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Impaired glucose tolerance predicts all-cause mortality among older men at high risk for cardiovascular disease in China

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ABSTRACT

Aims: To investigate the potential association between impaired glucose tolerance (IGT) and all-cause mortality among older men at high risk for cardiovascular disease (CVD) in China.
Methods: In this prospective observational study, 460 older men aged ≥60 years were determined to have either IGT or normal glucose tolerance (NGT) based on an oral glucose tolerance test conducted between May 2005 and May 2007. IGT and NGT were diagnosed according to the 1999 WHO diagnostic criteria. All subjects were followed until March 2017. The primary outcome studied was all-cause mortality. Multivariate Cox models were used to estimate relative risk for all-cause mortality.
Results: During a mean follow-up of 11.2 years, forty-three (21.4%) subjects in the IGT group and twenty-nine (11.2%) subjects in the NGT group died (HR 2.05, 95% CI 1.28–3.28, P = 0.003). Multivariate Cox proportional-hazards analysis demonstated that IGT was significantly associated with increased risk for all-cause mortality, composite cardiovascular outcome, nonfatal stroke and heart failure after adjusting for potential confounding factors. Logistic regression analysis showed that IGT at baseline (P < 0.05) rather than incident type 2 diabetes was a risk factor of all-cause mortality.
Conclusions: IGT was significantly associated with all-cause mortality in older Chinese men at high risk for CVD.

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1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has increased dramatically in China and elsewhere [1], and T2DM is associated with a substantial increase in all-cause mortality [2]. Impaired glucose tolerance (IGT), also known as pre-diabetic state, has been shown to be a significant risk factor for T2DM. Moreover, IGT itself is significantly associated with microvascular and cardiovascular complications [3]. Studies have shown increased prevalence of retinopathy and chronic kidney disease among subjects with IGT [4,5], and reversal of IGT to normal glucose regulation has been shown to significantly reduce the risk of cardiovascular diseases [6].

With regards to mortality, the relationship between IGT and mortality remains uncertain, especially in the elderly. Previous studies showed a significant association between IGT and mortality in the general population [7,8]. In contrast, Deedwania and colleagues observed that prediabetes was not an independent risk factor of mortality [9]. In addition, previous studies examining the relationship between IGT and all-cause mortality were conducted in diverse populations [10], and seldom focused on IGT subjects. Furthermore, data on such relationship is limited in the elderly, particularly among older adults in China. Therefore, the objective of the present study was to test the hypothesis that IGT would predict all-cause mortality in older men in China.

2. Methods

2.1. Study design

This is a prospective observational study. In this study, 460 community-dwelling older Chinese men were categorized as impaired glucose tolerance (IGT) or normal glucose tolerance (NGT) based on the results from an oral glucose tolerance test (OGTT) performed between May 2005 and May 2007. All subjects were followed without any intervention until March 1, 2017. Recruitment, study procedures for data collection, and prospective follow-up were conducted at Chinese PLA General Hospital in Beijing and approved by the local ethics committee. Informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

2.2. Inclusion and exclusion criteria

Major inclusion criteria were community-dwelling men aged 60 years or older. Subjects meeting this inclusion criteria were administered an OGTT and categorized as isolated IGT or NGT accordingly. Major exclusion criteria included type 1 or type 2 diabetes; isolated impaired fasting glucose (IFG); IFG plus IGT; use of medications that may affect glucose metabolism, such as glucocorticoids or thyroid hormones; history of an acute coronary, cerebrovascular accident, or other acute events such as operation, trauma, and infection within one month.

2.3. Study procedures

At baseline, an 8 h overnight fasting venous blood specimen was collected for the measurement of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol (HDL-c), and creatinine. Information on demographic characteristics, personal and family medical history, physical examination, laboratory test outcomes were obtained. All participants were given a steamed bun which contained approximately 75 g of complex carbohydrates, and 2 h postprandial glucose (PPG) after carbohydrate load was measured using a Roche Accu-chek ® glucometer. OGTT was performed in participants with PPG $\geq$ 7.2 mmol/L. Blood samples were drawn at 0 h, 1 h, and 2 h after glucose load to measure glucose and insulin concentration. IGT (0hPG < 6.1 mmol/L and 7.8 $\leq$ OGTT 2hPG < 11.1 mmol/L) and NGT (0hPG < 6.1 mmol/L and OGTT 2hPG < 7.8 mmol/L) were diagnosed according to the 1999 World Health Organization diagnostic criteria [11]. 2018 ESC/ESH Guidelines for the management of arterial hypertension was used to diagnose hypertension [12]. Dyslipidemia was diagnosed according to 2016 Chinese guideline for the management of dyslipidemia in adults [13]. Metabolic syndrome (MS) was defined according to the 2005 IDF consensus worldwide definition [14]. HOMA2 model was used to determine insulin resistance (HOMA2-IR), β cell function (HOMA2-%B), and insulin sensitivity (HOMA2-%S) [15,16]. Insulin sensitivity index [ISI (composite)] during the OGTT was used to evaluate the whole-body insulin sensitivity [17]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [18]. Plasma glucose was measured with a glucose oxidase method. Serum TC, TG, LDL-c and HDL-c were determined with enzymatic methods using Cobas® 8000 system (Roche Diagnostics). Serum insulin concentration was measured using a radioimmunoassay kit from American Diagnostic Products Corporation. The inter-assay coefficient of variability of insulin was 5.9–8.0%, and the intra-assay coefficient of variability was 5.2–6.4%.

