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Associations of three diagnostic glycemic measures with all-cause and cardiovascular mortality in people not on antidiabetic medications: A prospective cohort study

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ABSTRACT

Objective: This study aimed to investigate the value of three diagnostic glycemic measures, i.e., 2-hour plasma glucose (2hPG) during 75-g oral glucose tolerance test, fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c), in predicting risk of all-cause and cardiovascular mortality after adjusting for the influence of these glycemic measures on each other.

Methods: A total of 14,013 U.S. adults who were not on antidiabetic medications when recruited were identified from the Third National Health and Nutrition Examination Survey (NHANES III) and NHANES 2005–2016. High blood glucose was defined as 2hPG ≥11.1 mmol/L, FPG ≥7.0 mmol/L, or HbA1c ≥6.5 %, according to the American Diabetes Association 2023 standards. Two approaches were adopted to examine the value of each glycemic measure in predicting mortality risk while controlling the influence of the other two measures: (1) adjusting for 2hPG, HbA1c, and FPG in the same model, and (2) comparing individuals showing isolated elevation of 2hPG, HbA1c, or FPG with those being "normal" for all the three measures. Major non-glycemic risk factors were adjusted for in the multivariable regression analyses.

Results: During a median follow-up of 9.8 years, 2869 participants died, and 960 of the deaths were attributed to cardiovascular causes. When included in the model individually, elevated 2hPG, FPG, and HbA1c were all predictive of both all-cause and cardiovascular mortality (adjusted hazard ratios ranging from 1.32 to 1.55, all p values <0.05). After controlling the influence of the other two glycemic measures, elevated 2hPG was still statistically significantly associated with the outcomes (adjusted hazard ratios ranging from 1.04 to 1.33, depending on analytical approaches), whereas elevated FPG was not, and HbA1c was associated with cardiovascular mortality only when treated as a continuous variable and when 2hPG and FPG levels were in the normal range (adjusted hazard ratio 1.27 [1.04–1.55] for 1 % increase in HbA1c).

Conclusions: 2hPG, FPG, and HbA1c were all predictive of all-cause and cardiovascular mortality when used alone, but when combined only 2hPG retained its predictive value for both outcomes while HbA1c predicted cardiovascular mortality only when used as a continuous variable and when 2hPG and FPG were in the normal range.

1. Background

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose level, with type 2 diabetes accounting for >90 % of it. It affects around 537 million adults worldwide, and is the direct cause of 6.7 million deaths every year.[1] The ultimate goal of diagnosing and treating diabetes is to prevent macrovascular and microvascular complications and eventually reduce disability and mortality. Towards this end, diagnosis should aim to identify people at higher risk of diabetic complications. A wide range of glycemic measures, such as 2-hour plasma glucose (2hPG) during 75-g oral glucose tolerance test, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), HbA1c variability, and the time in range, are associated with risk of diabetic complications.[2,3] According to the current standards of American Diabetes

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Association, 2hPG, FPG, and HbA1c can be used to diagnose type 2 diabetes, and elevation of any of them could lead to a diagnosis under the prescribed conditions.[4] The assumption of these criteria is that each glycemic measure in itself is predictive of diabetic complications and thus represents a valid target of treatment.

While numerous studies have shown that each of the three glycemic measures was associated with diabetic complications after adjusting for non-glycemic risk factors such as age and hypertension,[5,6] whether the association is influenced by the other two glycemic measures (i.e., whether they are redundant in predicting the development of complications) is less understood, partly because few studies included the three measures in a single regression model to adjust for their influence on each other. The studies that did so reported inconsistent results. For example, Cavalot et al. observed that both 2hPG and HbA1c were associated with all-cause and cardiovascular mortality,[7] while most others found that only the result for 2hPG was statistically significant,[8–10] and few studies found that FPG could predict risk of all-cause or cardiovascular mortality after adjusting for 2hPG and HbA1c.

Of note, the above-mentioned method to control for confounding caused by the three glycemic measures on each other is subject to the potential multicollinearity among them, which can lead to unstable coefficient estimates, increased standard errors, and diminished statistical power.[11] To address this issue, it is necessary to assess the potential multicollinearity first and include only the glycemic measures that are not highly correlated into the regression model. However, such assessment was rarely done by previous studies. An alternative method which can preclude the confounding caused by elevation of other glycemic measures in the first place is to compare the individuals having only one glycemic measure elevated (and the other two being normal) with those who are normal for all the three glycemic measures. However, previous studies using this method mostly considered the levels of two glycemic measures only, leaving the potential confounding caused by the third one unaddressed.[12] Thus, more research is needed to better investigate the usefulness of each glycemic measure in predicting the development of diabetes complications.

