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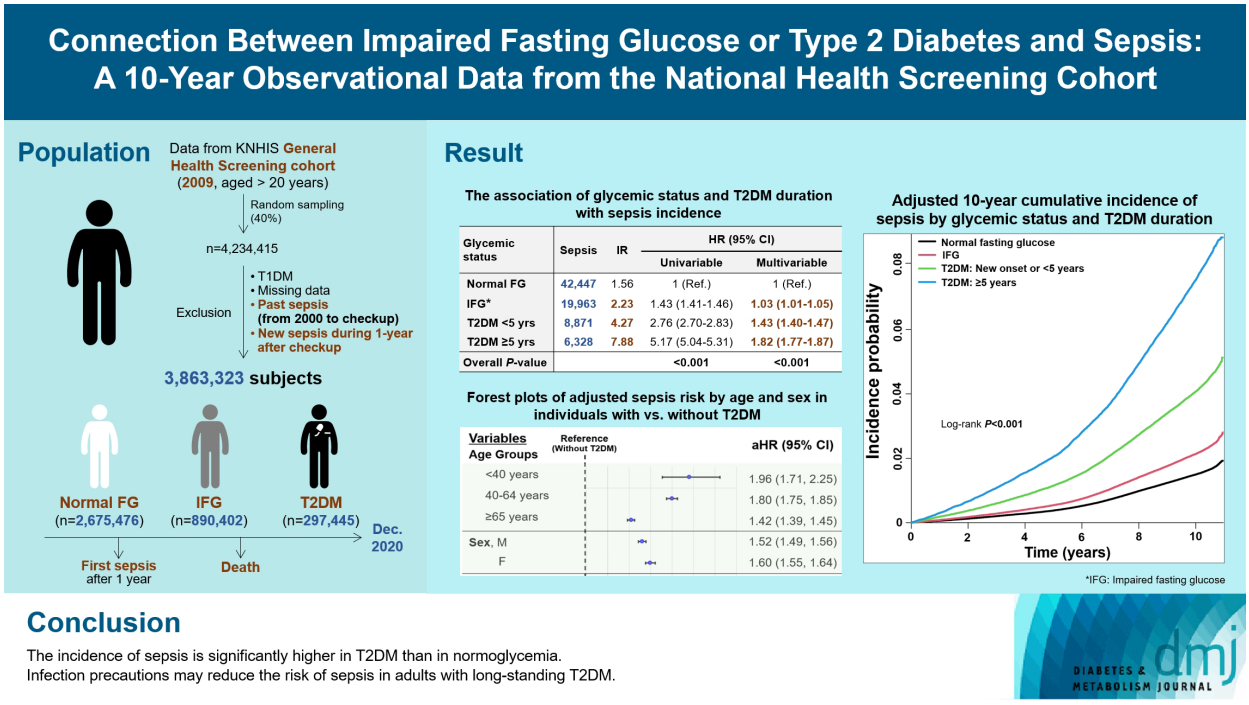
Diabetes Metab J 2025;49:485-497 | *https://doi.org/10.4093/dmj.2024.0387*



Highlights

- **Sepsis risk increases substantially in long-standing T2DM or young-onset T2DM.**
- **Obesity, smoking, drinking, and physical activity lack ties to sepsis risk in T2DM.**
- **Infection precautions and vaccination can reduce sepsis risk in long-standing T2DM.**

How to cite this article:
Lee EH, Lee KH, Lee KN, Park Y, Han KD, Han SH. Connection between Impaired Fasting Glucose or Type 2 Diabetes Mellitus and Sepsis: A 10-Year Observational Data from the National Health Screening Cohort. Diabetes Metab J 2025;49:485-497. https://doi.org/10.4093/dmj.2024.0387

Original Article
Complications

Diabetes Metab J 2025;49:485-497
https://doi.org/10.4093/dmj.2024.0387
pISSN 2233-6079 · eISSN 2233-6087

dmj
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Connection between Impaired Fasting Glucose or Type 2 Diabetes Mellitus and Sepsis: A 10-Year Observational Data from the National Health Screening Cohort

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Background: The mortality of sepsis without direct drugs is high. The association between prediabetes, based on a single fasting glucose (FG), or long-term type 2 diabetes mellitus (T2DM) and sepsis remains unclear.
Methods: Of the adults aged ≥20 years who were included in the National Health Screening Program (NHSP) in 2009, 40% were randomly sampled. After excluding patients with type 1 diabetes mellitus, with missing information, and who were diagnosed with sepsis during the wash-out (between 2001 and the NHSP) or 1-year lag period, a cohort comprised of 3,863,323 examinees. Body mass index (BMI) measurements, FG tests, and self-reported questionnaires on health-related behaviors were conducted. Individual information was followed up until 2020 and censored upon the first occurrence of sepsis or death. The incidence of sepsis was compared using a multivariable regression adjusted for age, sex, income, BMI, smoking, drinking, physical activity levels, and chronic diseases.
Results: The cohort was divided into those with normal FG (n=2,675,476), impaired fasting glucose (IFG) (n=890,402, 23.0%), T2DM <5 years (n=212,391, 5.5%), or T2DM for ≥5 years (n=85,054, 2.2%). The groups with IFG (adjusted hazard ratio [aHR], 1.03; 95% confidence interval [CI], 1.01 to 1.05), T2DM <5 years (aHR, 1.43; 95% CI, 1.40 to 1.47), and T2DM for ≥5 years (aHR, 1.82; 95% CI, 1.77 to 1.87) exhibited significantly higher incidence of sepsis (P<0.001), with the greatest risk in patients with T2DM aged <40 years (aHR, 1.96; 95% CI, 1.71 to 2.25).
Conclusion: Patients with long-standing and young-onset T2DM show a substantially high risk of sepsis, emphasizing the need for infection prevention and vaccination.

Keywords: Diabetes mellitus, type 2; Incidence; Prediabetic state; Risk; Sepsis

INTRODUCTION

The growing global prevalence and socioeconomic burden of type 2 diabetes mellitus (T2DM) in the aging population could bring about significant ripple effects on multifaceted public health sectors and disability-adjusted life-years [1-3]. Despite the probable underestimation of the real prevalence and the high proportion of undiagnosed T2DM [4,5], forecasts from the Global Burden of Disease dataset and the International Diabetes Federation Atlas suggest that the global T2DM preva-

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Received: Jul. 16, 2024; Accepted: Oct. 23, 2024

lence may reach approximately 7,000 per 100,000 individuals in 2030 and affect 11.2% of the global population in 2045 [3,6]. In addition to the well-documented and common complications of T2DM, including cardiovascular diseases, renal disease, and retinopathy [2], chronic low-grade systemic inflammation from hyperglycemia can lead to immune dysfunction and exhaustion. This results from the prolonged activation of mononuclear cells and neutrophils; reduced phagocytic activity; and alterations in the complement system, cytokines, and chemokines [7-9]. Therefore, patients with T2DM may be vulnerable to infections caused by several bacteria or viruses [8, 10-13], and have a higher risk of active tuberculosis compared with the general population [14].

