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Diabetes modifies the association of prehypertension with cardiovascular disease and all-cause mortality

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Abstract

Prehypertension is a risk factor for cardiovascular disease (CVD) and all-cause mortality. However, it is unclear whether prehypertension combined with diabetes associate with a higher risk for cardiovascular disease and all-cause mortality. The purpose of this study was to explore the relationship between prehypertension and the risk of CVD and all-cause mortality was different among individuals with or without diabetes. In the prospective community-based Kailuan study, 67 344 participants without hypertension or a history of CVD at baseline (2006) were included. Prehypertension was defined as systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg. The outcomes were CVD and all-cause mortality were followed up through December 31, 2017. We performed Cox proportional hazards models to evaluate the relationships between prehypertension and CVD and all-cause mortality by diabetes status. During a median follow-up of 11.03 years, 2981 CVD events and 4655 all-cause mortality occurred. After adjusting age, sex, and other factors, the associations of prehypertension with risk of CVD and all-cause mortality were significant in participants without diabetes (hazard ratio and 95% confidence interval: 1.54 [1.38–1.71] and 1.27 [1.17–1.38]), but not in participants with diabetes (1.20 [0.93–1.56] and 0.88 [0.73–1.07]). The interactions between prehypertension and diabetes for the risk of CVD and all-cause mortality were all significant (all $p < .05$). Prehypertension was only associated with an increased risk for

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CVD and all-cause mortality in non-diabetes participants. Diabetes modifies the relation of prehypertension with the risk of CVD and all-cause mortality.

1 | INTRODUCTION

Prehypertension, defined as "high normal," is a mild blood pressure (BP) state between normal BP and hypertension that is characterized by BP in the range of 120–139/80–89 mmHg.[1,2] It has been a predict factor for cardiovascular disease (CVD) events[3-6] and all-cause mortality.[7,8] However, inconsistent results have been reported.[5,6,8] A meta-analysis of 20 prospective cohort studies with 1 129 098 participants demonstrated that prehypertension was not associated with all-cause mortality, but was significantly associated with a great risk of CVD mortality.[9] Meanwhile, another meta-analysis from 396 200 participants, which were derived from 13 studies, showed that prehypertension was associated with CVD events.[10] In addition, a recent study suggested that the prehypertension was not independent risk factor for CVD events and all-cause mortality in non-diabetes participants.[11]

One reason for the inconsistent relationship between prehypertension and CVD in prior studies may be explained by whether concomitant diabetes was existent. The Action to Control Cardiovascular risk in Diabetes (ACCORD) trial, which compared CVD events with diabetes and hypertension who were randomized to standard therapy (Systolic blood pressure [SBP] target of <140 mmHg) or intensive therapy (SBP target of <120 mmHg), did not document CVD benefit differ between the two groups.[12] In contrast, there were several previous studies that have revealed participants with prehypertension and diabetes had a higher risk for CVD events compared with their counterparts without prehypertension or diabetes.[11,13] In addition, this is limited quality evidence to determine a precise BP target in adults with diabetes.[1,14] While several studies thus far focused on the joint effect of prehypertension and diabetes on the CVD risk,[11,15] few have systematically described the association between prehypertension and CVD risk in different degrees of metabolic risk. Beyond that, evidence regarding the interaction between prehypertension and diabetes on CVD risk is still limited.

Therefore, the objectives of this study were to examine the association between prehypertension and incident CVD and all-cause mortality among individuals with and without diabetes.

2 | METHODS

2.1 | Study design and population

The Kailuan study is a prospective community-based cohort study that was performed in the community of Kailuan in Tangshan, China.[16] This study was approved by Ethics Committees of Kailuan General Hospital and Beijing Tiantan Hospital, and followed the guidelines of the Helsinki Declaration. All participants in this study were conducted in the community of Kailuan in Tangshan and signed an informed consent. At baseline of this study from June 2006, we involved 101 510 individuals (81 110 men and 20 400 women) with an age ranging between 18 and 98 years. We performed re-examinations in 2-year intervals up to the end of the follow-up on December 31, 2017. For the present study, we excluded individuals with missing data on BP, with a history of MI or stroke, and with a history of hypertension or diagnosis hypertension or taking anti-hypertensive medication at baseline of the study.

