# One-Hour Plasma Glucose as a Long-Term Predictor of Cardiovascular Events and All-Cause Mortality in a Chinese Older Male Population Without Diabetes: A 20-year Retrospective and Prospective Study

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# Abstract

Background

The association between one-hour plasma glucose (1h-PG) and the incidence of type 2 diabetes has been investigated in previous studies. However, the predictive value of 1h-PG for the risk of cardiovascular disease (CVD) and all-cause mortality, especially in older Asians, has been investigated in only a few studies. Therefore, the influence of 1h-PG on the incidence of CVD and mortality was evaluated in the present study.

Methods

The participants were recruited from the Chinese People's Liberation Army General Hospital, and were categorized into 1h-PG tertiles. The primary outcomes were all-cause mortality, myocardial infarction, unstable angina, and stroke. Multivariate adjusted Cox proportional hazard regression models were performed to examine the association between risk factors and outcomes and to estimate the risk of CVD and all-cause mortality based on 1h-PG.

Results

The study included 862 male participants. Median age was 74.0 (25th–75th percentile: 68.0–79.0) years. There were 480 CVD events and 191 deaths during 15,527 person-years of follow-up. The adjusted hazard ratio (HR) of 1h-PG as a continuous variable was 1.097 (95% CI 1.027–1.172; P = 0.006) for CVD events and 1.196 (95% CI 1.115-1.281; P < 0.001) for higher risk of mortality. When compared with the lowest 1h-PG tertile, the other tertiles were associated with CVD events (HR 1.464, 95% CI 1.031–2.080; P = 0.033 and HR 1.538, 95% CI 1.092–2.166; P = 0.014, for tertile 2 and tertile 3 compared with tertile 1, respectively), and the highest 1h-PG tertile had a significantly higher risk of mortality (HR 2.384, 95% CI 1.631-3.485; P < 0.001) after full adjustment.

Conclusion

Higher 1h-PG is associated with an increased risk of all-cause mortality and CVD. 1h-PG might be a better predictor of CVD than 2h-PG in older adults.


# Background

Over the past century, life expectancy has risen dramatically. According to data released by the National Bureau of Statistics in 2018, the older population (≥ 60 years of age) in China accounted for 17.3% (240 million) of the total population in 2017, and the proportion of the older population is expected to exceed 30% by 2050[1]. In 2017, 4.38 million people died from cardiovascular diseases (CVDs) such as coronary heart disease, accounting for 42% of all deaths, and the cardiovascular burden exceeded 85 million disability-adjusted life years[2]. Aging and diabetes are two well-known risk factors for CVD. With age, many people develop asymptomatic hyperglycemia and an insipid, progressive metabolic disorder, which

increases susceptibility to many chronic age-related diseases over the years, including CVD and premature death from CVD. Once type 2 diabetes presents with permanent vascular changes, altering the pathologic trajectory by lowering average blood glucose levels may not be possible. Therefore, early intervention is necessary, especially during the postprandial period, to maintain blood sugar homeostasis to as close to normal as possible, and before people are diagnosed with diabetes. One-hour plasma glucose (1h-PG) concentration during the oral glucose tolerance test (OGTT) has emerged as a method to capture insulin resistance and β-cell dysfunction more accurately than two-hour plasma glucose (2h-PG) [3, 4] and is a better predictor of future type 2 diabetes than 2h-PG[5]. Therefore, 1h-PG is a potentially important predictor of hyperglycemia-related complications, which would be highly relevant for prognosis. Over the past decade, the superiority of the 1h-PG value *versus* the 2h-PG value for the prediction of type 2 diabetes has been suggested in several studies. However, the extant evidence on the association of 1h-PG and CVD events is limited, especially regarding older Asians. Therefore, in the present study, the prognostic value of 1h-PG and 2h-PG for predicting CVD events and all-cause mortality, both for isolated incidence and in a multivariable prediction model, were evaluated. In addition, whether 1h-PG was an independent risk factor for CVD events and all-cause mortality in older male Chinese subjects was assessed.

