Predictive Value of Fasting Glucose, Postload Glucose, and Hemoglobin A_{1c} on Risk of Diabetes and Complications in Chinese Adults

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Jieli Lu,[1] Jiang He,[2] Mian Li,[1] Xulei Tang,[3] Ruying Hu,[4] Lixin Shi,[5] Qing Su,[6] Kui Peng,[1] Min Xu,[1] Yu Xu,[1] Yuhong Chen,[1] Xuefeng Yu,[7] Li Yan,[8] Tiange Wang,[1] Zhiyun Zhao,[1] Guijun Qin,[9] Qin Wan,[10] Gang Chen,[11] Meng Dai,[1] Di Zhang,[1] Zhengnan Gao,[12] Guixia Wang,[13] Feixia Shen,[14] Zuojie Luo,[15] Yingfen Qin,[15] Li Chen,[16] Yanan Huo,[17] Qiang Li,[18] Zhen Ye,[4] Yinfei Zhang,[19] Rui Du,[1] Di Cheng,[1] Chao Liu,[20] Youmin Wang,[21] Shengli Wu,[22] Tao Yang,[23] Huacong Deng,[24] Donghui Li,[25] Shenghan Lai,[26] Zachary T. Bloomgarden,[27] Lulu Chen,[28] Jiajun Zhao,[29] Yiming Mu,[30] Guang Ning,[1] Weiqing Wang,[1] and Yufang Bi,[1] for the 4C Study Group

OBJECTIVE

Uncertainty remains regarding the predictive value of various glycemic measures as they relate to the risk of diabetes and its complications. Using the cutoffs recommended by the American Diabetes Association's 2010 criteria, we determined the associations of fasting plasma glucose (FPG), 2-h postload glucose (2h-PG), and HbA_{1c} with the outcomes.

RESEARCH DESIGN AND METHODS

Baseline medical history, FPG, 2h-PG, and HbA_{1c} were obtained from a population-based cohort of 193,846 adults aged ≥40 years in China during 2011–2012. A follow-up visit was conducted during 2014–2016 in order to assess incident diabetes, cardiovascular disease (CVD), cancer, and mortality.

RESULTS

We documented 8,063 cases of diabetes, 3,014 CVD-related events, 1,624 cases of cancer, and 2,409 deaths during up to 5 years of follow-up. Multivariable-adjusted risk ratios (95% CIs) of diabetes associated with prediabetes based on FPG of 100–125 mg/dL, 2h-PG of 140–199 mg/dL, or HbA_{1c} of 5.7–6.4% (39–47 mmol/mol) were 1.60 (1.43–1.79), 2.72 (2.43–3.04), and 1.49 (1.36–1.62), respectively. Restricted cubic spline analyses suggested J-shaped associations of FPG, 2h-PG, and HbA_{1c} levels with CVD, cancer, and mortality. Multivariable-adjusted hazard ratios (95% CIs) associated with untreated diabetes based on FPG ≥126 mg/dL, 2h-PG ≥200 mg/dL, or HbA_{1c} ≥6.5% (48 mmol/mol) were 1.18 (1.05–1.33), 1.31 (1.18–1.45), and 1.20 (1.07–1.34) for CVD; 1.10 (0.92–1.32), 1.44 (1.25–1.67), and 1.08 (0.92–1.28) for cancer; and 1.37 (1.20–1.57), 1.57 (1.41–1.76), and 1.33 (1.17–1.52) for mortality, respectively. 2h-PG remained significantly associated with outcomes in models including FPG and HbA_{1c} as spline terms. Furthermore, 2h-PG significantly improved the ability of the C statistic to predict diabetes, CVD, and mortality.

CONCLUSIONS

2h-PG remains independently predictive of outcomes in models including FPG and HbA_{1c}. Therefore, in addition to FPG and HbA_{1c}, routine testing of 2h-PG should be considered in order to better assess the risks of outcomes.

[1]Shanghai National Clinical Research Center for Endocrine and Metabolic Diseases, Key Laboratory for Endocrine Tumors of Ministry of Shanghai, Shanghai Institute for Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[2]Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA
[3]The First Hospital of Lanzhou University, Lanzhou, China
[4]Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China
[5]Affiliated Hospital of Guiyang Medical College, Guiyang, China
[6]Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China
[7]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[8]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
[9]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[10]The Affiliated Hospital of Southwest Medical University, Luzhou, China
[11]Fujian Provincial Hospital, Fujian Medical University, Fuzhou, China
[12]Dalian Municipal Central Hospital, Dalian, China
[13]The First Hospital of Jilin University, Changchun, China

Diabetes has become a major cause of death and disability worldwide (1). The prevalence of diabetes has more than quadrupled in China during the past two decades (2,3). It has been estimated that 113.9 million Chinese adults had diabetes and 493.4 million had prediabetes in 2010 (3).

Fasting plasma glucose (FPG), 2-h postload glucose (2h-PG), and HbA_{1c} have been used to test glycemia, but uncertainty remains regarding their predictive utility in determining the risk of incident diabetes, cardiovascular disease (CVD), cancer, and mortality (4–6). Only a few prospective studies have compared all three glycemic measures in the same participants, and they reported conflicting findings (7–9). The Atherosclerosis Risk in Communities (ARIC) study showed that prediabetes defined on the basis of HbA_{1c} provided better risk discrimination for clinical complications and all-cause mortality (9). Other studies, however, reported that 2h-PG better predicted CVD and mortality (7,8). These studies all had limited sample sizes. The values of the three glycemic measures in predicting risk of diabetes were not directly compared. In addition, the three glycemic measures were obtained from the ARIC study participants at different visits (9).

Using the established cutoffs for prediabetes and diabetes recommended by American Diabetes Association (ADA) 2010 criteria, we compared the associations of FPG, 2h-PG, and HbA_{1c} levels with the incidences of diabetes, CVD, and cancer, and all-cause mortality, among participants from the China Cardiometabolic Disease and Cancer Cohort (4C) Study, a prospective cohort study of Chinese adults aged ≥40 years.

RESEARCH DESIGN AND METHODS

Study Participants

The 4C Study was a multicenter, population-based, prospective cohort study investigating the associations of glucose homeostasis with clinical outcomes including diabetes, CVD, cancer, and all-cause mortality.

Between 2011 and 2012, a total of 259,657 individuals aged ≥40 years were recruited from 25 communities throughout various regions of China in order to participate in the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal (REACTION) Study (10,11). The main objectives of the REACTION Study were to demonstrate whether abnormal glucose metabolism (prediabetes and diabetes) was associated with increased risk for cancer in the Chinese population and to identify factors that modify the risk of cancer among individuals with abnormal glucose metabolism (10,11). Eligible men and women aged ≥40 years were identified from local resident registration systems. Trained community health workers visited eligible individuals' homes and invited them to participate in the study.

