Online-Only Supplemental Material

Tabel S1. Covariates included in multivariable analyses

Covariate	Unit	Definition	Source	Categories
Sex			NDR	Female
				Male
Age	Years		NDR	Age<55years
				55≤Age<65
				65≤Age<75
				Age≥75 years
Diabetes treatment			NDR	Diet only
				Non-insulin glucose lowering drugs only (tablets and/or GLP-1 analogues)
				Insulin only
				Insulin and non-insulin glucose lowering drugs (tablets and/or GLP-1 analogues)
BMI	kg/m^2	BMI closest to sepsis diagnosis	NDR	Underweight: BMI <18.5
				Normal: BMI 18.5-24.9
				Overweight: BMI 25-29.9
				Obese: BMI ≥30
Time-updated mean HbA1c	mmol/mol (%)	Mean value from all HbA1c taken last 12 months before first sepsis diagnosis	NDR	<43 mmol/mol (6.1%)
				43-47 mmol/mol (6.1-6.5%)
				48-52 mmol/mol (6.5-6.9%)
				53-62 mmol/mol (7.0-7.8%)
				63-72 mmol/mol (7.9-8.7%)
				73-82 mmol/mol (8.8-9.7%)
				>82 mmol/mol (9.7%)
Blood pressure interval	mmHg	Systolic blood pressure (SBP) and diastolic blood pressure (DBP) closest to sepsis diagnosis but max 3 years before sepsis diagnosis	NDR	**Normal**: SBP 120-129 mmHg and/or DBP 80-84 mmHg and SBP <120 mmHg and DBP <80 mmHg
				High normal: SBP 130-139 mmHg and/or DBP 85-89 mmHg
				Hypertension: SBP ≥140 mmHg and/or DBP ≥90 mmHg
eGFR	ml/min	Value closest to sepsis diagnosis but max 3 years before sepsis diagnosis	NDR	≥ 90 ml/min
				60-89 ml/min
				45-59 ml/min
				30-44 ml/min
				15-29 ml/min
				<15 ml/min

Albuminuria		Value closest to sepsis diagnosis, but max 3 years before sepsis diagnosis	NDR	Albuminuria categories in CKD AER ACR (approximate equivalent):
				A1-Normal: AER<30 mg/24 hours (ACR<3 mg/mmol or <30mg/g)
				A2-Moderately increased: AER 30-300 mg/24h (ACR 3-30mg/mmol or 30-300mg/g) (Microalbuminuria)
				A3-Severely increased: (Macroalbuminuria) AER>300mg/24h (ACR>30mg/mmol or >300mg/g)
Smoking status		Last recorded status before sepsis diagnosis	NDR	Smoker
				Non-smoker
Systemic corticosteroid treatment		ATC code up to 4 weeks before sepsis defined as a prescription for any of the listed drugs that was filled within the 4 weeks preceding sepsis diagnosis (sepsis group) or an NDR registration (no sepsis group).	Prescribed Drug Register	Defined using the following ATC codes:
				H02AB: Glucocorticoids for systemic use
				H02BX01: Glucocorticoids for systemic use, combinations
Statin use		ATC code up to 3 years before sepsis defined as a prescription for any of the listed drugs that was filled within the 3 years preceding sepsis diagnosis (sepsis group) or an NDR registration (no sepsis group).	Prescribed Drug Register	Defined using the following ATC codes:
				C10AA: HMG CoA reductase inhibitors
				C10BA: HMG CoA reductase inhibitors in combination with other lipid modifying agents
				C10BX: HMG CoA reductase inhibitors, other combinations)

