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ORIGINAL ARTICLE

Hypertension is an independent risk factor for type 2 diabetes: the Korean genome and epidemiology study

Min-Ju Kim, Nam-Kyoo Lim, Sun-Ja Choi and Hyun-Young Park

Hypertension and diabetes share common risk factors and frequently co-occur. Although high blood pressure (BP) was reported as a significant predictor of type 2 diabetes, little is known about this association in Korea. This study investigated the relationship of prehypertension and hypertension with type 2 diabetes in 7150 middle-aged Koreans, as well as the effect of BP control on diabetes development over 8 years. At 8 years, 1049 (14.7%) of the 7150 participants had newly developed diabetes, including 11.2, 16.7 and 21.5% of baseline normotensive, prehypertensive and hypertensive subjects, respectively. The overall incidence rate of diabetes was 22.3 events per 1000 person-years. Subjects with baseline prehypertension (hazard ratio (HR), 1.27; 95% confidence interval (CI), 1.09–1.48) and hypertension (HR 1.51; 95% CI, 1.29–1.76) were at higher risk of diabetes than normotensive subjects after controlling for potential confounders (P-value for trend <0.001). These associations persisted even when subjects were stratified by baseline glucose status, sex and body mass index (BMI). The risk of diabetes was significantly higher in subjects who had normal BP at baseline and progressed to prehypertention or hypertension at 8 years (HR, 1.48; 95% CI, 1.20–1.83) than those with controlled BP, but these associations were not observed in subjects with baseline prehypertension and hypertension. These findings showed that prehypertension and hypertension are significantly associated with the development of diabetes, independent of baseline glucose status, sex and BMI. Active BP control reduced incident diabetes only in normotensive individuals, suggesting the need for early BP management.

INTRODUCTION

The worldwide incidence of diabetes has increased significantly,[1] with the number of people of all ages with diabetes expected to approximately double between 2000 and 2030.[2] The prevalence of diabetes increased more among Asians than among whites in 2005.[3] In Korea, the prevalence of diabetes in subjects aged ⩾ 30 years was increased from 8.6% in 2001 to 11.0% in 2013.[4] Diabetes is associated with increased cardiovascular morbidity and mortality, with the risk of vascular diseases being about twofold higher in diabetic patients than without diabetes.[5] Early detection of patients at high risk for diabetes is particularly important in preventing cardiovascular diseases.

Age, ethnicity, obesity, blood pressure (BP), and fasting blood glucose and lipid concentrations were identified as risk factors for diabetes.[6] In particular, hypertension, which is also associated with cardiovascular disease, is emerging as a risk factor for diabetes.[7,8] A cross-sectional study from China showed that hypertensive subjects with diabetic risk had a greater risk of cardiovascular disease than normoglycemic subjects.[9] Hypertension and diabetes were found to share common risk factors, including obesity, lipid profile and BP; moreover, as both are factors of metabolic syndrome, they commonly occur together in individuals.[10–12] Although several longitudinal

studies indicated that higher BP is a significant predictor of type 2 diabetes,[7,8,13–16] most of these studies have limitations, including self-reporting of diabetes and/or BP,[13,16] inclusion of a single sex,[7,13,15,16] and lack of information on important baseline characteristics that may confound these relationships.[7,8,13,16]

Glucose surveillance may be important in both hypertensive and prehypertensive individuals. Despite findings showing the association between BP and diabetes, little is known about this association in Koreans or about the relationship between prehypertension and incident type 2 diabetes. Therefore, this study investigated the relationships between prehypertension and hypertension with type 2 diabetes in a prospective community-based epidemiologic cohort that had been followed-up for 8 years. The effect of BP control on development of diabetes was determined by evaluating the risk of incident diabetes relative to change in BP.