After the enrollment, participants were followed without any intervention except for a routine annual visit at which a physical examination and laboratory testing were performed. Laboratory tests included FPG, TC, TG, LDL-c, and HDL-c, and 2 h postprandial venous plasma glucose (2hPG). Participants with elevated FPG, elevated 2hPG, or history of increased plasma glucose during the follow-up would be recommended further laboratory evaluation including glycosylated hemoglobin (HbA1c) or OGTT. HbA1c was measured using routine HPLC with a Variant II HbA1c analyzer (Bio-Rad Laboratories, Hercules, CA, USA). According to current guideline [19] in which HbA1c $\geq$ 6.5% was used to diagnose T2DM. Information from participants' medical record was collected to confirm clinical diagnoses, medication use or events both at baseline and during follow-up.

2.4. Outcomes

The primary outcome in the time-to-event analysis was all-cause mortality. The secondary composite cardiovascular outcome was the first confirmed event of cardiovascular cause

of death, nonfatal myocardial infarction, or nonfatal stroke. Other secondary outcomes included the first occurrence of heart failure, unstable angina, and cancer. Additional outcomes included incidence of T2DM, changes in FPG, 2hPG and HbA1c.

2.5. Statistics analysis

Data were presented as mean ± standard deviation (SD) for normally distributed continuous variables, and median (5th and 95th percentiles) for non-normal continuous variables. Comparison of variables between groups was performed using unpaired Student's *t* test or χ^2 test; otherwise, non-parametric analysis was applied. The average HbA1c level in every following year was calculated in every subject. The HOMA2-IR level was divided into quartiles in the subgroup analyses, and subjects were categorized into two groups, the highest quartile and other quartiles. The main analysis used the time-to-first-event approach. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from Cox proportional-hazards models with number of years since baseline as the time scale. Person-time was calculated from the date of baseline until death or the end of follow-up (March 1, 2017). Multivariate Cox proportional-hazards models were adjusted for the baseline variables such as age, body mass index (BMI), smoking history, HOMA2-IR, eGFR, and history of hypertension, dyslipidemia, coronary heart disease, and cancer. Independent significant risk factors for all-cause mortality were evaluated by multivariate logistic regression analysis. *P* values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 460 participants were enrolled into the study. There were 3 participants among the NGT group who did not have data regarding BMI, smoking history, or blood pressure at baseline. Fifteen (3.3%) participants were lost to follow-up. Of the 460 participants enrolled, 201 subjects (43.7%) had IGT at baseline as determined by OGTT. 22 cases in IGT group and 32 cases in NGT group were not included in the calculation of metabolic syndrome because there was no data of waist circumference at baseline. Table 1 summarizes major baseline demographic and clinical characteristics of the participants. Age, BMI, SBP, FPG, and 2hPG level were higher in IGT group compared with those in the NGT group ($P < 0.05$), while the proportion of smokers, level of DBP, TC, TG, LDL-c, HDL-c and eGFR were similar. Both study groups had similar frequencies of common medical diagnoses except for a greater incidence of hypertension in the IGT group than that in the NGT group (69.7% vs 54.4%, $p < 0.01$).

3.2. Insulin resistance and β cell function

0hPG, 1hPG and 2hPG during OGTT at baseline in the IGT group were all significantly increased compared to the NGT group ($P < 0.001$, Table 2). The 0hINS and 2hINS level in the IGT group were higher than the NGT group ($P < 0.01$), and 1hINS

Table 1 – Baseline characteristics of the participants.