Other immunosuppressive drugs		ATC code up to 4 weeks before sepsis defined as a prescription for any of the listed drugs that was filled within the 4 weeks preceding sepsis diagnosis (sepsis group) or an NDR registration (no sepsis group).	Prescribed Drug Register	Defined using the following ATC codes:
				L04AA Selective immunosuppressants
				L04AB Tumor necrosis factor alpha (TNF-α) inhibitors
				L04AC Interleukin inhibitors
				L04AD Calcineurin inhibitors
				L04AX Other immunosuppressants: L04AX01 Azathioprine, L04AX02 Thalidomide, L04AX03 Methotrexate, L04AX04 Lenalidomide, L04AX05 Pirfenidone, L04AX06 Pomalidomide, L04AX07 Dimethyl fumarate, L04AX08 Darvadstrocel
Antihypertensive drugs		ATC code up to 4 weeks before sepsis defined as a prescription for any of the listed drugs that was filled within the 4 weeks preceding sepsis diagnosis (sepsis group) or an NDR registration (no sepsis group).	Prescribed Drug Register	Defined using the following ATC codes:
				C02: Antihypertensive agents
				C03: Diuretics
				C08: Calcium channel blockers
				C07: Beta blocking agents
				C09A: ACE inhibitors, plain
				C09B: ACE inhibitors combinations
				C09C: Angiotensin II Receptor Blockers, plain
				C09D: Angiotensin II Receptor Blockers, combinations
Recent antibiotic therapy		ATC code up to 4 weeks before sepsis defined as a prescription for any of the listed drugs that was filled within the 4 weeks preceding sepsis diagnosis (sepsis group) or an	Prescribed Drug Register	Defined using the following ATC codes:

		NDR registration (no sepsis group).		
				J01: Antibacterials for systemic use
				J02: Antimycotics for systemic use
				J04: Antimycobacterials
Coexisting condition		ICD-10	Patient Register	Defined using the following ICD-10 codes:
				Stroke: I61, I62.9, I63, I64, I67.9
				Coronary heart disease: I20-I25
				Heart failure: I50
				Atrial fibrillation: I48
				Cancer: C00-C97
				Renal dialysis and transplantation: Z94.0, Z49, Z99.2
				Lung disease: J40-J47, J60-J70, J85-J86
				Liver disease: K70-K77
				Hematologic disease: D50-D53, D60-D64, D70
				Immunologic deficiency: D80-D89
Income level			LISA	Low
				Intermediate
				High
Country of birth			LISA	Sweden
				Other
Education level		Education level at sepsis diagnosis	LISA	Low: Primary and secondary school (up to 9 years)
				Intermediate: Upper Secondary School
				High: Post-secondary Education and Doctoral Studies

Abbreviations: NDR, National Diabetes Register; BMI, Body Mass Index; HbA1c, glycated hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; ATC, Anatomical Therapeutic Chemical Classification System; ACE inhibitors, Angiotensin converting enzyme inhibitors; ICD, International Classification of Disease; LISA, Longitudinal integrated database for health insurance and labour market studies

