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Glycaemic measures and risk of mortality in older Chinese: the Guangzhou Biobank Cohort Study

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Abstract

Context: China has the largest number of people with type 2 diabetes mellitus (T2DM) in the world. Data from previous studies 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 hyperglycaemia with mortality in the general Chinese population.

Design: Prospective cohort study

Setting: China

Participants: 17,939 participants aged 50+ years

Exposures: Previously diagnosed diabetes and newly detected diabetes defined by fasting glucose (≥7.0 mmol/L), 2h post-load glucose (≥11.1 mmol/L), or haemoglobin 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 (standard deviation=1.5) years' follow-up, 1,439 deaths were recorded. Of 3,706 participants with T2DM, 2126 (57%) had known T2DM, 118 (3%) were identified by isolated elevated fasting glucose, 1022 (28%) had isolated elevated post-load glucose, and 440 (12%) had both elevated fasting and post-load glucose. Compared to normoglycaemia, the HR (95% CI) 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 four groups above, respectively. T2DM defined by elevated HbA_{1c} was not significantly associated with all-cause mortality (HR 1.17, 95%

0.81-1.69).

Conclusion: Individuals with isolated higher 2h post-load glucose had a higher risk of mortality by 43% than those with normoglycaemia. Under-use of OGTT leads to substantial under-detection of individuals with a higher mortality risk and lost opportunities for early intervention.

Introduction

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 hyperglycaemia facilitates early intervention to attenuate the development of complications, and reduce the associated mortality.(5) Current definitions recommend the use of the 2h post-load 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 2h post-load glucose in the diagnosis of T2DM was primarily based on evidence from the western populations that individuals with elevated 2h post-load glucose had a higher risk of mortality, independent of their fasting glucose levels.(6,8)

Although OGTT has been included as one 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 under-use of OGTT leads to substantial under-diagnosis of diabetes in China.(3) However, there is no information on the mortality risk of these individuals, since previous studies in China on the long-term effect of T2DM on mortality did not measure 2h post-load glucose.(9) In the present study we analysed data from the Guangzhou Biobank Cohort Study to assess the association of prediabetes and T2DM defined by FPG, 2h post-load 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 above for a nominal fee of 4 CNY (≈50 US cents) 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 2h post-load glucose was only measured in 1,303 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.

Glycaemic measures

Both fasting and 2h post-load glucose were measured. An OGTT was not performed for those with self-reported physician diagnosis of diabetes or with glucose-lowering treatment. Due to the constraints in funding, HbA_{1c} was measured only in 6,074 participants who returned after May 2010. T2DM was defined by FPG ≥7.0 mmol/l, 2h post-load glucose ≥11.1 mmol/l, or by a history of self-reported physician-diagnosed diabetes (known T2DM). Impaired fasting glucose (IFG) was defined by a FPG level of 5.6–6.9 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 2h post-load glucose of 7.8–11.0 mmol/L according to the definition by both WHO and ADA.(6,7) Elevated HbA_{1c} was defined by an HbA_{1c} of 5.7-6.4% by the ADA, or 6.0-6.4 % by the WHO.(13) Prediabetes was defined as the presence of IFG and/or IGT, and without T2DM. Normoglycaemia 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 (GCDC). Causes of death were coded according to the 10^{th} revisions of the International Classification of Diseases (ICD) by trained nosologists in each hospital. When the death certificates were not issued by medical institutions (and hence might have quality issue with the coding), the causes of death were verified by GCDC as part of their quality assurance programme by cross-checking past medical history and conducting verbal autopsy.

From 2015 to 2018, eleven 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 (ICD-10).

Statistical analysis

Associations of hyperglycaemia or glycaemic measures with mortality were estimated by Cox regression. As no evidence of violation for the proportional hazard assumption was found by checking Schoenfeld residuals using "stphtest" command in STATA, the Cox proportional hazards model was used to calculate adjusted hazard ratios (HRs) with 95% confidence interval (CI). As the current analysis included participants who attended the second examination from 2008 to 2012, to partly account for potential influence due to lost to follow-up for repeated physical examination, we used inverse probability weighting to adjust for non-response in estimation of relative mortality risk.(14) The characteristics for participants in the 1st examination (2003-8) and those who returned for the 2nd examination (2008-12) 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 CVD and cancer, smoking status and clinical parameters that could be common causes of both hyperglycaemia 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 31 December 2017. Potential interactions between glycaemic 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. As no significant interaction was found between glycaemic 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 0.08 to 0.89), 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<0.05 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 2h post-load glucose, giving 17,939 participants (13,055 women and 4,884 men) in this paper. Of the 17,939 participants, after an average follow-up of 7.8 (standard deviation (SD) =1.5) years, 1,439 (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 (Supplementary Table 1) (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 non-manual occupation),

