Glycemic Measures and Risk of Mortality in Older Chinese: The Guangzhou Biobank Cohort Study

Chao Qiang Jiang,[1] Lin Xu,[2,3] Tai Hing Lam,[1,3] Ya Li Jin,[1] Wei Sen Zhang,[1] Feng Zhu,[1] G. Neil Thomas,[4] and Kar Keung Cheng[4]

[1]Guangzhou No.12 Hospital, Guangzhou 510620, China; [2]School of Public Health, Sun Yat-sen University, Guangzhou, China; [3]School of Public Health, the University of Hong Kong, Hong Kong; and [4]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

ORCiD number: 0000-0002-0537-922X (Lin Xu).

Context: China has the largest number of people with type 2 diabetes mellitus (T2DM) in the world. Data from previous studies have suggested that up to one-fifth of individuals with diabetes would be missed without an oral glucose tolerance test (OGTT). To date, there is little information on the mortality risk of these individuals.

Objective: We estimated the association of different indicators of hyperglycemia with mortality in the general Chinese population.

Design: Prospective cohort study.

Setting: China.

Participants: A total of 17 939 participants aged 50+ years.

Exposures: Previously diagnosed diabetes and newly detected diabetes defined by fasting glucose (≥7.0 mmol/L), 2-hour postload glucose (≥11.1 mmol/L), or hemoglobin A_{1c} (HbA_{1c}, ≥6.5%).

Main Outcomes Measures: Deaths from all-cause, cardiovascular disease, and cancer were identified by record linkage with death registration.

Results: During 7.8 (SD, 1.5) years' follow-up, 1439 deaths were recorded. Of 3706 participants with T2DM, 2126 (57%) had known T2DM, 118 (3%) were identified by isolated elevated fasting glucose, 1022 (28%) had isolated elevated postload glucose, and 440 (12%) had both elevated fasting and postload glucose. Compared with normoglycemia, the hazard ratio (95% confidence interval) of all-cause mortality was 1.71 (1.46-2.00), 0.96 (0.47-1.93), 1.43 (1.15-1.78), and 1.82 (1.35-2.45) for the 4 groups, respectively. T2DM defined by elevated HbA_{1c} was not significantly associated with all-cause mortality (hazard ratio, 1.17; 95% confidence interval, 0.81-1.69).

Conclusion: Individuals with isolated higher 2-h postload glucose had a higher risk of mortality by 43% than those with normoglycemia. Underuse of OGTT leads to substantial underdetection of individuals with a higher mortality risk and lost opportunities for early intervention. ***(J Clin Endocrinol Metab* 105: e171–e180, 2020)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 30 August 2019. Accepted 31 October 2019.
First Published Online 3 November 2019.
Corrected and Typeset 17 February 2020.

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; CVD, cardiovascular disease; DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; FPG, fasting plasma glucose; GBCS, Guangzhou Biobank Cohort Study; GHHARE, The Guangzhou Health and Happiness Association for the Respectable Elders; HbA_{1c}, hemoglobin A1c; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization.

Type 2 diabetes mellitus (T2DM) constitutes a major disease burden (1). China has the largest number of diabetic patients in the world and the prevalence is rapidly rising, from <1% in 1980 (2) to 11.6% in 2010 (3, 4). Identifying individuals with hyperglycemia facilitates early intervention to attenuate the development of complications and reduce the associated mortality (5). Current definitions recommend the use of the 2-hour postload glucose levels from the oral glucose tolerance test (OGTT) and hemoglobin A_{1c} (HbA_{1c}) along with fasting plasma glucose (FPG) to diagnose T2DM and prediabetes (6, 7). The recommendation of 2-hour postload glucose in the diagnosis of T2DM was primarily based on evidence from the western populations that individuals with elevated 2-hour postload glucose had a higher risk of mortality, independent of their fasting glucose levels (6, 8).

Although OGTT has been included as 1 of the diagnostic tests for decades (6), it is rarely used in health checks or population-based studies for reasons of inconvenience. Previous data suggest that the underuse of OGTT leads to substantial underdiagnosis of diabetes in China (3). However, there is no information on the mortality risk of these individuals because previous studies in China on the long-term effect of T2DM on mortality did not measure 2-hour postload glucose (9). In the present study, we analyzed data from the Guangzhou Biobank Cohort Study to assess the association of prediabetes and T2DM defined by FPG, 2-hour postload glucose or HbA_{1c} with all-cause and cause-specific mortality.

Methods

Study subjects

All participants of the Guangzhou Biobank Cohort Study (GBCS) were recruited and first examined from 2003 to 2008. Details of the GBCS have been reported previously (10, 11). Briefly, the GBCS is a 3-way collaboration among Guangzhou 12th Hospital and the Universities of Hong Kong, China, and Birmingham, UK. Recruitment of participants was from "The Guangzhou Health and Happiness Association for the Respectable Elders" (GHHARE), a community social and welfare organization. GHHARE is unofficially aligned with the municipal government. Membership is open to Guangzhou permanent residents aged 50 years or older for a nominal fee of 4 CNY (~$US0.50) per month. GHHARE included about 7% of Guangzhou residents in this age group, with branches in all 10 districts of Guangzhou, the capital city of Guangdong province in southern China.

In the main analyses for the present paper, we used data from participants who returned for the second examination from March 2008 to December 2012, because 2-hour postload glucose was only measured in 1303 participants in the first examination. A computer-assisted questionnaire was used for the face-to-face interviews. Information collected included demographic characteristics, lifestyle, family and personal medical history, and detailed assessment of anthropometrics, blood pressure, fasting plasma glucose, lipids, and inflammatory markers. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed consent before participation.

