Glycemic Control and Risk of Sepsis and Subsequent Mortality in Type 2 Diabetes

Diabetes Care 2022;45:127–133 | https://doi.org/10.2337/dc21-1050

Anca Balintescu,1 Marcus Lind,2,3 Mikael Andersson Franko,1 Anders Oldner,4,5 Maria Cronhjort,1 Ann-Marie Svensson,2,6 Björn Eliasson,7 and Johan Mårtensson4,5

OBJECTIVE
To investigate the nature of the relationship between HbA1c and sepsis among individuals with type 2 diabetes, and to assess the association between sepsis and all-cause mortality in such patients.

RESEARCH DESIGN AND METHODS
We included 502,871 individuals with type 2 diabetes recorded in the Swedish National Diabetes Register and used multivariable Cox regression and restricted cubic spline analyses to assess the association between time-updated HbA1c values and sepsis occurrence between 1 January 2005 and 31 December 2015. The association between sepsis and death was examined using multivariable Cox regression analysis.

RESULTS
Overall, 14,534 (2.9%) patients developed sepsis during the study period. On multivariable Cox regression analysis, compared with an HbA1c of 48–52 mmol/mol (6.5–6.9%), the adjusted hazard ratio for sepsis was 1.15 (95% CI 1.07–1.24) for HbA1c <43 mmol/mol (6.1%), 0.93 (0.87–0.99) for HbA1c 53–62 mmol/mol (7.0–7.8%), 1.05 (0.97–1.13) for HbA1c 63–72 mmol/mol (7.9–8.7%), 1.14 (1.04–1.25) for HbA1c 73–82 mmol/mol (8.8–9.7%), and 1.52 (1.37–1.68) for HbA1c >82 mmol/mol (9.7%). In the cubic spline model, a reduction of the adjusted risk was observed within the lower HbA1c range until 53 mmol/mol (7.0%), with a hazard ratio of 0.78 (0.73–0.82) per SD; it increased thereafter (P for nonlinearity <0.001). As compared with patients without sepsis, the adjusted hazard ratio for death among patients with sepsis was 4.16 (4.03–4.30).

CONCLUSIONS
In a nationwide cohort of individuals with type 2 diabetes, we found a U-shaped association between HbA1c and sepsis and a fourfold increased risk of death among those developing sepsis.

In 2017, an estimated 48.9 million cases of sepsis were recorded worldwide and 11 million sepsis-related deaths were reported, representing 19.7% of all global deaths (1). In Sweden, the annual incidence of sepsis is 13–43 per 100,000 people depending on the definition (2). Among those patients with sepsis, >25,000 require admission to an intensive care unit each year. In this group of critically ill patients, mortality is close to 30% (3).
Because of its high prevalence (4) and association with impaired host defense against infections (5), diabetes is a particularly relevant risk factor for sepsis. The burden of diabetes is increasing worldwide and is expected to affect >500 million individuals by 2030, with a majority developing type 2 diabetes (6).

Type 2 diabetes is an established risk factor for a variety of infectious diseases (7–9). Despite such evidence, risk factors for sepsis, a potentially lethal host response to infections, have not been systematically investigated in individuals with type 2 diabetes. Some small studies suggest an association between insufficient glycemic control (glycated hemoglobin A1c [HbA1c] >53 mmol/mol [7.0%]) and the risk of severe infections (10,11). These findings are, however, inconsistent (12) and are difficult to interpret, because other potential confounders such as comorbidity, diabetes duration, and risk factor control were not considered in these studies.

Accordingly, we aimed to assess the association of glycemic control, quantified by the level of HbA1c, with sepsis among all individuals with type 2 diabetes in Sweden. In addition, we aimed to study the association between sepsis and mortality in this population. We hypothesized that the level of HbA1c is an independent risk factor for sepsis and that sepsis carries an independent association with mortality among individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This study was approved by the Swedish Ethical Review Authority, Uppsala, Sweden (approval no. 2017/213-31).

