)	1 (0.3%)	0.22
Renal, pre-eclampsia	18 (0.7%)	26 (1.7%)	10 (2.0%)	13 (1.8%)	3 (0.9%)	0.44
Other medical	1 (0.0%)	1 (0.1%)	1 (0.2%)	0	0	0.53
APACHE IIIj post-operative diagnostic group, <i>n</i> (% of group)						
All surgical	1344 (52.1%)	844 (53.8%)	268 (54.1%)	392 (53.6%)	184 (53.6%)	0.98
Musculoskeletal	6 (0.2%)	6 (0.4%)	2 (0.4%)	2 (0.3%)	2 (0.6%)	0.77
Vascular, cardiac	674 (26.0%)	486 (31.0%)	148 (29.9%)	231 (31.6%)	107 (31.2%)	0.82
Respiratory	285 (11.0%)	136 (8.7%)	48 (9.7%)	59 (8.1%)	29 (8.5%)	0.60
Gastrointestinal	106 (4.1%)	94 (6.0%)	35 (7.1%)	43 (5.9%)	16 (4.7%)	0.35
Neurosurgical	102 (4.0%)	38 (2.4%)	10 (2.0%)	20 (2.7%)	8 (2.3%)	0.72
Trauma, burns	121 (4.7%)	17 (1.1%)	5 (1.0%)	7 (1.0%)	5 (1.5%)	0.77
Urological, transplantation	14 (0.5%)	20 (1.3%)	10 (2.0%)	6 (0.8%)	4 (1.2%)	0.20
Gynaecological	3 (0.1%)	5 (0.3%)	1 (0.2%)	3 (0.4%)	1 (0.3%)	0.86
Orthopaedic	36 (1.4%)	45 (2.9%)	11 (2.2%)	22 (3.0%)	12 (3.5%)	0.53
Haematological	–	–	–	–	–	–
Metabolic	3 (0.1%)	3 (0.2%)	0	1 (0.1%)	2 (0.6%)	0.22
APACHE IIIj group, <i>n</i> (% of group)						
Cardiothoracic	605 (23.4%)	448 (28.6%)	131 (26.5%)	213 (29.1%)	104 (30.3%)	0.43
Trauma	380 (14.7%)	56 (3.6%)	15 (3.0%)	25 (3.4%)	16 (4.7%)	0.44

HbA_{1c} = glycated haemoglobin. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. * *P* values are for comparisons between diabetes subgroups, using Kruskal–Wallis, χ^2 or Fisher exact tests as appropriate.

recorded during ICU admission. A hyperglycaemic episode was identified as BG concentration > 11.1 mmol/L, and a hypoglycaemic episode was identified as BG concentration < 4.0 mmol/L, separated by at least 4 hours from any previous event.²²

Hospital mortality was recorded from the local ICU dataset, and 1-year mortality was recorded from the ISAAC database, both of which are routinely updated from the South Australian Births, Deaths and Marriages registry.

Table 2. Blood test result data, by study group and prior hyperglycaemia category

Blood test variable	Control	Diabetes	Prior hyperglycaemia category			P*
			HbA _{1c} < 6.5%	HbA _{1c} 6.5%–8.5%	HbA _{1c} > 8.5%	
Blood tests, <i>n</i> (IQR)	6 (4–10)	7 (5–9)	7 (5–9)	6 (5–9)	7 (5–9)	0.57
Median test interval, hours (IQR)	9.7 (5.4–14.6)	10.3 (5.8–14.7)	10.3 (6.2–14.6)	10.5 (5.7–15.0)	9.8 (5.2–14.7)	0.77
Median BG level, mmol/L (IQR)						
Mean BG level	7.2 (6.4–8.1)	8.6 (7.6–9.9)	7.9 (7.0–8.8)	8.7 (7.8–10.0)	9.6 (8.5–11.7)	< 0.001
Peak BG level	9.4 (8.0–11.1)	12.8 (10.5–15.9)	11.0 (9.2–13.6)	13.0 (11.0–15.8)	15.3 (12.7–19.7)	< 0.001
Minimum BG level	5.3 (4.7–6.1)	5.2 (4.3–6.2)	5.3 (4.3–6.2)	5.2 (4.3–6.2)	5.1 (4.3–6.1)	0.79
BG CoV	20.4 (14.9–27.5)	32.2 (22.7–42.8)	26.8 (18.9–37.7)	32.3 (23.5–43.3)	37.4 (29.9–50.5)	< 0.001
Median HbA _{1c} level, % (IQR)	5.5% (5.2%–5.8%)	6.9% (6.2%–8.2%)	5.8% (5.5%–6.1%)	7.1% (6.7%–7.7%)	9.8% (9.0%–11.3%)	–
Hyperglycaemic events, † <i>n</i> (%)						< 0.001
0	1945 (75.4%)	483 (30.8%)	258 (52.1%)	192 (26.3%)	33 (9.6%)	
1	367 (14.2%)	468 (29.8%)	121 (24.4%)	232 (31.7%)	115 (33.5%)	
2	160 (6.2%)	289 (18.4%)	71 (14.3%)	151 (20.7%)	67 (19.5%)	
3	76 (3.0%)	135 (8.6%)	20 (4.0%)	72 (9.9%)	43 (12.5%)	
4	16 (0.6%)	91 (5.8%)	14 (2.8%)	39 (5.3%)	38 (11.1%)	
Hypoglycaemic events, ‡ <i>n</i> (%)						0.79
0	2351 (91.2%)	1297 (82.7%)	413 (83.8%)	603 (82.5%)	279 (81.3%)	
1	156 (6.1%)	187 (11.9%)	54 (10.9%)	93 (12.7%)	43 (12.5%)	
2	52 (2.0%)	70 (4.5%)	23 (4.7%)	28 (3.8%)	16 (4.7%)	
≥ 3	20 (0.8%)	15 (1.0%)	3 (0.6%)	7 (1.0%)	5 (1.5%)	