Sepsis is a dysregulated pathophysiological response triggered to a microbial infection, leading to critical organ dysfunction with severe outcomes and irreversible functional disabilities [15]. Managing sepsis and septic shock remains a challenge as early intensive resuscitation aimed at restoring tissue hypoperfusion without distinct targets or goals does not substantially improve the survival rates [16,17]. Additionally, the lack of direct antiseptic drugs that can control organ or tissue injuries underscores the need for personalized approaches to prevent sepsis in patients with risk factors [18].

Recent investigations in the United Kingdom (UK), Denmark, and Sweden revealed that patients with uncontrolled T2DM along with elevated glycosylated hemoglobin (HbA1c) levels had an increased risk of various infections, including sepsis, and an elevated risk of mortality from such infections than those with well-managed T2DM or without T2DM [12, 13,19,20]. Understanding the link between prediabetes or the duration of T2DM and sepsis is crucial for developing individualized approaches to prevent sepsis through lifestyle modification and the adoption of infection prevention measures after the early detection of hyperglycemia; however, this relationship remains relatively unexplored. Hence, we aimed to provide evidence based on the largest health checkup cohort with a longitudinal follow-up to substantiate the association of T2DM duration or impaired fasting glucose (IFG) with the incidence of sepsis in South Korean individuals in non-Caucasian East Asia.

METHODS

Data source and study design

This retrospective longitudinal cohort study was based on the National Healthcare Promotion Project implemented by the Korean National Health Insurance Service (KNHIS), which serves as a singular public insurance system with mandatory registration [21,22]. The National Health Information Database (NHID) records various types of medical information, including the International Classification of Diseases 10th Revision (ICD-10) diagnostic codes, demographics, prescriptions, procedures, and dates of death for outpatient and inpatient usage, generated by the KNHIS for comprehensive claims system [21,22]. Since 2008, the KNHIS has conducted biennially free and voluntary National Health Screening Programs (NHSPs) (known as general health checkups) for individuals aged ≥20 years. These screenings consist essentially of gathering of basic sociodemographic data, anthropometric measurements (height, weight, waist circumference [WC], and blood pressure levels), fasting laboratory tests, and a self-administered survey capturing current diseases, medications used, and health-related behaviors (cigarette smoking, alcohol consumption, and physical activity [PA]) (Appendix 1) [23]. To ensure the reliability of plasma glucose and lipid levels, examinees were instructed to fast for at least 8 hours after dinner, the day before the checkup. Additional information on the examinees was obtained from the NHID-NHSP database using anonymized identifiers.

Forty percent (n=4,234,415) of the total participants who underwent the NHSP from January 2009 to December 2009 were randomly sampled. The checkup date was defined as the cohort start date. Patients with type 1 diabetes mellitus (T1DM; n=71,691), a prior diagnosis of sepsis during the washout period (between 2000 and the start date) (n=7,239), and missing values (n=281,520) were excluded. Additionally, participants newly diagnosed with sepsis during the 1-year lag period after the start date (n=10,642) were excluded to ensure accurate evaluation of the association between T2DM or IFG and sepsis. The checkup results of the final cohort (n=3,863,323) were collected from the NHSP database, and their clinical data were monitored in the NHID until December 2020. The participants were censored if the first occurrence of sepsis during hospitalization was identified or if they died. The median follow-up period of the cohort was 10.3 years (Fig. 1). This study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB No. 3-2023-0267), and the requirement for written consent was waived due to the retrospective design of the anonymized data. All research procedures adhered to the principles of the Declaration of Helsinki.

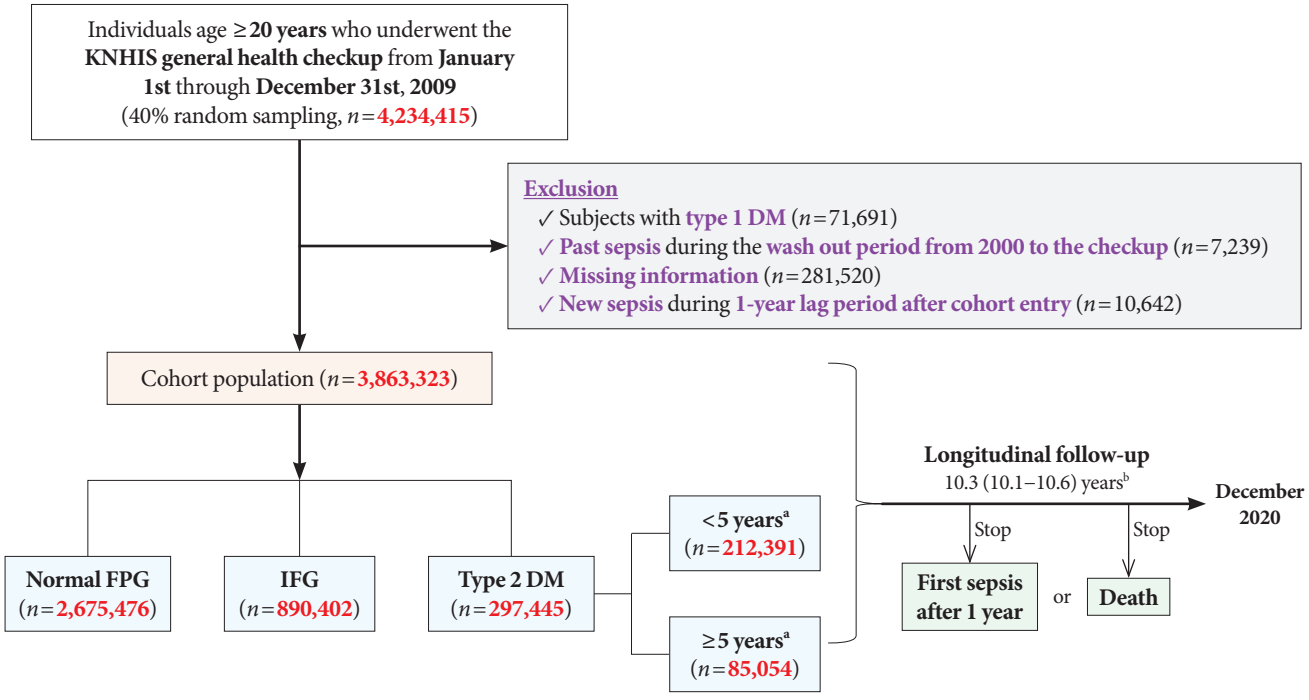

Fig. 1. Schematic diagram of cohort selection, group classification, and follow-up process. KNHIS, Korean National Health Insurance Service; DM, diabetes mellitus; FPG, fasting plasma glucose; IFG, impaired fasting glucose. [a]The duration of DM at the time of the health check-up was assessed by International Classification of Diseases 10th Revision code or start date of oral anti-diabetic drugs and/or insulin, [b]Median (interquartile range).

Operational definitions

Inpatient sepsis was diagnosed using the ICD-10 codes, except for P36 (bacterial sepsis in newborns) and O85 (puerperal sepsis) in the NHID (Supplementary Table 1) [24]. Outpatient sepsis codes were not considered to minimize diagnostic errors from code-based definitions.

