**SUPPLEMENTAL DIGITAL CONTENT FOR**

**Independent Association of Glucose Variability with Hospital Mortality in Adult Intensive Care Patients: Results From The ANZICS CORE Binational Registry**

**Hemant Kulkarni, MD1, Shailesh Bihari, MD, FCICM, PhD2, Shivesh Prakash, MD, MPH, EDIC, FCICM2, Sue Huckson, BAppSci (Health Promotion)3, Shaila Chavan, MSPH3, Manju Mamtani, MD1, David Pilcher, MRCP, FRACP, FCICM3-5**

1 M&H Research, LLC, San Antonio, Texas, USA

2 Flinders University and Flinders Medical Centre, Adelaide, Australia

3 The Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation (CORE), 277 Camberwell Road, Camberwell VIC 3124, Australia

4 The Department of Intensive Care, Alfred Health, Commercial Road, Prahran, VIC 3004, Australia

5 The Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Commercial Road, Prahran VIC 3004, Australia

**Corresponding author:**

Hemant Kulkarni, MD

12023 Waterway Rdg,

San Antonio, TX 78249, USA

Phone: +1 (210) 602 5537

Email: [hemant.kulkarni@mnhresearch.com](mailto:hemant.kulkarni@mnhresearch.com)

**CONTENTS**

|  |  |
| --- | --- |
| **Item** | **Page** |
| *Supplementary Notes* |  |
| Supplementary Note 1: Proof-of-concept studies to demonstrate that glucose width can adequately capture glucose variability | 4-5 |
| Supplementary Note 2: Sensitivity analyses for the potential influence of unmeasured confounding on the association of glucose width with hospital mortality | 6-7 |
| *Supplementary Figures* | |
| Supplementary Figure 1. Proof-of-concept studies for appropriateness of MinMax versus UAV methods to measure glucose variability | 8 |
| Supplementary Figure 2. Box plots showing distribution of glucose width in the study patients | 9 |
| *Supplementary Tables* |  |
| Supplementary Table 1: Mean BGL values based on quartiles of glucose width | 10 |
| Supplementary Table 2: Specificity of the association of glucose width quartiles with hospital mortality | 11 |
| Supplementary Table 3: Choice of the Г parameter using Rosenbaum’s method for sensitivity analysis for the association of high glucose variability with hospital mortality potentially confounded by an unmeasured confounding factor. | 12 |
| Supplementary Table 4. Greenland Sensitivity analysis for the potential influence of unmeasured confounding on the association of glucose variability with hospital mortality | 13-21 |
| Supplementary Table 5: Potential influence of measured, dichotomous confounders on the association of glucose width with hospital mortality estimated using the Greenland method of sensitivity analysis. | 22 |
| Supplementary Table 6: Comparison of clinical characteristics of patients belonging to the lowest and highest quartile of glucose width | 23 |
| *References* | 24 |

**Supplementary Note 1: Proof-of-concept studies to demonstrate that glucose width can adequately capture glucose variability**

**Background and Objective**

Constrained by the data structure of the ANZICS CORE APD dataset, we used glucose width (defined as the difference between the largest and smallest BGL value) as a measure of glucose variability. Rodbart has extensively reviewed the methods used for measuring glucose variability and their relative merits and demerits.([1-3](#_ENREF_1)) Glucose width is a simple measure, the accuracy and use of which is not known. Our objective in these proof-of-concept studies was to demonstrate the adequacy of using glucose width to capture glucose variability using publicly available recordings of continuous glucose monitoring (CGM).

**The dataset**

For these studies we used the AIM-94 (Artificial Intelligence in Medicine 1994) Diabetes dataset (https://archive.ics.uci.edu/ml/datasets/diabetes) generously provided for research purposes by Michael Kahn, MD, PhD, Washington University, St. Louis, MO. This dataset contains annotated BGL recordings from CGM on 70 diabetic patients. From this dataset, we extracted the BGL data and included patients on whom at least 30 measurements were available. Therefore, our studies use 63 (90% of the full dataset) CGM recordings.

**Methods**

For each of the 63 patients, we first extracted the minimum and maximum recorded BGL. Based on this we estimated the glucose width and mean glucose level. Considering the range rule of normal distribution, standard deviation (SD) can be approximated as range/4 and thus we estimated the SD as glucose width/4. We dubbed this method of deriving the mean and standard deviation as the MinMax method. Alternatively, we used all the recorded BGL values for a patient and calculated the actual mean and standard deviation from these observations (method dubbed as “Using All Values (UAV)”). We then statistically compared the results from these two methods. Statistical comparison was made using correlational plots, estimating Pearson’s correlation coefficient, generating Bland-Altman plots, determining the limits of agreement (LAG) and testing for equal variances using Pitman’s test. All analyses were done using Stata 12.0 (Stata Corp, College Station, Texas) software package.

**Results**

The results of our analyses are shown in Supplementary Figure 1. We found that the mean BGL levels estimated by the MinMax method and the UAV method showed a correlation of 67% with each other (p<0.0001, Supplementary Figure 1A). The Bland-Altman plot (Supplementary Figure 1B) showed a good agreement between the two although the MinMax method generally provided higher values of mean BAG as compared to the UAV method. However, only 2 (3.2%) of the observations fell outside the limits of agreement demonstrating that there was 96.8% agreement between the methods. Moreover, the Pitman’s test did not show any statistically significant difference in variance for the mean BAG with the two methods. Similarly, when we compared the standard deviations estimated using the MinMax and the UAV methods we found an even stronger Pearson’s correlation coefficient (81%, p<0.0001, Supplementary Figure 1C). The MinMax method continued to yield slightly higher values of SD (mean difference between the methods being 0.37 mmols/L) but the Bland-Altman plot (Supplementary Figure 1D) showed that only 3 (4.8%) observations were outside the limits of agreement indicating a 95.2% agreement between the two methods. The Pitman’s test was however significant indicating a possible difference in variance of the SD estimates. Together, these observations demonstrated that the MinMax method had a high agreement with true mean and SD of the data. It should be remembered however that the analyses presented here are from diabetic patients who tend to have a higher glucose variability than euglycemic or stress hyperglycemic patients.