Glycemic measures

Both fasting and 2-hour postload glucose levels were measured. An OGTT was not performed for those with self-reported physician diagnosis of diabetes or with glucose-lowering treatment. Because of constraints in funding, HbA_{1c} was measured in 6074 participants only who returned after May 2010. T2DM was defined by FPG ≥7.0 mmol/L, 2-hour postload glucose ≥11.1 mmol/L, or by a history of self-reported physician-diagnosed diabetes (known T2DM). Impaired fasting glucose (IFG) was defined by an FPG level of 5.6 to 6.9 mmol/L by the American Diabetes Association (ADA) (12), or 6.0–6.9 mmol/L by the World Health Organization (WHO) (7). Impaired glucose tolerance (IGT) was defined by 2-hour postload glucose of 7.8 to 11.0 mmol/L according to the definition by both WHO and ADA (6, 7). Elevated HbA_{1c} was defined by an HbA_{1c} of 5.7 to 6.4% by the ADA, or 6.0 to 6.4 % by the WHO (13). Prediabetes was defined as the presence of IFG and/or IGT, and without T2DM. Normoglycemia was defined as values below the cut points for IFG/IGT for ADA or WHO.

Mortality

Information on underlying causes of deaths up to December 2017 was mostly obtained via record linkage with Death Registry of the Guangzhou Center for Disease Control and Prevention. Causes of death were coded according to the 10th revisions of the International Classification of Diseases by trained nosologists in each hospital. When the death certificates were not issued by medical institutions (and hence might have a quality issue with the coding), the causes of death were verified by Guangzhou Center for Disease Control and Prevention as part of its quality assurance programme by cross-checking medical history and conducting verbal autopsy. From 2015 to 2018, 11 verbal autopsy meetings were conducted in the Guangzhou 12th Hospital to clarify the deaths with unclear causes. A physician panel including 5 chief physicians from various disciplines reviewed all available medical records of the same individuals and assigned in a standard manner a cause of death, with assistance of an epidemiologist in the last meeting for unsettled cases. Causes of deaths were coded using the 10th International Classification of Diseases.

Statistical analysis

Associations of hyperglycemia or glycemic measures with mortality were estimated by Cox regression. Because no evidence of violation for the proportional hazard assumption was found by checking Schoenfeld residuals using the "stphtest" command in STATA, the Cox proportional hazards model was used to calculate adjusted hazard ratios (HRs) with 95% confidence interval (CI). Because the current analysis included participants who attended the second examination from 2008 to 2012, to partly account for potential influence resulting from

lost to follow-up for repeated physical examination, we used inverse probability weighting to adjust for nonresponse in estimation of relative mortality risk (14). The characteristics for participants in the first examination (2003–2008) and those who returned for the second examination (2008–2012) were similar regarding proportions of men, education level, occupation, smoking, and physical activity, as reported elsewhere (15). Potential confounders adjusted for included demographic characteristics (age, sex), socioeconomic position (education and occupation), personal history of cardiovascular disease (CVD) and cancer, smoking status, and clinical parameters that could be common causes of both hyperglycemia and mortality (including body mass index, waist circumference (WC), triglycerides, and systolic blood pressure). Participants who died of any other causes were regarded as censored at the date of death (16, 17). Those who were alive were right-censored on December 31, 2017. Potential interactions between glycemic status and age group (<65/65+ years), sex, education (primary school or below/secondary school/college or above), and central obesity, defined by a WC ≥80 cm in women and ≥90 cm in men, were checked. Because no significant interaction was found between glycemic measures, as continuous or categorical variables classified by ADA/WHO criteria, and sex, age, education, or WC groups for the association with all-cause CVD or cancer mortality (P for interaction from .08 to .89), the main results pooling men and women together are presented. To enable comparability with other studies, stratified analyses by sex and age group were also conducted. $P < .05$ was considered statistically significant. All analysis was done by using STATA/IC 14.0.

Results

Of the 18 104 participants, 165 were excluded because of incomplete information on FPG or 2-hour postload glucose, resulting in 17 939 participants (13 055 women and 4884 men) in this paper. Of the 17 939 participants, after an average follow-up of 7.8 (SD, 1.5) years, 1439 (women 764 [5.9%] and men 675 [13.8%]) deaths were recorded. The numbers of participants and deaths from all-cause, CVD, and cancer are shown in the online repository (18). At baseline, the mean age of the participants was 65 (SD, 7.1) years. Table 1 shows that, compared with participants without T2DM, those with T2DM were older, had higher socioeconomic position (higher education and nonmanual occupation), more were smokers and alcohol users, and had a lower level of physical activity (all $P < .001$). Moreover, those with T2DM also had greater WC; higher systolic and diastolic blood pressure; higher levels of triglycerides, fasting, and 2-hour postload glucose; and HbA_{1c}, and higher prevalence of self-reported history of CVD and cancer (P from <.001 to .02).