MATERIALS AND METHODS

Study participants

The Korean Genome and Epidemiology Study is a population-based prospective cohort study designed to investigate the prevalence of and risk factors for chronic diseases in Korea and supported by the Korean National Institute of

Health. The baseline survey was started in 2001–2002 on 10 038 participants aged ⩾ 40 years, with all subjects undergoing follow-up examinations every 2 years. Specimens were collected from groups of residents representing local populations in a rural (Anseong) and an urban (Ansan) area.[17] Baseline and 8-year follow-up data were obtained from the Center for Genome Science in the National Institute of Health, Korea. The details of the present cohort have been described elsewhere.[17] Of the 10 038 participants initially enrolled, 9999 (99.6%) aged 40–69 years were assessed at baseline. Of the latter, 1334 with diabetes and 451 with incomplete data were excluded. The remaining 8214 participants were included in the baseline study; at 8 years, 847 were lost to follow-up and 217 with incomplete data were excluded. A total of 7150 people were included in the present study (Figure 1). Of these, 5537 subjects were divided into poorly controlled and controlled groups according to their BP changes determined at the baseline and after 8 years. The study protocol was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention. Written informed consent was obtained from all study participants.

Clinical and biochemical measurements

Body weight was measured to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm, with body mass index (BMI) calculated as body weight (kg) divided by height (m) squared. Trained examiners measured waist circumference at the midpoint between the ribs and the iliac crest in the standing position. BP was measured after a 5 min rest period in the supine position using standard protocols, with measurements taken at least twice at 30-s intervals and averaged.

Blood samples were collected after an 8–14 h fast. Fasting plasma glucose (FPG), total cholesterol, triglyceride and high-density lipoprotein cholesterol concentrations were measured enzymatically, and low-density lipoprotein cholesterol concentrations were estimated by the Friedwald formula.[18] Fasting insulin concentrations were measured by radioimmunoassay and hemoglobin A_{1C} (HbA$_{1C}$) concentrations by high-performance liquid chromatography. The homeostatic model for insulin resistance was calculated as fasting insulin $(\mu IU\,ml^{-1}) \times$ fasting glucose $(mg\,dl^{-1})/(22.5 \times 18)$.
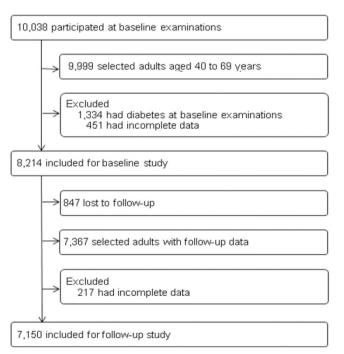

Figure 1 Study flow chart showing subjects screened, included and followed up.

(Flow chart contents:)
- 10,038 participated at baseline examinations
- 9,999 selected adults aged 40 to 69 years
- Excluded: 1,334 had diabetes at baseline examinations; 451 had incomplete data
- 8,214 included for baseline study
- 847 lost to follow-up
- 7,367 selected adults with follow-up data
- Excluded: 217 had incomplete data
- 7,150 included for follow-up study

Table 1 Demographic and clinical characteristics of the study subjects at baseline