Against this background, we conducted a cohort study to find out which one(s) of the three glycemic measures for diabetes diagnosis might be the most effective in identifying patients with higher risk of all-cause and cardiovascular mortality, which are the most severe diabetic complications. Both of the two analytical methods mentioned above were adopted to adjust for the confounding caused by non-glycemic risk factors and more importantly the influence of the three glycemic measures on each other. Due to lack of data, other glycemic measures than 2hPG, FPG, and HbA1c were not examined in this study.

2. Method

2.1. Study population

The study population was selected from the participants of Third National Health and Nutrition Examination Survey (NHANES III) and six continuous cycles from 2005–2006 to 2015–2016 of NHANES, which were all conducted by National Center for Health Statistics, the Centers for Disease Control and Prevention using a complex, stratified, multistage probability cluster design to obtain a representative sample of the civilian, noninstitutionalized U.S. population. Those cycles were chosen because they were the only NHANES cycles that had data on all the three glycemic measures, particularly 2hPG. The NHANES protocols were approved by the National Center for Health Statistics Research Ethics Review Board. All participants provided informed consent for the utilization of their data. The datasets are publicly available for downloading at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. The NHANES participants who (1) were 20 years or older, not pregnant, not on antidiabetic medications, and with complete data on 2hPG, FPG and HbA1c at baseline, (2) had data on mortality status by the end of follow-up (see below), and (3) were assigned sample weights by the NHANES team, were eligible to be included in this study. This study was approved by the Survey and Behavioural Research Ethics Committee of The Chinese University of Hong Kong (reference no. SBRE-23-0967).

2.2. Baseline data collection

In NHANES, 2hPG and FPG were measured only for those who had fasted for more than 9 h before blood sample collection, while HbA1c was measured for all participants who provided blood samples regardless of their fasting status. During 2005–2016, there were three HbA1c laboratory instruments used in NHANES, i.e., the Tosoh A1C 2.2 Plus during 2005–2006, the Tosoh A1C G7 during 2007–2012, and the Tosoh A1C G8 during 2013–2016. High blood glucose was defined as 2hPG $\geq$11.1 mmol/L, FPG $\geq$7.0 mmol/L, or HbA1c $\geq$6.5 %, according to the American Diabetes Association 2023 standards.[4]

Age, sex, race, marital status, education level, smoking status, drinking status, physical activity, current health status, existing cardiovascular disease, comorbidity, antihypertensive drugs, and lipid-lowering drugs were self-reported by participants at the time of survey. For smoking status, participants were categorized as never smokers, previous smokers, or current smokers based on their responses to the questions about whether they had smoked at least 100 cigarettes during their lifetime and whether they were currently smoking.[13,14] For alcohol consumption, participants were categorized as never drinkers, previous drinkers or current drinkers based on their responses to the questions about whether they had at least 12 alcoholic drinks in the entire lifetime and the quantity of alcohol consumption in the past year.[15] Physical activity levels were categorized as sedentary, moderate, or vigorous according to the weekly metabolic equivalents of task derived from participants' responses to the questions about type and duration of their physical activities.[16] Existing cardiovascular disease was ascertained by the following questions: "Has a doctor or other health professional ever told you that you had congestive heart failure/coronary heart disease/angina/heart attack/stroke?" The participants who answered "Yes" to any one of these questions were considered as having existing cardiovascular disease. Comorbidity was defined as presence of one or more of the following: asthma, emphysema, chronic bronchitis, liver condition, thyroid problem and cancer.

Body mass index (BMI) was calculated based on participants' height and weight measured through physical examination. Blood pressure was measured during the household interview or in the mobile examination centers after resting quietly in a seated position for 5 min. The mean blood pressure was calculated as the average of up to 3 readings in NHANES III and up to 4 readings in the continuous NHANES cycles. Total cholesterol was measured by an enzymatic assay based on serum sample.

2.3. Follow-up and ascertainment of outcomes

The follow-up of NHANES participants started from the date of survey participation. Mortality status was ascertained through linkage to the records from the National Death Index. The most updated public-use Linked Mortality Files of NHANES provide data on mortality that occurred between baseline survey and December 31, 2019. Due to the probabilistic nature of the linkage, those linked to the National Death Index were assumed deceased and those not were assumed alive. The "underlying cause of death" in the Linked Mortality Files, which was recoded based on ICD-10 and ICD-9, was used to determine the cause of the death. Cardiovascular mortality encompassed conditions classified under diseases of the heart and cerebrovascular diseases (underlying cause of death codes 054-068 and 070).