# Methods

Study subjects

This retrospective and prospective study included 862 subjects 60 years of age or older who visited the Chinese People's Liberation Army General Hospital of Beijing between May 1998 and August 2019 for regular physical examinations. For the study, only the participants with complete data on fasting plasma glucose (FPG), 1h-PG, and 2h-PG at baseline were included. Participants who had CVD events within 48 months before baseline records were excluded. Other major exclusion criteria were diabetes, a history of gastrointestinal surgery, advanced cancer, or other severe diseases. The study protocol was approved by the Chinese People's Liberation Army General Hospital Ethics Committee. Information related to the identities of the patients was concealed.

Measurements

Data including patient demographics such as age, height, weight, waist circumference (WC), blood pressure, past medical history, and laboratory results were obtained from hospital records. Body mass index (BMI) was calculated as weight (in kg)/height (in m)$^2$. Blood samples were taken after an overnight fast (> 8 h). Serum lipid profiles, including triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) levels, were measured using chemiluminescence on an autoanalyzer. The low-density lipoprotein cholesterol (LDL-C) level was computed with the Friedewald equation. All subjects underwent 75 g OGTT and venous plasma glucose measurements were taken before OGTT (FPG), and 1 h and 2 h after OGTT (1h-PG and 2h-PG, respectively). The enzymatic hexokinase method was used to measure FPG, 1h-PG, and 2h-PG. Glucose tolerance was determined according to the 1999 WHO criteria

as normal glucose tolerance (NGT) (FPG<6.1 mmol/L and 2h-PG<7.8 mmol/L) and prediabetes, including impaired fasting glucose (IFG) (6.1mmol/L≤FPG<7.0mmol/L and 2h-PG<7.8 mmol/L) and impaired glucose tolerance (IGT) (FPG < 7 mmol/L and 7.8 ≤ 2h-PG < 11.1 mmol/L). The TyG index was calculated using the following formula: ln [fasting TG (mg/dL) × FPG (mg/dL)/2][6], which is becoming an ideal surrogate variable for insulin resistance[7]. In previous studies, the TyG index was proven to be significantly correlated with homeostatic model assessment of insulin resistance (HOMA-IR) and the hyperinsulinemic-euglycemic clamp (HIEC)[6, 8, 9]. In the present study, the TyG index was used as a substitute for insulin resistance. As the Chinese guideline for the management of dyslipidemia in adults (revised in 2016)[10] suggests, dyslipidemia was defined as a fasting TC ≥5.2 mmol/L(200 mg/dL), LDL-c ≥3.4 mmol/L(130 mg/dL), TG ≥1.7 mmol/L(150 mg/dL), HDL-c <1.0mmol/L(40mg/dL). Overweight and obesity was defined as BMI ≥25kg/$m^2$.

Outcomes

Follow-up time for each subject was defined as time from baseline screening to the time of myocardial infarction, unstable angina, stroke, death, or the last follow-up date up to 20 years. The outcomes were CVD events defined as a composite of major cardiovascular events (including myocardial infarction, unstable angina, and stroke), and all-cause mortality. Relevant information regarding cardiovascular events was also collected from hospital records. For deaths and hospitalizations, copies of death certificates and hospital discharge summaries were requested. The definition of myocardial infarction was derived from the Fourth Universal Definition of Myocardial Infarction[11]. The diagnostic basis of unstable angina is focused on data elements needed for determining whether symptoms truly represent cardiovascular ischemia, including the character and duration of the presenting symptoms, the proximity of symptom onset to hospitalization, and the duration of hospitalization[12]. Stroke was defined based on the presence of acute infarction observed on imaging or the persistence of symptoms[12]. Death was defined as all-cause mortality.

