Glycaemic status, insulin resistance, and risk of infection-related mortality

Glycaemic status, insulin resistance, and risk of infection-related mortality: a cohort study

Short title: Glycaemic status and infection mortality

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Abstract

Background: The impact of non-diabetic hyperglycaemia and insulin resistance on infection-related mortality risk remains unknown. We investigated the association of glycaemic status and insulin resistance with infection-related mortality in individuals with and without diabetes.

Design: Cohort study based on Kangbuk Samsung Health Study and national death records.

Methods: 666,888 Korean adults who underwent fasting blood measurements including glucose, glycated hemoglobin (HbA1c), and insulin during health screening examinations were followed for up to 15.8 years. Vital status and infection-related mortality were ascertained through national death records. Variable categories were created based on established cutoffs for glucose and HbA1c levels and homeostatic model assessment of insulin resistance (HOMA-IR) quintiles. We used Cox proportional hazards regression analyses to estimate hazard ratios (HRs) and 95% CIs for infection-related mortality.

Results: During a median follow-up of 8.3 years, 313 infectious disease deaths were identified. The associations of glucose and HbA1c levels with infection-related mortality were J-shaped (*P* for quadratic trend<0.05). The multivariable-adjusted HR (95% CIs) for infection-related mortality comparing glucose levels <5, 5.6-6.9, and ≥7.0 mmol/L to 5.0-5.5 mmol/L (the reference) were 2.31 (1.47-3.64), 1.65 (1.05-2.60), and 3.41 (1.66-7.00), respectively. Among individuals without diabetes, the multivariable adjusted HR for infection-related mortality for insulin resistance (HOMA-IR ≥75^{th} centile versus <75^{th} centile) was 1.55 (1.04-2.32).

Conclusions: Both low and high glycaemic levels and insulin resistance were independently associated with increased infection-related mortality risk, indicating a possible role of abnormal glucose metabolism in increased infection-related mortality.

Keywords: infection; glucose; HbA1c; insulin resistance; infection-related mortality; cohort study

Significant Statement

To the best of our knowledge, this study is the first to demonstrate an independent positive association between non-diabetic hyperglycaemia and insulin resistance detected during the screening process and an increased risk of infection-related mortality. Insulin resistance measured by HOMA-IR was also positively associated with increased risk of infection-related mortality among individuals without diabetes. Individuals with hyperglycaemia even in the non-diabetic range and insulin resistance may benefit from preventive measures to reduce risk of infectious diseases and its related mortality.

Introduction

Diabetes is one of the leading causes of morbidity and mortality worldwide (1). In 2019, global diabetes prevalence was estimated to be 9.3% and is projected to rise to 10.9% by 2045(2). People with diabetes are at an increased risk for a wide range of diabetes-related complications including cardiovascular disease (CVD), retinopathy, neuropathy, and end-stage renal disease (1). Poorly controlled diabetes and its complications and co-morbidities are known risk factors for infectious diseases (3, 4). Indeed, previous studies have shown that people with diabetes are at increased risk of common infections, severe infections and infection-related mortality (5-7). Recently, patients with coronavirus disease 2019 (COVID-19) infection and diabetes reportedly had a significantly higher risk of COVID-19 disease severity and associated mortality (8).

People with pre-diabetes or non-diabetic hyperglycaemia, defined as glycaemic parameters above normal but below the diabetes diagnostic threshold, are not only at a high risk of developing diabetes but are also at increased risk of various adverse outcomes, including CVD, renal disease, and all-cause mortality (9-11). Although the impact of diabetes on infectious disease and infection-related mortality has been widely explored, very little is known about the role of non-diabetic hyperglycaemia as a risk factor for infection. To date, only a few studies have reported an association between non-diabetic hyperglycaemia and increased risk of pulmonary tuberculosis, and periodontitis (12-14). Notably, non-diabetic hyperglycaemia and metabolic syndrome, an insulin resistant phenotype, have been reported to be associated with alterations in cytokine responses and immune cell functions (15-17). Until now, the effect of insulin resistance, a key pathogenic feature of both diabetes and non-diabetic hyperglycaemia, on infection, remains uncertain. Therefore, since alterations in immune cell functions have been described with non-diabetic hyperglycaemia and insulin

resistance, we hypothesized that non-diabetic hyperglycaemia and insulin resistance, even in individuals without diabetes, increases the risk of infection-related mortality. To test this hypothesis, we investigated the associations between glycaemic status (including non-diabetic hyperglycaemia and diabetes) and insulin resistance and the development of infection-related mortality in a large sample of Korean adults who participated in a routine health check programme.