T2DM was defined using the ICD-10 code E11and/or prescription codes for oral antidiabetic drugs or (short- or long-acting) insulin only when the self-reported questionnaire responses and NHID information within 6 months from the cohort start date were identical. New-onset T2DM was defined as diabetes detected after an NHSP, which reported a fasting plasma glucose (FPG) level of ≥126 mg/dL [25], and the confirmation of the diagnostic and medication codes for T2DM within 3 months after the checkup. The duration of T2DM was assessed as the disease period prior to the cohort start date. To ascertain the T2DM duration, we confirmed the ICD-10 and/or antidiabetic drug codes from the NHID rather than from the responses to the self-questionnaire. The T2DM group (n=297,445) was divided into individuals with diabetes <5 years including those with new-onset (n=212,391) and individuals with diabetes ≥5 years (n=85,054). IFG (n=890,402) was defined as 100≤ FPG ≤125 mg/dL at the checkup and the lack of both diagnosis and drug codes for T2DM in the NHID during the total follow-up [25]. The normal FPG group (n=2,675,476) was defined as individuals with a checkup FPG level of <100 mg/dL and the absence of both diagnosis and drug codes for T2DM in the NHID in the entire observation period.

Alcohol consumption was classified as none, mild, or heavy, based on the average daily intake. The mild and heavy drinkers were defined as those who consumed <30 and ≥30 g/day, respectively [26]. By smoking status, the participants were divided into none, former, or current smokers at the start of the study. Regular PA was defined as engaging in light-intensity PA for ≥5 days/week, or vigorous-intensity PA for ≥3 days/week [27]. The last 7-day recall self-report for PA level (Appendix 1) was considered an appropriate tool for evaluating each participant's level of PA during national monitoring [28].

Chronic illnesses such as hypertension, dyslipidemia, and chronic kidney disease (CKD) were ascertained in the NHID by identifying relevant ICD-10 and/or drug codes within 6 months from the start date, adhering to established diagnostic

criteria for each condition (Supplementary Table 2). Body mass index (BMI) calculated based on the patient's height and weight at checkup were subdivided into underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), obese I (25–29.9 kg/m^2), and obese II (≥30 kg/m^2) according to the Asia-Pacific standard of the World Health Organization. Patients with a household income of below the 25th percentile, according to the 2010 National Population and Housing Census, were assigned to the lowest income group.

Statistical analysis

The baseline characteristics were expressed as the mean±standard deviation or median with the 25th and 75th interquartile ranges. To compare the four groups (normal FPG, IFG, T2DM <5 years including new onset, and T2DM for ≥5 years), the Kruskal-Wallis and one-way analysis of variance tests were employed for categorical and continuous variables, respectively. A two-tailed *P* value of less than 0.05 was considered significant. The incidence rate (IR) of sepsis per 1,000 person-year (PY) was also assessed. To examine the relationship between T2DM or IFG and sepsis using normal FPG levels as a reference, multivariable Cox proportional hazard regression models were used to obtain unadjusted or adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). Contrary to the unadjusted model 1, model 2 was adjusted for age and sex, while model 3 was adjusted for age, sex, income, BMI categories, smoking, drinking, regular PA, hypertension, dyslipidemia, and CKD. Adjusted Kaplan-Meier curves were utilized, and the statistical significance was determined using the log-rank test to compare the cumulative incidence of sepsis across distinct groups over a 10-year period. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Forest plots of various subgroups were created using Python version 3.12.3 (Python Software Foundation, Wilmington, DE, USA).

RESULTS

Baseline characteristics of cohort and subgroups

Among 3,863,323 of cohort population, participants with normal FPG levels (69.3%) had the highest proportion, followed by those with IFG (23.0%), T2DM <5 years (5.5%), and T2DM for ≥5 years (2.2%). The mean age of the entire cohort was 47 years, and 56% were aged between 40 and 64 years. The youngest group comprised participants with normal FPG levels (45.0±13.8 years), while the oldest group comprised those with T2DM for ≥5 years (61.4±9.9 years). The age increased sequentially from individuals with normal FPG levels to those with T2DM for ≥5 years (*P*<0.001). The proportion of older adults aged ≥65 years was the highest in the group with T2DM for ≥5 years (40.1%). The BMI and WC was highest in the group with T2DM for <5 years (25.2±3.4 kg/m^2 and 85.6±8.6 cm, respectively), showing a significantly higher incidence of abdominal obesity in patients with T2DM regardless of duration (all *P*<0.001). Hypertension, dyslipidemia, and CKD commonly developed in the group with T2DM for ≥5 years (64%, 43%, and 16%, respectively), showing a progressively higher prevalence compared with those with normal FPG levels (*P*<0.001). The proportion of participants who engaged in regular PA was significantly higher in the group with a T2DM for ≥5 years compared with the normal FPG group (25% vs. 17%, *P*<0.001) (Table 1).

In single-point checkup fasting blood tests, the FPG levels increased with the progression of T2DM, reflecting a hyperglycemic condition with prolonged duration of T2DM (normal FPG, IFG, T2DM for <5 years, and T2DM for ≥5 years: 87.5±7.7, 107.8±6.6, 146.2±45.9, and 147.5±52.2 mg/dL, respectively; *P*<0.001). The IFG group had the highest levels of total and low-density lipoprotein cholesterol among the four study groups (all *P*<0.001) (Table 1).

The prevalence of sepsis was significantly higher among individuals with T2DM for ≥5 years (7.4%) than among those with normal FPG levels (1.6%), IFG (2.2%), and T2DM for <5 years (4.2%) (*P*<0.001) (Table 1).

Differences of sepsis incidence among the impaired fasting glucose groups and two diabetes duration groups

The IFG group (IR, 2.23/1,000 PY) had a significantly higher IR of sepsis than the reference group among participants with normal FPG levels (1.56/1,000 PY) in the unadjusted model 1 (hazard ratio [HR], 1.43; 95% CI, 1.41 to 1.46), multivariable model 2 (HR, 1.03; 95% CI, 1.02 to 1.05), and model 3 (HR, 1.03; 95% CI, 1.01 to 1.05). The risk of sepsis was significantly higher in patients with T2DM for <5 years (4.27/1,000 PY) and T2DM for ≥5 years (7.88/1,000 PY) in all models compared with the normal FPG group. In the model 3 adjusted for potential confounding factors, the aHR was highest in the group with T2DM for ≥5 years (1.82; 95% CI, 1.77 to 1.87). In all three models, the incidence of sepsis differed significantly among the four groups (all *P*<0.001). In particular, the risk of

Table 1. Baseline characteristics of the cohort population and subgroups according to type 2 diabetes mellitus

