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ORIGINAL RESEARCH

Chronic Kidney Disease Risk of Isolated Systolic or Diastolic Hypertension in Young Adults: A Nationwide Sample Based-Cohort Study

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BACKGROUND: Hypertension among young adults is common. However, the effect of isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), or systolic and diastolic hypertension (SDH) among young adults on chronic kidney disease (CKD) development is unknown.

METHODS AND RESULTS: From a nationwide health screening database, we included 3 030 884 participants aged 20 to 39 years who were not taking antihypertensives at baseline examination in 2009 to 2010. Participants were categorized as having normal blood pressure (BP), elevated BP, stage 1 IDH, stage 1 ISH, stage 1 SDH, stage 2 IDH, stage 2 ISH, and stage 2 SDH. The primary outcome was incident CKD. A total of 5853 (0.19%) CKD events occurred. With normal BP as the reference, multivariable-adjusted hazard ratios (HRs) (95% CIs) for CKD were 1.14 (95% CI, 1.04–1.26), elevated BP; 1.19 (95% CI, 1.10–1.28), stage 1 IDH; 1.24 (95% CI, 1.08–1.42), stage 1 ISH; 1.39 (95% CI, 1.28–1.51), stage 1 SDH; 1.88 (95% CI, 1.63–2.16), stage 2 IDH; 1.84 (95% CI, 1.54–2.19), stage 2 ISH; 2.70 (95% CI, 2.44–2.98), stage 2 SDH. The HRs for CKD were attenuated in the patients who were antihypertensive and began medication within 1 year of medical checkup than in those without antihypertensives.

CONCLUSIONS: Among Korean young adults, those with elevated BP, stage 1 IDH, stage 1 ISH, stage 1 SDH, stage 2 IDH, stage 2 ISH, and stage 2 SDH were associated with a higher CKD risk than those with normal BP. The CKD risk in ISH and IDH groups was similar but lower than that in the SDH group. Antihypertensives attenuated the risk of CKD in young adults with hypertension.

Key Words: blood pressure ■ chronic kidney disease ■ hypertension ■ isolated diastolic hypertension ■ isolated systolic hypertension ■ young adult

Hypertension is the most important modifiable risk factor globally for overall mortality and morbidity.[1] Hypertension also plays a crucial role in the development and progression of kidney failure.[2,3] Blood pressure (BP) rises with a declining kidney function, which in turn aggravates the hypertension. Moreover, as chronic kidney disease (CKD) worsens, BP becomes more difficult to control. Thus, it becomes a vicious cycle. Therefore, early diagnosis and prompt treatment are crucial. However, hypertension

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study demonstrating the relationship between blood pressure and chronic kidney disease (CKD) development in young adults using a well-established and validated longitudinal national database.
- Blood pressure levels greatly influenced CKD development in young adults, including the elevated blood pressure group; the risk was greater in SDH than in the ISH or IDH group and for stage 2 than stage 1 hypertension.
- Increased blood pressure was associated with increased CKD risk in young adults; antihypertensives reduced CKD risk.

What Are the Clinical Implications?

- The 2017 American College of Cardiology/American Heart Association guidelines increased the prevalence of hypertension in young adults.
- Antihypertensives reduced the risk of CKD in young adults.

Nonstandard Abbreviations and Acronyms

IDH	isolated diastolic hypertension
ISH	isolated systolic hypertension
SDH	systolic and diastolic hypertension

is usually diagnosed late in young adults and this interdependence complicates the management of both diseases. In 2017, the American College of Cardiology/American Heart Association released an updated guideline with new criteria for hypertension defining stage 1 hypertension as a systolic BP (SBP) value of 130 mm Hg through 139 mm Hg or a diastolic BP (DBP) value of 80 mm Hg through 89 mm Hg.[4] Most of the study populations according to this guideline comprised middle-aged and elderly adults, leaving a relative lack of evidence for young adults aged 20 through 39 years.

Hypertension among young people is common and affects 1 in 8 adults aged between 20 and 40 years.[1] However, the effect of isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), or systolic and diastolic hypertension (SDH) among young adults on the development of CKD is unknown. Moreover, hypertension can have harmful health effects even at a young age. In the short term, it is associated with higher rates of left ventricular hypertrophy[5] and alterations in the brain volume, suggesting that hypertension in young adults may affect cardiovascular and brain health.[6,7]

Although previous cohort studies have investigated the association of BP with cardiovascular disease among young adults,[8,9] they have not studied the association of BP with CKD. Moreover, the new definition led to an increase in the prevalence rate of hypertension, particularly among young adults.[10,11] However, the awareness and level of treatment for hypertension remains poor.[12]

This nationwide sample-based study aimed to investigate the association between the BP categories according to the 2017 American College of Cardiology/American Heart Association guidelines and the risk of CKD among young adults using the Korean National Health Insurance Service database.

METHODS

Data Availability

Because of the confidentiality of data used in this study and the strict privacy policy of the data holder stating that these data can be kept only among the designated research personnel, these data cannot be made available to others, whether or not they are made anonymous.

Study Design and Database

The Korean National Health Insurance Service database comprises the complete health information pertaining to 50 million Koreans including an eligibility database, a medical treatment database, a health examination database, and a medical care institution database.[13–15] The National Health Insurance Corporation, managed by the Korean government, is the single insurer to which ≈97% of Koreans subscribe. Enrollees of the National Health Insurance Corporation are recommended to undergo a standardized medical examination at least once every 2 years. Among 4 944 387 young adults who enrolled from 2009 to 2010 (index year), 3 233 386 participants who were available for follow up from 2013 to 2016 were selected. To avoid confounders due to preexisting diseases and minimize the potential effects of reverse causality, those who had a history of CKD before the index year were also excluded (n=111 394). Ultimately, the study sample consisted of 3 030 884 subjects (Figure 1).

This study was approved by the Chonnam National University Hospital (study approval number: CNUH-EXP-2020-228) and National Health Insurance Service, and it was conducted according to the principles of the Declaration of Helsinki. The need for written informed consent was waived by our institutional review board.