Statistical analysis

The participants were categorized into 1h-PG tertiles and 2h-PG tertiles and their characteristics assessed across tertiles. Continuous variables were summarized using means and standard deviation (SD). Categorical variables were presented as frequencies and corresponding percentages. One-way analysis of variance (ANOVA) or Kruskal-Wallis test was used to compare continuous variables and the $\chi 2$-test for categorical variables, as appropriate. To define potential explanatory variables for each outcome, univariable Cox proportional-hazards regressions were applied on the following demographic and clinical continuous variables: age, BMI, WC, SBP, SDP, FPG, 1h-PG, 2h-PG, HDL-C, LDL-C, non-HDL-C, TG, TC, the TyG index, and the categorical variables: history of hypertension, history of CVD, overweight and obesity, dyslipidemia. We then used multivariable Cox proportional hazards regression models to calculate adjusted hazard ratios (HRs) for both outcomes associated with 1h-PG and 2h-PG. This was done modeling 1h-PG and 2h-PG as continuous variables and tertiles of variables with the lowest quartile serving as the reference. Three nested models were constructed: Model 1 (for both endpoints): age, WC,

SBP; Model 2(for both endpoints): model 1 + history of hypertension and history of CVD; Model 3: model 2 + HDL-c and TC for CVD events, model 2 + HDL-c for all-cause mortality. The predictive abilities both alone and in addition to the clinical prediction model were tested with Harrell's concordance index (C-index). Furthermore, subjects were stratified into subgroups according to glucose tolerance to separately explore the relationship between 1h-PG or 2h-PG and the outcomes. All analyses were performed using IBM SPSS Statistics 25 (IBM) and R. A *P*-value < 0.05 (two-sided) was considered to indicate statistical significance.

# Results

Baseline characteristics

At baseline, median age was 74.0 (25th–75th percentile: 68.0–79.0) years, mean systolic blood pressure 130.0 (120.0-140.0) mmHg and mean BMI 25.2±2.8kg/m2. Total cholesterol was 5.3±0.9mmol/L. Table 1 presents the anthropometric, laboratory, and clinical characteristics of the study population. Of 862 study participants, 491 had NGT, 53 had IFG, and 318 had IGT at baseline, respectively. 63 of 318 subjects with IGT also had IFG. Subjects with IGT at baseline generally had a worse risk profile than their counterparts with NGT. The characteristics of the participants included in this study across tertiles of 1h-PG and 2h-PG are presented in Table 2. The participants in the highest tertile of 1h-PG were older, more likely to have history of hypertension and dyslipidemia. They also had a higher BMI, blood pressure, FPG and 2h-PG. Similarly, a more adverse risk profile was present across 2h-PG tertiles.

As shown in Table 3 and Table 4, over 20 years of follow-up, 215 (24.9%) individuals had CVD events during 15,527 person-years of follow-up; 480 composite CVD events (myocardial infarction, unstable angina, stroke, or cardiovascular death, whichever came first) were detected, and the corresponding incidence density of CVD events was 30.9 per 1,000 person-years. There were 191 all-cause deaths and the corresponding incidence density of death was 12.3 per 1,000 person-years. IGT, the uppermost 1h-PG tertile and the uppermost 2h-PG tertile appeared to be associated with higher all-cause mortality and CVD events compared with NGT, the lower 1h-PG tertiles and the uppermost 2h-PG tertile, respectively. Due to the small number of cardiovascular deaths, we did not conduct a follow-up analysis.

The following variables were statistically significant on univariable analysis for prediction of incident CVD and all-cause mortality: age, WC, SBP, HDL-c, history of hypertension and history of CVD. TC was also significant for prediction of incident CVD. The final Cox regression model performed better than isolated 1h-PG measurement for the prediction of both endpoints, with C-index of 0.69 and 0.79 for CVD and all-cause mortality, respectively (Supplementary Table 1).