Characteristic	Total (n=3,863,323)	Fasting glucose level and diabetic status				*P* value
		Normal FPG (n=2,675,476, 69.3%)	IFG (n=890,402, 23.0%)	T2DM[a] for <5 years (n=212,391, 5.5%)	T2DM for ≥5 years (n=85,054, 2.2%)	
Age, yr	47.0±13.9	45.0±13.8	49.7±13.2	54.7±12.3	61.4±9.9	<0.001
<40	1,212,131 (31.4)	986,194 (36.9)	201,470 (22.6)	23,388 (11.0)	1,079 (1.3)	<0.001
40–64	2,165,045 (56.0)	1,417,667 (53.0)	556,861 (62.5)	140,618 (66.2)	49,899 (58.7)	
≥65	486,147 (12.6)	271,615 (10.2)	132,071 (14.8)	48,385 (22.8)	34,076 (40.1)	
Male sex	2,110,997 (54.6)	1,370,656 (51.2)	552,195 (62.0)	139,201 (65.5)	48,945 (57.6)	<0.001
BMI, kg/m^2	23.7±3.2	23.3±3.2	24.4±3.2	25.2±3.4	24.7±3.1	<0.001
<18.5	143,780 (3.7)	120,176 (4.5)	19,458 (2.2)	3,126 (1.5)	1,020 (1.2)	<0.001
<23	1,513,927 (39.2)	1,160,170 (43.4)	281,199 (31.6)	49,351 (23.2)	23,207 (27.3)	
<25	950,974 (24.6)	644,130 (24.1)	231,495 (26.0)	52,015 (24.5)	23,334 (27.4)	
<30	1,118,746 (29.0)	678,214 (25.4)	316,641 (35.6)	90,992 (42.8)	32,899 (38.7)	
≥30	135,896 (3.5)	72,786 (2.7)	41,609 (4.7)	16,907 (8.0)	4,594 (5.4)	
Waist circumference, cm	80.2±9.1	78.8±9.0	82.4±8.7	85.6±8.6	85.4±8.1	<0.001
Underlying diseases						
Hypertension	959,722 (24.8)	508,341 (19.0)	288,323 (32.4)	108,465 (51.1)	54,593 (64.2)	<0.001
Dyslipidemia	654,579 (16.9)	354,931 (13.3)	188,110 (21.1)	75,067 (35.3)	36,471 (42.9)	<0.001
CKD	260,725 (6.8)	155,993 (5.8)	70,072 (7.9)	21,042 (9.9)	13,618 (16.0)	<0.001
Income status						
Lowest quartile	751,765 (19.5)	523,490 (19.6)	166,987 (18.8)	44,384 (20.9)	16,904 (19.9)	<0.001
Smoking						
Non-smoker	2,299,615 (59.5)	1,652,590 (61.8)	485,899 (54.6)	109,323 (51.5)	51,803 (60.9)	<0.001
Ex-smoker	552,552 (14.3)	340,468 (12.7)	156,499 (17.6)	39,613 (18.7)	15,972 (18.8)	
Current smoker	1,011,156 (26.2)	682,418 (25.5)	248,004 (27.9)	63,455 (29.9)	17,279 (20.3)	
Alcohol consumption						
None	1,984,806 (51.4)	1,399,781 (52.3)	421,821(47.4)	108,389 (51.0)	54,815 (64.5)	<0.001
Mild to moderate	1,570,345 (40.7)	1,091,870 (40.8)	375,364 (42.2)	79,189 (37.3)	23,922 (28.1)	
Heavy	308,172 (8.0)	183,825 (6.9)	93,217 (10.5)	24,813 (11.7)	6,317 (7.4)	
Regular PA	692,063 (17.9)	458,362 (17.1)	168,672 (18.9)	43,733 (20.6)	21,296 (25.0)	<0.001
Laboratory findings, mg/dL						
Fasting glucose	96.7±22.5	87.5±7.7	107.8±6.6	146.2±45.9	147.5±52.2	<0.001
Total cholesterol	195.1±36.7	192.6±35.5	201.8±37.5	201.5±42.0	188.8±40.3	<0.001
HDL cholesterol	56.1±27.8	56.8±27.7	55.4±27.7	52.8±27.8	51.9±29.9	<0.001
LDL cholesterol	113.7±38.6	112.6±38.0	117.6±38.5	113.2±43.4	106.3±41.3	<0.001
Sepsis	77,609 (2.0)	42,447 (1.6)	19,963 (2.2)	8,871 (4.2)	6,328 (7.4)	<0.001

Values are presented as mean±standard deviation or number (%).
FPG, fasting plasma glucose; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; BMI, body mass index; CKD, chronic kidney disease; PA, physical activity; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Include new-onset T2DM.

Table 2. Diabetic status and duration in association with sepsis incidence

Glycemic status	Subjects	Sepsis	Duration, PY	IR, / 1,000 PY	HR (95% CI)		
					Univariable model 1	Multivariable	
						Model 2	Model 3
Normal FPG	2,675,476	42,447	27,161,552	1.56	1 (Ref)	1 (Ref)	1 (Ref)
IFG	890,402	19,963	8,948,872	2.23	1.432 (1.408–1.456)	1.034 (1.017–1.052)	1.029 (1.012–1.047)
T2DM for <5 years (including new-onset)	212,391	8,871	2,076,617	4.27	2.763 (2.702–2.827)	1.473 (1.439–1.507)	1.433 (1.398–1.467)
T2DM for ≥5 years	85,054	6,328	802,774	7.88	5.172 (5.037–5.310)	1.875 (1.825–1.925)	1.818 (1.769–1.868)
Overall *P* value[a]					<0.001	<0.001	<0.001

Univariable model 1: not adjusted. Multivariable model 2 was adjusted for age and sex. Multivariable model 3 was adjusted for age, sex, lowest income status, five categories of body mass index, smoking and drinking behaviors, regular physical activities, hypertension, dyslipidemia, and chronic kidney disease.
PY, person-year; IR, incidence rate; HR, hazard ratio; CI, confidence interval; FPG, fasting plasma glucose; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus.
[a]Comparison among the four groups.

sepsis progressively increased with higher aHR, from the IFG group to the group with T2DM for ≥5 years (Table 2). As the observation period progressed, the cumulative incidence probability of sepsis increased most steeply in the group with T2DM for ≥5 years, followed by those with T2DM <5 years and IFG (log-rank *P*<0.001) (Fig. 2).

Impact of T2DM between subgroups according to comorbidities or health-related behaviors on the risk of sepsis

A significant difference was observed in the aHR for sepsis depending on the diagnosis of T2DM in the multivariable model 2 by age group (*P*<0.001), sex (*P*=0.009), and the presence of hypertension (*P*<0.001). When the risk of sepsis was compared between participants with T2DM and those without T2DM, the risk was significantly high in patients aged <65 years. Notably, when T2DM was diagnosed, the aHR for sepsis increased by two-fold (95% CI, 1.7 to 2.25) in the group aged <40 years and by 1.8-fold (95% CI, 1.75 to 1.85) in the group aged 40–64 years. However, the relative risk of sepsis due to T2DM only increased by 1.4-fold in adults aged ≥65 years, apart from the highest prevalence of sepsis (12.4 cases/1,000 PY). In addition, women with T2DM exhibited a greater increase in aHR than men with T2DM (1.60 vs. 1.52, *P*=0.009). Furthermore, patients with T2DM without hypertension displayed a higher aHR than those with hypertension (1.62 vs. 1.52, *P*<0.001) (Fig. 3, Supplementary Table 3).

