Effects of Prediabetes Mellitus Alone or Plus Hypertension on Subsequent Occurrence of Cardiovascular Disease and Diabetes Mellitus

Longitudinal Study

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Abstract—Whether prediabetes mellitus alone or combined with other disorders means a higher risk for cardiovascular disease (CVD) is still controversial. This study aimed to investigate the association between prediabetes mellitus and CVD and diabetes mellitus and to explore whether prediabetes mellitus alone or combined with other syndromes, such as hypertension, could promote CVD risks significantly. This longitudinal population-based study of 1609 residents from Shanghai in Southern China was conducted between 2002 and 2014. Participants with a history of CVD at baseline were excluded from analysis. Multivariate log-binomial regression models were used to adjust possible coexisting factors. Incidence of CVD during follow-up was 10.1%. After adjusting for age, sex, and other factors, the association between prediabetes mellitus and CVD was not observed. When hypertension was incorporated in stratifying factors, adjusted CVD risk was elevated significantly (odds ratio, 2.41; 95% confidence interval, 1.25–4.64) in prediabetes mellitus and hypertension combined group, and coexistence of diabetes mellitus and hypertension made CVD risk highly significantly increased, reaching 3.43-fold higher than the reference group. Blood glucose level within prediabetic range is significantly associated with elevated risks for diabetes mellitus after multivariable adjustment, but only when it is concurrent with other disorders, such as hypertension, it will significantly increase CVD risk. **(*Hypertension*. 2015;65:525-530. DOI: 10.1161/HYPERTENSIONAHA.114.04632.)**

Key Words: cardiovascular diseases ■ diabetes mellitus ■ hypertension ■ prediabetic state

Prediabetes mellitus (Pre-DM) is a general term that refers to an intermediate state of abnormal glycemia. It is also known as impaired glucose regulation (IGR), involving 2 groups of individuals, subjects with impaired fasting glucose (IFG) and subjects with impaired glucose tolerance (IGT).[1] It has been increasing globally and the number of people with pre-DM worldwide is estimated to reach 472 million by the year 2025.[2] In the United States, the prevalence of pre-DM is also steadily increasing, with an estimated rate of pre-DM in adults reaching 36.2% in 2010.[3] In the Chinese adult population, a cross-sectional survey reported that in 2010, about 50.1% had pre-DM and 11.6% had DM, making China among the countries with the highest DM prevalence in Asia and having the largest absolute disease burden of DM in the world.[4] As is known to all, cardiovascular disease (CVD) is a leading cause of mortality and morbidity in the world, and DM is a risk factor for serious chronic disease, including CVD.[5–7] However, studies on the presence and accumulation of risk factors for CVD in the stage of IGR were insufficient and did not reach a general agreement.[8–13] Furthermore, few articles were found in the literature about the risk for CVD involved in blood glucose and hypertension combined.[14] Therefore, our study has 2 objectives: (1) to investigate the association between IGR and incident CVD or DM in a Chinese longitudinal study and (2) to explore whether IGR alone or coexistent with other syndromes, such as hypertension, could promote CVD risks significantly.

Methods

Study Population

This study was from a population-based prospective cohort study of 2132 men and women aged 18 to 76 years from Pingliang community, Yangpu district, Shanghai, a municipality in South China. The design of the study has been described previously.[15] The first examination of participants was conducted from November 2002 to January 2003. The follow-up visit, consisting of 1609 (75.5%) participants, lasted from July to December 2013, but an additional follow-up was made in September to October 2014 for those unavailable at that time. Formation of the study population is shown in the Figure. Written informed consent was

Received November 12, 2014; first decision November 26, 2014; revision accepted December 21, 2014.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.114.04632**