HbA_{1c} = glycated haemoglobin. IQR = interquartile range. BG = blood glucose. CoV = coefficient of variation. * *P* values are for comparisons between diabetes subgroups, using Kruskal–Wallis, χ^2 or Fisher exact tests as appropriate. † BG > 11.1 mmol/L. ‡ BG < 4.0 mmol/L.

Statistical analysis

We show data as frequencies with proportions for categorical variables, and means with standard deviations or medians with interquartile ranges (IQRs) for continuous variables. Proportions were compared using the χ^2 or Fisher exact tests. Between-group comparisons were performed with the *t*, Wilcoxon rank-sum or Kruskal–Wallis test, as indicated. Univariate and multivariate logistic regression analyses were used to assess factors associated with hospital mortality, with group-by-continuous interaction effects shown as marginal predictive plots. We used Cox proportional hazards regression to assess 1-year mortality.

Primary analyses of premorbid glycaemia were based on the three pre-defined HbA_{1c} subgroups, and secondary analyses were performed with HbA_{1c} as a continuous covariate. Between-group comparisons were considered statistically significant at *P* < 0.05. Inclusion of covariates in the multivariate models was set at *P* < 0.1. We performed all analyses using Stata, version 14 (StataCorp).

Results

From 8870 eligible ICU admissions, 8200 were matched index episodes, 4148 (51%) of which had sufficient HbA_{1c}

and BG data. From this group, 1569 patients (38%) met the criteria for diabetes, forming the primary study group. The remaining 2579 episodes (62%) acted as a reference control group for secondary analyses (Figure 1). Of the 2749 patients without a prior ICD-10-AM diagnosis of diabetes, 170 had an HbA_{1c} level > 6.5%, indicating a prevalence of unrecognised diabetes of about 6%. The lead time for HbA_{1c} measurement before ICU admission was a median of 2.9 days (IQR, –0.1 to 15.3 days) days. Of the 156 patients (9.9%) who had their HbA_{1c} level measured on the day after ICU admission, 122 (7.8%) had the measurement taken on Day 2 or Day 3 of ICU admission, and 34 (2.1%) had the measurement taken after Day 3.

Patients with diabetes were, overall, older and had higher APACHE III scores than control participants, but patients with more pronounced prior hyperglycaemia (HbA_{1c} > 8.5%) were younger and had lower APACHE III scores (Table 1). Prior insulin use was recorded for 203 patients (13%) with diabetes, with higher levels of use among those with prior hyperglycaemia (Table 1). There were some case-mix differences between patients with diabetes and control patients, but the distribution of diagnostic categories was relatively uniform across HbA_{1c} subgroups (Table 1).

Domains of dysglycaemia

The median number of BG measurements per patient was seven (IQR, 5–9 measurements), with a median between-test interval of 10.3 hours (IQR, 5.8–14.8 hours). Neither measure differed across HbA_{1c} subgroups. The mean, peak and number of hyperglycaemic episodes and coefficient of variation of BG level all increased significantly with increasing prior hyperglycaemia (Table 2). The minimum BG level and the number of hypoglycaemic events did not differ according to prior hyperglycaemia (Table 2), but more patients with diabetes had at least one hypoglycaemic event compared with control patients (17.3% v 8.8%, $P < 0.001$).