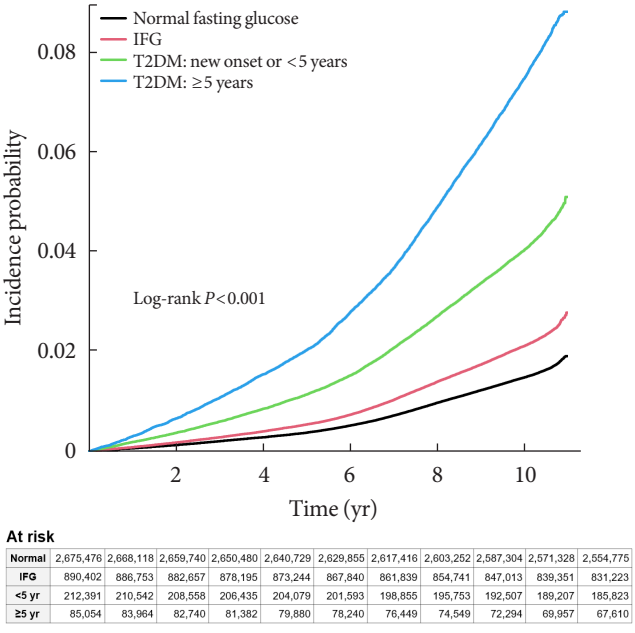

Fig. 2. Adjusted cumulative incidence probability of sepsis during the 10-year follow-up according to normal or impaired fasting glucose (IFG) or duration of type 2 diabetes mellitus (T2DM). The incidence risk in each group was adjusted for age, sex, lowest income status, five categories of body mass index, smoking and drinking behaviors, regular physical activities, hypertension, dyslipidemia, and chronic kidney disease.

DISCUSSION

The results of a large-scale NHSP cohort comprising approxi-

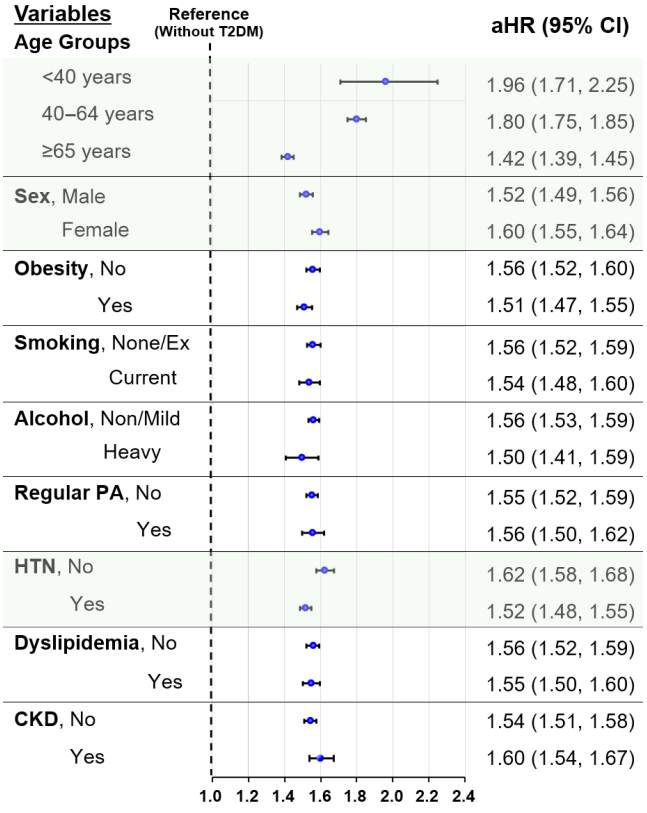

Fig. 3. Forest plots revealing the adjusted sepsis risk in patients with type 2 diabetes mellitus (T2DM) compared with patients without T2DM in the subgroups according to various clinical characteristics. Adjusted hazard ratios (aHRs) were obtained using the multivariable model 2. Obesity indicates obese I and II among the five categories based on body mass index. The light green boxes indicate that the aHRs were significantly different between the subgroups ($P<0.05$). CI, confidence interval; Ex, former smoker; PA, physical activity; HTN, hypertension; CKD, chronic kidney disease.

mately 4 million people nationwide revealed that T2DM or IFG (prediabetes) are independent risk factors of sepsis. The notable findings in our data are as follows: (1) the risk of sepsis substantially increases in individuals with T2DM for ≥5 years or young-onset T2DM (YOD), defined as onset before the age of 40 years; (2) modifiable lifestyle factors such as obesity, smoking, drinking, and PA did not show significant associations with the risk of sepsis in patients with T2DM; and (3) individuals with T2DM without hypertension or women with T2DM exhibited a higher vulnerability to sepsis compared with those with T2DM with hypertension or men with T2DM.

Additionally, recent studies, including one by Balintescu et al. [20], highlighted that both well- and poorly controlled hyperglycemia, measured through based on the mean HbA1c values within short intervals, increased the incidence of sepsis in patients with T2DM (lowest aHR at HbA1c of 7.0%–7.8%). A meta-analysis revealed a U-shaped relationship between in-hospital mortality rate after sepsis and blood glucose levels in patients with T2DM (with the lowest mortality observed at blood glucose levels of 145 to 155 mg/dL) [29]. Despite the nonlinear connection between blood glucose levels and the risk or outcome of sepsis, the precise pathophysiologic mechanism linking T2DM duration or IFG to sepsis incidence, relative to individuals with normal FPG, remain poorly understood and warrant further investigation. Our analyses showed that patients with IFG identified on a single blood test had an increased incidence of sepsis compared with those with normal FPG levels, although the adjusted risk ratio was slightly higher. The early detection of IFG or T2DM using a simple FPG test could therefore aid in predicting a higher risk of sepsis compared with the IR at normal FPG levels. Such proactive measures could potentially prevent sepsis by promoting education and adherence to infection prevention practices (e.g., pneumonia from hand washing or urinary tract infection [UTI] from toilet hygiene) in adults with IFG or T2DM. Therefore, the implementation of regular (annual or biennial) measurement of FPG levels as part of a health checkup could be one of the several cost-effective strategies to reduce community-acquired sepsis, especially in low- and middle-income countries.

The incidence of YOD has remarkably increased in various countries, especially among female [30]. A nationwide cohort analysis from the Korean NHID also showed that the incidence of YOD steadily increased from 1.3 in 2006 to 1.7/1,000 people in 2015, with a strikingly higher proportion of obese individuals [31]. Due to the rapid decline in β-cell function and poor compliance to clinic visit or treatment, YOD patients have the more aggressive clinical outcomes and complications including cardiovascular disease, retinopathy, CKD, mental illness and cancer compared with patients with usual-onset T2DM (occurring at age ≥40 years) and T1DM [30,32], ultimately leading to the higher all-cause hospitalization and mortality [30,32-34]. Herein, our report presents sepsis as an additional serious disease that requires attention among patients with YOD.