2.2 | Data collection

All data were collected by a standardized questionnaire interviews, anthropometric measurements, clinical examinations, and laboratory assessments. The questionnaire included questions on demographic and socioeconomic parameters, and on clinical parameters like history of diseases and use of medication. Additionally, we assessed the consumption of alcohol, current or former smoking and amount of physical activity and diet. Besides, family income and education were self-reported. Anthropometric measurements including height and weight, and body mass index (BMI) were calculated as weight in kilograms divided by height in meters squared.

SBP and diastolic blood pressure (DBP) were measured three times with the participants in the seated position at least 5 min using a mercury sphygmomanometer, and the average of three readings was used for further analysis. Prehypertension was defined as SBP of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg, according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[1]

Blood samples were collected after an overnight fast (8- to 12-h) and measured the fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) levels, uric acid (UA), high-sensitive C-reactive protein (CRP), and creatinine (Cr) by an automatic analyzer (Hitachi 747; Hitachi),[17] as well as the estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).[18] Diabetes was defined as a self-reported specialist-diagnosis history of diabetes mellitus or taking hypoglycemic drugs, or FBG ≥ 7.0 mmol/L according to criteria from the American Diabetes Association.[19]

Based on the baseline status of prehypertension and diabetes, the study participants were stratified into four groups: "without prehypertension or diabetes," "with prehypertension alone," "with diabetes alone," and "with both prehypertension and diabetes."

2.3 | Outcome assessment

The present study participants were followed up from the baseline examination at 2006 up to December 31, 2017, as the end of the follow-up period, or to the date of a CVD event, or death, whichever came first. The primary outcome in the current analysis was the first occurrence of CVD. The composite CVD outcome included incident nonfatal myocardial infarction (MI) and nonfatal stroke.[20] Stroke was diagnosed according to the World Health Organization criteria on the basis of clinical symptoms, images obtained by computed tomography or magnetic resonance imaging, and other diagnostic reports.[21] MI was diagnosed according to the criteria of the World Health Organization based on electrocardiogram (ECG) changes and cardiac enzymes levels, and clinical symptoms.[22] Death was confirmed by certificates reviewed by the study clinicians form vital statistics offices.[23]

2.4 | Statistical analyses

All data are presented as median and interquartile range (IQR) or numbers and percent. Continuous variables were compared using analysis of variance of the Kruskal-Wallis tests according to distribution, and categoric variables were compared with the chi-square test. Incidence of CVD and all-cause mortality was reported as rate/1000 person-years (PY) with 95% CIs. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD and all-cause mortality were used a Cox proportional hazards regression analysis after adjustments for covariates. The covariates were included age (categorical, <60 or ≥ 60), gender(categorical, male or female), the family average monthly income (categorical, <¥800" or "≥¥800"), education (categorical, literacy/primary, middle school or college/university), BMI (continuous), physical activity [categorical, very active (≥80 min of moderate or vigorous activity per week), moderately active (1–79 min), and inactive (0 min)], smoking (categorical, never, former, and current smokers), alcohol (categorical, never, former, and current drinkers [average daily strong spirit (alcohol content >50%) consumption of 100 ml or more than 100 ml for at least the previous year]), salt intake (categorical, <10 g/day and ≥10 g/day), TG (continuous, mg/dl), LDL(continuous, mg/dl), HDL(continuous, mg/dl), eGFR (continuous, ml/min/1.73 m^2), UA (continuous, μmol/L), CRP (continuous, mg/L), and lipid-lowering medication (categorical, never or yes).

To assess whether diabetes conditions modify the association between prehypertension and risk for CVD and all-cause mortality, we separated participants into two subgroups based on the status of diabetes and conducted Cox proportional hazards regression models in each subgroup to investigate the association between outcomes and prehypertension. To verify the robustness of the study finding, we performed two sensitivity analyses. First, considering participants would have developed hypertension during the long-term follow-up, we excluded the population with incident hypertension, which was defined as a self-reported specialist-diagnosis history
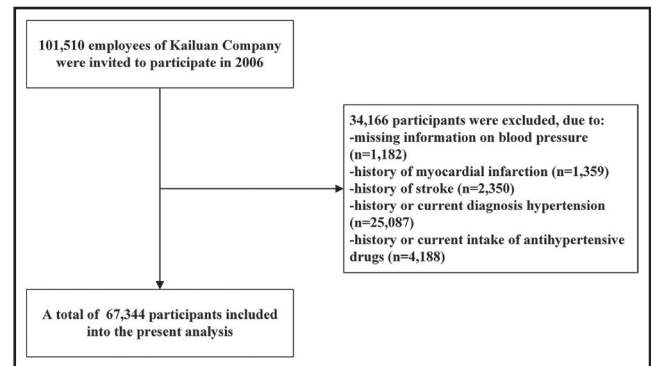