Variable	NGT (n = 5593) Normal BP (n = 3198)	Prehypertension (n = 1378)	Hypertension (n = 1017)	P-value for trend	Prediabetes (n = 1557) Normal BP (n = 732)	Prehypertension (n = 389)	Hypertension (n = 436)	P-value for trend
Age (years)	49.1 ± 7.8	53.4 ± 9.0	55.8 ± 8.4	<0.001	50.1 ± 8.3	54.3 ± 8.8	56.4 ± 8.4	<0.001
BMI (kg m⁻²)	23.8 ± 2.8	24.5 ± 3.1	25.4 ± 3.1	<0.001	24.5 ± 3.1	25.0 ± 3.1	25.7 ± 3.4	<0.001
WC (cm)	79.8 ± 8.1	83.4 ± 8.6	85.9 ± 8.2	<0.001	80.7 ± 8.4	84.2 ± 8.3	86.5 ± 9.0	<0.001
SBP (mm Hg)ᵃ	103.8 (103.5–104.1)	123.6 (123.2–124.0)	138.2 (137.2–139.2)	<0.001	104.2 (103.5–105.0)	124.8 (124.1–125.5)	136.5 (134.9–138.2)	<0.001
DBP (mm Hg)ᵃ	67.0 (66.7–67.3)	79.5 (79.1–79.8)	87.7 (87.1–88.3)	<0.001	67.0 (66.4–67.6)	79.8 (79.2–80.4)	86.0 (84.9–87.1)	<0.001
FPG (mg dl⁻¹)ᵃ	80.4 (80.2–80.6)	81.6 (81.2–82.0)	81.8 (81.4–82.3)	<0.001	86.4 (85.7–87.2)	88.3 (87.3–89.4)	88.0 (87.0–89.0)	0.013
PP2 glucose (mg dl⁻¹)ᵃ	99.2 (98.5–100.0)	99.6 (98.4–100.9)	102.5 (101.1–104.0)	<0.001	151.9 (150.2–153.6)	152.6 (149.9–155.2)	153.9 (151.5–156.3)	0.182
Fasting insulin (µIU ml⁻¹)ᵃ	6.2 (6.0–6.3)	6.5 (6.3–6.8)	7.1 (6.8–7.4)	<0.001	6.1 (5.9–6.4)	6.8 (6.4–7.2)	7.3 (6.9–7.7)	<0.001
PP2 insulin (µIU ml⁻¹)ᵃ	16.4 (15.9–16.9)	16.3 (15.6–17.2)	19.9 (18.8–21.1)	<0.001	25.4 (23.6–27.3)	24.2 (22.0–27.0)	26.7 (24.2–29.4)	0.414
HOMA-IRᵃ	1.2 (1.2–1.2)	1.3 (1.3–1.4)	1.4 (1.4–1.5)	<0.001	1.3 (1.2–1.4)	1.5 (1.4–1.6)	1.6 (1.5–1.7)	<0.001
HbA₁C (%)ᵃ	5.5 (5.4–5.5)	5.5 (5.5–5.5)	5.5 (5.5–5.6)	<0.001	5.6 (5.5–5.7)	5.7 (5.7–5.7)	5.7 (5.7–5.8)	<0.001
TC (mg dl⁻¹)ᵃ	182.0 (180.9–183.1)	185.7 (183.9–187.5)	189.7 (187.6–191.8)	<0.001	189.8 (187.5–192.3)	198.9 (195.6–202.4)	196.0 (192.7–199.4)	0.003
HDL-C (mg dl⁻¹)ᵃ	44.3 (44.0–44.7)	44.3 (43.8–44.8)	43.2 (42.6–43.7)	<0.001	44.3 (43.6–45.0)	44.2 (43.3–45.2)	43.5 (42.6–44.4)	0.146
LDL-C (mg dl⁻¹)ᵃ	109.1 (108.1–110.2)	108.5 (106.7–110.3)	111.0 (108.9–113.2)	0.104	114.2 (111.9–116.5)	117.8 (114.3–121.4)	113.3 (109.7–117.0)	0.665
TG (mg dl⁻¹)ᵃ	120.8 (119.1–122.5)	136.8 (133.7–139.9)	149.1 (145.4–153.0)	<0.001	132.0 (127.9–136.2)	154.1 (147.6–160.9)	163.1 (156.8–169.8)	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic BP; FPG, fasting plasma glucose; HbA$_{1C}$, hemoglobin A$_{1C}$; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model for insulin resistance; LDL-C, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; PP2, postprandial 2 h; SBP, systolic BP; TC, total cholesterol; TG, triglyceride; WC, waist circumference.
The data are expressed as mean ± s.d. or as geometric mean (95% confidence interval (CI)). Between group differences were analyzed by one-way analysis of variance.
ᵃLog-transformed values were analyzed, with the geometric means and 95% CIs back-transformed.