Table 2 shows that IFG defined by either WHO or ADA criteria was not associated with all-cause, CVD, or cancer mortality. Participants with known T2DM were associated with about 60% higher risk of all-cause, about 80% higher risk, of CVD and about 30% higher risk of cancer mortality. Compared with normoglycemia, the adjusted HR of all-cause mortality for diabetes defined by FPG using WHO and ADA criteria was 1.48 (95% CI, 1.13-1.94), and 1.49 (95% CI, 1.14-1.96), respectively. One-mmol/L increment in FPG was associated with 10% higher risk of all-cause, 12% higher risk of CVD, and 6% higher risk for cancer mortality. Compared with normal 2-hour postload glucose, IGT was associated with a higher risk of all-cause mortality by 19% (HR, 1.19; 95% CI, 1.04-1.37). New T2DM defined by elevated 2-hour postload glucose was associated with higher risk of all-cause, CVD, and cancer mortality, with the adjusted HR (95% CI) being 1.54 (1.28-1.86), 1.70 (1.25-2.32), and 1.44 (1.07-1.95), respectively. When FPG and 2-hour postload glucose (and potential confounders) were mutually adjusted for each other, the association of 2-hour postload glucose with the risk of all-cause (HR, 1.05; 95% CI, 1.02-1.07), CVD (HR, 1.05; 95% CI, 1.01-1.09), and cancer mortality (HR, 1.04; 95% CI, 1.00-1.08) remained significant, but the association of FPG was attenuated and became nonsignificant (18). Furthermore, prediabetes defined by elevated HbA_{1c} was not associated with all-cause or cause-specific mortality risk, and T2DM defined by elevated HbA_{1c} using either WHO or ADA criteria was associated with CVD mortality only (HR, 2.45; 95% CI, 1.39-4.3, and 2.22, 95% CI, 1.18-4.18, respectively), not with all-cause or cancer mortality (Table 2).

Among participants with IFG or IGT, one-half (54%) of them had IGT only, 23% had IFG only, and 23% had both IGT and IFG (18). Table 3 shows that compared with normoglycemia defined by normal fasting and 2-hour postload glucose, IFG only was not associated with all-cause, CVD, or cancer mortality, IGT was associated with a higher risk of all-cause mortality only (HR, 1.17; 95% CI, 1.00-1.38), and the presence of both IGT and IFG was associated with a higher risk of CVD mortality (HR, 1.44; 95% CI, 1.01-2.05) and a marginally significantly higher risk of all-cause mortality (HR, 1.23; 95% CI, 0.98-1.54). In those without known T2DM, 1580 were newly diagnosed with T2DM by the repeated examination. Of the participants with T2DM, 28% were diagnosed by high 2-hour postload glucose only, 3% by high FPG only, and 12% by both high 2-hour postload glucose and FPG (18). Table 3 shows that T2DM diagnosed by elevated 2-hour postload glucose only was associated with higher risk of all-cause (HR, 1.43; 95% CI, 1.15-1.78) and CVD mortality (HR, 1.51; 95% CI, 1.05-2.17), whereas new T2DM by elevated FPG

Table 1. Baseline Demographic Characteristics and Biochemical Parameters of 17 939 Participants

Characteristics	No. (n = 14 233)	Type 2 Diabetes by				*P* Value
		High FPG Only (n = 118)	High 2-h Postload Glucose Only (n = 1022)	Both High Fasting and 2-h Postload Glucose (n = 440)	Self-Reported Physician Diagnosed (n = 2126)	
Men, %	27.4	33.9	25.7	27.5	26.3	.30
Age[a], y	64.8 (7.1)	65.9 (7.1)	67 (6.5)	65.8 (7)	67.1 (6.6)	<.001
Education (college or above), %	9.1	9.3	9.1	8.6	10.1	<.001
Occupation (manual), %	60.4	59.8	59.5	66.3	58.0	<.001
Current smokers, %	9.0	11.1	6.3	5.9	6.2	<.001
Current drinkers, %	18.5	16.2	17.9	21.0	13.1	<.001
IPAQ physical activity (active), %	79.1	76.3	72.8	80.2	74.2	<.001
BMI[a], kg/m^2	23.6 (3.4)	24.9 (3.8)	25.2 (3.6)	25.7 (3.5)	24.4 (3.5)	<.001
WC[a], cm	81.5 (9.2)	85.9 (9.9)	85.8 (9)	87.6 (8.4)	84.4 (9.1)	<.001
Triglycerides[a], mmol/L	1.6 (1.1)	1.8 (1.2)	2.2 (1.6)	2.5 (2.7)	2.1 (1.9)	<.001
HDL-cholesterol[a], mmol/L	1.4 (0.4)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	<.001
LDL-cholesterol[a], mmol/L	3.5 (0.8)	3.5 (0.8)	3.6 (0.9)	3.6 (1)	3.4 (0.9)	<.001
Total cholesterol[a], mmol/L	5.8 (1.1)	5.8 (1)	5.9 (1.1)	6 (1.2)	5.7 (1.2)	.97
Systolic blood pressure[a], mm Hg	129.9 (38.4)	136.1 (19.1)	141.6 (32.1)	142.1 (21.5)	138.3 (29)	<.001
Diastolic blood pressure[a], mm Hg	72.6 (12.9)	75.7 (10.9)	76.2 (10.5)	77.1 (10.6)	73.8 (16.5)	<.001
Fasting plasma glucose[a], mmol/L	5.1 (0.5)	7.9 (1.2)	5.9 (0.6)	9.3 (3.1)	7.6 (2.7)	<.001
2-h postload glucose[a], mmol/L	6.9 (1.7)	8.4 (1.8)	13.1 (1.7)	18.3 (4.8)	9.6 (4.4)	<.001
HbA1c[a,b], %	5.9 (0.5)	6.2 (1.2)	6.4 (0.7)	8.6 (4)	7.3 (1.6)	<.001
Self-reported history of CVD, %	9.3	17.0	13.1	10.5	16.2	<.001
Self-reported history of cancer, %	1.7	1.7	1.9	2.1	2.5	.02

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; WC, waist circumference.
[a]Data were expressed as mean ± SD.
[b]A total of 6074 participants with HbA1c data were analyzed.

only was not associated with mortality. As expected, new T2DM defined by both high 2-hour postload glucose and FPG was associated with all-cause (HR, 1.82; 95% CI, 1.35-2.45), CVD (HR, 2.01; 95% CI, 1.22-3.29), and cancer mortality (HR, 1.75; 95% CI, 1.09-2.79).