Study Population

We conducted a prospective, observational study in adults (age ≥18 years) with type 2 diabetes recorded in the Swedish National Diabetes Register (NDR) between 1 January 2005 and 31 December 2015. The NDR is a nationwide register to which trained physicians and nurses report clinical information regarding patients with diabetes. It covers >90% of all adults with type 2 diabetes in Sweden. Recorded data include diabetes type, risk factors, medication and treatment, diabetes-associated complications, and level of glycemic control (HbA1c) (Supplementary Table 1). Consent is obtained from all patients before inclusion in the register.

Type 2 diabetes is defined in the register by the following epidemiological criteria: treatment with diet with or without additional treatment with non-insulin glucose-lowering drugs or treatment with insulin (with or without noninsulin glucose-lowering drugs). The latter category (insulin treatment) applies only to individuals who were diagnosed with diabetes at age ≥40 years. Patients were followed from baseline (1 January 2005) until the end of the study period (31 December 2015) or until death, whichever occurred first.

Data Collection

Additional information was retrieved by linking the unique 10-digit Swedish identity number to the following nationwide health care and administrative registers: the Inpatient Register, the Cause of Death Register, the Prescribed Drug Register, and the Register for Longitudinal Integration Database for Health Insurance and Labor Market Studies (Statistics Sweden). From the Inpatient Register, we obtained information on outpatient and emergency department visits and inpatient admissions to all public hospitals and private specialist care facilities and the corresponding ICD-10 codes (13). From the Cause of Death Register, we obtained information on date and ICD-10–coded cause of death. From the Prescribed Drug Register, we obtained data on the Anatomical Therapeutic Chemical code and date of dispensed drugs (available for all pharmacies in Sweden since July 2005) (14). Data on level of income, level of education, and country of birth (Sweden or other) were obtained from Statistics Sweden.

Operational Definitions

We used time-updated mean HbA1c to quantify glycemic control. Time-updated mean is the mean value of all HbA1c values recorded within 12 months before sepsis diagnosis. To test the robustness of our findings, we also quantified glycemic control using the following additional approaches: 1) baseline HbA1c at inclusion in the NDR, 2) updated mean HbA1c from all values recorded in the NDR until sepsis diagnosis, 3) updated time-weighted mean HbA1c from all values recorded in the NDR until sepsis diagnosis, and 4) latest updated HbA1c before sepsis diagnosis.

HbA1c was measured in mmol/mol (International Federation of Clinical Chemistry and Laboratory Medicine calibrated) and converted to percentage for dual reporting according to the NGSP standard (15). HbA1c values <20 mmol/mol (4%) and >100 mmol/mol (11.3%) were not considered. HbA1c was examined as a continuous variable and as a categorical variable. For the categorization of HbA1c, we considered the following cutoffs in accordance with values in clinical use for individuals with diabetes: threshold for diagnosis of prediabetes (43 mmol/mol [6.1%]) and diabetes (48 mmol/mol [6.5%]), and the goal for well-controlled diabetes (53 mmol/mol [7.0%]). Based on these cut-off values, the following categories were chosen: <43 mmol/mol (6.1%), 43–47 mmol/mol (6.1–6.5%), 48–52 mmol/mol (6.5–6.9%), and 10-unit strata >52 mmol/mol (6.9%) (Supplementary Table 1).

We quantified renal function from estimated glomerular filtration rate (eGFR) and albuminuria using the Kidney Disease: Improving Global Outcomes classification system: eGFR category (G1–5) and albuminuria category (A1–3) (16). eGFR was based on creatinine, age, and sex and was calculated according to the MDRD formula (17).

Definition and categorization of additional potential risk factors (demographics, nondiabetic comorbidities, blood pressure control, chronic medication, and socioeconomic status) are detailed in Supplementary Table 1.

Outcomes

Primary outcome was time from type 2 diabetes diagnosis (date of first entry in the NDR) to first sepsis episode during the study period. Sepsis was considered present if any of the ICD-10 codes for sepsis (A41.9), severe sepsis (R65.1), or septic shock (R57.2) were recorded in the Inpatient Register or Cause of Death Register during the study period. Secondary outcome was time to death.

