Diabetes, Glycemic Control, and Risk of Infection Morbidity and Mortality: A Cohort Study

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Objective: Diabetic patients have an elevated risk of infection, but the optimal level of glycemic control with the lowest infection risk remains unclear, especially among the elderly. We aimed to investigate the relation between fasting plasma glucose (FPG) level and risk of infection-related morbidity and mortality.

Method: The participants were from a community-based health screening program in northern Taiwan during 2005–2008 (n = 118 645) and were followed up until 2014. Incidence of hospitalization for infection and infection-related death was ascertained from the National Health Insurance Database and National Death Registry. Cox proportional hazards regression modelling was used to estimate the hazard ratio (HR) between FPG and risk of infection.

Results: During a median follow-up of 8.1 years, the incidence rate of hospitalization for any infection was 36.33 and 14.26 per 1000 person-years among diabetics and nondiabetics, respectively, in the total study population, but increased to 70.02 and 45.21 per 1000 person-years, respectively, in the elderly. In the Cox regression analysis, the adjusted HR comparing diabetics to nondiabetics was 1.59 (95% confidence interval [CI], 1.52–1.67) for any hospitalization for infection and 1.71 (95% CI, 1.36–2.16) for infection-related mortality. The hazard for infection morbidity and mortality was higher at both extremes (<90 and >200 mg/dl) of FPG. The excess risk associated with FPG ≤ 90 mg/dl was attenuated after controlling for multiple comorbidities.

Conclusions: Poor glycemic control (FPG > 200 mg/dl) was associated with a higher risk of infection-related morbidity and mortality, especially in the elderly population where the baseline infection risk was high.

Key words: community-based health screening; diabetes mellitus; glycemic control; mortality; risk of infection.

INTRODUCTION

Hyperglycemia has been extensively studied in cell model and animal studies for its effect on immune system against infections [1–4]. Several observational studies reported that diabetic patients with higher glycemic level were associated with an elevated risk of infections [5, 6]. However, these studies focused on diabetic patients alone (without nondiabetics as the comparison) and did not account for lifestyle risk factors, such as body mass index (BMI), cigarette smoking, and alcohol consumption. Therefore, the exact relation between blood glucose level and infection risk is yet to be determined, and it is unknown whether optimal glucose control could reduce the infection risk to the level comparable to that among nondiabetics. Although numerous studies examined the association between high blood glucose level and risk of infection at specific site, few studies fully examined the risks across different sites of infection [7–10]. Lastly, there were limited data on glucose control and infection risk in the elderly population, who have a higher infection risk and a less stringent A1c goal suggested by current practice guidelines. The answers to these questions have important clinical implications to set optimal glycemic control goal for infection prevention, as current recommendations regarding glycemic goal were based on micro-vascular complication prevention.

In the present study, we analyzed population-based community screening data to (1) investigate the risk of first hospitalization for any infection and individual site of infections across a wide range of fasting plasma glucose (FPG) level; (2) evaluate the relation between fasting glucose level and infection-related mortality; and (3) assess the relation between glycemic level and infection risk among older people. We hypothesized that a lower blood glucose level was associated with a lower risk of infection-related hospitalization and mortality.

METHODS

Data Source and Study Population

Potential participants of this prospective study came from a total of 125 865 individuals who voluntarily participated in a free community-based health screening service for the residents aged 40 years or older in New Taipei City for 2005–2008. In brief, the participants filled out the questionnaire about demographics, educational level, and lifestyle information. Each participant received a standard physical examination and blood and urine analyses. Overnight fasting blood and first morning voided urine were collected and analyzed. With participants' consent, the screening program database was linked to the National Health Insurance Database and the National Death Registry using each participant's unique national identification number. In Taiwan, national health insurance is compulsory for all residents, and the coverage rate for 2005–2008 was over 99%. After data linkage, information related to individual identification were removed and remained anonymous during the entire study process. The protocol was approved by the National Taiwan University Hospital Research Ethics Committee.

Participants were excluded if they did not have baseline measurement of FPG level or BMI; complete information about cigarette smoking, alcohol consumption, and education level; and any claims in the National Health Insurance Database. The final study population included 118 645 participants (see Supplementary Figure 1 for study flow diagram).

Measurement of Diabetes and Other Covariates

The main exposure of this study was diabetes, which was defined by the following criteria: (1) FPG over 126 mg/dL or (2) prescription of any hypoglycemic agent (verified from the health insurance claims database) for more than 28 days in the previous year before the baseline survey. Participants who had treated or untreated diabetes were further classified by their FPG levels. Body mass index was categorized into the following categories: <18.5, 18.5 to <25, ≥25 to <30, and ≥30 kg/m2. Age was categorized as 20 to 40 years, 41 to 50 years, 51 to 60 years, 61 to 70 years, and 71 to 100 years.

Information about other potential confounding factors were obtained from the questionnaire at cohort entry (BMI, age, sex, level of education, smoking and alcohol use) and from the National Health Insurance Database (comorbid diseases and prior hospitalization and drug use history during the 12-month period before study entry; the International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM] codes provided in Supplementary Table 1).

Outcome and Follow-Up Plan

The primary outcome of interest is incident hospitalization for all infections ascertained from the National Health Insurance Database after study beginning. Hospitalization for infection further was classified according to specific site of infection,

including septicemia, lower respiratory tract, intra-abdominal, reproductive and urinary tract, skin and soft tissue, osteomyelitis, necrotizing fasciitis, central nervous system, and invasive mold, as defined by ICD-9-CM codes listed in Supplementary Table 1. The patients may have more than 1 specific site of infection in their first hospitalization for infection. The secondary outcomes were overall mortality and infection-related mortality. The vital status and date of death for the study participants was obtained by linkage through the National Death Registry with the unique identification number. The cohort participants were followed up from the date of health screening until first hospitalization for infection, death (based on vital registry), or the end of 2014, whichever came first. Infection-related death was defined by the death certificates codes (underlying cause of death) according to ICD-9 and ICD-10, using data from the vital registry. In the analysis for infection-related deaths, all participants were followed from the date of health screening until death.

Statistical Analysis

We computed the incidence rate of hospitalization for infection and infection-related mortality rate by diabetes status and by site of infection. We used Cox regression modeling to estimate the adjusted hazard ratios (aHRs) and corresponding 95% confidence intervals (95% CIs) for diabetes (compared to nondiabetes) and infection outcome (hospitalization and death), adjusting for potential confounders of age category, sex, current smoking, current drinking, low educational level, BMI category, systemic steroids use within 1 year before study entry, and hospitalization history within 6 months before hospitalization for infection. We further conducted a dose-response analysis stratifying by the level of FPG. The analysis of hospitalization for infection was conducted for all infections and by site of infection. In the analysis for specific site of infection, participants who were hospitalized due to 1 site of infection were not allowed to contribute follow-up person-time for another site of infection. In separate analyses, we classified both diabetes and nondiabetes groups according to their FPG levels and calculated the associated risks using nondiabetics and diabetics with FPG between 90–99 mg/dL as the reference group.

