Independent effects of 2hPG, FPG and HbA1c on cardiovascular risk: analysis of a nationally representative sample from China

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Abstract

Aims: To evaluate the independence of the effect of 2-hour post-load plasma glucose (2hPG), fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) on cardiovascular disease (CVD) after adjusting for each other and non-glycemic factors.

Methods: We analyzed data from a nationally representative sample of 174,329 Chinese adults from a survey conducted in 2013–2014. The associations of glycemic measures with the risk of CVD were examined and compared by using logistic regression analyses.

Results: After adjusting for non-glycemic factors, the odds ratio for one standard-deviation increase of 2hPG, FPG and HbA1c was 1.08 (95% confidence interval [CI]: 1.05-1.11), 1.02 (95% CI: 0.99-1.06) and 1.05 (95% CI: 1.02-1.07), respectively. However, the odds ratio for 2hPG (1.10, 95% CI: 1.05-1.16) remained statistically significant after FPG and HbA1c were added to the models, whereas the odds ratios for FPG and HbA1c became statistically insignificant after 2hPG was adjusted for. The results remained consistent across various scenarios.

Conclusions: 2hPG showed an effect on cardiovascular risk which was independent from FPG and HbA1c, whereas whether the effects of FPG and HbA1c were independent from 2hPG was open to question. This finding calls for more research on how to better use FPG and HbA1c in diagnosing diabetes.

Keywords: Glycemic measures, 2-hour post-load plasma glucose, Fasting plasma glucose, Glycated hemoglobin, Cardiovascular disease, Cross-sectional study

1. Introduction

Diabetes mellitus is an increasingly important public health concern, affecting more than 422 million adults worldwide [1]. Macro-vascular complications, mainly cardiovascular disease (CVD), account for the majority of diabetes-related deaths [2-4]. Two-hour post-load glucose (2hPG) was the first glycemic measure used for diagnosing diabetes [5], with fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) added to diagnostic criteria later [6,7]. According to the current guidelines of American Diabetes Association (ADA), elevation of any of these glycemic measures may lead to a diagnosis of diabetes [8]. The implicit assumption underlying the criteria is that each glycemic measure is independently associated with the risk of diabetes complications. Although many studies have shown that each glycemic measure was associated with CVD risk after adjusting for non-glycemic risk factors such as age [9-11], whether their effects are independent from each other is actually not well understood, because the three glycemic measures were rarely all included in a single regression model.

A few cohort studies have tried to do so, but their results were inconsistent and most of them small in sample size [12-15]. For example, Lind et al found that when FPG, 1hPG, 2hPG and HbA1c were included in the same models, only 2hPG was independently associated with increased risk of CVD [12]. Lu et al had similar findings [15]. By contrast, the study by Cavalot et al with similar analysis found that both 2hPG and HbA1c were predictive of CVD [13], while Wild et al found that neither FPG nor 2hPG was associated with CVD mortality [14]. Although temporal order from baseline glycemic measures to future CVD events is clear in cohort studies, the association between them could be distorted by inevitable drug treatment and other interventions patients receive during the follow-up period, which are often hard to measure and adjust for. In contrast, cross-sectional studies do not have this problem and may help verify the findings of cohort studies from another angle. In fact, the evidence based on which clinical guidelines [7,16-18] supported the use of FPG and HbA1c in diagnosing diabetes is mainly from cross-sectional studies [19-21].

We therefore conducted this study to assess the independence of the effect of each of the diagnostic glycemic measures on the risk of major CVD by adjusting for major conventional confounders and more importantly other glycemic measures based on a nationally representative sample obtained from a cross-sectional survey in China.

2. Research Design and Methods

2.1. Study Design and Sample

The data used in this study came from the 2013–2014 survey of China Chronic Diseases and Risk Factors Surveillance (CCDRFS), which is an on-going nationally representative surveillance system administered by the National Center for Chronic and Non-communicable Disease Control and Prevention (NCNCD), the Chinese Center for Disease Control and Prevention. The CCDRFS was designed to investigate the epidemiology and temporal changes of major chronic diseases and their risk factors in the general population of China by conducting cross-sectional surveys every 3 years.

The 2013–2014 survey of CCDRFS conducted between August 2013 and July 2014 adopted a multistage, stratified random sampling scheme to obtain a nationally representative sample. The survey was approved by the ethical review committee of NCNCD (ref. no. 201307, scanned copy available upon request) and written informed consents were obtained from all study participants. For details of the sampling methods, survey questionnaires, standard operation procedures for physical measurements, laboratory tests and quality control programs, one could refer to previous publications.[22-25] Briefly, the 31 provinces, autonomous regions and municipalities in mainland China were all covered by the survey, with a varying number of survey sites in each of the 31 areas. In total, 177,099 participants from 298 survey sites were enrolled.[23] Among them, those without valid information on doctor-diagnosed CVD, doctor-diagnosed diabetes or all of the three glycemic measures were excluded, leaving 174,329 participants (98.44% of all) for the present study.

2.2. Measurements and Definitions of Study Variables

A standard questionnaire including questions about demographic characteristics (age, sex, ethnicity), socioeconomic status (education level), lifestyle risk factors (smoking, drinking, physical inactivity) and medical history (diabetes, CVD) was administered by trained interviewers at local centers for disease control and prevention and community clinics in the participants' residential area. Current smoking was defined as self-reported tobacco use every day or on some days at the time the survey was conducted. Former smoking was defined as self-reported previous tobacco use which had stopped by the time the survey was conducted. Heavy drinking was defined as daily consumption of pure alcohol >40 g for women and >60 g for men.[26] The computation for pure alcohol consumption from various kinds of alcoholic beverages is described in detail elsewhere.[27] The Global Physical Activity Questionnaire was used to evaluate physical activity of each respondent. Individuals with less than 150 minutes of moderate-intensity activity per week or equivalent were defined as insufficiently active. The height and weight were measured for all participants, from which body mass index (BMI) was computed. Those with a BMI ≥28 kg/m^2 were classified as obese based on Chinese criteria. Hypertension was defined as the presence of at least one of the following: a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or a prior diagnosis of hypertension. Dyslipidemia was defined as a total cholesterol level ≥6.22 mmol/L (240 mg/dl), triglyceride ≥2.26 mmol/L (200 mg/dl), low-density lipoprotein cholesterol ≥4.14 mmol/L (160 mg/dl), or high-density lipoprotein cholesterol <1.04 mmol/L (40 mg/dl).

The participants were also asked whether they had ever been diagnosed with diabetes mellitus, myocardial infarction and stroke by a secondary or tertiary (i.e., county-level or above) hospital. Those who answered 'yes' were considered as having doctor-diagnosed diabetes or CVD and further asked the time of or age at diagnosis. Those who answered 'no' but met any of the following criteria used by World Health Organization and ADA were considered as newly diagnosed diabetes: (1) 2hPG ≥11.1 mmol/L (200 mg/dl) during a 75-g oral glucose tolerance test; (2) FPG ≥7.0 mmol/L (126 mg/dl); and (3) HbA1c ≥6.5%.[1,16] Those who met any of the following criteria used by ADA were considered as prediabetes: (1) 2hPG 7.8-11.0 mmol/L (140-199 mg/dl) during a

75-g oral glucose tolerance test; (2) FPG 5.6-6.9 mmol/L (100-125 mg/dl); and (3) HbA1c 5.7%-6.4%. Blood samples were collected for all participants after an overnight fast of at least 10 hours. All participants without a history of doctor-diagnosed diabetes received a standard 75-g oral glucose tolerance test, during which plasma glucose was measured at 0 and 2 hours. Blood samples for the glucose test were collected using vacuum blood-collection tubes containing anticoagulant sodium fluoride and were centrifuged on site within 2 hours of collection. FPG and 2hPG were measured locally using glucose oxidase or hexokinase methods within 24 hours, as reported previously.[24,28] HbA1c was directly measured from venous blood samples in a single laboratory using quantitative high-performance liquid chromatography and the boronate affinity method (Bio-Rad D-10 Hemoglobin Analyzer).

2.3. Statistical Analysis

The basic characteristics were compared between people without diabetes, newly diagnosed diabetes, and doctor-diagnosed diabetes. Analysis of variance, χ^2 test and Kruskal Wallis test were used to compare continuous variables (e.g., age), binary variables (e.g., smoking status) and variables that were not normally distributed (e.g., total cholesterol), respectively. The association between glycemic status and CVD risk was assessed by using logistic regression analysis that took into account the stratification and intra-cluster correlation and expressed in odds ratio (OR) with 95% confidence interval (CI).