In a retrospective cohort study performed in the UK, patients with T2DM had the increased risk ratio of 2.3 (95% CI, 2.1 to 2.4) for sepsis than age-sex-practice-matched control

group without T2DM [13]. However, the total number of patients with T2DM (n=96,630) and sepsis events (n=2,612) was lower than that in our cohort, and analyses according to age groups and T2DM duration were not performed. Another cohort (n=443,764) in Hong Kong have shown a significantly higher admission rate caused by various infections (aHR, 1.7; 95% CI, 1.4 to 2.1) in patients with YOD compared with those with usual-onset T2DM, but data on sepsis were not included [34]. Our first study revealed the particularly alarming finding that the risk of sepsis was the highest in patients with YOD among all age groups or those with any clinical features, with a two-fold increased aHR compared with individuals aged 20 to 40 years without T2DM. The total burden of sepsis in patients with YOD might be lower than that in individuals with other chronic compilations [30,32,33]. Considering the unexpectedly high mortality or long-term disabilities after sepsis or septic shock even in the current era without direct antisepsis drugs, the long-life expectancy, and less attention to sepsis in patients with YOD, prospective studies on sepsis and sepsis-attributable mortality are warranted and should guide the development of multifaceted preventive strategies tailored to a specific population.

The higher risk of sepsis in patients with T2DM for ≥5 years could be interpreted as a more chronic inflammatory status caused by intermittent or persistent hyperglycemia, which intensify the dysregulation or impairment of the immune systems [8]. The interaction of advanced glycation end products (AGEs) with receptor for AGEs (RAGE) via MyD88 and toll-like receptor 4 in T2DM can activate the nuclear factor-κB. The activation of this key transcriptional factor can cause hyperinflammation, cytokine storm, and organ dysfunction in patients with sepsis [35,36]. In addition, insulin resistance in the skeletal muscles of patients with T2DM could induce higher expression of various genes related to immune mechanisms [37]. This vicious repetition between insulin resistance worsens with T2DM duration, and constant inflammation in obesity-associated adipose tissues, muscles, and hepatocytes could gradually aggravate vulnerability to sepsis [8,36-38].

The exact or potential reasons for our findings regarding the higher risk of sepsis in women with T2DM and patients with T2DM without hypertension are currently not clearly understood. There have been no studies conducted on the relationship between sex and infections or impairment of immune systems in T2DM patients. Several studies have reported that (recurrent) UTIs are commonly observed in female diabetes patients compared to women without T2DM [39,40]. In general, UTIs occur at a significantly higher prevalence in women compared to men regardless of T2DM [39]. Therefore, we could infer that female with T2DM may be at a higher risk of developing sepsis originated from UTIs compared to men. Hypertension, which commonly coexists with T2DM, in many preclinical *in vitro* or animal studies can have the complex impacts on the chronic immune system and cytokine secretion through various mechanisms [41]. It may be very difficult, to clearly explain the underlying causes of clinical phenomena that emerge as the final results of complex physiological processes between hypertension and sepsis in relation to a wide complicated immune response.

The study findings may have clinical implications for personalized prevention of sepsis and various infectious diseases in patients with T2DM or IFG. Although international guidelines such as the 'Surviving Sepsis Campaign,' including early intensive resuscitation and protocol-based bundle approaches, have contributed to reducing the mortality rate of sepsis [42], the mortality of sepsis in intensive care unit care and acquisition at the hospital is significantly high at 25% to 62%, particularly in resource-limited setting [15,35]. The dire outcome in high-severity sepsis originates considerably from the failure of bench-to-bedside research on innovative anti-sepsis medication [18,35]. Therefore, personalized approaches for individuals with risk factors for sepsis should be prioritized in the public health sector, warranting urgent attention [35,42]. The early detection of abnormal FPG levels through regular simple blood tests in health checkup and adherence to proper hygiene and precautions will help reduce the global burden of sepsis, particularly in low-income countries.

Our study has some limitations that are similar to the inherent disadvantages, including the operational definition in a large-scale retrospective cohort or registry with long-term observation [12,19,31,34]. Primarily, the diagnosis of sepsis may not be absolutely objective, and sepsis may be overestimated or underestimated depending on the decision of the physician based on different scoring methods for assessing systemic inflammation and organ dysfunction (i.e., quick Sequential Organ Failure Assessment or Acute Physiology and Chronic Health Evaluation II) [42]. Additionally, the definition of sepsis in the international guidelines was significantly changed following the introduction of the 'Sepsis-3 criteria' and the deletion of severe sepsis during the 10-year follow-up period [42]. However, to minimize misclassification errors arising from the identi-

fication of sepsis in big data, we operationally defined sepsis using only the ICD-10 codes for hospitalized patients. Because accurate documentation of diagnostic codes is crucial for medical expense reimbursement in the KNHIS, there is little tendency for ICD-10 codes related to severe infectious conditions like sepsis to be inaccurately recorded. Furthermore, the application of the same ICD-10 codes in previous studies on sepsis from a nationwide cohort may support the reliance on the extraction of sepsis diagnoses [24,43]. Second, the participants in the NHSP did not undergo a 75-g oral glucose tolerance test or measurement of HbA1c levels, which is another method of diagnosing T2DM or impaired glucose tolerance. Finally, owing to the retrospective design, not all potential confounding covariates could be captured by a single examination in the NHSP and may have changed during the observation period. However, this report from the largest cohort, encompassing over 300,000 patients with T2DM, represents one of the most extensive studies in diabetes registries. It recorded a significant number of sepsis events, with 78,000 occurring in the total cohort and 15,000 within the T2DM group specifically. Results from extensive numbers and observations over a long period of time can provide enough statistical power and strength to overcome the shortcomings of retrospective analysis.

In conclusion, the incidence of sepsis significantly increased in T2DM compared to normoglycemia, and was the highest in patients with T2DM of ≥5 years at approximately twice than people with normal FPG. Infection precautions, including education on preventive behaviors and vaccination, will help reduce the risk of sepsis in adults with long-standing T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0387.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: E.H.L., K.H.L., K.D.H., S.H.H.
Acquisition, analysis, or interpretation of data: E.H.L., K.L., Y.P., K.D.H., S.H.H.
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FUNDING

None

ACKNOWLEDGMENTS

None

REFERENCES

1. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2023;402:203-34.
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88-98.
3. Khan MA, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes: global burden of disease and forecasted trends. J Epidemiol Glob Health 2020;10:107-11.
4. Tönnies T, Rathmann W, Hoyer A, Brinks R, Kuss O. Quantifying the underestimation of projected global diabetes prevalence by the International Diabetes Federation (IDF) Diabetes Atlas. BMJ Open Diabetes Res Care 2021;9:e002122.
5. Ogurtsova K, Guariguata L, Barengo NC, Ruiz PL, Sacre JW, Karuranga S, et al. IDF Diabetes Atlas: global estimates of undiagnosed diabetes in adults for 2021. Diabetes Res Clin Pract 2022;183:109118.
6. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119.
7. Andreasen AS, Pedersen-Skovsgaard T, Berg RM, Svendsen KD, Feldt-Rasmussen B, Pedersen BK, et al. Type 2 diabetes mellitus is associated with impaired cytokine response and ad-