Table 2 Risk of incident diabetes over 8 years in subjects categorized by baseline BP

			Unadjusted		Model 1		Model 2	
BP groups	Number at risk	Diabetes cases	HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend
All								
Normal BP	3930	442	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
Prehypertension	1767	295	1.58 (1.37–1.83)**		1.44 (1.23–1.67)**		1.27 (1.09–1.48)*	
Hypertension	1453	312	2.12 (1.83–2.45)**		1.90 (1.63–2.22)**		1.51 (1.29–1.76)**	
Total	7150	1049						
NGT								
Normal BP	3198	197	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
Prehypertension	1378	126	1.58 (1.26–1.97)**		1.43 (1.14–1.80)*		1.29 (1.02–1.63)*	
Hypertension	1017	125	2.12 (1.69–2.65)**		1.91 (1.51–2.41)**		1.59 (1.25–2.03)**	
Total	5593	448						
Prediabetes								
Normal BP	732	245	1 (reference)	0.001	1 (reference)	0.002	1 (reference)	0.015
Prehypertension	389	169	1.40 (1.15–1.70)*		1.28 (1.05–1.57)*		1.24 (1.01–1.52)*	
Hypertension	436	187	1.49 (1.24–1.81)**		1.38 (1.13–1.68)*		1.29 (1.05–1.58)*	
Total	1557	601						

Abbreviations: BP, blood pressure; CI, confidence interval; HR, hazard ratio; NGT, normal glucose tolerance.
By glucose status and BP category at baseline examination.
Model 1: adjusted for age and sex.
Model 2: adjusted for the variables in model 1 and fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, body mass index, family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or above), alcohol use (current or non-current) and smoking status (current or non-current).
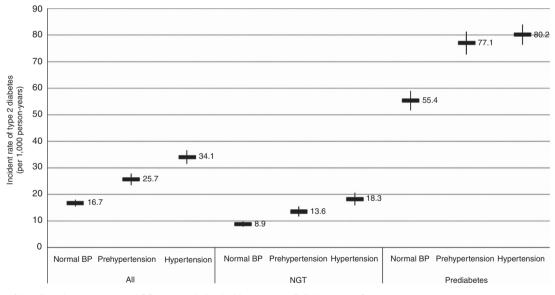*P<0.05, **P<0.001.

Figure 2 Effect of baseline glucose status and BP on cumulative incidence rates of diabetes over 8 years.

Definition of hypertension and diabetes mellitus

BP was classified according to the Seventh Report of the Joint National Committee on High BP categories[19] as normal (<120 mm Hg systolic and <80 mm Hg diastolic); prehypertension (120–139 mm Hg systolic or 80–89 mm Hg diastolic); or hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic or use of antihypertensive medication).

Diabetes mellitus was diagnosed according to the 2010 criteria of the American Diabetes Association as an FPG ≥126 mg dl^{−1}, a 2-h postchallenge plasma glucose (2-h PG) ≥200 mg dl^{−1}, HbA$_{1C}$ ≥6.5% or use of an oral hypoglycemic agent, and prediabetes as either impaired fasting glucose (FPG levels 100–125 mg dl^{−1}) and/or impaired glucose tolerance (2-h PG levels 140–199 mg dl^{−1}).[20]

Statistical analysis

Distribution testing for normality was performed using the Shapiro–Wilk test, with the data log-transformed to obtain normalized distributions. The baseline characteristics of subjects were expressed as means ± s.d. or geometric means with 95% confidence intervals (CIs). Differences between groups were compared by one-way analysis of variance for continuous variables and χ^2 tests for categorical variables. The geometric means of log-transformed variables were back-transformed for ease of interpretation and reported with their 95% CIs. The diabetes incidence rate was calculated per 1000 person-years for each BP category. Cox proportional hazards models were used to analyze time at risk and the association with BP categories, and reported as hazard ratios (HRs) and 95% CIs. Participants with normal BP at baseline were considered the reference