Hospital mortality

Of the patients with diabetes, 240 (15.3%) died during the index hospital admission. The degree of prior exposure to hyperglycaemia did not significantly affect hospital mortality (Table 3). Patients with diabetes were less likely to survive to hospital discharge than were patients in the control group (mortality, 15.3% v 11.7%; $P = 0.001$).

Univariate factors showing a significant positive association with hospital mortality included BG metrics (variability, mean, peak, minimum, number of hypoglycaemic and hyperglycaemic events), the diagnostic category of sepsis, increasing age and increasing APACHE III score ($P \leq 0.001$). The cardiothoracic surgery and post-operative diagnostic categories were associated with reduced risk ($P < 0.0001$).

Secondary analysis of prior hyperglycaemia, using continuous rather than stratified HbA_{1c} level, showed a reduced risk of hospital mortality with increasing HbA_{1c} level ($P = 0.017$). This unexpected observation was evaluated for the presence of confounding factors. Patients with higher HbA_{1c} levels were younger and had lower APACHE III scores. The association between prior hyperglycaemia and reduced mortality persisted when calculations were adjusted for these covariates, but there was a strong interaction with the diagnostic category of cardiothoracic surgery ($P = 0.01$) (Appendix, Figures 1A and 1B, online at cicm.org.au/Resources/Publications/Journal).

Interactions between prior hyperglycaemia, BG metrics and hospital mortality

Glycaemic variability

Increasing glycaemic variability was strongly associated with hospital mortality ($P < 0.001$), but there was a significant interaction effect with prior hyperglycaemia ($P = 0.013$), such that for those with HbA_{1c} > 8.5%, increasing glycaemic variability conferred no greater risk of mortality (Figure 2A). This interaction effect remained significant when adjusted for age, APACHE III score, use of insulin, APACHE III diagnostic subgroup and the diagnostic categories of cardiothoracic surgery, trauma, post-operative and sepsis. The interaction was also stronger when entering HbA_{1c} level into the model as a continuous covariate ($P = 0.001$), compared with the three pre-defined subgroups.

There was greater glycaemic variability in patients with diabetes compared with control patients ($P < 0.0001$) (Table 2). The interaction between the presence of diabetes, glycaemic variability and acute mortality was significant ($P < 0.0001$) (Appendix, Figure 2A).

Hyperglycaemia

Increasing peak BG level was strongly associated with hospital mortality ($P < 0.001$), but there was a significant interaction effect with prior hyperglycaemia ($P = 0.001$), such that for those with HbA_{1c} > 8.5%, increasing peak BG conferred no greater risk of mortality (Figure 2B). This interaction effect remained significant when adjusted for covariates. Mortality risk increased with an increasing number of hyperglycaemic events (Figure 3A).

Patients with diabetes had greater peak BG concentrations and more hyperglycaemic events compared with control patients ($P < 0.001$) (Table 2). The interaction between the presence of diabetes, hyperglycaemia and acute mortality was significant ($P < 0.0001$) (Appendix, Figure 2B).