Because older people were more susceptible to infections, we further conducted a subgroup analysis on the association between FPG level and infection hospitalization among those aged above 65 years.

Several sensitivity analyses were conducted for a comprehensive evaluation of the relation between FPG and the risks of infection hospitalization. To avoid overadjustment of potential intermediate variables on a causal pathway between glycemic control and infection risk, we did not control for comorbidities in our main analysis. To further explore the role of comorbidities in the relation between FPG and infection morbidity and mortality, we additionally adjusted the Charlson comorbidity score

to see if the association would change substantially. Because older adults (>65 years old) and those with liver and renal disease, autoimmune disease, and cancer were more likely to have low FPG levels and also were more susceptible to severe infections, we excluded these participants to avoid confounding by these conditions. Because the definition of diabetes and glycemic control was based on 1 single measurement of FPG at baseline, we conducted the following analyses to reduce the potential biases from misclassification of blood glucose level. First, we excluded those with untreated diabetes (FPG > 126 mg/dL but no prescription record for hypoglycemic agents) in order to remove the potential false-positive diabetes cases. Second, among the subgroup (~9%) of population who had repeated measurements of FPG over multiple years, we used a time-dependent Cox analysis to account for time-varying exposure of FPG. Because prior study suggested an association between infection risk and recent rather than remote glycemic level [6], we shortened the maximal follow-up period to 2 years after the baseline to avoid a long time lag between measurement of FPG and infection outcome. Lastly, because those who had early occult infections may have abnormal blood glucose levels, we conducted analyses excluding participants who were hospitalized for infections within 2 weeks after health screening program to reduce potential protopathic bias.

RESULTS

Of the total 118 645 study participants, 64% were women. The mean age was 51.9 years (standard deviation, 11.9) (Table 1). At the baseline, 9511 people (8.02%) had diabetes, and 59.8% of them were taking any antidiabetic medications. The prevalence of diabetes was 9.55% in men and 7.16% in women, respectively. Most of the diabetic participants included in our analysis had a duration of ≤4 years (mean diabetes duration, 2.1 years). In our study, only 3067 participants (2.6% of the total participants) had newly diagnosed diabetes. Among the diabetes patients, 29.07% had FPG < 130 mg/dL, 60.35% had FPG between 130–200 mg/dL, and 10.58% had FPG > 200 mg/dL. The differences in underlying disease between diabetic and nondiabetic participants can be seen in Table 1. As compared with nondiabetics, those diabetic patients with higher FPG were more likely to be overweight or obese and were more likely to use tobacco smoking and alcohol (Table 1), while a higher proportion of diabetic patients with FPG ≤ 90 mg/dL were male and elderly, had lower educational level, and more comorbidities.

During a median follow up of 8.13 years, 14 372 cases of hospitalization for infection occurred. The most frequent site of infection was reproductive and urinary tract (5802), followed by lower respiratory tract (4052), septicemia (3255), intra-abdominal (1874), and skin and soft tissue (1856) (Table 2). The incidence rate of any infection was 36.33 (34.92–37.81) per 1000 person-years among diabetics and 14.26 (14.01–14.52) among

nondiabetics. There were 5243 total deaths and 422 infection-related deaths during the follow-up period, with a rate of 15.39 (95% CI, 14.53–16.31) and 4.66 (95% CI, 4.52–4.80) per 1000 for overall mortality and 1.32 (1.08–1.61) and 0.37 (0.33–0.41) per 1000 for infection-related mortality among diabetics and nondiabetics, respectively (Table 2).

In the Cox regression analysis, the crude and adjusted HR of any hospitalization for infection comparing diabetics to nondiabetics was 2.56 (95% CI, 2.45–2.67) and 1.59 (95% CI, 1.52–1.67), respectively (Table 2). The association between diabetes and hospitalization for infection was similar across different sites of infection, except that the association between diabetes and osteomyelitis was weak and not statistically significant (aHR, 0.98; 95% CI, 0.68–1.43) and that between diabetes and invasive mold was not statistically significant (aHR, 1.45; 95% CI, 0.59–3.52). The aHR comparing diabetics to nondiabetics was 1.69 (95% CI, 1.58–1.81) for overall mortality and 1.71 (95% CI, 1.36–2.16) for infection-related mortality, respectively. Similar results were found in the analyses additionally controlled for Charlson comorbidity score, although the risk estimates associated with diabetes were slightly attenuated (Table 2).

Using FPG measured at baseline as a proxy for glycemic control, the HR for infection morbidity and mortality was higher at both extremes of FPG (<90 mg/dL and >200 mg/dL) with or without taking comorbidities into consideration (Table 2). Further detailed dose-response analysis of hospitalization for infection by 10 mg/dL interval of FPG revealed a U-shape curve (Figure 1). The risks of hospitalization for infection among the diabetics across all FPG levels were uniformly higher than nondiabetics. A similar pattern was found between FPG level and infection-related mortality, but most of the associations were not statistically significant due to the few numbers of deaths from infection (Figure 1).

In a separate analysis using nondiabetics with FPG between 90–99 mg/dL as the reference group, a similar U-shaped curve was observed among the diabetics (Supplementary Figure 2). Even at the same level of FPG, the infection risk among diabetics was consistently higher than that among the nondiabetics. In the nondiabetics, the risk of hospitalization for infection increased slightly at the 2 extremes (FPG < 80 mg/dL and >110 mg/dL). Importantly, the risk of infection was elevated in those with impaired fasting glucose (FPG between 100–126 mg/dL) when compared with nondiabetics with FPG between 90–99 mg/dL.

In older adults, the morbidity and mortality from infections were substantially increased when compared to the general population (Table 3). The incidence rate of any infection was 70.02 (95% CI, 66.32–73.92) and 45.21 (95% CI, 43.87–46.60) per 1000 person-years among diabetics and nondiabetics, respectively. The corresponding rate was 35.09 (95% CI, 32.73–37.62) and 23.64 (95% CI, 22.73–24.59) per 1000 for overall mortality, and 3.42 (95% CI, 2.73–4.27) and 2.49 (95% CI, 2.21–2.82)

Table 1. Baseline Characteristics of the Study Population, Stratified by Diabetes Status and Fasting Plasma Glucose (mg/dl) Level