Table 4 shows that of participants with normal FPG by ADA (<5.6 mmol/L), 22.7% had IGT and 3% had new diabetes defined by elevated 2-hour postload glucose levels. In such normal FPG, IGT was associated with a marginally higher risk of all-cause mortality (HR, 1.17; 95% CI, 0.99-1.38), and T2DM defined by 2-hour postload glucose levels was associated with a higher risk of all-cause and CVD mortality (HR, 1.68; 95% CI, 1.23-2.28, and 1.78; 95% CI, 1.07-2.95, respectively). However, in participants with normal FPG, no significant association of elevated HbA_{1c} with mortality was found, although the nonsignificant association with CVD mortality could be due to a small number of participants (HR, 2.02; 95% CI, 0.83-4.93) (Table 4). In participants with normal 2-hour postload glucose levels, no association of FPG or HbA_{1c} with all-cause mortality was found (18).

Increasing FPG, 2-hour postload glucose levels and HbA_{1c} was associated with a higher risk of mortality, and the optimum values for these glycemic measures were 5.0 mmol/L, 6.5 mmol/L, and 6.0%, respectively Figure 1 (18). Sensitivity analysis showed that the association of hyperglycemia, including T2DM (never *vs.* known and newly diagnosed T2DM), IFG, IGT, and high HbA_{1c} with all-cause mortality did not vary by sex and age groups (18). Reference (18) that adding FPG and/or HbA_{1c} did not improve predictive capability of postload glucose for all-cause mortality (area under the receiver operating characteristic curve increased by 0.001 to 0.002).

Table 2. Mortality Rate (per 10 000 Person-Years) and Adjusted HRs of Deaths From All-Cause, Cardiovascular Disease, and Cancer by Glycemic Indicators in 17 939 Participants of the Guangzhou Biobank Cohort Study Recruited During 2008–2012 and Followed Until December 2017

		All-cause (n = 1439)		Cardiovascular disease (n = 500)		Cancer	(n = 590)
	Person-years/No.	Rate	HR (95% CI)[a]	Rate	HR (95% CI)[a]	Rate	HR (95% CI)[a]
FPG, mmol/L	231 362/1439	113.9	1.1 (1.07-1.13)[b]	40.6	1.12 (1.08-1.16)[b]	45.0	1.06 (1.02-1.11)[c]
FPG groups by WHO, mmol/L							
<6.1	181 825/1019	101.2	1.00	34.9	1.00	42.3	1.00
6.1–6.9	12 663/83	119.2	1.13 (0.89-1.44)	38.9	1.07 (0.7-1.63)	48.1	1.09 (0.75-1.58)
≥7.0	7426/63	160.2	1.48 (1.13-1.94)[c]	56.0	1.57 (0.99-2.47)	63.3	1.40 (0.92-2.14)
Known T2DM	29 448/274	178.2	1.57 (1.36-1.82)[b]	72.5	1.81 (1.44-2.29)[b]	56.2	1.27 (1.00-1.62)[d]
FPG groups by ADA, mmol/L							
<5.6	156 304/866	99.8	1.00	34.1	1.00	41.4	1.00
5.6–6.9	38 185/236	112.9	1.08 (0.92-1.26)	39.6	1.12 (0.86-1.45)	47.8	1.1 (0.86-1.39)
≥7.0	7426/63	160.2	1.49 (1.14-1.96)[c]	56.0	1.6 (1.01-2.53)[d]	63.3	1.42 (0.93-2.18)
Known T2DM	29 448/274	178.2	1.58 (1.37-1.83)[b]	72.5	1.85 (1.46-2.35)[b]	56.2	1.29 (1.01-1.65)*
2-h postload glucose, mmol/L	231 362/1439	113.9	1.05 (1.03-1.07)[b]	40.6	1.06 (1.03-1.09)[b]	45.0	1.04 (1.01-1.07)[c]
2-h postload glucose groups, mmol/L							
<7.8	129 340/650	90.0	1.00	30.0	1.00	38.8	1.00
7.8–11.0	53 055/357	122.8	1.19 (1.04-1.37)[d]	43.2	1.21 (0.95-1.53)	49.0	1.19 (0.96-1.47)
≥11.1	19 519/158	151.1	1.54 (1.28-1.86)[b]	55.5	1.70 (1.25-2.32)[c]	58.8	1.44 (1.07-1.95)[d]
Known T2DM	294 48/274	178.2	1.71 (1.47-2)[b]	72.5	2.02 (1.57-2.6)[b]	56.2	1.38 (1.07-1.77)[d]
HbA1c,[e] %	86 623/1439	112.2	1.07 (1.02-1.11)[c]	40.5	1.08 (1.03-1.14)[c]	42.7	1.02 (0.89-1.17)
HbA_{1c} groups by WHO,[e] %							
<6.0	30 120/128	74.5	1.00	19.5	1.00	39.4	1.00
6.0–6.4	19 554/84	77.6	1.08 (0.81-1.44)	20.8	1.07 (0.61-1.87)	31.6	0.82 (0.54-1.25)
≥6.5	7501/39	94.1	1.17 (0.81-1.69)	51.0	2.45 (1.39-4.3)[c]	32.4	0.71 (0.39-1.3)
Known T2DM	29 448/274	178.2	1.68 (1.33-2.13)[b]	72.5	2.58 (1.69-3.95)[b]	56.2	1.20 (0.83-1.72)
HbA_{1c} groups by ADA,[e] %							
<5.7	16 306/80	88.1	1.00	21.6	1.00	46.9	1.00
5.7–6.4	33 367/132	69.7	0.84 (0.63-1.13)	19.2	0.91 (0.51-1.6)	31.2	0.69 (0.46-1.03)
≥6.5	7501/39	94.1	1.01 (0.68-1.50)	51.0	2.22 (1.18-4.18)[d]	32.4	0.60 (0.32-1.14)
Known T2DM	29 448/274	178.2	1.45 (1.11-1.91)[c]	72.5	2.35 (1.41-3.9)[c]	56.2	1.02 (0.68-1.53)
T2DM by FPG only[f]							
No	194 489/998	102.4	1.00	35.2	1.00	42.6	1.00
Yes	36 873/441	174.5	1.54 (1.35-1.76)[b]	69.2	1.76 (1.42-2.18)[b]	57.6	1.29 (1.04-1.6)[d]
T2DM by FPG+2-hour postload glucose[f]							
No	18 0761/1102	99.5	1.00	33.9	1.00	41.7	1.00
Yes	50 601/337	165.4	1.52 (1.35-1.72)[b]	64.4	1.73 (1.42-2.11)[b]	56.8	1.30 (1.06-1.58)[d]
T2DM by 2-h postload glucose only							
No	182 395/1007	99.5	1.00	33.9	1.00	42.0	1.00
Yes	48 967/432	167.4	1.54 (1.36-1.74)[b]	64.9	1.72 (1.41-2.12)[b]	57.7	1.32 (1.08-1.6)[c]