Hypoglycaemia

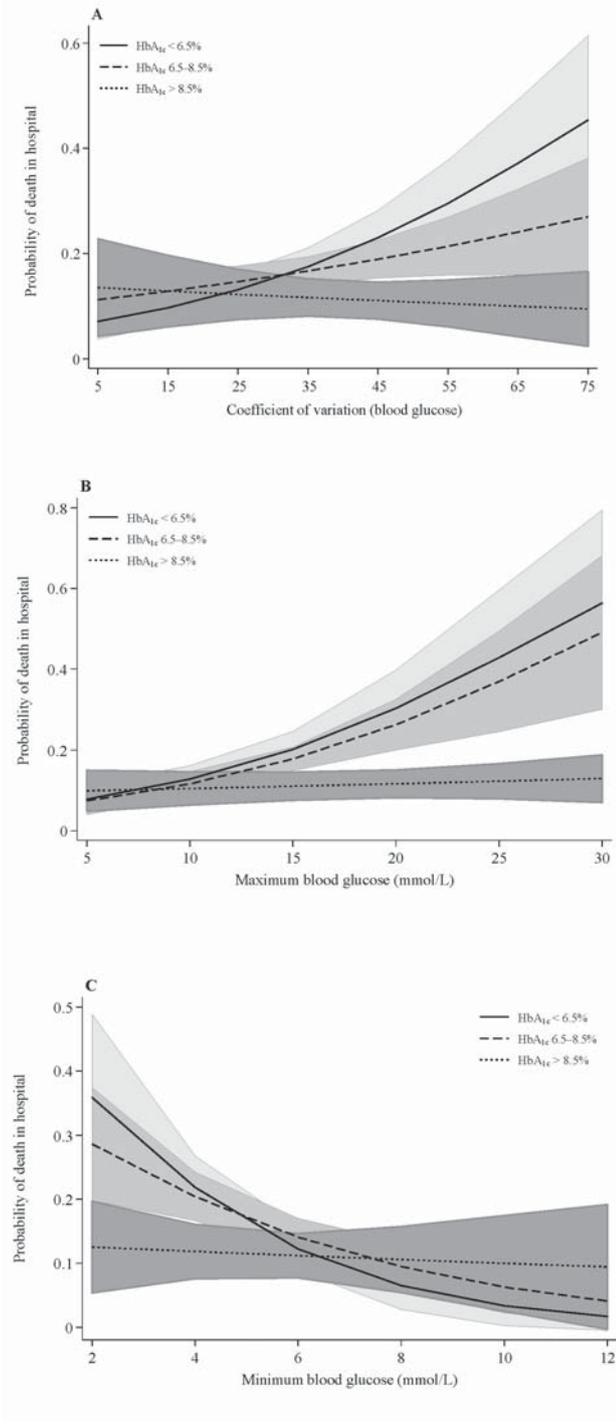
The minimum BG concentration and the number of hypoglycaemic episodes were strongly associated with hospital mortality ($P < 0.0001$), but neither differed

Table 3. Mortality outcomes, by study group and prior hyperglycaemia category

Outcome	Control	Diabetes	Prior hyperglycaemia category			P*
			HbA _{1c} < 6.5%	HbA _{1c} 6.5%–8.5%	HbA _{1c} > 8.5%	
Separations, <i>n</i> (% total)	2581 (62%)	1569 (38%)	495 (32%)	731 (47%)	343 (22%)	
Died in ICU	209 (8.1%)	145 (9.2%)	44 (8.9%)	76 (10.4%)	25 (7.3%)	0.25
Died in hospital	302 (11.7%)	240 (15.3%)	80 (16.2%)	121 (16.6%)	39 (11.4%)	0.07
Died at 12 months	453 (17.6%)	367 (23.4%)	132 (26.7%)	175 (23.9%)	60 (17.5%)	< 0.0001
Separations, alive, <i>n</i> (%)	2279 (63%)	1327 (37%)	415 (84%)	610 (83%)	304 (89%)	
Died at 12 months	159 (7.0%)	130 (9.8%)	53 (12.8%)	55 (9.0%)	22 (7.2%)	0.028

HbA_{1c} = glycated haemoglobin. ICU = intensive care unit. * P values are for comparisons between diabetes subgroups, using the χ^2 test for ICU and hospital mortality; and log-rank test for 12-month mortality.

Figure 2. Marginal model predictions evaluating impact of prior exposure to hyperglycaemia, by prior hyperglycaemia category, on associations between hospital death and glycaemic variability, hyperglycaemia and hypoglycaemia



A. Glycaemic variability (coefficient of variation). B. Hyperglycaemia (maximum blood glucose). C. Hypoglycaemia (minimum blood glucose). Shaded areas represent 95% CIs. HbA_{1c} = glycated haemoglobin.