Variables	IGT n = 201	NGT n = 259	P value
Age (year)	73.1 ± 8.0	71.4 ± 7.7	0.026
BMI (kg/m^2)	25.2 ± 2.8	24.6 ± 2.8	0.040
Smoking	66 (32.8)	72 (28.1)	0.242
SBP (mmHg)	133.0 ± 15.1	128.5 ± 14.2	0.001
DBP (mmHg)	76.6 ± 10.7	75.5 ± 10.0	0.251
FPG (mmol/L)	5.25 ± 0.42	5.08 ± 0.38	<0.001
PPG (mmol/L)	9.07 ± 1.23	8.49 ± 1.09	<0.001
TC (mmol/L)	4.95 ± 0.75	4.94 ± 0.87	0.934
TG (mmol/L)	1.56 ± 0.77	1.51 ± 0.83	0.472
HDL-c (mmol/L)	1.45 ± 0.29	1.46 ± 0.28	0.722
LDL-c (mmol/L)	2.87 ± 0.66	2.78 ± 0.78	0.188
eGFR (ml/min)	83.2 ± 18.4	84.9 ± 17.2	0.304
Medical diagnosis			
Hypertension	140 (69.7)	141 (54.4)	0.001
Hypertension on medication	124 (88.6)	126 (89.4)	0.833
Dyslipidemia	136 (67.7)	178 (68.7)	0.808
Dyslipidemia on medication	93 (68.4)	121 (68.0%)	0.939
Metabolic syndrome*	44 (24.6)	50 (22.0)	0.545
Coronary heart disease	101 (50.2)	126 (48.6)	0.734
Unstable angina	12 (6.0)	17 (6.6)	0.795
Acute myocardial infarction	10 (5.0)	17 (6.6)	0.472
Heart failure	0	1 (0.4)	–
Stroke	14 (7.0)	19 (7.3)	0.879
Cancer	16 (8.0)	17 (6.6)	0.565

Data were presented as mean ± SD or n (%).
The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.
* 22 cases in IGT group and 32 cases in NGT group were not included in the calculation of metabolic syndrome because there was no data of waist circumference at baseline.

Table 2 – Insulin resistance and β cell function of the participants at baseline.

Variables	IGT n = 201	NGT n = 259	P value
Oral glucose tolerance test (OGTT)			
0hPG (mmol/L)	5.20 ± 0.38	5.04 ± 0.36	<0.001
1hPG (mmol/L)	10.35 ± 1.94	8.85 ± 1.80	<0.001
2hPG (mmol/L)	9.07 ± 0.90	6.45 ± 0.91	<0.001
0hINS (mU/L)	5.6 (2.4, 15.6)	4.5 (2.0, 14.1)	0.006
1hINS (mU/L)	71.1 (21.9, 200.8)	66.5 (24.4, 183.0)	0.556
2hINS (mU/L)	82.5 (25.8, 265.9)	44.9 (14.0, 152.6)	<0.001
Insulin resistance and β cell function			
HOMA2-IR	0.75 (0.32, 2.04)	0.60 (0.26, 1.85)	0.004
HOMA2-%B	71.4 (39.2, 144.6)	67.8 (36.5, 141.5)	0.052
HOMA2-%S	135.4 (50.0, 316.9)	167.3 (54.1, 387.9)	<0.001
ISI (composite)	3.77 (1.38, 10.5)	5.54 (2.04, 13.2)	<0.001

Data were presented as mean ± SD or median (5th and 95th percentiles).
HOMA2 model was used to determine insulin resistance (IR), β cell function (%B), and insulin sensitivity (%S).
Insulin sensitivity index [ISI (composite)] during the OGTT was used to evaluate the whole-body insulin sensitivity.

was similar between both groups. Serum insulin response rose progressively from 1 h to 2 h in the IGT group, while it declined after 1 h in the NGT group.

Insulin resistance index HOMA2-IR in the IGT group was significantly higher than in the NGT group (P < 0.01, Table 2). β cell function demonstrated as HOMA2-%B in the IGT group was also higher than in the NGT group, nearly achieving statistical significance (P = 0.052). Insulin sensitivity index (ISI) and HOMA2-%S in the IGT group were both significantly lower than in the NGT group (P < 0.01).

3.3. Incident T2DM

The mean follow-up time was 11.2 years. Incident T2DM cases were 76 (37.8%) in the IGT group and 56 (21.6%) in the NGT group, and the risk for developing T2DM in the IGT group was 2.18 fold higher than in the NGT group (Fig. 1). After adjusting for age, BMI, smoking, HOMA2-IR, eGFR, and history of hypertension, dyslipidemia, and coronary heart disease, the IGT remained as a significant risk factor for developing T2DM compared to NGT (HR 2.26, 95%CI 1.58–3.22, P < 0.001).

3.4. Glycemic control

At baseline, the mean FPG in the IGT group was higher than in the NGT group (5.25 ± 0.42 vs. 5.08 ± 0.38 mmol/L, respectively, P < 0.001). During follow up, FPG increased gradually in both groups, though it remained higher in the IGT group than in the NGT group (e.g. FPG measurements at the end of the follow-up were 5.89 ± 0.89 vs. 5.64 ± 0.80 mmol/L, respectively, P = 0.017, Fig. A1).

Similarly, the mean 2hPG measured by glucometer in the IGT group was higher than in the NGT group (9.07 ± 1.23 vs. 8.49 ± 1.09 mmol/L, respectively, P < 0.001) at baseline (Table 1). While it increased gradually in both groups, the difference between the two groups remained statistically significant throughout follow-up (e.g., 2hPG measurements at the end of the follow-up were 9.86 ± 2.06 vs. 9.05 ± 1.96 mmol/L, respectively, P = 0.039).

