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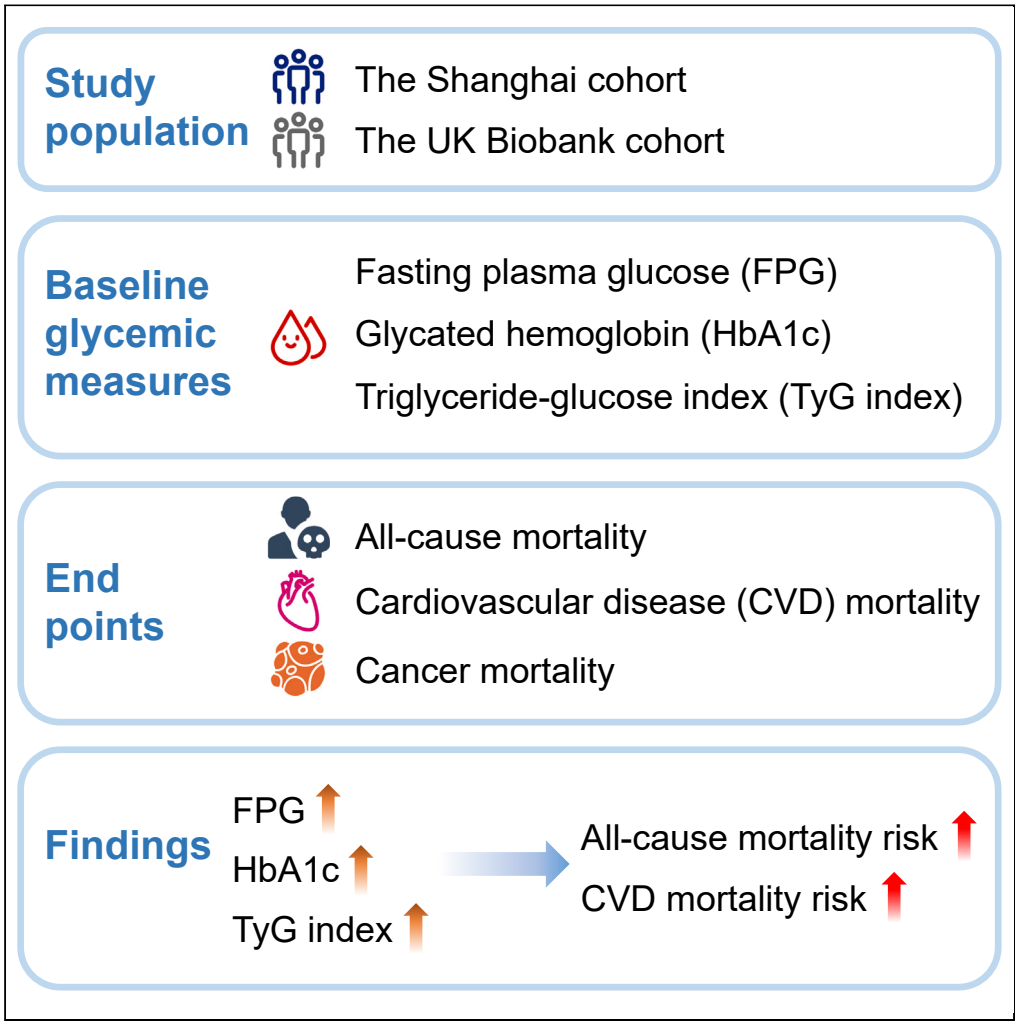

Juzhong Ke, Xiaonan Ruan, Wenbin Liu, ..., Xiaojie Tan, Zhitao Li, Guangwen Cao

gcao@smmu.edu.cn

Highlights

Higher FPG and HbA1c increase the risks of all-cause and CVD mortalities

U-shaped association of TyG index with all-cause and cause-specific mortalities exist

FPG and HbA1c increase the predicting capacity of mortality prognostic models

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Prospective cohort studies underscore the association of abnormal glycemic measures with all-cause and cause-specific mortalities

Juzhong Ke,[1,5] Xiaonan Ruan,[1,5] Wenbin Liu,[2,3,4] Xiaolin Liu,[1] Kang Wu,[1] Hua Qiu,[1] Xiaonan Wang,[1] Yibo Ding,[2,3,4] Xiaojie Tan,[2,3,4] Zhitao Li,[1] and Guangwen Cao[2,3,4,6,*]

SUMMARY

The role of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and triglyceride-glucose index (TyG index) in predicting all-cause and cause-specific mortalities remains elusive. This study included 384,420 adults from the Shanghai cohort and the UK Biobank (UKB) cohort. After multivariable adjustment in the Cox models, FPG $\geq$7.0 mmol/L or HbA1c $\geq$ 6.5% increased the risk of all-cause mortality, FPG $\geq$5.6 mmol/L or HbA1c $\geq$ 6.5% increased CVD-related mortality, and higher or lower TyG index increased all-cause and CVD-related mortalities in the Shanghai cohort; FPG $\geq$5.6 mmol/L, HbA1c $\geq$ 5.7%, TyG index <8.31 or $\geq$9.08 increased the risks of all-cause, CVD-related, and cancer-related mortalities in the UKB cohort. FPG or HbA1c increased the discrimination of the conventional risk model in predicting all-cause and CVD-related mortalities in both cohorts. Thus, increased levels of FPG and HbA1c and U-shaped TyG index increase the risks of all-cause especially CVD-related mortalities.