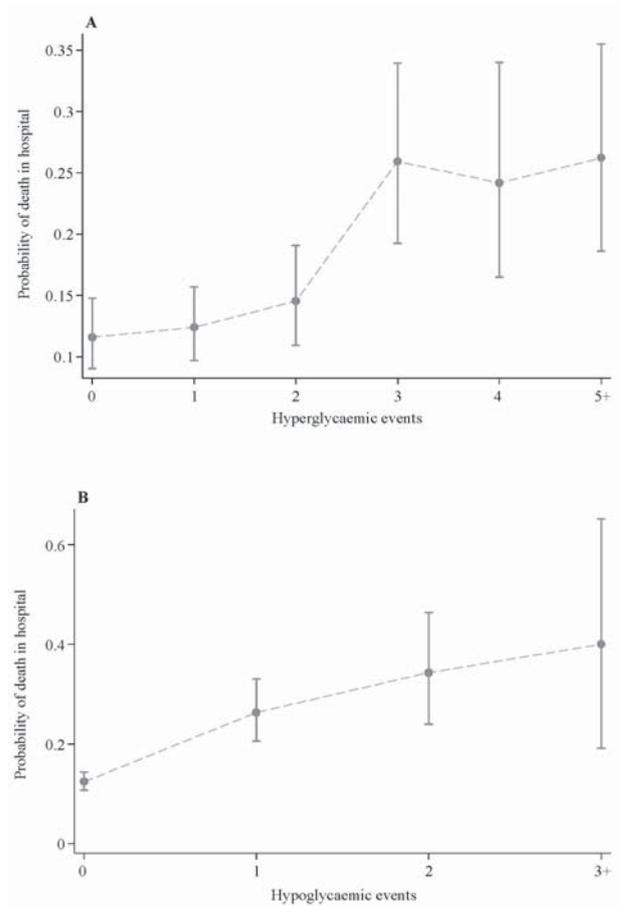
significantly across HbA_{1c} subgroups (Table 2). The interaction term between minimum BG, prior hyperglycaemia and mortality was significant, ($P = 0.035$) (Figure 2C), but this association was not significant with either glycaemic variability or peak BG added to the model. Mortality risk increased as the number of hypoglycaemic episodes increased (Figure 3B).

Minimum BG levels were similar in patients with diabetes and control patients, but patients with diabetes were more likely to have one or more episodes of hypoglycaemia ($P < 0.001$) (Table 2). The interaction between the presence of diabetes, minimum BG levels and acute mortality was not significant ($P = 0.26$) (Appendix, Figure 2C).

1-year mortality

Mortality at 1 year was lower across subgroups of increasing prior hyperglycaemia ($P < 0.01$) (Table 3 and Appendix, Figure 3A). When adjusted for the covariates of age, APACHE III score and cardiothoracic surgery, the lower

Figure 3. Model predictions of probability of hospital death, by number of hyperglycaemic and hypoglycaemic events



A. Hyperglycaemic events. B. Hypoglycaemic events. Bars represent 95% CIs.

risk of mortality with increasing HbA_{1c} subgroup remained significant ($P = 0.02$).

Within 1 year of ICU admission, 367 patients with diabetes (23.4%) and 453 control patients (17.6%) had died ($P < 0.001$) (Table 3 and Appendix, Figure 3B). The mortality rate at 1 year for patients with diabetes was 453 per 1000 patient-years (95% CI, 188–226 per 1000 patient-years), and for patients without diabetes was 367 per 1000 patient-years (95% CI, 261–320 per 1000 patient-years) (Appendix, Figure 3B).

Discussion

We undertook our single-centre, retrospective, observational study to evaluate the impact of prior exposure to hyperglycaemia (using HbA_{1c} as a marker) on the association between acute glycaemic variability during critical illness and hospital mortality. In our dataset, prior hyperglycaemia markedly attenuated the association between glycaemic variability and mortality. For patients with HbA_{1c} > 8.5%, increasing glycaemic variability had no detectable effect on mortality. Secondary observations included that:

- acute hyperglycaemia was associated with increased mortality and this effect was attenuated by prior hyperglycaemia, an observation consistent with previous studies
- hypoglycaemic episodes occurred more frequently in patients with diabetes
- more frequent episodes of hypoglycaemia were associated with increased mortality
- the 1-year mortality rate for patients with diabetes was significantly greater than the rate for control patients but, unexpectedly, the mortality rate was reduced in those with prior hyperglycaemia.

Comparison with other data

The strong association between increasing glycaemic variability and hospital mortality has been consistently reported,^{19,20,23,24} and this relationship appears to be independent of the deleterious effects of hypoglycaemic episodes.^{16,19} While previous studies have reported that this association may be attenuated in patients with diabetes,^{6,16,21,25} a limitation of previous work is that patients with diabetes have been viewed as a homogeneous cohort, irrespective of their preceding glycaemic control. Our study builds on these previous observations and identifies an exposure–response relationship between prior hyperglycaemia, glycaemic variability during critical illness and mortality. Our data are also complementary to findings from observational studies that evaluated associations between acute hyperglycaemia and hypoglycaemia and hospital mortality.^{7–11} They also support the hypothesis that dysglycaemia does not represent the same insult to all critically ill patients; rather, the impact is markedly influenced by prior exposure to hyperglycaemia.

Recent reports suggest that patients with prior hyperglycaemia have a greater risk of hypoglycaemic episodes and there is a stronger association between acute hypoglycaemia and mortality for those with prior hyperglycaemia (HbA_{1c} > 8%).¹¹ In our study, patients with diabetes were more likely to have hypoglycaemic episodes, but the frequency of these did not vary with prior hyperglycaemia. Taken together, these data suggest that, although a diagnosis of diabetes and prior exposure to hyperglycaemia may attenuate the harm associated with acute hyperglycaemia and increased glucose variability, the risks from hypoglycaemia persist.