hesion molecule expression in human endotoxemia. Intensive Care Med 2010;36:1548-55.
8. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The effects of type 2 diabetes mellitus on organ metabolism and the immune system. Front Immunol 2020;11:1582.
9. Dowey R, Iqbal A, Heller SR, Sabroe I, Prince LR. A bittersweet response to infection in diabetes; targeting neutrophils to modify inflammation and improve host immunity. Front Immunol 2021;12:678771.
10. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schonheyder HC, Sorensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care 2008;31:1541-5.
11. Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes and the risk of acute urinary tract infection among postmenopausal women. Diabetes Care 2002;25:1778-83.
12. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, 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;41:2127-35.
13. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care 2018;41:513-21.
14. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008;5:e152.
15. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801-10.
16. Osborn TM. Severe sepsis and septic shock trials (ProCESS, ARISE, ProMISe): what is optimal resuscitation? Crit Care Clin 2017;33:323-44.
17. Nguyen HB, Jaehne AK, Jayaprakash N, Semler MW, Hegab S, Yataco AC, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care 2016;20:160.
18. Cavaillon JM, Singer M, Skirecki T. Sepsis therapies: learning from 30 years of failure of translational research to propose new leads. EMBO Mol Med 2020;12:e10128.
19. Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sorensen 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;186:227-36.
20. Balintescu A, Lind M, Franko MA, Oldner A, Cronhjort M, Svensson AM, et al. Glycemic control and risk of sepsis and subsequent mortality in type 2 diabetes. Diabetes Care 2022;45:127-33.
21. Seong SC, Kim YY, Khang YH, Park JH, Kang HJ, Lee H, et al. Data resource profile: the national health information database of the national health insurance service in South Korea. Int J Epidemiol 2017;46:799-800.
22. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 2017;32:718-28.
23. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open 2017;7:e016640.
24. Tonai M, Shiraishi A, Karumai T, Endo A, Kobayashi H, Fushimi K, et al. Hospital-onset sepsis and community-onset sepsis in critical care units in Japan: a retrospective cohort study based on a Japanese administrative claims database. Crit Care 2022;26:136.
25. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. Diabetes Care 2024;47(Suppl 1):S20-42.
26. Jeon KH, Han K, Jeong SM, Park J, Yoo JE, Yoo J, et al. Changes in alcohol consumption and risk of dementia in a nationwide cohort in South Korea. JAMA Netw Open 2023;6:e2254771.
27. Lee KH, Lee EH, Lee KN, Park Y, Song YG, Han KD, et al. Physical activity and the incidence of sepsis: a 10-year observational study among 4 million adults. J Microbiol Immunol Infect 2024;57:354-64.
28. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-95.
29. Wang W, Chen W, Liu Y, Li L, Li S, Tan J, et al. Blood glucose levels and mortality in patients with sepsis: dose-response analysis of observational studies. J Intensive Care Med 2021;36:182-90.
30. Magliano DJ, Sacre JW, Harding JL, Gregg EW, Zimmet PZ, Shaw JE. Young-onset type 2 diabetes mellitus: implications for morbidity and mortality. Nat Rev Endocrinol 2020;16:321-31.
31. Choi HH, Choi G, Yoon H, Ha KH, Kim DJ. Rising incidence of diabetes in young adults in South Korea: a national cohort

study. Diabetes Metab J 2022;46:803-7.
32. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol 2018;6:69-80.
33. Cho Y, Park HS, Huh BW, Seo SH, Seo DH, Ahn SH, et al. Prevalence and risk of diabetic complications in young-onset versus late-onset type 2 diabetes mellitus. Diabetes Metab 2022;48:101389.
34. Ke C, Lau E, Shah BR, Stukel TA, Ma RC, So WY, et al. Excess burden of mental illness and hospitalization in young-onset type 2 diabetes: a population-based cohort study. Ann Intern Med 2019;170:145-54.
35. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392:75-87.
36. Nielsen TB, Pantapalangkoor P, Yan J, Luna BM, Dekitani K, Bruhn K, et al. Diabetes exacerbates infection via hyperinflammation by signaling through TLR4 and RAGE. mBio 2017;8:e00818-17.
37. Wu C, Xu G, Tsai SA, Freed WJ, Lee CT. Transcriptional profiles of type 2 diabetes in human skeletal muscle reveal insulin resistance, metabolic defects, apoptosis, and molecular signatures of immune activation in response to infections. Biochem Biophys Res Commun 2017;482:282-8.
38. Heo YJ, Choi SE, Jeon JY, Han SJ, Kim DJ, Kang Y, et al. Visfatin induces inflammation and insulin resistance via the NF-κB and STAT3 signaling pathways in hepatocytes. J Diabetes Res 2019;2019:4021623.
39. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269-84.
40. Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol 2019;202:282-9.
41. Harrison DG, Patrick DM. Immune mechanisms in hypertension. Hypertension 2024;81:1659-74.
42. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
43. Skei NV, Moe K, Nilsen TIL, Aasdahl L, Prescott HC, Damas JK, et al. Return to work after hospitalization for sepsis: a nationwide, registry-based cohort study. Crit Care 2023;27:443.

Appendix 1. Self-report questionnaires from the biennial health screening program (general health check-up) by the Korean National Health Insurance Service

Questions related to disease history (past history, family history)

Please read the questions below and mark '√' the information that corresponds to your **current status**.

1. Have you been **diagnosed with or currently taking medication** for any of the following diseases?

	Stroke	Heart disease (MI/angina)	HTN	Type 2 DM	Dyslipidemia	Others (Including malignancies)
Diagnosis						
Medication						

MI: Myocardial infarction, HTN: hypertension, DM: diabetes mellitus

2. Have any of your parents, brothers, or sisters suffered from or died from the following diseases?

	Stroke	Heart disease (MI/angina)	HTN	Type 2 DM	Dyslipidemia	Others (Including malignancies)
Yes						

Physical activities

Please read the following items and mark '√' on the response that corresponds to your activity status during the past week.

1. How many days in the past week did you engage in intense activities that made you breathe much harder than usual for more than 20 minutes? (e.g., running, aerobics, fast cycling, hiking, etc.)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

2. How many days in the past week did you engage in moderate activities that made you breathe slightly harder than usual for more than 30 minutes? (e.g., brisk walking, playing tennis, cycling at a regular pace, mopping, etc.) Exclude activities related to the response in 1.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

3. How many days in the past week did you walk for at least 30 minutes, combining walks of at least 10 minutes each time? (e.g., walking during commuting or leisure time) Exclude physical activities related to the responses in 1 and 2.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

(*Continued to the next page*)

Appendix 1. Continued

Smoking habits

Please read the following items and provide information that corresponds to your current condition.

1. Have you smoked a total of 5 packs (100 cigarettes) or more in your lifetime?

(1) No ☐ (2) Yes, but I quit. ☐ → Go to questionnaire 2 (3) Yes, I am smoking. ☐ → Go to questionnaire 3

2. If you are an ex-smoker,

How many years did you smoke?	Total _____ years
How many cigarettes per day?	_____ cigarettes

3. If you are a current smoker,

How many years have you been smoking?	Total _____ years
How many cigarettes per day?	_____ cigarettes

Drinking habits

Please read the following items and provide information that corresponds to your current condition.

