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Title

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Associations of Systolic Blood Pressure With Incident CKD G3-G5: A Cohort Study of South Korean Adults

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Rationale & Objective: Clinical practice guidelines recommend a target blood pressure (BP) < 130/80 mm Hg to reduce cardiovascular risk. However, the optimal BP to prevent chronic kidney disease (CKD) is unknown.

Study Design: Population-based retrospective cohort study.

Setting & Participants: 10.5 million adults who participated in the National Health Insurance Service National Health Checkup Program in South Korea between 2009 and 2015 and had an estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2 at the beginning of follow-up.

Predictors: Baseline and time-updated systolic BP (SBP) as a continuous variable and categorized as <110, 110 to 119, 120 to 129, 130 to 139, or ≥140 mm Hg.

Outcome: Incident CKD GFR categories 3 to 5 (CKD G3-G5), defined as de novo development of estimated GFR < 60 mL/min/1.73 m^2 for at least 2 consecutive assessments confirmed at least 90 days apart.

Analytical Approach: Cox proportional hazards regression for baseline BP and marginal structural analysis for time-updated BP.

Results: During 49,169,311 person-years of follow-up, incident CKD G3-G5 developed in 172,423 (1.64%) individuals with a crude event rate of 3.51 (95% CI, 3.49-3.52) per 1,000 person-years. Compared to a baseline SBP of 120 to 129 mm Hg, HRs for incident CKD G3-G5 for the <110, 110 to 119, 130 to 139, and ≥140 mm Hg categories were 0.84 (95% CI, 0.82-0.85), 0.92 (95% CI, 0.91-0.94), 1.11 (95% CI, 1.09-1.12), and 1.30 (95% CI, 1.28-1.31), respectively. For time-updated SBPs, corresponding HRs were 0.57 (95% CI, 0.56-0.59), 0.79 (95% CI, 0.78-0.80), 1.58 (95% CI, 1.55-1.60), and 2.49 (95% CI, 2.45-2.53), respectively. Treated as a continuous exposure, each 10–mm Hg higher SBP was associated with 35% higher risk for incident CKD G3-G5 (95% CI, 1.35-1.36).

Limitations: Use of *International Classification of Diseases* codes to assess comorbid condition burden; residual confounding, and potential selection bias cannot be excluded.

Conclusions: In this large national cohort study, higher SBPs were associated with higher risk for incident CKD G3-G5. These findings support evaluation of SBP-lowering strategies to reduce the development of CKD.

Hypertension is common worldwide and directly contributes to many public health problems, such as coronary artery disease, heart failure, stroke, and chronic kidney disease (CKD).[1] According to a World Health Organization report,[2] ~40% of adults in the age range of 25 years and older had an elevated blood pressure (BP) in 2008, defined as systolic BP (SBP) ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of antihypertensive medications. Therefore, BP control is of paramount importance in preventing hypertension-related complications. Many clinical trials have demonstrated the beneficial effects of lowering BP on major adverse cardiovascular events. However, there have been conflicting reports with respect to the optimal BP target.

The kidney is a major target organ affected by elevated BP, and hypertensive nephrosclerosis is the second-most common cause of kidney failure.[3] Long-term elevations in BP can lead to a decline in kidney function through various mechanisms.[4-6] Most guidelines recommend a BP target of <140/90 mm Hg for primary prevention of CKD.[7-11] In addition, it is also recommended that BP be lowered to <130/80 mm Hg in the presence of albuminuria according to the KDIGO (Kidney Disease: Improving Global Outcomes) CKD guideline.[7] However, it should be noted that these recommendations are largely based on secondary analyses of randomized controlled trial (RCT) data in which kidney disease outcomes were considered as secondary end points.[7] In addition, most of these studies included individuals who had SBPs > 130 mm Hg or received antihypertensive medications and were at heightened risk for cardiovascular disease. Interestingly, with respect to kidney disease outcomes, these mentioned RCTs have not demonstrated the beneficial effects of BP < 130/80 mm Hg in the prevention of incident CKD or attenuation of CKD progression.[12-18] This is in contrast to healthy people with few comorbid conditions, for whom observational studies have shown an incrementally lower risk for CKD at BP ranges even <120/80 mm Hg.[19-21]