Statistical Analysis

We analyzed data using R version 4.0.4 (18). Categorical data are presented as
numbers and percentages. Continuous data are summarized as medians with interquartile ranges (IQRs). Time from type 2 diabetes diagnosis to sepsis was assessed using Cox regression analysis and the following models: unadjusted, adjusted for age and sex, and fully adjusted. In the fully adjusted model, we included the following potential confounders: age, sex, smoking, country of birth, socioeconomic factors, diabetes treatment, other medications, BMI, blood pressure, eGFR, albuminuria, and coexisting conditions (Supplementary Table 1). Based on previous data showing a J-shaped relationship between HbA1c and infections (7), we also used restricted cubic splines with three knots at the 25th, 50th, and 75th percentiles to flexibly model the association of HbA1c with sepsis before and after full adjustment for covariates. In the spline analyses, we used HbA1c of 53 mmol/mol (7.0%) as reference. We tested for potential nonlinearity by using a likelihood ratio test comparing the model with only a linear term versus the model with linear and cubic spline terms. Because the association between HbA1c and sepsis was approximately log linear below and above the reference value, we used a log linear model to calculate hazard ratios per SD increase in HbA1c.

Because immunosuppressed patients are particularly prone to infections, we conducted two sensitivity analyses excluding such patients. In the first analysis, we did a complete case exclusion of individuals with an ICD-10 diagnosis associated with immunosuppression (cancer, renal dialysis and transplantation, and immunological deficiency) and/or individuals receiving treatment with immunosuppressive drugs (systemic glucocorticoids and/or other immunosuppressive drugs) (Supplementary Table 1 lists ICD-10 and Anatomical Therapeutic Chemical codes). In the second analysis, individuals were censored at the time point when an immunosuppressive disease was diagnosed or when immunosuppressive therapy commenced.

The association between sepsis and death was assessed using Cox regression analysis and covariates included in the fully adjusted model (Supplementary Table 1). We further explored the association between HbA1c and mortality among individuals with type 2 diabetes who developed sepsis using Cox regression analysis before and after adjustment.

All tests were two tailed and conducted at a significance level of 0.05.

RESULTS

Study Population
A total of 502,871 patients with type 2 diabetes were recorded in the NDR between 1 January 2005 and 31 December 2015. Overall, 14,534 (2.9%) patients developed sepsis during the study period. Baseline characteristics of patients with sepsis and those without sepsis are summarized in Table 1 and Supplementary Table 2. As compared with patients without sepsis, patients with sepsis were more likely to be male, were older, were more likely to have been born in Sweden, and were less likely to have a university education or higher. In addition, patients with sepsis had longer diabetes duration, were more likely to be treated with insulin, and were more likely to have insufficient glycemic control (HbA1c ≥53 mmol/mol [7.0%]) at baseline. Hypertension and renal dysfunction at baseline were more common among patients with sepsis. Coexisting conditions, except coronary heart disease, lung disease, and atrial fibrillation, and treatment with corticosteroids and/or other immunosuppressant drugs were also more common among patients with sepsis than among patients without sepsis.

Primary Outcome
Median (IQR) follow-up time to sepsis was 6.0 (3.6–8.3) years in the sepsis group and 5.8 (3.0–8.3) years in the no sepsis group. Median number of HbA1c measurements was 1.8 (1.2–4.1) times per year in the sepsis group and 1.7 (1.2–2.7) times per year in the no sepsis group. In the fully adjusted multivariable Cox regression analysis, compared with an HbA1c of 48–52 mmol/mol (6.5–6.9%), the adjusted hazard ratio for sepsis was 1.15 (95% CI 1.07–1.24) for HbA1c <43 mmol/mol (6.1%), 1.00 (0.93–1.07) for HbA1c 43–47 mmol/mol (6.1–6.5%), 0.93 (0.87–0.99) for HbA1c 53–62 mmol/mol (7.0–7.8%), 1.05 (0.97–1.13) for HbA1c 63–72 mmol/mol (7.9–8.7%), 1.14 (1.04–1.25) for HbA1c 73–82 mmol/mol (8.8–9.7%), and 1.52 (1.37–1.68) for HbA1c >82 mmol/mol (9.7%) (Table 2). In Fig. 1, we used restricted cubic splines to display the nature of the relationship between HbA1c and sepsis. In the adjusted analysis, we observed a U-shaped relationship with a marked risk reduction within the lower range of HbA1c, which reached the lowest risk at ~53 mmol/mol (7.0%) and then increased thereafter (P for nonlinearity <0.001). Below 53 mmol/mol (7.0%), the risk decreased, with a hazard ratio of 0.78 (95% CI 0.73–0.82) per SD. Above 53 mmol/mol (7.0%), the risk increased, with a hazard ratio of 1.18 (95% CI 1.15–1.22) per SD. Sensitivity analyses using four additional approaches to quantify glycemic control confirmed the U-shaped relationship between HbA1c and sepsis, with small differences between the five different approaches; lowest-risk estimates were observed with baseline HbA1c; highest-risk estimates in the lower range were observed with 12-month mean HbA1c (Supplementary Table 3 and Supplementary Fig. 1). The association between HbA1c and sepsis remained virtually unchanged after excluding or censoring individuals with immunosuppressive disease and/or individuals receiving immunosuppressive therapy (Supplementary Table 4).