INTRODUCTION

The global burden of type 2 diabetes mellitus (T2DM) and prediabetes keep growing, especially in high-income countries. The global prevalence of impaired glucose tolerance was 9.1% in 2021 and is projected to increase to 10.0% in 2045.[1] T2DM and prediabetes are often associated with immature death. It is critical to evaluate glycemic measures that can predict the mortality. Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) are crucial to the diagnosis and management of T2DM. World Health Organization recommends performing an oral glucose tolerance test (OGTT) to detect prediabetes and T2DM,[2] while the American Diabetes Association (ADA) recommends HbA1c,[3] and their diagnostic criteria for prediabetes differ slightly. As compared with OGTT, which needs the combination of FPG and 2-h prandial glucose to diagnose, HbA1c is less time-consuming and more cost-effective. However, the relationship between FPG or HbA1c and the mortality is inconsistent. Some studies showed J- or U-shaped curves between FPG or HbA1c and the mortality,[4,5] while others did not show any association between low glycemic measures and the mortality. The triglyceride (TG)-glucose (TyG) index is a reliable surrogate marker of insulin resistance and highly correlated to the euglycaemic-hyperinsulinaemic clamp test, a predictor of T2DM.[6] Recent cohort studies have recommended that TyG index is associated with incident cardiovascular disease (CVD) in patients with nondiabetes or diabetes.[1,7] However, the predictive values of different glycemic measures on CVD were inconsistent among studies.[8,9] Recent cohort studies have demonstrated that elevation in HbA1c level is unlikely to represent an effective strategy for screening pancreatic cancer, however, an elevated risk of colorectal cancer incidence is evident in people with higher TyG index.[10,11] Furthermore, the effects of FPG, HbA1c, and TyG index on the predicting of all-cause and cause-specific mortality are not simultaneously compared in the same batch of human population. Understanding the predicting roles of the three glycemic measures will help in the prophylaxis and control of the burden of the most frequent diseases including CVD and cancer worldwide. Here, we compared the effects of FPG, HbA1c, and TyG index on the prediction of all-cause and major cause-specific mortalities in two prospective cohort studies conducted in China and England, respectively.

RESULTS

The association of three glycemic measures with demographic characteristics and other parameters at baseline

Baseline characteristics of 9,448 participants in the Shanghai cohort are shown in Table 1. Mean age was 57.91 years (range: 15–93 years) at baseline. As shown in Table 2, the three glycemic parameters increased consecutively with age, increasing body mass index (BMI), increasing

[1]Center for Disease Control and Prevention of Pudong New Area, Pudong Institute of Preventive Medicine, Fudan University, Shanghai, P.R. China
[2]Department of Epidemiology, Second Military Medical University, Shanghai, P.R. China
[3]Shanghai Key Laboratory of Medical Bioprotection, Shanghai, P.R. China
[4]Key Laboratory of Biological Defense, Ministry of Education, Shanghai, P.R. China
[5]These authors contributed equally
[6]Lead contact
*Correspondence: gcao@smmu.edu.cn
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Table 1. Baseline characteristics and follow-up summaries of cohort participants in the two cohorts

Characteristics	The Shanghai cohort	The UKB cohort
No. of participants	9,448	374,792
Age (years)	57.9 (12.9)	56.2 (8.1)
Male (%)	3,575 (37.8)	174,244 (46.5)
Urban (%)	5,693 (60.3)	–
Married (%)	8,265 (87.5)	–
≥ 9 years of education (%)	7,438 (78.7)	–
Current smoking (%)	1,563 (16.5)	40,111 (10.8)
Alcohol intake (%)	1,134 (12.0)	344,154 (91.8)
Physical activity (%)	2,320 (24.6)	–
History of hypertension (%)	3,876 (41.0)	104,909 (28.0)
History of dyslipidemia (%)	4,547 (48.1)	–
FPG (mmol/L)	5.9 (1.7)	5.1 (1.2)
HbA1c (%)	5.6 (1.1)	5.5 (0.6)
TyG index	8.8 (0.7)	8.7 (0.6)
TG (mmol/L)	1.7 (1.4)	1.7 (1.0)
HDL (mmol/L)	1.4 (0.3)	1.4 (0.4)
LDL (mmol/L)	3.1 (1.0)	3.6 (0.9)
BMI (kg/m^2)	25.0 (3.8)	27.4 (4.8)
CRP (mg/L)	1.3 (4.7)	2.6 (4.3)
Follow-up time (months), IQR	10.5 (10.4, 10.6)	14.0 (13.2, 14.7)
No. of deaths, all-causes	942	28,992
No. of deaths, CVD, n (%)	398 (42.3)	6,632 (22.9)
No. of deaths, cancer, n (%)	291 (30.9)	13,054 (45.0)

Mean (SD) values and percentages are reported for continuous and categorical variables, respectively.
BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TyG index, triglyceride-glucose index; UKB, UK Biobank.

circulating levels of triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and C-reactive protein (CRP), increasing frequencies of smoking, alcohol intake, hypertension, and dyslipidemia, decreasing levels of education and decreasing circulating level of serum high-density lipoprotein (HDL) cholesterol.

Baseline characteristics of 374,792 participants in the UK Biobank (UKB) cohort are also shown in Table 1. Mean age was 56.22 years (range: 37–73 years) at baseline. As shown in Table 2, the three glycemic parameters increased consecutively with age, increasing BMI, increasing circulating levels of TG and CRP, increasing frequencies of males, smoking, and hypertension, decreasing circulating level of serum HDL, and decreasing frequency of alcohol intake. TyG index increased consecutively with increasing the level of circulating LDL.

Factors associated with all-cause or cause-specific mortality

In the Shanghai cohort, 942 deaths (9.82 per 1,000 person-years) occurred during a median follow-up of 10.52 years (interquartile range [IQR]: 10.43–10.56 years). Of those, 398 (42.25%) died of CVD, with a mortality rate of 4.15 per 1,000 person-years; 291 (30.89%) died of cancer, with a mortality of 3.03 per 1,000 person-years; and 253 (26.86%) died of other causes. Those who died of CVD were older than those who died of cancer [81.86 (8.61) vs. 74.55 (10.14) years, $p < 0.001$]. Participants with higher glycemic levels at baseline had a higher all-cause mortality. The cumulative all-cause mortality was the highest in participants with T2DM, followed by those with prediabetes, as compared with those with normal glucose. Participants with the top quartile of the TyG index had the highest risk of all-cause mortality. After multivariable adjustment in the Cox model, FPG ≥7.0 mmol/L or HbA1c ≥ 6.5% was associated with an increased risk of all-cause mortality, while FPG ≥5.6 mmol/L or HbA1c ≥ 6.5% was associated with an increased risk of CVD-related mortality. However, the difference in cancer-related mortality among various glycemic groups failed to reach statistical significance, possibly because of the small sample size (Table 3; Tables S1 and S2). The multivariable Cox regression analysis indicated that higher FPG, older age, adverse marriage status, current smoking, and higher circulating CRP independently increased the risk of all-cause mortality; higher FPG, older age, adverse marriage status, current smoking, hypertension, and higher CRP independently increased the risk of CVD-related mortality; and older age and current smoking independently increased the risk of cancer-related mortality (Tables S3, S4, and S5).