more smokers and alcohol users, and lower level of physical activity (all P <0.001). Moreover, those with T2DM also had greater WC, higher systolic and diastolic blood pressure, higher levels of triglycerides, fasting and 2h post-load glucose and HbA_{1c}, and higher prevalence of self-reported history of CVD and cancer (P from <0.001 to 0.02).

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 to normoglycaemia, the adjusted HR of all-cause mortality for diabetes defined by FPG using WHO and ADA 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 to normal 2h post-load 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 2h post-load 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 2h post-load glucose (and potential confounders) were mutually adjusted for each other, the association of 2h post-load 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 non-significant (Supplementary Table 2 of the online repository (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 only associated with CVD mortality (HR 2.45, 95% CI 1.39, 4.3 and 2.22, 95% CI 1.18, 4.18, respectively), but not with all-cause or cancer mortality (Table 2).

Among participants with IFG or IGT, half (54%) of them had IGT only, 23% had IFG only, and 23% had both IGT and IFG (Supplementary Table 3 of the online repository (18)). Table 3 shows that compared to normoglycaemia defined by normal fasting and 2h post-load glucose, IFG only was not associated with all-cause, CVD or cancer mortality, IGT only was associated with a higher risk of all-cause mortality (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, 1,580 were newly diagnosed T2DM by the repeated examination. Of the participants with T2DM, 28% were diagnosed by high 2h post-load glucose only, 3% by high FPG only, and 12% by both high 2h post-load glucose and FPG (Supplementary Table 3 of the online repository (18)). Table 3 shows that T2DM diagnosed by elevated 2h post-load 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 only was not associated with mortality. As expected, new T2DM defined by both high 2h post-load 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 2h post-load 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 2h post-load glucose levels was associated with a higher risk of all-cause and CVD mortality (HR 1.68 (1.23, 2.28) and 1.78 (1.07, 2.95), respectively). However, in participants with normal FPG, no significant association of elevated HbA_{1c} with mortality was found, although the non-significant association with CVD mortality could be due to small number of participants (HR 2.02, 95% CI 0.83, 4.93) (Table 4). In participants with normal 2h post-load glucose levels, no association of FPG or HbA_{1c} with all-cause mortality was found (Supplementary Table 4 of the online repository (18)).

Increasing FPG, 2h post-load glucose levels and HbA_{1c} was associated with a higher risk of mortality, and the optimum values for these glycaemic measures were 5.0 mmol/l, 6.5 mmol/l and 6.0%, respectively (Figure 1, Supplementary Figure 1 of the online repository (18)). Sensitivity analysis showed that the association of hyperglycaemia, including T2DM (never *versus* known and newly diagnosed T2DM), IFG, IGT and high HbA_{1c} with all-cause mortality did not vary by sex and age groups (Supplementary Figure 2 of the online repository (18)). Supplementary Figure 3 shows that adding FPG and/or HbA_{1c} did not improve predictive capability of post-load glucose for all-cause mortality (Area under ROC increased by 0.001-0.002).

Discussion

Our analysis of a large Chinese cohort with more than 140,000 person-years of follow-up showed that individuals with isolated elevated 2h post-load glucose had significantly increased risk of all-cause mortality by 43% than those with normoglycaemia. In our study, 28% of T2DM and 54% of prediabetes (IFG/IGT) would not have been identified without measuring 2h post-load glucose, highlighting its importance. Among participants with normal fasting glucose, 3.1% had T2DM defined by post-load glucose and were associated with a higher risk of all-cause mortality (HR 1.68, 95% 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 hyperglycaemia defined by 2h post-load glucose predicted premature death better than that defined by fasting glucose alone.(20-23) Our study showed that individuals with isolated elevated post-load 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 normoglycaemia and these individuals are likely to miss the opportunity for preventive interventions. Note that in our study, the comprehensive glycaemia 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 anti-diabetic 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 post-load hyperglycemia on mortality risk.