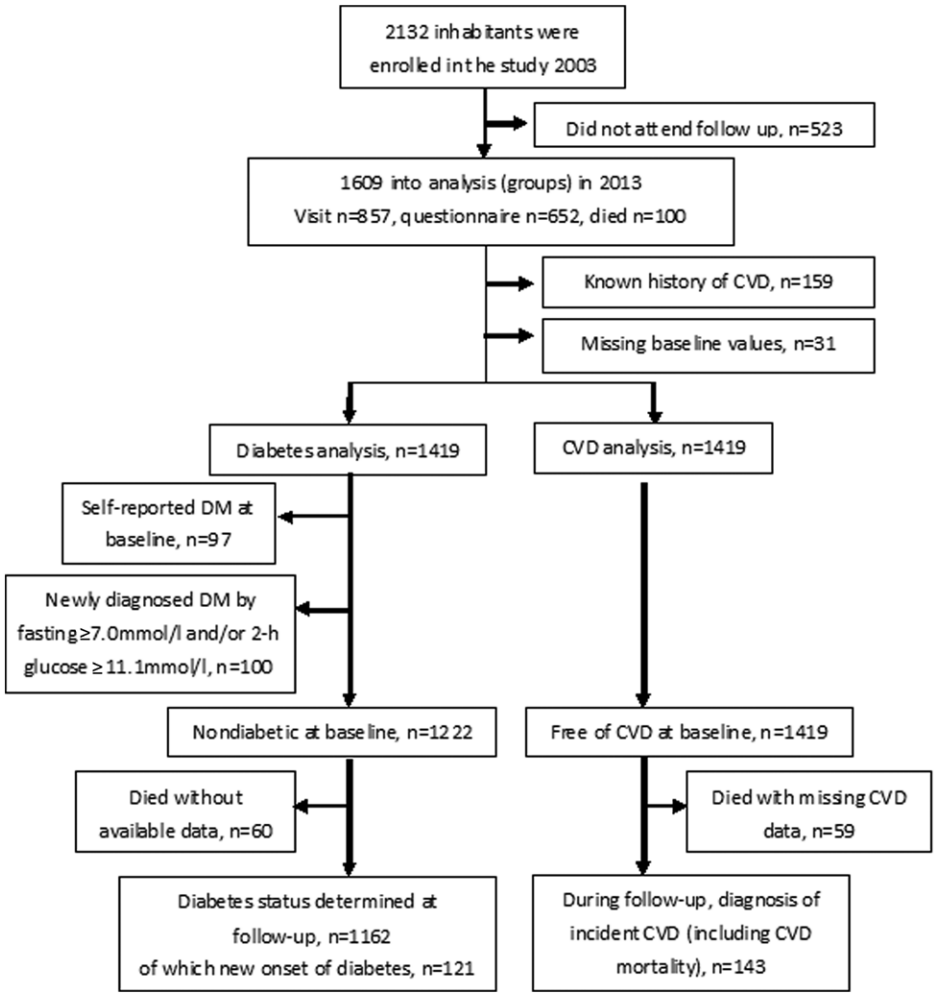

Figure. Formation of the study population for diabetes and cardiovascular disease (CVD) analysis.

obtained from all participants. The institutional review board or ethics committee of our hospital approved the study protocol.

Measurement of Blood Glucose

The serum glucose level was measured by means of glucose oxidase method. Venous blood samples were drawn both at baseline and follow-up. Blood for fasting glucose measurement was drawn between 6:30 and 9:30 after a 12-hour overnight fast. At baseline, we used 75-g liquid glucose load to assess 2-hour glucose for those without known DM and used 100-g steamed bread that contained approximately similar carbohydrates for those with self-reported DM. While at follow-up, 100-g steamed bread was used for all the participants. These 2 modes of assessment of glucose tolerance were proved to be of equal clinical significance of DM diagnosis and of equal effectiveness in evaluating residual β cell function in normal and diabetic subjects. In addition, steamed bread test showed extra benefits in keeping sensitive individuals from adverse effects, such as nausea, vomit, and wild fluctuations of glucose.[16–18] Blood samples were centrifuged to separate plasma and analyzed immediately after collection.