Table 2. Baseline characteristics stratified by the levels of FPG, HbA1c and TyG index in the participants of both cohorts

	FPG (mmol/L)				HbA1c (%)				TyG index				
Characteristics	<5.6	5.6–6.9	≥7.0	*p*	<5.7	5.7–6.4	≥6.5	*p*	Q1	Q2	Q3	Q4	*p*
The Shanghai cohort													
Number	5,360	2,882	1,206		6,054	2,091	1,303		2,408	2,342	2,339	2,359	
Age (years)	55.2 (13.8)	61.0 (10.8)	62.6 (10.4)	<0.001	56.1 (13.3)	60.2 (11.9)	62.7 (10.6)	<0.001	53.6 (14.8)	58.4 (12.4)	59.9 (11.8)	59.7 (11.5)	<0.001
Male (%)	38.2%	36.6%	39.1%	0.219	37.9%	36.9%	39.2%	0.389	37.3%	37.3%	38.5%	38.3%	0.730
Urban (%)	62.2%	58.2%	56.6%	<0.001	58.9%	64.3%	60.3%	<0.001	58.7%	61.7%	60.6%	60.0%	0.213
Married (%)	87.2%	88.2%	87.3%	0.402	87.6%	87.3%	87.0%	0.791	86.0%	88.3%	87.3%	88.3%	0.052
≥9 years education (%)	83.1%	74.9%	68.4%	<0.001	80.7%	77.7%	71.2%	<0.001	82.3%	79.2%	76.9%	76.6%	<0.001
Current smoking (%)	16.0%	15.8%	20.7%	<0.001	16.1%	15.6%	20.0%	0.002	12.4%	16.9%	16.2%	20.7%	<0.001
Alcohol intake (%)	10.5%	13.9%	14.3%	<0.001	11.3%	12.8%	14.0%	0.010	10.1%	12.4%	11.5%	14.1%	<0.001
Physical activity (%)	24.4%	24.6%)	24.9%	0.944	24.7%	24.0%	24.6%	0.797	23.2%	25.3%	25.0%	24.7%	0.341
History of hypertension (%)	31.8%	50.0%	60.8%	<0.001	35.9%	45.7%	57.2%	<0.001	24.9%	38.3%	45.7%	55.2%	<0.001
History of dyslipidemia (%)	41.7%	53.8%	63.2%	<0.001	43.2%	53.5%	62.2%	<0.001	18.0%	33.7%	51.4%	89.4%	<0.001
TG (mmol/L)	1.5 (1.2)	1.8 (1.3)	2.2 (2.1)	<0.001	1.6 (1.3)	1.8 (1.4)	2.1 (1.8)	<0.001	0.7 (0.2)	1.2 (0.2)	1.7 (0.3)	3.2 (2.1)	<0.001
HDL (mmol/L)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)	<0.001	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)	<0.001	1.6 (0.4)	1.4 (0.3)	1.3 (0.3)	1.2 (0.3)	<0.001
LDL (mmol/L)	3.0 (1.0)	3.2 (1.0)	3.4 (1.0)	<0.001	3.0 (1.0)	3.2 (1.0)	3.3 (1.0)	<0.001	2.6 (0.9)	3.1 (0.9)	3.4 (1.0)	3.5 (1.0)	<0.001
BMI (kg/m^2)	24.5 (3.5)	25.6 (4.1)	26.3 (3.7)	<0.001	24.7 (3.8)	25.4 (3.6)	26.0 (3.7)	<0.001	23.4 (3.4)	24.7 (3.4)	25.5 (3.4)	26.5 (4.1)	<0.001
CRP (mg/L)	1.1 (4.5)	1.6 (5.1)	1.8 (4.4)	<0.001	1.3 (5.1)	1.3 (3.7)	1.8 (4.5)	0.001	1.1 (5.9)	1.2 (4.5)	1.5 (4.6)	1.6 (3.5)	0.004
The UKB cohort													
Number	318,994	41,957	13,841		303,214	57,029	14,549		92,728	93,478	94,421	94,165	
Age (years)	55.9 (8.1)	58.2 (7.7)	58.7 (7.4)	<0.001	55.5 (8.2)	59.4 (7.1)	59.0 (7.3)	<0.001	54.0 (8.3)	56.4 (8.1)	57.2 (7.9)	57.2 (7.8)	<0.001
Male (%)	45.6%	49.4%	58.3%	<0.001	45.5%	47.7%	62.4%	<0.001	33.0%	41.7%	50.1%	61.0%	<0.001
Current smoking (%)	10.9%	9.8%	10.3%	<0.001	9.8%	15.5%	12.5%	<0.001	8.8%	10.1%	11.0%	13.1%	<0.001
Alcohol intake (%)	92.2%	91.0%	85.5%	<0.001	93.0%	88.1%	82.4%	<0.001	92.7%	92.2%	91.8%	90.6%	<0.001
Hypertension (%)	25.3%	38.7%	58.6%	<0.001	23.4%	42.4%	67.3%	<0.001	17.6%	24.8%	30.8%	38.7%	<0.001
TG (mmol/L)	1.7 (1.0)	1.9 (1.1)	2.3 (1.4)	<0.001	1.7 (1.0)	2.0 (1.1)	2.3 (1.4)	<0.001	0.8 (0.2)	1.3 (0.2)	1.8 (0.3)	3.1 (1.1)	<0.001
HDL (mmol/L)	1.5 (0.4)	1.4 (0.4)	1.3 (0.4)	<0.001	1.5 (0.4)	1.4 (0.4)	1.2 (0.3)	<0.001	1.7 (0.4)	1.5 (0.4)	1.4 (0.3)	1.2 (0.3)	<0.001
LDL (mmol/L)	3.6 (0.9)	3.5 (0.9)	3.1 (0.9)	<0.001	3.6 (0.8)	3.6 (1.0)	2.9 (0.9)	<0.001	3.2 (0.7)	3.5 (0.8)	3.7 (0.9)	3.8 (0.9)	<0.001
BMI (kg/m^2)	27.1 (4.6)	28.6 (5.2)	30.7 (5.9)	<0.001	26.9 (4.4)	29.2 (5.3)	31.7 (5.9)	<0.001	25.2 (4.0)	26.8 (4.5)	28.2 (4.7)	29.6 (4.8)	<0.001
CRP (mg/L)	2.5 (4.1)	3.0 (4.9)	3.8 (5.5)	<0.001	2.3 (4.0)	3.5 (5.2)	4.1 (5.6)	<0.001	1.9 (4.1)	2.4 (4.4)	2.8 (4.4)	3.1 (4.1)	<0.001

Mean (SD) values and percentages are reported for continuous and categorical variables, respectively.
BMI, body mass index; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TyG index, triglyceride-glucose index; UKB, UK Biobank.