Methods

Study population

This cohort study was performed in a subsample of the Kangbuk Samsung Health Study, a cohort study of Korean men and women who underwent a comprehensive annual or biennial health examination at one of the Kangbuk Samsung Hospital Total Healthcare Center clinics in Seoul and Suwon, South Korea as described previously (18, 19). This study population was restricted to individuals who participated in a comprehensive health-screening examination between 2005 and 2019 (n = 682,030). A total of 15,142 participants met the exclusion criteria at baseline, including unknown vital status (n = 3), missing data on fasting blood glucose (FBG) level, glycated hemoglobin (HbA1c) or BMI (n = 1,432), or a history of malignancy (n = 13,734). Finally, 666,888 participants were included in the analysis. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No. KBSMC 2020-04-011) the requirement for informed consent was waived because the study was designed to use anonymized, retrospective data that were collected during a routine health examination process and linked to mortality data from the Korea National Statistical Office (KNSO). All procedures used in this study adhered to the ethical principles of the Declaration of Helsinki for Medical Research Involving Human Subjects outlined in 2013.

Measurements

At baseline and follow-up visits, data on demographic factors, lifestyle factors, medical history, and medication use were collected using a standardized, self-administered questionnaire as described previously (18, 19). Smoking status was categorized as never, former, and current smoking. Average alcohol use was categorized as none, < 20 g, and ≥ 20 g of ethanol/day and the frequency of moderate or vigorous intense physical activity was categorized as < 3 and ≥ 3 times/week.

Anthropometry and sitting blood pressure (BP) were measured by trained nurses. BMI was categorized according to Asian criteria, and BMI ≥ 25 kg/m^2 was classified as obesity (20). Hypertension was defined as BP ≥ 140/90 mmHg, a history of physician-diagnosed hypertension, or use of BP-lowering medication.

At least a 10-hour fast was required for the health examinations, which included blood measurements of glycemic parameters (FBG, HbA1c and insulin), lipid profiles, and high-sensitivity C-reactive protein (hsCRP) level (18). Serum insulin levels were measured on the day of blood collection by immunoradiometric assays (Biosource, Nivelles, Belgium) between 2002 and 2009, and thereafter using an electrochemiluminescence immunoassay with the Modular E170 system (Roche Diagnostics, Tokyo, Japan). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: fasting blood insulin (IU/L) × FBG (mg/dL)/405 (21).

Previously diagnosed diabetes was defined as a history of physician-diagnosed diabetes or the current use of glucose-lowering medication as indicated on a self-administered, structured questionnaire. Among those without previously diagnosed diabetes, participants were categorized into four groups as follows: FBG level (<5.0, 5.0–5.5, 5.6–6.9, or ≥7.0

mmol/L) and HbA1c level (<36, 36-38, 39–46, or ≥48 mmol/mol). The cut-off values used in this study were applied according to the American Diabetes Association guideline clasification(22). Since previous studies have reported an elevated risk of infection-related mortality in individuals with low FBG levels, participants with FBG levels below 5.6 mmol/L were further divided into groups of <5.0 and 5.0-5.5 mmol/L (23). An HbA1c of 36 mmol/mol corresponds to an FBG of approximately 5.6 mmol/L according to a previous report of an adult population without diabetes and corresponds to approximately the 25th percentile of HbA1c of our population (24). An FBG level of 5.0-5.5 mmol/L and an HbA1c level of 36-38 mmol/mol were used as the reference group, which had the lowest risk of infection-related mortality in our population.

Insulin and HOMA-IR were categorized into quintiles based on their distributions within the study participants without previously diagnosed diabetes. Insulin resistance was defined as HOMA-IR ≥ 75th percentile of nondiabetic individuals (the respective 75th percentile values: 2.41 for immunoradiometric assay and 1.84 for electrochemiluminescence immunoassay) (25, 26).

Mortality follow-up

Vital status until December 31, 2020 was ascertained through linkage to nationwide death certificate data from the KNSO. In South Korea, all deaths are legally required to be reported to the KNSO. The cause of death is classified according to the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Concordance between the cause of death on the death certificate and patient diagnosis in the medical utilization data was 72.2-91.9% across all causes of deaths, and was 94.9% for cancer deaths (27, 28). Infection-related mortality was defined as underlying cause of death including

certain infectious and parasitic diseases (ICD-10 A00-B99) and organ-specific infectious diseases (Supplemental Table S1).

Statistical analysis

The baseline characteristics of the participants are presented stratified by the primary endpoint, infection-related mortality. As there was a large difference in age and sex between participants with infection-related mortality and participants without, all baseline characteristics other than age and sex are presented as age- and sex-adjusted means or proportions with 95% CIs.

Each participant was followed from their first examination until either the date of death or the end of follow-up (December 31, 2020), whichever came first. Participants who died from other causes were censored at the date of death. Cox proportional hazards regression analyses using the age as time scale were used to estimate hazard ratios (HRs) and 95% CIs for infection-related mortality. The proportional hazards assumption was assessed by examining graphs of estimated log (-log [SURVIVAL]); no violation of the assumption was identified.