Our results are consistent with previous Danish data on long-term outcomes showing that 1-year mortality after ICU admission is increased in patients with diabetes.²⁶ The inverse relationship between HbA_{1c} and mortality, such that prior exposure to hyperglycaemia was associated with a reduction in mortality, was unexpected, and there is no immediate plausible physiological rationale. This novel observation should be interpreted cautiously as it may reflect confounding from some unmeasured factor and be a spurious result.²⁷ However, if this relationship is observed in other datasets, it should provide an impetus for further epidemiological work.

Potential mechanism for attenuation of glycaemic variability with prior hyperglycaemia

There are *in vitro* studies to support the mechanistic plausibility that acute fluctuations in BG level have a deleterious biological effect. Acute marked fluctuations of BG levels have been shown to trigger oxidative stress in isolated umbilical vein cells,²⁸ increase apoptosis²⁹ and promote endothelial dysfunction through monocyte activation.³⁰ These results have been replicated in patients with type 2 diabetes and prior exposure to hyperglycaemia, with increasing glycaemic variability associated with increased markers of oxidative stress.^{31,32} The mechanisms governing any protective effect of prior hyperglycaemia remain poorly understood, but conditioning with prior hyperglycaemia may cause cellular adaptation with preferential down-regulation of insulin-independent GLUT-1 and GLUT-3 glucose transporters, thus limiting intracellular glucotoxicity.³³ Patients with prior hyperglycaemia may be protected from hyperglycaemia and, possibly, glycaemic variability, as long as hypoglycaemia is strictly avoided.

Study strengths

The strengths of our study include that we obtained a relatively large number of HbA_{1c} measurements, allowing for stratification of diabetes into three clinically relevant cohorts of patients with prior exposure to hyperglycaemia. The number of glucose measurements per patient was sufficient to allow adequate assessment of glycaemic variability, and 1 year is a longer follow-up period than most epidemiological work in this area.

Limitations

Our study has several important limitations. First, as with any retrospective observational study, systematic error, observation bias and the potential for unmeasured confounding factors are possible.³⁴ However, data were collected prospectively and measured independently, so observation bias should be limited. Second, the data were collected from a single centre, which introduces the potential for recruitment bias based on the prevalence of diabetes in the surrounding community.³⁵ Third, no information was available on the time since patients had been diagnosed with diabetes, the treatment of dysglycaemia before hospital admission, or the adequacy of glycaemic control after discharge from the ICU. We were therefore unable to exclude the possibility that management of glycaemic control before or after ICU admission may have biased our results. Fourth, our study population was a subset of critically ill patients with diabetes for whom both HbA_{1c} and BG data were available, which introduces potential selection bias.²⁶ Finally, only central pathology results were available, and incorporating results from bedside glucometer testing may have altered our estimates.

Clinical implications

These data are complementary to recent observational and interventional studies indicating that patients with diabetes may be more tolerant of hyperglycaemia and increased glycaemic variability than patients with normal glucose tolerance, and that this tolerance is influenced by their degree of prior glycaemic control.^{36,37} However, hypoglycaemia occurred more frequently in critically ill patients with diabetes, and the strong association with mortality was not attenuated in this group. Therefore, avoidance of hypoglycaemia warrants particular vigilance in critically ill patients with diabetes.¹⁷

Future directions

Future prospective observational studies, incorporating measurement of prior hyperglycaemia and comorbidities on ICU admission and a prolonged follow-up period, would be complementary. Interventional studies aimed at avoiding hypoglycaemia in patients with diabetes during critical illness also appear warranted.

Conclusions

Prior exposure to hyperglycaemia attenuates the relationship between glycaemic variability during critical illness and mortality. For patients with prior exposure to hyperglycaemia, avoidance of hypoglycaemia may represent a greater priority than treating hyperglycaemia or limiting glycaemic variability.

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Competing interests

None declared.