In 2014, funding allowed the study to do a follow-up examination visit. Because of limited funds, however, only 193,846 participants from 20 communities from various geographic regions in China, selected to represent the general population, were invited to participate. In addition, the objectives of the study were extended in order to investigate the association of glycemia measures with the incidence of diabetes, CVD, and cancer, and with mortality. Therefore, the study was renamed as the 4C Study.

The study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University. All study participants provided written informed consent.

Baseline Data Collection

The study visits took place in the mornings at local community clinics. Participants were required to fast for ≥10 h before their clinic visits. Trained study personnel used a standard questionnaire to obtain data on participants' sociodemographic information, lifestyle risk factors, and medical history. Physical activity was assessed using the International Physical Activity Questionnaire (12). Moderate and vigorous physical activity was defined as ≥150 min/week of moderate-intensity physical activity, or 75 min/week of vigorous aerobic activity, or an equivalent combination of moderate-intensity and vigorous aerobic activities (13). Trained study nurses measured body weight, height, waist circumference, and blood pressure according to a standard protocol (14). Three blood pressure measurements were obtained with participants in a seated position after 5 min of quiet rest. In addition, participants were required to avoid alcohol, cigarettes, coffee/tea, and exercise for ≥30 min before their blood pressure was measured. An automated blood pressure and pulse monitor (model HEM-752 FUZZY; OMRON, Dalian, China) was used for obtaining measurements, and one of four cuff sizes (pediatric, regular adult, large, or thigh)

[14]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[15]The First Affiliated Hospital of Guangxi Medical University, Nanning, China
[16]Qilu Hospital of Shandong University, Jinan, China
[17]Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Nanchang, China
[18]The Second Affiliated Hospital of Harbin Medical University, Harbin, China
[19]Central Hospital of Shanghai Jiading District, Shanghai, China
[20]Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing, China
[21]The First Affiliated Hospital of Anhui Medical University, Hefei, China
[22]Karamay Municipal People's Hospital, Xinjiang, China
[23]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[24]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[25]Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX
[26]Johns Hopkins University School of Medicine, Baltimore, MD
[27]Icahn School of Medicine at Mount Sinai, New York, NY
[28]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[29]Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China
[30]Chinese People's Liberation Army General Hospital, Beijing, China

Corresponding authors: Yufang Bi, byf10784@rjh.com.cn, Weiqing Wang, wqingw61@163.com, Guang Ning, gning@sibs.ac.cn, Yiming Mu, muyiming@301hospital.com.cn, Jiajun Zhao, jjzhao@medmail.com.cn, and Lulu Chen, cheria_chen@126.com

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J.L., J.H., M.L., X.T., and R.H. contributed equally to this work.

was chosen on the basis of the participant's arm circumference.

All participants underwent an oral glucose tolerance test, and plasma glucose was obtained at 0 and 2 h during the test. Plasma glucose concentrations were analyzed locally by using the glucose oxidase or the hexokinase method within 2 h after collecting the blood sample under a stringent quality control program. Previous research has shown these two methods of glucose measurement to be highly consistent (15,16). All regional laboratories passed a national standardization program and a study-specific quality assurance program. A Hemoglobin Capillary Collection System (Bio-Rad Laboratories, Hercules, CA) was used to collect capillary whole blood from a finger. Blood was shipped at 2–8°C to a certified central laboratory at Ruijin Hospital, Shanghai, China. This clinical laboratory is certificated by the U.S. National Glycohemoglobin Standardization Program and passed the Laboratory Accreditation Program of the College of American Pathologists. HbA_{1c} was determined by using high-performance liquid chromatography (VARIANT II System; Bio-Rad Laboratories). Serum insulin, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were measured at the central laboratory by using an ARCHITECT ci16200 autoanalyzer (Abbott Laboratories, Abbott Park, IL).

Follow-up and Outcome Assessment

During 2014–2016, all participants were invited to attend an in-person follow-up visit. Trained staff queried lifestyle risk factors and medical history using the same standard questionnaire as was used at baseline. Anthropometric values and blood pressure were measured, oral glucose tolerance tests performed, and blood samples obtained by using the same protocols that were used during the baseline examination. If patients were hospitalized or had visited an emergency department, trained staff used a standard form to obtain data—including medical history, physical examination findings, laboratory tests, treatments, and diagnosis at discharge—from the participants' medical records. In addition, photocopies were obtained of selected sections of a given participant's inpatient record, discharge summary, electrocardiogram, and pathology reports.

Information on vital status and clinical outcomes was collected from local death and disease registries of the National Disease Surveillance Point System and National Health Insurance System. Two members of the outcome adjudication committee independently verified each clinical event, and discrepancies were adjudicated through discussion involving other members of the committee. All members of the committee were unaware of the baseline risk factors of study participants.

Incident diabetes was defined as any one or a combination of FPG $\geq$126 mg/dL, 2h-PG $\geq$200 mg/dL, HbA_{1c} $\geq$6.5% (48 mmol/mol), or a self-reported previous diagnosis by health care professionals at a follow-up visit among participants without diabetes at baseline.

Incident CVD was defined as the first instance of myocardial infarction, stroke, hospitalization or treatment for heart failure, and cardiovascular death during follow-up. Myocardial infarction was defined by characteristic changes in levels of troponin T and the creatine kinase–MB isoform, symptoms of myocardial ischemia, changes in electrocardiogram results, or a combination of these. Stroke was defined as a fixed neurological deficit lasting $>$24 h and having a presumably vascular cause. Heart failure was identified by hospitalization, or an emergency department visit with medical therapy, for a clinical syndrome presenting with multiple signs and symptoms consistent with cardiac decompensation or inadequate cardiac pump function. Incident cancer was defined as the first occurrence of any type of cancer at any site during follow-up.

Statistical Analyses

Cumulative incidence (95% CI) of diabetes was calculated for a mean of 3.8 years' follow-up. We used relative risk regression to examine the associations between glycemic measures at baseline and risk of incident diabetes (17). We adjusted multivariable models for baseline age, sex, BMI, family history of diabetes, cigarette smoking, alcohol consumption, education, physical activity, systolic blood pressure, HDL cholesterol, LDL cholesterol, and triglycerides.