Measurement of Blood Pressure

Blood pressure was measured through a mercury sphygmomanometer after checking for the device accuracy. It was measured for 3 times consecutively, with 1-minute interval between the measurements. Systolic blood pressure (SBP) and diastolic blood pressure were the mean of last 2 of the 3 measurements taken in participants in sitting position after 5 minutes of rest at the time of survey.[19]

Assessment of Major Outcomes

DM was confirmed by diabetic 2-hour glucose value and fasting values or self-reported DM at baseline. IFG was defined as a fasting glucose range from 5.6 to <7.0 mmol/L, as well as 2-hour glucose <7.8 mmol/L. IGT was defined as a 2-hour glucose range from 7.8 to <11.1 mmol/L. Both IFG and IGT were confined to nondiabetic fasting and 2-hour concentrations.[20] IGR represented a status of IFG or IGT alone or combined. Hypertension was defined as the average of the blood pressure values (with a SBP≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) or self-reported hypertension at baseline. CVD was based on self-reported diagnosis or medication use during visit, and if available, medical records were reviewed. It included coronary heart disease and cerebrovascular disease. Coronary heart disease was further defined as angina pectoris, myocardial infarctions, abnormal coronary arteriography, a cardiac procedure, and a death directly from or accompanied by coronary heart disease. Cerebrovascular disease includes transient cerebral ischemic attack, cerebral hemorrhage, cerebral infarction from any cause, and a death directly from or accompanied by above causes. Information on deaths was obtained from the official death certificates of the district.

Other Variables of Interest

Triglycerides and serum cholesterol levels were measured enzymatically. Anthropometric measurements were conducted by trained nurses or clinical postgraduates. Waist:hip ratio is the waist circumference in centimeter divided by the hip circumference in centimeter. Smoking and alcohol consumption, educational background, daytime napping, diet and physical activity were acquired through well-designed questionnaires. Smoking and drinking status were classified

Table 1. Characteristics of the Study Participants, According to the Blood Glucose Value at Baseline

	Blood Glucose Category				
Value	Overall (n=1419)	NGR (n=719)	IGR (n=503)	DM (n=197)	*P* Value
Fasting glucose, mmol/L	5.9±1.7	5.1±0.3	6.0±0.4	9.0±2.8	*
2-h glucose, mmol/L	5.9±2.8	5.0±1.0	5.9±1.6	11.5±5.6	*
Age, y	54.2±12.1	50.6±12.4	56.8±10.8	60.3±9.7	*
Male prevalence, %	41.2	38.9	41.9	47.2	NS
LDL-C, mmol/L	2.84±0.81	2.72±0.76	2.94±0.77	3.05±0.99	*
HDL-C, mmol/L	1.44±0.44	1.48±0.38	1.40±0.34	1.37±0.73	*
Triglycerides, mmol/L† median	1.3 (0.8–1.8)	1.1 (0.8–1.6)	1.4 (1.0–2.0)	1.5 (1.1–2.3)	*
Total cholesterol, mmol/L	4.9±1.0	4.8±0.9	5.1±0.9	5.2±1.3	*
Waist:hip ratio	0.84±0.06	0.83±0.07	0.84±0.06	0.86±0.06	*
SBP, mm Hg	129.6±18.6	125.1±17.3	132.8±18.6	137.4±18.8	*
DBP, mm Hg	82.9±10.7	81.4±10.2	84.3±11.0	85.1±11.1	*
Hypertension, %	51.8	41.2	59.2	71.6	*
Family history of DM, %	19.1	17.5	19.7	23.4	NS
Alcohol use, %					*
Currently	14.2	14.9	15.9	7.6	
Formerly	1.7	0.7	2.2	4.1	
Never	84.1	84.4	81.9	88.3	
Smoking status, %					NS
Current smoker	20.0	20.9	18.7	20.3	
Former smoker	3.6	2.9	4.2	4.6	
Never smoked	76.4	76.2	77.1	75.1	
Physical activity, %					NS
Inactive	38.1	38.2	37.2	39.6	
Medium	34.9	33.8	37.2	33.0	
Active	27.1	28.0	25.6	27.4	

Results are given mean±SD or n (%).