FIGURE 1 Flowchart of the study cohort

of, or using of anti-hypertensive drugs or SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, during the follow-up period. Second, we excluded the population with diabetic treatment. Third, to examine the potential effect of non–CVD-related death as a competing, risk rather than a censoring event, which impeded the occurrence of CVD, competing risk model (also called the Fine and Gray model) was conducted. We further calculated the hazard ratios for subtypes of CVD events, including MI and stroke.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc). All reported *p* values were based on two-sided test of significance, and *p* <.05 was deemed statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 67 344 participants (men, 77.49%; median age, 50.05 [41.63–56.84]) were eventually analyzed in our study, after excluding those with missing information on BP (*n* = 1182), a history of MI (*n* = 1310), and previous stroke (*n* = 2344), and those with a history or hypertension or diagnosis hypertension, or taking anti-hypertensive therapy (*n* = 29 330) (Figure 1).

Among them, 18 678 were defined as without prehypertension or diabetes, 44 031 as with prehypertension alone, 857 as with diabetes alone, and the rest 3778 as with prehypertension and diabetes at baseline. Participants with both prehypertension and diabetes had a higher age, were more likely men, had a lower self-reported education, and had a higher SBP, DBP, BMI, prevalence of dyslipidemia, FPG, TC, TG, and LDL concentrations compared with their counterparts in the other three groups (Table 1).

3.2 | Risk for incident CVD and all-cause mortality

During a median follow-up of 11.03 years (IQR: 10.73–11.21 years), 2981 participants had CVD events (rate 4.21 per 1000 person-year, [95% CI 4.06–4.36]), and 4655 participants died (6.46 per 1000 person-year, [95% CI 6.28–6.65]). Regardless of the status of

diabetes, the HRs (95% CIs) for CVD events were 1.50 (95% CI, 1.36–1.66) and all-cause mortality were 1.22 (95% CI, 1.13–1.31) for prehypertension group compared with no-prehypertension group, after adjusting for potential confounding factors (Table 2).

Rates per 1000 person-years were calculated among four groups: "without prehypertension or diabetes," "with prehypertension alone," "with diabetes alone," and "with both prehypertension and diabetes." (Figure 2) Without adjustment of confounders, the cumulative incidence of CVD events and all-cause mortality was the highest in the both prehypertension and diabetes group and decreased toward the without prehypertension or diabetes group (Table S1). After multivariable adjustment, the HRs (95% CIs) for CVD events were 1.55 (95% CI, 1.39–1.72) for prehypertension alone, 2.73 (95% CI, 2.12–3.53) for diabetes alone, and 3.09 (95% CI, 2.67–3.55) for both prehypertension and diabetes compared with their counterparts without prehypertension or diabetes (Table S1). In the multivariable model, the HRs for all-cause mortality were 1.28 (95% CI, 1.18–1.39) for prehypertension alone, 2.71 (95% CI, 2.25–3.26) for diabetes alone, and 2.30 (95% CI, 2.05–2.58) for both prehypertension and diabetes (Table S1). Sensitivity analyses showed similar results (Table S1).