Hence there remains considerable uncertainty regarding the optimal BP level in the primary prevention of CKD, particularly among healthy adults without underlying kidney disease. To address this knowledge gap, we sought to determine the association between SBP and the

development of incident CKD glomerular filtration rate (GFR) categories 3 to 5 (CKD G3-G5) using a large and contemporary national database with detailed longitudinal data and exceptional capture of a large proportion of the Korean population (~10.5 million residents, or ~20% of the nation's population).

Methods

Data Source and Study Population

We obtained data from the Korean National Health Insurance Service (NHIS) database. The NHIS covers compulsory health insurance for all citizens in Korea and provides cost-free annual or biennial health screening examinations to all insured individuals. Because Korea has a single-payer national health system, all medical records of covered in- and outpatient visits and results from the national health examinations are centralized in the NHIS database, which includes diagnostic codes, procedures, prescriptions, medical costs, and personal information.[22,23]

Participants who underwent NHIS health examination during January 1, 2009, to December 31, 2015, were included in the study. We first identified 10,810,233 individuals who at their first examination (baseline examination), were 40 years or older, had estimated GFR (eGFR) ≥ 60 mL/min/1.73 m^2, and had at least 3 or more eGFR assessments during follow-up. We then excluded individuals who had extremely high eGFR (defined as >99.75th percentile, ie, >130.3 mL/min/1.73 m^2; n = 23,380) or had missing data for core study variables (eg, smoking status, alcohol consumption, physical activity, height, weight, lipid profiles, or urinalysis; n = 277,084) at the time of baseline examination. We also excluded those with outlier SBPs at baseline (defined as <0.1st percentile or >99.9th percentile of observed values, ie, <85 or >190 mm Hg, respectively; n = 14,199). Therefore, the final study population comprised 10,495,570 participants (Fig S1).

The study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of NHIS Ilsan Hospital. Given the large sample size, nonintrusive nature of the research study, and anonymity of subjects, the requirement for written consent was waived.

Data Collection and Measurements

Data for lifestyle behaviors, body anthropometry, and laboratory results were longitudinally collected at every health examination visit from the general health examinations database. Information regarding smoking status, alcohol consumption, and physical activity were ascertained by self-administered questionnaires. Comorbid conditions (eg, diabetes [E10~14], ischemic heart disease [I20~I25], congestive heart failure [I10.1, I13.0, I13.2, I25.5, I42, and I50], peripheral artery disease [I702],

cerebrovascular disease [I60~I64 and G459], chronic obstructive pulmonary disease [J43 and J44], and malignancy [C00~C97]) were assessed using the *International Statistical Classification of Disease and Related Health Problems, Tenth Revision* (ICD-10) coding algorithms from the medical claim database. At least 2 or more diagnostic codes identified from January 1, 2008, to the date of baseline examination were used to determine these comorbid conditions. Use of antihypertensives or HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase inhibitors (ie, statins) was defined as the presence of a prescription for these medications identified for 3 or more months within the year before each examination.

BP was measured in the same manner following the standard protocol during the entire follow-up period using digital or automatic monitors after a 5-minute rest in the sitting position. If the initially measured SBP was ≥120 mm Hg or diastolic BP was ≥80 mm Hg, BP was re-measured with at least 2-minute intervals and the mean of 3 BP readings was used as the BP value for each visit. Body mass index was calculated as weight in kilograms divided by height in meters squared. Lipid levels and serum creatinine concentrations were measured from specimens collected while fasting. Serum creatinine was measured using the isotope-dilution mass spectrometry–traceable method and GFR was estimated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation.[24] Urinalysis was performed by urine dipstick based on random spot urine measurements, and the presence of proteinuria was defined as trace or ≥1+.