Potential nonlinear associations between the levels of glycemia and the incidence of clinical outcomes were examined with restricted cubic splines (18). Analyses adjusted for multiple variables, and the highest and lowest 0.5% was trimmed for each glycemic measure. A knot was located at the 5th, 50th, and 95th percentiles for each of the three glycemic measures. Tests for nonlinearity, which compared a model containing only the linear term with a model containing the linear and restricted cubic spline terms, were conducted by using likelihood ratio tests. If a test for nonlinearity was not significant, we conducted a test for linearity, comparing a model containing the linear term with a model containing only the covariates of interest.

We calculated incidence rate (95% CI) per 1,000 person-years, and we used Cox proportional hazards models to investigate the associations of baseline glycemic measures and subsequent CVD, cancer, and all-cause mortality (19). In the time-to-event analysis, data were censored at the time of the clinical event, death, or the end of follow-up—whichever occurred first. In addition to the aforementioned covariables, we included baseline glycemic measures as spline terms in the mutually adjusted model to compare the strength of associations with clinical outcomes.

To assess the added value of individual or a combination of glycemic measures in prediction models, we included continuous glycemic measures in the models of subsequent diabetes and categorized glycemic measures using the cutoffs recommended by the 2019 ADA criteria; these measures were added to the models of subsequent CVD, cancer, and all-cause mortality. We calculated the difference (C statistic) with or without glycemic measures, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) (20). The C statistic measures concordance between model-based risk estimates and observed events. NRI and IDI measure the incremental prognostic effect that a new biomarker will have when added to an existing prediction model. We used bootstrapping methods to obtain 95% CIs.

We used SAS version 9.2 (SAS Institute) to conduct statistical analyses and R version 3.4.2 (R Foundation for Statistical Computing) to create Cox models with restricted cubic splines.

RESULTS

Among 193,846 study participants, 170,240 (87.8%) were followed up in 2014–2016. We excluded 12,677 with

treated diabetes and 6,074 with one or more glycemic measures missing at baseline, leaving 151,489 for this analysis. Additionally, 22,632 participants with untreated diabetes at baseline and 22,364 without glucose measures at follow-up were excluded from diabetes analyses, 7,503 participants with CVD and 2,148 with cancer at baseline were excluded from the respective analyses, and 22,652 participants without follow-up data on CVD and cancer were also excluded (Supplementary Fig. 1).

Baseline characteristics of participants without treated diabetes are presented in Table 1 according to categories of glycemic measures. In addition, baseline characteristics of participants without a history of diagnosed diabetes (including treated and untreated diabetes) are reported in Supplementary Table 1. Baseline characteristics of participants who were and who were not lost to follow-up are shown in Supplementary Table 2.

Glycemic Measures and Incident Diabetes

During up to 5 years of follow-up (mean 3.8 years), 8,063 incident cases of diabetes were counted among 106,493 participants without a history of diabetes at baseline. The cumulative incidence of diabetes increased with the number of abnormal glycemic measures and was higher in individuals with isolated impaired glucose tolerance (8.8%) than in those with isolated impaired fasting glucose (5.0%) or isolated elevated HbA_{1c} (4.7%) ($P < 0.001$ for group difference). Furthermore, the incidence of diabetes was higher in individuals with impaired glucose tolerance and impaired fasting glucose (12.7%) and in those with impaired glucose tolerance and elevated HbA_{1c} (13.3%) than in those with combined impaired fasting glucose and elevated HbA_{1c} (9.2%). Individuals with three abnormal glycemic measures had the highest incidence of diabetes (21.3%) (Table 2).

After adjusting for important covariables, we found that elevated FPG, 2h-PG, and HbA_{1c} are significant predictive indicators of incident diabetes. The risk ratio (95% CI) of diabetes associated with isolated impaired glucose tolerance (2.72 [2.43–3.04]) was significantly greater than that associated with isolated impaired fasting glucose (1.60 [1.43–1.79]) or isolated elevated HbA_{1c}

Table 1—Baseline characteristics of 151,489 study participants without treated diabetes, according to plasma glucose and HbA_{1c} levels