2.4. Statistical analyses

The baseline characteristics of study participants, both overall and stratified by the levels of the three glycemic measures, were summarized

using counts and proportions for categorical variables or means with standard deviations for continuous variables. Sample weights were used in calculating means and proportions to account for the complex, stratified probability sampling design and produce estimates that were representative of the U.S. population. The value of glycemic measures in predicting risk of all-cause and cardiovascular mortality was assessed by using Cox regression analysis and expressed as hazard ratio (HR) with 95 % confidence interval (CI).

Specifically, two analytical approaches were adopted. The first one involved three variables for glycemic measures, one for each. A crude HR without any adjustment and an HR adjusted for non-glycemic risk factors, including age, sex, race, marital status, education level, smoking status, drinking status, physical activity level, current health status, existing cardiovascular disease, comorbidity, antihypertensive drugs, lipid-lowering drugs, BMI, systolic blood pressure, and total cholesterol, were estimated for each glycemic measure. Then, to adjust for the influence of the three glycemic measures on each other, we tried to include all of them in a single regression model. However, before that, the potential multicollinearity among them were assessed by variance inflation factor (VIF). Only the glycemic measures that were not highly correlated with each other (VIF < 5) were eligible to enter the final model. From this final model, a third HR adjusted for both non-glycemic risk factors and other glycemic measures was generated for each glycemic measure to examine its value in predicting risk of mortality.

In the second analysis approach, only one variable representing the blood glucose status of participants was included in the regression model. The variable had six possible values which corresponded to the following glycemic statuses (or subgroups) respectively: (1) all the three glycemic measures in normal ranges; (2) only 2hPG elevated; (3) only FPG elevated; (4) only HbA1c elevated; (5) any two measures elevated; (6) all the three measures elevated. The Kaplan-Meier survival curves were generated for all of the subgroups. Then, subgroup (1) was used as reference group, and the other 5 subgroups were compared with it separately. For each subgroup, a crude HR without any adjustment and an HR adjusted for non-glycemic risk factors were generated. In subgroups (2) to (4), there was only one glycemic measure elevated, precluding the confounding caused by elevation of the other two glycemic measures in the first place. Thus, comparisons of them with subgroup (1) could help reveal the added predictive value of each glycemic measure.

Sensitivity analyses were conducted by using the glycemic measures as continuous variables to examine the robustness of results from the two above approaches. All p values were 2-tailed. A p value <0.05 was indicative of statistical significance. All statistical analyses were performed with R version 4.3.1 (R Foundation for Statistical Computing).

3. Results

A total of 80,985 participants were included in the baseline survey of NHANES III and NHANES 2005–2016, and 14,013 of them who were not on anti-diabetic medications met the inclusion criteria for this study (see Supplementary Figure for the flow of selection). Among the included participants, the weighted prevalence of elevated 2hPG, elevated FPG, and elevated HbA1c in the U.S. general adults were 6.1 %, 4.2 % and 2.7 %, respectively. The overlapping among the three glycemic measures is shown in Fig. 1. Specifically, 79.7 % had elevated 2hPG (regardless of their FPG and HbA1c levels), 15.7 % had normal 2hPG but elevated FPG (regardless of their HbA1c levels), and 4.6 % had normal 2hPG and normal FPG but elevated HbA1c. The weighted prevalence of elevation in any glycemic measures was 7.7 %. The characteristics of participants stratified by levels of the three glycemic measures are shown in Table 1. The follow-up periods ranged from 2 months to 373 months, with a median of 117 months (or 9.8 years). During the follow-up, 2869 participants died, and 960 of these deaths were attributed to cardiovascular causes. The median survival time was 353 months (or 29.4 years), and the 10-year survival rate was 91.5 %.

The results of Cox regression analysis involving three variables for glycemic measures are shown in Table 2. When the three variables were included individually in the model, each measure showed statistically significant associations with both all-cause mortality (HR ranging from 1.51 to 1.55) and cardiovascular mortality (HR ranging from 1.32 to 1.52) after adjusting for non-glycemic risk factors. However, when all the three measures were included in the model (all VIFs <2) to adjust for their influence on each other, the associations were all attenuated, and only elevated 2hPG remained statistically significantly associated with all-cause mortality. Specifically, for all-cause mortality, the HRs for 2hPG, FPG and HbA1c were 1.33 (95%CI: 1.10–1.61), 1.23 (95%CI: 0.99–1.53) and 1.06 (95%CI: 0.82–1.36), respectively, and for cardiovascular mortality, the corresponding numbers were 1.08 (95%CI: 0.81–1.43), 1.36 (95%CI: 0.96–1.93) and 1.11 (95%CI: 0.78–1.59), respectively (Table 2).