Characteristics	Total		No Diabetes		Diabetes, Overall		Diabetes, Stratified by FPG Level (mg/dl)							
							≤90		90–130		130–200		>200	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Characteristics	118 645	(100.0%)	109 134	(92.0%)	9511	(8.0%)	174	(0.1%)	2591	(2.2%)	5740	(4.8%)	1006	(0.8%)
Male	42 380	(35.7%)	38 332	(35.1%)	4048	(42.6%)	85	(48.9%)	1163	(44.9%)	2401	(41.8%)	399	(39.7%)
Age in year, mean (SD)	51.9	(11.9)	51.1	(11.7)	60.4	(10.7)	63.7	(10.4)	61.7	(11.0)	60.0	(10.7)	58.3	(10.1)
Duration of diabetes in years, mean (SD)	NA	NA	NA	NA	2.08	(1.15)	2.12	(1.23)	2.02	(1.17)	2.10	(1.15)	2.10	(1.10)
Newly diagnosed	3067	(2.6%)	NA	NA	3067	(32.2%)	7	(4.0%)	598	(23.1%)	2159	(37.6%)	303	(30.1%)
≤4 years	5902	(5.0%)	NA	NA	5902	(62.1%)	146	(83.9%)	1822	(70.3%)	3288	(57.3%)	646	(64.2%)
>4 years	542	(0.5%)	NA	NA	542	(5.7%)	21	(12.1%)	171	(6.6%)	293	(5.1%)	57	(5.7%)
Type 1 diabetes	NA	NA	NA	NA	326	(3.4%)	9	5.2	92	3.6	181	3.2	44	4.4
BMI (kg/m²), mean (SD)	24.4	(3.6)	24.2	(3.6)	26.3	(3.9)	25.1	(3.9)	26.2	(3.8)	26.5	(3.9)	26.0	(3.8)
<18.5	3321	(2.8%)	3234	(3.0%)	87	(0.9%)	5	(2.9%)	22	(0.8%)	51	(0.9%)	9	(0.9%)
18.5–25.0	68 876	(58.1%)	65 215	(59.8%)	3661	(38.5%)	93	(53.4%)	1006	(38.8%)	2144	(37.4%)	418	(41.6%)
25.0–30.0	38 383	(32.4%)	34 123	(31.3%)	4260	(44.8%)	54	(31.0%)	1165	(45.0%)	2595	(45.2%)	446	(44.3%)
>30.0	8065	(6.8%)	6562	(6.0%)	1503	(15.8%)	22	(12.6%)	398	(15.4%)	950	(16.6%)	133	(13.2%)
Current smoker	17 548	(14.8%)	16 031	(14.7%)	1517	(15.9%)	31	(17.8%)	386	(14.9%)	903	(15.7%)	197	(19.6%)
Current alcohol use	8429	(7.1%)	7647	(7.0%)	782	(8.2%)	13	(7.5%)	184	(7.1%)	475	(8.3%)	110	(10.9%)
Education														
High school and above	58 291	(49.1%)	55 611	(51.0%)	2680	(28.2%)	38	(21.8%)	751	(29.0%)	1635	(28.5%)	256	(25.4%)
Junior high school and below	60 354	(50.9%)	53 523	(49.0%)	6831	(71.8%)	136	(78.2%)	1840	(71.0%)	4105	(71.5%)	750	(74.6%)
Comorbidities														
Hypertension	21 755	(18.3%)	17 043	(15.6%)	4712	(49.5%)	113	(64.9%)	1451	(56.0%)	2700	(47.0%)	448	(44.5%)
Ischemic heart disease	6992	(5.9%)	5575	(5.1%)	1417	(14.9%)	40	(23.0%)	453	(17.5%)	804	(14.0%)	120	(11.9%)
Myocardial infarction	259	(0.2%)	195	(0.2%)	64	(0.7%)	NA	NA	23	(0.9%)	37	(0.6%)	NA	NA
Cardiac dysrhythmia	3208	(2.7%)	2771	(2.5%)	437	(4.6%)	12	(6.9%)	148	(5.7%)	245	(4.3%)	32	(3.2%)
Congestive heart failure	1528	(1.3%)	1193	(1.1%)	335	(3.5%)	16	(9.2%)	120	(4.6%)	169	(2.9%)	30	(3.0%)
Ischemic stroke	1417	(1.2%)	1100	(1.0%)	317	(3.3%)	10	(5.7%)	124	(4.8%)	159	(2.8%)	24	(2.4%)
Hemorrhagic stroke	225	(0.2%)	197	(0.2%)	28	(0.3%)	NA	NA	14	(0.5%)	10	(0.2%)	NA	NA
Peripheral arterial disease	511	(0.4%)	401	(0.4%)	110	(1.2%)	3	(1.7%)	32	(1.2%)	65	(1.1%)	10	(1.0%)
Lipid metabolism disorder	13 773	(11.6%)	10 469	(9.6%)	3304	(34.7%)	65	(37.4%)	1066	(41.1%)	1860	(32.4%)	313	(31.1%)
Chronic lung disease	9068	(7.6%)	7947	(7.3%)	1121	(11.8%)	35	(20.1%)	338	(13.0%)	642	(11.2%)	106	(10.5%)
Chronic liver disease	8397	(7.1%)	7337	(6.7%)	1060	(11.1%)	27	(15.5%)	325	(12.5%)	597	(10.4%)	111	(11.0%)
Autoimmune disease	3179	(2.7%)	2873	(2.6%)	306	(3.2%)	4	(2.3%)	109	(4.2%)	170	(3.0%)	23	(2.3%)
Dementia	264	(0.2%)	203	(0.2%)	61	(0.6%)	NA	NA	37	(1.4%)	21	(0.4%)	NA	NA
Cancer	2254	(1.9%)	1954	(1.8%)	300	(3.2%)	4	(2.3%)	111	(4.3%)	157	(2.7%)	28	(2.8%)
Charlson comorbidity score, mean (SD)	0.4	(0.9)	0.3	(0.7)	1.40	(1.43)	2.3	(1.8)	1.6	(1.5)	1.3	(1.4)	1.3	(1.4)
Systemic steroids use within 1 year prior to study entry	1523	(1.3%)	1330	(1.2%)	193	(2.0%)	9	(5.2%)	68	(2.6%)	101	(1.8%)	15	(1.5%)

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation.

NA indicates that the exact case number was too small to be retrieved because of the authority's policy regulation.

Table 2. Association Between Fasting Plasma Glucose (mg/dl) Level at Baseline and the Risk of Infection Hospitalization by Site and Infection-Related Mortality Using Nondiabetics as the Reference Group