Associations between 1h-PG or 2h-PG and incident CVD

At 20 years, 1h-PG and 2h-PG alone as continuous variables were significant predictors of incident CVD (HR 1.129, 95% CI 1.058–1.204; *P* < 0.001 and HR 1.108, 95% CI 1.025-1.198; *P* = 0.009, respectively) (Supplementary Table 1). FPG alone did not predict incident CVD. Likewise, when compared with the

lowest 1h-PG tertile, the other tertiles were associated with CVD events (HR 1.519, 95% CI 1.070-2.158; P = 0.019 and HR 1.799, 95% CI 1.281-2.526; P = 0.001, for 1h-PG tertile 2 and tertile 3 compared with tertile 1, respectively) (Table 5). However, as a categorical variable, 2h-PG did not predict incident CVD. When compared with NGT, neither IFG nor IGT could predict incident CVD. The pattern of results was similar for the cumulative risk of CVD (Figure 1). When 1h-PG was examined continuously in the fully adjusted model, each unit change in 1h-PG was associated with a higher risk of CVD events (HR 1.097, 95% CI 1.027–1.172; P = 0.006), while 2h-PG was not (Supplementary Table 1). After full multivariable adjustment, when compared with the lowest 1h-PG tertile, the other tertiles were associated with CVD events (HR 1.464, 95% CI 1.031–2.080; P = 0.033 and HR 1.538, 95% CI 1.092–2.166; P = 0.014, for 1h-PG tertile 2 and tertile 3 compared with tertile 1, respectively) (Table 5).

Associations between 1h-PG or 2h-PG and all-cause mortality

At 20 years, 1h-PG and 2h-PG alone as continuous variables were significant predictors of all-cause mortality (HR 1.228, 95% CI 1.147-1.314; *P* < 0.001 and HR 1.291, 95% CI 1.186-1.404; *P* < 0.001, respectively) (Supplementary Table 1). C-index for 1h-PG and 2h-PG alone were 0.63(0.020) and 0.63(0.021), respectively. FPG alone did not predict all-cause mortality. Likewise, when compared with the lowest 1h-PG tertile, the other tertiles were associated with all-cause mortality (HR 1.539 95% CI 1.013-2.338; P = 0.043 and HR 2.963, 95% CI 2.032-4.321; P < 0.001, for 1h-PG tertile 2 and tertile 3 compared with tertile 1, respectively). when compared with the lowest 2h-PG tertile, participants in the highest tertile were at a significantly higher risk of mortality (HR 2.493, 95% CI 1.738-3.577; *P* < 0.001) (Table 6). The pattern of results was similar for the cumulative risk of all-cause mortality (Figure 2). When 1h-PG or 2h=PG was examined continuously in the fully adjusted model, each unit change in 1h-PG or 2h=PG was associated with a higher risk of all-cause mortality (HR 1.196, 95% CI 1.115-1.281; P < 0.001 and HR 1.207, 95% CI 1.110-1.311; P < 0.001, respectively). Both C-index for the two clinical prediction models were 0.79 (Supplementary Table 1). After full multivariable adjustment, when compared with the lowest tertile, participants in the highest tertile of 1h-PG and 2h-PG were at a significantly higher risk of mortality (HR 2.384, 95% CI 1.631-3.485; P < 0.001 and HR 1.847, 95% CI 1.285-2.656; P < 0.001, respectively). Likewise, after full multivariable adjustment, when compared with NGT, participants with IFG or IGT were at a significantly higher risk of mortality (HR 2.188, 95% CI 1.213-3.947; P = 0.009 and HR 1.676, 95% CI 1.244-2.258; P = 0.001, respectively) (Table 6).