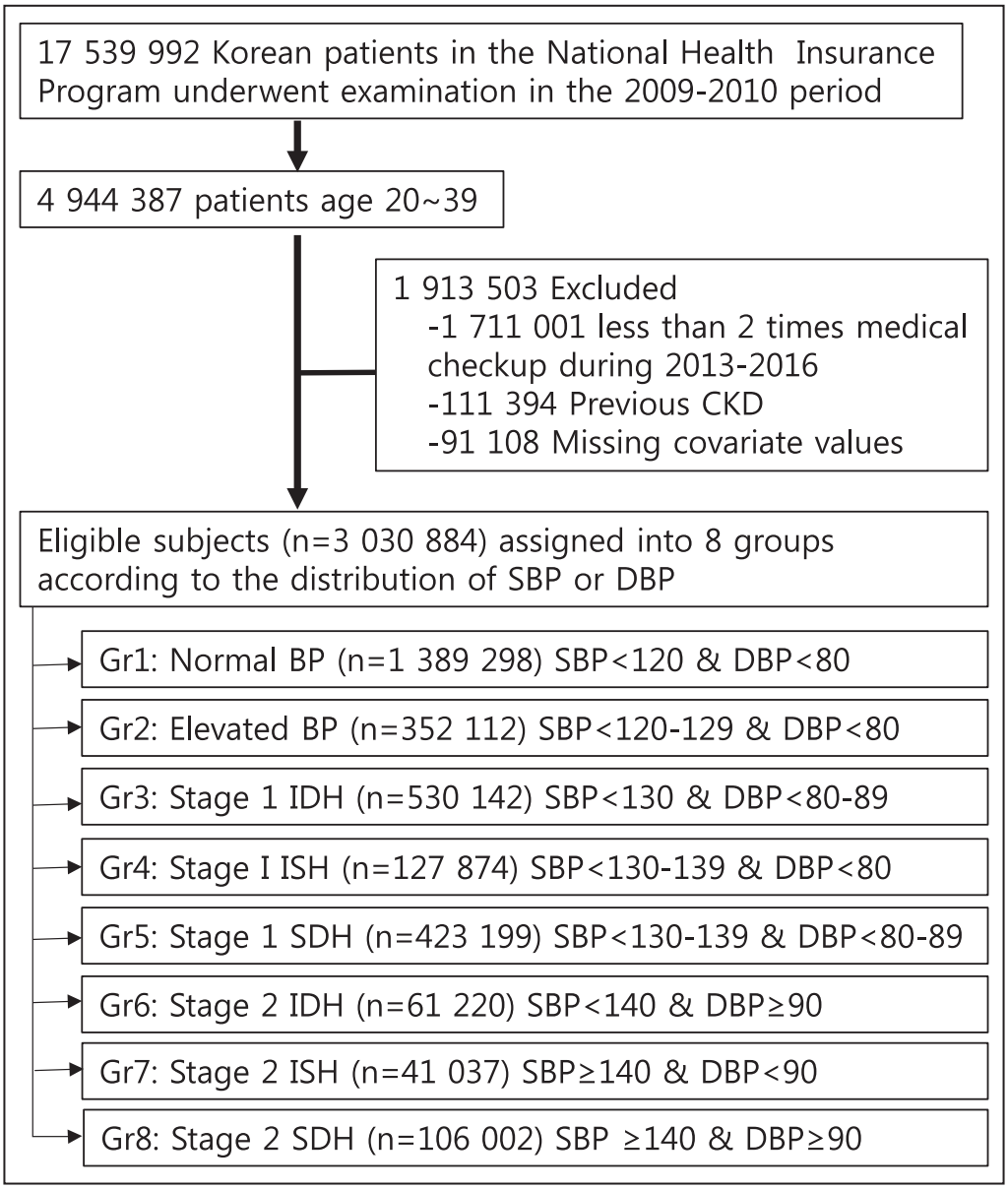

Figure 1. Flow diagram of the study.
BP indicates blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; Gr, group; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SBP, systolic blood pressure; and SDH, systolic and diastolic hypertension.

Measurements and Definitions

BP measurements were performed during the health checkup by trained medical staff using the auscultatory or oscillometric methods. The BP measurement protocol recommending at least 5 minutes of rest in a seated position followed by 2 repeated measurements at 5-minute intervals was followed.[16] Participants were categorized into 8 mutually exclusive groups: (1) normal BP (untreated SBP <120/DBP <80 mm Hg; n=1 389 298); (2) elevated BP (SBP 120–129/DBP <80 mm Hg; n=352 112); (3) stage 1 IDH (SBP <130/DBP 80–89 mm Hg; n=530 142); (4) stage 1 ISH (SBP 130–139/DBP <80 mm Hg; n=124 874); (5) stage 1 SDH (SBP 130–139/DBP 80–89 mm Hg; n=423 199); (6) stage 2 IDH (SBP <140/DBP ≥90 mm Hg; n=61 220); (7) stage 2 ISH (SBP ≥140/DBP <90 mm Hg; n=41 037); (8) stage 2 SDH (SBP ≥140/DBP ≥90 mm Hg; n=106 002). Body mass index was calculated as the participant's weight in kilograms divided by the square of the participant's height in meters. Information on the current smoking and alcohol consumption habits was obtained by a questionnaire. Heavy alcohol consumption was defined as alcohol consumption more than 30 g per day.

Regular exercise was defined as physical activity that was performed at least 5 times per week. The income level was dichotomized at the lower 25%. Blood samples for the measurement of serum glucose and total cholesterol levels were collected after overnight fasting. Proteinuria was tested by the dipstick method and defined as negative, trace, and 1+ to 4+. Comorbidities were identified using information gathered in the 1 year preceding the index date. Hypertension was defined as a previous diagnosis of hypertension as per the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes (I10–13, I15) and a history of using at least 1 antihypertensive drug, or a recorded SBP of ≥140 mm Hg, or a DBPe of ≥90 mm Hg in the health examination database. Diabetes mellitus (DM) was identified using the appropriate diagnostic codes (E11–14) and a medical history of DM or a recorded fasting serum glucose concentration of ≥126 mg/dL in the health examination database. Dyslipidemia was identified using the appropriate diagnostic code (E78) and a history of lipid-lowering drug use or a total serum cholesterol concentration of ≥240 mg/dL in the health examination database. CKD was defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2 calculated using the CKD Epidemiology Collaboration equation. The participants' blood glucose (mg/dL) and total cholesterol (mg/dL) concentrations were measured in a fasting state. The quality of the laboratory tests was warranted by the Korean Association for Laboratory Medicine, and the hospitals participating in the National Health Insurance health checkup programs are certified by the National Health Insurance Service.

Study Outcomes and Follow-Up

The study sample was followed up from the baseline period up to the date of CKD diagnosis or until December 31, 2016. The primary end point was incident CKD; it was defined using a combination of *ICD-10* codes (N18-19) and an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2 calculated using the CKD Epidemiology Collaboration equation on more than 2 occasions during the medical checkup from 2013 to 2016.

Statistical Analysis

We report the mean±SD with intervals for continuous variables and the numbers (with percentages) for categorical variables. To identify the risk of CKD using the SBP and DBP levels, we calculated the hazard ratios (HRs) with 95% CIs and analyzed these data using the Cox proportional hazard regression model. We analyzed the associations between BP levels and CKD development using 5 models—Model 1: nonadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for model 2 plus smoking, alcohol drinking, physical activity, body mass index, and low income; Model 4 adjusted for Model 3 plus dyslipidemia, DM, and estimated glomerular filtration rate. Model 5 adjusted for Model 4 and the Charlson Comorbidity Index.[17,18] We also performed subgroup analyses for clinically important variables. A $P<0.05$ was considered to reflect statistical significance. SAS version 9.3 software and SAS survey procedures (SAS Institute, Inc., Cary, NC, USA) were used for all statistical analyses.

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of the participants with respect to the development of CKD. Of the total, 5853 (0.19%) subjects developed CKD. The mean age of those who developed CKD was higher than that of those who did not. The proportion of men (72.29%), obesity (body mass index ≥25), and abdominal obesity (waist circumference ≥90 in men, ≥85 in women) was higher in the incident CKD than in the non-CKD group. Comorbidities such as DM, hypertension, dyslipidemia, CKD, and proteinuria were more prevalent in the CKD group than in the non-CKD group. The estimated glomerular filtration rate was lower and BP, total cholesterol, and glucose levels were higher in the CKD than in the non-CKD group (Table 1).

Of the total number of participants, 530 142 (17.5%) had stage 1 IDH, 127 874 (4.2%) had stage 1 ISH, 423 199 (14.0%) had stage 1 SDH, 61 220 (2.0%) had stage 2 IDH, 41 037 (1.4%) had stage 2 ISH, and 106 002 (3.5%) had stage 2 SDH. Participants across all stages and subtypes of hypertension had higher body mass index, waist circumference, fasting glucose, and triglycerides levels; more severe DM and dyslipidemia; and were more likely to be male, current smokers, and frequent alcohol users than those in the normal BP group (Table 2).