To evaluate the effects of different glycemic measures and their impact on each other, analyses were restricted to the participants without a history of doctor-diagnosed diabetes and the three measures were included into logistic regression models progressively. In total, seven models were used, including three models containing any single glycemic measures, another three containing any two measures, and the last containing all three measures. In each model, the OR corresponding to 1 standard deviation increase in every glycemic measure included in that model was estimated so that the effect of different glycemic measures could be compared using a common metric. To control for potential confounding caused by non-glycemic risk factors of CVD such as age, sex, smoking and hypertension, multivariate analyses adjusting for those factors were conducted for each of the above models as well. Pearson correlation coefficients and variance inflation factors were estimated to assess potential collinearity in the models containing two or three glycemic measures. To examine the robustness of results, the above univariate and multivariate analyses were repeated by converting glycemic measures into binary variables (i.e. above or below current diagnostic cutoffs) or by further adjusting for BMI and dyslipidemia instead of obesity and total cholesterol.

To examine the potential dose-response relationship between glycemic concentrations and CVD, the participants without doctor-diagnosed diabetes were divided into around 20 groups. Using the group with lowest glycemic concentration as reference group, the OR for CVD in each of the other groups was estimated, plotted against glycemic concentration, connected with line, and tested for trend. Similarly, both univariate and multivariate analyses were conducted. All P values were 2-tailed. A p value ≤ 0.05 was indicative of statistical significance. All statistical analyses were

performed with SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.6.0 (R Foundation for Statistical Computing).

3. Results

3.1. Characteristics of Participants

The characteristics of participants are shown in Table 1. Doctor-diagnosed (n=10,226) and newly diagnosed (n=14,025) diabetes accounted for 5.87% and 8.05% of the 174,329 participants, respectively. Compared with the participants without diabetes, those with diagnosed diabetes were older and more likely to be ethnically Han, former smoker, physically inactive, obese, hypertensive, and blood lipid dysregulated (Table 1). Doctor-diagnosed CVD was reported by 4,897 participants (2.81%) and their characteristics can be found in supplemental Table S1.

Table 1. Characteristics of the participants without diabetes, newly diagnosed diabetes, and doctor-diagnosed diabetes

Variables	Participants free of doctor-diagnosed diabetes			Doctor-diagnosed diabetes (N=10226)	*P*-value
	Total (N=164103)	Without diabetes (N=150078)	Newly diagnosed diabetes (N=14025)		
Age (years)	51.09±14.24	50.59±14.23	56.44±13.20	59.34±11.28	<0.001[a]
Male (%)	70368 (42.9)	63719 (42.5)	6649 (47.4)	4135 (40.4)	<0.001[b]
Ethnicity (Han, %)	144601 (88.2)	131884 (87.9)	12717 (90.7)	9581 (93.7)	<0.001[b]
College or above (%)	10762 (6.6)	10018 (6.7)	744 (5.3)	689 (6.7)	<0.001[b]
Current smokers (%)	40548 (24.7)	36963 (24.6)	3585 (25.6)	1896 (18.6)	<0.001[b]
Former smokers (%)	8436 (5.1)	7443 (5.0)	993 (7.1)	867 (8.5)	<0.001[b]
Heavy drinkers (%)	5257 (3.2)	4554 (3.0)	703 (5.0)	209 (2.0)	<0.001[b]
Physical inactivity (%)	23250 (14.2)	20889 (13.9)	2361 (16.8)	1801 (17.6)	<0.001[b]
BMI (kg/m^2)	24.21±3.62	24.08±3.56	25.60±3.91	25.70±3.60	<0.001[a]
Obesity (%)	23493 (14.4)	19985 (13.4)	3508 (25.2)	2477 (24.5)	<0.001[b]
SBP (mmHg)	130.88±20.73	129.93±20.34	141.09±22.14	141.90±21.73	<0.001[a]
DBP (mmHg)	77.44±11.58	77.09±11.48	81.12±11.97	80.40±11.31	<0.001[a]
Hypertension (%)	56651 (34.8)	48854 (32.8)	7797 (56.0)	6268 (61.7)	<0.001[b]
TC (mmol/L, median, IQR)	4.73 (4.12-5.42)	4.70 (4.09-5.38)	5.13 (4.46-5.86)	4.96 (4.29-5.69)	<0.001[c]
TG (mmol/L, median, IQR)	1.19 (0.85-1.75)	1.16 (0.84-1.68)	1.62 (1.10-2.44)	1.56 (1.08-2.34)	<0.001[c]
LDL-C (mmol/L, median, IQR)	2.89 (2.35-3.49)	2.87 (2.34-3.46)	3.16 (2.55-3.81)	3.07 (2.48-3.70)	<0.001[c]
HDL-C (mmol/L, median, IQR)	1.33 (1.10-1.61)	1.34 (1.11-1.61)	1.22 (1.00-1.49)	1.19 (0.98-1.42)	<0.001[c]
Dyslipidemia (%)	53816 (32.8)	46603 (31.1)	7213 (51.5)	5226 (51.1)	<0.001[b]

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; IQR, interquartile range; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; 2hPG, 2-hour postload glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin. P values

were derived for differences between participants without diabetes, newly diagnosed diabetes, and doctor-diagnosed diabetes. [a]ANOVA. [b]Chi-square test. [c]Kruskcal Wallis test.

3.2. Percentage of Diabetes Identified by Different Glycemic Measures

Of the newly diagnosed diabetes, 59.55% were positive for elevated 2hPG regardless of the concentration of the other two measures, 32.65% were negative for elevated 2hPG but positive for elevated FPG regardless of the concentration of HbA1c, and 7.80% were negative for both elevated 2hPG and elevated FPG but positive for elevated HbA1c (Figure 1). Put it differently, the prevalence of newly diagnosed diabetes was increased by 54.82% by adding FPG to 2hPG and by 8.46% by adding HbA1c to 2hPG and FPG. The correlation coefficient was 0.432 between 2hPG and FPG, 0.307 between 2hPG and HbA1c, and 0.274 between FPG and HbA1c.

3.3. Increased CVD Risk in Diabetes

In the participants free of diabetes by any diagnostic methods, the prevalence of CVD was 2.28% (3,359/147,067). Using this as reference, the crude OR for CVD was 3.99 (95% CI: 3.67-4.35) in those with doctor-diagnosed diabetes, 1.86 (95% CI: 1.70-2.04) in newly diagnosed diabetes, and 2.74 (95% CI: 2.56-2.93) in the two groups combined. After adjusting for non-glycemic risk factors of CVD, the corresponding ORs were 2.38 (95% CI: 2.18-2.61), 1.20 (95% CI: 1.09-1.32), and 1.73 (95% CI: 1.62-1.86), respectively. However, after further dividing newly diagnosed diabetes according to the combination of different glycemic measures, the adjusted ORs were statistically significant only in the participants with elevated 2hPG alone and those with all the three glycemic measures elevated (Figure 2). When normoglycemic participants were alternatively used as reference, the significant findings in above two subgroups persisted (supplemental Figure S1). Besides, statistically higher ORs were also observed in the participants with impaired glucose tolerance.

3.4. Independent Effect of Different Glycemic Measures on CVD Risk

In the logistic regression analyses containing a single glycemic measure, the adjusted ORs corresponding to 1-SD increase of 2hPG, FPG, and HbA1c were 1.08 (95% CI: 1.05-1.11, $p<0.001$), 1.02 (95% CI: 0.99-1.06, $p=0.203$), and 1.05 (95% CI: 1.02-1.07, $p=0.002$), respectively (Table 2). The OR for 2hPG was little changed in magnitude and remained statistically significant after FPG, HbA1c, or both were adjusted, whereas the ORs for FPG and HbA1c became smaller and statistically insignificant after 2hPG was adjusted. The results using glycemic measures on their original scale are shown in supplemental Table S2. Similar trends were also observed when the regression analyses were repeated by taking glycemic measures as binary variables, with or without excluding participants with prediabetes (Table 2 and supplemental Table S3). The magnitude of above associations attenuated slightly but remained statistically significant in models where obesity and total cholesterol were removed and BMI and dyslipidemia were instead included (supplemental Table S4).