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoprotein; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

[a]Adjusted for age, sex, education, occupation, smoking, BMI, waist circumference, HDL cholesterol, triglycerides, systolic blood pressure, and self-reported history of cancer and cardiovascular disease.

[b]$P < .001$.

[c]$P < .01$.

[d]$P < .05$.

[e]A total of 6074 participants with HbA1c data were analyzed.

[f]T2DM was defined by FPG ≥7.0 mmol/L (by FPG only), 2-h postload glucose ≥11.1 mmol/L (by FPG+2-h postload glucose), or by a history of self-reported physician-diagnosed diabetes (known T2DM).

doi:10.1210/clinem/dgz173

Table 3. Mortality Rate (per 10 000 Person-years) and Adjusted HR of Deaths From All-Cause, Cardiovascular Disease, and Cancer by Status of DM, IFG, and IGT[a] in 17 939 Participants of the Guangzhou Biobank Cohort Study Recruited During 2008–2012 and Followed until December 2017

		All-Cause (n = 1439)			Cardiovascular Disease (n = 500)		Cancer	(n = 590)
	N (%)	Person-years	Rate	HR (95% CI)[b]	Rate	HR (95% CI)[b]	Rate	HR (95% CI)[b]
Normal	9105 (50.8)	114 722	89.4	1.00	30.7	1.00	38.3	1.00
IFG only	1151 (6.4)	14 079	95.2	1.00 (0.77-1.29)	25.7	0.79 (0.48-1.29)	43.1	1.07 (0.73-1.56)
IGT only	2777 (15.5)	36 563	122.4	1.17 (1.00-1.38)[c]	40.4	1.06 (0.81-1.41)	47.3	1.17 (0.91-1.50)
IFG+IGT	1200 (6.7)	15 397	123.6	1.23 (0.98-1.54)	50.3	1.44 (1.01-2.05)[c]	53.0	1.29 (0.92-1.80)
New T2DM by:								
High FPG only	118 (0.7)	1634	106.4	0.96 (0.47-1.93)	25.1	0.72 (0.18-2.83)	45.5	0.85 (0.27-2.69)
High 2-h postload glucose only	1022 (5.7)	13 727	140.9	1.43 (1.15-1.78)[d]	51.6	1.51 (1.05-2.17)[c]	54.8	1.33 (0.93-1.92)
Both high fasting and 2-h postload glucose	440 (2.5)	5792	175.4	1.82 (1.35-2.45)[e]	64.8	2.01 (1.22-3.29)[d]	68.3	1.75 (1.09-2.79)[c]
Self-reported physician diagnosed	2126 (11.9)	29 448	178.2	1.71 (1.46-2.00)[e]	72.5	1.96 (1.52-2.53)[e]	56.2	1.39 (1.08-1.80)[c]

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HDL, high-density cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

[a]IFG was defined according to the ADA criteria as FPG 5.6–6.9 mmol/L, and IGT as 2-h postload glucose 7.8–11.0 mmol/L; DM was defined as FPG ≥7.0 mmol/L (high FPG), 2-h postload glucose ≥11.1 mmol/L (high 2-h postload glucose), both high fasting and 2-h postload glucose, or self-reported physician diagnosed T2DM; normoglycemia was defined as values below the cut points for IGT and IFG.

[b]Adjusted for age, sex, education, occupation, smoking, BMI, waist circumference, HDL-cholesterol, triglycerides, systolic blood pressure, and self-reported history of cancer and cardiovascular disease.

[c]$P < .05$.

[d]$P < .01$.