While HbA1c was not measured at baseline, the two study groups did not differ significantly in the first year (5.76 ± 0.33 vs. 5.58 ± 0.31%, respectively, P = 0.166). However, HbA1c was measured in only a limited number of participants. Throughout follow-up, HbA1c increased gradually in both groups and became significantly higher in the IGT group than in the NGT group (e.g., HbA1c at the end of the follow-up were 6.22 ± 0.71 vs. 5.98 ± 0.42%, respectively, P = 0.009).

3.5. Cardiovascular outcomes and cancer

Compared with the NGT group, the IGT group had significantly increased risk for composite cardiovascular outcome, nonfatal stroke, and heart failure (Fig. 1). The risks of nonfatal myocardial infarction or unstable angina did not differ between the two groups.

Multivariable models were constructed to assess the risk between the two study groups after adjusting for a number of important variables (Table 3). Model 1 was adjusted for age, BMI, and smoking. Model 2 was further adjusted for HOMA2-IR and eGFR based on model 1. Model 3 was further adjusted for history of hypertension, dyslipidemia, coronary heart disease and cancer based on model 2. The risks of composite cardiovascular outcome, nonfatal stroke and heart failure in the IGT group remained significantly increased in all models (all P < 0.05) compared to the NGT group.

On the other hand, incident cancer cases were 54 (26.9%) in the IGT group and 55 (21.2%) in the NGT group, and the risk of cancer was not significantly different between the two groups (HR = 1.40, 95%CI 0.96–2.04, P = 0.079).

3.6. All-cause mortality

The primary outcome, all-cause mortality, was significantly higher in the IGT group (43, 21.4%) than in the NGT group (29, 11.2%) with a hazard ratio (HR) of 2.05 (95%CI 1.28–3.28, P = 0.003) (Fig. 1). After adjusting for age, BMI, smoking, HOMA2-IR, eGFR, hypertension, dyslipidemia, coronary heart disease, and cancer, risk for all-cause mortality in the IGT group remained significantly higher than in the NGT group, with a HR of 1.94 (95%CI 1.19–3.14, P = 0.008).

Further analyses have identified even higher risk for all-cause mortality in subsets of participants in the IGT group compared to the same subsets in the NGT group (Table 4). For example, HR for those BMI ≥25 kg/m^2 was 2.81 (95%CI 1.25–6.32, P = 0.013); HR for non-smokers was 2.55 (95%CI 1.18–5.52, P = 0.017); HR for those with HOMA2-IR in the highest quartile was 4.03 (95%CI 1.25–13.0, P = 0.020); HR for those with hypertension was 2.84 (95%CI 1.49–5.41, P = 0.001); HR for those with dyslipidemia was 2.04 (95%CI 1.16–3.60, P = 0.014). When stratified by eGFR, compared with NGT group, the risk of all-cause mortality was significantly higher among those with eGFR ≧90 ml/min in the IGT group (HR 5.75, 95%CI 1.51–21.9, P = 0.010). However, no such subgroup difference was identified when stratified by age or coronary heart disease.

3.7. Risk factors of all-cause mortality

To identify independent risk factors for all-cause mortality, a multivariate logistic model was performed. Risk factors such as baseline age (≥75 year, <75 year), baseline BMI (≥25 kg/m^2, <25 kg/m^2), baseline glucose metabolism (IGT, NGT), incident T2DM (yes, no), incident composite cardiovascular outcome (yes, no), and incident cancer (yes, no) were included in the model. Logistic regression analysis showed that baseline age (OR 15.3, 95%CI 7.14–32.8, P < 0.001), baseline glucose metabolism (OR 1.97, 95%CI 1.05–3.69, P = 0.035), incident composite cardiovascular outcome (OR 4.00, 95%CI 2.03–7.88, P < 0.001), incident cancer (OR 4.86, 95%CI 2.51–9.41, P < 0.001) were significant risk factors for all-cause mortality in the study, but not baseline BMI (OR 0.86, 95%CI 0.46–1.60, P = 0.635) or incident T2DM (OR 0.69, 95%CI 0.33–1.46, P = 0.338).

4. Discussion

This study reports, for the first time, that IGT at baseline was associated with significantly increased risk for all-cause mortality in community-dwelling older Chinese men at high risk for CVD. In addition, IGT was associated with significantly increased risk for incident T2DM, composite cardiovascular