Exposure and Outcome Ascertainment

The exposure of interest was time-updated SBP, which was analyzed as: (1) a continuous variable in 10–mm Hg increments, and (2) a categorical variable in which SBP was parsed into 5 groups (<110, 110-119, 120-129, 130-139, and ≥140 mm Hg) to determine the association of longitudinal SBP measurements with risk for incident CKD G3-G5. In the latter analyses, we defined the 120– to 129–mm Hg category as the reference group based on thresholds for defining hypertension recommended by the recent clinical practice guidelines[11] to granularly investigate CKD risk associated with low and high SBP categories. In secondary analyses, we also examined baseline SBP.

The primary outcome of interest was de novo development of incident CKD G3-G5, defined as eGFR < 60 mL/min/1.73 m^2 for at least 2 consecutive measurements at least 90 days apart. At-risk time began the day after the baseline examination and the study observation closed on December 31, 2015. Participants were censored at the date of the last health examination.

Statistical Analysis

To determine the effects of SBP on incident CKD G3-G5 while accounting for changes in SBP over time and to address potential time-dependent confounding based on

examination of other time-dependent covariates, we conducted marginal structural Cox models (MSMs) with stabilized inverse probability of treatment and censoring weights (Item S1).[25–27] We first fit multinomial logistic regression models to obtain the inverse probability of treatment (exposure to SBP categories) and censoring weights (being uncensored) in each visit from the date of baseline examination to end of follow-up (date of CKD G3-G5 diagnosis or last health examination, whichever came first), as a function of both baseline (age, sex, comorbid conditions, smoking status, alcohol intake, physical activity, and eGFR) and time-dependent covariates (use of any antihypertensive medications, use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, use of statins, body mass index, proteinuria, low-density lipoprotein cholesterol level, triglyceride level, and high-density lipoprotein cholesterol level). These inverse weights were stabilized by each inverse probability multiplied by the probability of treatment (for treatment weights) and censoring (for censoring weights) estimated by logistic regression including baseline covariates. After calculating the final stabilized weight by multiplying the treatment and censoring weights, we finally truncated stabilized weights at below the 0.1st or above the 99.9th percentiles to improve precision. This method creates a pseudo-population using inverse probability of treatment and censoring weights by which the covariate distributions become balanced across a priori selected SBP categories.[28–32]

In the main analyses of MSM, we used mean SBP up to the current study visit (ie, by averaging all previous SBP measurements) to summarize the exposure history over an extended period (ie, exposure window). To test the robustness of association between SBPs during the entire study period and risk for incident CKD G3-G5, we additionally performed sensitivity analyses using the percentage of time being spent in each SBP category.[27,28]

Furthermore, we also conducted Cox proportional hazard models with baseline SBP as a predictor, adjusting for all baseline covariates that were described in the MSMs as above. We then performed competing-risk analyses with subdistribution hazard modeling to confirm the associations observed in Cox models.[33] In this model, all participants were followed up until the date of the studied event, death, or end of the study period, whichever occurred first.

For sensitivity analyses, we additionally explored the continuous potentially nonlinear relationship by using adjusted restricted cubic spline models with 4 knots. The risk for incident CKD G3-G5 was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Data from descriptive analyses were summarized using mean ± standard deviation, median with interquartile range (IQR), or proportions. All analyses were performed using SAS, version 9.4 (SAS Institute Inc), and Stata, version 15.1 (Stata Corp).

Results

Study Population

Baseline characteristics of the 10,495,570 participants who met eligibility criteria for the study are shown in Table 1. Median age of study participants was 53 (IQR, 44-60) years, among whom 50% were men, 10% had diabetes, and 8% had receipt of antihypertensive medications at the time of cohort entry. Mean and median baseline SBP values were 123 ± 15 mm Hg and 120 (IQR, 112-131) mm Hg, respectively. Individuals in the higher baseline SBP categories were more likely to be older, have a higher prevalence of comorbid conditions, and have higher body mass index than those in the lower SBP categories. In addition, those with higher SBPs were more likely to have dyslipidemia, lower eGFRs, and proteinuria.