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Appendix

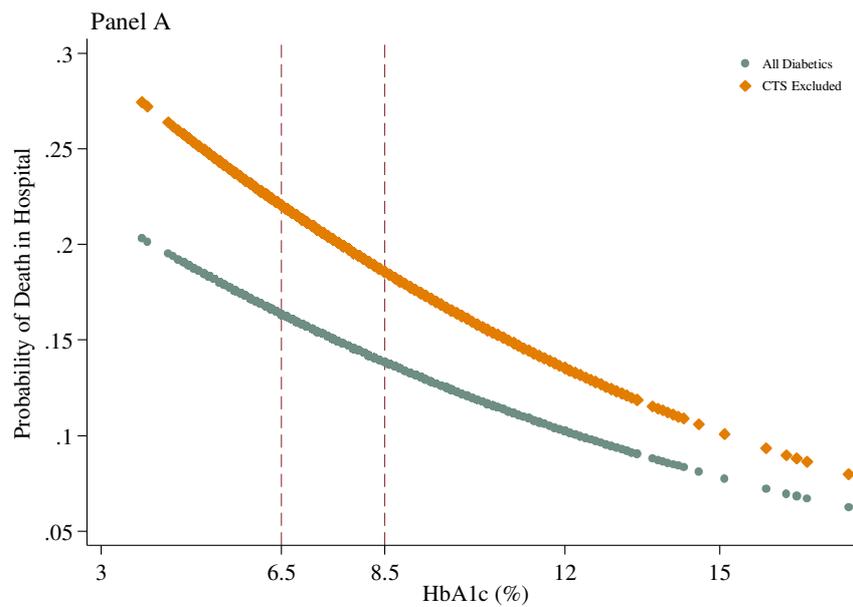
This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

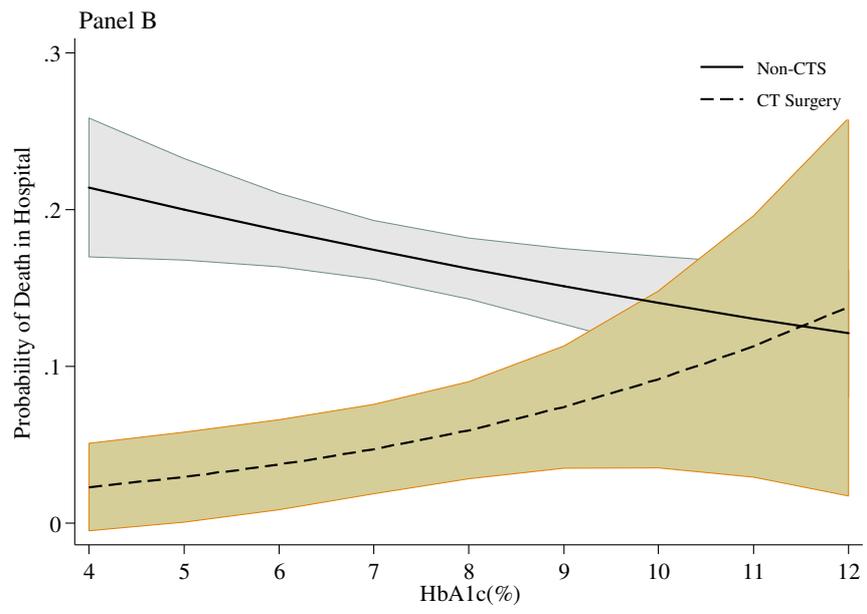
Supplemental Tables and Figures

Supplemental Figure 1

A) Logistic regression for hospital death against HbA1c as a continuous variable for the entire cohort and with patients admitted with a diagnostic category of cardiothoracic surgery (CTS) excluded.

B) Marginal model predictions (with 95% confidence bands) for hospital death for the entire cohort and with patients admitted with a diagnostic category of cardiothoracic surgery.