	No. of cases	Person-years	Incidence rate	Crude HR	Adjusted HR[a]	Adjusted HR[b]
Any infection						
No DM	11 938	837 015	14.26 (14.01~14.52)	Reference	Reference	Reference
DM	2434	66 988	36.33 (34.92~37.81)	2.56 (2.45~2.67)	1.59 (1.52~1.67)	1.33 (1.27~1.39)
DM and FPG ≤ 90	62	1094	56.70 (44.20~72.72)	4.03 (3.14~5.17)	1.89 (1.47~2.42)	1.34 (1.04~1.73)
DM and 90 < FPG ≤ 130	694	17 949	38.66 (35.89~41.65)	2.73 (2.53~2.95)	1.56 (1.45~1.69)	1.27 (1.17~1.37)
DM and 130 < FPG ≤ 200	1387	40 967	33.86 (32.12~35.69)	2.38 (2.25~2.52)	1.52 (1.43~1.61)	1.29 (1.21~1.37)
DM and FPG > 200	291	6978	41.70 (37.18~46.78)	2.94 (2.61~3.30)	2.09 (1.86~2.35)	1.78 (1.58~2.00)
Septicemia						
No DM	2592	837 015	3.10 (2.98~3.22)	Reference	Reference	Reference
DM	663	66 988	9.90 (9.17~10.68)	3.23 (2.96~3.51)	1.86 (1.70~2.03)	1.54 (1.40~1.69)
DM and FPG ≤ 90	19	1094	17.37 (11.08~2724)	5.77 (3.68~9.06)	2.51 (1.60~3.95)	1.77 (1.12~2.79)
DM and 90 < FPG ≤ 130	188	17 949	10.47 (9.08~12.08)	3.42 (2.95~3.97)	1.82 (1.56~2.11)	1.46 (1.25~1.71)
DM and 130 < FPG ≤ 200	372	40 967	9.08 (8.20~10.05)	2.95 (2.65~3.29)	1.74 (1.56~1.95)	1.47 (1.31~1.65)
DM and FPG > 200	84	6978	12.04 (9.72~14.91)	3.92 (3.16~4.87)	2.61 (2.10~3.24)	2.20 (1.77~2.74)
Lower respiratory tract infection						
No DM	3299	837 015	3.94 (3.81~4.08)	Reference	Reference	Reference
DM	753	66 988	11.24 (10.47~12.07)	2.88 (2.66~3.12)	1.53 (1.41~1.66)	1.25 (1.14~1.36)
DM and FPG ≤ 90	19	1094	17.37 (11.08~2724)	4.52 (2.88~7.09)	1.55 (0.99~2.43)	1.05 (0.67~1.66)
DM and 90 < FPG ≤ 130	214	17 949	11.92 (10.43~13.63)	3.06 (2.67~3.52)	1.44 (1.25~1.66)	1.14 (0.99~1.31)
DM and 130 < FPG ≤ 200	432	40 967	10.54 (9.60~11.59)	2.70 (2.44~2.98)	1.50 (1.35~1.66)	1.24 (1.11~1.37)
DM and FPG > 200	88	6978	12.61 (10.23~15.54)	3.23 (2.61~3.99)	2.11 (1.70~2.61)	1.76 (1.42~2.18)
Intra-abdominal infection						
No DM	1640	837 015	1.96 (1.87~2.06)	Reference	Reference	Reference
DM	234	66 988	3.49 (3.07~3.97)	1.79 (1.56~2.05)	1.37 (1.19~1.58)	1.20 (1.03~1.39)
DM and FPG ≤ 90	5	1094	4.57 (1.90~10.99)	2.36 (0.98~5.67)	1.54 (0.64~3.70)	1.19 (0.49~2.89)
DM and 90 < FPG ≤ 130	64	17 949	3.57 (2.79~4.56)	1.83 (1.42~2.35)	1.34 (1.04~1.73)	1.15 (0.88~1.49)
DM and 130 < FPG ≤ 200	135	40 967	3.30 (2.78~3.90)	1.69 (1.41~2.01)	1.31 (1.09~1.56)	1.16 (0.97~1.40)
DM and FPG > 200	30	6978	4.30 (3.01~6.15)	2.20 (1.53~3.16)	1.79 (1.25~2.58)	1.59 (1.10~2.29)
Reproductive and urinary tract infection						
No DM	4800	837 015	5.73 (5.57~5.90)	Reference	Reference	Reference
DM	1002	66 988	14.96 (14.06~15.91)	2.62 (2.44~2.80)	1.79 (1.67~1.92)	1.52 (1.41~1.64)
DM and FPG ≤ 90	18	1094	16.46 (10.37~26.13)	2.90 (1.83~4.61)	1.57 (0.99~2.50)	1.15 (0.72~1.83)
DM and 90 < FPG ≤ 130	290	17 949	16.16 (14.40~18.13)	2.83 (2.51~3.19)	1.81 (1.61~2.05)	1.50 (1.32~1.69)
DM and 130 < FPG ≤ 200	577	40 967	14.08 (12.98~15.28)	2.46 (2.26~2.68)	1.72 (1.57~1.88)	1.48 (1.35~1.62)
DM and FPG > 200	117	6978	16.77 (13.99~20.10)	2.93 (2.44~3.52)	2.25 (1.87~2.70)	1.93 (1.61~2.33)
Skin and soft tissue infection, including necrotizing fasciitis						
No DM	1508	837 015	1.80 (1.71~1.89)	Reference	Reference	Reference
DM	348	66 988	5.19 (4.68~5.77)	2.89 (2.57~3.25)	1.64 (1.45~1.85)	1.35 (1.19~1.54)
DM and FPG ≤ 90	12	1094	10.97 (6.23~19.32)	6.13 (3.48~10.83)	2.84 (1.60~5.01)	2.00 (1.12~3.55)
DM and 90 < FPG ≤ 130	87	17 949	4.85 (3.93~5.98)	2.70 (2.17~3.35)	1.43 (1.15~1.78)	1.14 (0.91~1.43)
DM and 130 < FPG ≤ 200	200	40 967	4.88 (4.25~5.61)	2.72 (2.34~3.15)	1.56 (1.34~1.82)	1.31 (1.12~1.53)
DM and FPG > 200	49	6978	7.02 (5.31~9.29)	3.91 (2.94~5.19)	2.54 (1.91~3.38)	2.12 (1.59~2.84)
Osteomyelitis						
No DM	221	837 015	0.26 (0.23~0.30)	Reference	Reference	Reference
DM	34	66 988	0.51 (0.36~0.71)	1.91 (1.33~2.74)	0.98 (0.68~1.43)	0.85 (0.58~1.26)
DM and FPG ≤ 90	NA	1094	NA	3.42 (0.48~24.39)	1.29 (0.18~9.23)	1.00 (0.14~7.22)
DM and 90 < FPG ≤ 130	10	17 949	0.56 (0.30~1.04)	2.10 (1.11~3.96)	0.97 (0.51~1.84)	0.82 (0.43~1.58)
DM and 130 < FPG ≤ 200	17	40 967	0.41 (0.26~0.67)	1.56 (0.95~2.56)	0.83 (0.50~1.37)	0.73 (0.44~1.21)
DM and FPG > 200	NA	6978	NA	3.23 (1.44~7.27)	2.00 (0.89~4.51)	1.78 (0.78~4.03)