P for difference: **P*<0.01, †values of fasting triglycerides did not follow Gaussian distribution, thus medium and interquartile ranges were used instead of mean and SD to describe central and discrete tendency. DBP indicates diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; IGR, impaired glucose regulation; LDL-C, low-density lipoprotein-cholesterol; NGR, normal glucose regulation; NS, nonsignificant; and SBP, systolic blood pressure.

into currently, formerly, and never consumed. Physical activity was calculated as the product of the duration and frequency of each activity (in hours per day) weighted by an estimate of the metabolic equivalent of that activity.[21]

Statistical Analyses

All data were analyzed using SPSS for Windows, version 18.0 (SPSS, Chicago, IL). Baseline characteristics were analyzed for significance of differences between groups using 1-way ANOVA for continuous variables and the χ^2 test for categorical variables. Student *t* test was applied for comparisons of basic characteristics in those at follow-up and those who were lost at follow-up. Binary logistic regression models were used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CI) for CVD and DM. The analyses were performed primarily to assess the association between pre-DM and risk of CVD and DM and then to analyze the risk for CVD by pre-DM and high blood pressure (HBP) alone or combined (−IGR/−HBP [reference], +IGR/−HBP, DM/−HBP, −IGR/+HBP, +IGR/+HBP, and DM/+HBP).

The analyses were initially performed adjusting for age and sex in model 1 and model 3; further adjustments were subsequently made for waist:hip ratio, triglycerides, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, total cholesterol, family history of DM, smoking and drinking status, educational background, daytime napping, diet and physical activity at baseline in model 4. Model 2 adjusted all the factors in model 4 plus SBP.

Data were expressed as mean±SD, n (%), or OR (95% CI), all statistical tests were 2 sided, and a *P* value of <0.05 was considered to be statistically significant.

Results

The follow-up time was 10.5 to 12.0 years (mean, 10.9 years). A total of 1609 participants (75.5%) were included in follow-up, among which 159 subjects with previous CVD and 31 subjects with missing data were excluded from analyses.

Selected characteristics of the study population at baseline are shown in Table 1, both overall and according to blood glucose

levels. Participants with DM were more likely to be old, to have adverse lipid profile and to have higher waist:hip ratio, blood pressure, and more daytime napping compared with those without IGR or DM at baseline. The overall incidence of known hypertension was 51.8%, individuals with DM have a higher prevalence of hypertension (71.6%) than with IGR (59.2%) or normal glucose regulation (NGR; 41.2%). Among the baseline hypertensive populations, 36.8% applied antihypertensive treatment currently, among which 35.1% used angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, and 48.6% of treated patients have their blood pressure successfully controlled (SBP<140 mm Hg and diastolic blood pressure, <90 mm Hg). Family history of DM, cigarette consumption, physical activity, and antihypertensive therapy were of no significant difference among the 4 groups (P>0.05). Sex difference was not observed in our study. Moreover, we did comparisons between the visited and the unvisited in terms of basic characteristics, which revealed no significant difference in glucose levels, blood lipid profile, blood pressure, and any other factors between these 2 groups (data not shown).