**Supplementary Note 2: Sensitivity analyses for the potential influence of unmeasured confounding on the association of glucose width with hospital mortality**

**Background**

Our study is observational in nature and is thus prone to confounding bias such that measured or unmeasured confounders may strengthen or weaken the true association. Two approaches have been recommended and widely used in the literature to address this issue and re together combined in an integrated approach to sensitivity analyses. These approaches estimate the potential influence of a confounder (Z) on the association of exposure (E) on outcome (D). In our case, E and D represent glucose width and hospital mortality. To make our data amenable to these sensitivity analyses, we dichotomized glucose width as highest quartile compared to the rest of the patients.

**Methods**

The first approach suggested by Rosenbaum ([4](#_ENREF_4)) attempts to identify the value of the parameter Г (representing the magnitude of unmeasured confounder to the exposure) which makes the observed association (ORDE) statistically non-significant. The approach is similar to a Mantel-Haenszel procedure and estimates the summary effect size (odds ratio) contingent upon a pre-selected value of Г. The second approach developed by Greenland ([5](#_ENREF_5)) is also referred to as the external adjustment method ([6](#_ENREF_6)) and quantifies the variation in association when adjusted for a potential confounder. The method simulates various plausible values for confounder prevalence and the magnitude of the confounder-outcome association. While the Greenland method assumes that the confounder must be associated with both the exposure and outcome, the Rosenbaum method only utilizes the association between the confounder and the exposure. It has been recommended that as an integrated approach, the Rosenbaum method should be first used to estimate the Г parameter which should be used as a guiding, starting point for the Greenland method. We used this approach in our sensitivity analyses. For these analyses, we used the spreadsheet approach outlined by Cabral and Luiz.([7](#_ENREF_7))

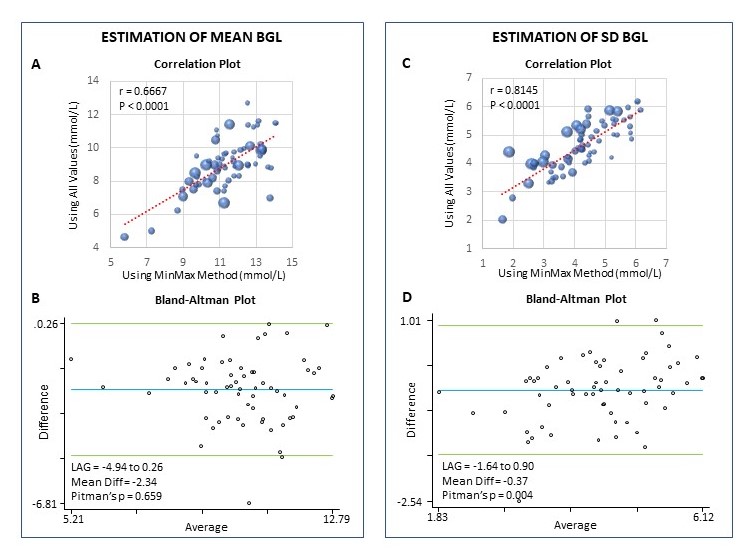
**Results**

The unadjusted, raw odds ratio for the association of glucose width (E) with hospital mortality (D) was 1.87 (95% CI 1.81 – 1.92), p<<0.0001. Using the Rosenbaum method, the critical value of Г that yielded statistically non-significant association was estimated to be 1.83 (Supplementary Table 3). Next, we varied the ORDZ value over the range of 1.5 through 5 (which included the estimated Г parameter in the previous step) and the prevalence of confounder in exposed and unexposed over the ranges of 0.2-0.7 and 0.1-0.6, respectively. These ranges were consistent with the distribution of measured confounders in the study. The results showed that only when the ORDZ values exceeded 4, was the ED association substantially influenced (Supplementary Table 4). Consistent with this interpretation, we estimated the potential impact of 11 putative, dichotomous, observed confounders on the association of glucose width with hospital mortality. We found (Supplementary Table 5) that with the exception of hypoglycemic event none of the putative confounders substantially influenced the ORED association.

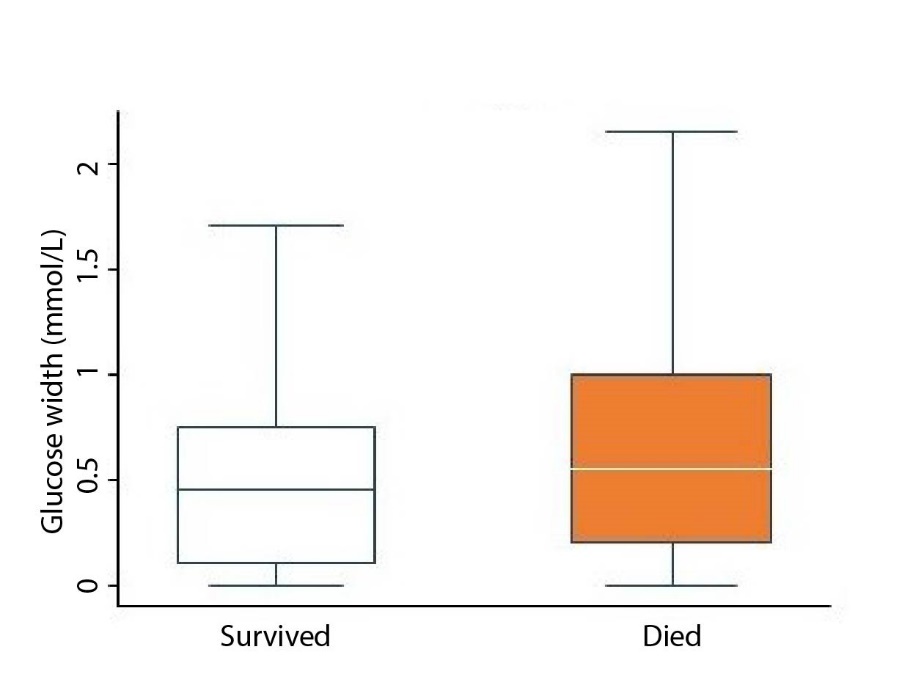
**Conclusion**

Together, these results indicate that our interpretations are unlikely to be greatly influenced by known or unknown confounders.