Models were initially adjusted for age (as the timescale) and sex and then further adjusted for study center (Seoul or Suwon); year of screening; smoking status (never, former, current, or unknown); alcohol intake (0, <20, ≥20 g/day, or unknown); physical activity (< 3, ≥ 3 times a week, or unknown); education level (< 12 years, ≥ 12 years, or unknown); medication for lowering serum lipids, and immunosuppressive agents ; BMI; history of hypertension, CVD, respiratory disease, kidney disease, psychiatric disorder (multivariable-adjusted model 1); and hsCRP (model 2). To evaluate the impact of the updated status of FBG, HbA1c, HOMA-IR and confounders during follow-up, we conducted additional analyses

introducing FBG, HbA1c and HOMA-IR (separately) levels and other confounders as a time-varying covariate in the models. Among individuals without diabetes, the multivariable adjusted HR for infection-related mortality for insulin resistance (defined by HOMA-IR≥75th centile versus <75th centile) was investigated. To test for linear trends, the median value of each category was included in each model as a continuous variable. We also assessed the relationship between the glycaemic parameters as a continuous factor and outcome using restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the sample distribution to provide a flexible estimate of the concentration-response relationship between the exposure and infection-related mortality. We also performed analyses whilst introducing BMI categories. BMI was categorized according to Asian-specific criteria(29) as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2), obesity stage I (BMI 25–29.9 kg/m^2) and obesity stage II (BMI ≥30 kg/m^2). Statistical analyses were performed using STATA version 16.0 (StataCorp LP, College Station, TX, USA). All reported *P* values were two-tailed. Differences with a *P* value <0.05 were considered statistically significant.

Results

Out of 666,888 participants, 313 infection-related deaths were identified (Table 1). The three most common causes of infection-related deaths (Supplemental Table S1) were respiratory tract infections (n = 161), hepatobiliary tract infections (n = 38), and bacterial infections including sepsis (n = 35). Compared to participants who not die, those who died of infection were more likely to be older, male, current smokers, less educated, and more likely to have non-communicable diseases including diabetes, CVD, respiratory disease, kidney

disease. In addition, compared to non-infection death cases, infection-death cases were older and had a higher prevalence of underweight and higher levels of hsCRP and glycaemic parameters, including glucose, HbA1C, HOMA-IR, and insulin (Table 1).

During a total of 5,681,158 person-years of follow-up, the infection-related mortality rate was 5.5 (95% CI, 4.9-6.2) per 10^5 person-years (Table 2). The median duration of follow-up was 8.3 years (interquartile range, 4.6-12.7 years; maximum, 15.8 years). Previously diagnosed diabetes was associated with over two-fold increased risk of infection-related mortality. Both low and high levels of FBG and HbA1c were associated with an increased risk of infection-related mortality compared to reference categories, showing a J-shaped association. After adjustment for possible confounders (model 1), multivariable-adjusted HRs (95% CI) for infection-related mortality comparing FBG levels <5.0, 5.6-6.9, and ≥ 7.0 mmol/L with FBG level 5.0-5.5 mmol/L (reference) were 2.31 (1.47-3.64), 1.65 (1.05-2.60), and 3.41 (1.66-7.00), respectively (*P* for quadratic trend = 0.001). The corresponding HRs (95% CI) comparing HbA1c <36, 39-46, and ≥48 mmol/mol with HbA1c 36-38 mmol/mol (reference) were 1.50 (0.92-2.46), 1.25 (0.80-1.95), and 2.45 (1.24-4.83), respectively (*P* for quadratic trend = 0.010). After adjustment for hsCRP level, the multivariable-adjusted HRs for infection-related mortality were slightly attenuated but remained significant (model 2). In the spline regression models, both low and high levels of FBG and HbA1c were associated with an increased infection-related mortality (Figure 1). When the association was evaluated after introducing changes in glucose and HbA1c levels (separately) and confounders during follow-up as time-varying covariates, the associations of glucose and HbA1c levels with infection-related mortality were similar to the analysis limited to baseline measures.

Table 3 shows the risk of infection-related mortality according to HOMA-IR categories among individuals without either previously diagnosed diabetes or screen-detected diabetes.

High levels of HOMA-IR compared with the third quintile were positively associated with increased risk of infection-related mortality. Multivariable-adjusted HRs (95% CI) for infection-related mortality comparing the highest to third (middle) quintiles of HOMA-IR was 2.83 (1.49-5.39) (model 1). Similarly, multivariable-adjusted HRs (95% CI) for infection-related mortality for insulin resistance defined as HOMA-IR $\geq 75^{th}$ percentile with $<75^{th}$ percentile was 1.55 (1.04-2.32) (model 1), but this association became insignificant after adjustment for hsCRP. In time-dependent analyses with changes in HOMA-IR levels and confounders during follow-up treated as time-varying covariates, the associations of insulin resistance with infection-related mortality were consistently observed.