Table 2. Continued

	No. of cases	Person-years	Incidence rate	Crude HR	Adjusted HR[a]	Adjusted HR[b]
Infection of central nervous system						
No DM	NA	837 015	NA	Reference	Reference	Reference
DM	NA	66 988	NA	1.05 (0.25~4.42)	0.93 (0.21~4.10)	1.09 (0.24~5.09)
DM and FPG ≤ 90	0	1094	NA	NA	NA	NA
DM and 90 < FPG ≤ 130	NA	17 949	NA	3.91 (0.92~16.55)	3.25 (0.72~14.63)	4.04 (0.84~19.53)
DM and 130 < FPG ≤ 200	0	40 967	NA	NA	NA	NA
DM and FPG > 200	0	6978	NA	NA	NA	NA
Invasive fungal infection						
No DM	39	837 015	0.05 (0.03~0.06)	Reference	Reference	Reference
DM	6	66 988	0.09 (0.04~0.20)	1.94 (0.82~4.59)	1.45 (0.59~3.52)	1.08 (0.41~2.85)
DM and FPG ≤ 90	0	1094	NA	NA	NA	NA
DM and 90 < FPG ≤ 130	NA	17 949	NA	6.07 (2.39~15.40)	4.39 (1.67~11.53)	3.27 (1.19~9.02)
DM and 130 < FPG ≤ 200	NA	40 967	NA	0.53 (0.07~3.85)	0.40 (0.05~2.96)	0.27 (0.03~2.18)
DM and FPG > 200	0	6978	NA	NA	NA	NA
Total mortality						
No DM	4088	877 270	4.66 (4.52~4.80)	Reference	Reference	Reference
DM	1155	75 034	15.39 (14.53~16.31)	3.31 (3.10~3.53)	1.69 (1.58~1.81)	1.37 (1.27~1.47)
DM and FPG ≤ 90	35	1304	26.83 (19.27~37.37)	6.37 (4.63~8.77)	2.11 (1.53~2.91)	1.45 (1.05~2.00)
DM and 90 < FPG ≤ 130	355	20 166	1760 (15.86~19.53)	3.80 (3.41~4.24)	1.71 (1.54~1.91)	1.34 (1.20~1.50)
DM and 130 < FPG ≤ 200	643	45 526	14.12 (13.07~15.26)	3.03 (2.79~3.29)	1.61 (1.48~1.75)	1.33 (1.22~1.45)
DM and FPG > 200	119	8038	14.80 (12.37~17.72)	3.17 (2.64~3.80)	2.01 (1.68~2.42)	1.66 (1.38~1.99)
Mortality from any infection						
No DM	323	877 270	0.37 (0.33~0.41)	Reference	Reference	Reference
DM	99	75 034	1.32 (1.08~1.61)	3.59 (2.86~4.49)	1.71 (1.36~2.16)	1.45 (1.14~1.85)
DM and FPG ≤ 90	3	1304	2.30 (0.74~7.13)	6.40 (2.06~19.94)	1.78 (0.57~5.57)	1.33 (0.42~4.21)
DM and 90 < FPG ≤ 130	29	20 166	1.44 (1.00~2.07)	3.95 (2.70~5.77)	1.57 (1.07~2.31)	1.30 (0.88~1.92)
DM and 130 < FPG ≤ 200	52	45 526	1.14 (0.87~1.50)	3.10 (2.31~4.15)	1.56 (1.16~2.10)	1.34 (0.99~1.82)
DM and FPG > 200	15	8038	1.87 (1.13~3.10)	5.03 (3.00~8.45)	3.36 (1.99~5.65)	2.87 (1.70~4.86)

Abbreviations: DM, Diabetes mellitus; FPG, fasting plasma glucose; HR, hazard ratio.

NA indicates that the exact case number was too small to be retrieved, because of the authority's policy regulation or the hazard ratio could not be estimated.

[a]Adjusting for age (categorical), sex, tobacco smoking, alcohol use, education, body mass index (categorical), systemic steroids use 1 year before study entry, and hospitalization in the previous 6 months.

[b]Adjusting for age (categorical), sex, tobacco smoking, alcohol use, education, body mass index (categorical), systemic steroids use 1 year before study entry, hospitalization in the previous 6 months, and Charlson comorbidity score.
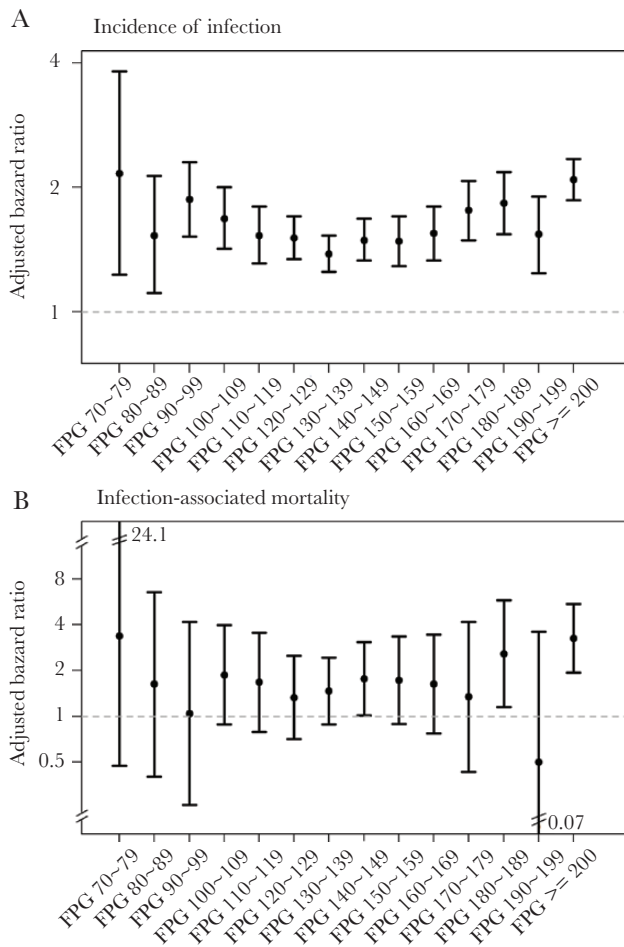
Figure 1. Dose-Response Relation Between Fasting Plasma Glucose (mg/dl) at Baseline and (a) Incidence of Any Infection or (b) Infection-Associated Mortality From the Multivariable Cox Regression Analysis The nondiabetics were used as the reference group; aHR indicates adjusted hazard ratio; FPG, fasting plasma glucose. Adjusted hazard ratios were adjusted for age (categorical), sex, tobacco smoking, alcohol use, education, body mass index (categorical), systemic steroids use 1 year before study entry, and hospitalization in the previous 6 months.

per 1000 for infection-related mortality among diabetics and nondiabetics, respectively. In the Cox regression analysis, the aHR of any hospitalization for infection, overall mortality, and infection-related mortality was 1.55 (95% CI, 1.45–1.65), 1.61 (95% CI, 1.48–1.74), and 1.59 (95% CI,1.23–2.06), respectively (Table 3). The risk estimates associated with diabetes were slightly attenuated after adjustment of comorbidity. The dose-response analysis of hospitalization for infection by 10 mg/dL interval of FPG also revealed a U-shape curve in this population (Figure 2).