**Supplementary Figure 1. Proof-of-concept studies for appropriateness of MinMax versus UAV methods to measure glucose variability**. (A-B) Estimation of mean blood glucose levels and (C-D) estimation of standard deviation of blood glucose levels (BGL). Panels A and C represent weigted correlation plots shown as bubbles. Each bubble represents a patient and the radius of the bubble is proportional to the number of BGL observations. Panels B and D show Bland-Altman plots (difference versus average plots). Green lines in panels B and D represent the limits of agreement and blue line represents the mean difference. LAG, limits of agreement



**Supplementary Figure 2. Box plots showing distribution of glucose width in the study patients.** Empty boxes are for survivors and filled boxes are for patients who died in hospital.



**Supplementary Table 1: Mean BGL values based on quartiles of glucose width.** Cells show mean (SD) mid-point BGL values in mmol/L.

|  |  |
| --- | --- |
| Glucose width  quartile | MBGL  mmol/L |
| 1 | 6.02 (0.93) |
| 2 | 5.99 (0.75) |
| 3 | 5.83 (0.65) |
| 4 | 5.25 (0.68) |

**Supplementary Table 2. Specificity of the association of glucose width quartiles with hospital mortality\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Width covariate** | **OR (95% CI) for width covariate** | **OR (95% CI) for glucose width quartile**  **2nd vs 1st** | **OR (95% CI) for glucose width quartile**  **3rd vs 1st** | **OR (95% CI) for glucose width quartile**  **4th vs 1st** |
| Hemoglobin | 0.99  (0.98 – 1.01) | 1.09  (1.05 – 1.15) | 1.20  (1.14 – 1.27) | 1.46  (1.33 – 1.60) |
| Hematocrit | 1.01  (0.99 – 1.02) | 1.08  (1.03 – 1.13) | 1.21  (1.15 – 1.27) | 1.41  (1.29 – 1.54) |
| Systolic blood pressure | 0.99  (0.98 – 1.01) | 1.08  (1.04 – 1.13) | 1.19  (1.14 – 1.25) | 1.48  (1.36 – 1.61) |
| Diastolic blood pressure | 0.96  (0.95 – 0.98) | 1.09  (1.05 – 1.13) | 1.19  (1.14 – 1.25) | 1.48  (1.36 – 1.61) |
| White cell count | 0.98  (0.96 – 1.00) | 1.09  (1.04 – 1.13) | 1.21  (1.15 – 1.27) | 1.48  (1.36 – 1.61) |
| Platelet count | 1.01  (0.99 – 1.03) | 1.09  (1.04 – 1.14) | 1.19  (1.13 – 1.26) | 1.44  (1.31 – 1.59) |

\*, Results are from mixed effects logistic regression models that included all the covariates mentioned in the last model in Table 2 and the additional width covariates indicated here. Width for each covariate is defined as the difference between the highest and lowest value within 24 hours of ICU admission

**Supplementary Table 3: Choice of the Г parameter using Rosenbaum’s method for sensitivity analysis for the association of high glucose variability with hospital mortality potentially confounded by an unmeasured confounding factor.**

|  |  |  |
| --- | --- | --- |
| Г | Z value | P value |
| 1.0 | 43.41 | <<0.0001 |
| 1.1 | 36.65 | <<0.0001 |
| 1.2 | 30.53 | <<0.0001 |
| 1.3 | 24.96 | <<0.0001 |
| 1.4 | 19.82 | <<0.0001 |
| 1.5 | 15.07 | <<0.0001 |
| 1.6 | 10.62 | <<0.0001 |
| 1.7 | 6.46 | 5.2x10-11 |
| 1.8 | 2.54 | 0.0056 |
| 1.83 | 1.41 | 0.0799 |
| 1.9 | 1.15 | 0.1241 |

**Supplementary Table 4. Greenland Sensitivity analysis for the potential influence of unmeasured confounding on the association of glucose variability with hospital mortality**

*Key to column titles:*

Inputs to sensitivity analyses:

ORDZ – Odds ratio for association of the outcome (D) with the unmeasured confounder (Z);

Zexp – prevalence of the confounder in patients with high glucose variability (highest quartile);

Zunexp – prevalence of the confounder in patients with low glucose variability (quartiles 1-3);

Outputs from sensitivity analyses

ORDE1 – adjusted odds ratio for association of glucose variability with hospital mortalty in patients with the confounder;

ORDE0 – adjusted odds ratio for association of glucose variability with hospital mortality in patients without the confounder