Table 3 Sex-stratified risk of incident diabetes over 8 years in subjects categorized by baseline BP

					Unadjusted		Model 1		Model 2	
BP groups	Number at risk	Diabetes cases	Person-years	Diabetes incidence rate per 1000 person-years	OR (95% CI)	P-value for trend	OR (95% CI)	P-value for trend	OR (95% CI)	P-value for trend
Men										
Normal BP	1774	229	11 717.1	19.5	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
Prehypertension	949	168	6069.2	27.7	1.43 (1.17–1.75)**		1.38 (1.13–1.69)*		1.24 (1.01–1.52)*	
Hypertension	671	165	4136.8	39.9	2.09 (1.71–2.55)**		1.98 (1.61–2.42)**		1.65 (1.34–2.05)**	
Total	3394	562	21 923.1	25.6						
Women										
Normal BP	2156	216	14 759.2	14.6	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	0.018
Prehypertension	818	127	5418.1	23.4	1.69 (1.35–2.10)**		1.49 (1.19–1.88)*		1.30 (1.03–1.64)*	
Hypertension	782	147	5008.6	29.3	2.13 (1.73–2.64)**		1.79 (1.42–2.25)**		1.34 (1.05–1.70)*	
Total	3756	487	25 185.9	19.3						

Abbreviations: BP, blood pressure; CI, confidence interval; OR, odds ratio.
By glucose status and BP category at baseline examination.
Model 1: adjusted for age.
Model 2: adjusted for the variables in model 1 and fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, body mass index, family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or above), alcohol use (current or non-current) and smoking status (current or non-current).
*$P<0.05$, **$P<0.001$.

group. To assess the effect of BP control on incident diabetes, participants were categorized as those with poorly controlled and controlled BP. Values of $P<0.05$ were considered statistically significant. All data were analyzed using SPSS software (version 21.0; SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics
The baseline characteristics of the participants are shown in Table 1. Of the 7150 subjects, 5593 (78.2%) had normal glucose tolerance (NGT) and 1557 (21.8%) had prediabetes. The mean age of subjects at baseline was 52 years, and 52.5% were female. The proportions of subjects having normal BP, prehypertension and hypertension were 57.2, 24.6 and 18.2%, respectively, in the NGT group, and 47.0, 25.0 and 28.0%, respectively, in the prediabetes group. Higher BP levels were associated with older age, higher BMI and increased waist circumference. FPG, fasting insulin, homeostatic model for insulin resistance, hemoglobin A_{1C}, total cholesterol and triglyceride levels were significantly associated with increases in BP in both the NGT and prediabetes groups.

Risk of incident diabetes over 8 years according to baseline BP category
Table 2 shows the risk of incident type 2 diabetes by BP categories. During the 8-year follow-up period, 1049 (14.7%) of the 7150 participants had newly developed diabetes, including 442 (11.2%), 295 (16.7%) and 312 (21.5%) subjects with baseline normal BP, prehypertension and hypertension, respectively. The overall incidence rate for diabetes was 22.3 events per 1000 person-years, which increased from 16.7 per 1000 person-years in baseline normotensive to 34.1 per 1000 person-years in hypertensive subjects (Figure 2). The incidence of diabetes after 8 years was higher in subjects with baseline prediabetes than NGT. Compared with subjects having baseline normal BP, those with baseline prehypertension (HR, 1.27; 95% CI, 1.09–1.48) and hypertension (HR, 1.51; 95% CI, 1.29–1.76) were at higher risk for incident diabetes (P-value for trend <0.001, Table 2); these associations persisted even when subjects were stratified by baseline glucose status. For further analysis, prehypertension category was divided into two groups: those with systolic BP of 120–129 mm Hg or diastolic BP of 80–84 mm Hg and those with systolic BP of

130–139 mm Hg or diastolic BP of 85–89 mm Hg. Relative to normotensive subjects, diabetes risk was significantly higher in subjects with BP of 130–139/85–89 mm Hg (HR, 1.48; 95% CI, 1.20–1.82), but not for those with BP of 120–129/80–84 mm Hg (data not shown).