In analyses using BMI categories, the results were similar to the results of multivariable analysis with BMI as a continuous variable (Supplemental Table S2). In the analyses to assess the association between glycaemic indices and non-infection mortality (Supplemental Tables S3 and S4), J-shape association (elevated risk in the low-level category) was not observed for non-infection mortality, and the amplitude of association was smaller than that of the association with infection mortality.

Discussion

In this large cohort study of young and middle-aged Korean adults, we found that diabetes, non-diabetic hyperglycaemia and insulin resistance were associated with increased risk of infection-related mortality. These associations remained significant after adjustment for potential confounders and when changes in glycaemic parameters and confounders over time were incorporated as time-varying covariates. Our novel findings indicate that individuals with non-diabetic hyperglycaemia or insulin resistance may be at increased risk for developing infection-related mortality.

Several studies have suggested increased mortality risk from infection in people with diabetes (30-34). The increased risk of death from infectious disease in patients with diabetes might be explained by diabetic complications or hyperglycaemia. In a US cohort study, the risk of death owing to infection was doubled in individuals with diabetes compared with those without and appeared to be largely mediated by CVD-related complications (30). However, recent studies in the UK and Italy have reported significantly increased risk of mortality from infections among people with diabetes, even after adjustment for comorbidities, which supports an independent role of diabetes in the development of infection-related mortality (32, 33). Until now, there have been no studies investigating associations between non-diabetic hyperglycaemia, insulin resistance, and infection-related mortality. Furthermore, only a few studies have demonstrated the relationship of prediabetes with specific infectious diseases (12, 35-38). Prediabetes was found to be associated with an increased prevalence of latent and active tuberculosis (12, 35, 36). Additionally, several cross-sectional studies have reported a positive association of impaired glucose tolerance with moderate-to-severe periodontitis (37) and severity of periodontal inflammatory parameters (38). In a recent study of patients with infective endocarditis in China, both diabetes and prediabetes were found to be associated with increased risk for in-hospital and long-term mortality (39). Thus, although several studies have focused on the association between hyperglycaemia at the time of active infection and the outcome of infectious diseases; the present study is unique in that it demonstrates the association between random fasting blood glucose at the time of a routine health check and subsequent death from infectious diseases. To the best of our knowledge, this study is the first to demonstrate an independent positive association between non-diabetic hyperglycaemia and insulin resistance detected during the screening process and an increased risk of infection-related mortality. Previous studies have reported an association between

hyperglycaemia at the time of infection diagnosis and adverse outcomes related to infection (40), or an association between pre-infection glucose levels and severe COVID-19 among patients diagnosed with COVID-19 (41).

This study demonstrated that non-diabetic hyperglyacemia and insulin resistance, in addition to diabetes, significantly increased the risk of infection-related death. The positive association between insulin resistance and infection-related mortality was consistently observed among individuals without either previously diagnosed or screen detected diabetes. Therefore, our findings support the notion that hyperglycaemia or insulin resistance itself, even in the absence of overt diabetes, may increase risk of infection-related mortality.

The underlying mechanisms for the increased infection-related mortality among people with hyperglycaemia or insulin resistance have not been fully elucidated. There is some evidence to suggest that hyperglycaemia, even in the pre-diabetic range, could be related to a compromised immune system as with diabetes. A population-based study of 1653 individuals in Southern Germany showed that serum pro-inflammatory cytokine interleukin-6 and co-regulated acute-phase protein levels were higher in patients with than without impaired glucose tolerance or type 2 diabetes (42). In addition, hyperglycaemia induces active pro-inflammatory conditions in neutrophils, leading to reduced responses to external stimuli, thereby making patients with hyperglycaemia vulnerable to infections (43). A recent study has showed that systemic inflammation, defined as an CRP elevation, was associated with a greater relative risk of infection-related death (44). Similarly, in our study, hsCRP levels were higher in the infection-related mortality group than other groups, but after adjustment for hsCRP, the association between glycemic parameters and infection-related mortality remained significant. Furthermore, obesity and metabolic syndrome, the clinical phenotype of insulin resistance, appear to adversely affect immunity and pathogen defenses, including the

disruption of lymphoid tissue integrity; alterations in cytokine responses, immune cell functions, and innate and adaptive immune responses; and decreased vaccine efficacy (17). The presence of insulin resistance may suppress insulin signaling, leading to insufficient T cell activation in response to pathogens and inhibit the anti-inflammatory role of insulin, which may contribute to promoting anti-inflammatory T helper cell 2 differentiation (17, 45). Conversely, systemic insulin resistance can be induced during infection, particularly sepsis; insulin resistance may interfere with the appropriate metabolic response induced by sepsis and adversely affect the activation of T-cells and macrophages, leading to immunologic dysfunction (46, 47). Further research is required to elucidate the mechanisms underlying the association between insulin resistance and abnormal glucose metabolism with infection-related mortality.