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

In our study, 28% of the participants who had diabetes according to the 2-hour post-load glucose criteria were classified as normal according to the fasting glucose criteria. These participants had a 51% higher risk for CVD mortality compared to participants who had strictly normal levels for both fasting and OGTT glucose criteria. Inclusion of the 2-hour post-load 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 glycaemic 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 glycaemic markers especially 2h post-load 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, i.e., subgroups of FPG within participants with normal 2h post-load 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 2h post-load glucose and HbA1c measured during the first examination (2003-8). Thus we could not compare the effects of progression in these glycaemic measures on death. Third, assessments of glycaemic status during the second examination relied on repeated measurements but not all participants returned for the second examination. Compared to those who participated in the second examination (who must be survivors and healthy enough to come back), non-participants 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 glycaemic measures and mortality risk and attenuated the results towards 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 2h post-load glucose alone. Participants with elevated 2h post-load 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.

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Conflict of interest

The authors have no competing interests.

Contribution statement

CQJ, LX, THL, KKC, GNT and YLJ have substantial contributions to conception and design, acquisition of funding, data and interpretation of data; YLJ and LX analyzed the data, CQJ, LX, THL, KKC, GNT and YLJ drafted the article, CQJ, LX, THL, KKC, GNT, WSZ, FZ and YLJ revised it critically for important intellectual content, and all authors contributed to final approval of the paper.

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Figure Legend:

Figure 1. Association of fasting plasma glucose, 2h post-load glucose and HbA1c with all-cause mortality in 17,939 participants of the Guangzhou Biobank Cohort Study recruited during 2008-12 and followed up till December 2017.

Note: (1) All HRs and 95% CIs (dash lines) were adjusted for age, sex, education, occupation, smoking, BMI, waist circumference, triglycerides, systolic blood pressure and self-reported history of cancer and cardiovascular disease.

(2) 6,074 participants with HbA1c data were analysed.

Table1. Baseline demographic characteristics and biochemical parameters of 17,939 participants

Characteristics	Type 2 Diabetes by					
	No (n=14,233)	High FPG only (n=118)	High 2h post-load glucose only (n=1,022)	Both high fasting and 2h post-load glucose (n=440)	Self-reported Physician diagnosed (n=2,126)	P-value
Men, %	27.4	33.9	25.7	27.5	26.3	0.30
Age[#], years	64.8 (7.1)	65.9 (7.1)	67 (6.5)	65.8 (7)	67.1 (6.6)	<0.001
Education (college or above), %	9.1	9.3	9.1	8.6	10.1	<0.001
Occupation (manual), %	60.4	59.8	59.5	66.3	58.0	<0.001
Current smokers, %	9.0	11.1	6.3	5.9	6.2	<0.001
Current drinkers, %	18.5	16.2	17.9	21.0	13.1	<0.001
IPAQ Physical activity (active), %	79.1	76.3	72.8	80.2	74.2	<0.001
BMI[#], kg/m^2	23.6 (3.4)	24.9 (3.8)	25.2 (3.6)	25.7 (3.5)	24.4 (3.5)	<0.001
WC[#], cm	81.5 (9.2)	85.9 (9.9)	85.8 (9)	87.6 (8.4)	84.4 (9.1)	<0.001
Triglycerides[#], mmol/l	1.6 (1.1)	1.8 (1.2)	2.2 (1.6)	2.5 (2.7)	2.1 (1.9)	<0.001
HDL-cholesterol[#], mmol/l	1.4 (0.4)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	<0.001
LDL-cholesterol[#], mmol/l	3.5 (0.8)	3.5 (0.8)	3.6 (0.9)	3.6 (1)	3.4 (0.9)	<0.001
Total cholesterol[#], mmol/l	5.8 (1.1)	5.8 (1)	5.9 (1.1)	6 (1.2)	5.7 (1.2)	0.97
Systolic blood pressure[#], mmHg	129.9 (38.4)	136.1 (19.1)	141.6 (32.1)	142.1 (21.5)	138.3 (29)	<0.001
Diastolic blood pressure[#], mmHg	72.6 (12.9)	75.7 (10.9)	76.2 (10.5)	77.1 (10.6)	73.8 (16.5)	<0.001
Fasting plasma glucose[#], mmol/l	5.1 (0.5)	7.9 (1.2)	5.9 (0.6)	9.3 (3.1)	7.6 (2.7)	<0.001
2h post-load glucose[#], mmol/l	6.9 (1.7)	8.4 (1.8)	13.1 (1.7)	18.3 (4.8)	9.6 (4.4)	<0.001
HbA1c[#†], %	5.9 (0.5)	6.2 (1.2)	6.4 (0.7)	8.6 (4)	7.3 (1.6)	<0.001
Self-reported history of CVD, %	9.3	17.0	13.1	10.5	16.2	<0.001
Self-reported history of cancer, %	1.7	1.7	1.9	2.1	2.5	0.02