	FPG, mg/dL				2h-PG, mg/dL				HbA_{1c}, %			
	<100	100–125	≥126	*P* value	<140	140–199	≥200	*P* value	<5.7% (39 mmol/mol)	5.7–6.4% (39–47 mmol/mol)	≥6.5% (48 mmol/mol)	*P* value
Participants	84,260 (55.6)	55,365 (36.6)	11,864 (7.8)	<0.001	96,394 (63.6)	37,784 (25.0)	17,311 (11.4)	<0.001	58,996 (39.0)	76,082 (50.2)	16,411 (10.8)	<0.001
Age, years	55.6 ± 9.2	57.7 ± 8.9	58.7 ± 8.8	<0.001	55.4 ± 8.9	58.3 ± 9.1	59.60 ± 8.9	<0.001	54.3 ± 9.1	57.8 ± 8.7	59.6 ± 8.6	<0.001
Male sex	26,003 (30.9)	20,162 (36.4)	5,187 (43.7)	<0.001	32,243 (33.5)	12,261 (32.5)	6,848 (39.6)	<0.001	20,911 (35.4)	24,517 (32.2)	5,924 (36.1)	<0.001
BMI, kg/m^2	24.2 ± 3.5	25.1 ± 3.6	26.0 ± 3.6	<0.001	24.22 ± 3.5	25.18 ± 3.6	25.82 ± 3.7	<0.001	24.0 ± 3.4	24.8 ± 3.6	26.2 ± 3.6	<0.001
High school or higher education	31,904 (37.9)	18,721 (33.8)	3,954 (33.3)	<0.001	35,562 (36.9)	13,179 (34.9)	5,838 (33.7)	0.02	21,212 (36.0)	27,697 (36.4)	5,670 (34.6)	0.10
Current cigarette smoking	12,057 (14.3)	7,772 (14.0)	2,033 (17.1)	<0.001	14,672 (15.2)	4,574 (12.1)	2,616 (15.1)	<0.001	9,065 (15.4)	10,412 (13.7)	2,385 (14.5)	<0.001
Current alcohol drinking	7,349 (8.7)	6,364 (11.5)	1,604 (13.5)	<0.001	9,620 (10.0)	3,736 (9.9)	1,961 (11.3)	<0.001	6,803 (11.5)	7,009 (9.2)	1,505 (9.2)	<0.001
Moderate and vigorous physical activity	11,221 (13.3)	7,401 (13.4)	1,411 (11.9)	0.005	12,871 (13.4)	5,072 (13.4)	2,090 (12.1)	<0.001	7,199 (12.2)	10,712 (14.1)	2,122 (12.9)	<0.001
Family history of diabetes	9,012 (10.7)	6,519 (11.8)	1,945 (16.4)	<0.001	10,034 (10.4)	4,733 (12.5)	2,709 (15.7)	<0.001	5,602 (9.5)	9,102 (12.0)	2,772 (16.9)	<0.001
Systolic blood pressure, mmHg	130.2 ± 20.4	135.7 ± 20.4	141.4 ± 20.9	<0.001	130.7 ± 20.4	135.8 ± 20.5	140.8 ± 20.8	<0.001	131.3 ± 20.7	133.2 ± 20.7	138.9 ± 20.6	<0.001
Fasting HDL cholesterol, mg/dL	53.1 ± 14.0	51.4 ± 14.1	49.1 ± 13.2	<0.001	53.3 ± 14.2	50.6 ± 13.6	49.3 ± 13.7	<0.001	53.9 ± 14.5	51.6 ± 13.8	48.4 ± 12.7	<0.001
Fasting LDL cholesterol, mg/dL	110.6 ± 33.2	113.8 ± 34.5	118.3 ± 35.9	<0.001	110.8 ± 33.3	114.2 ± 34.5	117.4 ± 35.9	<0.001	107.5 ± 32.0	114.6 ± 34.4	119.5 ± 36.2	<0.001
Fasting triglycerides, mg/dL	107.2 (78.0–153.2)	124.0 (87.7–179.8)	150.6 (104.5–223.2)	<0.001	106.3 (77.1–150.6)	131.1 (93.0–188.7)	149.7 (104.5–217.9)	<0.001	104.5 (76.2–149.7)	119.6 (85.0–171.0)	150.6 (105.4–217.5)	<0.001
FPG, mg/dL	92.0 ± 6.2	108.87 ± 6.4	160.70 ± 44.9	<0.001	97.0 ± 11.2	104.5 ± 13.7	138.1 ± 46.2	<0.001	96.3 ± 11.5	101.5 ± 13.0	139.2 ± 46.9	<0.001
2-h PG, mg/dL	119.6 ± 33.6	145.9 ± 45.7	260.4 ± 99.2	<0.001	108.4 ± 19.6	162.8 ± 16.2	268.2 ± 71.7	<0.001	119.4 ± 34.4	135.9 ± 42.2	235.7 ± 97.0	<0.001
HbA_{1c}, %	5.7 ± 0.4	5.9 ± 0.5	7.5 ± 1.8	<0.001	5.7 ± 0.5	5.9 ± 0.5	7.1 ± 1.6	<0.001	5.3 ± 0.3	6.0 ± 0.2	7.5 ± 1.5	<0.001

Values are number (percent), mean ± SD, or median (interquartile range). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

(1.49 [1.36–1.62]) (Table 2). The risk ratio associated with combined impaired glucose tolerance and either impaired fasting glucose (3.71 [3.33–4.13]) or elevated HbA_{1c} (3.87 [3.53–4.23]) was significantly greater than that associated with combined impaired fasting glucose and elevated HbA_{1c} (2.68 [2.46–2.92]). The risk ratio associated with three abnormal glycemic measures (5.84 [5.40–6.32]) was significantly greater than that for any two abnormal measures.

The multivariable-adjusted risk ratio (95% CI) of incident diabetes associated with prediabetes based on fasting glucose of 100–125 mg/dL was 2.03 (1.94–2.12); that based on 2h-PG of 140–199 mg/dL was 2.78 (2.66–2.90), and that based on HbA_{1c} of 5.7–6.4% was 1.85 (1.76–1.95) (Supplementary Table 3). When all three glycemic measures were included in the same model simultaneously, the risk ratio (95% CI) of diabetes associated with prediabetes based on 2h-PG of 140–199 mg/dL (2.20 [2.10–2.30]) was significantly greater than those associated with prediabetes based on FPG of 100–125 mg/dL (1.46 [1.40–1.53]) or elevated HbA_{1c} (1.44 [1.37–1.51]) (Supplementary Table 3). Results of a sensitivity analysis that use self-reported physician-diagnosed diabetes are shown in Supplementary Table 4; the associations between glycemic measures and incident diabetes were similar.

Glycemic Measures and CVD, Cancer, and Mortality

Among 151,489 participants not receiving antidiabetes treatment at baseline, we identified 3,014 incident cardiovascular events (450 myocardial infarctions, 1,787 strokes, 195 cases of heart failure, and 582 cardiovascular deaths), 1,624 incident cases of cancer (325 lung, 167 breast, 156 colorectal, 135 liver, 134 stomach, 83 thyroid, 57 pancreatic, and 49 esophageal cancers, and 518 cancers at other sites), and 2,409 deaths.

Multivariable-adjusted restricted cubic spline analyses suggested "J-shaped" associations of glycemic markers with CVD, cancer, and all-cause mortality. We found evidence of nonlinear associations of FPG and HbA_{1c} with CVD, cancer, and all-cause mortality. The analyses also suggested significant nonlinear relationships between 2h-PG and both CVD and all-cause mortality, but not cancer. Evidence indicated a significant linear

Table 2—Cumulative incidence and risk ratio of diabetes according to glucose tolerance status over a mean follow-up of 3.8 years among study participants without diagnosed diabetes and without undiagnosed diabetes at baseline

Variable	Glucose tolerance			Study participants, *n* (%)	Incident diabetes		Age- and sex-adjusted model		Multivariable-adjusted model[a]	
	FPG, mg/dL	2h-PG, mg/dL	HbA_{1c}, % (mmol/mol)		Participants, *n*	Cumulative incidence, %	Risk ratio (95% CI)	*P* value	Risk ratio (95% CI)	*P* value
Normal glucose tolerance	<100	<140	<5.7 (39)	30,291 (28.4)	880	2.9	1.00 (reference)		1.00 (reference)	
Isolated impaired fasting glucose	100–125	<140	<5.7 (39)	9,138 (8.6)	454	5.0	1.66 (1.49–1.86)	<0.001	1.60 (1.43–1.79)	<0.001
Isolated impaired glucose tolerance	<100	140–199	<5.7 (39)	4,970 (4.7)	437	8.8	2.93 (2.62–3.27)	<0.001	2.72 (2.43–3.04)	<0.001
Isolated elevated HbA_{1c}	<100	<140	5.7–6.4 (39–47)	25,380 (23.8)	1,184	4.7	1.56 (1.43–1.70)	<0.001	1.49 (1.36–1.62)	<0.001
Combined impaired fasting glucose and impaired glucose tolerance	100–125	140–199	<5.7 (39)	3,983 (3.7)	507	12.7	4.21 (3.79–4.68)	<0.001	3.71 (3.33–4.13)	<0.001
Combined impaired fasting glucose and elevated HbA_{1c}	100–125	<140	5.7–6.4 (39–47)	14,433 (13.6)	1,320	9.2	3.00 (2.76–3.26)	<0.001	2.68 (2.46–2.92)	<0.001
Combined impaired glucose tolerance and elevated HbA_{1c}	<100	140–199	5.7–6.4 (39–47)	7,727 (7.3)	1,030	13.3	4.37 (4.00–4.77)	<0.001	3.87 (3.53–4.23)	<0.001
Combined impaired fasting glucose, impaired glucose tolerance, and elevated HbA_{1c}	100–125	140–199	5.7–6.4 (39–47)	10,571 (9.9)	2,251	21.3	6.91 (6.40–7.46)	<0.001	5.84 (5.40–6.32)	<0.001