Table 2. Independent effects of 2hPG, FPG and HbA1c in predicting cardiovascular disease in 164103 adults free of doctor-diagnosed diabetes

Models and glycemic measures	Per 1-standard-deviation increase[a]					Above vs. below the current diagnostic cutoff[b]				
	Unadjusted OR (95% CI)[c]	*P*-value	Adjusted OR (95% CI)[d]	*P*-value	VIF	Unadjusted OR (95% CI)[c]	*P*-value	Adjusted OR (95% CI)[d]	*P*-value	VIF
Model 1										
2hPG	1.25 (1.22-1.28)	<0.001	1.08 (1.05-1.11)	<0.001	-	2.21 (2.00-2.45)	<0.001	1.31 (1.17-1.46)	<0.001	-
Model 2										
FPG	1.12 (1.09-1.14)	<0.001	1.02 (0.99-1.06)	0.203	-	1.50 (1.33-1.68)	<0.001	1.08 (0.96-1.22)	0.179	-
Model 3										
HbA1c	1.17 (1.15-1.19)	<0.001	1.05 (1.02-1.07)	0.002	-	1.79 (1.57-2.05)	<0.001	1.20 (1.04-1.38)	0.013	-
Model 4										
2hPG	1.34 (1.29-1.39)	<0.001	1.11 (1.07-1.16)	<0.001	1.72	2.24 (1.97-2.54)	<0.001	1.34 (1.18-1.51)	<0.001	1.30
FPG	0.91 (0.87-0.95)	<0.001	0.96 (0.91-1.01)	0.094	1.66	0.98 (0.84-1.14)	0.782	0.94 (0.82-1.09)	0.420	1.29
Model 5										
2hPG	1.23 (1.17-1.28)	<0.001	1.08 (1.03-1.13)	<0.001	1.51	2.15 (1.89-2.45)	<0.001	1.29 (1.13-1.46)	<0.001	1.36
HbA1c	1.03 (0.99-1.07)	0.168	1.00 (0.96-1.05)	0.895	1.52	1.08 (0.90-1.29)	0.433	1.04 (0.87-1.24)	0.653	1.34
Model 6										
FPG	0.99 (0.94-1.04)	0.553	0.99 (0.94-1.05)	0.710	1.64	1.22 (1.05-1.42)	0.011	1.00 (0.87-1.15)	0.970	1.38
HbA1c	1.19 (1.14-1.24)	<0.001	1.05 (1.00-1.11)	0.039	1.71	1.57 (1.32-1.88)	<0.001	1.20 (1.02-1.42)	0.031	1.38
Model 7										
2hPG	1.30 (1.24-1.36)	<0.001	1.10 (1.05-1.16)	<0.001	1.87	2.18 (1.90-2.51)	<0.001	1.31 (1.15-1.50)	<0.001	1.48
FPG	0.86 (0.81-0.92)	<0.001	0.95 (0.89-1.01)	0.084	1.92	0.95 (0.80-1.12)	0.530	0.92 (0.79-1.07)	0.298	1.45
HbA1c	1.10 (1.04-1.16)	<0.001	1.03 (0.97-1.08)	0.369	1.75	1.11 (0.90-1.35)	0.328	1.08 (0.89-1.31)	0.425	1.51

OR, odds ratio; CI, confidence interval; VIF, variance inflation factor. [a]ORs and 95% CIs corresponding to every 1-standard-deviation increase in 2hPG (2.60mmol/L), FPG (1.19mmol/L) and HbA1c (0.67%) were estimated. [b]2hPG, FPG and Hba1c were used as binary variables, i.e. above vs. below the diagnostic cutoffs. [c]Non-glycemic risk factors of CVD were not adjusted for. [d]Age, sex, ethnicity, education level, physical inactivity, current smoking, former smoking, harmful drinking, systolic blood pressure, total cholesterol and obesity were adjusted for.

3.5. Dose-response Relationship between Glycemic Measures and CVD Risk

In the participants free of doctor-diagnosed diabetes, the risk of CVD started to increase when the mean 2hPG, FPG, and HbA1c concentrations were well below the current cutoff values used for diagnosis of diabetes (Figure 3 (A), (C) and (E)). After adjusting for non-glycemic risk factors, the curves were substantially depressed towards the null-effect line. The rising trend remained statistically significant for 2hPG and HbA1c (P_{trend} <0.0001 for both; Figure 3 (B) and (F)), but not for FPG (P_{trend}=0.224; Figure 3 (D)). The adjusted ORs started to reach statistical significance in the group with a mean 2hPG of 10.31 mmol/L or a mean HbA1c of 5.00%, but were not statistically significant for any group defined by FPG.

4. Discussion

Diabetes defined according to the latest World Health Organization and American Diabetes Association criteria was prevalent in 13.94% of the participants of this study. Over the past decades, the diagnostic criteria of diabetes have been modified for several times. For example, the number of glycemic measures for diagnosing diabetes has increased gradually from one (i.e., 2hPG alone) [5] to three (i.e., plus FPG and HbA1c).[6,7,16] This has inevitably increased the number of patients and costs for diagnosis and treatment in the population, as abnormality of any of these glycemic measures may lead to a diagnosis of diabetes. As shown in Figure 1, the number of patients was increased by two-thirds when FPG and HbA1c were added to the diagnosis using 2hPG only. Of note, previous modifications of diagnostic criteria of diabetes were predominantly focused on concerns about microvascular complications, in particular retinopathy.[7,16-18] Whether FPG and HbA1c were independently associated with the risk of macrovascular complications (mainly CVD) is less understood.

A few studies have tried to elicit the independent contribution of glycemic measures by adjusting for each other with inconsistent findings, as described in the introduction section. Our study found that 2hPG was independently associated with CVD after FPG and HbA1c were adjusted for, whereas FPG and HbA1c failed to show an effect on CVD risk after 2hPG was controlled for. This is consistent with findings of previous large studies that compared all three glycemic measures in the same participants, including those by Medcalf et al and Lu et al [15,29], and implies that the associations of FPG and HbA1c with CVD are likely to be a result of confounding by 2hPG.

Collinearity among glycemic measures may cause a problem in the multivariate analyses including two or three glycemic measures in one model. However, in this study the correlation coefficients between glycemic measures and the variance inflation factors in logistic models were both well below the commonly accepted rule of thumb for high collinearity.[30,31] In addition, sizable attenuation, which may result from significant collinearity was not observed in the ORs for 2hPG in the models containing other glycemic measures. Furthermore, the same phenomenon was also observed when the three groups with isolated hyperglycemia defined by 2hPG, FPG and HbA1c respectively were compared with the reference group without diabetes, in which collinearity does not pose a problem (Figure 2).

A possible explanation for this finding is that transient increase of blood glucose (e.g., elevated 2hPG) might be more deleterious than the increased usual blood glucose, which is relatively stable over time (e.g., elevated FPG and HbA1c) and easier for the body to adjust to. Another possible explanation is that people with elevated 2hPG are likely at a later stage of diabetes than those with elevated FPG or HbA1c alone[32] so that they had been exposed to high glucose for a longer time than the others and should have a higher CVD risk.

A second issue raised by this study is what cutoff value of a glycemic measure should be used in diagnosing diabetes. Our analyses showed that the risk of CVD was relatively stable only in the 3-4 groups with lowest 2hPG or HbA1c concentrations and started to steadily increase thereafter. This pattern is similar to those observed by previous studies, including meta-analysis of individual

patient data from cohort studies, although the points of starting to increase differ slightly.[9-11,33,34] In any case, the glycemic thresholds for CVD risk that can be used to define diabetes are lower than the current retinopathy-based cutoffs. Importantly, it is very likely drugs can cause more harms than benefits in those with a blood glucose below the current recommended cutoffs.[35] Given the fact that CVD risk continues to increase as blood glucose increases, the cutoff cannot be determined by the glycemia-CVD relation itself but through establishing the benefit-harm balance from interventions. It is important to note that a small decrease in the cutoff will result in a greater number of new patients with diabetes. For example, the cutoff of FPG was changed from 7.8 mmol/L to 7.0 mmol/L and this change alone doubled the prevalence of diabetes in China, which has raised great concerns.[36]

The present study is almost the largest one that has evaluated the independent effect of each glycemic measure on CVD by adjusting for other glycemic measures in the same models. Data on all three glycemic measures in some 170,000 people identified through random sampling is rare. It is a cross-sectional study and by design is free of possible bias that can arise due to inevitable glucose-lowering interventions in patients with diabetes during a long follow-up period in cohort studies. Thus, we believe that the evidence it provides can help verify cohort studies in the investigation of glycemia-CVD relationship. Indeed, this study yielded similar results to those of the large cohort study by Lu et al [15], while being faster and cheaper than the latter. This implies that well-designed cross-sectional studies have their own merit.

