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

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## OBJECTIVE

**To investigate the nature of the relationship between $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ <43 mmol/mol (6.1%), 0.93 (0.87–0.99) for $HbA_{1c}$ 53–62 mmol/mol (7.0–7.8%), 1.05 (0.97–1.13) for $HbA_{1c}$ 63–72 mmol/mol (7.9–8.7%), 1.14 (1.04–1.25) for $HbA_{1c}$ 73–82 mmol/mol (8.8–9.7%), and 1.52 (1.37–1.68) for $HbA_{1c}$ >82 mmol/mol (9.7%). In the cubic spline model, a reduction of the adjusted risk was observed within the lower $HbA_{1c}$ 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 $HbA_{1c}$ 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).

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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 $A_{1c}$ [$HbA_{1c}$] >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 $HbA_{1c}$, 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 $HbA_{1c}$ 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 ($HbA_{1c}$) (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 noninsulin 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 $HbA_{1c}$ to quantify glycemic control. Time-updated mean is the mean value of all $HbA_{1c}$ 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 $HbA_{1c}$ at inclusion in the NDR, *2*) updated mean $HbA_{1c}$ from all values recorded in the NDR until sepsis diagnosis, *3*) updated time-weighted mean $HbA_{1c}$ from all values recorded in the NDR until sepsis diagnosis, and *4*) latest updated $HbA_{1c}$ before sepsis diagnosis.

$HbA_{1c}$ 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). $HbA_{1c}$ values <20 mmol/mol (4%) and >100 mmol/mol (11.3%) were not considered. $HbA_{1c}$ was examined as a continuous variable and as a categorical variable. For the categorization of $HbA_{1c}$, 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 $HbA_{1c}$ 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 $HbA_{1c}$ with sepsis before and after full adjustment for covariates. In the spline analyses, we used $HbA_{1c}$ 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 against the model with linear and cubic spline terms. Because the association between $HbA_{1c}$ 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 $HbA_{1c}$.

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 $HbA_{1c}$ 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 ($HbA_{1c}$ $\geq$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 $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ $<$43 mmol/mol (6.1%), 1.00 (0.93–1.07) for $HbA_{1c}$ 43–47 mmol/mol (6.1–6.5%), 0.93 (0.87–0.99) for $HbA_{1c}$ 53–62 mmol/mol (7.0–7.8%), 1.05 (0.97–1.13) for $HbA_{1c}$ 63–72 mmol/mol (7.9–8.7%), 1.14 (1.04–1.25) for $HbA_{1c}$ 73–82 mmol/mol (8.8–9.7%), and 1.52 (1.37–1.68) for $HbA_{1c}$ $>$82 mmol/mol (9.7%) (Table 2). In Fig. 1, we used restricted cubic splines to display the nature of the relationship between $HbA_{1c}$ and sepsis. In the adjusted analysis, we observed a U-shaped relationship with a marked risk reduction within the lower range of $HbA_{1c}$, which reached the lowest risk at $\sim$53 mmol/mol (7.0%) and then increased thereafter ($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 $HbA_{1c}$ and sepsis, with small differences between the five different approaches; lowest-risk estimates were observed with baseline $HbA_{1c}$; highest-risk estimates in the lower range were observed with 12-month mean $HbA_{1c}$ (Supplementary Table 3 and Supplementary Fig. 1). The association between $HbA_{1c}$ 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 $HbA_{1c}$ 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/m$^2$‡ | 29.1 (26.0–33.0) | 29.2 (26.2–32.9) |
| $HbA_{1c}$, mmol/mol | 52 (45–62) | 50 (45–59) |
| $HbA_{1c}$ interval, mmol/mol (%) | | |
| <43 (<6.1) | 2,108/14,283 (14.8) | 81,845/484,905 (16.9) |
| 43–47 (6.1–6.5) | 2,568/14,283 (18.0) | 100,405/484,905 (20.7) |
| 48–52 (6.5–6.9) | 2,598/14,283 (18.2) | 95,978/484,905 (19.8) |
| 53–62 (7–7.8) | 3,450/14,283 (24.2) | 104,265/484,905 (21.5) |
| 63–72 (7.9–8.7) | 1,856/14,283 (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 | | |
| Microalbuminuria | 2,118/14,534 (14.6) | 45,377/488,337 (9.3) |
| Macroalbuminuria | 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 | | |
| Recent antibiotic therapy | 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.

**Table 2—Cox regression analysis showing the association with sepsis in individuals with type 2 diabetes**

| $HbA_{1c}$ interval, mmol/mol (%) | Unadjusted | Adjusted for age and sex | Fully adjusted* |
|---|---|---|---|
| <43 (<6.1) | 1.21 (1.14–1.28) | 1.23 (1.16–1.31) | 1.15 (1.07–1.24) |
| 43–47 (6.1–6.5) | 1.03 (0.97–1.09) | 1.01 (0.95–1.07) | 1.00 (0.93–1.07) |
| 48–52 (6.5–6.9) | 1.00 | 1.00 | 1.00 |
| 53–62 (7–7.8) | 0.97 (0.92–1.03) | 1.01 (0.96–1.07) | 0.93 (0.87–0.99) |
| 63–72 (7.9–8.7) | 1.10 (1.03–1.17) | 1.22 (1.15–1.30) | 1.05 (0.97–1.13) |
| 73–82 (8.8–9.7) | 1.20 (1.11–1.29) | 1.41 (1.31–1.52) | 1.14 (1.04–1.25) |
| >82 (>9.7) | 1.61 (1.48–1.74) | 2.02 (1.86–2.20) | 1.52 (1.37–1.68) |

Data are presented as hazard ratio (95% CI). *Analysis was adjusted for age, sex, smoking, country of birth, socioeconomic factors, diabetes treatment, other medications, BMI, blood pressure, eGFR, albuminuria, and coexisting conditions (Supplementary Table 1).