Secondary Outcome
Overall, 9,292 (63.9%) patients in the sepsis group and 88,093 (18.0%) patients in the no sepsis group died during the study period. Median (IQR) follow-up time to death was 4.38 (2.22–6.68) years in the sepsis group and 2.75 (0.81–5.20) years in the no sepsis group. On multivariable Cox regression analysis, we observed an independent association between sepsis and mortality (adjusted hazard ratio 4.16; 95% CI 4.03–4.30). Among individuals with type 2 diabetes who developed sepsis, we observed no significant association between HbA1c and mortality (Supplementary Material and Supplementary Table 5).

CONCLUSIONS

Key Findings
We conducted a nationwide, observational study in more than half a million individuals with type 2 diabetes to assess the independent association of
Table 1—Baseline characteristics of individuals with type 2 diabetes with and without sepsis

| Characteristic                                      | Sepsis (n = 14,534) | No sepsis (n = 488,337) |
|-----------------------------------------------------|----------------------|-------------------------|
| Male sex                                            | 8,925/14,534 (61.4)  | 277,375/488,337 (56.8) |
| Age, years                                          | 71 (64–78)           | 65 (57–74)              |
| Born in Sweden                                      | 12,541/14,421 (86.9)| 392,841/486,623 (80.7) |
| Smoker                                              | 2,101/14,165 (14.8)  | 72,888/479,965 (15.2)  |
| Education level*                                    |                      |                         |
| Low                                                 | 6,995/13,748 (50.9)  | 192,585/474,944 (40.5) |
| Intermediate                                        | 5,037/13,748 (36.6)  | 199,725/474,944 (42.1) |
| High                                                | 1,716/13,748 (12.5)  | 82,634/474,944 (17.4)  |
| Diabetes duration, years †                          | 6 (1–12)             | 2 (0–8)                 |
| Diabetes treatment                                  |                      |                         |
| Diet only                                           | 3,640/14,222 (25.6)  | 166,766/486,140 (34.3) |
| Noninsulin glucose-lowering drugs                   | 5,347/14,222 (37.6)  | 217,793/486,140 (44.8) |
| Insulin only                                        | 2,837/14,222 (19.9)  | 49,502/486,140 (10.2)  |
| Insulin and noninsulin glucose-lowering drugs       | 2,398/14,222 (16.9)  | 52,079/486,140 (10.7)  |
| BMI, kg/m²‡                                         | 29.1 (26.0–33.0)     | 29.2 (26.2–32.9)        |
| HbA1c, mmol/mol                                      |                      |                         |
| <43 (<6.1)                                          | 2,108/14,228 (14.8)  | 81,845/486,905 (16.9)  |
| 43–47 (6.1–6.5)                                     | 2,568/14,228 (18.0)  | 100,405/486,905 (20.7) |
| 48–52 (6.5–6.9)                                     | 2,598/14,228 (18.2)  | 95,978/484,905 (19.8)  |
| 53–62 (7–7.8)                                       | 3,450/14,228 (24.2)  | 104,265/484,905 (21.5) |
| 63–72 (7.9–8.7)                                     | 1,856/14,228 (13.0)  | 53,615/484,905 (11.1)  |
| 73–82 (8.8–9.7)                                     | 1,015/14,283 (7.1)   | 26,851/484,905 (5.5)   |
| >82 (≥9.7)                                          | 688/14,283 (4.8)     | 21,946/484,905 (4.5)   |
| Hypertension                                        | 7,697/14,154 (54.4)  | 245,870/483,176 (50.9) |
| eGFR interval, mL/min                               |                      |                         |
| ≥90                                                 | 3,134/13,794 (22.7)  | 159,611/475,462 (33.6) |
| 60–89                                               | 6,280/13,794 (45.5)  | 235,643/475,462 (49.6) |
| 45–59                                              | 2,549/13,794 (18.5)  | 55,670/475,462 (11.7)  |
| 30–44                                              | 1,335/13,794 (9.7)   | 19,667/475,462 (4.1)   |
| 15–29                                              | 365/13,794 (2.6)     | 4,223/475,462 (0.9)    |
| <15                                                | 131/13,794 (0.9)     | 648/475,462 (0.1)      |
| Albuminuria                                         | 2,118/14,534 (14.6)  | 45,377/488,337 (9.3)   |
| Microalbuminuria                                    | 1,449/14,534 (10.0)  | 21,767/488,337 (4.5)   |
| Coexisting conditions                               |                      |                         |
| Stroke                                              | 452 (3.1)            | 11,280 (2.3)            |
| Coronary heart disease                              | 523 (3.6)            | 24,066 (4.9)            |
| Heart failure                                       | 418 (2.9)            | 9,963 (2.0)             |
| Atrial fibrillation                                 | 319 (2.2)            | 11,658 (2.4)            |
| Cancer                                              | 398 (2.7)            | 12,609 (2.6)            |
| Renal dialysis or transplantation                   | 30 (0.2)             | 349 (0.1)               |
| Lung disease                                        | 244 (1.7)            | 8,484 (1.7)             |
| Liver disease                                       | 69 (0.5)             | 1,758 (0.4)             |
| Hematological disease                               | 393 (2.7)            | 7,564 (1.5)             |
| Immunological deficiency                            | 8 (0.06)             | 335 (0.07)              |
| Medications                                         | 927 (6.4)            | 20,248 (4.1)            |
| Corticosteroid                                      | 491 (3.4)            | 7,210 (1.5)             |
| Immunosuppressant                                   | 162 (1.1)            | 2,390 (0.5)             |
| Statin                                              | 5,629 (38.7)         | 198,195 (40.6)          |
| Antihypertensive drug                               | 9,672 (66.5)         | 307,382 (62.9)          |