During the follow-up, 143 (10.1%) participants reported a diagnosis of CVD, and the corresponding incidence rates of CVD in NGR, IGR, and DM group were 6.6%, 11.1%, and 23.2%, respectively. The adjusted ORs and 95% CI of 10-year risk of DM and CVD according to the glucose level are shown in Table 2. A baseline IGR had a 4.40 times higher risk of developing DM in the crude model. Additional adjustment for multivariable only slightly attenuated this association, and the glucose category was still strongly and significantly associated with diagnosed DM. However, IGR did not significantly elevate CVD risk when compared with the reference group after adjusting for age, sex, SBP, blood lipid level, and other factors, with OR of 1.16 and 95% CI 0.72–1.87. Diagnosed DM was independently and significantly associated with the development of CVD (OR, 1.93; 95% CI, 1.12–3.32) in model 2.

Because prevalence of hypertension has reached as high as 51.8% in our population, we have further assessed the association of 3 categories of blood glucose (NGR, IGR, and DM) with the risk of major outcomes among participants stratified according to the presence or absence of hypertension (–IGR/–HBP [reference], +IGR/–HBP, DM/–HBP, –IGR/+HBP, +IGR/+HBP, and DM/+HBP). As expected, coexistence of DM and hypertension was associated with the most significant increases in the incidences of both DM and CVD compared with the reference group. Table 3 depicts the adjusted OR and 95% CI for DM and CVD according to blood glucose and blood pressure. Isolated IGR was not associated with elevated CVD risk in the adjusted models (OR, 1.10; 95% CI, 0.47–2.58); however, IGR and hypertension in the same individual considerably increased the risk for developing both CVD and DM when compared with the reference group, with adjusted OR of 2.41 (95% CI, 1.25–4.64) for CVD and 6.37 (95% CI, 3.41–11.89) for DM. Isolated DM increased CVD risk for 2.72 times (95% CI, 1.03–7.14), and a DM and hypertension combined state was even higher, up to 3.43 times (95% CI, 1.66–7.11), compared with –IGR/-HBP group.

Table 2. Adjusted Odds Ratio for Diabetes Mellitus and Cardiovascular Disease According to the Blood Glucose at Baseline

Blood Glucose Category (n, Events/Subjects): Odds Ratio (95% CI)			
Outcome	Unadjusted Model	Model 1	Model 2
DM			
NGR* (n=34/719)	1.00	1.00	1.00
IGR (n=87/503)	4.40 (2.90–6.66)†	3.90 (2.54–5.98)†	3.88 (2.44–6.19)†
Cardiovascular disease			
NGR* (n=46/719)	1.00	1.00	1.00
IGR (n=53/503)	1.76 (1.16–2.66)†	1.32 (0.86–2.02)	1.16 (0.72–1.87)
DM (n=44/197)	4.24 (2.70–6.65)†	2.74 (1.71–4.41)†	1.93 (1.12–3.32)‡

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, waist:hip ratio, triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, total cholesterol, family history of DM, blood pressure, smoking and drinking status, daytime napping, educational background, diet and physical activity. CI indicates confidence interval; DM, diabetes mellitus; IGR, impaired glucose regulation; and NGR, normal glucose regulation.

*Reference group, †P<0.01, and ‡P<0.05.

Discussion

More and more attention is focused on pre-DM because it has been a huge burden in China, where the incidence of pre-DM

Table 3. Adjusted Odds Ratio for Diabetes Mellitus and Cardiovascular Disease According to the Blood Glucose and Hypertension at Baseline