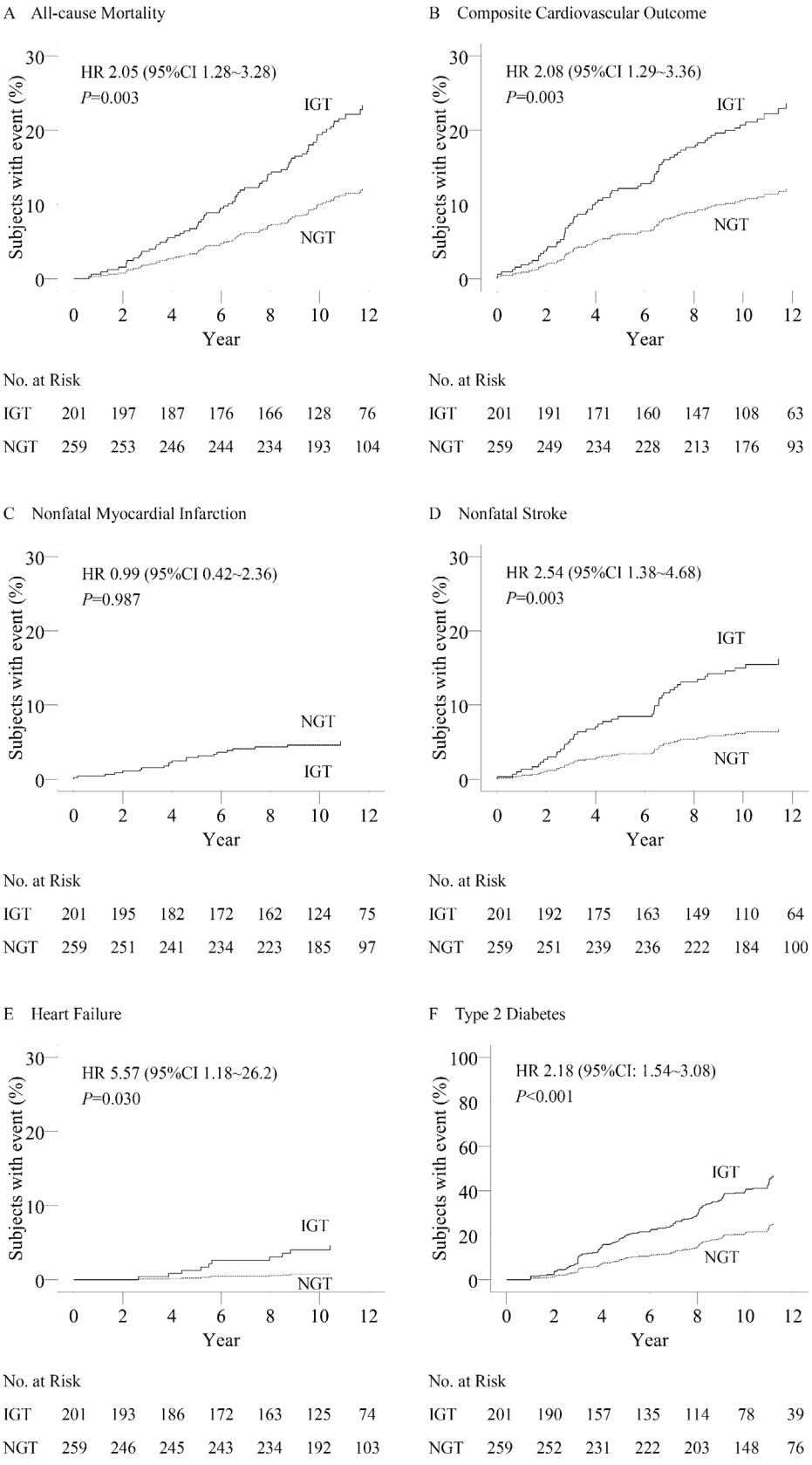

Fig. 1 – The cumulative incidence during the follow-up.
Shown are the cumulative incidence of all-cause mortality (Panel A), composite cardiovascular outcome (Panel B), nonfatal myocardial infarction (Panel C), nonfatal stroke (Panel D), heart failure (Panel E), and type 2 diabetes (Panel F). Hazard Ratios (HR) and 95% confidence intervals (CI) are based on Cox regression analyses.

Table 3 – Adjusted hazard ratios for all-cause mortality, cardiovascular outcomes and cancer during the follow-up.

Variables	IGT n = 201	NGT n = 259	Model 1		Model 2		Model 3	
	n (%)	n (%)	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
All-cause mortality	43 (21.4)	29 (11.2)	1.85 (1.15–2.97)	0.012	1.88 (1.16–3.03)	0.010	1.94 (1.19–3.14)	0.008
Composite cardiovascular outcome	42 (20.9)	28 (10.8)	1.89 (1.17–3.07)	0.010	1.90 (1.17–3.09)	0.010	1.88 (1.15–3.06)	0.012
Nonfatal myocardial infarction	9 (4.5)	12 (4.6)	0.89 (0.37–2.14)	0.800	0.89 (0.37–2.13)	0.785	0.89 (0.36–2.17)	0.791
Non-fatal stroke	29 (14.4)	16 (6.2)	2.36 (1.27–4.39)	0.006	2.44 (1.31–4.56)	0.005	2.41 (1.29–4.49)	0.006
Heart failure	8 (4.0)	2 (0.8)	5.01 (1.05–23.9)	0.043	5.14 (1.07–24.7)	0.041	5.04 (1.00–25.4)	0.050
Unstable angina	29 (14.4)	33 (12.7)	1.10 (0.66–1.82)	0.718	1.04 (0.62–1.73)	0.892	1.03 (0.61–1.73)	0.908
Cancer	54 (26.9)	55 (21.2)	1.33 (0.91–1.94)	0.147	1.34 (0.91–1.96)	0.136	1.32 (0.90–1.95)	0.161