Our study also has some limitations. First, the temporality of glycemia-CVD relation in this cross-sectional study may be weaker than in cohort studies.[12,29] However, in cohort studies, the association between a baseline glycemic measure and future CVD event could be distorted by drug treatment and other interventions patients with diabetes will receive during follow-up, as mentioned above. Cross-sectional studies do not have this problem. In fact, the evidence based on which current guidelines justify the use of FPG and HbA1c in diagnosing diabetes is mainly from cross-sectional studies.[7,16-21] Another limitation of our study is that the CVD cases were identified by self-reporting rather than screening of all study participants and limited to diagnosed myocardial infarction and stroke. Thus, some mild, undiagnosed cases and those with peripheral artery disease might have been misclassified as non-CVD participants, and fatal CVD cases could not be recruited. The misclassification is likely to cause under-estimation of the true glycemia-CVD relation in this circumstance and consequently make the conclusion from our study more conservative. With regard to fatal CVD cases, the conclusions of previous studies using CVD death as outcome were consistent with ours.[37] This suggests missing of fatal CVD cases be unlikely to have caused severe bias in our study.

5. Conclusions

In this study, 2hPG showed an effect on cardiovascular risk which was independent from FPG and HbA1c, whereas whether the effects of FPG and HbA1c were independent from 2hPG was open to question. The finding calls for discussion about how to better use FPG and HbA1c in diagnosing diabetes. This study also shed new light on the dose-response relation between glycemic measures and cardiovascular risk.

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Conflict of interest

Authors have disclosed no conflicts of interest.

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Authors' Contributions
JT and LW conceived and designed the study. MZ, ZH, and LW developed the surveillance instruments and collected the data. MZ did data cleaning. XZ did the statistical analyses with the guidance of JT, ZY, LW and AJF. ZY wrote the first draft with the help of XZ and YZ. XZ revised the draft with the guidance of ZY, JT, and LW. All authors critically reviewed the manuscript and approved the final version for submission.

Ethics Approval
This study complied with the Declaration of Helsinki. As stated in the Methods section, this study was approved by the ethical review committee of the National Center for Chronic and Non-communicable Disease Control and Prevention, the Chinese Center for Disease Control and Prevention (ref. no. 201307, scanned copy available upon request) and written informed consents were obtained from all study participants.

Data Availability Statement
The data are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. The numbers of new patients with diabetes identified by different glycemic measures and their overlapping relationship. In parenthesis is the proportion of each part out of all patients with diabetes. The total number did not sum to 164,103 because there were 4,255 participants who did not have complete data on all the three glycemic measures.

Figure 2. Odds ratio and 95% confidence interval for cardiovascular risk in the participants free of doctor-diagnosed diabetes, according to combinations of status of 2hPG, FPG and HbA1c. The total number did not sum to 164,103 because there were 4,255 participants who did not have complete data on all the three glycemic measures. Adjusted factors include age, sex, ethnicity, education level, physical inactivity, current smoking, former smoking, harmful drinking, systolic blood pressure, total cholesterol and obesity. The asterisks indicate statistical significance where $p<0.05$.

Figure 3. Odds ratio and 95% confidence interval for cardiovascular risk in the participants free of doctor-diagnosed diabetes, according to the concentration of three glycemic measures (A, C, E: unadjusted; B, D, F: adjusted). The values on X-axis denote the mean glycemic concentrations of the corresponding groups. The groups with lowest glycemic concentrations were used as reference groups. The vertical dotted lines denote the current diagnostic cutoffs, i.e., 2hPG=11.1 mmol/L, FPG=7.0 mmol/L, and HbA1c=6.5%. Adjusted factors include age, sex, ethnicity, education level, physical inactivity, current smoking, former smoking, harmful drinking, systolic blood pressure, total cholesterol and obesity. The asterisks indicate statistical significance where $p<0.05$.

Independent effects of 2hPG, FPG and HbA1c on cardiovascular risk: analysis of a nationally representative sample from China

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Abstract

Aims: To evaluate the independence of the effect of 2-hour post-load plasma glucose (2hPG), fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) on cardiovascular disease (CVD) after adjusting for each other and non-glycemic factors.

Methods: We analyzed data from a nationally representative sample of 174,329 Chinese adults from a survey conducted in 2013–2014. The associations of glycemic measures with the risk of CVD were examined and compared by using logistic regression analyses.

Results: After adjusting for non-glycemic factors, the odds ratio for one standard-deviation increase of 2hPG, FPG and HbA1c was 1.08 (95% confidence interval [CI]: 1.05-1.11), 1.02 (95% CI: 0.99-1.06) and 1.05 (95% CI: 1.02-1.07), respectively. However, the odds ratio for 2hPG (1.10, 95% CI: 1.05-1.16) remained statistically significant after FPG and HbA1c were added to the models, whereas the odds ratios for FPG and HbA1c became statistically insignificant after 2hPG was adjusted for. The results remained consistent across various scenarios.

Conclusions: 2hPG showed an effect on cardiovascular risk which was independent from FPG and HbA1c, whereas whether the effects of FPG and HbA1c were independent from 2hPG was open to question. This finding calls for more research on how to better use FPG and HbA1c in diagnosing diabetes.

Keywords: Glycemic measures, 2-hour post-load plasma glucose, Fasting plasma glucose, Glycated hemoglobin, Cardiovascular disease, Cross-sectional study

1. Introduction

Diabetes mellitus is an increasingly important public health concern, affecting more than 422 million adults worldwide [1]. Macro-vascular complications, mainly cardiovascular disease (CVD), account for the majority of diabetes-related deaths [2-4]. Two-hour post-load glucose (2hPG) was the first glycemic measure used for diagnosing diabetes [5], with fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) added to diagnostic criteria later [6,7]. According to the current guidelines of American Diabetes Association (ADA), elevation of any of these glycemic measures may lead to a diagnosis of diabetes [8]. The implicit assumption underlying the criteria is that each glycemic measure is independently associated with the risk of diabetes complications. Although many studies have shown that each glycemic measure was associated with CVD risk after adjusting for non-glycemic risk factors such as age [9-11], whether their effects are independent from each other is actually not well understood, because the three glycemic measures were rarely all included in a single regression model.

A few cohort studies have tried to do so, but their results were inconsistent and most of them small in sample size [12-15]. For example, Lind et al found that when FPG, 1hPG, 2hPG and HbA1c were included in the same models, only 2hPG was independently associated with increased risk of CVD [12]. Lu et al had similar findings [15]. By contrast, the study by Cavalot et al with similar analysis found that both 2hPG and HbA1c were predictive of CVD [13], while Wild et al found that neither FPG nor 2hPG was associated with CVD mortality [14]. Although temporal order from baseline glycemic measures to future CVD events is clear in cohort studies, the association between them could be distorted by inevitable drug treatment and other interventions patients receive during the follow-up period, which are often hard to measure and adjust for. In contrast, cross-sectional studies do not have this problem and may help verify the findings of cohort studies from another angle. In fact, the evidence based on which clinical guidelines [7,16-18] supported the use of FPG and HbA1c in diagnosing diabetes is mainly from cross-sectional studies [19-21].

We therefore conducted this study to assess the independence of the effect of each of the diagnostic glycemic measures on the risk of major CVD by adjusting for major conventional confounders and more importantly other glycemic measures based on a nationally representative sample obtained from a cross-sectional survey in China.

2. Research Design and Methods

2.1. Study Design and Sample

The data used in this study came from the 2013–2014 survey of China Chronic Diseases and Risk Factors Surveillance (CCDRFS), which is an on-going nationally representative surveillance system administered by the National Center for Chronic and Non-communicable Disease Control and Prevention (NCNCD), the Chinese Center for Disease Control and Prevention. The CCDRFS was designed to investigate the epidemiology and temporal changes of major chronic diseases and their risk factors in the general population of China by conducting cross-sectional surveys every 3 years.