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ORDZ | Zexp | Zunex | ORDE1 | ORDE0 |
| 1.5 | 0.2 | 0.1 | 1.783566 | 1.783096 |
| 1.5 | 0.2 | 0.2 | 1.868174 | 1.868051 |
| 1.5 | 0.2 | 0.3 | 1.953063 | 1.952969 |
| 1.5 | 0.2 | 0.4 | 2.037964 | 2.03789 |
| 1.5 | 0.2 | 0.5 | 2.122925 | 2.122734 |
| 1.5 | 0.2 | 0.6 | 2.20781 | 2.207679 |
| 1.5 | 0.3 | 0.1 | 1.706117 | 1.705505 |
| 1.5 | 0.3 | 0.2 | 1.78705 | 1.786763 |
| 1.5 | 0.3 | 0.3 | 1.868253 | 1.867986 |
| 1.5 | 0.3 | 0.4 | 1.949467 | 1.949212 |
| 1.5 | 0.3 | 0.5 | 2.030739 | 2.030363 |
| 1.5 | 0.3 | 0.6 | 2.111938 | 2.111612 |
| 1.5 | 0.4 | 0.1 | 1.634867 | 1.634542 |
| 1.5 | 0.4 | 0.2 | 1.712421 | 1.712419 |
| 1.5 | 0.4 | 0.3 | 1.790233 | 1.790263 |
| 1.5 | 0.4 | 0.4 | 1.868055 | 1.868109 |
| 1.5 | 0.4 | 0.5 | 1.945933 | 1.945884 |
| 1.5 | 0.4 | 0.6 | 2.023741 | 2.023752 |
| 1.5 | 0.5 | 0.1 | 1.5695 | 1.569143 |
| 1.5 | 0.5 | 0.2 | 1.643953 | 1.643904 |
| 1.5 | 0.5 | 0.3 | 1.718653 | 1.718633 |
| 1.5 | 0.5 | 0.4 | 1.793364 | 1.793364 |
| 1.5 | 0.5 | 0.5 | 1.868128 | 1.868027 |
| 1.5 | 0.5 | 0.6 | 1.942825 | 1.942779 |
| 1.5 | 0.6 | 0.1 | 1.509215 | 1.508623 |
| 1.5 | 0.6 | 0.2 | 1.580808 | 1.5805 |
| 1.5 | 0.6 | 0.3 | 1.652639 | 1.652347 |
| 1.5 | 0.6 | 0.4 | 1.724481 | 1.724196 |
| 1.5 | 0.6 | 0.5 | 1.796373 | 1.795979 |
| 1.5 | 0.6 | 0.6 | 1.868201 | 1.867849 |
| 1.5 | 0.7 | 0.1 | 1.453207 | 1.453018 |
| 1.5 | 0.7 | 0.2 | 1.522144 | 1.522246 |
| 1.5 | 0.7 | 0.3 | 1.591309 | 1.591445 |
| 1.5 | 0.7 | 0.4 | 1.660484 | 1.660646 |
| 1.5 | 0.7 | 0.5 | 1.729709 | 1.729783 |
| 1.5 | 0.7 | 0.6 | 1.798871 | 1.799004 |
| 1.5 | 0.8 | 0.1 | 1.401374 | 1.40082 |
| 1.5 | 0.8 | 0.2 | 1.467852 | 1.467561 |
| 1.5 | 0.8 | 0.3 | 1.53455 | 1.534274 |
| 1.5 | 0.8 | 0.4 | 1.601258 | 1.600989 |
| 1.5 | 0.8 | 0.5 | 1.668014 | 1.667643 |
| 1.5 | 0.8 | 0.6 | 1.734709 | 1.734377 |
| 2 | 0.2 | 0.1 | 1.712002 | 1.712566 |
| 2 | 0.2 | 0.2 | 1.867942 | 1.868152 |
| 2 | 0.2 | 0.3 | 2.023582 | 2.023803 |
| 2 | 0.2 | 0.4 | 2.179053 | 2.179676 |
| 2 | 0.2 | 0.5 | 2.3347 | 2.335418 |
| 2 | 0.2 | 0.6 | 2.49032 | 2.491275 |
| 2 | 0.3 | 0.1 | 1.58062 | 1.580659 |
| 2 | 0.3 | 0.2 | 1.724593 | 1.724262 |
| 2 | 0.3 | 0.3 | 1.868288 | 1.867925 |
| 2 | 0.3 | 0.4 | 2.011829 | 2.011792 |
| 2 | 0.3 | 0.5 | 2.155531 | 2.155538 |
| 2 | 0.3 | 0.6 | 2.299208 | 2.29939 |
| 2 | 0.4 | 0.1 | 1.467753 | 1.467647 |
| 2 | 0.4 | 0.2 | 1.601445 | 1.600983 |
| 2 | 0.4 | 0.3 | 1.73488 | 1.734374 |
| 2 | 0.4 | 0.4 | 1.868171 | 1.867955 |
| 2 | 0.4 | 0.5 | 2.001611 | 2.001424 |
| 2 | 0.4 | 0.6 | 2.135029 | 2.134991 |
| 2 | 0.5 | 0.1 | 1.369883 | 1.369788 |
| 2 | 0.5 | 0.2 | 1.494661 | 1.494234 |
| 2 | 0.5 | 0.3 | 1.619199 | 1.618731 |
| 2 | 0.5 | 0.4 | 1.743601 | 1.743405 |
| 2 | 0.5 | 0.5 | 1.868144 | 1.867974 |
| 2 | 0.5 | 0.6 | 1.992666 | 1.992635 |
| 2 | 0.6 | 0.1 | 1.2842 | 1.284316 |
| 2 | 0.6 | 0.2 | 1.401173 | 1.400996 |
| 2 | 0.6 | 0.3 | 1.517921 | 1.517725 |
| 2 | 0.6 | 0.4 | 1.634542 | 1.634619 |
| 2 | 0.6 | 0.5 | 1.751295 | 1.751416 |
| 2 | 0.6 | 0.6 | 1.868028 | 1.868298 |
| 2 | 0.7 | 0.1 | 1.208584 | 1.209056 |
| 2 | 0.7 | 0.2 | 1.31867 | 1.318898 |
| 2 | 0.7 | 0.3 | 1.428544 | 1.428787 |
| 2 | 0.7 | 0.4 | 1.538298 | 1.538832 |
| 2 | 0.7 | 0.5 | 1.648177 | 1.648784 |
| 2 | 0.7 | 0.6 | 1.758036 | 1.758817 |
| 2 | 0.8 | 0.1 | 1.141574 | 1.14104 |
| 2 | 0.8 | 0.2 | 1.245556 | 1.244704 |
| 2 | 0.8 | 0.3 | 1.349338 | 1.348411 |
| 2 | 0.8 | 0.4 | 1.453007 | 1.452265 |
| 2 | 0.8 | 0.5 | 1.556794 | 1.556032 |
| 2 | 0.8 | 0.6 | 1.660562 | 1.659875 |
| 2.5 | 0.2 | 0.1 | 1.652717 | 1.652402 |
| 2.5 | 0.2 | 0.2 | 1.868386 | 1.867889 |
| 2.5 | 0.2 | 0.3 | 2.083969 | 2.083391 |
| 2.5 | 0.2 | 0.4 | 2.299432 | 2.299078 |
| 2.5 | 0.2 | 0.5 | 2.515102 | 2.514425 |
| 2.5 | 0.2 | 0.6 | 2.730575 | 2.730303 |
| 2.5 | 0.3 | 0.1 | 1.481478 | 1.481683 |
| 2.5 | 0.3 | 0.2 | 1.674802 | 1.674907 |
| 2.5 | 0.3 | 0.3 | 1.868048 | 1.868144 |
| 2.5 | 0.3 | 0.4 | 2.061187 | 2.061547 |
| 2.5 | 0.3 | 0.5 | 2.254511 | 2.254646 |
| 2.5 | 0.3 | 0.6 | 2.44766 | 2.448219 |
| 2.5 | 0.4 | 0.1 | 1.34263 | 1.342713 |
| 2.5 | 0.4 | 0.2 | 1.517834 | 1.517814 |
| 2.5 | 0.4 | 0.3 | 1.692969 | 1.692927 |
| 2.5 | 0.4 | 0.4 | 1.868007 | 1.86819 |
| 2.5 | 0.4 | 0.5 | 2.043212 | 2.043178 |
| 2.5 | 0.4 | 0.6 | 2.218258 | 2.218596 |
| 2.5 | 0.5 | 0.1 | 1.22763 | 1.227455 |
| 2.5 | 0.5 | 0.2 | 1.387828 | 1.387525 |
| 2.5 | 0.5 | 0.3 | 1.547962 | 1.547606 |
| 2.5 | 0.5 | 0.4 | 1.708007 | 1.707825 |
| 2.5 | 0.5 | 0.5 | 1.868206 | 1.867792 |
| 2.5 | 0.5 | 0.6 | 2.028259 | 2.028152 |
| 2.5 | 0.6 | 0.1 | 1.13063 | 1.130815 |
| 2.5 | 0.6 | 0.2 | 1.27817 | 1.278283 |