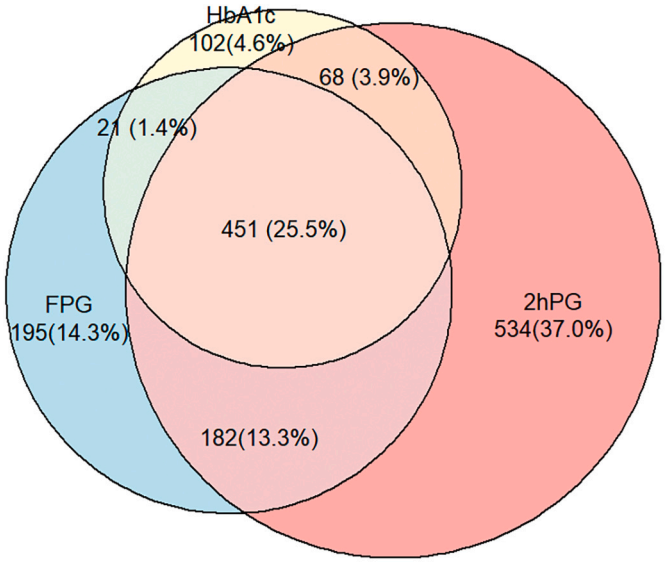

Fig. 1. The numbers of patients with diabetes identified by different glycemic measures and their overlapping pattern.

In the second analysis approach, the study population was divided into six subgroups according to the combination of levels of the three glycemic measures. The survival curves of these subgroups are shown in Fig. 2. It can be seen that (1) the subgroup with the three measures all being normal was at the top (highest survival probability), (2) the subgroups with isolated FPG elevation or isolated HbA1c elevation were in the middle, and (3) the subgroup with all the three glycemic measures elevated was at the bottom (lowest survival probability). Notably, for all-cause mortality, the subgroups with elevation of 2hPG only or any two glycemic measures (250/271 or 92 % of them had 2hPG elevation, according to Fig. 1) showed similar survival probabilities to the subgroup with elevation of all the three glycemic measures. Using the "all normal" subgroup as reference and after adjusting for non-glycemic risk factors, isolated 2hPG elevation (HR =1.26, 95 % CI:1.01–1.56), elevation of two glycemic measures (HR = 1.60, 95 % CI:1.16–2.20), and elevation of all the three glycemic measures (HR = 1.67, 95 % CI:1.32–2.10) were associated with an increased risk of all-cause mortality, whereas neither isolated FPG elevation nor isolated HbA1c elevation was statistically significantly associated with all-cause or cardiovascular mortality (Table 3).

In sensitivity analyses where the glycemic measures were treated as continuous variables, the results were in general consistent with those from the main analyses. Specifically, 2hPG was still statistically significantly associated with risk of all-cause and even cardiovascular mortality (HR 1.04 for every 1-mmol/L increase in 2hPG, Supplementary Tables 1 & 2), while FPG and HbA1c were not statistically associated with either outcome, with only one exception: in the participants with

Table 1
Baseline characteristics of the 14,013 study participants according to 2hPG, FPG and HbA1c levels.