In the UKB cohort, 28,992 deaths (5.66 per 1,000 person-years) occurred during a median follow-up of 13.95 years (IQR: 13.21–14.69 years). Of those, 6,632 (22.88%) died of CVD, with a mortality rate of 1.29 per 1,000 person-years; 13,054 (45.03%) died of cancer, with a mortality of 2.55 per 1,000 person-years; and 9306 (32.10%) died of other causes. Those who died of CVD were older than those who died of cancer (70.76 [7.57] vs. 70.13 [7.13] years, $p < 0.001$). Participants with higher glycemic levels had a higher risk of all-cause mortality. The cumulative all-cause mortality was the highest in participants with T2DM, followed by those with prediabetes, as compared with those with normal glucose measure. Participants with the top quartile of the TyG index had the highest risk of all-cause mortality. After the multivariable adjustment in the Cox model, FPG ≥5.6 mmol/L, HbA1c ≥ 5.7%, TyG index< 8.31 or ≥9.08 was associated with increased risks of all-cause, CVD-related, and cancer-related mortalities (Table 3; Tables S1 and S2). The multivariable Cox regression analysis indicated that higher glycemic measures,

Table 3. The risk of all-cause mortality according to baseline glycemic measures in cohort participants

Variable	Persons at risk	Death cases	Person-years	Mortality (1/1000)	Univariable analysis HR (95% CI)	*p*	Multivariable analysis[a] HR (95% CI)	*p*
The Shanghai cohort								
FPG (mmol/L)								
<5.6	5,360	387	54,930	7.05	Ref.		Ref.	
5.6–6.9	2,882	330	29,177	11.31	1.62 (1.40–1.87)	<0.001	1.14 (0.99–1.33)	0.074
≥7.0	1,206	225	11,787	19.09	2.77 (2.35–3.26)	<0.001	1.70 (1.44–2.00)	<0.001
HbA1c (%)								
<5.7	6,054	476	61,941	7.68	Ref.		Ref.	
5.7–6.4	2,091	229	21,190	10.81	1.41 (1.21–1.66)	0.001	1.02 (0.87–1.20)	0.785
≥6.5	1,303	237	12,763	18.57	2.46 (2.11–2.88)	<0.001	1.52 (1.30–1.78)	<0.001
TyG index								
Q2 (8.33–8.72)	2,342	243	23,779	10.22	Ref.		Ref.	
Q1 (<8.33)	2,408	182	24,651	7.38	0.73 (0.60–0.88)	0.001	0.95 (0.79–1.16)	0.629
Q3 (8.73–9.16)	2,339	234	23,747	9.85	0.97 (0.81–1.16)	0.716	0.86 (0.72–1.03)	0.100
Q4 (≥9.17)	2,359	283	23,717	11.93	1.18 (0.99–1.40)	0.062	1.13 (0.96–1.35)	0.150
The UKB cohort								
FPG (mmol/L)								
<5.6	318,994	22,255	4,375,483	5.09	Ref.		Ref.	
5.6–6.9	41,957	4,274	564,680	7.57	1.51 (1.46–1.56)	<0.001	1.13 (1.09–1.17)	<0.001
≥7.0	13,841	2,463	182,187	13.52	2.71 (2.60–2.82)	<0.001	1.64 (1.57–1.71)	<0.001
HbA1c (%)								
<5.7	303,214	19,248	4,167,723	4.62	Ref.		Ref.	
5.7–6.4	57,029	6,803	765,733	8.88	1.95 (1.90–2.00)	<0.001	1.19 (1.15–1.22)	<0.001
≥6.5	14,549	2,941	188,894	15.57	3.47 (3.34–3.60)	<0.001	1.76 (1.68–1.83)	<0.001
TyG index								
Q2 (8.31–8.67)	93,478	6,589	1,279,159	5.15	Ref.		Ref.	
Q1 (<8.31)	92,728	5,344	1,278,904	4.18	1.00 (0.96–1.03)	0.797	1.10 (1.06–1.14)	<0.001
Q3 (8.68–9.07)	94,421	7,711	1,287,247	5.99	1.10 (1.06–1.13)	<0.001	0.99 (0.96–1.03)	0.719
Q4 (≥9.08)	94,165	9,348	1,277,041	7.32	1.36 (1.31–1.40)	<0.001	1.07 (1.03–1.10)	<0.001

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HR, Hazard ratio; TyG index, triglyceride-glucose index; UKB, UK Biobank.
[a]In the Shanghai cohort, the risk was adjusted for age, sex, rural/urban, marriage status, education, current smoking, alcohol intake, physical activity, body mass index, hypertension, dyslipidemia, and C-reactive protein. In the UKB cohort, the risk was adjusted for age, sex, current smoking, alcohol intake, body mass index, hypertension, and C-reactive protein.

older age, male, current smoking, higher BMI, hypertension, and higher circulating level of CRP independently increased the risk of all-cause, CVD-related, and cancer-related mortalities (Tables S3, S4, and S5).

Effects of three glycemic measures on the risks of all-cause and cause-specific mortalities using the restricted cubic spline regression adjusted for covariates

In the Shanghai cohort, the risks of all-cause mortality increased with increasing levels of FPG and HbA1c; however, the U-shaped association of the TyG index with all-cause mortality was evident. Non-linear associations of TyG index levels with all-cause mortality were demonstrated after the multivariable adjustments in the Cox model (Figure 1). Similar associations were also observed between each of the three glycemic measurements with the risk of CVD-related mortality; however, the risk of cancer-related mortality did not increase significantly with increasing levels of FPG, HbA1c, and TyG index. The U-shaped association of the TyG index with the risk of cancer-related mortality was marginally significant ($P_{non\text{-}linear}$ = 0.047) (Figures S2 and S3).

In the UKB cohort, higher serum levels of FPG and HbA1c increased the risks of all-cause, CVD-related, and cancer-related mortalities; furthermore, the U-shaped association of the TyG index with the risks of all-cause, CVD-related, cancer-related mortalities were significant. The U-shaped association of the TyG index with the risk of cancer-related mortality was more apparent in the UKB cohort than in the Shanghai cohort, possibly because of the different sample size (Figure 1; Figures S2 and S3).