Associations between 1h-PG or 2h-PG and outcomes for stratified subgroups

Stratified analyses were conducted in subgroups divided according to glucose tolerance to further validate the abovementioned results. Among those with normal glucose tolerance, the results were similar. As shown in Supplementary Table 2, each unit change in 1h-PG was significantly associated with incident CVD and death (HR 1.112, 95% CI 1.015-1.219; P = 0.023 and HR 1.302, 95% CI 1.173-1.444; P <0.001, respectively) in the fully adjusted models. Each unit change in 2h-PG was significantly associated with incident death (HR 1.260, 95% CI 1.088-1.458; P = 0.002) but not with incident CVD in the fully

adjusted models. however, among those with impaired fasting glucose or impaired glucose tolerance, neither 1h-PG nor 2h-PG could predict any of the endpoints.

# Discussion

To the best of our knowledge, this is the first study in which the associations of 1h-PG and 2-PG with CVD events and all-cause mortality were investigated in a Chinese older population with long-term follow-up. A positive association was observed between 1h-PG and CVD events and/or overall mortality, in apparently healthy, older males with normal glucose tolerance, for both isolated incidence and in a clinical prediction model after 20 years of follow-up. 2h-PG was as effective as 1h-PG for predicting overall mortality, but it did not predict CVD events after adjusting for the variables included in the clinical prediction model.

Diabetes is a coronary heart disease risk equivalent. However, for some patients with undiagnosed diabetes, especially those without a clinical glucose metabolism disorder such as normal glucose tolerance (NGT), serious adverse events may still occur. In the present study, after 9,063 person-years of follow-up, the overall incidence of CVD events and all-cause mortality in the NGT subjects was 29.6/1,000 person-years and 8.7/1,000 person-years, respectively, indicating that higher rates of CVD events and all-cause mortality can still occur in the older population without diabetes in China. Therefore, finding indicators that identify a high risk of CVD events and all-cause mortality in diabetes-free patients is important.

The lack of association between impaired glucose tolerance or 2h-PG with CVD events is in disagreement with results of previous studies[13-17]. The predictive capacity of 2h-PG may decline over time or for older adults. The main focus in previous studies was on middle-aged subjects, and some were conducted over a shorter follow-up period. On the other hand, our subjects were followed up regularly for a long time and received good diabetes education. Most of the patients with abnormal glucose metabolism underwent lifestyle changes or drug therapy during the follow-up, which may reduce the incidence of cardiovascular events. This may also explain the importance of early detection and intervention of glucose metabolism abnormalities. In several previous studies, the 1h-PG was shown to be closely associated with cardiovascular risk in different populations. In large epidemiological studies, the area under the receiver-operating curve (ROC) of 1h-PG for predicting type 2 diabetes was significantly greater than FPG and 2h-PG[3, 18]. In a study conducted on Latinos and Hispanics, a high prevalence of 1h-PG was associated with cardiovascular and metabolic risk factors[19]. In a study that included hypertensive patients, subjects with 1h-PG $\geq$ 8.6 mg/mL, compared with 1h-PG $\leq$ 8.6 mg/mL, had higher pulse wave velocity (PWV), which is a surrogate end-point for cardiovascular morbidity and mortality[20]. Higher 1h-PG was also characterized by a worse cardiovascular risk profile[21-23], and associated with whole blood viscosity[24], left ventricular hypertrophy[25], and carotid atherosclerosis[26], all independent predictors of CVD. Furthermore, in a recent study, subjects with higher 1h-PG had altered markers of cardiovascular risk such as intima-media thickness and arterial stiffness and exhibited low endogenous secretory receptor for advanced glycation end product levels[27]. These markers were shown to be associated with coronary heart disease or atherosclerosis in nondiabetic males[28] and predicted cardiovascular mortality in

diabetic and nondiabetic subjects[29]. Several aspects of the present study differ from prior investigations, including differences in age and ethnicity; however, the results have provided additional information to support previous studies, indicating the clinical importance of 1h-PG for predicting the risk of CVD events and overall mortality.