Diabetes was defined as FPG ≥126 mg/dL (7.0 mmol/L), 2h-PG ≥200 mg/dL (11.1 mmol/L), HbA_{1c} ≥6.5% (48 mmol/mol), or self-report of a physician diagnosis of diabetes and use of antidiabetes medications at the follow-up visits. [a]Adjusted for age, sex, BMI, family history of diabetes, smoking, drinking, education status, physical activity, systolic blood pressure, HDL cholesterol, LDL cholesterol, and triglycerides.

relationship between 2h-PG and cancer ($P < 0.001$) (Fig. 1). In a sensitivity analysis among individuals without a history of diabetes, the associations between glycemic measures and clinical outcomes were similar (Supplementary Fig. 2).

Multivariable-adjusted hazard ratios (95% CIs) associated with untreated diabetes based on fasting glucose ≥126 mg/dL, 2h-PG ≥200 mg/dL, or HbA_{1c} ≥6.5% (48 mmol/mol) were 1.18 (1.05–1.33), 1.31 (1.18–1.45), and 1.20 (1.07–1.34) for CVD; 1.10 (0.92–1.32), 1.44 (1.25–1.67), and 1.08 (0.92–1.28) for cancer; and 1.37 (1.20–1.57), 1.57 (1.41–1.76), and 1.33 (1.17–1.52) for all-cause mortality, respectively (model 2, Table 3). When all three glycemic measures were included as spline terms in the same model simultaneously (model 3, Table 3), the hazard ratios (95% CIs) for 2h-PG remained significantly and positively associated with CVD (1.30 [1.14–1.49]), cancer (1.62 [1.36–1.93]), and all-cause mortality (1.58 [1.38–1.81]). In addition, prediabetes defined as 2h-PG of 140–199 mg/dL remained consistently and significantly associated with risk of CVD and all-cause mortality. Further adjustments for additional risk factors and study site did not alter our findings (Supplementary Tables 5–8). The risk estimates for CVD, cancer, and all-cause mortality based on the higher cutoffs of 6.1 mmol/L for impaired fasting glucose and 6.0% for elevated HbA_{1c} did not change significantly (Supplementary Table 9). In a sensitivity analysis, among individuals without a history of diagnosed diabetes, the associations between glycemic measures and clinical outcomes were similar (Supplementary Table 10). Moreover, sensitivity analyses using a common population that excluded individuals with diabetes, CVD, and cancer at baseline did not change the study findings (Supplementary Tables 11 and 12).

We also performed stratified analyses according to age, sex, BMI, and smoking status (Supplementary Tables 13–16). We found that the risk estimates were generally similar for incident cancer and all-cause mortality across subgroups. For incident CVD, we observed significant differences in age ($P = 0.01$ for interaction) and BMI ($P < 0.001$ for interaction) across strata.

Predictive Values of Glycemic Measures

The C statistic (95% CI) of the predictive models of conventional risk factors was 0.652 (0.646–0.658) for incident diabetes. The addition of continuous glycemic