The 2013–2014 survey of CCDRFS conducted between August 2013 and July 2014 adopted a multistage, stratified random sampling scheme to obtain a nationally representative sample. The survey was approved by the ethical review committee of NCNCD (ref. no. 201307, scanned copy available upon request) and written informed consents were obtained from all study participants. For details of the sampling methods, survey questionnaires, standard operation procedures for physical measurements, laboratory tests and quality control programs, one could refer to previous publications.[22-25] Briefly, the 31 provinces, autonomous regions and municipalities in mainland China were all covered by the survey, with a varying number of survey sites in each of the 31 areas. In total, 177,099 participants from 298 survey sites were enrolled.[23] Among them, those without valid information on doctor-diagnosed CVD, doctor-diagnosed diabetes or all of the three glycemic measures were excluded, leaving 174,329 participants (98.44% of all) for the present study.

2.2. Measurements and Definitions of Study Variables

A standard questionnaire including questions about demographic characteristics (age, sex, ethnicity), socioeconomic status (education level), lifestyle risk factors (smoking, drinking, physical inactivity) and medical history (diabetes, CVD) was administered by trained interviewers at local centers for disease control and prevention and community clinics in the participants' residential area. Current smoking was defined as self-reported tobacco use every day or on some days at the time the survey was conducted. Former smoking was defined as self-reported previous tobacco use which had stopped by the time the survey was conducted. Heavy drinking was defined as daily consumption of pure alcohol >40 g for women and >60 g for men.[26] The computation for pure alcohol consumption from various kinds of alcoholic beverages is described in detail elsewhere.[27] The Global Physical Activity Questionnaire was used to evaluate physical activity of each respondent. Individuals with less than 150 minutes of moderate-intensity activity per week or equivalent were defined as insufficiently active. The height and weight were measured for all participants, from which body mass index (BMI) was computed. Those with a BMI ≥28 kg/m^2 were classified as obese based on Chinese criteria. Hypertension was defined as the presence of at least one of the following: a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or a prior diagnosis of hypertension. Dyslipidemia was defined as a total cholesterol level ≥6.22 mmol/L (240 mg/dl), triglyceride ≥2.26 mmol/L (200 mg/dl), low-density lipoprotein cholesterol ≥4.14 mmol/L (160 mg/dl), or high-density lipoprotein cholesterol <1.04 mmol/L (40 mg/dl).

The participants were also asked whether they had ever been diagnosed with diabetes mellitus, myocardial infarction and stroke by a secondary or tertiary (i.e., county-level or above) hospital. Those who answered 'yes' were considered as having doctor-diagnosed diabetes or CVD and further asked the time of or age at diagnosis. Those who answered 'no' but met any of the following criteria used by World Health Organization and ADA were considered as newly diagnosed diabetes: (1) 2hPG ≥11.1 mmol/L (200 mg/dl) during a 75-g oral glucose tolerance test; (2) FPG ≥7.0 mmol/L (126 mg/dl); and (3) HbA1c ≥6.5%.[1,16] Those who met any of the following criteria used by ADA were considered as prediabetes: (1) 2hPG 7.8-11.0 mmol/L (140-199 mg/dl) during a

75-g oral glucose tolerance test; (2) FPG 5.6-6.9 mmol/L (100-125 mg/dl); and (3) HbA1c 5.7%-6.4%. Blood samples were collected for all participants after an overnight fast of at least 10 hours. All participants without a history of doctor-diagnosed diabetes received a standard 75-g oral glucose tolerance test, during which plasma glucose was measured at 0 and 2 hours. Blood samples for the glucose test were collected using vacuum blood-collection tubes containing anticoagulant sodium fluoride and were centrifuged on site within 2 hours of collection. FPG and 2hPG were measured locally using glucose oxidase or hexokinase methods within 24 hours, as reported previously.[24,28] HbA1c was directly measured from venous blood samples in a single laboratory using quantitative high-performance liquid chromatography and the boronate affinity method (Bio-Rad D-10 Hemoglobin Analyzer).

2.3. Statistical Analysis

The basic characteristics were compared between people without diabetes, newly diagnosed diabetes, and doctor-diagnosed diabetes. Analysis of variance, χ^2 test and Kruskal Wallis test were used to compare continuous variables (e.g., age), binary variables (e.g., smoking status) and variables that were not normally distributed (e.g., total cholesterol), respectively. The association between glycemic status and CVD risk was assessed by using logistic regression analysis that took into account the stratification and intra-cluster correlation and expressed in odds ratio (OR) with 95% confidence interval (CI).

To evaluate the effects of different glycemic measures and their impact on each other, analyses were restricted to the participants without a history of doctor-diagnosed diabetes and the three measures were included into logistic regression models progressively. In total, seven models were used, including three models containing any single glycemic measures, another three containing any two measures, and the last containing all three measures. In each model, the OR corresponding to 1 standard deviation increase in every glycemic measure included in that model was estimated so that the effect of different glycemic measures could be compared using a common metric. To control for potential confounding caused by non-glycemic risk factors of CVD such as age, sex, smoking and hypertension, multivariate analyses adjusting for those factors were conducted for each of the above models as well. Pearson correlation coefficients and variance inflation factors were estimated to assess potential collinearity in the models containing two or three glycemic measures. To examine the robustness of results, the above univariate and multivariate analyses were repeated by converting glycemic measures into binary variables (i.e. above or below current diagnostic cutoffs) or by further adjusting for BMI and dyslipidemia instead of obesity and total cholesterol.

To examine the potential dose-response relationship between glycemic concentrations and CVD, the participants without doctor-diagnosed diabetes were divided into around 20 groups. Using the group with lowest glycemic concentration as reference group, the OR for CVD in each of the other groups was estimated, plotted against glycemic concentration, connected with line, and tested for trend. Similarly, both univariate and multivariate analyses were conducted. All P values were 2-tailed. A p value ≤ 0.05 was indicative of statistical significance. All statistical analyses were

performed with SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.6.0 (R Foundation for Statistical Computing).

3. Results

3.1. Characteristics of Participants

The characteristics of participants are shown in Table 1. Doctor-diagnosed (n=10,226) and newly diagnosed (n=14,025) diabetes accounted for 5.87% and 8.05% of the 174,329 participants, respectively. Compared with the participants without diabetes, those with diagnosed diabetes were older and more likely to be ethnically Han, former smoker, physically inactive, obese, hypertensive, and blood lipid dysregulated (Table 1). Doctor-diagnosed CVD was reported by 4,897 participants (2.81%) and their characteristics can be found in supplemental Table S1.

Table 1. Characteristics of the participants without diabetes, newly diagnosed diabetes, and doctor-diagnosed diabetes

Variables	Participants free of doctor-diagnosed diabetes			Doctor-diagnosed diabetes (N=10226)	*P*-value
	Total (N=164103)	Without diabetes (N=150078)	Newly diagnosed diabetes (N=14025)		
Age (years)	51.09±14.24	50.59±14.23	56.44±13.20	59.34±11.28	<0.001[a]
Male (%)	70368 (42.9)	63719 (42.5)	6649 (47.4)	4135 (40.4)	<0.001[b]
Ethnicity (Han, %)	144601 (88.2)	131884 (87.9)	12717 (90.7)	9581 (93.7)	<0.001[b]
College or above (%)	10762 (6.6)	10018 (6.7)	744 (5.3)	689 (6.7)	<0.001[b]
Current smokers (%)	40548 (24.7)	36963 (24.6)	3585 (25.6)	1896 (18.6)	<0.001[b]
Former smokers (%)	8436 (5.1)	7443 (5.0)	993 (7.1)	867 (8.5)	<0.001[b]
Heavy drinkers (%)	5257 (3.2)	4554 (3.0)	703 (5.0)	209 (2.0)	<0.001[b]
Physical inactivity (%)	23250 (14.2)	20889 (13.9)	2361 (16.8)	1801 (17.6)	<0.001[b]
BMI (kg/m^2)	24.21±3.62	24.08±3.56	25.60±3.91	25.70±3.60	<0.001[a]
Obesity (%)	23493 (14.4)	19985 (13.4)	3508 (25.2)	2477 (24.5)	<0.001[b]
SBP (mmHg)	130.88±20.73	129.93±20.34	141.09±22.14	141.90±21.73	<0.001[a]
DBP (mmHg)	77.44±11.58	77.09±11.48	81.12±11.97	80.40±11.31	<0.001[a]
Hypertension (%)	56651 (34.8)	48854 (32.8)	7797 (56.0)	6268 (61.7)	<0.001[b]
TC (mmol/L, median, IQR)	4.73 (4.12-5.42)	4.70 (4.09-5.38)	5.13 (4.46-5.86)	4.96 (4.29-5.69)	<0.001[c]
TG (mmol/L, median, IQR)	1.19 (0.85-1.75)	1.16 (0.84-1.68)	1.62 (1.10-2.44)	1.56 (1.08-2.34)	<0.001[c]
LDL-C (mmol/L, median, IQR)	2.89 (2.35-3.49)	2.87 (2.34-3.46)	3.16 (2.55-3.81)	3.07 (2.48-3.70)	<0.001[c]
HDL-C (mmol/L, median, IQR)	1.33 (1.10-1.61)	1.34 (1.11-1.61)	1.22 (1.00-1.49)	1.19 (0.98-1.42)	<0.001[c]
Dyslipidemia (%)	53816 (32.8)	46603 (31.1)	7213 (51.5)	5226 (51.1)	<0.001[b]