Blood Glucose and Blood Pressure Category (n, Events/Subjects): Odds Ratio (95% CI)			
Outcome	Unadjusted Model	Model 3	Model 4
DM			
–IGR/–HBP* (n=17/422)	1.00	1.00	1.00
+IGR/–HBP (n=18/202)	2.38 (1.20–4.72)†	2.25 (1.13–4.51)†	2.46 (1.19–5.09)†
–IGR/+HBP (n=17/297)	1.48 (0.74–2.96)	1.43 (0.71–2.88)	1.15 (0.54–2.47)
+IGR/+HBP (n=69/301)	7.67 (4.40–13.38)‡	6.91 (3.84–12.43)‡	6.37 (3.41–11.89)‡
Cardiovascular disease			
–IGR/–HBP* (n=18/422)	1.00	1.00	1.00
+IGR/–HBP (n=9/202)	1.07 (0.47–2.42)	0.93 (0.41–2.12)	1.10 (0.47–2.58)
DM/–HBP (n=8/56)	3.63 (1.50–8.80)‡	2.58 (1.04–6.38)†	2.72 (1.03–7.14)†
–IGR/+HBP (n=28/297)	2.39 (1.30–4.41)‡	1.95 (1.04–3.63)†	2.18 (1.12–4.24)†
+IGR/+HBP (n=44/301)	3.99 (2.26–7.07)‡	2.53 (1.39–4.62)‡	2.41 (1.25–4.64)‡
DM/+HBP (n=36/141)	8.00 (4.36–14.69)‡	4.74 (2.50–8.97)‡	3.43 (1.66–7.11)‡

Model 3 adjusted for age and sex; model 4 adjusted for age, sex, waist:hip ratio, triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, total cholesterol, family history of DM, smoking and drinking status, daytime napping, educational background, diet and physical activity. CI indicates confidence interval; DM, diabetes mellitus; HBP, high blood pressure; and IGR, impaired glucose regulation.

*Reference group, †P<0.05, and ‡P<0.01.

has reached 50.1% among adults. It has become a point of concern about the effect of pre-DM on macrovascular events, and research is urgently needed to strengthen the evidence-based treatment guidelines for Chinese patients with pre-DM. However, whether IGR alone could increase CVD risk was still uncertain.[11,12] A recent systematic review concluded that IGR did not increase or only slightly increased the risk for CVD,[8] and a community-based study showed that glycohemoglobin rather than fasting glucose was significantly associated with CVD.[13] Another large Korean study reported that the increased risk for myocardial infarction could only be observed in the diabetic glucose level.[22] Meanwhile, other investigators thought that hyperglycemia within nondiabetic glucose range was associated with increased CVD risk.[9,12] Therefore, we investigated the association between IGR and incident CVD and DM and explored whether IGR alone or coexistent with other syndrome, such as hypertension, could promote CVD risks significantly as well.

The current analysis indicates that people with IGR are at a high risk of developing DM. When compared with people without abnormal glucose metabolism, people with IGR had 3.88 times the risk of DM. However, IGR was not associated with elevated CVD, with similar risks for CVD in subjects with NGR and IGR (OR, 1.16; 95% CI, 0.72–1.87). Our results lend support to a recent meta-analysis depending on a set of studies, which concluded that there was no increase in risk for CVD or at most a modest increase in risk. They further explained that the possible reason for a small increase in risk in some countries with a sizeable and growing percentage of adults with pre-DM might be the substantial numbers of adults developing or dying from CVD.[8]

Population-based longitude data on incident CVD among individuals with combined pre-DM and hypertension are few although both elevated blood pressure and DM are well-known risk factors for CVD morbidity.[23,24] Our study lasting for a decade provides a chance to observe the 10-year cardiovascular outcomes in natural population and enables us to explore the association between IGR alone or combined with other disorders and future CVD or DM risk, thus adding to the understanding of pre-DM in the general population.

Our study showed IGR alone did not promote CVD risk, but when it occurred in the hypertensive subjects, the risk for CVD was increased by 2.41-fold when compared with normotensive nondiabetic participants. Hypertension, as is well established, increased CVD risk significantly either alone or concurrent with IGR, indicating elevated blood pressure a more important role than IGR in the development of CVD. Whether IGR placed an additive independent effect on CVD in patients with hypertension, or acted as a causal product of hypertension as a previous research suggested, remain unclear.[25] Few studies are found involved in the combined effects of blood pressure and blood glucose on CVD risk. A previous study conducted in Arizona taking prehypertension and DM into consideration had drawn a similar conclusion that IFG or IGT alone did not promote the risk of developing CVD, whereas IFG and IGT in subjects with SBP between 120 and 139 mm Hg (prehypertension) increased the CVD risk for 2.12- and 2.06-fold, respectively, when compared with NGR in normotensive subjects (blood pressure, <120/80 mm Hg).[14] However, their study was aimed at individuals aged 45 to 74 years, and they did not include people with hypertension into analysis. Our study was based on a wider range of population aged 18 to 76 years and included normotensive and hypertensive subjects with different glucose categories, thus showing a generalization to the general population.