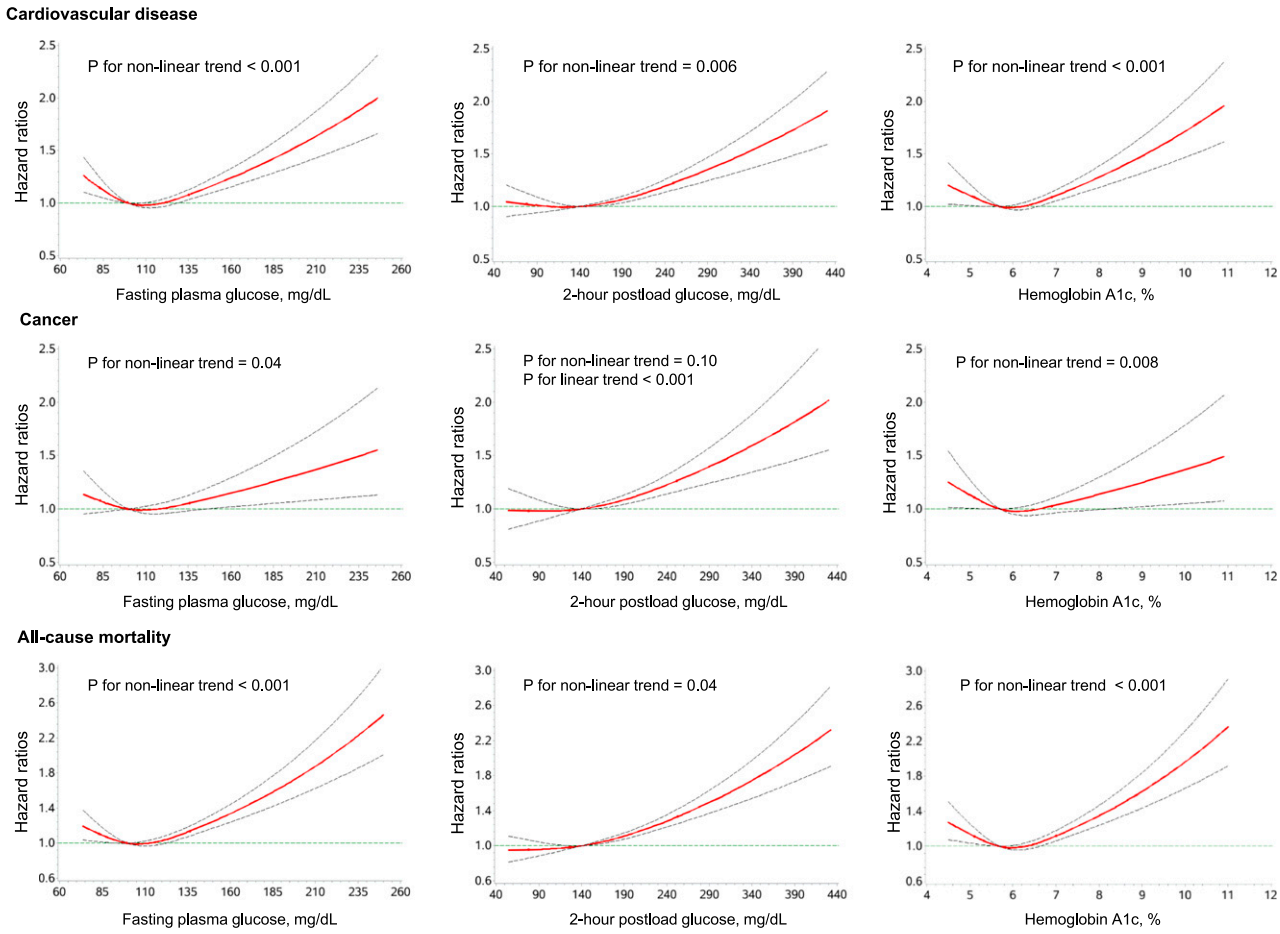

Figure 1—Multivariable-adjusted hazard ratios of CVD (top row), cancer (middle row), and all-cause mortality (bottom row) in participants without treated diabetes at baseline. The solid lines indicate multivariate-adjusted hazard ratios and the dashed lines indicate the 95% CIs derived from restricted cubic spline regression. A knot is located at the 5th, 50th, and 95th percentiles for each of the three glycemic measures (FPG [left], 2h-PG [middle], HbA_{1c} [right]), and the highest and lowest 0.5% of each glycemic measure was trimmed. The Cox regression was adjusted for age, sex, BMI, family history of diabetes, smoking, drinking, education status, physical activity, systolic blood pressure, HDL cholesterol, LDL cholesterol, and triglycerides.

Table 3—Incidence and hazard ratios of CVD, cancer, and all-cause mortality among participants without treated diabetes at baseline

	Person-years, *n*	Events, *n*	Incidence per 1,000 person-years (95% CI)	Model 1[a]		Model 2[b]		Model 3[c]	
				Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
CVD incidence									
FPG, mg/dL									
<100	248,463	1,568	6.31 (6.00–6.63)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
100–125	156,344	1,086	6.94 (6.54–7.37)	0.98 (0.90–1.05)	0.53	0.90 (0.83–0.97)	0.009	0.87 (0.79–0.94)	<0.001
≥126	32,561	360	11.06 (9.94–12.26)	1.42 (1.27–1.59)	<0.001	1.18 (1.05–1.33)	0.007	0.89 (0.75–1.06)	0.19
2h-PG, mg/dL									
<140	282,942	1,598	5.65 (5.37–5.93)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
140–199	107,041	875	8.17 (7.64–8.73)	1.18 (1.08–1.28)	0.001	1.12 (1.03–1.22)	0.009	1.14 (1.05–1.25)	0.002
≥200	47,384	541	11.42 (10.48–12.42)	1.49 (1.35–1.64)	<0.001	1.31 (1.18–1.45)	<0.001	1.30 (1.14–1.49)	<0.001
HbA_{1c}, %									
<5.7	174,245	1,040	5.97 (5.61–6.34)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
5.7–6.4	218,596	1,496	6.84 (6.50–7.20)	0.92 (0.85–1.00)	0.05	0.93 (0.86–1.01)	0.09	0.93 (0.85–1.01)	0.09
≥6.5	44,527	478	10.74 (9.79–11.74)	1.28 (1.15–1.43)	<0.001	1.20 (1.07–1.34)	0.002	1.07 (0.92–1.24)	0.39
Cancer incidence									
FPG, mg/dL									
<100	258,903	895	3.45 (3.23–3.69)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
100–125	165,591	580	3.50 (3.22–3.80)	0.93 (0.84–1.03)	0.17	0.96 (0.86–1.06)	0.40	0.92 (0.82–1.03)	0.13
≥126	35,045	149	4.25 (3.60–4.99)	1.05 (0.88–1.25)	0.60	1.10 (0.92–1.32)	0.29	0.82 (0.64–1.05)	0.16
2h-PG, mg/dL									
<140	293,722	919	3.13 (2.93–3.34)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
140–199	114,118	430	3.77 (3.42–4.14)	1.04 (0.93–1.17)	0.51	1.08 (0.96–1.21)	0.21	1.11 (0.99–1.26)	0.08
≥200	51,699	275	5.32 (4.71–5.99)	1.35 (1.18–1.54)	<0.001	1.44 (1.25–1.67)	<0.001	1.62 (1.36–1.93)	<0.001
HbA_{1c}, %									
<5.7	180,094	606	3.36 (3.10–3.64)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
5.7–6.4	230,654	806	3.49 (3.26–3.74)	0.89 (0.80–0.99)	0.03	0.92 (0.82–1.03)	0.13	0.90 (0.81–1.01)	0.08
≥6.5	48,791	212	4.35 (3.78–4.97)	1.01 (0.86–1.18)	0.94	1.08 (0.92–1.28)	0.35	0.88 (0.72–1.09)	0.25
All-cause mortality									
FPG, mg/dL									
<100	326,893	1,268	3.88 (3.67–4.10)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
100–125	207,835	855	4.11 (3.84–4.40)	0.91 (0.83–0.99)	0.03	0.95 (0.87–1.04)	0.26	0.90 (0.82–0.99)	0.04
≥126	44,847	286	6.38 (5.66–7.16)	1.25 (1.10–1.42)	0.001	1.37 (1.20–1.57)	<0.001	0.99 (0.83–1.20)	0.98
2h-PG, mg/dL									
<140	368,432	1,243	3.37 (3.19–3.57)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
140–199	144,726	681	4.71 (4.36–5.07)	1.05 (0.95–1.15)	0.33	1.13 (1.02–1.24)	0.02	1.15 (1.04–1.27)	0.005
≥200	66,416	485	7.30 (6.67–7.98)	1.41 (1.27–1.57)	<0.001	1.57 (1.41–1.76)	<0.001	1.58 (1.38–1.81)	<0.001
HbA_{1c}, %									
<5.7	226,004	836	3.70 (3.45–3.96)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
5.7–6.4	290,789	1,197	4.11 (3.89–4.36)	0.87 (0.80–0.96)	0.003	0.99 (0.90–1.08)	0.78	0.97 (0.88–1.06)	0.47
≥6.5	62,782	376	5.99 (5.40–6.63)	1.08 (0.95–1.22)	0.23	1.33 (1.17–1.52)	<0.001	1.06 (0.89–1.26)	0.47