Isolated SBP or DBP and the Risk of CKD

With normal BP as the reference, the multivariable-adjusted hazard ratios (95% CIs) for CKD as the outcome were 1.14 for elevated BP, 1.19 for stage 1 IDH, 1.24 for stage 1 ISH, 1.39 for stage 1 SDH, 1.88 for stage 2 IDH, 1.84 for stage 2 ISH, and 2.70 for stage 2 SDH groups (Table 3). We also evaluated the effect of antihypertensive medications on the CKD event. Antihypertensive medications within 1 year of medical checkup reduced the CKD risk in all groups significantly (Table 3). In order to excluding the effect of baseline proteinuria between BP and CKD risk, the analysis was performed only in patients without baseline proteinuria. The result were similar to those with baseline proteinuria (Table S1).

Table 1. Baseline Characteristics of Subjects According to the Incident CKD

Group	None CKD (N=3 025 031)	CKD (N=5853)	*P* Value
Age, y	31.82±4.81	35.02±3.82	<0.0001
Sex, male (%)	2 026 248 (66.98)	4231 (72.29)	<0.0001
Current smoker	1 116 411 (36.91)	1905 (32.55)	<0.0001
Heavy drinker*	275 023 (9.09)	453 (7.74)	0.0003
Physical activity-regular	430 539 (14.23)	1084 (18.52)	<0.0001
Income-low†	449 356 (14.85)	855 (14.61)	0.596
BMI, kg/m^2	23.22±3.45	24.63±3.69	<0.0001
Obesity (BMI ≥25)	843 632 (27.89)	2585 (44.17)	<0.0001
BMI 5 level			<0.0001
<18.5	190 167 (6.29)	179 (3.06)	
18.5–23	1 358 376 (44.9)	1854 (31.68)	
23–25	632 856 (20.92)	1235 (21.1)	
25–30	727 403 (24.05)	2107 (36)	
≥30	116 229 (3.84)	478 (8.17)	
Waist circumference, cm‡	78.41±9.56	81.62±9.91	<0.0001
Abdominal obesity	401 559 (13.27)	1324 (22.62)	<0.0001
Waist circumference 5 level			<0.0001
M:<70/F:<65	277 050 (9.16)	305 (5.21)	
M:70–79/F:65–74	1 226 510 (40.55)	1785 (30.5)	
M:80–89/F:75–84	1 119 912 (37.02)	2439 (41.67)	
M:90–99/F:85–94	337 567 (11.16)	1089 (18.61)	
M:≥100/F:≥95	63 992 (2.12)	235 (4.02)	
Diabetes mellitus	57 867 (1.91)	445 (7.6)	<0.0001
Hypertension	266 654 (8.81)	1664 (28.43)	<0.0001
Dyslipidemia	219 937 (7.27)	1029 (17.58)	<0.0001
CCI score	0.32±0.66	0.64±1.1	<0.0001
CCI grade			<0.0001
0	2 299 590 (76.02)	3826 (65.37)	
1	560 852 (18.54)	1049 (17.92)	
2	120 310 (3.98)	550 (9.4)	
≥3	44 279 (1.46)	428 (7.31)	
Proteinuria			<0.0001
Negative	2 917 819 (96.7)	4865 (83.3)	
Trace	56 642 (1.88)	191 (3.27)	
1+	31 342 (1.04)	321 (5.5)	
2+	9589 (0.32)	305 (5.22)	
3+	1738 (0.06)	134 (2.29)	
4+	284 (0.01)	24 (0.41)	
Height, cm	169.13±8.17	169.63±7.86	<0.0001
Weight, cm	66.82±13.06	71.3±13.85	<0.0001
Fasting blood glucose, mg/dL	91.05±15.43	97.71±33.39	<0.0001
Systolic blood pressure, mm Hg	118.5±12.87	123.85±15.68	<0.0001
Diastolic blood pressure, mm Hg	74.38±9.27	78.29±11.13	<0.0001
Pulse pressure, mm Hg	44.12±8.23	45.55±9.16	<0.0001
Total cholesterol, mg/dL	186.4±33.74	197.74±37.97	<0.0001
Estimated glomerular filtration rate, mL/min/1.73 m^2	96.31±51.36	80.26±51.93	<0.0001

Data are presented as mean±SD or frequency (%). BMI indicates body mass index; CCI, Charlson Comorbidity Index; and CKD, chronic kidney disease.
*Alcohol consumptions ≥30 g/day.
†Low income 25%, abdominal obesity: waist circumference ≥90 in men, ≥85 in women.