Stratification by sex showed that, relative to normotensive men, those with prehypertension (adjusted HR, 1.24; 95% CI, 1.01–1.52) and hypertension (adjusted HR, 1.65; 95% CI, 1.34–2.05) were at higher risk for diabetes (Table 3). Similarly, women with prehypertension (adjusted HR, 1.30; 95% CI, 1.03–1.64) and hypertension (adjusted HR, 1.34; 95% CI, 1.05–1.70) were at higher risk for diabetes than normotensive women.

Stratification by BMI category showed that, of the 7150 subjects, 32.2% had a normal BMI, 26.7% were overweight and 41.4% were obese (Table 4). The effect of BP on risk of diabetes was similar in these three subgroups. For example, the risk of diabetes was ~1.5-fold higher among hypertensive than normotensive individuals, regardless of BMI.

BP control and incident diabetes
Table 5 shows the HRs for diabetes according to change in BP over 8 years. Of the 5537 subjects with available BP measurements at baseline and at 8 years, 2768 had controlled BP (normal BP) and 2769 had poorly controlled BP (prehypertension or hypertension). Multivariate analysis Cox proportional hazard models showed that the latter group had a significantly higher risk of diabetes (HR, 1.28; 95% CI, 1.11–1.47) than the former. When the subjects were stratified by BP category at baseline, those who had normal BP at baseline and progressed to prehypertension or hypertension at 8 years had a significantly higher risk of diabetes (HR, 1.48; 95% CI, 1.20–1.83) than subjects with controlled BP. However, no association was observed between BP control and incident diabetes in subjects with prehypertension and hypertension at baseline.

DISCUSSION
The purpose of this study was to examine the relationships of BP and BP progression with type 2 diabetes in a middle-aged Korean population followed-up for 8 years. Prehypertension, as well as hypertension, were strongly and independently associated with type

Table 4 BMI-stratified risk of incident diabetes over 8 years in subjects categorized by baseline BP

BP groups	Number at risk	Diabetes cases	Person-years	Diabetes incidence rate per 1000 person-years	Unadjusted OR (95% CI)	P-value for trend	Model 1 OR (95% CI)	P-value for trend	Model 2 OR (95% CI)	P-value for trend
BMI < 23 kg m^{-2}										
Normal BP	1489	134	10 067.7	13.3	1 (reference)	<0.001	1 (reference)	0.003	1 (reference)	0.041
Prehypertension	517	58	3295.3	17.6	1.37 (1.01–1.87)*		1.17 (0.85–1.62)		0.98 (0.70–1.35)	
Hypertension	294	47	1855.5	25.3	1.98 (1.42–2.76)**		1.71 (1.20–2.43)*		1.45 (1.02–2.08)*	
Total	2300	239	15 218.5	15.7						
BMI 23–24.9 kg m^{-2}										
Normal BP	1108	111	7434.9	14.9	1 (reference)	<0.001	1 (reference)	0.016	1 (reference)	0.016
Prehypertension	460	85	3051.9	27.9	1.91 (1.44–2.53)**		1.62 (1.21–2.17)*		1.52 (1.13–2.04)*	
Hypertension	341	60	2204.1	27.2	1.85 (1.35–2.54)**		1.50 (1.08–2.09)*		1.51 (1.08–2.11)*	
Total	1909	256	12 690.9	20.2						
BMI ⩾ 25 kg m^{-2}										
Normal BP	1333	197	8973.7	22.0	1 (reference)	<0.001	1 (reference)	<0.001	1 (reference)	<0.001
Prehypertension	790	152	5140.1	29.6	1.38 (1.11–1.70)*		1.28 (1.03–1.59)*		1.29 (1.04–1.60)*	
Hypertension	818	205	5085.9	40.3	1.92 (1.58–2.33)**		1.74 (1.41–2.13)**		1.52 (1.23–1.88)**	
Total	2941	554	19 199.7	28.9						

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; OR, odds ratio.
By BMI and BP category at baseline examination.
Model 1: adjusted for age and sex.
Model 2: adjusted for the variables in model 1 and fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, body mass index, family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or above), alcohol use (current or non-current) and smoking status (current or non-current).
*P<0.05, **P<0.001.