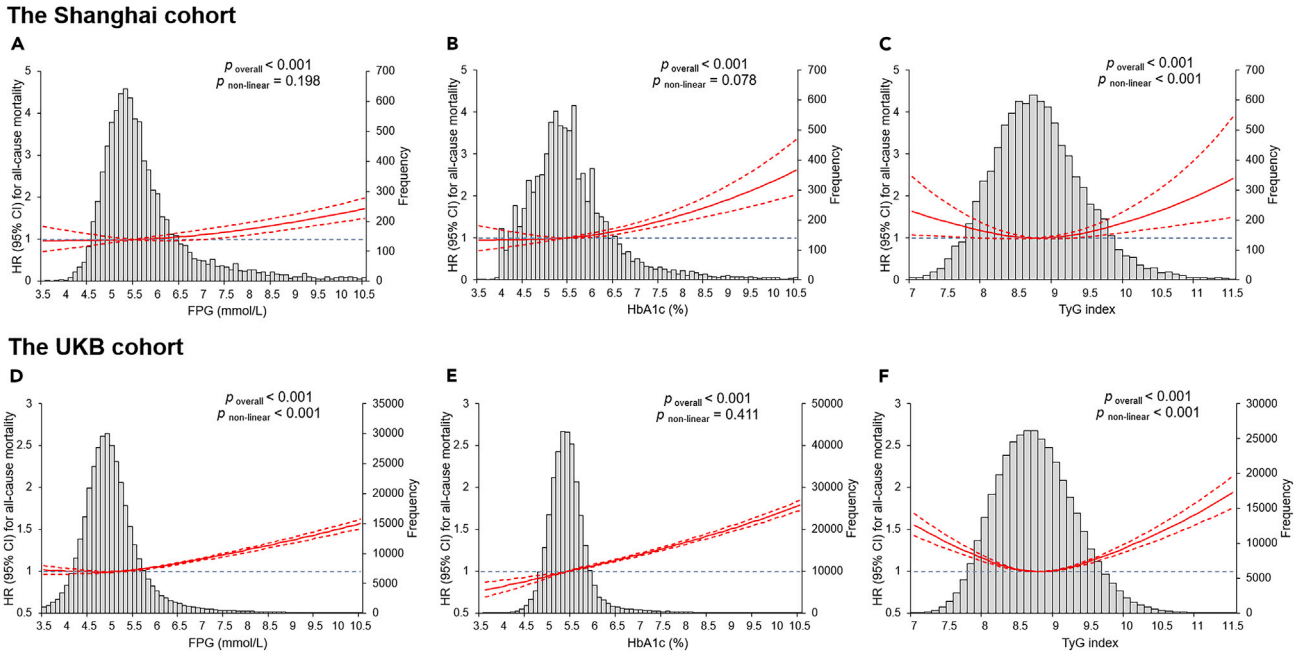

Figure 1. Associations of three glycemic measures with the risks of all-cause mortality according to restricted cubic spline regression in the Shanghai and UKB cohorts

The associations of FPG, HbA1c, and TyG index with all-cause mortality in two cohorts were shown in (A–C), and (D–F) respectively. HR in the Shanghai cohort was adjusted for age, sex, rural/urban, marriage status, education, current smoking, alcohol intake, physical activity, body mass index, hypertension, dyslipidemia, and C-reactive protein. Reference was set at the median glycemic level (FPG, 5.47 mmol/L; HbA1c, 5.4%; TyG index, 8.73). HR in the UKB cohort was adjusted for age, sex, current smoking, alcohol intake, body mass index, hypertension, and C-reactive protein. Reference was set at the median glycemic level (FPG, 4.93 mmol/L; HbA1c, 5.4%; TyG index, 8.68). Knots were set at the 5th, 50th, and 95th percentile. The bar graph shows the distribution of glycemic measures among study participants. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HR, Hazard ratio; TyG index, triglyceride-glucose index; UKB, UK Biobank.

Subgroup analyses

In the Shanghai cohort, participants were stratified into FPG ≥7.0 mmol/L only, HbA1c ≥ 6.5% only, TyG index ≥9.17 only, and those with combined two or all of the three elevated glycemic measures. The multivariable Cox regression analysis demonstrated that, as compared with participants with FPG <7.0 mmol/L, HbA1c < 6.5%, and TyG index <9.17 at baseline, The risk of all-cause mortality was significantly higher in participants with combined elevated FPG and HbA1c, combined elevated FPG and TyG index, and those with combined all three elevated glycemic measures. The risk of CVD-related mortality was significantly higher in participants with combined all three elevated glycemic measures, while the risk of cancer-related mortality was significantly higher in participants with combined elevated FPG and HbA1c (Tables S6–S8). The risks of all-cause and cause-specific mortalities in the participants with FPG-defined prediabetes, HbA1c-defined prediabetes, FPG- and HbA1c-defined prediabetes, FPG-defined T2DM, HbA1c-defined T2DM, and FPG- and HbA1c-defined T2DM were compared to the mortalities of those with FPG- and HbA1c-defined normal glucose tolerance. It was found that the risk of all-cause mortality was significantly higher in those with FPG-defined T2DM and FPG- and HbA1c-defined T2DM; while the risk of CVD-related mortality was significantly higher in those with FPG- and HbA1c-defined prediabetes, HbA1c-defined T2DM, and FPG- and HbA1c-defined T2DM, after multivariable adjustment in the Cox model (Tables S9–S11).

In the UKB cohort, the multivariable Cox regression analysis demonstrated that the risks of all-cause and CVD-related mortalities were significantly higher in those with elevated FPG or HbA1c, and those with combined two or three elevated glycemic measures, as compared with participants with FPG <7.0 mmol/L, HbA1c < 6.5%, and TyG index <9.17 at baseline, except for those with FPG <7.0 mmol/L, HbA1c < 6.5% and TyG index ≥9.08. Interestingly, the risk of cancer-related mortality was significantly higher in those with elevated FPG, combined elevated FPG and TyG index, combined elevated HbA1c and TyG index, and combined all three elevated glycemic measures (Tables S6–S8). The risk of all-cause mortality was significantly higher in those with FPG-defined prediabetes, HbA1c-defined prediabetes, FPG- and HbA1c-defined prediabetes, FPG-defined T2DM, HbA1c-defined T2DM, and FPG- and HbA1c-defined T2DM. The risks of CVD-related and cancer-related mortalities were significantly higher in those with HbA1c-defined prediabetes, FPG- and HbA1c-defined prediabetes, FPG-defined T2DM, HbA1c-defined T2DM, and FPG- and HbA1c-defined T2DM (Tables S9–S11).