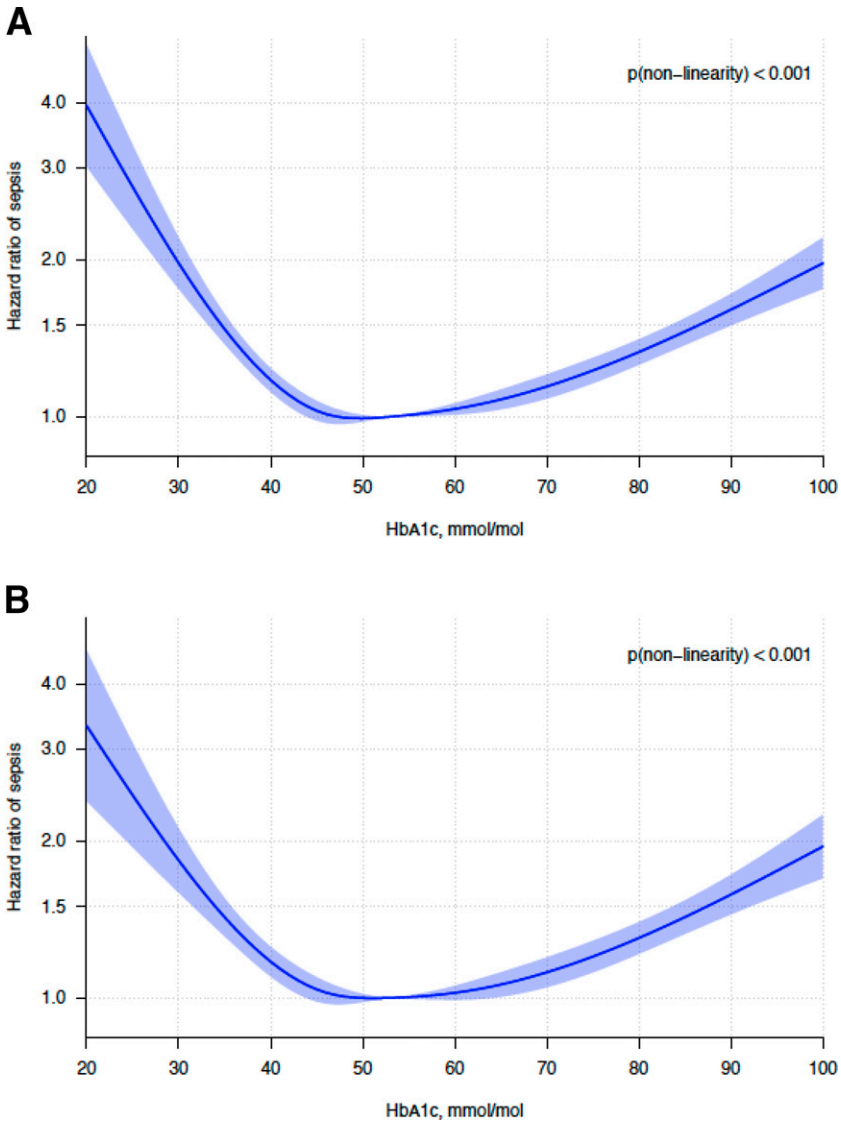


**Figure 1**—*A–B*: Unadjusted (*A*) and adjusted (*B*) restricted cubic spline curves showing the hazard ratios and 95% CIs for sepsis risk by time-updated mean $HbA_{1c}$ level. All hazard ratios are with respect to a reference $HbA_{1c}$ of 53 mmol/mol. *B*: Adjusted for the confounders listed in the Supplementary Table 1. Formula for conversion: $HbA_{1c}$ (%) = (0.09148 $HbA_{1c}$ [mmol/mol]) + 2.152.

glycemic control ($HbA_{1c}$ level) with sepsis and subsequent mortality. On adjusted analyses, we found a strong U-shaped relationship between $HbA_{1c}$ and sepsis, with the lowest risk observed at ~53 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. $HbA_{1c}$ 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 $HbA_{1c}$ level and, mainly, less severe infections was observed. For example, in a cohort of ~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 $HbA_{1c}$ >53 mmol/mol (7.0%). Also in accordance with our results, $HbA_{1c}$ <42 mmol/mol (6.0%) was independently associated with a greater risk than $HbA_{1c}$ 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 $HbA_{1c}$ within 3 years of ≥53 mmol/mol vs. <53 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 $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ and increased sepsis risk. However, the mechanistic link between low $HbA_{1c}$ 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 $HbA_{1c}$ (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 $HbA_{1c}$ 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 ($HbA_{1c}$) and sepsis, a syndrome associated with a markedly increased risk of death. Our results imply that current recommendations to maintain $HbA_{1c}$ 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 $HbA_{1c}$ is a strong and independent predictor of sepsis. Additional investigations of factors that may affect $HbA_{1c}$ are needed to understand the nature of the association between low levels of $HbA_{1c}$ 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 $HbA_{1c}$ and sepsis, with the lowest risk observed at an $HbA_{1c}$ 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. $HbA_{1c}$ was not associated with mortality among those individuals who developed sepsis.

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**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.

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