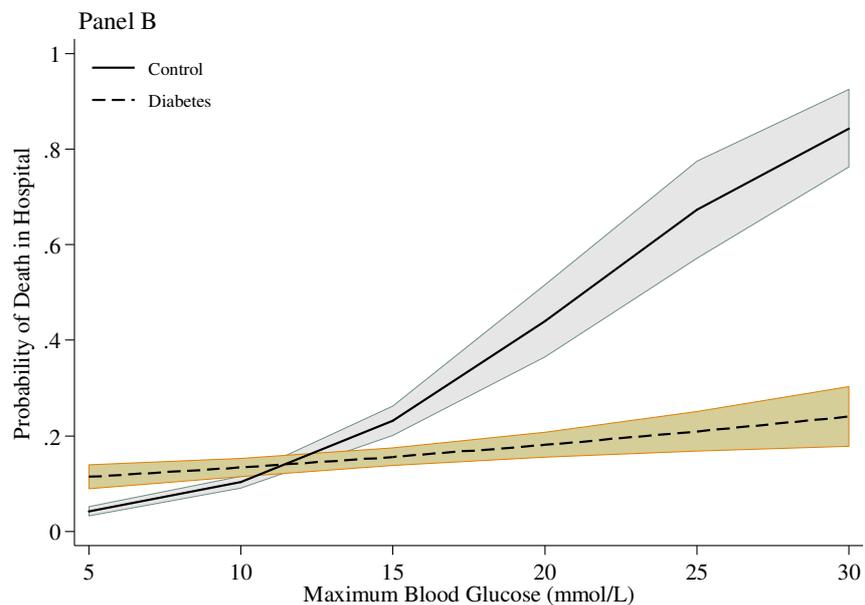
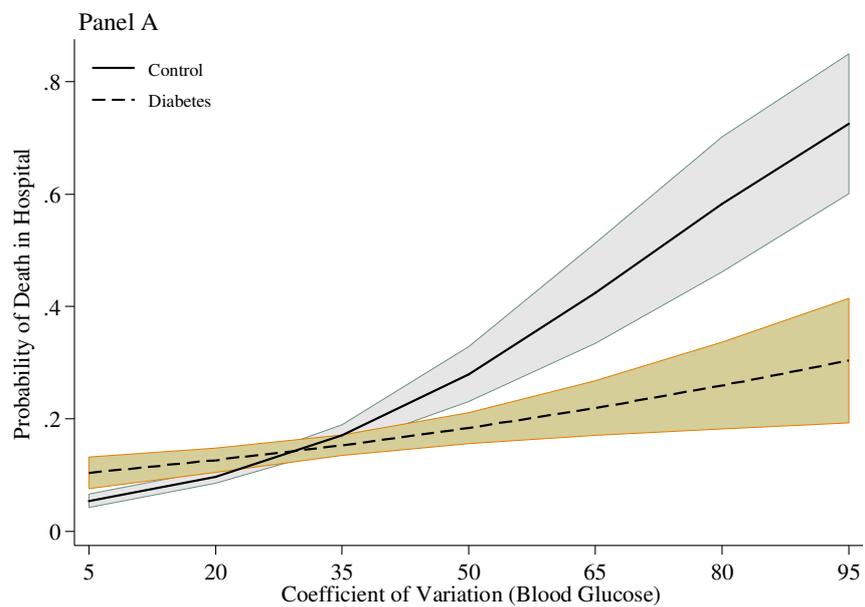
Supplemental Figure 2

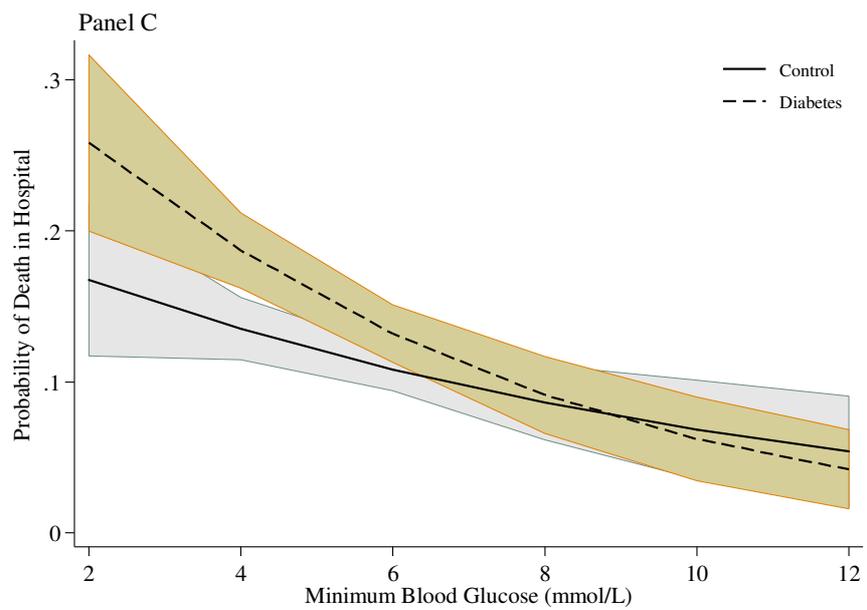
Marginal model predictions (with 95% confidence bands) of probability of hospital death for patients with a diabetes flag compared to controls for

A) Glycaemic variability (coefficient of variation);

B) Hyperglycaemia (peak blood glucose); and

C) Hypoglycaemia.





Supplemental Figure 3

Kaplan-Meier survival curves at one year according to:

A) Prior exposure to hyperglycaemia.

B) For patients with diabetes compared to controls