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; IQR, interquartile range; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; 2hPG, 2-hour postload glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin. P values

were derived for differences between participants without diabetes, newly diagnosed diabetes, and doctor-diagnosed diabetes. [a]ANOVA. [b]Chi-square test. [c]Kruskcal Wallis test.

3.2. Percentage of Diabetes Identified by Different Glycemic Measures

Of the newly diagnosed diabetes, 59.55% were positive for elevated 2hPG regardless of the concentration of the other two measures, 32.65% were negative for elevated 2hPG but positive for elevated FPG regardless of the concentration of HbA1c, and 7.80% were negative for both elevated 2hPG and elevated FPG but positive for elevated HbA1c (Figure 1). Put it differently, the prevalence of newly diagnosed diabetes was increased by 54.82% by adding FPG to 2hPG and by 8.46% by adding HbA1c to 2hPG and FPG. The correlation coefficient was 0.432 between 2hPG and FPG, 0.307 between 2hPG and HbA1c, and 0.274 between FPG and HbA1c.

3.3. Increased CVD Risk in Diabetes

In the participants free of diabetes by any diagnostic methods, the prevalence of CVD was 2.28% (3,359/147,067). Using this as reference, the crude OR for CVD was 3.99 (95% CI: 3.67-4.35) in those with doctor-diagnosed diabetes, 1.86 (95% CI: 1.70-2.04) in newly diagnosed diabetes, and 2.74 (95% CI: 2.56-2.93) in the two groups combined. After adjusting for non-glycemic risk factors of CVD, the corresponding ORs were 2.38 (95% CI: 2.18-2.61), 1.20 (95% CI: 1.09-1.32), and 1.73 (95% CI: 1.62-1.86), respectively. However, after further dividing newly diagnosed diabetes according to the combination of different glycemic measures, the adjusted ORs were statistically significant only in the participants with elevated 2hPG alone and those with all the three glycemic measures elevated (Figure 2). When normoglycemic participants were alternatively used as reference, the significant findings in above two subgroups persisted (supplemental Figure S1). Besides, statistically higher ORs were also observed in the participants with impaired glucose tolerance.

3.4. Independent Effect of Different Glycemic Measures on CVD Risk

In the logistic regression analyses containing a single glycemic measure, the adjusted ORs corresponding to 1-SD increase of 2hPG, FPG, and HbA1c were 1.08 (95% CI: 1.05-1.11, $p<0.001$), 1.02 (95% CI: 0.99-1.06, $p=0.203$), and 1.05 (95% CI: 1.02-1.07, $p=0.002$), respectively (Table 2). The OR for 2hPG was little changed in magnitude and remained statistically significant after FPG, HbA1c, or both were adjusted, whereas the ORs for FPG and HbA1c became smaller and statistically insignificant after 2hPG was adjusted. The results using glycemic measures on their original scale are shown in supplemental Table S2. Similar trends were also observed when the regression analyses were repeated by taking glycemic measures as binary variables, with or without excluding participants with prediabetes (Table 2 and supplemental Table S3). The magnitude of above associations attenuated slightly but remained statistically significant in models where obesity and total cholesterol were removed and BMI and dyslipidemia were instead included (supplemental Table S4).

Table 2. Independent effects of 2hPG, FPG and HbA1c in predicting cardiovascular disease in 164103 adults free of doctor-diagnosed diabetes

Models and glycemic measures	Per 1-standard-deviation increase[a]					Above vs. below the current diagnostic cutoff[b]				
	Unadjusted OR (95% CI)[c]	*P*-value	Adjusted OR (95% CI)[d]	*P*-value	VIF	Unadjusted OR (95% CI)[c]	*P*-value	Adjusted OR (95% CI)[d]	*P*-value	VIF
Model 1										
2hPG	1.25 (1.22-1.28)	<0.001	1.08 (1.05-1.11)	<0.001	-	2.21 (2.00-2.45)	<0.001	1.31 (1.17-1.46)	<0.001	-
Model 2										
FPG	1.12 (1.09-1.14)	<0.001	1.02 (0.99-1.06)	0.203	-	1.50 (1.33-1.68)	<0.001	1.08 (0.96-1.22)	0.179	-
Model 3										
HbA1c	1.17 (1.15-1.19)	<0.001	1.05 (1.02-1.07)	0.002	-	1.79 (1.57-2.05)	<0.001	1.20 (1.04-1.38)	0.013	-
Model 4										
2hPG	1.34 (1.29-1.39)	<0.001	1.11 (1.07-1.16)	<0.001	1.72	2.24 (1.97-2.54)	<0.001	1.34 (1.18-1.51)	<0.001	1.30
FPG	0.91 (0.87-0.95)	<0.001	0.96 (0.91-1.01)	0.094	1.66	0.98 (0.84-1.14)	0.782	0.94 (0.82-1.09)	0.420	1.29
Model 5										
2hPG	1.23 (1.17-1.28)	<0.001	1.08 (1.03-1.13)	<0.001	1.51	2.15 (1.89-2.45)	<0.001	1.29 (1.13-1.46)	<0.001	1.36
HbA1c	1.03 (0.99-1.07)	0.168	1.00 (0.96-1.05)	0.895	1.52	1.08 (0.90-1.29)	0.433	1.04 (0.87-1.24)	0.653	1.34
Model 6										
FPG	0.99 (0.94-1.04)	0.553	0.99 (0.94-1.05)	0.710	1.64	1.22 (1.05-1.42)	0.011	1.00 (0.87-1.15)	0.970	1.38
HbA1c	1.19 (1.14-1.24)	<0.001	1.05 (1.00-1.11)	0.039	1.71	1.57 (1.32-1.88)	<0.001	1.20 (1.02-1.42)	0.031	1.38
Model 7										
2hPG	1.30 (1.24-1.36)	<0.001	1.10 (1.05-1.16)	<0.001	1.87	2.18 (1.90-2.51)	<0.001	1.31 (1.15-1.50)	<0.001	1.48
FPG	0.86 (0.81-0.92)	<0.001	0.95 (0.89-1.01)	0.084	1.92	0.95 (0.80-1.12)	0.530	0.92 (0.79-1.07)	0.298	1.45
HbA1c	1.10 (1.04-1.16)	<0.001	1.03 (0.97-1.08)	0.369	1.75	1.11 (0.90-1.35)	0.328	1.08 (0.89-1.31)	0.425	1.51

OR, odds ratio; CI, confidence interval; VIF, variance inflation factor. [a]ORs and 95% CIs corresponding to every 1-standard-deviation increase in 2hPG (2.60mmol/L), FPG (1.19mmol/L) and HbA1c (0.67%) were estimated. [b]2hPG, FPG and Hba1c were used as binary variables, i.e. above vs. below the diagnostic cutoffs. [c]Non-glycemic risk factors of CVD were not adjusted for. [d]Age, sex, ethnicity, education level, physical inactivity, current smoking, former smoking, harmful drinking, systolic blood pressure, total cholesterol and obesity were adjusted for.