[e]$P < .001$.

doi:10.1210/clinem/dgz173

Table 4. Mortality Rate (per 10 000 Person-years) and Adjusted HRs of Deaths From All-Cause, Cardiovascular Disease, and Cancer by 2-h Postload Glucose and HbA1c Status in 12 258 Participants of the Guangzhou Biobank Cohort Study With Normal Fasting Plasma Glucose (<5.6 mmol/L) Recruited During 2008–2012 and Followed Until December 2017

			All-Cause (n = 866)		Cardiovascular Disease (n = 290)		Cancer	(n = 372)
	N (%)	Person-years	Rate	HR (95% CI)[a]	Rate	HR (95% CI)[a]	Rate	HR (95% CI)[a]
2-h postload glucose groups								
<7.8	9105 (74.3)	114 722	89.4	1.00	30.7	1.00	38.3	1.00
7.8–11.0	2777 (22.7)	36 563	122.4	1.17 (0.99-1.38)	40.4	1.04 (0.78-1.39)	47.3	1.15 (0.9-1.48)
≥11.1	375 (3.1)	5019	172.4	1.68 (1.23-2.28)[b]	66.1	1.78 (1.07-2.95)[c]	69.8	1.61 (0.99-2.63)
HbA_{1c} groups by WHO,[d] %								
<6.0	2558 (61.8)	25 858	74.3	1.00	20.9	1.00	39.2	1.00
6.0–6.4	1326 (32)	14 703	84.5	1.25 (0.90-1.72)	23.6	1.23 (0.67-2.25)	31.0	0.83 (0.5-1.36)
≥6.5	258 (6.2)	2914	94.4	1.26 (0.72-2.21)	41.8	2.02 (0.83-4.93)	41.6	1.00 (0.45-2.23)
HbA_{1c} groups by ADA,[d] %								
<5.7	1489 (36)	14 293	83.6	1.00	21.4	1.00	43.7	1.00
5.7–6.4	2395 (57.8)	26 268	74.9	0.99 (0.71-1.37)	22.1	1.16 (0.63-2.14)	32.2	0.75 (0.47-1.19)
≥6.5	258 (6.2)	2914	94.4	1.15 (0.64-2.06)	41.8	2.06 (0.78-5.43)	41.6	0.89 (0.38-2.04)

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; HDL, high-density cholesterol; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

[a]Adjusted for age, sex, education, occupation, smoking, BMI, waist circumference, HDL-cholesterol, triglycerides, systolic blood pressure and self-reported history of cancer and cardiovascular disease.

[b]$P < .01$.

[c]$P < .05$.

[d]4143 participants with normal fasting glucose measured HbA1c were included.

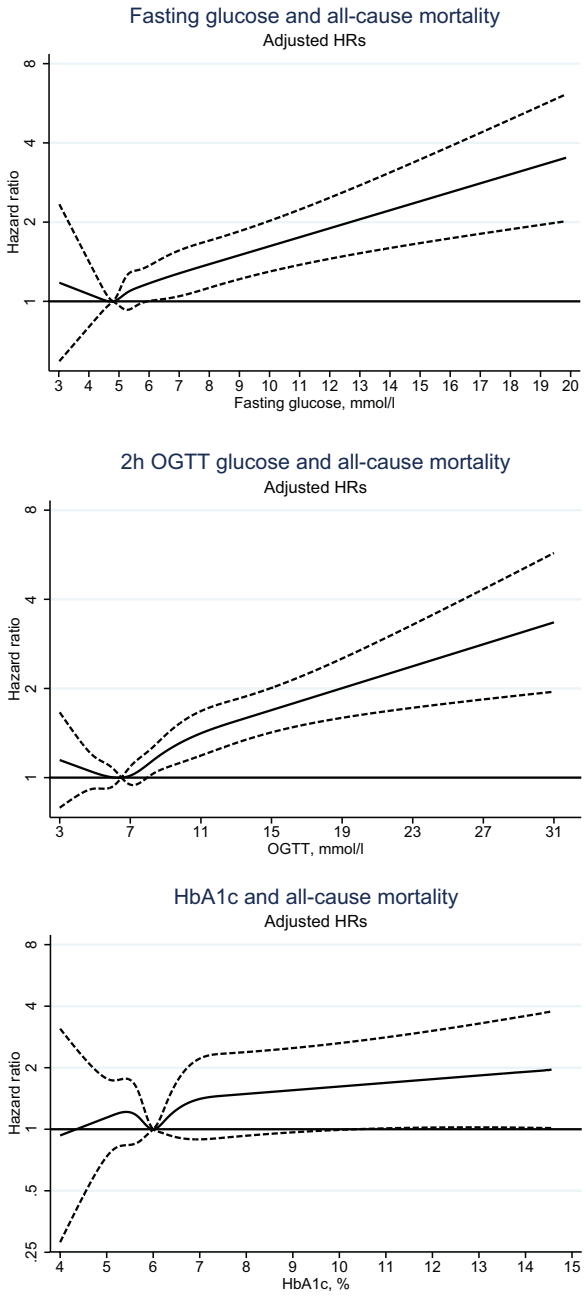

Figure 1. Association of fasting plasma glucose, 2-hour postload glucose, and hemoglobin A1c with all-cause mortality in 17 939 participants of the Guangzhou Biobank Cohort Study recruited during 2008–2012 and followed until December 2017. All hazard ratios and 95% confidence intervals (dashed lines) were adjusted for age, sex, education, occupation, smoking, body mass index, waist circumference, triglycerides, systolic blood pressure, and self-reported history of cancer and cardiovascular disease. A total of 6074 participants with hemoglobin A1c data were analyzed.