Variable	2hPG, mmol/L		FPG, mmol/L		HbA1c, %		Total
	<11.1	≥11.1	<7.0	≥7.0	<6.5	≥6.5	
Overall, n (%)	12,778 (93.9)	1235 (6.1)	13,164 (95.8)	849 (4.2)	13,371 (97.3)	642 (2.7)	14,013
Age, mean (SD)	49.0 (15.8)	61.0 (13.9)	49.5 (16.0)	58.7 (13.0)	49.7 (16.0)	58.5 (12.4)	50.1 (16.0)
Male, n (%)	6317 (48.1)	629 (48.2)	6453 (47.6)	493 (59.7)	6603 (47.9)	343 (54.8)	6946 (48.1)
Race, n (%)							
Non-Hispanic White	5890 (70.1)	544 (71.6)	6087 (70.3)	347 (67.9)	6232 (70.5)	202 (58.1)	6434 (70.2)
Non-Hispanic Black	2554 (10.6)	202 (8.5)	2592 (10.5)	164 (9.7)	2572 (10.3)	184 (16.9)	2756 (10.5)
Hispanic	3205 (12.1)	406 (14.1)	3332 (12.1)	279 (15.6)	3402 (12.1)	209 (16.7)	3611 (12.2)
Others	1129 (7.2)	83 (5.8)	1153 (7.2)	59 (6.8)	1165 (7.1)	47 (8.4)	1212 (7.1)
Married, n (%)	7147 (58.3)	755 (61.3)	7398 (58.5)	504 (59.0)	7510 (58.3)	392 (63.5)	7902 (58.5)
College degree or higher, n (%)	2925 (29.9)	144 (16.6)	2960 (29.5)	109 (20.2)	3012 (29.6)	57 (13.1)	3069 (29.1)
Smoking, n (%)							
Never smokers	6712 (53.0)	585 (45.8)	6813 (11.8)	384 (15.7)	7011 (52.8)	286 (42.0)	7297 (52.5)
Previous smokers	3178 (25.2)	421 (34.5)	3308 (25.3)	291 (36.5)	3385 (25.5)	214 (34.7)	3599 (25.8)
Current smokers	2880 (21.8)	227 (19.7)	2935 (21.7)	172 (20.0)	2966 (21.6)	141 (23.3)	3107 (21.7)
Alcohol consumption, n (%)							
Never drinkers	1604 (11.5)	228 (18.3)	1686 (11.8)	146 (15.7)	1703 (11.8)	129 (18.0)	1832 (11.9)
Previous drinkers	1740 (11.4)	254 (17.5)	1806 (11.4)	188 (20.9)	1834 (11.4)	160 (23.4)	1994 (11.8)
Current drinkers	8013 (77.1)	584 (64.3)	8182 (76.8)	415 (63.4)	8322 (75.8)	275 (58.6)	8597 (76.3)
Physical activity, n (%)							
Sedentary	5907 (40.8)	724 (56.0)	6148 (41.2)	483 (53.5)	6242 (41.3)	389 (59.0)	6631 (41.8)
Moderate	4113 (32.8)	406 (33.8)	4228 (32.6)	291 (37.5)	4313 (32.8)	206 (33.3)	4519 (32.8)
Vigorous	2712 (26.4)	98 (10.1)	2740 (26.1)	70 (9.0)	2765 (25.9)	45 (7.7)	2810 (25.4)
Current health status							
Excellent/very good/good	9818 (85.4)	768 (71.5)	10,054 (85.0)	532 (72.5)	10,210 (85.0)	376 (66.0)	10,586 (84.5)
Fair/poor	2509 (14.6)	434 (28.5)	2664 (15.0)	299 (27.5)	2696 (15.0)	247 (34.0)	2943 (15.5)
Existing cardiovascular disease							
Yes	780 (5.4)	137 (13.0)	838 (5.7)	79 (10.8)	863 (5.8)	54 (9.6)	917 (5.9)
No/unclear	11,998 (94.6)	1098 (87.0)	12,326 (94.3)	770 (89.2)	12,508 (94.2)	588 (90.4)	13,096 (94.1)
Comorbidity							
0	9620 (72.3)	917 (69.0)	9869 (72.1)	668 (73.3)	10,011 (72.0)	526 (76.7)	10,537 (72.1)
1	2401 (21.1)	217 (20.0)	2488 (21.1)	130 (19.4)	2534 (21.2)	84 (16.2)	2618 (21.0)
≥2	757 (6.6)	101 (11.0)	807 (6.8)	51 (7.3)	826 (6.9)	32 (7.1)	858 (6.9)
Taking antihypertensive drugs							
Yes	2124 (16.0)	362 (34.9)	2294 (16.7)	192 (27.6)	2358 (16.9)	128 (25.6)	2486 (17.2)
No/unclear	10,654 (84.0)	873 (65.1)	10,870 (83.3)	657 (72.4)	11,013 (83.1)	514 (74.4)	11,527 (82.8)
Taking lipid-lowering drugs							
Yes	1337 (10.8)	221 (22.8)	1443 (11.2)	115 (17.4)	1485 (11.4)	73 (13.9)	1558 (11.5)
No/unclear	11,441 (89.2)	1014 (77.2)	11,721 (88.8)	734 (82.6)	11,886 (88.6)	569 (86.1)	12,455 (88.5)
BMI (kg/m^2), mean (SD)	28.3 (6.5)	30.6 (6.7)	28.3 (6.5)	31.6 (6.8)	28.3 (6.5)	32.1 (7.1)	28.5 (6.5)
Systolic blood pressure (mmHg), mean (SD)	123.0 (16.1)	134.8 (19.1)	123.3 (16.3)	134.4 (18.3)	123.4 (16.3)	136.0 (19.0)	124.0 (16.6)
Total cholesterol (mmol/l), mean (SD)	5.2 (1.1)	5.5 (1.2)	5.2 (1.1)	5.5 (1.2)	5.2 (1.1)	5.6 (1.3)	5.2 (1.1)
Follow-up period, month (median (interquartile range))	118 (76–161)	112 (67–166)	117 (75–161)	118 (70–175)	117 (75–160)	124 (74–197)	117 (82–231)
Number of all-cause deaths	2328 (12.1)	541 (37.5)	2500 (12.6)	369 (36.3)	2571 (12.9)	298 (39.4)	2869 (13.6)
Number of cardiovascular deaths	781 (3.7)	179 (12.5)	830 (3.9)	130 (12.7)	853 (4.0)	107 (14.0)	960 (4.3)