Interestingly, in our study, significantly increased risk of infection-related mortality was also observed among individuals with low levels of FBG (<5.0 mmol/L) and HbA1c (<36 mmol/mol), supporting the nortion of a J-shaped association between FBG/HbA1c and infection-related mortality. This result is in agreement with a recent, large, population-based study from Taiwan (23). The study from Taiwan found that an FBG level <5.0 mmol/L was associated with an elevated risk of both infection-related hospitalization and mortality, and that the excess risk associated with FBG levels <5.0 mmol/L was attenuated after controlling for multiple comorbidities (23). Studies have found that lower BMI was associated with nondiabetic hypoglycaemia and was frequently accompanied by comorbidities such as malnutrition, chronic liver diseases, renal failure, heart failure, poor functional status and malignancies (48, 49). However, in our study, the independent association between low FBG and HbA1c levels with infection-related mortality persisted after adjustment for confounders, including BMI; however, we cannot fully exclude the possibility that unmeasured factors

associated with low fat and lean mass, may increase the risk of infection-related mortality.

A question arising from our observations is what is the cause of infection-related cause of death in our study. In our study, respiratory tract infections were the most common cause of death, followed by hepatobiliary tract infections and bacterial infections including sepsis. The high mortality rate of hepatobiliary tract infection is attributed to the high prevalence of hepatitis B infection in Korea. According to recent statistics on the infectious causes of death in Korea, viral hepatitis was the fourth leading cause of infection-related deaths(50). In our study, 20 of the 38 deaths from hepatobiliary tract infection were due to viral hepatitis.

This study had limitations and strengths that should be discussed. First, glycaemic status at each time points was defined by a single measure of FBG and HbA1c without an oral glucose tolerance test. Therefore, some people with non-diabetic hyperglycaemia or diabetes based on an oral glucose tolerance test might have been incorrectly classified as those with normoglycaemia. However, it should be noted that any misclassification bias would attenuate the strength of the associations that we observed towards the null. Furthermore, participants with a level of hyperglycaemia commensurate with the diagnosis of diabetes detected during the screening programme were referred for further confirmation and subsequent management by physicians or endocrinologists, and detailed data collected by clinicians were not available in our screening dataset. However, subsequent visits within the screening programme include the assessment of glycaemic parameters, and the use of glucose-lowering medications is updated after a diagnosis of screen-detected hyperglycaemia. In our time-dependent analyses that allowed for changes in status between baseline and follow-up, both previously diagnosed and screen-detected diabetes were consistently associated with an increased risk of infection-related mortality. Second, insulin resistance was determined by HOMA-IR instead of hyperinsulinemic euglycaemic clamp as the gold standard method for the determination of

whole body insulin sensitivity. Moreover, HOMA-IR is a reliable and validated measure of insulin sensitivity/resistance in various populations (51). Third, the infection-related mortality can be affected by non-communicable diseases and socio-economic deprivation (52). We adjusted for educational level as a proxy measure of socio-economic status, as well as other comorbidities, including a history of hypertension, CVD, respiratory disease, chronic kidney disease and psychiatric disorders, which were assessed using a self-administered, structured questionnaire used in the health check-up programme in Korea. However, the possibility of unmeasured confounders as well as measurement errors may not be fully excluded in our findings. Finally, our findings were derived from a large cohort of young and middle-aged Koreans, mostly employees and their spouses, who regularly participated in health check-up examinations and had easy access to health care, possibly limiting the generalizability of our results to other populations of different ages, ethnicity/race, socioeconomic status, and comorbidities. Nevertheless, our findings are less likely to be affected by survivor bias or biases related to comorbidities and medication use compared with results derived from older individuals. Furthermore, our cohort study provides a large sample size, utilizes standardized clinical and laboratory measurements, and used ICD-10 codes to identify infection-related mortality. Finally, the analyses included adjustment for a wide range of confounders at baseline and follow-up visits.

In conclusion, this cohort study demonstrated that hyperglycaemia, whether in the non-diabetic or diabetic range, and insulin resistance were associated with an increased risk of infection-related mortality. These findings suggest an independent role for hyperglycaemia even in the non-diabetic range and also insulin resistance, on increased risk of infection-related mortality. Future studies are needed to determine how hyperglycaemia and insulin resistance contribute to the development of infectious diseases and the poor prognoses of

infectious diseases and to identify effective interventions.

Supplementary materials

This is linked to the online version of the paper at

Declaration of interest

The authors declare that there is no conflicts of interest that could be perceived as prejudicing the impartiality of this article.

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Authorship contribution statement: HSC, EJ, MK, YC and SR planned, designed, and directed the study, including quality assurance and control. SR and YK analyzed data and designed the analytic strategy. SHW and CDB provided intellectual input, critically reviewed

and edited the manuscript. All authors conducted the literature review and prepared the Research Design and Methods and Discussion sections of the text. HSC and YC drafted the manuscript. All authors interpreted the results and contributed to the critical revision of the manuscript.