Discussion

Our analysis of a large Chinese cohort with more than 140 000 person-years of follow-up showed that individuals with isolated elevated 2-hour postload glucose had significantly increased risk of all-cause mortality by 43% than those with normoglycemia. In our study, 28% of T2DM and 54% of prediabetes (IFG/IGT) would not have been identified without measuring 2-hour postload glucose, highlighting its importance. Among participants with normal fasting glucose, 3.1% had T2DM defined by postload glucose and were associated with a higher risk of all-cause mortality (HR, 1.68; 95% CI, 1.23-2.28). T2DM defined by elevated HbA1c was significantly associated with a higher risk of CVD mortality.

Our results are consistent with previous studies showing that using fasting glucose only to define T2DM might fail to identify up to one-fifth of the newly diagnosed diabetes (3, 19), and hyperglycemia defined by 2-hour postload glucose predicted premature death better than that defined by fasting glucose alone (20–23). Our study showed that individuals with isolated elevated postload glucose had a higher all-cause mortality risk by 43% (95% CI, 15-78). OGTT is much less frequently used. Using solely FPG to rule out abnormal glucose tolerance would falsely reassure a large proportion of individuals as having normoglycemia, and these individuals are likely to miss the opportunity for preventive interventions. Note that, in our study, the comprehensive glycemia measures at baseline were likely to have helped to deliver a warning to those who were diabetic or had prediabetes and changes in lifestyles or antidiabetic medication might have been taken up in this group. These may lead to a reduced mortality in these individuals and therefore the risk we observed could well be an underestimation of the true effect of postload hyperglycemia on mortality risk.

In earlier reports from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, one-half of the patients with newly diagnosed T2DM were defined by the 2-hour postload glucose criteria (24, 25). In our study, 40% of participants with newly diagnosed T2DM had elevated postload glucose by 2-hour OGTT, and of these participants with postload glucose diabetes, 26% had normal fasting glucose. We found a slightly higher proportion of individuals with newly diagnosed T2DM who had elevated 2-hour postload glucose than that reported in the DECODE study, supporting perhaps a more important role of postload glucose measurement in the diagnosis of diabetes and mortality risk prediction in Chinese patients (2).

In our study, 28% of the participants who had diabetes according to the 2-hour postload glucose criteria were classified as normal according to the fasting glucose criteria. These participants had a 51% higher risk for CVD mortality compared with participants who had strictly normal levels for both fasting and OGTT glucose criteria. Inclusion of the 2-hour postload

glucose with the fasting glucose criteria significantly improved the predictions. Moreover, our study found that T2DM was associated with a 30% increased risk of total cancer, which was comparable to results from a pooled analysis of 19 prospective cohort studies in the Asia (the HR for cancer mortality from T2DM was 1.26) (26). In another previous meta-analysis of studies conducted mainly in the West, T2DM was associated with a 21% higher risk for cancer mortality (27). Overall, our findings and others support a robust and reliable association of diabetes with CVD and cancer in the Chinese population.

HbA1c has been used as an objective marker of average glycemic control in patients with diabetes for many years but has also been recommended by the ADA as a method to diagnose diabetes since 2009 (13). However, controversies about the diagnosis of T2DM using HbA_{1c} exist (28, 29). On the basis of mortality risk over approximately 8 years of follow-up of those with isolated elevated HbA_{1c}, our results do not support the use of HbA_{1c} in addition to OGTT or fasting glucose in risk classification in the community. The adoption of the HbA_{1c} as a diagnostic method in community settings needs to be further assessed.

The strengths of our study included comprehensive measurements of glycemic markers especially 2-hour postload glucose level in a large sample, detailed, and accurate information on deaths, and controlling for a wide range of potential confounding factors. However, there were some limitations. First, the duration of follow-up may not be sufficient, especially for some subgroup analyses (ie, subgroups of FPG within participants with normal 2-hour postload glucose levels or groups of HbA_{1c}). However, increased mortality risks with the relatively short follow-up highlight the considerable impact on life expectancy from T2DM. Second, only a limited number of participants had both 2-hour postload glucose and HbA1c measured during the first examination (2003–2008). Thus, we could not compare the effects of progression in these glycemic measures on death. Third, assessments of glycemic status during the second examination relied on repeated measurements, but not all participants returned for the second examination. Compared with those who participated in the second examination (who must be survivors and healthy enough to come back), nonparticipants tended to be older and have poorer health status at the first examination (15). Such a potential selection bias might have influenced the association between glycemic measures and mortality risk and attenuated the results toward the null. However, we used inverse probability weighting to account for this potential selection bias, although the true effect on mortality risk might be clearer with a longer duration of follow-up.

In conclusion, our study showed that 28% of participants with T2DM in our cohort were identified by 2-hour postload glucose alone. Participants with elevated 2-hour postload glucose levels had a higher risk of mortality than those with elevated fasting glucose or HbA_{1c}. The OGTT remains the most valuable test in diagnosing T2DM. Relying only on fasting glucose or HbA_{1c} misses a substantial proportion of people with higher risk of mortality. Consideration should be given to the use of OGTT, despite being cumbersome, in regular health checks in China.

Acknowledgments

The Guangzhou Biobank Cohort Study investigators include: Guangzhou No. 12 Hospital: W.S. Zhang, M. Cao, T. Zhu, B. Liu, C.Q. Jiang (co-principal investigator); The University of Hong Kong: C.M. Schooling, S.M. McGhee, G.M. Leung, R. Fielding, T.H. Lam (co-principal investigator); The University of Birmingham: P. Adab, G.N. Thomas, K.K. Cheng (co-principal investigator).