3.3 | Interaction effects of prehypertension and diabetes on CVD and all-cause mortality

To examine whether the interaction effect existed between prehypertension and diabetes status on both incident CVD and all-cause mortality, we did interaction analyses, which were shown in Table 3. After adjustment for potential confounders, prehypertension was significantly associated with CVD and all-cause mortality in participants without diabetes, the HRs were 1.54 (95% CI, 1.38–1.71) and 1.27 (95% CI, 1.17–1.38), the associations were not significant for participants with diabetes, the HRs were 1.20 (95% CI, 0.93–1.56) and 0.88 (95% CI, 0.73–1.07), compared with participants without prehypertension. Furthermore, there were significant interactions between prehypertension and diabetes in relation to CVD events and all-cause mortality (each p for interaction <0.05). Further analyses excluded participants with hypertension before event occurred during the follow-up, excluded participants with diabetic treatment, and analyzed the relationship between prehypertension and CVD events using competing risk model, with similar results. In the subtype analyses of CVD events, similar results were yielded for stroke and MI (Table S2).

Then, we divided all of the participants into subgroups according to age and gender. After adjustment for potential confounders, the HRs for all-cause mortality with prehypertension alone were 1.41 (95% CI, 1.24–1.59) for younger than 60 years and 1.14 (95% CI, 1.02–1.27) for those 60 years and older compared with participants without prehypertension or diabetes (p for interaction <0.01). No interaction was found in other subgroups (all p for interaction >0.05; Table S3).

4 | DISCUSSION

In this community-based study, we found that participants with prehypertension had an increased risk of CVD and all-cause mortality compared to those without prehypertension. However, in the stratified results by diabetes status, prehypertension was only associated with the risk of CVD and all-cause mortality in non-diabetes participants, not in diabetes participants. There has a significant interaction between prehypertension and diabetes on the risk of CVD and all-cause mortality.

An association between prehypertension and increased risk for CVD and all-cause mortality has been reported in some, but not all, studies.[10,24,25] In the Physician's Health Study (PHS) study of 53 163 healthy adults, the adjusted odds ratios for CVD mortality among participants with prehypertension were 1.02 (95% CI 0.73–1.42), compared with those with normal blood pressure. The results indicated that the JNC 7 categorization of prehypertension was not associated with a significantly increased risk of CVD mortality.[24] However, an investigation on almost 15 000 Iranian residents, the adjusted HR of CVD were 1.62 (95% CI 1.11–2.37) and 0.89 (95% CI 0.51–1.54) for middle-aged and elderly, respectively, with high normal BP (SBP of 130–139 mmHg or DBP of 85–89 mmHg), and when prehypertension was defined by 2007 European guidelines.[26,27] In a meta-analysis of twenty-nine articles (n = 1 010 858 participants), showed that prehypertension to be associated with a greater risk of incident stroke, MI, and total CVD events, defined by JNC 7 report.[25] Our study also found that prehypertension may elevated the risk of CVD and all-cause mortality compared to those without prehypertension.

In a prospective cohort study, they found that patients with prehypertension and diabetes were associated with an increased risk for CVD and all-cause mortality, but not with prehypertension alone.[11] Another cohort study also showed BP of 130–139/80–89 mmHg may result in significantly higher CVD risk with diabetes but not in those with normoglycemia or prediabetes.[28] However, the ACCORD trial has supported a SBP goal lower than 120 mmHg compared with <140 mmHg did not reduce the rate of CVD in adults with diabetes.[12] And the Systolic Blood Pressure Intervention Trial (SPRINT) conducted among adults without diabetes also demonstrated CVD benefit from intensive treatment of BP to goal of <120 mmHg as compared with <140 mmHg.[29] Results from the current analysis are consistent with these two trials, showing prehypertension was only associated with the risk of CVD and all-cause mortality in non-diabetes participants, not in diabetes participants. We also found that the interaction between prehypertension and diabetes for the risk of CVD and all-cause mortality were significant, which suggested that diabetes modifies the relation of prehypertension with the risk of CVD and all-cause mortality. It means that further studies are required to confirm the anticipated benefits of identifying and intervening in persons with prehypertension among non-diabetic patients.