We conducted additional analyses to compare the risk of hospitalization due to infection among all and elderly diabetic participants using diabetics with FPG 90–130 mg/dl as the reference group. As shown in Supplementary Table 2, diabetic patients with FPG > 200 mg/dl still were associated with a significantly higher risk, while those with FPG ≤ 90 mg/dl also

were associated a similar magnitude of excess risk, although not attaining statistically significant. Similar findings were observed among elderly diabetic participants despite risks estimates that were not statistically significant due to smaller numbers of participants included in the analysis (Supplementary Table 3). After additionally controlling for Charlson comorbidity score, a slight increase in risk estimates for those diabetic patients with FPG > 200 mg/dl and a decrease in risk estimates for those with FPG ≤ 90 mg/dl was observed (Supplementary Table 2). For elderly diabetic patients, those with FPG > 200 mg/dl had a significantly higher risk of hospitalization for any infection after controlling for Charlson score (Supplementary Table 3). In contrast, the infection risk associated with FPG ≤ 90 mg/dl almost was abolished after controlling for Charlson score.

In a sensitivity analysis, the U-shape relation between FPG and infection risk among diabetics remained unchanged when we excluded those with untreated diabetes (Supplementary Figure 3). We also reexamined the dose-response relation between FPG and infection risk after excluding the elderly (>65 years old) and those with liver and renal disease, autoimmune disease, and cancer. The higher risk of infection at both extremes was still observed (e Figure 4). In a subset of our study population who had repeated measurement of FPG at least 1 year after the first measurement (~9% of the original study population), the Pearson correlation coefficient between the first and second FPG measurement was 0.73 (P < .001). The time-dependent Cox regression analysis in this subset revealed a similar dose-response relation between the FPG level and infection risk, but most of the associations were not statistically significant because of the much smaller sample size (Supplementary Figure 5). No substantial changes in results were found when we excluded participants who were hospitalized for infections within 2 weeks after health screening program and shortened the maximal follow-up period to 2 years after the baseline (Supplementary Figures 6 and 7).

DISCUSSION

In this large population-based community screening cohort, we found that diabetes was associated with not only an increased risk of hospitalization for infection, but also a higher risk of overall mortality and infection-related mortality. A U-shaped relation between FPG level and infection-related hospitalization and mortality was observed, and FPG level of <90 mg/dL was associated with an increased risk of first hospitalization for infection and a trend of higher infection-related mortality. However, this increased risk was not observed when multiple comorbidities were further adjusted, suggesting that comorbidity may play a role in the excess risk associated with low FPG level. In the elderly, the hazard ratio between poor glycemic control and infection was similar to that observed in the general population. Given the high incidence rate of infection

Table 3. Association Between Fasting Plasma Glucose (mg/dl) Level at Baseline and the Risk of Infection Hospitalization by Site and Infection-Related Mortality Among Elderly Participants Aged > 65 Years, Using Elderly Nondiabetics as the Reference Group

	No. of cases	Person-years	Incidence rate	Crude HR	Adjusted HR[a]	Adjusted HR[b]
Any infection						
No DM	4208	93 067	45.21 (43.87~46.60)	Reference	Reference	Reference
DM	1304	18 624	70.02 (66.32~73.92)	1.57 (1.47~1.67)	1.55 (1.45~1.65)	1.33 (1.24~1.42)
DM and FPG ≤ 90	38	497	76.42 (55.61~105.02)	1.72 (1.25~2.37)	1.65 (1.19~2.27)	1.24 (0.90~1.71)
DM and 90 < FPG ≤ 130	421	5911	71.23 (64.74~78.37)	1.60 (1.45~1.77)	1.54 (1.40~1.71)	1.29 (1.17~1.44)
DM and 130 < FPG ≤ 200	729	10 804	67.48 (62.75~72.56)	1.51 (1.39~1.63)	1.50 (1.39~1.62)	1.31 (1.20~1.42)
DM and FPG > 200	116	1412	82.14 (68.47~98.54)	1.84 (1.53~2.21)	1.92 (1.60~2.31)	1.69 (1.40~2.03)
Septicemia						
No DM	1037	93 067	11.14 (10.48~11.84)	Reference	Reference	Reference
DM	343	18 624	18.42 (16.57~20.47)	1.68 (1.48~1.90)	1.69 (1.49~1.91)	1.42 (1.25~1.62)
DM and FPG ≤ 90	13	497	26.14 (15.18~45.02)	2.40 (1.39~4.15)	2.34 (1.36~4.05)	1.69 (0.97~2.95)
DM and 90 < FPG ≤ 130	122	5911	20.64 (17.28~24.65)	1.89 (1.56~2.28)	1.87 (1.55~2.25)	1.54 (1.27~1.87)
DM and 130 < FPG ≤ 200	180	10 804	16.66 (14.40~19.28)	1.51 (1.29~1.77)	1.53 (1.30~1.79)	1.31 (1.11~1.55)
DM and FPG > 200	28	1412	19.83 (13.69~28.72)	1.81 (1.24~2.64)	1.93 (1.33~2.82)	1.68 (1.15~2.45)
Lower respiratory tract infection						
No DM	1733	93 067	18.62 (17.76~19.52)	Reference	Reference	Reference
DM	465	18 624	24.97 (22.80~2734)	1.36 (1.23~1.51)	1.41 (1.27~1.56)	1.19 (1.07~1.33)
DM and FPG ≤ 90	13	497	26.14 (15.18~45.02)	1.44 (0.83~2.48)	1.36 (0.79~2.36)	1.00 (0.58~1.74)
DM and 90 < FPG ≤ 130	145	5911	24.53 (20.85~28.87)	1.34 (1.13~1.59)	1.34 (1.13~1.59)	1.11 (0.93~1.32)
DM and 130 < FPG ≤ 200	269	10 804	24.90 (22.09~28.06)	1.36 (1.19~1.54)	1.41 (1.24~1.61)	1.22 (1.07~1.39)
DM and FPG > 200	38	1412	26.91 (19.58~36.98)	1.47 (1.07~2.03)	1.69 (1.22~2.33)	1.47 (1.07~2.04)
Intra-abdominal infection						
No DM	340	93 067	3.65 (3.28~4.06)	Reference	Reference	Reference
DM	95	18 624	5.10 (4.17~6.24)	1.40 (1.12~1.76)	1.39 (1.11~1.75)	1.23 (0.97~1.57)
DM and FPG ≤ 90	NA	497	NA	1.11 (0.28~4.44)	1.06 (0.26~4.26)	0.84 (0.21~3.40)
DM and 90 < FPG ≤ 130	NA	5911	NA	1.40 (0.96~2.03)	1.36 (0.93~1.98)	1.18 (0.80~1.74)
DM and 130 < FPG ≤ 200	54	10 804	5.00 (3.83~6.53)	1.37 (1.03~1.83)	1.37 (1.02~1.83)	1.23 (0.91~1.65)
DM and FPG > 200	9	1412	6.37 (3.32~12.25)	1.75 (0.90~3.39)	1.84 (0.95~3.57)	1.66 (0.85~3.24)
Reproductive and urinary tract infection						
No DM	1445	93 067	15.53 (14.75~16.35)	Reference	Reference	Reference
DM	556	18 624	29.85 (2747~32.44)	1.95 (1.77~2.15)	1.88 (1.71~2.08)	1.63 (1.47~1.81)
DM and FPG ≤ 90	13	497	26.14 (15.18~45.02)	1.72 (0.99~2.96)	1.65 (0.96~2.85)	1.26 (0.73~2.19)
DM and 90 < FPG ≤ 130	179	5911	30.28 (26.16~35.06)	1.98 (1.70~2.31)	1.88 (1.61~2.20)	1.59 (1.36~1.87)
DM and 130 < FPG ≤ 200	312	10 804	28.88 (25.85~32.27)	1.88 (1.66~2.13)	1.83 (1.62~2.07)	1.60 (1.41~1.82)
DM and FPG > 200	52	1412	36.82 (28.06~48.32)	2.41 (1.83~3.18)	2.38 (1.80~3.14)	2.09 (1.58~2.77)
Skin and soft tissue infection, including necrotizing fasciitis						
No DM	504	93 067	5.42 (4.96~5.91)	Reference	Reference	Reference
DM	164	18 624	8.81 (756~10.26)	1.64 (1.37~1.96)	1.53 (1.28~1.83)	1.37 (1.13~1.66)
DM and FPG ≤ 90	6	497	12.07 (5.42~26.86)	2.26 (1.01~5.06)	2.23 (0.99~4.99)	1.83 (0.81~4.14)
DM and 90 < FPG ≤ 130	46	5911	7.78 (5.83~10.39)	1.45 (1.07~1.96)	1.34 (0.99~1.81)	1.18 (0.87~1.61)
DM and 130 < FPG ≤ 200	94	10 804	8.70 (7.11~10.65)	1.62 (1.30~2.02)	1.50 (1.20~1.88)	1.36 (1.08~1.71)
DM and FPG > 200	18	1412	12.75 (8.03~20.23)	2.38 (1.49~3.81)	2.33 (1.45~3.73)	2.11 (1.31~3.40)
Osteomyelitis						
No DM	87	93 067	0.93 (0.76~1.15)	Reference	Reference	Reference
DM	15	18 624	0.81 (0.49~1.34)	0.86 (0.50~1.49)	0.80 (0.46~1.39)	0.71 (0.40~1.27)
DM and FPG ≤ 90	0	497	NA	NA	NA	NA
DM and 90 < FPG ≤ 130	5	5911	0.85 (0.35~2.03)	0.90 (0.37~2.22)	0.82 (0.33~2.02)	0.71 (0.28~1.79)