| 2.5 | 0.6 | 0.3 | 1.425651 | 1.425761 |
| 2.5 | 0.6 | 0.4 | 1.573051 | 1.573365 |
| 2.5 | 0.6 | 0.5 | 1.720591 | 1.720738 |
| 2.5 | 0.6 | 0.6 | 1.867998 | 1.868472 |
| 2.5 | 0.7 | 0.1 | 1.0479 | 1.048081 |
| 2.5 | 0.7 | 0.2 | 1.184645 | 1.184759 |
| 2.5 | 0.7 | 0.3 | 1.321334 | 1.321447 |
| 2.5 | 0.7 | 0.4 | 1.457948 | 1.458252 |
| 2.5 | 0.7 | 0.5 | 1.594693 | 1.594842 |
| 2.5 | 0.7 | 0.6 | 1.731314 | 1.731768 |
| 2.5 | 0.8 | 0.1 | 0.97643 | 0.976981 |
| 2.5 | 0.8 | 0.2 | 1.103848 | 1.104388 |
| 2.5 | 0.8 | 0.3 | 1.231215 | 1.231803 |
| 2.5 | 0.8 | 0.4 | 1.358511 | 1.359327 |
| 2.5 | 0.8 | 0.5 | 1.48593 | 1.486652 |
| 2.5 | 0.8 | 0.6 | 1.613232 | 1.614289 |
| 3 | 0.2 | 0.1 | 1.600781 | 1.601445 |
| 3 | 0.2 | 0.2 | 1.867902 | 1.868211 |
| 3 | 0.2 | 0.3 | 2.134745 | 2.135049 |
| 3 | 0.2 | 0.4 | 2.401406 | 2.40222 |
| 3 | 0.2 | 0.5 | 2.6682 | 2.669307 |
| 3 | 0.2 | 0.6 | 2.93521 | 2.935569 |
| 3 | 0.3 | 0.1 | 1.400743 | 1.401321 |
| 3 | 0.3 | 0.2 | 1.634484 | 1.63475 |
| 3 | 0.3 | 0.3 | 1.867981 | 1.868242 |
| 3 | 0.3 | 0.4 | 2.10132 | 2.102027 |
| 3 | 0.3 | 0.5 | 2.334774 | 2.335737 |
| 3 | 0.3 | 0.6 | 2.568419 | 2.568726 |
| 3 | 0.4 | 0.1 | 1.245287 | 1.245304 |
| 3 | 0.4 | 0.2 | 1.453086 | 1.452744 |
| 3 | 0.4 | 0.3 | 1.66067 | 1.66024 |
| 3 | 0.4 | 0.4 | 1.868112 | 1.867996 |
| 3 | 0.4 | 0.5 | 2.075657 | 2.075686 |
| 3 | 0.4 | 0.6 | 2.283372 | 2.282735 |
| 3 | 0.5 | 0.1 | 1.120707 | 1.120901 |
| 3 | 0.5 | 0.2 | 1.307718 | 1.307619 |
| 3 | 0.5 | 0.3 | 1.494535 | 1.494387 |
| 3 | 0.5 | 0.4 | 1.681224 | 1.681388 |
| 3 | 0.5 | 0.5 | 1.868007 | 1.86833 |
| 3 | 0.5 | 0.6 | 2.054941 | 2.054696 |
| 3 | 0.6 | 0.1 | 1.018879 | 1.018791 |
| 3 | 0.6 | 0.2 | 1.188898 | 1.1885 |
| 3 | 0.6 | 0.3 | 1.358741 | 1.358254 |
| 3 | 0.6 | 0.4 | 1.528467 | 1.52822 |
| 3 | 0.6 | 0.5 | 1.698278 | 1.698133 |
| 3 | 0.6 | 0.6 | 1.868228 | 1.867521 |
| 3 | 0.7 | 0.1 | 0.933918 | 0.934095 |
| 3 | 0.7 | 0.2 | 1.08976 | 1.089695 |
| 3 | 0.7 | 0.3 | 1.24544 | 1.245337 |
| 3 | 0.7 | 0.4 | 1.401013 | 1.401173 |
| 3 | 0.7 | 0.5 | 1.556664 | 1.55696 |
| 3 | 0.7 | 0.6 | 1.712442 | 1.712266 |
| 3 | 0.8 | 0.1 | 0.862122 | 0.861783 |
| 3 | 0.8 | 0.2 | 1.005983 | 1.005338 |
| 3 | 0.8 | 0.3 | 1.149695 | 1.148931 |
| 3 | 0.8 | 0.4 | 1.293309 | 1.292703 |
| 3 | 0.8 | 0.5 | 1.436995 | 1.43643 |
| 3 | 0.8 | 0.6 | 1.580797 | 1.579714 |
| 3.5 | 0.2 | 0.1 | 1.556838 | 1.55663 |
| 3.5 | 0.2 | 0.2 | 1.868292 | 1.867888 |
| 3.5 | 0.2 | 0.3 | 2.179641 | 2.179203 |
| 3.5 | 0.2 | 0.4 | 2.491057 | 2.490383 |
| 3.5 | 0.2 | 0.5 | 2.802282 | 2.802106 |
| 3.5 | 0.2 | 0.6 | 3.113676 | 3.1134 |
| 3.5 | 0.3 | 0.1 | 1.334351 | 1.334347 |
| 3.5 | 0.3 | 0.2 | 1.601296 | 1.601158 |
| 3.5 | 0.3 | 0.3 | 1.868149 | 1.868018 |
| 3.5 | 0.3 | 0.4 | 2.135061 | 2.134762 |
| 3.5 | 0.3 | 0.5 | 2.40181 | 2.401971 |
| 3.5 | 0.3 | 0.6 | 2.668702 | 2.668813 |
| 3.5 | 0.4 | 0.1 | 1.167524 | 1.167572 |
| 3.5 | 0.4 | 0.2 | 1.401094 | 1.401036 |
| 3.5 | 0.4 | 0.3 | 1.634584 | 1.634542 |
| 3.5 | 0.4 | 0.4 | 1.868125 | 1.867947 |
| 3.5 | 0.4 | 0.5 | 2.101523 | 2.101759 |
| 3.5 | 0.4 | 0.6 | 2.335048 | 2.33525 |
| 3.5 | 0.5 | 0.1 | 1.037798 | 1.037895 |
| 3.5 | 0.5 | 0.2 | 1.245416 | 1.245429 |
| 3.5 | 0.5 | 0.3 | 1.452962 | 1.453001 |
| 3.5 | 0.5 | 0.4 | 1.660554 | 1.660483 |
| 3.5 | 0.5 | 0.5 | 1.868019 | 1.868326 |
| 3.5 | 0.5 | 0.6 | 2.075596 | 2.075884 |
| 3.5 | 0.6 | 0.1 | 0.93399 | 0.934324 |
| 3.5 | 0.6 | 0.2 | 1.12084 | 1.121149 |
| 3.5 | 0.6 | 0.3 | 1.307626 | 1.308007 |
| 3.5 | 0.6 | 0.4 | 1.494453 | 1.494784 |
| 3.5 | 0.6 | 0.5 | 1.681166 | 1.681887 |
| 3.5 | 0.6 | 0.6 | 1.86798 | 1.868733 |
| 3.5 | 0.7 | 0.1 | 0.849162 | 0.848788 |
| 3.5 | 0.7 | 0.2 | 1.019042 | 1.018509 |
| 3.5 | 0.7 | 0.3 | 1.188864 | 1.18826 |
| 3.5 | 0.7 | 0.4 | 1.358723 | 1.357938 |
| 3.5 | 0.7 | 0.5 | 1.528478 | 1.527912 |
| 3.5 | 0.7 | 0.6 | 1.698324 | 1.697653 |
| 3.5 | 0.8 | 0.1 | 0.778331 | 0.778848 |
| 3.5 | 0.8 | 0.2 | 0.934041 | 0.934584 |
| 3.5 | 0.8 | 0.3 | 1.089697 | 1.090348 |
| 3.5 | 0.8 | 0.4 | 1.245387 | 1.246045 |
| 3.5 | 0.8 | 0.5 | 1.400983 | 1.402013 |
| 3.5 | 0.8 | 0.6 | 1.556662 | 1.557767 |
| 4 | 0.2 | 0.1 | 1.51777 | 1.517839 |
| 4 | 0.2 | 0.2 | 1.868055 | 1.868096 |
| 4 | 0.2 | 0.3 | 2.218304 | 2.218384 |
| 4 | 0.2 | 0.4 | 2.568555 | 2.568687 |
| 4 | 0.2 | 0.5 | 2.918742 | 2.919279 |
| 4 | 0.2 | 0.6 | 3.268991 | 3.269805 |
| 4 | 0.3 | 0.1 | 1.278065 | 1.278329 |
| 4 | 0.3 | 0.2 | 1.573029 | 1.573316 |
| 4 | 0.3 | 0.3 | 1.867962 | 1.86833 |
| 4 | 0.3 | 0.4 | 2.162897 | 2.163357 |
| 4 | 0.3 | 0.5 | 2.457778 | 2.458626 |
| 4 | 0.3 | 0.6 | 2.752712 | 2.753841 |
| 4 | 0.4 | 0.1 | 1.103816 | 1.103937 |