1. On average, how many days a week do you drink alcohol?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

2. How much do you usually drink per day (regardless of the type of alcohol)?

_____ glasses

Supplementary Table 1. List of ICD-10 codes in extracting patients diagnosed with sepsis from the National Health Information Database

ICD-10 code	Diagnosis
A02.1	Salmonella sepsis
A20.7	Septicemic plague
A22.7	Anthrax sepsis
A26.7	Erysipelothrix sepsis
A32.7	Listerial sepsis
A40	*Streptococcal* sepsis
A40.0	Sepsis due to *Streptococcus*, group A
A40.1	Sepsis due to *Streptococcus*, group B
A40.2	Sepsis due to *Streptococcus*, group D and *enterococcus*
A40.3	Sepsis due to *Streptococcus pneumoniae* (pneumococcal sepsis)
A40.8	Other *Streptococcal* sepsis
A40.9	*Streptococcal* sepsis, unspecified
A41	Other sepsis
A41.0	Sepsis due to *Staphylococcus aureus*
A41.1	Sepsis due to other specified *Staphylococcus* (sepsis due to coagulase-negative *Staphylococcus*)
A41.2	Sepsis due to unspecified *Staphylococcus*
A41.3	Sepsis due to *Haemophilus influenzae*
A41.4	Sepsis due to anaerobes
A41.5	Sepsis due to other Gram-negative organisms (Gram-negative sepsis NOS)
A41.8	Other specified sepsis
A41.9	Sepsis, unspecified (septicemia)
A42.7	Actinomycotic sepsis
B37.7	Candidal sepsis
R57.2	Septic shock
R65	Systemic inflammatory response syndrome
R65.0	Systemic inflammatory response syndrome of infectious origin without organ failure
R65.1	Systemic inflammatory response syndrome of infectious origin with organ failure (severe sepsis)

No patients were defined by ICD-10 codes A20.7 and A22.7.
ICD-10, International Classification of Diseases 10th Revision; NOS, not otherwise specified.

Supplementary Table 2. List of diagnosis codes and criteria to identify underlying chronic medical conditions

Disease	ICD-10 code	Diagnostic criteria
Hypertension	I10: Essential (primary) hypertension I11: Hypertensive heart disease I12: Hypertensive renal disease I13: Hypertensive heart and renal disease I15: Secondary hypertension	Systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg
Dyslipidemia	E78.0: Pure hypercholesterolaemia E78.1: Pure hyperglyceridaemia E78.2: Mixed hyperlipidaemia E78.4: Other hyperlipidaemia E78.5: Hyperlipidaemia, unspecified	Fasting total cholesterol ≥240 mg/dL
CKD	N18.3: Chronic kidney disease, stage 3, GFR (30–59 mL/min) N18.4: Chronic kidney disease, stage 4, GFR (15–29 mL/min) N18.5: Chronic kidney disease, stage 5, end stage kidney disease N18.9: Chronic kidney disease, unspecified	Estimated GFR <60 mL/min/1.73 m^2, as calculated by the Modification of Diet in Renal Disease equation

ICD-10, International Classification of Diseases 10th Revision; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate.

Supplementary Table 3. Impact T2DM on sepsis risk adjusted with demographic, co-morbidities, and social habits

Characteristic	T2DM	Subjects	Sepsis	Duration, PY	IR, /1,000 PY	aHR[a] (95% CI)	*P* for interaction
Age, yr							<0.001
<40	No	1,187,664	4,114	12,202,232	0.34	1 (Ref)	
	Yes	24,467	220	249,289	0.88	1.96 (1.71–2.25)	
40–64	No	1,974,528	25,515	20,161,271	1.27	1 (Ref)	
	Yes	190,517	5,983	1,901,793	3.15	1.80 (1.75–1.85)	
≥65	No	403,686	32,781	3,746,921	8.75	1 (Ref)	
	Yes	82,461	8,996	728,308	12.35	1.42 (1.39–1.45)	
Sex							0.009
Male	No	1,922,851	33,981	19,372,687	1.75	1 (Ref)	
	Yes	188,146	8,840	1,809,557	4.89	1.52 (1.49–1.56)	
Female	No	1,643,027	28,429	16,737,738	1.70	1 (Ref)	
	Yes	109,299	6,359	1,069,833	5.94	1.60 (1.55–1.64)	
Obesity							0.110
No	No	2,456,628	41,696	24,856,468	1.68	1 (Ref)	
	Yes	152,053	8,381	1,450,054	5.78	1.56 (1.52–1.60)	
Yes	No	1,109,250	20,714	11,253,956	1.84	1 (Ref)	
	Yes	145,392	6,818	1,429,336	4.77	1.51 (1.47–1.55)	
Current smoking							0.579
No	No	2,635,456	47,944	26,727,418	1.79	1 (Ref)	
	Yes	216,711	11,727	2,100,986	5.58	1.56 (1.52–1.59)	
Yes	No	930,422	14,466	9,383,007	1.54	1 (Ref)	
	Yes	80,734	3,472	778,404	4.46	1.54 (1.48–1.60)	
Heavy alcohol drinking							0.182
No	No	3,288,836	57,418	33,318,640	1.72	1 (Ref)	
	Yes	266,315	13,831	2,577,743	5.37	1.56 (1.53–1.59)	
Yes	No	277,042	4,992	2,791,784	1.79	1 (Ref)	
	Yes	31,130	1,368	301,648	4.54	1.50 (1.41–1.59)	
Regular PA							0.868
No	No	2,938,844	51,524	29,746,284	1.73	1 (Ref)	
	Yes	232,416	12,139	2,243,895	5.41	1.55 (1.52–1.59)	
Yes	No	627,034	10,886	6,364,141	1.71	1 (Ref)	
	Yes	65,029	3,060	635,495	4.82	1.56 (1.50–1.62)	
HTN							<0.001
No	No	2,769,214	33,685	28,226,287	1.19	1 (Ref)	
	Yes	134,387	4,823	1,326,158	3.64	1.62 (1.58–1.68)	
Yes	No	796,664	28,725	7,884,137	3.64	1 (Ref)	
	Yes	163,058	10,376	1,553,232	6.68	1.52 (1.48–1.55)	
Dyslipidemia							0.775
No	No	3,022,837	48,338	30,642,668	1.58	1 (Ref)	
	Yes	185,907	9,290	1,792,601	5.18	1.56 (1.52– 1.59)	
Yes	No	543,041	14,072	5,467,757	2.57	1 (Ref)	
	Yes	111,538	5,909	1,086,790	5.44	1.55 (1.50–1.60)	
CKD							0.111
No	No	3,339,813	53,832	33,877,636	1.59	1 (Ref)	
	Yes	262,785	12,011	2,565,521	4.68	1.54 (1.51–1.58)	
Yes	No	226,065	8,578	2,232,788	3.84	1 (Ref)	
	Yes	34,660	3,188	313,870	10.16	1.60 (1.54–1.67)	

T2DM, type 2 diabetes mellitus; PY, person-year; IR, incidence rate; aHR, adjusted hazard ratio; CI, confidence interval; PA, physical activities; HTN, hypertension; CKD, chronic kidney disease.

[a]Adjusted for age, sex, income status of the lowest quartile, categories of body mass index, behaviors of smoking and drinking, regular PA, HTN, dyslipidemia, and CKD.