Literature has documented an increase in microvascular risk with increases in glycemic levels within the nondiabetic range,[26] although macrovascular risk was not observed in prediabetic subjects. This is probably because microvascular dysfunction is correlated with plasma insulin levels, and elevated insulin levels in pre-DM may damage microvascular blood flow and contribute to microvascular diseases. However, larger vessels may need a longer duration, a higher level of insulin and blood glucose, or other accompanied lesions to induce the damage.[26] In other words, when pre-DM converts to overt DM or occurs with other metabolic syndromes, such as hypertension, in the same individual, it will then significantly promote CVD risk. Noteworthily, when IGR progresses to DM, the risk for CVD increases markedly and get even higher when accompanied by hypertension.

In our study, we implemented a strict quality control and assurance program at every step and adjusted multiple confounding factors including most of the traditional CVD risk factors, such as serum lipid profile, physical activity, daytime napping, and blood pressure.[24,27] What is more, our participants were from a homogeneous population and had no intervention during the visit. Such natural course would be good enough to reflect human's natural development of disease, and our results may be referred to a wider range of population. Most importantly, it may provide evidence for further treatment strategies toward pre-DM in China, which have further enhanced the significance of our work.

However, our findings are limited by several facts: We did not perform a baseline glycohemoglobin test in every participant and might therefore have missed some diabetic cases detected by HbA1c alone.[28] However, the clinical diagnosis of both pre-DM and DM in the majority of hospital are mainly fasting and 2-hour glucose, and HbA1c was more commonly used for the evaluation of the average blood glucose in the most recent 2 to 3 months. In addition, our sample size was relatively small, and our follow-up rate was relatively low because of uncertain factors. However, we followed the principle of randomization in baseline enrollment to ensure the representativeness of the sample, and compared the participants who attended follow-up with those who were lost. We found no significant differences in basic characteristics, which may strengthen the reliability of the statistical power of the analyses.

Perspectives

Pre-DM markedly increased the risk for DM and independently did not exhibit increased risk for incident CVD. However, subjects with IGR and coexistent hypertension demonstrated significantly higher risk for CVD in our study. Our research may contribute to evidence-based treatment guidelines of pre-DM in China: to prevent CVD morbidity and mortality, it is reasonable for prediabetic patients to have individualized treatment. For subjects with pre-DM alone, moderate lifestyle intervention, regular monitoring of glycemia, blood pressure, and blood lipid are recommended. But for subjects with combined pre-DM and hypertension, more active intervention is needed. Lifestyle modification should be

strengthened and pharmacological intervention for blood pressure and blood glucose control may be warranted.

Acknowledgments

We are grateful to the field staff and the participants of our study.

Sources of Funding

This study was supported by grants from the National Natural Science Foundation of China (81270935, 91439113, and 81130016).

Disclosures

None.

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Novelty and Significance

What Is New?

- Few articles were found in the literature about the risk for cardiovascular disease (CVD) involved in blood glucose and hypertension combined. Our study aimed to explore whether impaired glucose regulation alone or combined with other syndromes, such as hypertension, could promote CVD risks significantly.

What Is Relevant?

- Pre-diabetes mellitus with or without hypertension showed different effects on long-term CVD risk.

Summary

Blood glucose level within prediabetic range is significantly associated with elevated risks for diabetes mellitus, but only when it is concurrent with other disorders, such as hypertension, it will significantly increase CVD risk.