The exact mechanisms linking increased 1h-PG with an increased risk of adverse outcomes are unknown, however, there are several hypotheses. A strong correlation exists between insulin resistance and the risk of developing CVD. In previous studies, insulin resistance was suggested to promote the production of CVD through two independent pathways: the formation of atherosclerotic plaques[30-34] and abnormal ventricular hypertrophy[35] and diastole[36]. Both of these effects can lead to heart failure. In several studies, higher 1h-PG values had a strong correlation with lower insulin secretion, higher insulin resistance, reduced β-cell glucose sensitivity, and reduced β-cell rate sensitivity[3, 4, 37]. Furthermore, in the Botnia Study, the group of subjects with normal glucose tolerance with a 1h-PG > 8.6 mg/dL and metabolic syndrome, had a high risk of developing type 2 diabetes, and the risk exceeded that of subjects with IFG or IGT[38]. Similar results were reported in the Insulin Sensitivity and Cardiovascular Risk (RISC) study; participants with normal glucose tolerance with a 1h-PG > 8.95 mmol/L had lower basal and total insulin secretion than subjects with IGT. These data indicate that 1h-PG may be an earlier biomarker of dysglycemia than IFG and IGT in the lengthy trajectory from normal glucose tolerance to type 2 diabetes and the related complications. Based on these factors, 1h-PG is an important predictor for cardiovascular risk.

The present study had several limitations that should be considered. First, a time-dependent analysis could not be performed because only a single OGTT was conducted at baseline and the data regarding insulin secretion measurement and HbA1c level could not be obtained because they were not widely used in the late 1990s in China. Second, the exclusion of a significant proportion of the original study population constitutes a major limitation and prevents extending the results beyond older Chinese males; additionally, all subjects were well educated, which may have resulted in a selection bias. Whether the present findings could be applied to other populations and to females warrants further study. Third, we did not have data on lifestyle intervention or glucose-lowering medications, and the modification of therapeutic regimen may influence postprandial blood sugar, thus underestimating the predictive function of 1h-PG in patients with prediabetes.

# Conclusion

The findings of the present study indicate that a higher 1h-PG value is associated with an increased risk of all-cause mortality and CVD. 1h-PG might be a better predictor of CVD than 2h-PG in older adults. Future studies are needed to determine whether lower 1h-PG values are associated with reduced risk of mortality and CVD.

# Abbreviations

CVD, cardiovascular disease; OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 1h-PG, one hour plasma glucose; 2h-PG, two hour plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HIEC, hyperinsulinemic-euglycemic clamp; PWV, pulse wave velocity.

# Declarations


### Acknowledgements

Not applicable


### Authors' contributions

CL and BS contributed to the conception and design of the study. LR and XM analyzed the data. YG supervised the study. LR wrote the initial draft of the paper. LR and XM contributed equally to this work. CL and BS contributed to the writing, reviewing, and revising of the manuscript. All authors read and approved the final manuscript.


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### Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The study protocol was approved by the Chinese People's Liberation Army General Hospital Ethics Committee. Information related to the identity of the patient was concealed.

### Consent for publication

Not applicable

### Competing interests

The authors declare no competing interests.

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*[10] PMID: 29434622 DOI: 10.11909/j.issn.1671-5411.2018.01.011

*[27] PMID:31426413 DOI: 10.33901cells8080910

## Tables

Due to technical limitations, table 1, 2, 3, 4, 5 and 6 is only available as a download in the Supplemental Files section.