Data sharing/availability statement: The data are not available to be shared publicly as we do not have IRB permission for distributing the data. However, supporting information or analytic code is available from the corresponding author on reasonable request.

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Table legends

Table 1. Estimated* mean values (95% CI) and adjusted* proportions (95% CI) of baseline characteristics of study participants according to infection-related mortality (N = 666,888)

Table 2. Hazard ratios (95% CIs) for infection-related mortality by glucose category in the overall population (N = 666,888)

Table 3. Hazard ratios (95% CIs) for infection-related mortality by HOMA-IR and insulin level without screen-detected diabetes or previously diagnosed diabetes (N=639,751)

Figure legend

Figure 1. Multivariable-adjusted hazard ratios (95% CI) for infection-related mortality by fasting blood glucose (a) and HbA1c (b) among subjects without previously diagnosed diabetes. The curves represent adjusted hazard ratios (solid line) and their 95% confidence intervals (dashed lines) for infection-related mortality based on restricted cubic splines for fasting blood glucose or HbA1c with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, and 95^{th} percentiles of their sample distribution. The reference value was set at the 50^{th} percentile (5.2 mmol/L) for fasting blood glucose and the 75^{th} percentile (39 mmol/mol) for HbA1c. The model was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, BMI, education level, history of CVD, history of respiratory disease, history of chronic kidney disease, medication for psychiatric disorder, use of immunosuppressive agents and lipid lowering medication.

Table 1. Estimated[*] mean values (95% CI) and adjusted[*] proportions (95% CI) of baseline characteristics of study participants according to infection-related mortality (N = 666,888)

Characteristics	Survivors	Infection death	Non-infection death
Number	660,769	313	5,806
Age (years)	39.8 (39.8-39.8)	63.0 (61.8-64.2)	55.0 (54.7-55.2)
Male (%)	52.2 (52.1-52.3)	60.4 (55.0-65.8)	68.2 (67.0-69.4)
High education level (%)[†]	75.9 (75.8-76.0)	62.8 (55.5-70.2)	65.5 (64.1-66.9)
Current smoker (%)	21.8 (21.7-21.8)	24.8 (20.5-29.1)	28.6 (27.7-29.6)
Alcohol intake (%)[‡]	19.4 (19.3-19.5)	17.1 (13.2-21.1)	20.6 (19.6-21.5)
Regular exercise (%)[§]	15.1 (15.0-15.2)	12.0 (9.0-15.0)	14.2 (13.4-15.1)
Hypertension (%)	13.9 (13.9-14.0)	15.4 (12.7-18.1)	15.4 (14.7-16.1)
Previously diagnosed diabetes (%)	3.0 (3.0-3.1)	3.4 (2.5-4.2)	3.6 (3.3-3.9)
History of CVD (%)	3.3 (3.3-3.4)	6.4 (4.7-8.0)	5.1 (4.7-5.4)
History of respiratory disease (%)	2.1 (2.1-2.2)	3.8 (2.2-5.5)	2.6 (2.3-3.0)
History of kidney disease (%)	3.2 (3.1-3.2)	7.4 (5.5-9.3)	5.7 (5.3-6.2)
History of psychiatric disorder (%)	2.4 (2.3-2.4)	2.2 (1.0-3.4)	2.7 (2.4-3.1)
Immunosuppressant (%)	0.2 (0.2-0.2)	0.4 (-0.4-1.2)	0.2 (0.1-0.3)
Lipid lowering medication (%)	3.0 (2.9-3.0)	0.9 (0.4-1.4)	0.9 (0.8-1.0)
Fatty liver (%)	27.9 (27.8-28.0)	17.7 (14.3-21.0)	20.2 (19.3-21.0)
Obesity (%)[‖]	29 (28.9-29.1)	22.6 (18.6-26.6)	23.9 (22.9-24.8)
BMI category (%)			
<18.5 kg/m^2	5.3 (5.3-5.4)	21.6 (15.0-28.1)	8.4 (7.3-9.5)
18.5~22.9 kg/m^2	43.0 (42.9-43.1)	44.7 (38.2-51.2)	49.6 (48.2-51.0)
23.0~24.9 kg/m^2	22.7 (22.6-22.8)	13.2 (10.1-16.3)	18.3 (17.4-19.2)
25.0~29.9 kg/m^2	25.5 (25.4-25.6)	17.0 (13.7-20.3)	20.3 (19.4-21.2)
≥30 kg/m^2	3.5 (3.4-3.5)	3.7 (1.7-5.8)	3.5 (3.0-3.9)
BMI (kg/m^2)	23.4 (23.4-23.4)	22.2 (21.9-22.6)	22.8 (22.7-22.8)
Waist circumference (cm)	80.8 (80.8-80.8)	78.4 (77.4-79.5)	79.6 (79.3-79.8)
Systolic BP (mmHg)	111.3 (111.3-111.4)	115.6 (114.2-117.0)	114.5 (114.2-114.8)
Diastolic BP (mmHg)	71.4 (71.4-71.4)	70.5 (69.5-71.5)	72.1 (71.9-72.3)
Total cholesterol (mmol/L)	191.6 (191.6-191.7)	181.6 (177.8-185.3)	186.0 (185.2-186.9)
LDL-C (mmol/L)	117.4 (117.3-117.5)	98.8 (95.3-102.2)	105.1 (104.3-105.9)
HDL-C (mmol/L)	58.0(57.9-58.0)	58.4 (56.9-60.0)	57.5 (57.2-57.9)
Triglycerides (mmol/L)	114.3 (114.1-114.5)	117.2 (108.8-125.6)	118.0 (116.0-119.9)
ALT (U/L)	24.7 (24.6-24.7)	25.0 (22.5-27.5)	25.7 (25.1-26.3)
GGT (U/L)	30.6 (30.5-30.7)	54.2 (49.8-58.6)	48.3 (47.3-49.3)
hsCRP (mg/L)	1.12 (1.11-1.13)	2.40 (2.02-2.78)	2.14 (2.05-2.23)
Glycemic and insulin parameters			
Glucose (mmol/L)	95.3 (95.2-95.3)	100.5 (98.8-102.2)	98.4 (98.0-98.8)
HbA1c (mmol/mol)	5.5 (5.5-5.5)	5.8 (5.7-5.9)	5.7 (5.6-5.7)
HOMA-IR [#]	1.67 (1.67-1.67)	1.92 (1.78-2.06)	1.86 (1.83-1.89)
Insulin (uIU/mL) [#]	7.16 (7.15-7.18)	8.33 (7.76-8.91)	8.01 (7.88-8.14)

Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; CVD, cardiovascular disease; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin; HDL-C, HDL cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, LDL cholesterol
[*]Adjusted for age and sex; [†]≥College graduate; [‡]≥20 g/day; [§]≥3 times/week; [‖]BMI ≥25 kg/m^2; [#]among 639,751 subjects with available insulin data and without diabetes

Table 2. Hazard ratios (95% CIs) for infection-related mortality by glucose category in the overall population (N = 666,888)

	Person-years (PY)	Number of events	Mortality rate (10^5 PY)	Age, sex-adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI)		HR (95% CI)† in model using time-dependent variables
					Model 1	Model 2	
FBG category (mmol/L)							
<5.0	1,916,655	70	3.7	1.80 (1.29-2.51)	2.31 (1.47-3.64)	2.33 (1.48-3.67)	2.16 (1.39-3.35)
5.0-5.5	2,428,299	68	2.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
5.6-6.9	1,112,086	101	9.1	1.75 (1.28-2.38)	1.65 (1.05-2.6)	1.63 (1.03-2.56)	1.28 (0.83-2.00)
≥7.0 (screen-detected diabetes)	72,886	14	19.2	2.27 (1.28-4.05)	3.41 (1.66-7)	3.09 (1.50-6.35)	2.81 (1.38-5.72)
P for quadratic trend				<0.001	<0.001	0.001	0.001
Previously diagnosed diabetes	151,233	60	39.7	2.47 (1.74-3.52)	2.57 (1.57-4.23)	2.51 (1.53-4.13)	2.16 (1.34-3.49)
HbA1c category (mmol/mol)							
<36	1,976,245	66	3.3	1.55 (1.11-2.18)	1.50 (0.92-2.46)	1.58 (0.97-2.59)	1.58 (0.96-2.57)
36-38	2,143,239	71	3.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
39-46	1,331,660	98	7.4	0.98 (0.72-1.34)	1.25 (0.80-1.95)	1.20 (0.77-1.87)	1.07 (0.70-1.65)
≥48 (screen-detected diabetes)	78,782	18	22.8	1.66 (0.99-2.80)	2.45 (1.24-4.83)	2.17 (1.10-4.30)	2.32 (1.18-4.55)
P for quadratic trend				0.044	0.010	0.023	0.013
Previously diagnosed diabetes	151,233	60	39.7	1.85 (1.30-2.63)	2.07 (1.25-3.43)	2.00 (1.21-3.32)	1.83 (1.12-3.00)

*Cox proportional hazard models using age as a timescale were used to estimate HRs and 95% CIs; multivariable Model 1 was adjusted for age (timescale), sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, BMI, education level, history of hypertension, history of CVD, history of respiratory disease, history of kidney disease, history of psychiatric disorder, immunosuppressive agents and lipid lowering medication; model 2: model 1 plus adjustment for quintile of hsCRP.