Table 3. Continued

	No. of cases	Person-years	Incidence rate	Crude HR	Adjusted HR[a]	Adjusted HR[b]
DM and 130 < FPG ≤ 200	NA	10 804	NA	0.79 (0.38~1.63)	0.75 (0.36~1.55)	0.67 (0.32~1.41)
DM and FPG > 200	NA	1412	NA	1.51 (0.37~6.14)	1.40 (0.34~5.72)	1.27 (0.31~5.22)
Infection of central nervous system						
No DM	4	93 067	0.04 (0.02~0.11)	Reference	Reference	Reference
DM	0	18 624	NA	NA	NA	NA
DM and FPG ≤ 90	0	497	NA	NA	NA	NA
DM and 90 < FPG ≤ 130	0	5911	NA	NA	NA	NA
DM and 130 < FPG ≤ 200	0	10 804	NA	NA	NA	NA
DM and FPG > 200	0	1412	NA	NA	NA	NA
Invasive fungal infection						
No DM	9	93 067	0.10 (0.05~0.19)	Reference	Reference	Reference
DM	3	18 624	0.16 (0.05~0.50)	1.68 (0.46~6.22)	2.08 (0.55~7.80)	1.86 (0.45~7.63)
DM and FPG ≤ 90	0	497	NA	NA	NA	0.00 (0.00~0.00)
DM and 90 < FPG ≤ 130	3	5911	0.51 (0.16~1.57)	5.30 (1.43~19.60)	6.98 (1.83~26.53)	6.34 (1.49~27.10)
DM and 130 < FPG ≤ 200	0	10 804	NA	NA	NA	NA
DM and FPG > 200	0	1412	NA	NA	NA	NA
Total mortality						
No DM	2483	105 043	23.64 (22.73~24.59)	Reference	Reference	Reference
DM	791	22 543	35.09 (32.73~37.62)	1.50 (1.38~1.62)	1.61 (1.48~1.74)	1.36 (1.25~1.48)
DM and FPG ≤ 90	26	609	42.67 (29.05~62.67)	1.84 (1.25~2.71)	1.90 (1.29~2.79)	1.41 (0.95~2.09)
DM and 90 < FPG ≤ 130	265	7137	37.13 (32.92~41.88)	1.60 (1.41~1.81)	1.63 (1.44~1.86)	1.34 (1.17~1.53)
DM and 130 < FPG ≤ 200	436	13 023	33.48 (30.48~36.77)	1.43 (1.29~1.58)	1.54 (1.39~1.71)	1.34 (1.21~1.49)
DM and FPG > 200	64	1773	36.11 (28.26~46.13)	1.53 (1.19~1.96)	1.86 (1.45~2.39)	1.62 (1.26~2.08)
Mortality from any infection						
No DM	262	105 043	2.49 (2.21~2.82)	Reference	Reference	Reference
DM	77	22 543	3.42 (2.73~4.27)	1.39 (1.08~1.80)	1.59 (1.23~2.06)	1.43 (1.09~1.87)
DM and FPG ≤ 90	NA	609	NA	1.35 (0.33~5.41)	1.46 (0.36~5.90)	1.21 (0.30~4.94)
DM and 90 < FPG ≤ 130	NA	7137	NA	1.50 (1.01~2.25)	1.57 (1.05~2.36)	1.37 (0.90~2.08)
DM and 130 < FPG ≤ 200	40	13 023	3.07 (2.25~4.19)	1.25 (0.89~1.74)	1.46 (1.04~2.05)	1.33 (0.94~1.88)
DM and FPG > 200	9	1773	5.08 (2.64~9.76)	2.04 (1.05~3.96)	2.89 (1.48~5.65)	2.64 (1.35~5.18)

Abbreviations: DM, DM, Diabetes mellitus; FPG, fasting plasma glucose; HR, hazard ratio.

NA indicates that the exact case number was too small to be retrieved, because of the authority's policy regulation or the hazard ratio could not be estimated.

[a]Adjusting for age (categorical), sex, tobacco smoking, alcohol use, education, body mass index (categorical), systemic steroids use 1 year before study entry, and hospitalization in the previous 6 months.