normal 2hPG and FPG, elevation of HbA1c was associated with higher cardiovascular mortality (HR = 1.27 for every 1 % increase in HbA1c, 95 % CI: 1.04–1.55, Supplementary Table 2).

4. Discussion

Whether a glycemic measure can predict risk of diabetic complications is critical for determining its value as a diagnostic measure. Mortality represents the most severe complication of diabetes. This study employed two approaches to examining the value of 2hPG, FPG, and HbA1c in predicting risk of all-cause and cardiovascular mortality. After adjusting for non-glycemic risk factors and the influence of the other two glycemic measures, 2hPG was consistently found to be able to predict risk of all-cause mortality regardless of the analytical approach, and in some analyses, it also predicted risk of cardiovascular mortality. HbA1c and FPG were predictive of all-cause and cardiovascular mortality when used alone, but after adjusting for the effects of 2hPG and FPG by stratification, HbA1c predicted cardiovascular mortality only when used as a continuous variable, while FPG no longer showed a statistically significant association with mortality. The higher risk of mortality in people with elevation of two or three glycemic measures (701/722 or 97 % of them had elevated 2hPG) further supported the significant predictive value of elevated 2hPG. However, as the corresponding HRs (1.60 and 1.67) in these subgroups were apparently higher than that for isolated elevated 2hPG (1.26), the results suggested that there was interaction (synergistic effect) among the three glycemic measures when they were all elevated.

Our findings about the predictive value of 2hPG align well with previous studies. For instance, Lu et al.,[8] the DECODE study[12] and Qiao et al.[9] found that when two or three glycemic measures were included in a single regression model, only 2hPG remained statistically significantly associated with risk of all-cause mortality. A possible explanation for this finding is that glycemic spikes (as reflected by 2hPG level) might be more deleterious to the blood vessels compared with mean or basal glycaemia (as reflected by FPG and HbA1c levels).[17,18] Another possible explanation is that individuals with elevated 2hPG might be at a more advanced stage of diabetes and thus have been exposed to hyperglycemia for a longer period compared to those with elevated FPG or HbA1c only,[19] which heightens their risks of various complications, including mortality. The statistically insignificant association between 2hPG and cardiovascular mortality in some of our analyses could be a result of insufficient statistical power caused by the limited number of cardiovascular deaths (54 cases, see Table 3) in the subgroup with isolated elevated 2hPG.

HbA1c was chosen as a diagnostic measure primarily for its convenience (no need for fasting) rather than because there was solid evidence

Table 2
The association of each glycemic measure with all-cause and cardiovascular mortality, with or without adjustment for the other two glycemic measures in the same regression model.