Data are presented as n/total N with available data (%), n (%), or median (IQR). *Educational level was categorized as low (compulsory only), intermediate, or high (university level or similar). †Data available for 14,492 individuals in the sepsis group and 487,771 in the no sepsis group. ‡Data available for 13,410 individuals in the sepsis group and 466,434 in the no sepsis group.
glycemic control (HbA1c level) with sepsis and subsequent mortality. On adjusted analyses, we found a strong U-shaped relationship between HbA1c and sepsis, with the lowest risk observed at \( \approx 53 \text{ mmol/mol} \) (7.0%). Furthermore, we observed that sepsis was independently associated with a fourfold increased risk of death among individuals with type 2 diabetes. HbA1c was, however, not associated with mortality among individuals who developed sepsis.

Comparison With Previous Studies
To our knowledge, this is the first nationwide study assessing the relationship between glycemic control and sepsis in individuals with type 2 diabetes. However, in previous cohorts, an association between HbA1c level and, mainly, less severe infections was observed. For example, in a cohort of \( \approx 85,000 \) primary care patients with diabetes (90% with type 2 diabetes) in the U.K., the risk of a variety of infections (requiring outpatient antibiotic prescription or hospital admission), including sepsis, increased with increasing baseline HbA1c \( >53 \text{ mmol/mol} \) (7.0%). Also in accordance with our results, HbA1c \( <42 \text{ mmol/mol} \) (6.0%) was independently associated with a greater risk than HbA1c within the reference range (42–52 mmol/mol [6.0–6.9%]) (8). However, potential confounders such as drug treatment, level of kidney dysfunction, and blood pressure control were not considered in the multivariable analysis. Another U.K.-based primary care study of 34,000 individuals with type 2 diabetes found an association between insufficient glycemic control (a most recent HbA1c \( >53 \text{ mmol/mol} \) within 3 years of \( \approx 53 \text{ mmol/mol} \) vs. \( <53 \text{ mmol/mol} \) [7.0%]) and presentation to primary care with infection (9).