IPAQ: International Physical Activity Questionnaire; BMI: body mass index; WC, waist circumference; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein; CVD: cardiovascular disease.

[#]: Data were expressed as mean± SD

[†]: 6,074 participants with HbA1c data were analysed.

Table 2 Mortality rate (per 10000 Person-years) and adjusted hazard ratios (HRs) of deaths from all-cause, cardiovascular disease and cancer by glycaemic indicators in 17,939 participants of the Guangzhou Biobank Cohort Study recruited during 2008-12 and followed up till December 2017.

	Person-years/ Number	All-cause (n=1,439)		Cardiovascular disease (n=500)		Cancer (n=590)	
		Rate	HR (95% CI)[†]	Rate	HR (95% CI)[†]	Rate	HR (95% CI)[†]
FPG, mmol/l	231362/1439	113.9	1.1 (1.07, 1.13)***	40.6	1.12 (1.08, 1.16)***	45.0	1.06 (1.02, 1.11)**
FPG groups by WHO, mmol/l							
<6.1	181825/1019	101.2	1.00	34.9	1.00	42.3	1.00
6.1-6.9	12663/83	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)**	56.0	1.57 (0.99, 2.47)	63.3	1.40 (0.92, 2.14)
Known T2DM	29448/274	178.2	1.57 (1.36, 1.82)***	72.5	1.81 (1.44, 2.29)***	56.2	1.27 (1.00, 1.62)*
FPG groups by ADA, mmol/l							
<5.6	156304/866	99.8	1.00	34.1	1.00	41.4	1.00
5.6-6.9	38185/236	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)**	56.0	1.6 (1.01, 2.53)*	63.3	1.42 (0.93, 2.18)
Known T2DM	29448/274	178.2	1.58 (1.37, 1.83)***	72.5	1.85 (1.46, 2.35)***	56.2	1.29 (1.01, 1.65)*
2h post-load glucose, mmol/l	231362/1439	113.9	1.05 (1.03, 1.07)***	40.6	1.06 (1.03, 1.09)***	45.0	1.04 (1.01, 1.07)**
2h post-load glucose groups, mmol/l							
<7.8	129340/650	90.0	1.00	30.0	1.00	38.8	1.00
7.8-11.0	53055/357	122.8	1.19 (1.04, 1.37)*	43.2	1.21 (0.95, 1.53)	49.0	1.19 (0.96, 1.47)
≥11.1	19519/158	151.1	1.54 (1.28, 1.86)***	55.5	1.70 (1.25, 2.32)**	58.8	1.44 (1.07, 1.95)*
Known T2DM	29448/274	178.2	1.71 (1.47, 2)***	72.5	2.02 (1.57, 2.6)***	56.2	1.38 (1.07, 1.77)*
HbA1c,[‡] %	86623/1439	112.2	1.07 (1.02, 1.11)**	40.5	1.08 (1.03, 1.14)**	42.7	1.02 (0.89, 1.17)
HbA_{1c} groups by WHO,[‡] %							
<6.0	30120/128	74.5	1.00	19.5	1.00	39.4	1.00
6.0-6.4	19554/84	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)**	32.4	0.71 (0.39, 1.3)
Known T2DM	29448/274	178.2	1.68 (1.33,	72.5	2.58 (1.69, 3.95)***	56.2	1.20 (0.83, 1.72)