3.5. Dose-response Relationship between Glycemic Measures and CVD Risk

In the participants free of doctor-diagnosed diabetes, the risk of CVD started to increase when the mean 2hPG, FPG, and HbA1c concentrations were well below the current cutoff values used for diagnosis of diabetes (Figure 3 (A), (C) and (E)). After adjusting for non-glycemic risk factors, the curves were substantially depressed towards the null-effect line. The rising trend remained statistically significant for 2hPG and HbA1c (P_{trend} <0.0001 for both; Figure 3 (B) and (F)), but not for FPG (P_{trend}=0.224; Figure 3 (D)). The adjusted ORs started to reach statistical significance in the group with a mean 2hPG of 10.31 mmol/L or a mean HbA1c of 5.00%, but were not statistically significant for any group defined by FPG.

4. Discussion

Diabetes defined according to the latest World Health Organization and American Diabetes Association criteria was prevalent in 13.94% of the participants of this study. Over the past decades, the diagnostic criteria of diabetes have been modified for several times. For example, the number of glycemic measures for diagnosing diabetes has increased gradually from one (i.e., 2hPG alone) [5] to three (i.e., plus FPG and HbA1c).[6,7,16] This has inevitably increased the number of patients and costs for diagnosis and treatment in the population, as abnormality of any of these glycemic measures may lead to a diagnosis of diabetes. As shown in Figure 1, the number of patients was increased by two-thirds when FPG and HbA1c were added to the diagnosis using 2hPG only. Of note, previous modifications of diagnostic criteria of diabetes were predominantly focused on concerns about microvascular complications, in particular retinopathy.[7,16-18] Whether FPG and HbA1c were independently associated with the risk of macrovascular complications (mainly CVD) is less understood.

A few studies have tried to elicit the independent contribution of glycemic measures by adjusting for each other with inconsistent findings, as described in the introduction section. Our study found that 2hPG was independently associated with CVD after FPG and HbA1c were adjusted for, whereas FPG and HbA1c failed to show an effect on CVD risk after 2hPG was controlled for. This is consistent with findings of previous large studies that compared all three glycemic measures in the same participants, including those by Medcalf et al and Lu et al [15,29], and implies that the associations of FPG and HbA1c with CVD are likely to be a result of confounding by 2hPG.

Collinearity among glycemic measures may cause a problem in the multivariate analyses including two or three glycemic measures in one model. However, in this study the correlation coefficients between glycemic measures and the variance inflation factors in logistic models were both well below the commonly accepted rule of thumb for high collinearity.[30,31] In addition, sizable attenuation, which may result from significant collinearity was not observed in the ORs for 2hPG in the models containing other glycemic measures. Furthermore, the same phenomenon was also observed when the three groups with isolated hyperglycemia defined by 2hPG, FPG and HbA1c respectively were compared with the group without diabetes, in which collinearity does not pose a problem (Figure 2).

A possible explanation for this finding is that transient increase of blood glucose (e.g., elevated 2hPG) might be more deleterious than the increased usual blood glucose, which is relatively stable over time (e.g., elevated FPG and HbA1c) and easier for the body to adjust to. Another possible explanation is that people with elevated 2hPG are likely at a later stage of diabetes than those with elevated FPG or HbA1c alone[32] so that they had been exposed to high glucose for a longer time than the others and should have a higher CVD risk.

A second issue raised by this study is what cutoff value of a glycemic measure should be used in diagnosing diabetes. Our analyses showed that the risk of CVD was relatively stable only in the 3-4 groups with lowest 2hPG or HbA1c concentrations and started to steadily increase thereafter. This pattern is similar to those observed by previous studies, including meta-analysis of individual

patient data from cohort studies, although the points of starting to increase differ slightly.[9-11,33,34] In any case, the glycemic thresholds for CVD risk that can be used to define diabetes are lower than the current retinopathy-based cutoffs. Importantly, it is very likely drugs can cause more harms than benefits in those with a blood glucose below the current recommended cutoffs.[35] Given the fact that CVD risk continues to increase as blood glucose increases, the cutoff cannot be determined by the glycemia-CVD relation itself but through establishing the benefit-harm balance from interventions. It is important to note that a small decrease in the cutoff will result in a greater number of new patients with diabetes. For example, the cutoff of FPG was changed from 7.8 mmol/L to 7.0 mmol/L and this change alone doubled the prevalence of diabetes in China, which has raised great concerns.[36]

The present study is almost the largest one that has evaluated the independent effect of each glycemic measure on CVD by adjusting for other glycemic measures in the same models. Data on all three glycemic measures in some 170,000 people identified through random sampling is rare. It is a cross-sectional study and by design is free of possible bias that can arise due to inevitable glucose-lowering interventions in patients with diabetes during a long follow-up period in cohort studies. Thus, we believe that the evidence it provides can help verify cohort studies in the investigation of glycemia-CVD relationship. Indeed, this study yielded similar results to those of the large cohort study by Lu et al [15], while being faster and cheaper than the latter. This implies that well-designed cross-sectional studies have their own merit.

Our study also has some limitations. First, the temporality of glycemia-CVD relation in this cross-sectional study may be weaker than in cohort studies.[12,29] However, in cohort studies, the association between a baseline glycemic measure and future CVD event could be distorted by drug treatment and other interventions patients with diabetes will receive during follow-up, as mentioned above. Cross-sectional studies do not have this problem. In fact, the evidence based on which current guidelines justify the use of FPG and HbA1c in diagnosing diabetes is mainly from cross-sectional studies.[7,16-21] Another limitation of our study is that the CVD cases were identified by self-reporting rather than screening of all study participants and limited to diagnosed myocardial infarction and stroke. Thus, some mild, undiagnosed cases and those with peripheral artery disease might have been misclassified as non-CVD participants, and fatal CVD cases could not be recruited. The misclassification is likely to cause under-estimation of the true glycemia-CVD relation in this circumstance and consequently make the conclusion from our study more conservative. With regard to fatal CVD cases, the conclusions of previous studies using CVD death as outcome were consistent with ours.[37] This suggests missing of fatal CVD cases be unlikely to have caused severe bias in our study.

5. Conclusions

In this study, 2hPG showed an effect on cardiovascular risk which was independent from FPG and HbA1c, whereas whether the effects of FPG and HbA1c were independent from 2hPG was open to question. The finding calls for discussion about how to better use FPG and HbA1c in diagnosing diabetes. This study also shed new light on the dose-response relation between glycemic measures and cardiovascular risk.

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Conflict of interest

Authors have disclosed no conflicts of interest.

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Authors' Contributions
JT and LW conceived and designed the study. MZ, ZH, and LW developed the surveillance instruments and collected the data. MZ did data cleaning. XZ did the statistical analyses with the guidance of JT, ZY, LW and AJF. ZY wrote the first draft with the help of XZ and YZ. XZ revised the draft with the guidance of ZY, JT, and LW. All authors critically reviewed the manuscript and approved the final version for submission.

Ethics Approval
This study complied with the Declaration of Helsinki. As stated in the Methods section, this study was approved by the ethical review committee of the National Center for Chronic and Non-communicable Disease Control and Prevention, the Chinese Center for Disease Control and Prevention (ref. no. 201307, scanned copy available upon request) and written informed consents were obtained from all study participants.

Data Availability Statement
The data are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. The numbers of new patients with diabetes identified by different glycemic measures and their overlapping relationship. In parenthesis is the proportion of each part out of all patients with diabetes. The total number did not sum to 164,103 because there were 4,255 participants who did not have complete data on all the three glycemic measures.

Figure 2. Odds ratio and 95% confidence interval for cardiovascular risk in the participants free of doctor-diagnosed diabetes, according to combinations of status of 2hPG, FPG and HbA1c. The total number did not sum to 164,103 because there were 4,255 participants who did not have complete data on all the three glycemic measures. Adjusted factors include age, sex, ethnicity, education level, physical inactivity, current smoking, former smoking, harmful drinking, systolic blood pressure, total cholesterol and obesity. The asterisks indicate statistical significance where $p<0.05$.