## Figures

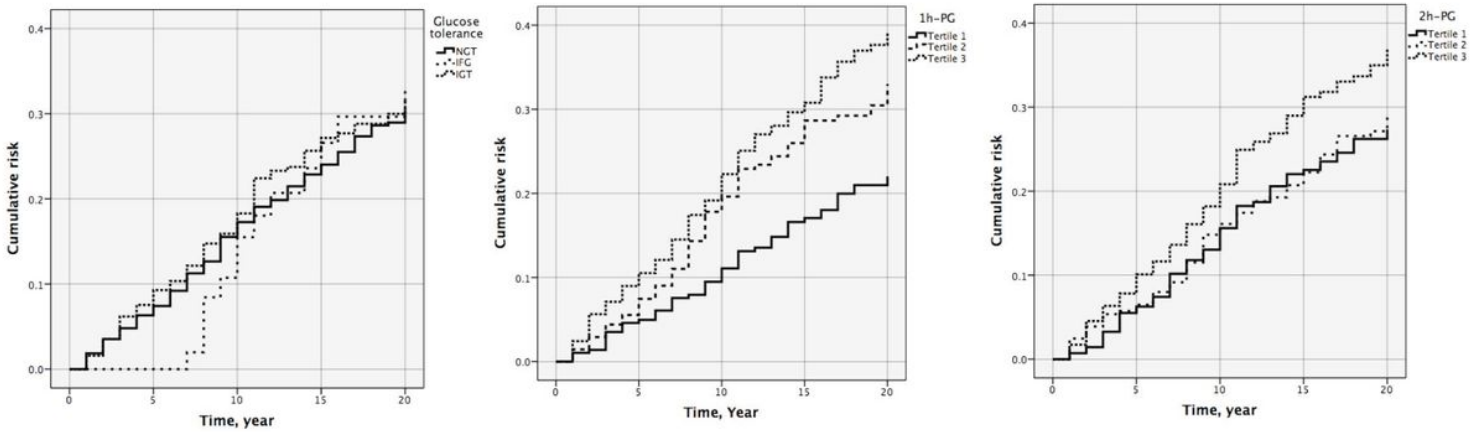

**Figure 1**

Cumulative risk of cardiovascular diseases by glucose tolerance (P=902), 1h-PG (P=0.002) and 2h – PG (P=0.119) at 20 years of follow-up

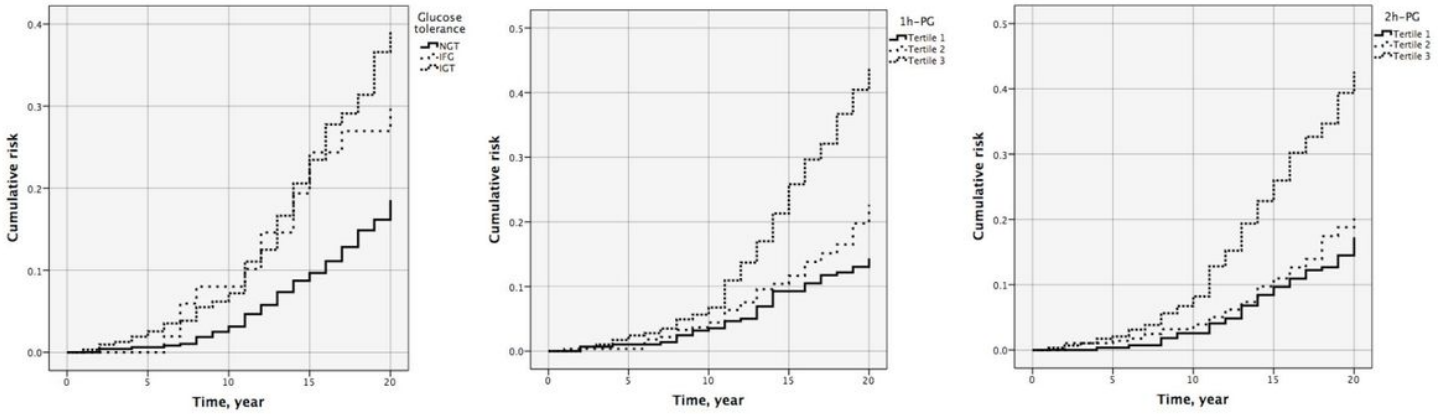


**Figure 2**

Cumulative risk of all-cause mortality by glucose tolerance (P<0.001), 1h-PG (P<0.001) and 2h-PG (P<0.001) at 20 years of follow-up

# Supplementary Files

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