There are several potential explanations for why prehypertension may be a risk factor for incident CVD in non-diabetes individuals,

TABLE 1 Characteristics of the study participants at baseline with and without prehypertension stratified by diabetes status

	Total	Participants without diabetes		Participants with diabetes		p value
		No prehypertension	Prehypertension	No prehypertension	Prehypertension	
Cases, n	67 344	18 678	44 031	857	3778	
Age, years, median (IQR)	50.02 (41.63–56.84)	45.16 (36.21–53.28)	50.9 (42.93–57.7)	52.94 (47.46–60.39)	54.69 (48.67–62.28)	<.01
Male sex, n (%)	52 186 (77.49)	12 340 (66.07)	36 024 (81.82)	662 (77.25)	3160 (83.64)	<.01
Smoke, n (%)						
Never smoker	41 218 (61.21)	11 381 (60.93)	26 959 (61.23)	483 (56.36)	2395 (63.39)	<.01
Former smoker	3175 (4.71)	811 (4.34)	2076 (4.71)	55 (6.42)	233 (6.17)	
Current smoker	22 951 (34.08)	6486 (34.73)	14 996 (34.06)	319 (37.22)	1150 (30.44)	
Current alcohol, n (%)	25 208 (37.43)	7387 (39.55)	16 331 (37.09)	307 (35.82)	1183 (31.31)	<.01
Salt intake g/day, ≥10, n (%)	6620 (10.20)	1954 (10.74)	4191 (9.91)	91 (11.14)	384 (10.69)	<.01
Education, n (%)						
Literacy/Primary	5506 (8.18)	1183 (6.50)	3772 (8.91)	99 (12.12)	452 (12.58)	<.01
Middle school	53 886 (80.02)	14 179 (75.90)	36 033 (85.12)	668 (81.76)	3006 (83.69)	
College/University	5550 (8.24)	2839 (15.60)	2527 (5.98)	50 (6.12)	134 (3.73)	
Income						
<¥800	57 727 (85.72)	15 203 (81.40)	38 490 (87.42)	706 (82.38)	3328 (88.09)	<.01
≥¥800	9617 (14.28)	3475 (18.60)	5541 (12.58)	151 (17.62)	450 (11.91)	
Physical activity, n (%)						
Inactive	8372 (12.43)	2299 (12.31)	5518 (12.53)	108 (12.60)	447 (11.83)	<.01
Moderately active	50 179 (74.51)	14 168 (75.85)	32 711 (74.29)	598 (69.78)	2702 (71.52)	
Very active	8793 (13.06)	2211 (11.84)	5802 (13.18)	151 (17.62)	629 (16.65)	
Dyslipidemia, n (%)	20 832 (30.93)	4531 (24.26)	14 115 (32.06)	386 (45.04)	1800 (47.64)	<.01
FBG, mmol/L, median (IQR)	5.07 (4.63–5.60)	4.93 (4.53–5.36)	5.05 (4.62–5.51)	8.55 (7.30–11.34)	8.53 (7.40–10.95)	<.01
LDL, mmol/L, median (IQR)	2.30 (1.79–2.80)	2.21 (1.75–2.7)	2.32 (1.81–2.81)	2.30 (1.83–2.83)	2.40 (1.88–2.91)	<.01
HDL, mmol/L, median (IQR)	1.50 (1.27–1.75)	1.48 (1.27–1.72)	1.50 (1.28–1.76)	1.45 (1.22–1.72)	1.48 (1.26–1.77)	<.01
TG, mmol/L, median (IQR)	1.21 (0.84–1.79)	1.03 (0.73–1.51)	1.24 (0.88–1.85)	1.43 (0.96–2.16)	1.61 (1.11–2.55)	<.01
TC, mmol/L, median (IQR)	4.87 (4.24–5.52)	4.73 (4.13–5.37)	4.90 (4.27–5.54)	5.05 (4.38–5.84)	5.11 (4.41–5.85)	<.01
SBP, mmHg, median (IQR)	120.00 (110.00–130.00)	109.30 (100.00–110.70)	125.00 (120.00–130.00)	110.00 (102.00–112.70)	130.00 (120.00–136.30)	<.01
DBP, mmHg, median (IQR)	80.00 (71.70–81.30)	70.00 (69.30–72.70)	80.00 (80.00–84.70)	70.00 (68.70–72.70)	80.00 (80.00–85.00)	<.01
hs-CRP, mg/L, median (IQR)	0.76 (0.29–2.20)	0.70 (0.26–2.00)	0.76 (0.29–2.16)	1.18 (0.40–2.64)	1.20 (0.45–2.90)	<.01
BMI, kg/m^2, median (IQR)	24.34 (22.15–26.61)	23.30 (21.22–25.40)	24.62 (22.53–26.91)	24.61 (22.53–26.49)	25.59 (23.51–27.68)	<.01
eGFR (ml/min/1.73 m^2), median (IQR)	83.66 (70.26–97.47)	86.42 (74.23–99.79)	82.41 (68.97–96.59)	82.97 (70.80–95.00)	80.24 (65.63–95.01)	<.01
Uric acid, μmol/L, median (IQR)	276.00 (227.00–331.31)	271.00 (222.00–326.00)	280.00 (230.00–335.00)	266.00 (217.00–319.00)	268.00 (220.00–320.00)	<.01
Lipid-lowering medication, n (%)	233 (0.35)	61 (0.33)	121 (0.27)	19 (2.22)	32 (0.85)	<.01