Outcomes and glycemic measures	Only one glycemic measure was included in the model				All the three glycemic measures were included in the model		
	HR (95 % CI) without adjustment for non-glycemic risk factors (n = 14,013)	P	HR (95 % CI) adjusted for non-glycemic risk factors[a] (n = 12,095)	P	HR (95 % CI) adjusted for non-glycemic risk factors[a] (n = 12,095)	P	VIF
All-cause mortality							
2hPG: ≥11.1 vs. <11.1 mmol/L	3.41 (2.97–3.93)	**<0.001**[b]	1.51 (1.29–1.76)	**<0.001**	1.33 (1.10–1.61)	**0.003**	1.779
FPG: ≥7.0 vs. <7.0 mmol/L	2.79 (2.33–3.35)	**<0.001**	1.55 (1.29–1.85)	**<0.001**	1.23 (0.99–1.53)	0.057	1.929
HbA1c: ≥6.5 % vs. <6.5 %	2.78 (2.33–3.31)	**<0.001**	1.51 (1.24–1.84)	**<0.001**	1.06 (0.82–1.36)	0.674	1.850
Cardiovascular mortality							
2hPG: ≥11.1 vs. <11.1 mmol/L	3.66 (3.00–4.45)	**<0.001**	1.32 (1.06–1.63)	**0.013**	1.08 (0.81–1.43)	0.599	1.779
FPG: ≥7.0 vs. <7.0 mmol/L	3.16 (2.43–4.12)	**<0.001**	1.52 (1.16–2.00)	**0.003**	1.36 (0.96–1.93)	0.080	1.929
HbA1c: ≥6.5 % vs. <6.5 %	3.16 (2.38–4.21)	**<0.001**	1.47 (1.08–2.00)	**0.014**	1.11 (0.78–1.59)	0.559	1.850

[a] The non-glycemic risk factors adjusted for included age, sex, race, education level, marital status, physical activity, smoking status, drinking status, current health status, existing cardiovascular disease, comorbidity, antihypertensive drugs, lipid-lowering drugs, BMI, systolic blood pressure, and total cholesterol.
[b] In this table, P values ≤0.05 were indicative of statistical significance.

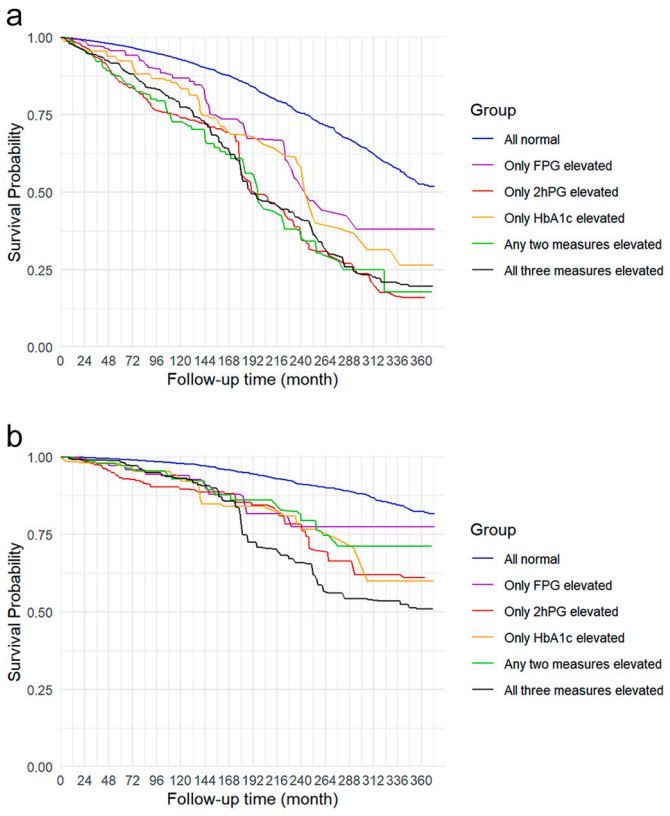

Fig. 2. Survival curves for a) all-cause mortality and b) cardiovascular mortality according to the different combinations of 2hPG, FPG, and HbA1c levels.

that it has added value in predicting risk of diabetic complications on top of other glycemic measures.[21] Previous studies yielded conflicting results about the predictive value of HbA1c. For example, Cavalot et al.[22] and Metcalf et al.[23] found that HbA1c was still associated with all-cause mortality after adjustment for FPG and 2hPG, while Barr et al.[24] found that it was associated with neither all-cause nor cardiovascular mortality after adjustment for 2hPG or FPG. In the present study, HbA1c predicted cardiovascular mortality only when used as a continuous variable and when 2hPG and FPG were in the normal range. One possible reason for the statistically insignificant results when HbA1c was analyzed as a binary variable was the limited number of outcome events in those with isolated elevated HbA1c, which was 37 for all-cause deaths and 16 for cardiovascular deaths (Table 3). Another possible reason is that people with very high HbA1c values were pooled together with people with "good glycemic control" (i.e., HbA1c <7 %) in the "elevated" group, which means that most people in that group were not really exposed to poor glycemic control, thus resulting in an overall weak association.