Model 1 was adjusted for age, BMI, and smoking.
Model 2 included the adjustment in model 1 and was also adjusted for HOMA2-IR and eGFR.
Model 3 included the adjustment in model 2 and was also adjusted for previous history of hypertension, dyslipidemia, coronary heart disease and cancer.
Data were presented as n (%).
Hazard Ratios (HR) and 95% confidence intervals (CI) are based on Cox regression analyses.

Table 4 – Subgroup analyses for all-cause mortality during the follow-up.

Subgroup	IGT (n = 201)	NGT (n = 259)	HR (95%CI)	P value
Age				
≧75 year (n = 171)	34/82 (41.5)	27/89 (30.3)	1.78 (1.06–2.99)	0.031
<75 year (n = 289)	9/119 (7.6)	2/170 (1.2)	5.43 (1.16–25.5)	0.032
BMI				
≧25 kg/m^2 (n = 215)	19/99 (19.2)	11/116 (9.5)	2.81 (1.25–6.32)	0.013
<25 kg/m^2 (n = 242)	24/102 (23.5)	18/140 (12.9)	1.63 (0.88–3.02)	0.124
Smoking				
Yes (n = 138)	21/66 (31.8)	18/72 (25.0)	1.63 (0.84–3.17)	0.150
No (n = 319)	22/135 (16.3)	11/184 (6.0)	2.55 (1.18–5.52)	0.017
HOMA2-IR				
Highest quartile (n = 115)	16/64 (25.0)	4/51 (7.8)	4.03 (1.25–13.0)	0.020
Other quartiles (n = 345)	27/137 (19.7)	25/208 (12.0)	1.58 (0.90–2.75)	0.109
eGFR				
≧90 ml/min (n = 177)	12/74 (16.2)	3/103 (2.9)	5.75 (1.51–21.9)	0.010
60 ~ 90 ml/min (n = 248)	26/113 (23.0)	20/135 (14.8)	1.44 (0.77–2.67)	0.255
<60 ml/min(n = 35)	5/14 (35.7)	6/21 (28.6)	3.27 (0.71–15.0)	0.128
Hypertension				
Yes (n = 281)	34/140 (24.3)	17/141 (12.1)	2.84 (1.49–5.41)	0.001
No (n = 179)	9/61 (14.8)	12/118 (10.2)	0.88 (0.34–2.24)	0.786
Dyslipidemia				
Yes (n = 314)	30/136 (22.1)	21/178 (11.8)	2.04 (1.16–3.60)	0.014
No (n = 146)	13/65 (20.0)	8/81 (9.9)	1.00 (0.37–2.75)	0.994
Coronary heart disease				
Yes (n = 227)	34/101 (33.7)	27/126 (21.4)	1.60 (0.95–2.71)	0.079
No (n = 233)	9/100 (9.0)	2/133 (1.5)	5.09 (0.95–27.3)	0.058

Shown are the results of subgroup analyses for all-cause mortality during the follow-up categorized by age, BMI, smoking, HOMA2-IR, eGFR, and previous history of hypertension, dyslipidemia, and coronary heart disease.
In the multivariate Cox proportional-hazards model, baseline variables other than subgroup variable were adjusted, including age, BMI, smoking, HOMA2-IR, eGFR, hypertension history, dyslipidemia history, coronary heart disease history and cancer history.
Data were presented as no. of events / no. of subgroup (%).
Hazard Ratios (HR) and 95% confidence intervals (CI) are based on Cox regression analyses.
There were 3 cases among NGT group who did not have the data of BMI and smoking at baseline.

outcome, nonfatal stroke and heart failure, with no significantly increased risk for nonfatal myocardial infarction, unstable angina, or cancer.

Increased risk of all-cause mortality in type 1 and type 2 diabetes has been well described in the literature [20,21]. Data from the Emerging Risk Factors Collaboration study [22] has shown independent associations of diabetes with substantial premature death from vascular disease, several cancers, infectious diseases, and other causes. However, fewer studies have investigated the risk of all-cause mortality and disease-specific mortality in individuals with IGT, especially in older adults. One systematic review and meta-analysis sug-