| 4 | 0.4 | 0.2 | 1.358564 | 1.358682 |
| 4 | 0.4 | 0.3 | 1.613286 | 1.613449 |
| 4 | 0.4 | 0.4 | 1.868011 | 1.868228 |
| 4 | 0.4 | 0.5 | 2.122688 | 2.123216 |
| 4 | 0.4 | 0.6 | 2.37741 | 2.378157 |
| 4 | 0.5 | 0.1 | 0.97139 | 0.971413 |
| 4 | 0.5 | 0.2 | 1.195576 | 1.195576 |
| 4 | 0.5 | 0.3 | 1.419739 | 1.41976 |
| 4 | 0.5 | 0.4 | 1.643904 | 1.643953 |
| 4 | 0.5 | 0.5 | 1.868027 | 1.86833 |
| 4 | 0.5 | 0.6 | 2.09219 | 2.092666 |
| 4 | 0.6 | 0.1 | 0.86734 | 0.867209 |
| 4 | 0.6 | 0.2 | 1.067513 | 1.067326 |
| 4 | 0.6 | 0.3 | 1.267665 | 1.267462 |
| 4 | 0.6 | 0.4 | 1.467819 | 1.467605 |
| 4 | 0.6 | 0.5 | 1.667935 | 1.667914 |
| 4 | 0.6 | 0.6 | 1.868087 | 1.868185 |
| 4 | 0.7 | 0.1 | 0.78341 | 0.783078 |
| 4 | 0.7 | 0.2 | 0.964213 | 0.963782 |
| 4 | 0.7 | 0.3 | 1.144996 | 1.144501 |
| 4 | 0.7 | 0.4 | 1.325782 | 1.325228 |
| 4 | 0.7 | 0.5 | 1.506533 | 1.506104 |
| 4 | 0.7 | 0.6 | 1.687317 | 1.686947 |
| 4 | 0.8 | 0.1 | 0.714283 | 0.713903 |
| 4 | 0.8 | 0.2 | 0.879131 | 0.878643 |
| 4 | 0.8 | 0.3 | 1.043963 | 1.043398 |
| 4 | 0.8 | 0.4 | 1.208796 | 1.20816 |
| 4 | 0.8 | 0.5 | 1.373598 | 1.373058 |
| 4 | 0.8 | 0.6 | 1.53843 | 1.537925 |
| 4.5 | 0.2 | 0.1 | 1.483511 | 1.483486 |
| 4.5 | 0.2 | 0.2 | 1.868098 | 1.868048 |
| 4.5 | 0.2 | 0.3 | 2.252505 | 2.252942 |
| 4.5 | 0.2 | 0.4 | 2.637067 | 2.637737 |
| 4.5 | 0.2 | 0.5 | 3.021835 | 3.02172 |
| 4.5 | 0.2 | 0.6 | 3.406416 | 3.406247 |
| 4.5 | 0.3 | 0.1 | 1.23031 | 1.230136 |
| 4.5 | 0.3 | 0.2 | 1.549256 | 1.549022 |
| 4.5 | 0.3 | 0.3 | 1.868054 | 1.868184 |
| 4.5 | 0.3 | 0.4 | 2.18698 | 2.187264 |
| 4.5 | 0.3 | 0.5 | 2.506078 | 2.505669 |
| 4.5 | 0.3 | 0.6 | 2.825019 | 2.824527 |
| 4.5 | 0.4 | 0.1 | 1.050849 | 1.050777 |
| 4.5 | 0.4 | 0.2 | 1.323273 | 1.323169 |
| 4.5 | 0.4 | 0.3 | 1.595569 | 1.595795 |
| 4.5 | 0.4 | 0.4 | 1.867974 | 1.868352 |
| 4.5 | 0.4 | 0.5 | 2.140526 | 2.140333 |
| 4.5 | 0.4 | 0.6 | 2.412946 | 2.4127 |
| 4.5 | 0.5 | 0.1 | 0.917159 | 0.916859 |
| 4.5 | 0.5 | 0.2 | 1.154925 | 1.154534 |
| 4.5 | 0.5 | 0.3 | 1.392579 | 1.392415 |
| 4.5 | 0.5 | 0.4 | 1.630329 | 1.630236 |
| 4.5 | 0.5 | 0.5 | 1.868206 | 1.867553 |
| 4.5 | 0.5 | 0.6 | 2.105968 | 2.105208 |
| 4.5 | 0.6 | 0.1 | 0.813596 | 0.813405 |
| 4.5 | 0.6 | 0.2 | 1.024513 | 1.024263 |
| 4.5 | 0.6 | 0.3 | 1.235332 | 1.235302 |
| 4.5 | 0.6 | 0.4 | 1.446235 | 1.446288 |
| 4.5 | 0.6 | 0.5 | 1.657253 | 1.656828 |
| 4.5 | 0.6 | 0.6 | 1.868167 | 1.867667 |
| 4.5 | 0.7 | 0.1 | 0.731052 | 0.730792 |
| 4.5 | 0.7 | 0.2 | 0.920571 | 0.920234 |
| 4.5 | 0.7 | 0.3 | 1.110001 | 1.109839 |
| 4.5 | 0.7 | 0.4 | 1.299508 | 1.299397 |
| 4.5 | 0.7 | 0.5 | 1.489116 | 1.488553 |
| 4.5 | 0.7 | 0.6 | 1.678632 | 1.677978 |
| 4.5 | 0.8 | 0.1 | 0.663704 | 0.663713 |
| 4.5 | 0.8 | 0.2 | 0.835763 | 0.835766 |
| 4.5 | 0.8 | 0.3 | 1.007743 | 1.007968 |
| 4.5 | 0.8 | 0.4 | 1.17979 | 1.180126 |
| 4.5 | 0.8 | 0.5 | 1.351931 | 1.35192 |
| 4.5 | 0.8 | 0.6 | 1.523988 | 1.523958 |
| 5 | 0.2 | 0.1 | 1.452746 | 1.453117 |
| 5 | 0.2 | 0.2 | 1.867864 | 1.868334 |
| 5 | 0.2 | 0.3 | 2.283005 | 2.283499 |
| 5 | 0.2 | 0.4 | 2.698237 | 2.698296 |
| 5 | 0.2 | 0.5 | 3.11335 | 3.113283 |
| 5 | 0.2 | 0.6 | 3.528463 | 3.528159 |
| 5 | 0.3 | 0.1 | 1.188644 | 1.188957 |
| 5 | 0.3 | 0.2 | 1.528297 | 1.528692 |
| 5 | 0.3 | 0.3 | 1.867967 | 1.868384 |
| 5 | 0.3 | 0.4 | 2.207712 | 2.207775 |
| 5 | 0.3 | 0.5 | 2.54736 | 2.547323 |
| 5 | 0.3 | 0.6 | 2.887008 | 2.886778 |
| 5 | 0.4 | 0.1 | 1.005785 | 1.005991 |
| 5 | 0.4 | 0.2 | 1.293186 | 1.293444 |
| 5 | 0.4 | 0.3 | 1.580601 | 1.580862 |
| 5 | 0.4 | 0.4 | 1.86808 | 1.868025 |
| 5 | 0.4 | 0.5 | 2.155477 | 2.15532 |
| 5 | 0.4 | 0.6 | 2.442874 | 2.442538 |
| 5 | 0.5 | 0.1 | 0.871662 | 0.872031 |
| 5 | 0.5 | 0.2 | 1.120738 | 1.121207 |
| 5 | 0.5 | 0.3 | 1.369826 | 1.370351 |
| 5 | 0.5 | 0.4 | 1.61897 | 1.619276 |
| 5 | 0.5 | 0.5 | 1.868042 | 1.868314 |
| 5 | 0.5 | 0.6 | 2.117115 | 2.117285 |
| 5 | 0.6 | 0.1 | 0.769213 | 0.768846 |
| 5 | 0.6 | 0.2 | 0.989014 | 0.988538 |
| 5 | 0.6 | 0.3 | 1.208826 | 1.208202 |
| 5 | 0.6 | 0.4 | 1.428687 | 1.427671 |
| 5 | 0.6 | 0.5 | 1.648485 | 1.647242 |
| 5 | 0.6 | 0.6 | 1.868283 | 1.866753 |
| 5 | 0.7 | 0.1 | 0.688225 | 0.687819 |
| 5 | 0.7 | 0.2 | 0.884884 | 0.884358 |
| 5 | 0.7 | 0.3 | 1.081553 | 1.080872 |
| 5 | 0.7 | 0.4 | 1.278266 | 1.277213 |
| 5 | 0.7 | 0.5 | 1.474922 | 1.473643 |
| 5 | 0.7 | 0.6 | 1.671578 | 1.67002 |
| 5 | 0.8 | 0.1 | 0.622654 | 0.622634 |
| 5 | 0.8 | 0.2 | 0.800576 | 0.800547 |
| 5 | 0.8 | 0.3 | 0.978507 | 0.978437 |
| 5 | 0.8 | 0.4 | 1.156477 | 1.15617 |
| 5 | 0.8 | 0.5 | 1.334397 | 1.333984 |
| 5 | 0.8 | 0.6 | 1.512317 | 1.51175 |