[a]Model 1 was adjusted for age and sex. [b]Model 2 included model 1 variables plus BMI, family history of diabetes, cigarette smoking (current, former, and never smoker), alcohol consumption (current, former, and never), high school or higher education, moderate and vigorous physical activity, systolic blood pressure, HDL cholesterol, LDL cholesterol, and triglycerides. [c]Model 3 included model 2 variables plus baseline 2h-PG and HbA_{1c} (as spline terms) for the FPG category, model 2 variables plus baseline FPG and HbA_{1c} (as spline terms) for the 2h-PG category, and model 2 variables plus baseline FPG and 2h-PG (as spline terms) for the HbA_{1c} category.

measures to diabetes-predictive models significantly improved discrimination (Table 4). The C statistic, IDI, and NRI were significantly increased by adding FPG, 2h-PG, or HbA_{1c}. The addition of two or three glycemic measures simultaneously further improved discrimination, especially for models including 2h-PG.

The C statistic (95% CI) of the predictive models of conventional risk factors was 0.740 (0.732–0.749) for incident CVD, 0.657 (0.643–0.671) for cancer, and 0.792 (0.783–0.802) for all-cause mortality. The addition of categorized 2h-PG or a combination of 2h-PG and other glycemic measures slightly but significantly increased the C statistic, IDI, and NRI for predicting CVD (Table 4). Likewise, the addition of categorized 2h-PG significantly increased IDI and NRI for predicting cancer risk. Adding categorized 2h-PG or HbA_{1c} slightly but significantly increased the C statistic, IDI, and NRI for predicting all-cause mortality. The addition of categorized 2h-PG improved discrimination most; also including FPG and HbA_{1c} did not further improve the model. We observed similar predictive values of different glycemic measures among individuals without a history of diagnosed diabetes in a sensitivity analysis (Supplementary Table 17).

Table 4—Improvement in predicting diabetes, CVD, cancer, and all-cause mortality by adding FPG, 2h-PG, and HbA_{1c} to conventional risk factors[a]

	Diabetes incidence[c]			CVD incidence[d]			Cancer incidence[d]			All-cause mortality[d]		
	Δ C statistic (95% CI)	IDI, % (95% CI)	NRI, % (95% CI)	Δ C statistic (95% CI)	IDI, % (95% CI)	NRI, % (95% CI)	Δ C statistic (95% CI)	IDI, % (95% CI)	NRI, % (95% CI)	Δ C statistic (95% CI)	IDI, % (95% CI)	NRI, % (95% CI)
Adding a single glycemic measure[b]												
FPG	0.043 (0.038–0.048)	2.208 (2.086–2.331)	37.694 (35.420–39.967)	0.001 (0.0005–0.002)	0.034 (0.015–0.054)	1.250 (−2.289 to 4.789)	0.000 (−0.001 to 0.002)	0.006 (0.0001–0.011)	1.778 (−2.983 to 6.593)	0.001 (0.0002–0.002)	0.051 (0.020–0.081)	−0.892 (−4.951 to 3.168)
2h-PG	0.064 (0.058–0.070)	3.442 (3.288–3.596)	51.415 (49.171–53.658)	0.001 (0.0003–0.002)	0.044 (0.016–0.072)	20.322 (16.660–23.985)	0.002 (−0.001 to 0.004)	0.039 (0.022–0.055)	8.242 (3.780–12.703)	0.003 (0.002–0.005)	0.112 (0.056–0.169)	17.859 (13.885–21.833)
HbA_{1c}	0.034 (0.029–0.038)	1.527 (1.439–1.615)	34.959 (32.709–37.209)	0.001 (0.0003–0.002)	0.024 (0.006–0.042)	1.300 (−2.389 to 4.988)	0.001 (−0.001 to 0.002)	0.007 (0.001–0.014)	1.322 (−3.640 to 6.285)	0.001 (0.0002–0.002)	0.034 (0.005–0.062)	5.571 (1.963–9.180)
Adding two glycemic measures[b]												
FPG and 2h-PG	0.080 (0.074–0.086)	4.560 (4.373–4.746)	56.856 (54.633–59.080)	0.003 (0.002–0.005)	0.058 (0.030–0.085)	−6.717 (−10.398 to 3.035)	0.003 (−0.001 to 0.006)	0.057 (0.036–0.079)	−1.090 (−6.031 to 3.850)	0.004 (0.002–0.005)	0.151 (0.093–0.211)	15.308 (11.337–19.279)
FPG and HbA_{1c}	0.058 (0.052–0.063)	3.131 (2.983–3.278)	46.620 (44.376–48.863)	0.002 (0.001–0.004)	0.047 (0.023–0.071)	2.620 (−0.968 to 6.208)	0.001 (−0.001 to 0.003)	0.012 (0.004–0.020)	3.853 (−1.037 to 8.744)	0.001 (0.0004–0.003)	0.065 (0.030–0.101)	2.813 (−1.230 to 6.854)
2h-PG and HbA_{1c}	0.078 (0.072–0.083)	4.434 (4.254–4.614)	55.761 (53.538–57.985)	0.002 (0.001–0.003)	0.044 (0.019–0.069)	−5.87 (−9.532, 2.213)	0.003 (−0.001 to 0.006)	0.049 (0.030–0.068)	3.10 (−1.842 to 8.047)	0.004 (0.002–0.005)	0.118 (0.061–0.175)	14.945 (10.981–18.908)
Adding all three glycemic measures[b] (FPG, 2h-PG, and HbA_{1c})	0.088 (0.082–0.094)	5.247 (5.043–5.450)	59.472 (57.260–61.683)	0.004 (0.002–0.005)	0.069 (0.039–0.098)	8.456 (4.7787–12.1339)	0.004 (−0.00002 to 0.007)	0.063 (0.041–0.0847)	8.223 (3.263–13.183)	0.004 (0.002–0.006)	0.155 (0.095–0.214)	11.594 (7.557–15.632)

[a]Conventional risk factors included age, sex, BMI, family history of diabetes, smoking, drinking, high school or higher education, moderate or vigorous physical activity, systolic blood pressure, LDL cholesterol, HDL cholesterol, and triglycerides. [b]Continuous glycemic measures were included in the models of subsequent diabetes, and categorized glycemic measures—including FPG (<100, 100–125, and ≥126 mg/dL), 2h-PG (<140, 140–199, and ≥200 mg/dL), and HbA_{1c} (<5.7, 5.7–6.4, and ≥6.5%)—were added in the models of subsequent CVD, subsequent cancer, and all-cause mortality. [c]Excludes participants at baseline. [d]Excludes participants receiving antidiabetes treatment (oral hypoglycemic agents or insulin) at baseline.