†Estimated from Cox proportional hazard models with glucose/HbA1c category, alcohol intake, smoking status, regular exercise, BMI, history of hypertension, history of CVD, history of respiratory disease, history of kidney disease, history of psychiatric disorder, immunosuppressive agents and medication for dyslipidemia as time-dependent categorical variables, and baseline age, sex, center, year of screening exam, and education level as time-fixed variables.

Abbreviations: CVD, cardiovascular disease; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HR, hazard ratio

Table 3. Hazard ratios (95% CIs) for infection-related mortality by HOMA-IR and insulin level without screen-detected diabetes or previously diagnosed diabetes (N=639,751)

		Person-years (PY)	Number of events	Mortality rate (10^5 PY)	Age, sex-adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI)		HR (95% CI)† in model using time-dependent variables
						Model 1	Model 2	
HOMA-IR quintile‡								
Q1		1,153,520	51	4.4	1.28 (0.84-1.96)	1.61 (0.84-3.10)	1.61 (0.84-3.10)	1.36 (0.71-2.57)
Q2		1,107,324	43	3.9	1.18 (0.76-1.83)	1.80 (0.92-3.53)	1.80 (0.92-3.52)	1.88 (1.01-3.50)
Q3		1,082,927	37	3.4	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q4		1,058,952	45	4.2	1.20 (0.78-1.86)	1.72 (0.86-3.46)	1.69 (0.84-3.38)	1.21 (0.61-2.40)
Q5		1,069,402	73	6.8	1.66 (1.12-2.46)	2.83 (1.49-5.39)	2.67 (1.40-5.09)	2.30 (1.25-4.21)
P for quadratic trend					0.023	0.028	0.037	0.077
Insulin Resistance§								
HOMA-IR percentile	<75	4,139,608	167	4.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
HOMA-IR percentile	≥75	1,332,516	82	6.2	1.31 (1.00-1.70)	1.55 (1.04-2.32)	1.47 (0.98-2.20)	1.52 (1.03-2.25)

*Cox proportional hazard models using age as a timescale were used to estimate HRs and 95% CIs; multivariable Model was adjusted for age (timescale), sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, BMI, education level, history of CVD, history of respiratory disease, history of kidney disease, history of psychiatric disorder, immunosuppressive agents and medication for dyslipidemia; model 2: model 1 plus adjustment for quintile of hsCRP.

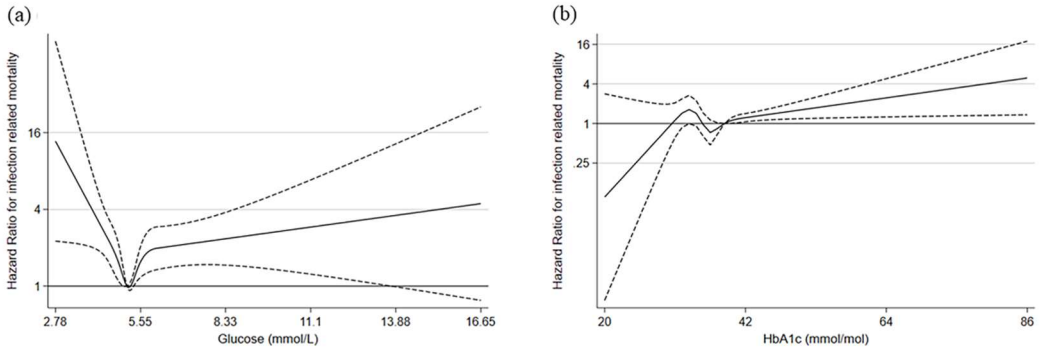
†Estimated from Cox proportional hazard models with HOMA-IR category, alcohol intake, smoking status, regular exercise, BMI, history of hypertension, history of CVD, history of respiratory disease, history of chronic kidney disease, medication for psychiatric disorder, use of immunosuppressive agents and lipid lowering medication, as a time-dependent categorical variables and baseline age, sex, center, year of screening exam and education level as time-fixed variables.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; FBG, fasting blood glucose; HR, hazard ratio; HOMA-IR, homeostasis model assessment of insulin resistance

‡HOMA-IR quintile levels. EIA: quintile 1, < 0.74; quintile 2, 0.74 to 1.05; quintile 3, 1.06 to 1.42; quintile 4, 1.43 to 2.01 ; quintile 5, ≥2.02

RIA: quintile 1, < 1.50; quintile 2, 1.51 to 1.80; quintile 3, 1.81 to 2.16; quintile 4, 2.17 to 2.70 ; quintile 5, ≥2.71

§HOMA -IR 75 percentile level. RIA: 2.54, EIA : 1.83


(a)
Hazard Ratio for infection related mortality
16
4
1
2.78
5.55
8.33
11.1
13.88
16.65
Glucose (mmol/L)
(b)
Hazard Ratio for infection related mortality
16
4
1
25
20
42
64
86
HbA1c (mmol/mol)