Table S2. Baseline characteristics of type 2 diabetes individuals 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)
Age interval		
<55 years	968/14,534 (6.6%)	96,606/488,337 (19.8%)
55-64 years	3,080/14,534 (21.2%)	135,979/488,337 (27.8%)
65-74 years	5,105/14,534 (35.1%)	145,866/488,337 (29.9%)
≥75 years	5,381/14,534 (37.0%)	109,886/488,337 (22.5%)
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%)
Income level		
Low	5,801/14,003 (41.4%)	166,121/483,369 (34.4%)
Intermediate	5,470/14,003 (39.1%)	164,581/483,369 (34.0%)
High	2,732/14,003 (19.5%)	152,667/483,369 (31.6%)
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%)
Non-insulin 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 non-insulin glucose lowering drugs	2,398/14,222 (16.9%)	52,079/486,140 (10.7%)
Body mass index, kg/m^2	29.1 (26.0 – 33.0)	29.2 (26.2 – 32.9)
Body mass index interval		
Underweight	81/13,410 (0.6%)	1,584/466,436 (0.3%)
Normal	2,324/13,410 (17.3%)	74,026/466,436 (15.9%)
Overweight	5,098/13,410 (38.0%)	183,617/466,436 (39.4%)
Obese	5,907/13,410 (44.0%)	207,209/466,436 (44.4%)
Glycated hemoglobin A1c, mmol/mol	52 (45 – 62)	50 (45 –59)
Glycated hemoglobin A1c interval		
<43 mmol/mol (<6.1%)	2,108/14,283 (14.8%)	81,845/484,905 (16.9%)
43-47 mmol/mol (6.1-6.5%)	2,568/14,283 (18.0%)	100,405/484,905 (20.7%)
48-52 mmol/mol (6.5-6.9%)	2,598/14,283 (18.2%)	95,978/484,905 (19.8%)
53-62 mmol/mol (7-7.8%)	3,450/14,283 (24.2%)	104,265/484,905 (21.5%)
63-72 mmol/mol (7.9-8.7%)	1,856/14,283 (13.0%)	53,615/484,905 (11.1%)
73-82 mmol/mol (8.8-9.7%)	1,015/14,283 (7.1%)	26,851/484,905 (5.5%)
>82 mmol/mol (>9.7%)	688/14,283 (4.8%)	21,946/484,905 (4.5%)
Diastolic blood pressure, mmHg†	79 (70 – 80)	80 (70 – 85)
Systolic blood pressure, mmHg‡	140 (128 – 150)	138 (126 – 150)
Blood pressure interval		
Normal	3,395/14,154 (24.0%)	120,625/483,176 (25.0%)
High normal	3,062/14,154 (21.6%)	116,681/483,176 (24.1%)
Hypertension	7,697/14,154 (54.4%)	245,870/483,176 (50.9%)
eGFR, ml/min	71 (55 – 88)	81 (66 – 96)
eGFR interval		
≥90 ml/min	3,134/13,794 (22.7%)	159,611/475,462 (33.6%)
60-89 ml/min	6,280/13,794 (45.5%)	235,643/475,462 (49.6%)
45-59 ml/min	2,549/13,794 (18.5%)	55,670/475,462 (11.7%)
30-44 ml/min	1,335/13,794 (9.7%)	19,667/475,462 (4.1%)
15-29 ml/min	365/13,794 (2.6%)	4,223/475,462 (0.9%)
<15 ml/min	131/13,794 (0.9%)	648/475,462 (0.1%)
Albuminuria		
Normoalbuminuria	10,967/14,534 (75.5%)	421,193/488,337 (86.3%)
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 and 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%)
Hematologic disease	393 (2.7%)	7,564 (1.5%)

Immunologic deficiency	8 (0.06%)	335 (0.07%)
Medications		
Recent antibiotic therapy	927 (6.4%)	20,248 (4.1%)
Corticosteroids	491 (3.4%)	7,210 (1.5%)
Immunosuppressants	162 (1.1%)	2,390 (0.5%)
Statin	5,629 (38.7%)	198,195 (40.6%)
Antihypertensive drugs	9,672 (66.5%)	307,382 (62.9%)
Beta blockers	6,199 (42.7%)	179,188 (36.7%)
ACE inhibitors	4,798 (33.0%)	152,035 (31.1%)
Angiotensin II receptor blockers	2,853 (19.6%)	95,619 (19.6%)
Others	7,197 (49.5%)	200,839 (41.1%)

Data are number/total number (%) or median (IQR). eGFR, estimated glomerular filtration rate. Educational level was categorized as low (compulsory only), intermediate, or high (university level or similar). *Data available in 14,492 persons in the sepsis group and 487,771 persons in the no sepsis group. †Data available in 14,131 persons in the sepsis group and 482,967 persons in the no sepsis group. ‡ Data available in 14,134 persons in the sepsis group and 483,077 persons in the no sepsis group

Table S3. Cox regression analysis showing the association with sepsis in individuals with type 2 diabetes using five different approaches to quantify HbA1c