Table 2. Baseline Characteristics of Study Population by Blood Pressure Group

Characteristics	Normal BP (N=1 389 298) 45.8%	Elevated BP (N=352 112) 11.6%	Stage 1 Hypertension			Stage 2 Hypertension		
			Stage 1 IDH (N=530 142) 17.5%	Stage 1 ISH (N=127 874) 4.2%	Stage 1 SDH (N=423 199) 14.0%	Stage 2 IDH (N=61 220) 2.0%	Stage 2 ISH (N=41 037) 1.4%	Stage 2 SDH (N=106 002) 3.5%
Systolic BP, mm Hg	108.01±7.25	122.65±2.99	119.63±4.89	132.6±2.89	132.22±3.07	129.35±5.77	144.66±5.82	148.64±9.41
Diastolic BP, mm Hg	67.6±5.94	71.58±4.26	80.94±2.1	73.21±4.09	82.39±3.09	91.88±3.53	81.66±4.9	96.52±6.99
Age, y	31.36±4.96	31.88±4.73	32.05±4.73	31.82±4.63	32.31±4.56	33.36±4.27	32.78±4.39	33.47±4.2
Sex (male)	692 596 (49.85)	261 205 (74.18)	400 704 (75.58)	110 465 (86.39)	376 524 (88.97)	53 459 (87.32)	37 632 (91.7)	97 894 (92.35)
Smoking								
None	868 263 (62.5)	165 406 (46.98)	238 497 (44.99)	48 718 (38.1)	146 305 (34.57)	21 780 (35.58)	13 651 (33.27)	32 562 (30.72)
Ex-	134 694 (9.7)	47 560 (13.51)	72 193 (13.62)	19 683 (15.39)	67 599 (15.97)	10 326 (16.87)	6941 (16.91)	18 390 (17.35)
Current	386 341 (27.81)	139 146 (39.52)	219 452 (41.39)	59 473 (46.51)	209 295 (49.46)	29 114 (47.56)	20 445 (49.82)	55 050 (51.93)
Drinking								
None	604 227 (43.49)	120 207 (34.14)	171 915 (32.43)	37 207 (29.1)	108 476 (25.63)	15 748 (25.72)	10 485 (25.55)	22 780 (21.49)
Mild	705 938 (50.81)	200 170 (56.85)	303 697 (57.29)	75 515 (59.05)	255 511 (60.38)	36 187 (59.11)	24 034 (58.57)	63 311 (59.73)
Heavy	79 133 (5.7)	31 735 (9.01)	54 530 (10.29)	15 152 (11.85)	59 212 (13.99)	9285 (15.17)	6518 (15.88)	19 911 (18.78)
Exercise*	178 062 (12.82)	52 651 (14.95)	79 894 (15.07)	20 899 (16.34)	67 876 (16.04)	9549 (15.6)	6604 (16.09)	16 088 (15.18)
Income†	213 877 (15.39)	55 522 (15.77)	82 512 (15.56)	18 771 (14.68)	55 067 (13.01)	7730 (12.63)	5387 (13.13)	11 345 (10.7)
Diabetes mellitus	14 286 (1.03)	6018 (1.71)	10 808 (2.04)	3058 (2.39)	13 389 (3.16)	2373 (3.88)	1954 (4.76)	6426 (6.06)
Hypertension	21 682 (1.56)	7017 (1.99)	12 495 (2.36)	3321 (2.6)	15 544 (3.67)	61 220 (100)	41 037 (100)	106 002 (100)
Dyslipidemia	66 584 (4.79)	23 737 (6.74)	42 695 (8.05)	10 775 (8.43)	46 006 (10.87)	8229 (13.44)	5526 (13.47)	17 414 (16.43)
Weight, kg	61.67±11.57	68.09±11.8	68.67±12.25	72.15±11.85	73.6±12.17	74.86±12.82	77.24±12.87	78.8±13.33
Height, cm	166.78±8.26	170.23±7.87	170.25±7.78	172.02±7.25	172.15±7.02	171.69±7.14	172.66±6.89	172.42±6.86
Waist circumference, cm	74.88±8.77	79.27±8.7	79.69±8.97	81.85±8.56	82.95±8.75	84.54±9.29	85.68±9.13	87.04±9.36
Body mass index, kg/m^2	22.04±3	23.4±3.15	23.59±3.31	24.31±3.28	24.77±3.46	25.32±3.63	25.85±3.69	<0.0001
Glucose, mg/dL	88.93±12.86	91.19±14.47	91.44±15.86	92.96±15.84	93.94±18.06	95.02±19.98	96.94±21.04	98.46±23.61
Total cholesterol, mg/dL	180.99±31.91	185.9±33.11	188.73±33.78	189.21±34.07	194.2±34.82	197.79±35.66	197.65±35.95	202.53±36.63
Estimated glomerular filtration rate, mL/min/1.73 m^2	97.22±52.97	98.25±62.55	94.86±46.11	96.87±52.56	93.6±39.82	95.17±49.71	98.46±68.25	94.25±45.57
Pulse pressure, mm Hg	40.41±5.93	51.07±4.42	38.69±4.75	59.4±4.28	49.83±3.01	37.48±6.04	62.99±7.05	52.12±8.58
Charlson Comorbidity Index	0.32±0.66	0.31±0.66	0.32±0.67	0.3±0.66	0.3±0.67	0.35±0.72	0.33±0.71	0.33±0.73
0	1 046 126 (75.3)	268 295 (76.2)	403 979 (76.2)	99 179 (77.56)	327 356 (77.35)	45 956 (75.07)	31 402 (76.52)	81 123 (76.53)
1	267 269 (19.24)	65 179 (18.51)	97 252 (18.34)	22 133 (17.31)	73 242 (17.31)	11 321 (18.49)	7182 (17.5)	18 323 (17.29)
2	57 030 (4.1)	13 782 (3.91)	20 718 (3.91)	4745 (3.71)	16 012 (3.78)	2682 (4.38)	1630 (3.97)	4261 (4.02)
≥3	18 873 (1.36)	4856 (1.38)	8193 (1.55)	1817 (1.42)	6589 (1.56)	1261 (2.06)	823 (2.01)	2295 (2.17)
Chronic kidney disease event	1940 (0.14)	597 (0.17)	1041 (0.2)	240 (0.19)	1037 (0.25)	236 (0.39)	140 (0.34)	622 (0.59)

Data are presented as mean±SD, or frequency (%).BP indicates blood pressure; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; and SDH, systolic and diastolic hypertension.
*Regular exercise: midterm exercise ≥5 days or vigorous exercise ≥3 days in a week.
†Low income 25%. *P* value for all categories <0.0001.

Table 3. Multivariable Cox Analysis for Incident CKD by Isolated Systolic or Diastolic Hypertension

BP Group	Total (n)	CKD (n)	%	HR (95% CI)				
				Model 1	Model 2	Model 3	Model 4	Model 5
Total population								
Normal	1 389 298	1940	0.14	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Elevated BP	352 112	597	0.17	1.22 (1.11–1.33)	1.17 (1.07–1.29)	1.10 (1.00–1.21)	1.14 (1.04–1.25)	1.14 (1.04–1.26)
Stage 1 IDH	530 142	1041	0.20	1.41 (1.31–1.52)	1.33 (1.23–1.43)	1.24 (1.15–1.34)	1.19 (1.10–1.28)	1.19 (1.10–1.28)
Stage 1 ISH	127 874	240	0.19	1.35 (1.17–1.54)	1.33 (1.16–1.53)	1.20 (1.05–1.38)	1.23 (1.07–1.41)	1.24 (1.08–1.42)
Stage 1 SDH	423 199	1037	0.25	1.76 (1.63–1.89)	1.63 (1.51–1.77)	1.46 (1.35–1.58)	1.38 (1.27–1.50)	1.39 (1.28–1.51)
Stage 2 IDH	61 220	236	0.39	2.77 (2.42–3.17)	2.25 (1.96–2.58)	1.94 (1.69–2.23)	1.88 (1.64–2.16)	1.88 (1.63–2.16)
Stage 2 ISH	41 037	140	0.34	2.45 (2.06–2.91)	2.15 (1.81–2.56)	1.80 (1.51–2.14)	1.82 (1.53–2.17)	1.84 (1.54–2.19)
Stage 2 SDH	106 002	622	0.59	4.22 (3.86–4.62)	3.41 (3.10–3.75)	2.81 (2.55–3.10)	2.66 (2.41–2.93)	2.70 (2.44–2.98)
P for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Population without antihypertensive medication within 1-yr after medical checkup								
Normal	1 367 616	1739	0.13	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Elevated BP	345 095	516	0.15	1.18 (1.07–1.30)	1.15 (1.04–1.27)	1.08 (0.98–1.20)	1.12 (1.02–1.24)	1.13 (1.02–1.24)
Stage 1 IDH	517 647	884	0.17	1.34 (1.24–1.46)	1.29 (1.18–1.40)	1.21 (1.11–1.31)	1.15 (1.06–1.25)	1.15 (1.06–1.25)
Stage 1 ISH	124 553	201	0.16	1.27 (1.10–1.47)	1.29 (1.11–1.49)	1.16 (1.00–1.35)	1.20 (1.03–1.39)	1.20 (1.03–1.39)
Stage 1 SDH	407 655	849	0.21	1.64 (1.51–1.78)	1.57 (1.44–1.71)	1.40 (1.28–1.53)	1.34 (1.23–1.46)	1.34 (1.23–1.47)
Stage 2 IDH	58 011	188	0.32	2.55 (2.20–2.97)	2.13 (1.83–2.49)	1.85 (1.59–2.16)	1.82 (1.56–2.13)	1.83 (1.57–2.13)
Stage 2 ISH	38 444	102	0.27	2.09 (1.71–2.55)	1.90 (1.55–2.32)	1.59 (1.30–1.95)	1.65 (1.35–2.03)	1.67 (1.36–2.04)
Stage 2 SDH	96 678	480	0.5	3.92 (3.54–4.34)	3.27 (2.94–3.63)	2.71 (2.43–3.02)	2.62 (2.35–2.93)	2.65 (2.38–2.96)
P for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Population with antihypertensive medication within 1-yr after medical checkup								
Normal	21 682	201	0.93	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Elevated BP	7017	81	1.15	1.25 (0.96–1.62)	1.14 (0.88–1.48)	1.14 (0.87–1.48)	1.17 (0.90–1.52)	1.16 (0.89–1.51)
Stage 1 IDH	12 495	157	1.26	1.36 (1.10–1.68)	1.22 (0.98–1.51)	1.22 (0.99–1.52)	1.18 (0.95–1.47)	1.19 (0.96–1.48)
Stage 1 ISH	3321	39	1.17	1.27 (0.90–1.79)	1.13 (0.79–1.60)	1.12 (0.79–1.59)	1.16 (0.82–1.65)	1.19 (0.83–1.69)
Stage 1 SDH	15 544	188	1.21	1.31 (1.07–1.60)	1.13 (0.92–1.39)	1.15 (0.93–1.42)	1.12 (0.91–1.39)	1.17 (0.94–1.44)
Stage 2 IDH	3209	48	1.50	1.62 (1.18–2.23)	1.36 (0.98–1.88)	1.37 (0.99–1.89)	1.34 (0.96–1.85)	1.37 (0.99–1.90)
Stage 2 ISH	2593	38	1.47	1.59 (1.12–2.25)	1.36 (0.96–1.94)	1.37 (0.95–1.96)	1.40 (0.98–2.01)	1.51 (1.05–2.17)
Stage 2 SDH	9324	142	1.52	1.65 (1.33–2.05)	1.41 (1.13–1.77)	1.44 (1.14–1.82)	1.44 (1.14–1.81)	1.55 (1.23–1.95)
P for trend				<0.0001	0.0037	0.007	0.0082	0.0007