CONCLUSIONS

This large, population-based prospective study found that elevated FPG, 2h-PG, and HbA_{1c} are significant predictive indicators of incident diabetes and its complications. 2h-PG remained significantly associated with the risk of diabetes, CVD, and cancer, and with all-cause mortality, in models including FPG and HbA_{1c}. Furthermore, 2h-PG significantly improved the prediction of diabetes, CVD, and all-cause mortality over conventional risk factors. These findings have important clinical implications.

FPG, 2h-PG, and HbA_{1c} have all been shown to be related to the risk of diabetes in epidemiological studies (21–24). Our study, however, contributes new knowledge about the relative importance of individual measures and their combinations in predicting the risk of incident diabetes. Specifically, these findings indicate that 2h-PG or combinations of 2h-PG with other glycemic measures better predict risk than

FPG, HbA_{1c}, or their combination. The combination of three glycemic measures best predicts risk of diabetes.

Our study observed nonlinear associations of glycemic measures with CVD and all-cause mortality, which is consistent with findings from other observational studies (24,25). In the Emerging Risk Factors Collaboration (ERFC), which included data from 73 prospective studies involving 294,998 participants, nonlinear associations with CVD were reported for fasting glucose, postload glucose, and HbA_{1c} (25). Prediabetes defined on the basis of fasting glucose, postload glucose, and HbA_{1c} was associated with higher risk of CVD and all-cause mortality in prospective studies (5,6). In our study, only prediabetes defined by 2h-PG was significantly associated with increased risk of CVD and all-cause mortality. It has been reported that compared to FPG, the glucose tolerance test is more sensitive in identifying individuals who are at high risk for prediabetes and diabetes among Asian populations (2,26). Intriguingly, we also observed differences in the associations of the different glycemic measures across age and BMI strata. Further investigations are warranted in order to validate our findings and explore the detailed relationship and potential mechanisms.

Postload hyperglycemia differs from fasting hyperglycemia with regard to pathophysiology and the risk of diabetes-related clinical outcomes, and it mainly results from moderate to severe insulin resistance and from an impaired late-phase insulin secretory response to oral glucose. Our findings indicated that 2h-PG remained independently associated with risk of CVD and all-cause mortality in models with FPG and HbA_{1c}, and it improved risk prediction more than did FBG or HbA_{1c}. When using the same cutoffs, the ARIC study and ERFC reported that HbA_{1c} better predicts risk for CVD (9,24,25). In those studies, however, not all three glycemic measures were obtained at the same visit. Methodological and study population differences notwithstanding, the reasons why our results do not agree with the ARIC study and ERFC findings are unclear. By contrast, several prospective studies—including the Australian Diabetes, Obesity, and Lifestyle (AusDiab) Study, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study, and the Framingham Offspring Study—reported that 2h-PG better predicted risk for CVD and mortality than did FPG or HbA_{1c} (8,27,28).

Elevated blood glucose has been associated with an increased risk of cancer in several prospective studies (29–31). In ~1.3 million men and women in Korea, elevated fasting serum glucose levels and a diagnosis of diabetes were independent risk factors for cancer overall and for several prevalent cancers (29). In a pooled analysis of 274,126 men and 275,818 women from six European cohorts, fasting glucose was associated with an increased risk of cancer overall and at several sites (30). In 29,629 Japanese adults aged 46–80 years, elevated HbA_{1c} was associated with overall cancer risk (31). In our study, 2h-PG, but not FPG or HbA_{1c}, was associated with overall cancer.

The primary strengths of this study are its population-based design, its large sample size, and its ability to compare the risks of FPG, 2h-PG, and HbA_{1c} as they relate to CVD, cancer, and all-cause mortality simultaneously. Although comparisons of the strength of the relationships between the glycemic variables and outcome must take into account their collinearity, the given analysis suggests that postload glucose may be a stronger predictor than the other two variables. Our study does have a number of important limitations. First, the study participants were only followed for a mean of 3.8 years. This relatively short follow-up duration reduced the number of clinical events and the study's statistical power, especially for determining cancer incidence and all-cause mortality. However, we have counted 1,624 incident cancer cases and 2,409 total deaths. Second, the study participants only had one follow-up visit, and glycemic measures were obtained at only two time points (the baseline and follow-up visits). This could limit the accuracy of the timing of diagnoses, especially diabetes. The methods by which we collected data regarding clinical outcomes may also limit the sensitivity of ascertaining outcomes. Third, 12.2% of study participants were lost to follow-up. Rural-to-urban migration and urban redevelopment in China have contributed to this loss. In the diabetes analysis, 13.1% participants did not have an OGTT and an HbA_{1c} test at follow-up and thus were excluded from the final analysis for incident diabetes. Fourth, anemia and hemoglobin might affect HbA_{1c} measurement, but that was not measured in this study. Nevertheless, this study was conducted among the general population. In a sensitivity analysis, further adjustment for self-reported anemia did not change the study findings. Single measurements of FPG, 2h-PG, and HbA_{1c} are subject to within-person variability. High variability in any of the measures could lead to imprecise associations and regression dilution bias of associations between glycemic measures and study outcomes (32). Fifth, microvascular complications, which are more specific complications of diabetes than cardiovascular events, cancer, or all-cause mortality, were not included as an outcome. Finally, the interpretations and conclusions of this study and others in the literature are fundamentally dependent on the approach used to model the three glycemic markers. In this study we used cutoffs established by 2010 ADA criteria for prediabetes and diabetes based on FPG, 2h-PG, and HbA_{1c} to compare their associations with the outcomes. Although the risk estimates did not change significantly for CVD, cancer, and all-cause mortality based on the higher cutoffs of 6.1 mmol/L for impaired fasting glucose and 6.0% for elevated HbA_{1c}, additional caution should be taken to balance the appropriate sensitivity and specificity of a glycemic marker.

In conclusion, our findings suggest that 2h-PG remains independently predictive of the outcomes in models including FPG and HbA_{1c}. Therefore, in addition to FPG and HbA_{1c} measurements, 2h-PG should be considered for routine testing in order to better assess the risks of diabetes, CVD, cancer, and all-cause mortality.

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