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL, high-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; N, number; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

	No prehypertension	Prehypertension
CVD events		
Number of events, N (%)	502 (2.57)	2479 (5.19)
Incidence rate, per 1000-person, y	2.41 (2.21–2.63)	4.95 (4.76–5.15)
Unadjusted HR[a]	Reference	2.05 (1.86–2.26)
Adjusted HR[b]	Reference	1.50 (1.36–1.66)
All-Cause mortality		
Number of events, N (%)	879 (4.50)	3776 (7.90)
Incidence rate, per 1000-person, y	4.18 (3.91–4.47)	7.40 (7.16–7.64)
Unadjusted HR[a]	Reference	1.77 (1.64–1.90)
Adjusted HR[b]	Reference	1.22 (1.13–1.31)

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; y, years.
[a]Unadjusted hazard ratio (95% CI).; [b]Adjusted for age, gender, income, education, body mass index, physical activity, current smoker, alcohol, salt intake and triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, estimated glomerular filtration rate, uric acid, and high-sensitive C-reactive protein.
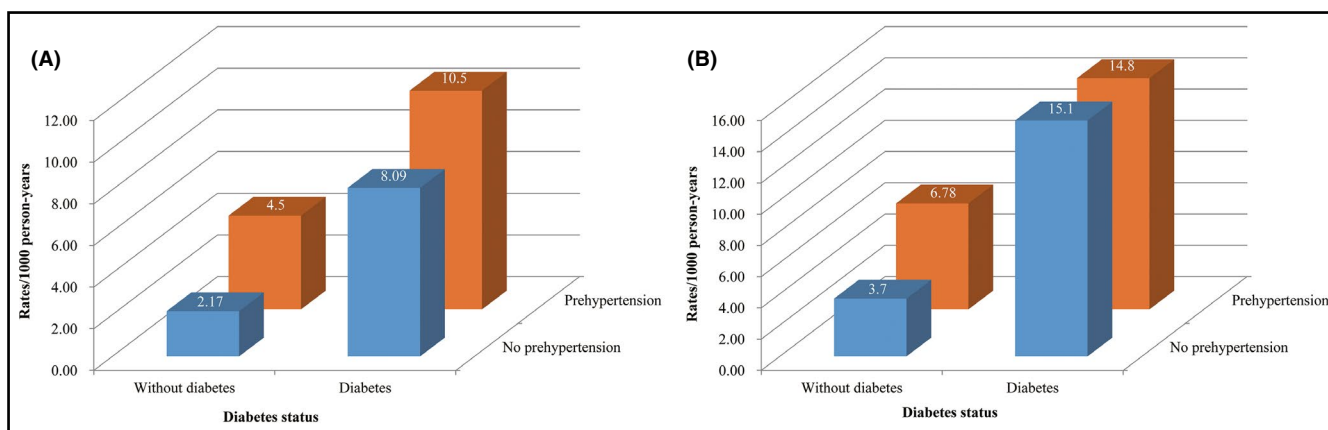

FIGURE 2 The effect of various diabetes categories and prehypertension categories combined on the prevalence of (A) CVD and (B) all-cause mortality. Rates per 1000 person-years were calculated in these four groups

but not in diabetes. First, the risk could be attributable to the fact that many individuals with prehypertension eventually progress to overt hypertension.[30,31] Second, prehypertension individuals might suffer from longer exposure to high BP levels and resulted in end-organ damage, leading to higher CVD risk.[32,33] Third, diabetes also represents an independent risk factor for CVD.[34] Diabetes increased the risk of CVD higher than prehypertension.[13] Diabetes plus pre-hypertension does not increase the extra risk more than diabetes alone.