Model 1: nonadjusted model. Model 2: adjusted for age, sex. Model 3: adjusted for Model 2 plus smoking, alcohol drinking, physical activity, body mass index, low income. Model 4 adjusted for Model 3 plus dyslipidemia, diabetes mellitus, and estimated glomerular filtration rate. Model 5 adjusted for Model 4 plus and Charlson Comorbidity Index. BP indicates blood pressure; CKD, chronic kidney disease; HR, hazard ratio; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; and SDH, systolic and diastolic hypertension.

BP and the Risk of CKD

We also analyzed the risk of developing CKD according to the SBP or DBP level. The risk of CKD increased with an increase in the SBP or DBP level. Patients taking antihypertensive medication within 1 year of medical checkup showed a lower risk of CKD than those not taking antihypertensive medication (Table 4, Figure 2).

Pulse Pressure and the Risk of CKD

Highest pulse pressure (Q5, pulse pressure quintile-highest) increased the risk of developing CKD. The risk of CKD was attenuated by antihypertensive medication use within 1 year of medical checkup in pulse pressure quintile (Table 5, Figure 2).

Subgroup Analyses

Subgroup analysis for the ISH and IDH groups showed that the increased CKD risk was attenuated by antihypertensive medication use within 1 year of medical checkup (Figure 3A).

In the DM and dyslipidemia subgroup analysis, the HRs for incident CKD were higher in the DM and dyslipidemia groups than in the non-DM and nondyslipidemia groups. The relative risks associated with high BP were higher in women than in men among young adults (Figure 3B).

Table 4. Multivariable Cox Analysis for Incident CKD by Systolic or Diastolic Blood Pressure Level

BP Group	Total (n)	CKD (n)	%	HR (95% CI)				
				Model 1	Model 2	Model 3	Model 4	Model 5
Systolic BP, mm Hg								
Total population								
<100	122 509	123	0.10	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
100–119	1 362 150	2009	0.15	1.47 (1.23–1.76)	1.46 (1.21–1.75)	1.35 (1.13–1.63)	1.30 (1.09–1.57)	1.31 (1.09–1.58)
120–139	1 399 186	2959	0.21	2.11 (1.76–2.53)	1.98 (1.64–2.38)	1.69 (1.41–2.04)	1.60 (1.33–1.93)	1.62 (1.35–1.95)
140–159	128 216	536	0.42	4.18 (3.43–5.08)	3.45 (2.82–4.21)	2.67 (2.18–3.27)	2.51 (2.04–3.08)	2.55 (2.08–3.13)
≥160	18 823	226	1.20	12.09 (9.70–15.07)	9.42 (7.52–11.79)	6.98 (5.55–8.77)	6.35 (5.05–7.98)	6.57 (5.22–8.26)
Population without antihypertensive medication within 1 y after medical checkup								
<100	120 834	115	0.10	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
100–119	1 340 208	1788	0.13	1.40 (1.16–1.69)	1.42 (1.17–1.71)	1.32 (1.09–1.59)	1.27 (1.05–1.53)	1.27 (1.05–1.53)
120–139	1 359 535	2474	0.18	1.91 (1.59–2.31)	1.86 (1.54–2.25)	1.60 (1.32–1.94)	1.52 (1.25–1.84)	1.53 (1.26–1.85)
140–159	118 627	401	0.34	3.56 (2.89–4.38)	3.09 (2.50–3.82)	2.41 (1.94–2.99)	2.31 (1.86–2.87)	2.34 (1.88–2.90)
≥160	16 495	181	1.10	11.65 (9.21–14.72)	9.50 (7.48–12.07)	7.10 (5.57–9.06)	6.65 (5.21–8.49)	6.80 (5.32–8.67)
Population with antihypertensive medication within 1 y after medical checkup								
<100	1675	8	0.48	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
100–119	21 942	221	1.01	2.12 (1.05–4.30)	1.87 (0.92–3.80)	1.85 (0.91–3.77)	1.79 (0.88–3.64)	1.78 (0.87–3.63)
120–139	39 651	485	1.22	2.58 (1.30–5.19)	2.04 (1.00–4.13)	2.03 (0.10–4.13)	1.96 (0.96–3.99)	1.99 (0.98–4.06)
140–159	9589	135	1.41	2.97 (1.46–6.08)	2.27 (1.10–4.69)	2.28 (1.10–4.73)	2.24 (1.08–4.64)	2.39 (1.15–4.96)
≥160	2328	45	1.93	4.10 (1.93–8.73)	3.19 (1.49–6.84)	3.26 (1.51–7.03)	3.18 (1.47–6.86)	3.47 (1.60–7.50)
Diastolic BP, mm Hg								
Total population								
<70	670 954	845	0.13	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
70–79	1 205 401	1952	0.16	1.29 (1.19–1.39)	1.27 (1.17–1.38)	1.21 (1.12–1.31)	1.12 (1.03–1.22)	1.13 (1.04–1.22)
80–89	987 307	2198	0.22	1.77 (1.63–1.92)	1.65 (1.51–1.79)	1.49 (1.37–1.62)	1.33 (1.22–1.45)	1.34 (1.23–1.45)
90–99	117 199	473	0.4	3.21 (2.87–3.60)	2.62 (2.33–2.94)	2.20 (1.95–2.48)	1.98 (1.76–2.23)	2.00 (1.77–2.25)
≥100	50 023	385	0.77	6.15 (5.45–6.94)	4.81 (4.25–5.45)	3.88 (3.41–4.41)	3.37 (2.96–3.83)	3.43 (3.01–3.90)
Population without antihypertensive medication within 1 y after medical checkup								
<70	661 231	771	0.12	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
70–79	1 182 732	1701	0.14	1.23 (1.13–1.34)	1.23 (1.13–1.34)	1.18 (1.08–1.29)	1.09 (1.00–1.19)	1.09 (1.00–1.19)
80–89	957 047	1819	0.19	1.63 (1.50–1.78)	1.56 (1.43–1.70)	1.41 (1.29–1.55)	1.27 (1.16–1.39)	1.27 (1.16–1.39)
90–99	109 457	364	0.33	2.86 (2.52–3.24)	2.41 (2.12–2.74)	2.04 (1.79–2.33)	1.87 (1.64–2.14)	1.88 (1.65–2.15)
≥100	45 232	304	0.67	5.80 (5.08–6.62)	4.70 (4.10–5.39)	3.82 (3.31–4.40)	3.39 (2.94–3.91)	3.43 (2.98–3.95)
Population with antihypertensive medication within 1 y after medical checkup								
<70	9723	74	0.76	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
70–79	22 669	251	1.11	1.46 (1.13–1.89)	1.33 (1.02–1.73)	1.34 (1.03–1.74)	1.29 (0.99–1.69)	1.31 (1.00–1.71)
80–89	30 260	379	1.25	1.65 (1.29–2.12)	1.41 (1.09–1.83)	1.43 (1.10–1.86)	1.35 (1.04–1.75)	1.40 (1.07–1.82)
90–99	7742	109	1.41	1.86 (1.38–2.51)	1.54 (1.13–2.09)	1.57 (1.15–2.14)	1.50 (1.10–2.05)	1.58 (1.16–2.16)
≥100	4791	81	1.69	2.24 (1.63–3.08)	1.86 (1.34–2.58)	1.93 (1.38–2.69)	1.82 (1.31–2.55)	2.01 (1.43–2.81)