During a median follow-up of 4.7 (IQR, 3.9-5.8) years (49,169,311 patient-years of follow-up), 172,423 (1.64%) incident CKD G3-G5 events occurred, with a crude incident rate of 3.51 (95% CI, 3.49-3.52) per 1,000 person-years. In the baseline SBP categories of <110, 110 to 119, 120 to 129, 130 to 139, and ≥140 mm Hg, crude incident rates were 1.61 (95% CI, 1.58-1.64), 2.39 (95% CI, 2.36-2.41), 3.06 (95% CI, 3.03-3.09), 4.36 (95% CI, 4.32-4.39), and 6.85 (95% CI, 6.79-6.92) per 1,000 person-years, respectively. A total of 11.2%, 13.8%, 13.2%, 14.3%, and 9.7% of participants consistently were within each of these SBP categories, respectively, at all study visits.

SBP and Risk for Incident CKD G3-G5

In the primary analyses adjusted for sociodemographic, comorbid condition, anthropometric, medication, and laboratory covariates, there was a graded association between incrementally higher SBP and increasingly higher risk for incident CKD G3-G5 (Fig 1). In analyses examining SBP as a continuous variable, each 10–mm Hg increment in time-updated SBP was significantly associated with 35% higher risk for incident CKD G3-G5. Multivariable-adjusted Cox models of baseline SBP also showed similar findings (9% higher risk for every 10–mm Hg greater value). In categorical analyses, compared with the time-updated SBP reference group of 120 to 129 mm Hg, HRs among a priori defined SBP categories (<110, 110-119, 130-139, and ≥140 mm Hg) were 0.57 (95% CI, 0.56-0.59), 0.79 (95% CI, 0.78-0.80), 1.58 (95% CI, 1.55-1.60), and 2.49 (95% CI, 2.45-2.53), respectively (Table 2). Furthermore, individuals with persistent time-updated SBPs of 130 to 139 and ≥140 mm Hg had 1.30- and 1.79-fold higher risks for incident CKD G3-G5 than those with the time-updated SBP reference group of 120 to 129 mm Hg (Table S1).

Similar associations were also observed in traditional Cox models with baseline SBP; the corresponding HRs were 0.84 (95% CI, 0.82-0.85), 0.92 (95% CI, 0.91-0.94), 1.11 (95% CI, 1.09-1.12), and 1.30 (95% CI,

Table 1. Baseline Characteristics of 10,495,570 Individuals Stratified by Baseline SBP