The effect of glycemic measures on the prediction of all-cause and cause-specific mortalities

In the Shanghai cohort, the C-index (95% CI) of the predicting models constructed with conventional risk factors (age, adverse marriage status, current smoking, and CRP) (conventional model) were 0.834 (0.821–0.846) for all-cause mortality, 0.899 (0.823–0.908) for CVD-related

Table 4. Improvement in predicting all-cause mortality by adding glycemic measures to conventional risk factors in cohort participants

	C-index (95% CI)	ΔC statistic (95% CI)	IDI, % (95% CI)	NRI, % (95% CI)
The Shanghai cohort				
Conventional risk factors	0.834 (0.821–0.846)	Ref.	Ref.	Ref.
Plus FPG	0.838 (0.826–0.850)	0.004 (0.002–0.008)*	0.657 (0.172–1.114)*	23.237 (17.477–30.212)*
Plus HbA1c	0.838 (0.825–0.849)	0.004 (0.002–0.007)*	0.587 (0.195–1.067)*	18.042 (12.798–29.293)*
Plus TyG index	0.834 (0.824–0.848)	0.000 (0.000–0.007)	0.029 (−0.009–1.009)	14.126 (8.594–28.971)*
The UKB cohort				
Conventional risk factors	0.755 (0.744–0.765)	Ref.	Ref.	Ref.
Plus FPG	0.757 (0.746–0.767)	0.002 (0.001–0.007)*	0.139 (0.121–0.165)*	2.421 (0.891–3.865)*
Plus HbA1c	0.757 (0.746–0.767)	0.002 (0.001–0.007)*	0.055 (0.041–0.157)	4.411 (1.109–5.731)*
Plus TyG index	0.755 (0.744–0.765)	0.000 (−0.001–0.001)	−0.004 (−0.005–0.154)	5.780 (1.211–6.981)*

*$p < 0.05$.

Conventional risk factors included age, marriage status, current smoking, and C-reactive protein in Shanghai cohort; age, sex, current smoking, alcohol intake, body mass index, hypertension, and C-reactive protein in the UKB cohort.

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IDI, Integrated Discrimination Improvement; NRI, Net Reclassification Improvement; TyG index, triglyceride-glucose index; UKB, UK Biobank.

mortality, and 0.778 (0.754–0.797) for cancer-related mortality, respectively. For the prediction of all-cause mortality, FPG or HbA1c slightly but significantly increased the C-index, Integrated Discrimination Improvement (IDI), and Net Reclassification Improvement (NRI) in the conventional model, while the TyG index significantly increased NRI in the conventional model. FPG and HbA1c yielded similar improvements. For the prediction of CVD-related mortality, FPG or HbA1c slightly but significantly increased the C-index, IDI, and NRI in the conventional model, while the TyG index yielded little improvement. Adding the TyG index significantly increased IDI for the prediction of cancer-related mortality, whereas FPG or HbA1c did not significantly improve the model discrimination (Table 4; Tables S12 and S13).

In the UKB cohort, the C-index (95% CI) of the predicting models constructed with conventional risk factors (age, sex, current smoking, alcohol intake, BMI, hypertension, and CRP) were 0.755 (0.744–0.765) for all-cause mortality, 0.796 (0.775–0.816) for CVD-related mortality, and 0.727 (0.711–0.743) for cancer-related mortality, respectively. For predicting all-cause and CVD-related mortalities, FPG significantly increased the C-index, IDI, and NRI, HbA1c significantly increased the C-index and NRI, and TyG index significantly increased NRI in the conventional model. FPG and HbA1c yielded similar improvement in the discrimination. FPG, HbA1c, or TyG index did not significantly improve the discrimination for predicting cancer-related mortality in the conventional model (Table 4; Tables S12 and S13).

DISCUSSION

In this two-cohort study with participants of different human races, the effects of three glycemic measures on all-cause and major cause-specific mortalities were systemically evaluated. The scientific and medical issues addressed consistently in both cohorts are: (i) the three glycemic parameters increased consecutively with age, BMI, smoking, alcohol intake, hypertension, dyslipidemia, and systemic inflammation; (ii) FPG ≥5.6 mmol/L, HbA1c ≥ 5.7%, TyG index <8.31 or ≥9.08 increased the risks of all-cause and CVD-related mortalities; (iii) the U-shaped association of the TyG index with the risks of all-cause, CVD-related, and cancer-related mortalities were significant; (iv) the risk of all-cause mortality was significantly higher in those with FPG-defined T2DM and FPG- and HbA1c-defined T2DM; while the risk of CVD-related mortality was significantly higher in those with FPG- and HbA1c-defined prediabetes, HbA1c-defined T2DM, and FPG- and HbA1c-defined T2DM; (v) FPG or HbA1c increased the power of conventional risk model for the prediction of all-cause and CVD-related mortalities, rather than cancer-related mortality in both cohorts. The prevention and control of abnormalities in the three glycemic measures via public health intervention should be important in preventing immature death for all people worldwide in the era of the sedentary behavior epidemic.

The study population in the Shanghai cohort was randomly recruited from Pudong New Area, the biggest district with urban and rural Chinese populations at various levels of socioeconomic status in Shanghai, China, which is highly representative. The levels of FPG, HbA1c, and TG were simultaneously detected at baseline, with strict quality controls. Therefore, the effects of glycemic measures on all-cause and cause-specific mortality are accurate. The UKB cohort study is a well-established nationwide cohort, the large sample size also allows us to perform stratified analyses with sufficient statistical power. The findings in both cohorts are generally consistent; however, there are a few differences. The conventional risk factors that independently increased the risk of all-cause mortality were somehow different although age, current smoking, and CRP kept consistent in the two cohorts. TyG index at Q4 (≥9.08) was independently associated with increased risks of all-cause, CVD-related, and cancer-related mortalities, whereas this effect is generally weak in the UKB cohort, with an HR ranging from 1.07 to 1.11. This effect is not evident in the Shanghai cohort. The inconsistencies are possibly due to big differences in sample size, rather than participants of different races, between the two cohorts. We believe that the two cohort studies are mutually validating. The outcomes of this study can be generalized to the general population worldwide.