gests an association between IGT and all-cause mortality in a combined but diverse populations [7]. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) Study has shown that IGT, not IFG, was predictive for all-cause mortality and deaths from cardiovascular disease [23]. In the Australian Diabetes, Obesity, and Lifestyle Study, while IGT was shown to be associated with all-cause mortality, it had no association with death from cardiovascular disease [24]. However, a previous study in 637 older Finnish men investigated the association of glucose intolerance with death during a 5-year follow-up, and found that the relative risk of mortality among diabetic men (RR 2.10, 95% CI 1.26–3.49) and among IGT men (RR 1.17, 95% CI 0.71–1.94) was greater than compared to NGT men. This study demonstrated a significantly increased risk of death among older men with T2DM, but a non-statistically significant increased risk among older men with IGT [25]. Our study also focused on older men, but the difference between the 5 year Finnish study and our 11 year study may be the length of follow-up. T2DM had a much greater impact on participants compared to IGT, which may take longer to observe changes in outcomes. Furthermore, the duration of IGT may also be important given the well-established relationship between the duration of T2DM and mortality [26]. The Whitehall II study enrolled 5427 non-diabetic participants aged 50–79 years with a median of 11.5 years of follow-up, and suggested that prediabetes defined by FPG or 2hPG was not associated with an increased risk of cardiovascular disease or all-cause mortality [27]. Similar to this study, our research had a participant follow-up of 11.2 years. The difference between the Whitehall II study and our study may be attributed to the age of participants. We found that the risk of mortality in older men aged ≥75 years was significantly higher than that in older men aged <75 years. Other inconsistencies between the results of these studies may be attributed to a number of variables including different diagnostic criteria and whether or not major risk factors were adjusted for. In addition, the average age of the participants at baseline was over 70 years old in the present study. This may have contributed to an effect on mortality in IGT subjects due to the increasing incidence with age of cardiovascular events, cancer, etc. Importantly, the participants in this study were at high risk for CVD due to a high prevalence of previous coronary heart disease, hypertension, and dyslipidemia at baseline, which may be another factor contributing to the difference between groups.

A recent study showed that IGT was associated with increased risk of mortality, but much of this increased risk was attributable to the development of T2DM [28]. Because the participants in this study were all IGT subjects, the development of T2DM during follow-up should play a significant role in mortality. However, our study focused on the different associated risk factors between IGT and NGT subjects. When logistic regression analysis was performed, we found that IGT, but not incident T2DM, was associated with increased all-cause mortality compared with NGT. During follow-up, development of T2DM occurred in both IGT and NGT groups. Nevertheless, in the IGT group, insulin resistance, baseline glucose abnormalities, and a higher incidence of diabetes during follow-up increased the likelihood of cardiovascular events. This finding from our work suggests a strong correlation between IGT and mortality. In addition, we also found that baseline age was the most important factor associated with death, except for composite cardiovascular outcome and incidence of cancer during follow-up.

An increased risk of composite cardiovascular outcome observed in participants with IGT in the present study is consistent with findings reported by previous studies [23,29]. Endothelial dysfunction and increased oxidative stress have been described in individuals with IGT [30] and is suggested to predict the risk of cardiovascular events in patients with coronary artery disease [31]. Other cardiovascular risk factors such as hypertension and dyslipidemia are closely associated with IGT and taken together may also contribute to cardiovascular damage. In the present study, we report IGT as an independent predictor of nonfatal stroke and heart failure. This is consistent with previous studies demonstrating a significant association between prediabetes and an increased future risk of stroke [32,33]. We did not observe increased events of coronary heart disease, i.e. nonfatal myocardial infarction or unstable angina in this study. This is likely due to the requirement of PPG ≥ 7.2 mmol/L for all participants prior to administration of OGTT. This stringent criterion may have led to missing participants with NGT, attenuating the difference between IGT group and NGT group. Alternatively, clustering of hypertension, dyslipidemia, and hyperglycemia rather than hyperglycemia alone may significantly influence such cardiovascular events.

The primary difficulty encountered during this study is subject follow-up. The mean follow-up time in the present study was 11.2 years. Participants showed good compliance with just fifteen (3.3%) participants lost to follow-up. The remaining participants were followed throughout the study until death or the completion of the trial, and received at least one visit per year to perform physical examination and laboratory tests. The major strengths of this study include the longitudinal nature of the study with a follow-up period of over 11 years and minimal lost to follow-up of study participants. In addition, all clinical diagnoses and events during follow-up were closely monitored and confirmed. We also carefully adjusted a number of potential confounding factors in our analyses. However, this study also has several limitations. For example, a participant PPG ≥ 7.2 mmol/L measured by glucometer was required prior to performing OGTT. This requirement may be biased towards IGT detection and ultimately attenuate the differences between the IGT and NGT study groups. Other limitations include the reliance on a single OGTT to discern glucose metabolism at baseline, and a limited number of 2 h plasma glucose measurements during follow-up. In addition, the possibility of other confounding factors cannot be completely eliminated due to the observational nature of this study.