**Supplementary Table 5: Potential influence of measured, dichotomous confounders on the association of glucose width with hospital mortality estimated using the Greenland method of sensitivity analysis.\***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Confounder | ORDZ | Zexp | Zunex | ORDE1 | ORDE0 |
| Age ≥60 y [n (%)] | 2.9731 | 0.5099 | 0.5231 | 1.8922 | 1.8926 |
| Male [n (%)] | 1.0926 | 0.5478 | 0.5670 | 1.8711 | 1.8714 |
| Indigenous [n (%)] | 1.1297 | 0.0809 | 0.0795 | 1.8683 | 1.8677 |
| Obesity (BMI ≥30 Kg/m2) | 0.7776 | 0.2573 | 0.2945 | 1.8516 | 1.8517 |
| Emergency surgery | 4.6233 | 0.6919 | 0.6126 | 1.7151 | 1.7141 |
| Hypertension | 0.4507 | 0.4166 | 0.5072 | 1.7476 | 1.7470 |
| Glasgow coma scale score <10 | 3.2628 | 0.1514 | 0.1076 | 1.7303 | 1.7301 |
| Anemia (Hb <11g/dl) | 2.2074 | 0.5028 | 0.4271 | 1.7617 | 1.7621 |
| Leukocytosis (WBC ≥11x109/L) | 1.4536 | 0.4420 | 0.4296 | 1.8592 | 1.8594 |
| Thrombocytosis (≥500x109/L) | 1.5506 | 0.0306 | 0.0306 | 1.8658 | 1.8682 |
| Hypoglycemic episode | 6.6948 | 0.0928 | 0.0061 | 1.2643 | 1.2647 |