Table 5 Risk of incident diabetes according to change in BP over 8 years in subjects categorized by baseline BP

BP change after 8 years	Number at risk	Diabetes cases (%)	Unadjusted HR (95% CI)	P-value	Model 1 HR (95% CI)	P-value	Model 2 HR (95% CI)	P-value
All	5537	884 (16.0)						
Controlled BP[a]	2768	346 (12.5)	1 (reference)		1 (reference)		1 (reference)	
Poorly controlled BP[b]	2769	538 (19.4)	1.60 (1.40–1.83)	<0.001	1.45 (1.26–1.66)	<0.001	1.28 (1.11–1.47)	<0.001
Normal at baseline	3100	372 (12.0)						
Controlled BP[a]	2032	195 (9.6)	1 (reference)		1 (reference)		1 (reference)	
Poorly controlled BP[b]	1068	177 (16.6)	1.78 (1.45–2.18)	<0.001	1.65 (1.34–2.03)	<0.001	1.48 (1.20–1.83)	<0.001
Prehypertension at baseline	1343	238 (17.7)						
Controlled BP[a]	446	73 (16.4)	1 (reference)		1 (reference)		1 (reference)	
Poorly controlled BP[b]	897	165 (18.4)	1.10 (0.84–1.45)	0.486	1.11 (0.84–1.46)	0.470	1.05 (0.80–1.39)	0.717
Hypertension at baseline	1094	274 (25.0)						
Controlled BP[a]	290	78 (26.9)	1 (reference)		1 (reference)		1 (reference)	
Poorly controlled BP[b]	804	196 (24.4)	0.89 (0.68–1.15)	0.361	0.88 (0.68–1.14)	0.339	0.93 (0.71–1.22)	0.607

Abbreviations: BP, blood pressure; CI, confidence interval; HR, hazard ratio.
By glucose status at baseline examination and BP change after 8 years.
Model 1: adjusted for age and sex.
Model 2: adjusted for the variables in model 1 and fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, body mass index, family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or above), alcohol use (current or non-current) and smoking status (current or non-current).
[a]Normal BP at 8-year follow-up.
[b]Prehypertensive or hypertensive at 8-year follow-up.

2 diabetes, even after controlling for potential confounders. Moreover, the risk of incident diabetes was significantly greater when BP was poorly controlled than well-controlled, with this association observed only in subjects with normal BP at baseline.

During the 8-year follow-up period, about 14.7% of all participants developed type 2 diabetes, with incidence rates in baseline normotensive, prehypertensive and hypertensive subjects of 16.7, 25.7 and 34.1 per 1000 person-years, respectively. These results indicated that participants with normal BP had the lowest risk of type 2 diabetes,

with the risk steadily increasing as BP increased. In addition, these associations persisted after stratification by glucose status, sex and BMI.

Our findings are consistent with previous studies of the association between BP and the risk of type 2 diabetes.[7,8,13–15] For example, the Osaka Health Survey reported that high normal BP and hypertension were associated with an increased risk of diabetes.[7] Moreover, the Women's Health Initiative Study found that subjects with high normal BP and hypertension were at about 1.5- and 2.0-fold higher risk of

developing diabetes than normotensive subjects.[13] A recent study from Sweden showed that hypertension and high normal systolic BP at midlife was a significant predictor of type 2 diabetes.[15] In the present study, Cox proportional hazards models indicated that prehypertensive and hypertensive participants were at 1.3- and 1.5-fold higher risk of type 2 diabetes than normotensive subjects, indicating that the increased risk of diabetes starts at near-normal BP. These associations remained significant after stratification by baseline glucose status and sex. Stratification by BMI showed that prehypertension and hypertension were associated with increased risk of diabetes among overweight (BMI, 23–24.9 kg m^{-2}) and obese (BMI, $\geqslant$ 25 kg m^{-2}) individuals, emphasizing the importance of BP control in prehypertensive subjects with BMI $\geqslant$ 23 kg m^{-2}.