This study indicates that elevated FPG and HbA1c levels are significantly associated with higher risks of all-cause mortality, especially CVD-related mortality. FPG and HbA1c represent different conditions in the process of glucose metabolism. FPG reflects hepatic glucose production in the fasting state, while HbA1c encompasses glycemic levels both in the fasting and post-prandial state.[12] As a fairly crude measurement of glycemic control, HbA1c reflects the average blood glucose concentrations over the preceding 2 to 3 months, therefore often fails to properly account for extreme glucose values and short-term glucose excursions.[13] Compared to FPG, HbA1c is susceptible to false elevations and reductions secondary to various medical comorbidities[14] and prone to be distorted in subjects with sickle cell trait, chronic malaria, hemolytic anemia, and other anemias.[3] Our data are partially consistent with several previous studies. A nationwide cohort study in Korea indicates all-cause mortality increases with an increase in FPG level and a J-shaped relationship exists between FPG levels and all-cause mortality.[5] A longitudinal study[15] in Australian women indicates that T2DM, rather than FPG-defined prediabetes, increases the risk of all-cause mortality. U-shaped relationship is found between FPG or HbA1c levels and the risk of all-cause mortality.[16] It has been demonstrated that low and high HbA1c are associated with increased all-cause mortality among older patients with insulin-treated T2DM.[17] A study using the US national database[4] indicates that low HbA1c is associated with an increased risk of all-cause mortality but not CVD-related mortality among residents without diabetes. The increased mortality risk in old individuals with lower FPG or HbA1c is also explained by multiple comorbidities.[18] Here, we do not find the U-shaped relationship of FPG levels and HbA1c with the risks of all-cause, CVD-related, and cancer-related mortalities, possibly because of differences in age and comorbidities among study populations. In a cohort of Japanese workers,[19] FPG- and HbA1c-defined prediabetes are both associated with increased risks of all-cause and cancer-related mortalities. Here, the association of FPG- and HbA1c-defined prediabetes with cancer-related mortality is weak, possibly because of the difference in age of the study population. The Japanese worker cohort participants are younger (42.0–52.1 years on average) and have a higher proportion of males (81.1%–94.1%) than do the participants (57.9 years on average, 37.8% males) in the Shanghai cohort. Residents who died of cancer are much younger and more males than those died of CVD.[20] Thus, the association of FPG and HbA1c with the risk of all-cause and cause-specific mortality might be related to the characteristics of the study population such as age, sex, multiple comorbidities, and prophylactic options.

In contrast to FPG and HbA1c, we observed a U-shaped association of the TyG index with all-cause and cause-specific mortalities. As a surrogate marker of insulin resistance, the TyG index reflects lipotoxicity and glucotoxicity.[21] A Chinese study[22] indicates that elevated TyG index significantly increases stroke recurrence and all-cause mortality. In the US population, the elevated TyG index is associated with all-cause and CVD-related mortalities.[23] It is understandable that the elevated TyG index is associated with a higher risk of CVD-related mortality, because elevated TyG index is considered as an effective marker for predicting adverse cardiovascular outcomes including coronary artery calcification, cardiac and cerebral events, ischemic stroke, and myocardial infarction.[24,25] Interestingly, declined TyG index is associated with increased risks of all-cause, CVD-related, and cancer-related mortalities. It has been demonstrated that the elevated TyG index is associated with an increased risk of obesity-related cancers.[10,11,26] However, the relationship of low TyG index with cancer is not reported. A cohort study[27] has demonstrated that TG < 1.70 mmol/L is associated with increased risk of cancer in patients with T2DM and in statin nonusers. The mechanism by which lower and higher TyG index increase the risk of cancer-related mortality remains to be investigated.

Our data of stratified analyses indicate that elevated FPG or HbA1c, and those with combined two or three elevated glycemic measures better predict the risks of all-cause and CVD-related mortalities, while cancer-related mortality was significantly higher in participants with elevated FPG, combined elevated FPG and TyG index, combined elevated HbA1c and TyG index, and those with combined all three elevated glycemic measures. Recent studies have demonstrated that greater variability of FPG is associated with increased risks of all-cause and cancer-specific mortalities.[28] HbA1c variability has a consistent dose-response relationship with all-cause mortality, especially non-cancer-related mortality including CVD-related mortality.[29,30] Increase in circulating HbA1c is independently associated with CVD, but the association of HbA1c with cancer is weak.[28–30] These data imply that CVD-related mortality is affected by both short-term and long-term glucose excursions, cancer-related mortality is more affected by short-term glucose excursions than long-term glycemic variability. A low-carbohydrate dietary intervention can lead to a greater 6-month reduction in HbA1c, FPG, and body weight.[31] FPG, HbA1c, and TyG index represent different pathological abnormalities in glucose metabolism, possibly reflecting the common and diverse mechanisms by which CVD and cancer develop. Healthy lifestyle such as the low-carbohydrate diet may help decrease the risks of CVD and cancer-related mortalities.

Our analyses indicate that the associations of the three glycemic measures with the risk of CVD-related mortality are stronger than those with cancer-related mortality. From the baseline data, each of the three glycemic measures is correlated to hypertension, dyslipidemia, BMI, and CRP. Metabolic syndrome is independently associated with CVD-related and all-cause mortalities.[32] As a biomarker of inflammation, CRP is established as an independent risk factor for CVD.[33] Thus, metabolic syndrome and systemic inflammation are key risk factors of CVD-related mortality. Here, we identified that current smoking and adverse marriage status independently increased CVD-related mortality. Smoking and high stress have been proven to increase the risk of CVD-related mortality.[34] Thus, family care and smoking cessation are important in preventing CVD death. We also found that age, current smoking, and <9 years of education independently increased cancer death, indicating that the ability of obtaining knowledge on cancer prevention is important in preventing cancer death.

Conclusions

Elevated FPG, HbA1c, and TyG index are associated with increased risks of all-cause and CVD-related mortalities. Adding FPG and HbA1c to the prognostic model constructed with conventional risk factors offers an additional benefit for the prediction of all-cause and CVD-related mortalities. These findings support the potential role of FPG and HbA1c as major predictors of all-cause and CVD-related mortalities. Risk

assessments of FPG and HbA1c may be beneficial for the management and interventions of high-risk population to prevent all-cause and CVD-related mortalities.

Limitations of the study

This study had several limitations. First, the follow-up period was relatively short. Second, due to ethical considerations, individuals with a history of T2DM (n = 1570) in the Shanghai cohort did not complete OGTT at baseline, leading to failure in comparing the predictive value of 2-h prandial glucose with other glycemic measures. Third, we did not analyze the glycemic measure variation during follow-up. Fourth, dietary habits, social and psychological factors were not included in the baseline survey.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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AUTHOR CONTRIBUTIONS

JK, XR, and GC had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and contribute equally to this work.