Model 1: nonadjusted model. Model 2: adjusted for age, sex. Model 3: adjusted for Model 2 plus smoking, alcohol drinking, physical activity, body mass index, low income. Model 4 adjusted for Model 3 plus dyslipidemia, diabetes mellitus, and estimated glomerular filtration rate. Model 5 adjusted for Model 4 plus and Charlson Comorbidity Index. BP indicates blood pressure; CKD, chronic kidney disease; and HR, hazard ratio.

DISCUSSION

The present study demonstrated that increased levels of both SBP and DBP were associated with a higher risk of CKD in young adults aged 20 to 39 years. Not only the SBP but also the DBP level was associated with an increased risk of CKD. Moreover, patients not taking any antihypertensives within 1 year of medical checkup showed a higher CKD risk than those commencing antihypertensive medication within 1 year of medical checkup. Young adults with stage 1 ISH, IDH, or SDH all had a significantly higher risk for CKD events than those with normal BP. The risk of CKD associated with stage 1 ISH and stage 1 IDH was similar but lower

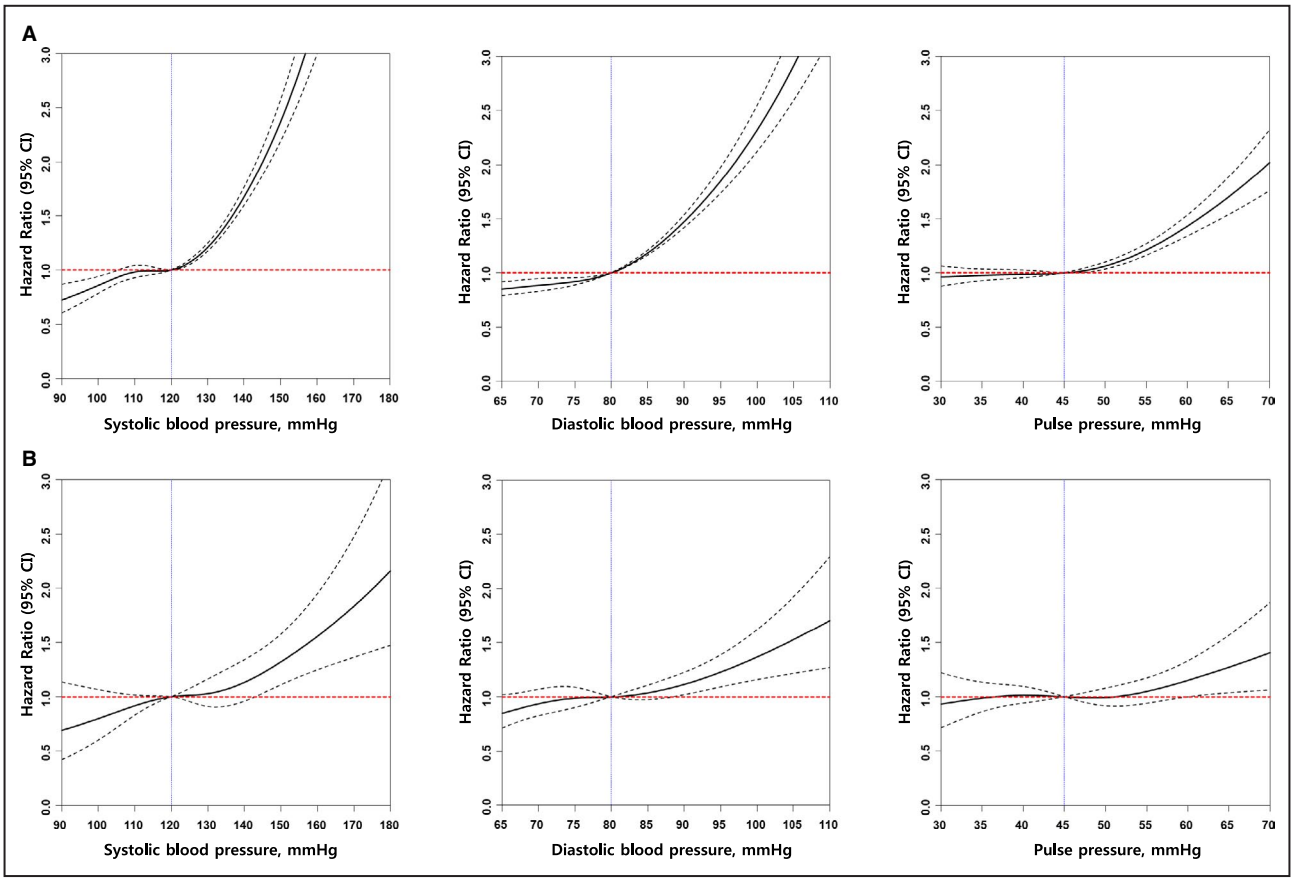

Figure 2. Hazard ratios for chronic kidney disease according to index systolic blood pressure, diastolic blood pressure and pulse pressure in young adult without anti-hypertensive medication within 1 y after medical checkup (A) and with anti hypertensive medication within 1 y after medical checkup (B).
Adjusted for age, sex, income-low 25%, diabetes mellitus, hypertension, dyslipidemia, current smoker, alcohol consumption, regular exercise, and estimated glomerular filtration rate.

than the risk of CKD associated with stage 1 SDH. As expected, the increase in the risk of CKD associated with ISH, IDH, and SDH was greater in participants with stage 2 than in those with stage 1 hypertension.