Similar to HbA1c, FPG was also introduced as a diagnostic measure for its convenience rather than proven added value for predicting diabetic complications.[25] Most previous studies found that FPG was not associated with macrovascular complications and mortality after controlling for other glycemic measures,[7,9,24] which was further corroborated by this study. However, Metcalf et al.[23] found that elevated FPG was associated with higher risks of microvascular complications such as retinopathy and nephropathy, although its effect was smaller than those of 2hPG and HbA1c. Therefore, further studies on the value of FPG, particularly in predicting risk of microvascular complications, are warranted to better inform the use of it in diagnosing and managing diabetes.

This study has some limitations. Firstly, as with most cohort studies, NHANES collected the data on medication use only at baseline and was not able to adjust for the potential confounding caused by medication use during follow-up. Thus, the results of this study were subject to residual confounding. Secondly, the sample size and number of outcome events of some subgroups (e.g., that with isolated HbA1c elevation) were relatively small, which might have led to insufficient power and the statistically insignificant results. Thirdly, this study only focused on mortality, the most severe outcome, but non-fatal microvascular and macrovascular complications which could lead to disability and decrease quality of life are also important for patients. Thus, further studies to illustrate the predictive value of each glycemic measure, particularly in predicting risk of microvascular complications, are warranted.

5. Conclusion

2hPG, FPG, and HbA1c were all predictive of all-cause and

Table 3
The association of different combinations of levels of the three glycemic measures with all-cause and cardiovascular mortality.

Glycemic measures	Not adjusted for non-glycemic risk factors				Adjusted for non-glycemic risk factors[a]			
	n	N	HR (95 % CI)	P	n	N	HR (95 % CI)	P
All-cause mortality								
All normal	2226	12,460	1		1942	10,795	1	
Only 2hPG elevated	208	534	3.61 (2.99–4.35)	**<0.001**[b]	174	436	1.26 (1.01–1.56)	**0.039**
Only FPG elevated	51	195	1.84 (1.20–2.83)	**0.006**	45	169	1.18 (0.79–1.77)	0.425
Only HbA1c elevated	44	102	2.41 (1.47–3.97)	**<0.001**	37	87	1.00 (0.69–1.45)	0.990
Any two measures elevated	115	271	3.62 (2.63–4.99)	**<0.001**	94	218	1.60 (1.16–2.20)	**0.004**
All three measures elevated	225	451	3.20 (2.60–3.94)	**<0.001**	201	390	1.67 (1.32–2.10)	**<0.001**
Cardiovascular mortality								
All normal	743	12,460	1		660	10,795	1	
Only 2hPG elevated	66	534	4.02 (3.00–5.38)	**<0.001**	54	436	1.10 (0.79–1.54)	0.561
Only FPG elevated	17	195	2.38 (1.27–4.48)	**0.007**	16	169	1.32 (0.72–2.51)	0.352
Only HbA1c elevated	19	102	3.34 (1.68–6.62)	**<0.001**	16	87	1.00 (0.57–1.73)	0.988
Any two measures elevated	31	271	2.77 (1.74–4.40)	**<0.001**	25	218	0.95 (0.58–1.54)	0.826
All three measures elevated	84	451	3.93 (2.88–5.36)	**<0.001**	79	390	1.75 (1.23–2.48)	**0.002**

[a] The non-glycemic risk factors adjusted for included age, sex, race, marital status, education level, physical activity, smoking status, drinking status, current health status, existing cardiovascular disease, comorbidity, antihypertensive drugs, lipid-lowering drugs, BMI, systolic blood pressure, and total cholesterol.
[b] In this table, P values ≤0.05 were indicative of statistical significance.

cardiovascular mortality when used alone, but when combined only 2hPG retained its predictive value for both outcomes while HbA1c predicted cardiovascular mortality only when used as a continuous variable and when 2hPG and FPG were in the normal range. Of note, when the three glycemic measures were all elevated, the risk of mortality was higher than when only 2hPG was elevated, suggesting potential interaction of them. In the future, more studies on the value of different glycemic measures in predicting risk of microvascular complications are warranted to better inform the diagnosis and management of diabetes.

CRediT authorship contribution statement

Jiayue Zhang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Wenxiao Zheng:** Formal analysis, Data curation. **Shuting Wang:** Writing – review & editing. **Xiangyang Gao:** Writing – review & editing. **Ying Xiao:** Writing – review & editing. **Zuyao Yang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

The NHANES protocols were approved by the National Center for Health Statistics Research Ethics Review Board. This study was approved by the Survey and Behavioural Research Ethics Committee of The Chinese University of Hong Kong (reference no. SBRE-23-0967).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2025.108970.

Data availability

The datasets generated and/or analyzed during the current study are available in the NHANES repository, https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

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