Concept and design: JK, XR, and GC.
Acquisition, analysis, or interpretation of data: JK, XR, XL, KW, HQ, XW, ZL, WL, XT, YD, and GC.
Drafting of the article: JK, GC.
Critical revision of the article for important intellectual content: All authors.
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DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Shanghai cohort	This study	N/A
UK Biobank	https://www.ukbiobank.ac.uk	application number 101971
Software and algorithms		
SPSS version 22.0	IBM Corp.	N/A
SAS version 9.4	SAS Institute Inc.	N/A

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Guangwen Cao (gcao@smmu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The dataset of Shanghai cohort will be shared by the lead contact upon reasonable request.
- The UK Biobank dataset was downloaded from https://www.ukbiobank.ac.uk.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study population

The community-based prospective cohort study conducted in Shanghai, China (the Shanghai cohort) was performed in Pudong New Area, Shanghai, China. Baseline participant recruitment and data collection using questionnaire, physical examination, and laboratory tests were carried out between January 2013 and July 2013.[35] Of 10,657 residents participated in the baseline survey, 1209 were excluded due to lack of permanent residency (difficult to follow-up) and complete questionnaire and/or physical examination (Figure S1A). The remaining 9,448 (3,575 men and 5,873 women) were successfully followed-up until the date of death, or September 30, 2023. Research ethics approval was obtained from the Center for Disease Control and Prevention of the Pudong New Area, Shanghai, China. All participants were self-reported Han Chinese. Each participant provided a written consent.

In total, 502,370 participants aged 37 to 73 years were recruited in the UKB cohort from 22 assessment centers across England, Scotland, and Wales between 2006 and 2010.[36] Of the participants, we excluded those without death information (n=1,297), glycemic measures (n=35,034), and other covariates (n=92,544). Overall, 374,792 participants were finally included in the analysis (Figure S1B). The UKB cohort was approved by the North West Multi-Centre Research Ethics Committee, National Information Governance Board for Health and Social Care in England and Wales, and Community Health Index Advisory Group in Scotland. This study was officially registered with the UK Biobanking Resource Center under application number 101971.

METHOD DETAILS

Baseline measurements

In the Shanghai cohort, glucose, lipids, and CRP levels were measured using a HITACHI 7170A automatic biochemical analyzer. Current smoking was defined as smoking at least one cigarette a day in the past 6 months. Alcohol intake was defined as consuming alcohol at least three times per week in the past 6 months. Physical activity was defined as participating in athletic activity for at least once per week in the past 5 years. History of hypertension was defined as blood pressure ≥140/90mmHg or taking a blood pressure-lowering medication. History of dyslipidemia was defined as plasma TG ≥2.26mmol/L, LDL ≥4.13mmol/L, HDL <1.03mmol/L or taking a cholesterol lowering medication. In the UKB cohort, Current smoking was defined as smoking regularly. Alcohol intake was defined as consuming alcohol at least once or twice a

week currently. History of hypertension was collected using the questionnaire. TyG index was calculated as Ln [fasting TG (mg/dL) × FPG (mg/dL)/2].[6] BMI was calculated as weight (kg)/height (m^2).

Outcomes

In the Shanghai cohort, the primary outcomes included all-cause, CVD-related, and cancer-related mortalities derived from the vital registration system, covering the fully registered permanent residents of Shanghai, China. Death causes were coded according to the International Classification of Diseases, Tenth Revision (ICD-10): codes I00 to I99 for CVD death, and C00 to D48 for cancer death. In the UKB cohort, the primary outcomes were all-cause, CVD-related, and cancer-related mortalities. Data of deaths were obtained through death certificates held within the NHS Information Centre (England and Wales) and the NHS Central Register (Scotland) to 30 November 2022. Outcomes were classified using ICD-9 and ICD-10 codes.

QUANTIFICATION AND STATISTICAL ANALYSIS

Continuous variables were presented as mean (standard deviation) and were compared using the One-way ANOVA test or Kruskal-Wallis test. Categorical variables were presented as number (percentage) and compared using the Pearson χ^2 test. We used the Cox proportional hazard model to estimate the association of glycemic measures and other variables with all-cause or cause-specific mortality. Levels of FPG and HbA1c were categorized using the cutoffs recommended by the 2020 ADA criteria.[12] Participants with FPG $\geq$ 7.0 mmol/L or HbA1c $\geq$ 6.5% were categorized as T2DM, Participants with FPG between 5.6 and 6.9 mmol/L or HbA1c between 5.7% and 6.4% were categorized as prediabetes. Participants with FPG < 5.6 mmol/L or HbA1c < 5.7% were categorized as normal glucose tolerance. Level of TyG index was categorized using the quartiles (< 8.33, 8.33–8.72, 8.73–9.16, and $\geq$ 9.17 in the Shanghai cohort, < 8.31, 8.31–8.67, 8.68–9.07, and $\geq$ 9.08 in the UKB cohort). The glycemic levels, together with age, sex, rural or urban areas, marriage status, current smoking, alcohol intake, physical activity, BMI, hypertension, dyslipidemia, and CRP were introduced into the Cox model in the Shanghai cohort to obtain factors independently associated with mortality. In the UKB cohort, the associations of the glycemic levels with mortality were assessed in the Cox model. The significant factors in the univariable Cox analysis were introduced into the multivariable Cox model, adjusted for age, sex, current smoking, alcohol intake, BMI, hypertension, and CRP, to determine the factors independently contributing to all-cause and cause-specific mortalities, respectively. We used restricted cubic splines in the Cox models to test whether a non-linear association existed between glycemic measures as a continuous variable and the risk of all-cause or cause-specific mortality, with the medians of FPG (5.47 mmol/L), HbA1c (5.4%), and TyG index (8.73) as the reference values. Differences in the area under the receiver operating characteristic curve (ΔC statistic), IDI, and NRI were applied to analyze the performance of the multivariable conventional risk factors together with or without each glycemic measure in predicting all-cause or cause-specific mortality in the following 10 years.[37] The ΔC statistic measured the improvement in concordance between model-based risk estimates and observed events when a new marker was added to an existing prediction model. The IDI measured the improvement in average sensitivity without sacrificing average specificity. The NRI measured the improvement in correctness of reclassification of subjects. Statistical analyses were two-side and performed using SPSS version 22.0 and SAS version 9.4. A p value of <0.05 was considered statistical significance.