			2.13)***					
HbA_{1c} groups by ADA,‡ %								
<5.7	16306/80	88.1	1.00		21.6	1.00	46.9	1.00
5.7-6.4	33367/132	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)*	32.4	0.60 (0.32, 1.14)
Known T2DM	29448/274	178.2	1.45 (1.11, 1.91)**		72.5	2.35 (1.41, 3.9)**	56.2	1.02 (0.68, 1.53)
T2DM by FPG only#								
No	194489/998	102.4	1.00		35.2	1.00	42.6	1.00
Yes	36873/441	174.5	1.54	(1.35,	69.2		57.6	
			1.76)***			1.76 (1.42, 2.18)***		1.29 (1.04, 1.6)*
T2DM by FPG+2h post-load glucose#								
No	180761/1102	99.5	1.00		33.9	1.00	41.7	1.00
Yes			1.52 (1.35,					
	50601/337	165.4	1.72)***		64.4	1.73 (1.42, 2.11)***	56.8	1.30 (1.06, 1.58)*
T2DM by2h post-load glucose only								
No	182395/1007	99.5	1.00		33.9	1.00	42.0	1.00
Yes			1.54 (1.36,		64.9			
	48967/432	167.4	1.74)***			1.72 (1.41, 2.12)***	57.7	1.32 (1.08, 1.6)**

FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; WHO: World Health Organization; ADA: American Diabetes Association; HbA1c: glycosylated haemoglobin A1c; T2DM: Type 2 diabetes mellitus

†: 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.

‡: 6,074 participants with HbA1c data were analysed.

#: T2DM was defined by FPG ≥7.0 mmol/l (by FPG only), 2h post-load glucose≥11.1 mmol/l (by FPG+2h post-load glucose), or by a history of self-reported physician-diagnosed diabetes (known T2DM).

*: P<0.05; **: P<0.01; ***: P<0.001

Table 3 Mortality rate (per 10000 Person-years) and adjusted hazard ratios (HRs) of deaths from all-cause, cardiovascular disease and cancer by status of diabetes mellitus (DM), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) in 17,939 participants of the Guangzhou Biobank Cohort Study recruited during 2008-12 and followed up till December 2017.

		All-cause (n=1,439)			Cardiovascular disease (n=500)		Cancer	(n=590)
	N (%)	Person-years	Rate	HR (95% CI)[†]	Rate	HR (95% CI)[†]	Rate	HR (95% CI)[†]
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)*	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)*	53.0	1.29 (0.92, 1.80)
New T2DM by:								
high FPG only	118 (0.7)	1,634	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 2h post-load glucose only	1022 (5.7)	13,727	140.9	1.43 (1.15, 1.78)**	51.6	1.51 (1.05, 2.17)*	54.8	1.33 (0.93, 1.92)
both high fasting and 2h post-load glucose	440 (2.5)	5,792	175.4	1.82 (1.35, 2.45)***	64.8	2.01 (1.22, 3.29)**	68.3	1.75 (1.09, 2.79)*
Self-reported physician diagnosed	2126 (11.9)	29,448	178.2	1.71 (1.46, 2.00)***	72.5	1.96 (1.52, 2.53)***	56.2	1.39 (1.08, 1.80)*

IFG: Impaired fasting glucose; IGT: impaired glucose tolerance; FPG: fasting plasma glucose; ADA: American Diabetes Association

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

[†]: 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.

*: P<0.05; **: P<0.01; ***: P<0.001

Table 4 Mortality rate (per 10000 Person-years) and adjusted hazard ratios (HRs) of deaths from all-cause, cardiovascular disease and cancer by 2h post-load glucose and HbA1c status in 12,258 participants of the Guangzhou Biobank Cohort Study with normal fasting plasma glucose (<5.6mmol/l) recruited during 2008-12 and followed up till December 2017.

			All-cause (n=866)		Cardiovascular disease (n=290)		Cancer (n=372)	
	N (%)	Person-years	Rate	HR (95% CI)[†]	Rate	HR (95% CI)[†]	Rate	HR (95% CI)[†]
2h post-load 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)	5,019	172.4	1.68 (1.23, 2.28)**	66.1	1.78 (1.07, 2.95)*	69.8	1.61 (0.99, 2.63)
HbA_{1c} groups by WHO,[‡] %								
<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)	2,914	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,[‡] %								
<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)	2,914	94.4	1.15 (0.64, 2.06)	41.8	2.06 (0.78, 5.43)	41.6	0.89 (0.38, 2.04)

WHO: World Health Organization; ADA: American Diabetes Association; HbA1c: glycosylated haemoglobin A1c

[†]: 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.

[‡]: 4,143 participants with normal fasting glucose measured HbA1c were included.

*: P<0.05; **: P<0.01; ***: P<0.001