[b]Adjusting for age (categorical), sex, tobacco smoking, alcohol use, education, body mass index (categorical), systemic steroids use 1 year before study entry, hospitalization in the previous 6 months, and Charlson comorbidity score.
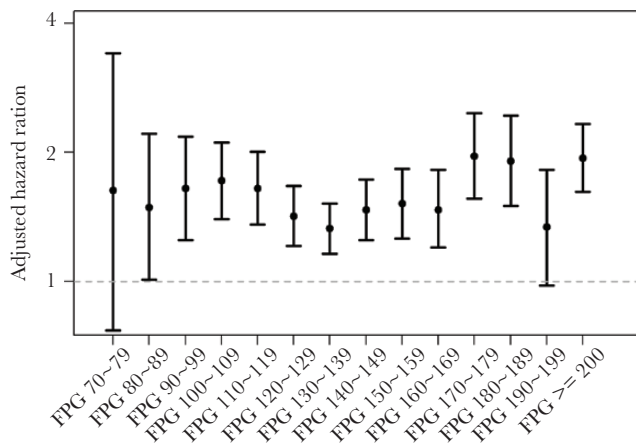
Figure 2. Dose-Response Relation Between Fasting Plasma Glucose (mg/dl) at Baseline and Incidence of Any Infection From the Multivariable Cox Regression Analysis While Restricting to Participants Aged Above 65 Years The nondiabetics were used as the reference group; aHR indicates adjusted hazard ratio; FPG, fasting plasma glucose. Adjusted hazard ratios were adjusted for age (categorical), sex, tobacco smoking, alcohol use, education, body mass index (categorical), systemic steroids use 1 year before study entry, and hospitalization in the previous 6 months.

morbidity and mortality in the elderly, the absolute burden of infection attributable to poor glycemic control in this population would be substantial.

Prior studies in the United Kingdom and northern Denmark have reported that the risks of urinary tract infection, genital tract infection, hospitalization for pneumonia, and streptococci bacteremia were higher for diabetic patients compared with those without diabetes [7–10]. In a Danish nationwide cohort study [11], type 2 diabetic patients had a higher rate of hospital-treated infection during a median follow-up of 2.8 years, with a HR of 1.49 (95% CI, 1.47–1.52); the risks were increased particularly for urinary tract infection (HR, 1.41), skin infection (HR, 1.50), and septicemia (HR, 1.60). In a recent UK cohort, in comparison with patients without diabetes mellitus (DM), those with DM and optimal control (HbA1c 6–7%), and poor control (≥11%) had increased hospitalization risks for infection [12]. We observed that diabetic patients had a nearly 60% increase in the risk of hospitalization for any infection, an approximately 80% excess risk of septicemia and urogenital tract infection, and a 64% higher risk of skin and soft tissue infection. The risk of hospitalization for infection became substantially higher in particular among those diabetic patients with FPG > 200 mg/dL. Furthermore, we found that diabetics had a 71% elevated risk of infection-related mortality, while those with FPG level > 200 mg/dL had a 3-fold increased risk of death due to infection as compared with those without diabetes.

In addition to the substantial evidence that high blood glucose level was associated with an elevated hazard, our study indicated that low blood glucose level also was associated with an increased risk of incident infection. Evidence on the dose-response relation between glycemic control and risk of infection

has been limited and inconclusive [13]. In the Diabetes Control and Complications Trial, intensive glucose control was associated with a nearly 50% reduction in vaginal infection among patients with type 1 diabetes. However, there was no association between glycemic control and the occurrence of foot, urinary, respiratory, and gastrointestinal infections [14]. In a Dutch study of diabetic patients from general practices, the mean A1c level was similar in those with infection and those without infection [15]. Another German study examined the relation between A1c and first occurrence of urinary tract infection. Compared with diabetic patients with A1c 7.0–7.5%, those with a high A1c level (>9.5%) and those with a low A1c level of 6.0–6.5% were both associated with a significantly higher risk of infection [5]. In a Denmark cohort of type 2 diabetics, Mor and colleagues also reported a J-shaped relation between blood glucose level and infection risk [6].

Some researchers speculated that a higher infection risk for those diabetic patients with low blood glucose level may be due to malnutrition, multiple comorbidities, impaired kidney and liver function, and poor functional status or frailty. Nonetheless, a similar U-shape dose-response relation in our cohort remained even after excluding the elderly and those with liver, renal, and autoimmune diseases (Supplementary Figure 4). Sufficient data have concluded that diabetic patients with low baseline A1c level was associated with an increased overall mortality [16, 17]. Several observational studies and 1 post-hoc analysis of a randomized trial also showed that hypoglycemia was associated with a higher risk of mortality and morbidity among diabetic patients hospitalized for infectious or noninfectious causes, in a critically ill or noncritically ill setting [18–21]. To our knowledge, little is known about the effect of low blood glucose level on immune function in response to infections. Additional research is needed to explore the influence of hypoglycemia on infection among diabetics and the optimal level of glycemic control in terms of infection outcomes.

The strengths of this study included enrolling a large number of participants from a community health screening program and prospectively following them for several years. A comprehensive list of potential confounding factors, including BMI, educational level, smoking, and alcohol consumption, were considered in the analyses. Outcome occurrence was obtained by linkage to the National Health Insurance Database for any clinically important infection event with very low missing rate.

Several important limitations also should be considered in the present study. First, participants of this study were categorized based on a single measurement of FPG level instead of a series of hemoglobin A1c. Although the correlation between FPG level and A1c is generally good, exposure misclassification may still occur [22]. We believe the misclassification bias of glycemic level would be nondifferential with regard to infection status, and this bias would have underestimated the true association between glycemic control and infection risk.

Nonetheless, we excluded participants with untreated diabetes and considered time-varying glucose information among those who had repeated measurements of FPG level in the sensitivity analyses, and we found very similar results. Second, we could not exclude the possibility that physicians were more likely to admit diabetic patients or those with poorly controlled diabetes into the hospital for infectious disease management. However, this could not explain the observed increased risk of infection among those with low blood glucose. Third, although we have adjusted for major important risk factors, confounding from unmeasured variables, such as diabetes duration or socioeconomic status, may still possibly influence the results. Fourth, including only the first hospitalization as outcome, but not all hospitalization, would lose some statistical power. However, given the large sample size of the present study (14 372 cases of first hospitalizations), we still had sufficient power to analyze the dose-response relation between glucose level and infection hospitalization. We did not include all hospitalizations in our analysis, because there were assumptions while using either Poisson regression or negative binomial regression model for count data to handle overdispersion or underdispersion [23, 24]. Fifth, in this study, we described the relation between FPG and risk of hospitalization due to infection without applying any statistical test. Finally, whether our study findings can be generalized to whole population needs to be confirmed in the upcoming population-based studies or even randomized controlled trials.

Our study revealed that diabetes was associated with not only a higher risk of hospitalization for infection, but also a significantly increased risk of infection-related mortality both in the general population and in the elderly. A U-shaped relation between FPG level and infection-related outcome was observed. After controlling for comorbidity, the increased risk among those with low FPG was not observed, suggesting that multiple comorbidities may play a role in the excess risk associated with low FPG level. Fasting plasma glucose > 200 mg/dl was consistently associated with a significantly higher risk of infection morbidity and mortality. We suggest that more efforts should be given to find the optimal level of glucose control to reduce the burden of infectious disease in diabetics, in particular for the elderly patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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