Financial Support: This work was funded by the Guangdong Natural Science Foundation (2018A030313140) and the Guangzhou Science and Technology Bureau, Guangzhou, China (201704030132).

Author Contributions: C.Q.J., L.X., T.H.L., K.K.C., G.N.T., and Y.L.J. have substantial contributions to conception and design, acquisition of funding, data, and interpretation of data; Y.L.J. and L.X. analyzed the data; C.Q.J., L.X., T.H.L., K.K.C., G.N.T., and Y.L.J. drafted the article; C.Q.J., L.X., T.H.L., K.K.C., G.N.T., W.S.Z., F.Z., and Y.L.J. revised it critically for important intellectual content; and all authors contributed to final approval of the paper.

Additional Information

Correspondence and Reprint Requests: Lin Xu, PhD, or Tai Hing Lam, MD, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong Province, China. E-mail: xulin27@mail.sysu.edu.cn.

Disclosure Summary: The authors have nothing to disclose.

Data availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;**87**(1):4–14.
2. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;**301**(20):2129–2140.

3. Xu Y, Wang L, He J, et al.; 2010 China Noncommunicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. *JAMA*. 2013;**310**(9):948–959.
4. Yang W, Lu J, Weng J, et al.; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med*. 2010;**362**(12):1090–1101.
5. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol*. 2014;**2**(6):474–480.
6. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997;**20**:1183–1197.
7. World Health Organization/International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. Geneva: World Health Organization; 2006. https://apps.who.int/iris/handle/10665/43588. Deposited 21 December 2019.
8. Balkau B. New diagnostic criteria for diabetes and mortality in older adults. DECODE study group. European Diabetes Epidemiology Group. *Lancet*. 1999;**353**(9146):68–69.
9. Bragg F, Holmes MV, Iona A, et al.; China Kadoorie Biobank Collaborative Group. association between diabetes and cause-specific mortality in rural and Urban Areas of China. *JAMA*. 2017;**317**(3):280–289.
10. Jiang C, Thomas GN, Lam TH, et al. Cohort profile: the Guangzhou Biobank Cohort Study, a Guangzhou-Hong Kong-Birmingham collaboration. *Int J Epidemiol*. 2006;**35**(4):844–852.
11. Xu L, Jiang C, Schooling C, Zhang W, Cheng K, Lam T. Liver enzymes and incident diabetes in China: a prospective analysis of 10 764 participants in the Guangzhou Biobank Cohort Study. *J Epidemiol Commun Health*. 2015;**69**(11):1040–1044.
12. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;**37**(Supplement 1):S14–S80.
13. World Health Organization. Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. 2011. https://apps.who.int/iris/handle/10665/70523. Deposited 21 December 2019.
14. Hogan JW, Roy J, Korkontzelou C. Handling drop-out in longitudinal studies. *Stat Med*. 2004;**23**(9):1455–1497.
15. Xu L, Lam TH, Jiang CQ, et al. Adiposity and incident diabetes within 4 years of follow-up: the Guangzhou Biobank Cohort Study. *Diabet Med*. 2017;**34**(10):1400–1406.
16. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. *Br J Cancer*. 2004;**91**(7):1229–1235.
17. Andersen PK, Abildstrom SZ, Rosthøj S. Competing risks as a multi-state model. *Stat Methods Med Res*. 2002;**11**(2):203–215.
18. Xu L. Supporting information from "Glycaemic measures and risk of mortality in older Chinese: the Guangzhou Biobank Cohort Study." https://datadryad.org/stash/dataset/doi:10.5061/dryad.mkkwh70v9 Dryad Digital Repository 2017. Deposited 25 September 2019.
19. Xu Y, Zhao W, Wang W, et al.; 2010 China Noncommunicable Disease Surveillance Group. Plasma glucose and hemoglobin A1c for the detection of diabetes in Chinese adults. *J Diabetes*. 2016;**8**(3):378–386.
20. Barrett-Connor E. The oral glucose tolerance test, revisited. *Eur Heart J*. 2002;**23**(16):1229–1231.
21. Bartoli E, Fra GP, Carnevale Schianca GP. The oral glucose tolerance test (OGTT) revisited. *Eur J Intern Med*. 2011;**22**(1):8–12.
22. Nakagami T; DECODA Study Group. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia*. 2004;**47**(3):385–394.
23. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *Bmj*. 2017;**356**:i6538.
24. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes epidemiology: collaborative analysis of diagnostic criteria in europe. *Lancet*. 1999;**354**(9179):617–621.
25. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. *BMJ*. 1998;**317**(7155):371–375.
26. Chen Y, Wu F, Saito E, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771 000 individuals in the Asia Cohort Consortium. *Diabetologia*. 2017;**60**(6):1022–1032.
27. Noto H, Tsujimoto T, Noda M. Significantly increased risk of cancer in diabetes mellitus patients: a meta-analysis of epidemiological evidence in Asians and non-Asians. *J Diabetes Investig*. 2012;**3**(1):24–33.
28. Mostafa SA, Davies MJ, Srinivasan BT, Carey ME, Webb D, Khunti K. Should glycated haemoglobin (HbA1c) be used to detect people with type 2 diabetes mellitus and impaired glucose regulation? *Postgrad Med J*. 2010;**86**(1021):656–662.
29. Misra A, Garg S. HbA1c and blood glucose for the diagnosis of diabetes. *Lancet*. 2011;**378**(9786):104–106.