	Updated mean HbA1c (12 months)[a]	**Baseline HbA1c[b]**	**Updated mean HbA1c (all values)[c]**	**Updated time-weighted mean HbA1c (all values)[d]**	**Latest updated HbA1c[e]**
Variable	**HR (95% CI)[f]**	**HR (95% CI)[f]**	**HR (95% CI)[f]**	**HR (95% CI)[f]**	**HR (95% CI)[f]**
HbA1c interval, mmol/mol					
<43	1.15 (1.07-1.24)	1.09 (1.02-1.17)	1.04 (0.96-1.12)	1.14 (1.06-1.23)	1.12 (1.04-1.21)
43-47	1.00 (0.93-1.07)	1.02 (0.95-1.09)	0.96 (0.90-1.03)	1.01 (0.94-1.08)	0.99 (0.92-1.06)
48-52	1.00	1.00	1.00	1.00	1.00
53-62	0.93 (0.87-0.99)	1.06 (0.99-1.13)	1.01 (0.95-1.07)	1.01 (0.95-1.07)	0.93 (0.88-0.99)
63-72	1.05 (0.97-1.13)	1.04 (0.96-1.12)	1.11 (1.04-1.20)	1.12 (1.04-1.20)	1.07 (1.00-1.15)
73-82	1.14 (1.04-1.25)	1.28 (1.17-1.40)	1.41 (1.29-1.56)	1.25 (1.14-1.37)	1.20 (1.09-1.31)
>82	1.52 (1.37-1.68)	1.45 (1.31-1.61)	1.71 (1.47-1.99)	1.65 (1.46-1.86)	1.51 (1.36-1.68)

[a]Updated mean HbA1c is the mean value of all HbA1c values recorded within 12 months before sepsis diagnosis
[b]Baseline HbA1c is the first recorded value in the National Diabetes Register
[c]Updated mean HbA1c is the mean of all values recorded in the National Diabetes Register until sepsis diagnosis
[d]Updated time-weighted (TW) mean HbA1c is the time-weighted average of all values recorded in the National Diabetes Register until sepsis diagnosis
[e]Latest updated HbA1c value before sepsis diagnosis
[f]The analyses were adjusted for age, sex, smoking, country of birth, socioeconomic factors, diabetes treatment, other medications, body mass index, blood pressure, eGFR, albuminuria, and coexisting conditions (Supplemental Table S1)