\*, the ORDZ estimates shown here are crude and unadjusted for inter-ICU variation and baseline SOI.

**Supplementary Table 6. Comparison of clinical characteristics of patients belonging to the lowest and highest quartile of glucose width.**

|  |  |  |
| --- | --- | --- |
| Characteristic | Lowest Quartile  Of Glucose Width | Highest Quartile  Of Glucose Width |
| Age [mean (SD)] y | 57.91 (20.49) | 57.69 (19.955) |
| Age ≥60 y [n (%)] | 39,500 (52.09) | 33,661 (50.99) |
| Females [n (%)] | 34,025 (44.88) | 29,846 (45.22) |
| Indigenous [n (%)] | 4,864 (8.08) | 4,394 (8.09) |
| BMI [mean (SE)] Kg/m2 | 30.36 (0.54) | 27.83 (0.14) |
| Elective surgery [n (%)]\* | 29,240 (38.622) | 20,226 (30.81) |
| Average blood pressure mmHg |  |  |
| Systolic BP [mean (SE)] | 125.78 (0.13) | 116.60 (0.15) |
| Diastolic BP [mean (SE)] | 65.47 (0.07) | 60.53 (0.07) |
| Glasgow coma scale score |  |  |
| Eye [mean (SE)] | 3.66 (0.003) | 3.46 (0.004) |
| Motor [mean (SE)] | 5.65 (0.004) | 5.41 (0.006) |
| Verbal [mean (SE)] | 4.50 (0.004) | 4.19 (0.006) |
| Total [mean (SE)] | 13.81 (0.01) | 13.06 (0.01) |
| Blood counts |  |  |
| Hemoglobin [mean (SE)] g/dL | 11.62 (0.009) | 11.05 (0.009) |
| Hematocrit [mean (SE)] % | 0.35 (0.0002) | 0.33 (0.0003) |
| White cell count [mean (SE)] x109/L | 11.33 (0.03) | 11.79 (0.03) |
| Platelet count [mean (SE)] x 109/L | 222.89 (0.41) | 211.91 (0.47) |
| Severity of illness score [mean (SE)] x 100 |  |  |
| Raw | 0.06 (0.0005) | 0.11 (0.0007) |
| Corrected for glucose | 0.06 (0.0004) | 0.10 (0.0007) |
| Hospital deaths [n (%)] | 5,052 (6.66) | 7,960 (12.06) |

**REFERENCES**

1. Rodbard D: Glucose Variability: A Review of Clinical Applications and Research Developments. Diabetes technology & therapeutics 2018;20:S25-S215

2. Rodbard D: The challenges of measuring glycemic variability. Journal of diabetes science and technology 2012;6:712-715

3. Rodbard D: Glycemic variability: measurement and utility in clinical medicine and research--one viewpoint. Diabetes technology & therapeutics 2011;13:1077-1080

4. Rosenbaum PR: Discussing hidden bias in observational studies. Annals of internal medicine 1991;115:901-905

5. Greenland S: Basic methods for sensitivity analysis of biases. International journal of epidemiology 1996;25:1107-1116

6. Huesch MD: External adjustment sensitivity analysis for unmeasured confounding: an application to coronary stent outcomes, Pennsylvania 2004-2008. Health services research 2013;48:1191-1214

7. Cabral MD, Luiz RR: Sensitivity analysis for unmeasured confounders using an electronic spreadsheet. Revista de saude publica 2007;41:446-452