Figure 3. Odds ratio and 95% confidence interval for cardiovascular risk in the participants free of doctor-diagnosed diabetes, according to the concentration of three glycemic measures (A, C, E: unadjusted; B, D, F: adjusted). The values on X-axis denote the mean glycemic concentrations of the corresponding groups. The groups with lowest glycemic concentrations were used as reference groups. The vertical dotted lines denote the current diagnostic cutoffs, i.e., 2hPG=11.1 mmol/L, FPG=7.0 mmol/L, and HbA1c=6.5%. Adjusted factors include age, sex, ethnicity, education level, physical inactivity, current smoking, former smoking, harmful drinking, systolic blood pressure, total cholesterol and obesity. The asterisks indicate statistical significance where $p<0.05$.

Figure 1

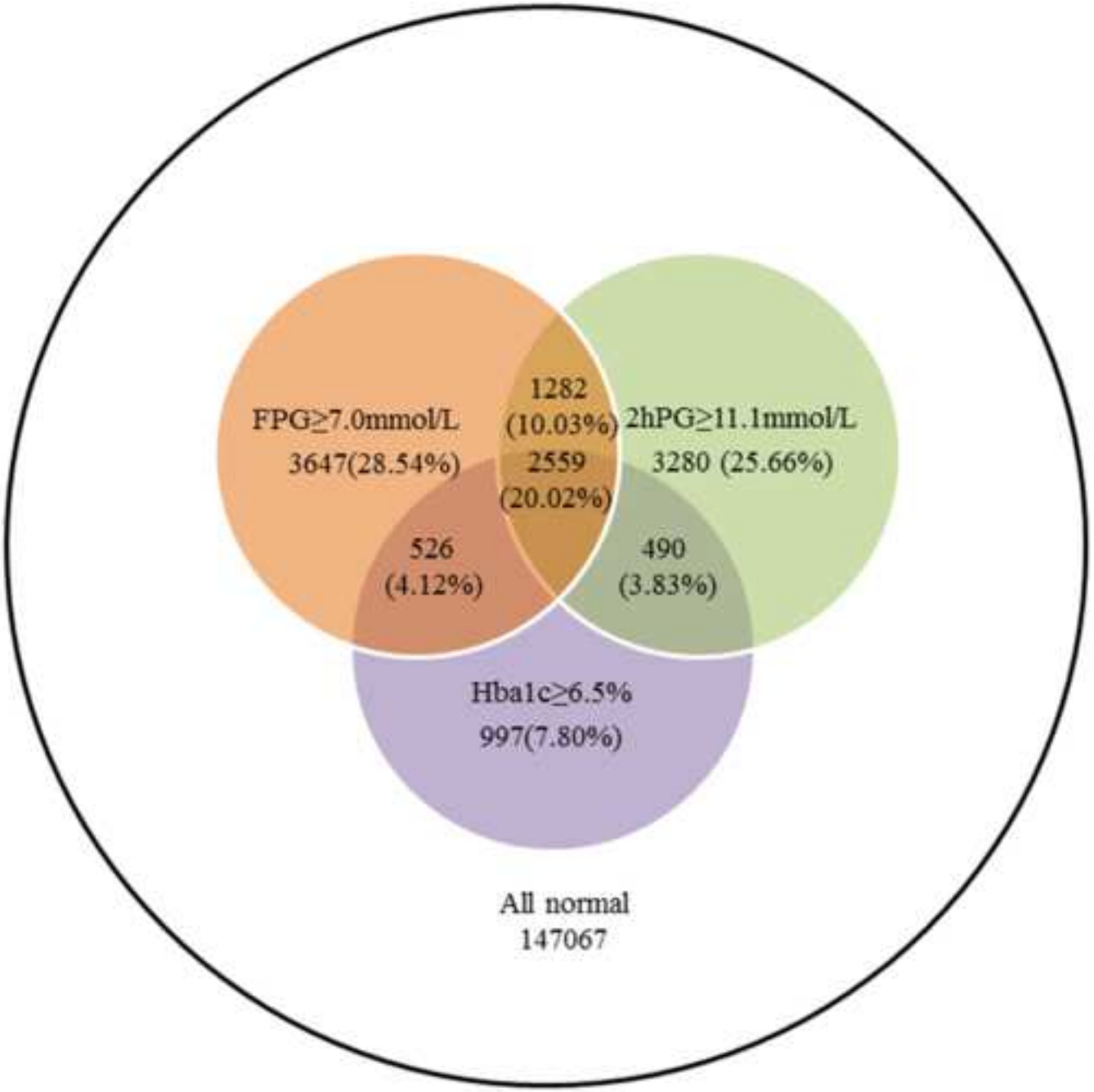

Figure 2

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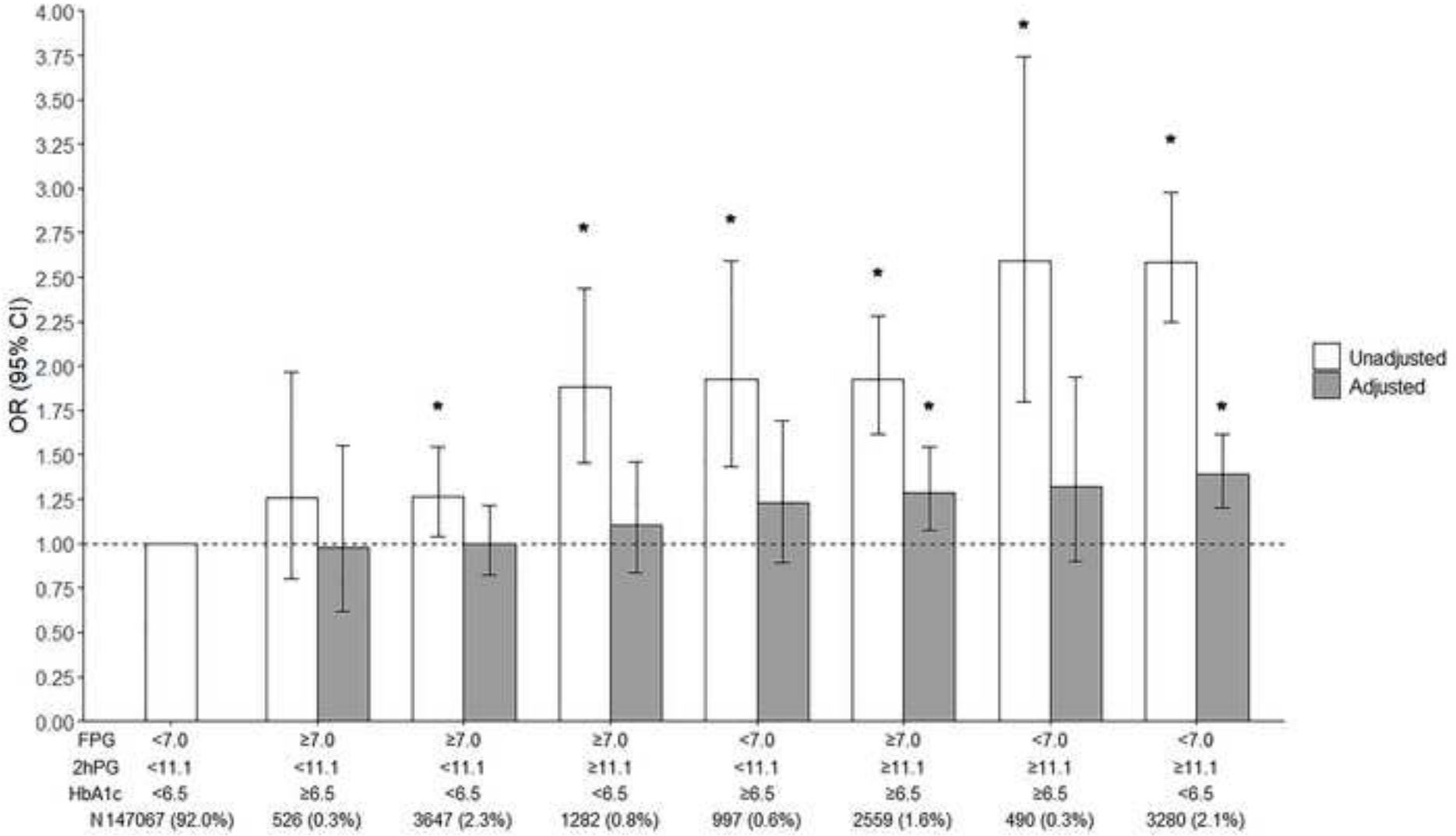

Figure 3

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