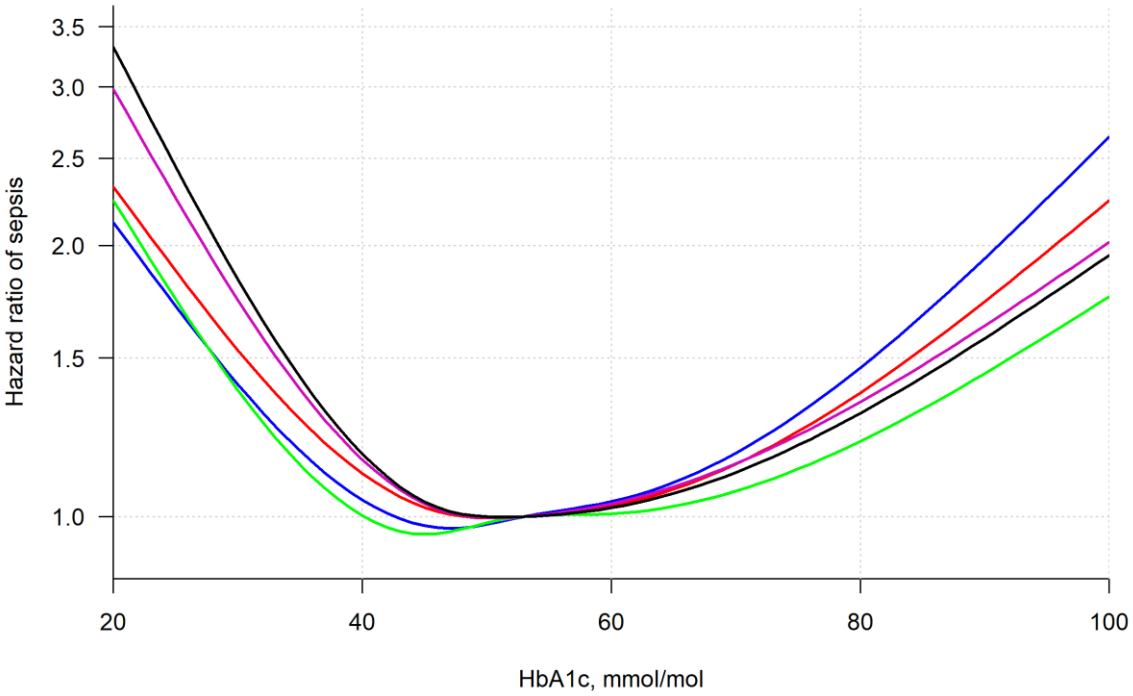

Figure S1. Adjusted restricted cubic spline curves showing the hazard ratio for sepsis risk by HbA1c level. HbA1c was assessed using five different approaches: as updated mean HbA1c using the mean value of all HbA1c values recorded within 12 months before sepsis diagnosis (black curve); as baseline HbA1c using the first recorded value in the National Diabetes Register (green curve); as updated mean HbA1c using all values recorded in the National Diabetes Register until sepsis diagnosis (blue curve); as updated time-weighted mean HbA1c from all values recorded in the National Diabetes Register until sepsis diagnosis (red curve); and as latest updated HbA1c value before sepsis diagnosis (purple curve). All hazard ratios are with respect to a reference HbA1c of 53 mmol/mol. The spline curves were adjusted for the confounders listed in the Supplemental Table S1.

Table S4. Cox regression analysis showing the association with sepsis in individuals with type 2 diabetes after excluding or censoring patients being immunosuppressed by disease or receiving immunosuppressive medication

	Immunosuppressed individuals excluded[a]	**Indiduals censored at immunosuppression[a]**
Variable	**HR (95% CI)[b]**	**HR (95% CI)[b]**
HbA1c interval, mmol/mol		
<43	1.14 (1.05-1.24)	1.16 (1.06-1.26)
43-47	0.99 (0.92-1.07)	0.99 (0.92-1.07)
48-52	1.00	1.00
53-62	0.92 (0.86-0.99)	0.93 (0.86-1.00)
63-72	1.03 (0.95-1.12)	1.04 (0.96-1.13)
73-82	1.16 (1.04-1.28)	1.18 (1.06-1.30)
>82	1.54 (1.37-1.72)	1.57 (1.40-1.76)

[a]Immunosuppression was defined as cancer (ICD-10 codes C00-C97), renal dialysis and transplantation (ICD-10 codes Z94.0, Z49, and Z99.2), immunologic deficiency (ICD-10 codes D80-D89), and/or treatment with immunosuppressive drugs (ATC codes L04, H02AB, and H02BX01)

[b]The analyses were adjusted for age, sex, smoking, country of birth, socioeconomic factors, diabetes treatment, other medications, body mass index, blood pressure, eGFR, albuminuria, and coexisting conditions (Supplemental Table S1)

Table S5. Cox regression analysis showing the association between HbA1c and all-cause mortality in individuals with type 2 diabetes and sepsis

Variable	**Unadjusted HR (95% CI)**	**HR adjusted for age and sex (95% CI)**	**Fully adjusted* HR (95% CI)**
HbA1c interval			
<43 mmol/mol	1.07 (0.98-1.16)	1.11 (1.02-1.20)	1.03 (0.92-1.15)
43-47 mmol/mol	1.05 (0.97-1.14)	1.05 (0.97-1.14)	1.01 (0.91-1.13)
48-52 mmol/mol	1.00	1.00	1.00
53-62 mmol/mol	1.06 (0.98-1.14)	1.04 (0.97-1.12)	0.99 (0.90-1.10)
63-72 mmol/mol	1.03 (0.95-1.13)	1.04 (0.96-1.14)	0.97 (0.86-1.09)
73-82 mmol/mol	1.03 (0.92-1.14)	1.08 (0.97-1.20)	1.07 (0.93-1.24)
>82 mmol/mol	1.04 (0.92-1.16)	1.15 (1.03-1.29)	1.06 (0.90-1.24)

*The analysis was adjusted for age, sex, smoking, country of birth, socioeconomic factors, diabetes treatment, other medications, body mass index, blood pressure, eGFR, albuminuria, and coexisting conditions (Supplemental Table S1)