The presence of hypertension at a young age increases the risk of cardiovascular events at middle age.[19] It contributes to early-onset coronary heart disease, heart failure, stroke, and transient ischemic attacks.[20] Although good national guidelines exist, the guidelines do not serve low-risk young patients with hypertension as effectively as they do older patients. Furthermore, risk assessment is challenging in young patients because of the limited validity of and a greater focus on SBP that is less well correlated with cardiovascular disease outcomes.[19,21] Furthermore, the mechanisms underlying ISH and those underlying IDH among young adults may differ. A higher systemic vascular resistance is a major contributor to high DBP, whereas increased aortic stiffness and a reduced aortic diameter contribute to high SBP among young adults.[22] However, in the current study, the CKD risk associated with stage 1 ISH and IDH was comparable.

Whether ISH of the young is a benign condition caused by increased SBP amplification with increased brachial but normal central SBP[23,24] or results from increased arterial stiffness and a larger stroke volume that may evolve into sustained hypertension is debatable.[22,25,26] Consequently, it is still unclear whether BP-lowering therapy would benefit young adults with ISH. Most young adults with stage 1 hypertension have a low absolute 10-year atherosclerotic cardiovascular disease risk and thus would not be suitable candidates for pharmacological interventions.[10,11] However, after cumulative exposure to high BP levels, a decrease in BP levels later in life may not completely restore the risk of cardiovascular disease to normal levels in such individuals.[27] Therefore, young adults with stage 1 hypertension should be subjected to further risk stratification to identify those individuals who would benefit from pharmacological therapy in conjunction with lifestyle changes. In the current study, stage 1 hypertension group subjects were associated with a significantly higher risk of CKD than those with normal BP or elevated BP. Moreover, the risk of CKD

Table 5. Multivariable Cox Analysis for Incident CKD by Pulse Pressure Quintile

Pulse Pressure Quintile	Total (n)	CKD (n)	%	HR (95% CI)				
				Model 1	Model 2	Model 3	Model 4	Model 5
Systolic blood pressure								
Total population								
Q1	440 377	753	0.17	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2	679 067	1202	0.18	1.04 (0.95–1.13)	1.02 (0.93–1.11)	0.99 (0.90–1.09)	0.95 (0.86–1.04)	0.95 (0.87–1.05)
Q3	687 095	1210	0.18	1.03 (0.94–1.13)	1.07 (0.98–1.17)	1.02 (0.93–1.12)	1.03 (0.94–1.13)	1.03 (0.94–1.13)
Q4	633 211	1280	0.20	1.18 (1.08–1.29)	1.18 (1.08–1.29)	1.09 (0.99–1.19)	1.07 (0.98–1.18)	1.09 (0.99–1.19)
Q5	591 134	1408	0.24	1.39 (1.28–152)	1.38 (1.27–1.51)	1.22 (1.12–1.34)	1.27 (1.16–1.39)	1.29 (1.18–1.41)
P for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Population without antihypertensive medication within 1 y after medical checkup								
Q1	431 789	659	0.15	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2	664 736	1025	0.15	1.01 (0.92–1.11)	1.02 (0.92–1.12)	0.99 (0.90–1.10)	0.95 (0.86–1.05)	0.95 (0.86–1.05)
Q3	671 842	1018	0.15	0.99 (0.9–1.10)	1.03 (0.94–1.14)	0.99 (0.90–1.09)	0.99 (0.90–1.09)	0.99 (0.90–1.10)
Q4	615 220	1087	0.18	1.16 (1.05–1.28)	1.17 (1.06–1.29)	1.08 (0.98–1.19)	1.08 (0.98–1.19)	1.08 (0.98–1.19)
Q5	572 112	1170	0.20	1.34 (1.22–1.48)	1.35 (1.22–1.48)	1.20 (1.09–1.32)	1.26 (1.14–1.38)	1.26 (1.15–1.39)
P for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Population with antihypertensive medication within 1 yr after medical checkup								
Q1	9196	99	1.08	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2	23 061	277	1.20	1.12 (0.89–1.41)	1.07 (0.85–1.35)	1.07 (0.85–1.35)	1.04 (0.83–1.32)	1.05 (0.83–1.33)
Q3	8073	100	1.24	1.15 (0.87–1.52)	1.04 (0.78–1.38)	1.03 (0.77–1.36)	1.05 (0.79–1.40)	1.06 (0.79–1.40)
Q4	18 819	212	1.13	1.05 (0.82–1.33)	0.95 (0.74–1.21)	0.94 (0.73–1.19)	0.93 (0.73–1.19)	0.96 (0.75–1.23)
Q5	16 036	206	1.28	1.20 (0.94–1.52)	1.14 (0.90–1.46)	1.12 (0.88–1.43)	1.15 (0.90–1.47)	1.20 (0.94–1.53)
P for trend				0.3673	0.6902	0.8583	0.5599	0.3338

Model 1: nonadjusted model. Model 2: adjusted for age, sex. Model 3: adjusted for Model 2 plus smoking, alcohol drinking, physical activity, body mass index, low income. Model 4 adjusted for Model 3 plus dyslipidemia, diabetes mellitus, and estimated glomerular filtration rate. Model 5 adjusted for Model 4 plus and Charlson Comorbidity Index. BP indicates blood pressure; and HR, hazard ratio.

posed by simultaneous elevation of the SBP and DBP (SDH group) was higher than that posed by isolated elevation of either. In addition, in our study antihypertensive therapy reduced the risk of CKD even in young adults with stage 1 ISH. These results may support the new 2017 American College of Cardiology/American Heart Association BP guideline regarding the CKD risk among young adults. This guideline was based on the fact that the SPRINT (Systolic Blood Pressure Intervention Trial) was prematurely ceased because ofthe benefit of being able to control the SBP levels of hypertensive patients to <120 mm Hg rather than <140 mm Hg, thus supporting the aim for a low SBP.[28]

Previous studies have reported that compared with the BP pattern in men, women tend to show a steeper elevation in BP with age, starting from young adulthood and continuing throughout life.[29] The possible explanations include sex differences in the vascular biology, hormonal factors, and social determinants of health.[30] The relative risk of cardiovascular disease associated with high BP levels is also higher in women than in men among young to middle-aged adults.[31] In this study, the subgroup analysis for sex also showed that the CKD risk was higher in women than in men, but the antihypertensive medication group did not reveal any differences between men and women. Our results warrant further testing in an independent cohort to verify if CKD outcomes associated with BP differ according to the sex.

The strengths of this study include the large nationwide longitudinal health screening database with high participation and outcome ascertainment rates owing to electronic linkages to universal health insurance records. This database covers a wide range of the Korean sample over a long follow-up duration and, hence, allows inclusion of a sizable number of young adults. The events in these young participants are considered premature CKD, an important sample health outcome measure, yet one that has rarely been studied in a large sample size.