Similarly, among almost 70,000 individuals with type 2 diabetes from northern Denmark, a time-updated HbA1c above or below a reference range of 37–47 mmol/mol (5.5–6.5%) was independently associated with a progressively increased risk of hospital-treated infections. However, the risk of sepsis was not specifically reported in that study (7). A similar J-shaped or U-shaped relationship has been identified
by others, linking low HbA1c levels with higher mortality (19) and risk of cardiovascular disease (20). Previous clinical and experimental data support a link between hyperglycemia and innate and adaptive immune system dysfunction (5). These findings likely explain the observed association between higher HbA1c and increased sepsis risk. However, the mechanistic link between low HbA1c and sepsis remains uncertain. It is possible that this relationship is generated by unmeasured confounders reflecting underlying conditions or treatments, which may affect both the level of HbA1c (independent of plasma glucose) and the risk of sepsis. Such conditions/treatments may include (1) blood loss, hemolytic anemia, hypersplenism, or genetic hemoglobin disorders, which reduce the number of circulating erythrocytes; (2) transfusion of red blood cells containing normal levels of glycated hemoglobin; (3) heavy alcohol consumption, potentially by reducing the affinity of glucose on hemoglobin; and (4) liver disease, malnourishment, renal failure, and other conditions associated with reduced erythropoiesis (21,22).

In agreement with previous studies in various populations, we observed a strong relationship between sepsis and mortality (23,24). The level of glycemic control was, however, not a significant mortality predictor in our cohort of patients with sepsis. Conversely, previous studies observed an independent association between higher HbA1c and sepsis-related mortality (25,26). However, these studies were small (n < 300) and did not consider the burden of comorbidity, diabetes duration, or socioeconomic factors. Indeed, our assessment suggests that factors other than the level of glycemic control per se are responsible for the high mortality seen in patients with sepsis with type 2 diabetes.

Implications of Study Findings

Our study has implications for public health, because its results apply to millions of individuals with type 2 diabetes worldwide, and also because it describes the relationship between a potentially modifiable risk factor (HbA1c) and sepsis, a syndrome associated with a markedly increased risk of death. Our results imply that current recommendations to maintain HbA1c at ~53 mmol/mol (7.0%) for prevention of microvascular complications may also apply for prevention of sepsis in individuals with type 2 diabetes. Our findings also imply that a very low level of HbA1c is a strong and independent predictor of sepsis. Additional investigations of factors that may affect HbA1c are needed to understand the nature of the association between low levels of HbA1c and sepsis risk.

Strengths and Limitations

Our study has several strengths. We included >90% of the entire adult population with type 2 diabetes in Sweden, thus providing a high degree of external validity for generalizing our results to other developed countries. By linking data with other national health care and administrative databases, we were able to control for a large number of potential confounders. Finally, our results were robust across multiple analyses.

Our study has limitations. It is an observational study and does not imply causation. However, it has several features that describe associations with potential for causality: strength of association that persists after adjustment, face validity based on prior knowledge, temporality between risk factors and outcome, presence of a biological gradient, and results consistent with findings in similar cohorts (27). Using ICD coding to identify sepsis is imperfect (2) and carries a risk that sepsis cases are included in the no sepsis group. However, such misclassification would bias the results toward the null.

In conclusion, in this nationwide cohort of individuals with type 2 diabetes, we found a strong and independent U-shaped relationship between HbA1c and sepsis, with the lowest risk observed at an HbA1c level of ~53 mmol/mol (7.0%). Mortality was markedly higher among patients with sepsis than among those without sepsis in our type 2 diabetes population. HbA1c was not associated with mortality among those individuals who developed sepsis.