5. Conclusions

The findings in this study support our original hypothesis that IGT predicts all-cause mortality in community-dwelling older Chinese men at high risk for CVD. In addition, our results indicate that IGT entails increased risk of progression to T2DM and increased risk of composite cardiovascular outcomes in

this elderly population after adjusting for major confounding factors. These findings help advance our knowledge about IGT and its adverse impact on overall health and specific cardiovascular outcomes in older men. They also highlight the need for further studies of risk factors that lead to IGT and effective interventional strategies for IGT prevention in this vulnerable older adult population.

Conflict of interest

The authors state that they have no conflict of interest.

Author contributions

H. T. and C. L. designed the study, reviewed the manuscript and interpreted the data. S. L. participated in the study design, reviewed the manuscript, and interpreted the data. F. F., G. P, and H. L. conducted the study, performed statistical analysis and wrote the manuscript. N. W, S. Y., L. W., Y. L., and J. L. conducted the study, and collected data.

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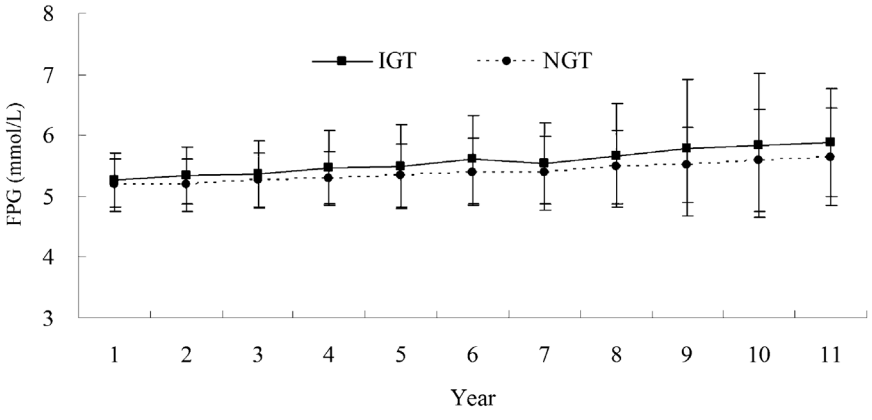
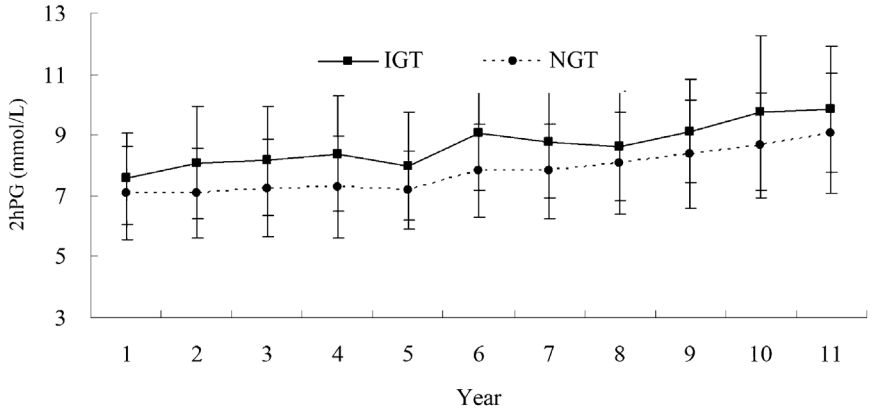
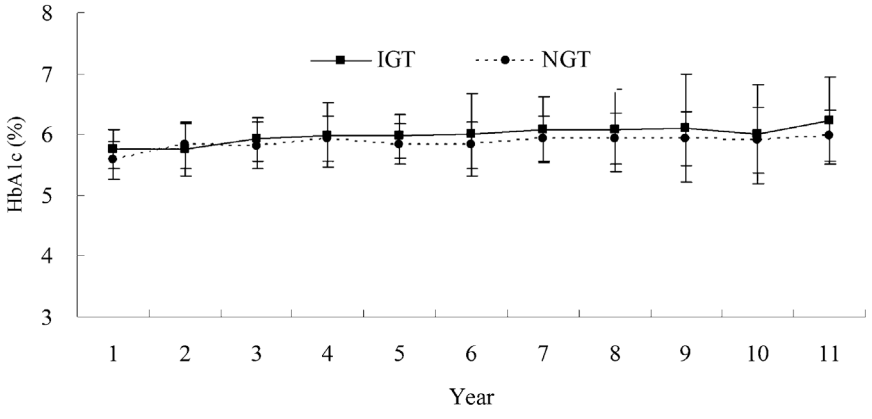
Appendix A.



IGT	174	188	185	182	176	169	165	160	157	126	76
NGT	223	232	229	230	228	226	224	217	214	185	105



IGT	31	79	123	108	94	96	96	96	89	73	44
NGT	30	85	168	165	162	157	156	156	155	123	67



IGT	24	52	79	86	82	80	96	114	135	105	70
NGT	9	43	55	70	72	75	106	144	193	159	90

Fig. A1 – The change of FPG, 2hPG, and HbA1c during the follow-up.

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