However, our study also has some limitations. First, although the 2017 American College of Cardiology/American Heart Association guidelines recommend that ≥2 BP readings be obtained before determining the stage of BP, in the current study, participants were classed based on their BP readings assessed during a single visit. The examination protocol recommends that the BP be measured twice and the average reading be

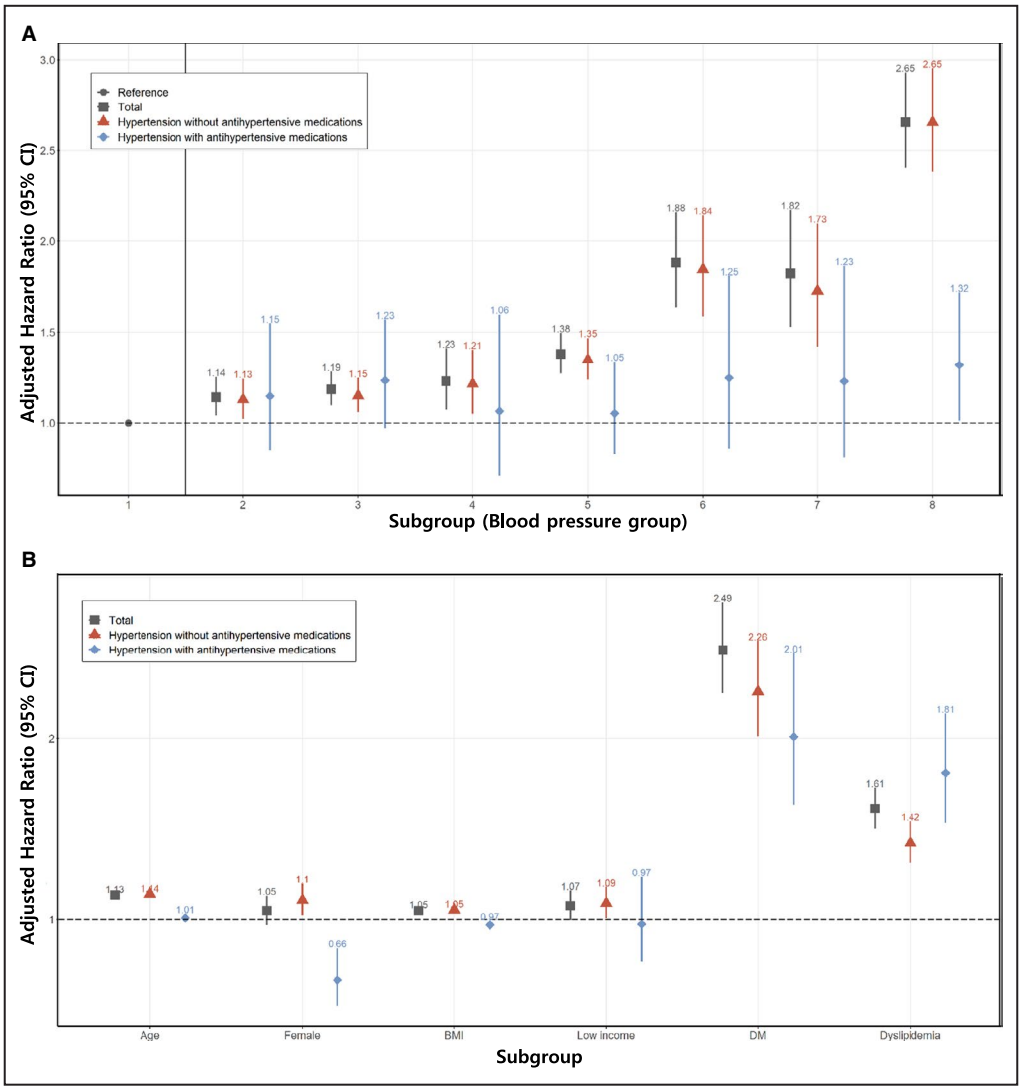

Figure 3. Subgroup analysis for chronic kidney disease risk.
A, Blood pressure group. **B**, Age, sex, BMI, DM, dyslipidemia. BMI indicates body mass index; and DM, diabetes mellitus.

used for the analysis. However, in a real-world screening environment taking place on a nationwide scale, adherence to the protocol may be limited. Therefore, the BP measurements used for the classification might not have fully reflected an individual's BP phenotype. Second, possible residual confounding, including sodium intake and psychological factors, may affect the association between BP and CKD events. Third, our study was based on Korean adults subscribing to a universal health insurance and screening program; the results should be interpreted with caution when applied to different populations or healthcare systems. Fourth, because cause and effect are not established, there is a possibility that worsening hypertension was the result of CKD in some of the people in the database. Finally, the role of antihypertensives such as renin-angiotensin-aldosterone system blockers in delaying the progression of CKD is known, but the impact of the type of antihypertensive medication prescribed was not considered in this study.

CONCLUSIONS

In conclusion, among Korean young adults, those with elevated BP, stage 1 IDH, stage 1 ISH, stage 1 SDH, stage 2 IDH, stage 2 ISH, and stage 2 SDH were associated with a higher CKD risk than those with normal BP. The CKD risk associated with ISH and IDH was comparable but lower than the risk associated with SDH. Antihypertensive medications attenuated the risk of CKD in young adults with hypertension.

PERSPECTIVES

This is the first study describing the relationship between BP and the development of CKD in young adults using a well-established and validated longitudinal national database. Our study demonstrated the enormous impact of BP on the development of CKD in young adults, even in those with elevated BP. The risk was greater in the SDH group than in the ISH or IDH group and more prominent for stage 2 hypertension than for stage 1 hypertension. Although antihypertensive therapy reduced the risk of CKD, we did not evaluate the impact of the class of the drug, and further studies are needed to clearly establish the effect of antihypertensive medication on the risk of CKD events in hypertension of the young.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable cox analysis for incident CKD by isolated systolic or diastolic hypertension excluding patients with baseline proteinuria.

BP group	Total (n)	CKD (n)	%	HR (95% Confidence interval)				
				Model1	Model2	Model3	Model4	Model5
Total population								
Normal	1 367 524	1 764	0.13	1(ref.)	1(ref.)	1(ref.)	1(ref.)	1(ref.)
Elevated BP	346 756	516	0.15	1.12(1.02-1.24)	1.09(0.98-1.20)	1.03(0.93-1.14)	1.06(0.96-1.18)	1.06(0.96-1.18)
Stage 1 IDH	521 413	931	0.18	1.36(1.25-1.47)	1.28(1.18-1.39)	1.21(1.12-1.32)	1.15(1.06-1.25)	1.16(1.06-1.25)
Stage 1 ISH	125 934	200	0.16	1.23(1.07-1.43)	1.23(1.06-1.42)	1.12(0.96-1.30)	1.14(0.98-1.33)	1.15(0.99-1.33)
Stage 1 SDH	415 750	867	0.21	1.64(1.51-1.78)	1.53(1.40-1.66)	1.38(1.27-1.51)	1.31(1.20-1.43)	1.31(1.21-1.43)
Stage 2 IDH	59 815	196	0.33	2.58(2.23-2.99)	2.09(1.80-2.43)	1.84(1.58-2.14)	1.78(1.53-2.11)	1.78(1.53-2.07)
Stage 2 ISH	40 062	115	0.29	2.28(1.89-2.75)	2.01(1.66-2.42)	1.71(1.41-2.06)	1.73(1.43-2.10)	1.74(1.44-2.11)
Stage 2 SDH	102 263	467	0.46	3.58(3.23-3.96)	2.89(2.60-3.21)	2.42(2.17-2.70)	2.30(2.06-2.57)	2.33(2.08-2.60)
P for trend				<.0001	<.0001	<.0001	<.0001	<.0001

HR, hazard ratio; BP, blood pressure; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic and diastolic hypertension. Model 1: non-adjusted model. Model 2: adjusted for age, sex. Model 3: adjusted for model 2 plus smoking, alcohol drinking, physical activity, BMI, low income. Model 4 adjusted for model 3 plus dyslipidemia, DM and eGFR. Model 5 adjusted for model 4 plus and Charlson Comorbidity Index.