The current study has several strengths. The Kailuan study enrolled a large population-based cohort of Chinese adults. Standardized protocols were used for data collection, including BP, FBG, and potential confounders such as BMI, income, health behaviors, and blood lipids. Additionally, long-term follow-up was available during which CVD events were identified and adjudicated by trained staff. Despite these strengths, several limitations should be taken into consideration. Although we included multivariable-adjusted studies to minimize the impacts, it remains a possibility that residual confounding and bias across the studies caused overestimation of

the associations. Second, we did not have data on HbA$_{1c}$ and post-prandial blood glucose after 2 h, which might result in bias in estimation of the total amount of diabetes. Third, many confounders were self-reported, such as smoking, previous disease history, and medication history, which might be susceptible to self-report bias. In addition, we did not collect the types of drugs used in the treatment of diabetes patients, so the impact of types of drugs cannot be assessed on cardiovascular risk. Finally, the population of this study came from a single country may cannot directly promote the results on other ethnicities. Further studies, including other geographic regions, ethnicities, and races, are needed to confirm the generalizability of the current results.

5 | CONCLUSIONS

Prehypertension was an independent risk factor for CVD and all-cause mortality in non-diabetes participants, but not among diabetes participants. Our study indicated that diabetes modifies the

TABLE 3 Risk for cardiovascular events and all-cause mortality associated with prehypertension stratified by diabetes status

	Participants without diabetes		Participants with diabetes		
	No prehypertension	Prehypertension	No prehypertension	Prehypertension	p-interaction
CVD events					
Unadjusted HR[a]	Reference	2.07 (1.87–2.30)	Reference	1.30 (1.00–1.68)	<.01
Adjusted HR[b]	Reference	1.54 (1.38–1.71)	Reference	1.20 (0.93–1.56)	.01
Sensitivity analysis[c]	Reference	1.64 (1.47–1.84)	Reference	1.27 (0.97–1.66)	.01
Sensitivity analysis[d]	Reference	1.56 (1.40–1.73)	Reference	1.06 (0.79–1.44)	<.01
Sensitivity analysis[e]	Reference	1.34 (1.26–1.44)	Reference	1.01 (0.86–1.19)	<.01
All-Cause mortality					
Unadjusted HR[a]	Reference	1.86 (1.72–2.01)	Reference	1.03 (0.86–1.24)	<.01
Adjusted HR[b]	Reference	1.27 (1.17–1.38)	Reference	0.88 (0.73–1.07)	<.01
Sensitivity analysis[c]	Reference	1.41 (1.30–1.53)	Reference	0.96 (0.79–1.16)	<.01
Sensitivity analysis[d]	Reference	1.28 (1.18–1.39)	Reference	0.96 (0.76–1.22)	<.01

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.
[a]Unadjusted hazard ratio (95% CI).; [b]Adjusted for age, gender, income, education, body mass index, physical activity, current smoker, alcohol, salt intake and triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, estimated glomerular filtration rate, uric acid, and high-sensitive C-reactive protein.; [c]Sensitivity analysis was adjusted for above covariables and further excluded participants with incident hypertension before event occurred.; [d]Sensitivity analysis was adjusted for above covariables and further excluded participants with diabetic treatment.; [e]Sensitivity analysis was adjusted for above covariables and used competing risk model.

relation of prehypertension with the risk of CVD and all-cause mortality. An understanding of the clinical significance of this relationship may prompt earlier surveillance of the blood pressure level in non-diabetes individuals, and result in the identification of populations at high risk of CVD and all-cause mortality.

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CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

AUTHOR CONTRIBUTIONS

YR and YZ wrote the manuscript. AW, SC, XT and HL collected the data. SC, XT and HL researched data and contributed to discussion. SW and YH reviewed and edited the manuscript. CM contributed to the discussion and reviewed/edited the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Kailuan Hospital (approval number: 2006-05) and Beijing Tiantan Hospital (approval number: 2010-014-01).

DATA AVAILABILITY STATEMENT

Data are available to researchers on request for purposes of reproducing the results or replicating the procedure by directly contacting the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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