Acknowledgments. A.-M.S. is deceased. Funding and Duality of Interest. A.B. and J.M. were supported by Region Stockholm (Stockholms Län Landsting) (clinical research appointment and Avtal om Läkarutbildning och Forsknings projekt grant ALF 592073). M.L. has received research grants from DexCom and Novo Nordisk and personal fees from AstraZeneca, Boehringer Ingelheim, DexCom, Eli Lilly, Merck Sharp & Dohme, and Novo Nordisk outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.B., M.L., A.O., M.C., A.-M.S., B.E., and J.M. were responsible for study concept and design. A.B., A.-M.S., and J.M. were responsible for acquisition and interpretation of data. M.A.F. performed the statistical analysis and takes responsibility for the accuracy of the data analysis, and all authors discussed the analysis plan and results. A.B. and J.M. drafted the manuscript. All authors critically reviewed and approved the manuscript. A.B. and J.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:201–211
2. Wilhelms SB, Huss FR, Granath G, Sjöberg F. Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: difficulties with methods and interpretation of results. Crit Care Med 2010;38:1442–1449
3. De Geer L, Oscarsson Tibblin A, Fredriksson M, Walther SM. No association with cardiac death after sepsis: a nationwide observational cohort study. Acta Anaesthesiol Scand 2019;63:344–351
4. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271–281
5. Schuetz P, Castro P, Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. Diabetes Care 2011;34:771–778
6. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Accessed 27 March 2021. Available at https://www.diabetesatlas.org
7. Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of glycemic control on risk of infections in patients with type 2 diabetes: a population-based cohort study. Am J Epidemiol 2017;186:227–236
8. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FI, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes Care 2018;41:2127–2133
9. Hine JL, de Lusignan S, Burleigh D, et al. Association between glycaemic control and common infections in people with type 2 diabetes: a cohort study. Diabet Med 2017;34:551–557
10. McKane CK, Marmarelis M, Mendu ML, Moromizato T, Gibbons FK, Christopher KB. Diabetes mellitus and community-acquired bloodstream infections in the critically ill. J Crit Care 2014;29:70–76
11. Dronge AS, Perkal MF, Kanic S, Concato J, Aslan M, Rosenthal RA. Long-term glycemic control and postoperative infectious complications. Arch Surg 2006;141:375–380; discussion 380
12. Blankush JM, Leitman IM, Soleiman A, Tran T. Association between elevated pre-operative glycosylated hemoglobin and post-operative infections after non-emergent surgery. Ann Med Surg (Lond) 2016;10:77–82
13. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450
14. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months [published correction appears in Pharmacoepidemiol Drug Saf. 2008;17:533]. Pharmacoepidemiol Drug Saf 2007;16:726–735
15. Hanas R; International HBA1c Consensus Committee. 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care 2010;33:1903–1904
16. Kidney Disease: Improving Global Outcomes. KDIGO guidelines. Accessed 2 February 2021. Available at https://kdigo.org/guidelines/ckd-evaluation-and-management/
17. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate [published correction appears in Ann Intern Med. 2021;174:584]. Ann Intern Med 2006;145:247–254
18. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Accessed 6 May 2021. Available at https://www.R-project.org/
19. Arnold LW, Wang Z. The HbA1c and all-cause mortality relationship in patients with type 2 diabetes is J-shaped: a meta-analysis of observational studies. Rev Diabet Stud 2014;11:138–152
20. Östgren CJ, Sundström J, Svennblad B, Lohm L, Nilsson PM, Johansson G. Associations of HbA1c and educational level with risk of cardiovascular events in 32,871 drug-treated patients with Type 2 diabetes: a cohort study in primary care. Diabet Med 2013;30:e170–e177
21. Christman AL, Lazo M, Clark JM, Selvin E. Low glycated hemoglobin and liver disease in the U.S. population. Diabetes Care 2013;34:2548–2550
22. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes. J Diabetes 2009;1:9–17
23. Lee C-C, Yo C-H, Lee MG, et al. Adult sepsis—a nationwide study of trends and outcomes in a population of 23 million people. J Infect 2017;75:409–419
24. Zoppini G, Fedeli U, Schievano E, et al. Mortality from infectious diseases in diabetes. Nutr Metab Cardiovasc Dis 2018;28:444–450
25. Gornik I, Gornik O, Gasparovič V. HbA1c is outcome predictor in diabetic patients with sepsis. Diabetes Res Clin Pract 2007;77:120–125
26. Lee YS, Min KH, Lee SY, et al. The value of glycated hemoglobin as predictor of organ dysfunction in patients with sepsis. PLoS One 2019;14:e0216397
27. Hill AB. The environment and disease: association or causation? 1965. J R Soc Med 2015;108:32–37