Prehypertension is associated with increased cardiovascular risk and insulin resistance.[21,22] For example, results from the San Antonio Heart Study indicated that subjects with prehypertension are at greater risk of diabetes than those with normal BP.[23] In particular, a BP of 130–139/85–89 mm Hg was associated with incident type 2 diabetes, indicating that prehypertension subcategories may differ in diabetes risk.[23,24] Our study also found that type 2 diabetes development was associated with a BP of 130–139/85–89 mm Hg (HR, 1.48; 95% CI, 1.20–1.82) but not a BP of 120–129/80–84 mm Hg. Although the clinical impact of these BP categories requires further analysis, active BP control in the former subcategory should be considered to reduce the development of diabetes. These findings indicate the importance of glucose surveillance in prehypertensive, as well as in hypertensive subjects.

This study also found that subjects with poorly controlled BP were more likely to develop type 2 diabetes than those with controlled BP. The risk of incident diabetes was significantly higher among subjects with poorly controlled than well-controlled baseline BP, in agreement with results showing that women with BP progression over 48 months had a higher risk of developing type 2 diabetes than women without BP progression.[13] The United Kingdom Prospective Diabetes Study trial showed that strict BP control significantly reduced the risk of diabetes-related end points compared with less-tight control.[25] By contrast, we found no significant associations between BP control and incident diabetes in baseline prehypertensive and hypertensive subjects, suggesting that the relative risk-reductions observed in subjects with controlled BP are lost once the BP is higher than the normal range. Continuous monitoring of BP levels during follow-up may elucidate the mechanisms underlying these results.

The pathophysiological mechanisms explaining the association between BP and incident type 2 diabetes are not clear, but several hypotheses were proposed. High BP was shown to induce microvascular dysfunction, which may contribute to the pathophysiology of diabetes development.[26,27] Endothelial dysfunction which is related to insulin resistance is also closely associated with hypertension, and biomarkers of endothelial dysfunction were found to be independent predictors of type 2 diabetes.[28] Insulin resistance constitutes a common soil for BP, type 2 diabetes and cardiovascular disease.[29] Thus it could be other potential links between BP and type 2 diabetes.[30] In addition, inflammatory markers, especially C-reactive protein, are related to both incident type 2 diabetes and increased BP levels.[31,32]

The strengths of this study include its assessment of a prospectively enrolled community-based cohort study from the general populations followed-up for 8 years. However, this study also had several limitations. First, the study population consisted only of those aged 40–69 years. Nevertheless, our results may be representative of the general population in Korea because the data were from a community-based prospective cohort study, which may have minimized the sampling-bias effect. Second, BP control was based on measured BP values at baseline and at 8 years, and not at intermediate time points. This may have led to a misclassification of BP, with under or overestimations of the prevalence of controlled and poorly controlled BP. Because of the limitations inherent in observational studies, further intervention trials will be needed to confirm these findings. Third, some antihypertensive drugs may increase the risk of type 2 diabetes. This should be further examined. Finally, the follow-up time examining the relationship between BP and diabetes was < 10 years. Longitudinal studies with longer follow-up are needed to confirm these findings.

In conclusion, prehypertension, as well as hypertension, was a significant risk factor for incident diabetes, independent of baseline glucose status, sex and BMI. These results indicate that active BP control, including early BP management, is needed to prevent incident diabetes.

CONFLICT OF INTEREST

The authors declare no conflict interest.

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