Characteristic	Overall	SBP, mm Hg				
		<110	110-119	120-129	130-139	≥140
No.	10,495,570	1,423,596	2,545,558	2,621,866	2,520,637	1,383,913
Age, y	52.7 ± 9.9	49.5 ± 8.4	51.1 ± 9.3	52.3 ± 9.6	54.3 ± 10.1	57.2 ± 10.3
Male sex	49.7%	31.9%	46.2%	52.6%	57.6%	55.7%
Comorbid conditions						
Diabetes	10.3%	6.0%	8.1%	10.1%	12.3%	15.1%
IHD	5.0%	3.3%	4.1%	4.9%	5.7%	7.1%
CHF	0.8%	0.5%	0.7%	0.7%	0.9%	1.2%
CBVD	2.6%	1.6%	2.0%	2.5%	3.2%	4.1%
PAD	0.4%	0.3%	0.3%	0.4%	0.5%	0.6%
COPD	1.8%	1.3%	1.6%	1.7%	2.0%	2.3%
Malignancy	2.6%	2.7%	2.5%	2.5%	2.5%	2.6%
Antihypertensives at BL	8.1%	2.8%	5.0%	7.4%	10.7%	15.3%
ACEi or ARB	3.5%	1.1%	2.1%	3.3%	4.7%	6.8%
CCB	2.2%	0.5%	1.2%	2.0%	3.0%	4.6%
Diuretics	1.7%	0.6%	1.1%	1.6%	2.3%	3.2%
Antihypertensives at last visit	15.0%	4.2%	8.3%	12.9%	20.1%	33.2%
ACEi or ARB	6.6%	1.8%	3.6%	5.6%	8.8%	14.8%
CCB	4.8%	0.9%	2.3%	4.0%	6.7%	11.6%
Diuretics	2.7%	0.8%	1.5%	2.4%	3.6%	6.0%
Statins at BL	4.0%	2.5%	3.3%	4.1%	4.8%	5.5%
Statins at last visit	8.3%	5.1%	6.8%	8.2%	9.9%	11.7%
Smoking status						
Never	63.6%	73.7%	65.4%	61.6%	59.2%	61.5%
Former	15.8%	9.9%	14.1%	16.8%	18.5%	18.2%
Current	20.6%	16.4%	20.5%	21.6%	22.3%	20.2%
Alcohol intake						
0 g/d	57.1%	65.9%	59.2%	55.7%	53.3%	53.9%
1-19 g/d	30.2%	27.8%	30.4%	31.3%	31.0%	28.5%
≥20 g/d	12.7%	6.3%	10.4%	13.1%	15.7%	17.6%
Physical activity						
<600 MET-min/wk	48.2%	50.4%	48.1%	47.4%	47.2%	49.3%
600-3,000 MET-min/wk	43.4%	42.3%	43.8%	44.1%	43.8%	41.7%
>3,000 MET-min/wk	8.4%	7.3%	8.1%	8.5%	8.9%	9.0%
Proteinuria	4.6%	3.8%	3.8%	4.3%	4.8%	6.9%
SBP, mm Hg	123.3 ± 15.0	101.2 ± 5.2	113.2 ± 3.4	122.5 ± 3.1	132.7 ± 3.2	149.1 ± 9.8
BMI, kg/m²	24.0 ± 3.4	22.5 ± 2.7	23.5 ± 2.8	24.1 ± 2.9	24.6 ± 4.5	25.1 ± 3.2
eGFR, mL/min/1.73 m²	88.2 ± 14.3	90.6 ± 14.6	89.0 ± 14.4	88.4 ± 14.3	87.2 ± 14.1	86.1 ± 14.0
LDL-C, mg/dL	118.6 ± 73.0	116.2 ± 65.0	118.2 ± 79.8	118.9 ± 61.9	119.5 ± 75.2	119.7 ± 82.4
HDL-C, mg/dL	55.5 ± 26.9	57.2 ± 25.7	55.9 ± 26.8	55.3 ± 26.6	54.8 ± 27.0	54.9 ± 28.4
Triglycerides, mg/dL	137.6 ± 101.8	106.7 ± 75.8	125.9 ± 90.7	138.9 ± 101.2	151.6 ± 108.5	163.0 ± 120.0

Note: Data are presented as mean ± standard deviation or percentage.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BL, baseline; BMI, body mass index; CBVD, cerebrovascular disease; CCB, calcium channel blocker; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; PAD, peripheral artery disease; SBP, systolic blood pressure.

1.28-1.31), respectively (Table 2). This association was largely consistent in additional competing-risk analysis with subdistribution hazard modeling (Table S2).

Sensitivity Analyses

We also treated time-updated and baseline SBPs as a continuous variable and modeled a nonlinear effect by using a restricted cubic spine function. In these sensitivity analyses, a similar trend was also confirmed, such that incrementally higher SBP was associated with higher risk for incident CKD G3-G5 (Fig 2).

Discussion

In this large national cohort study of 10.5 million Korean adults—capturing one-fifth of the nation's population—we found a significant relationship between incrementally higher SBP and risk for incident CKD G3-G5.
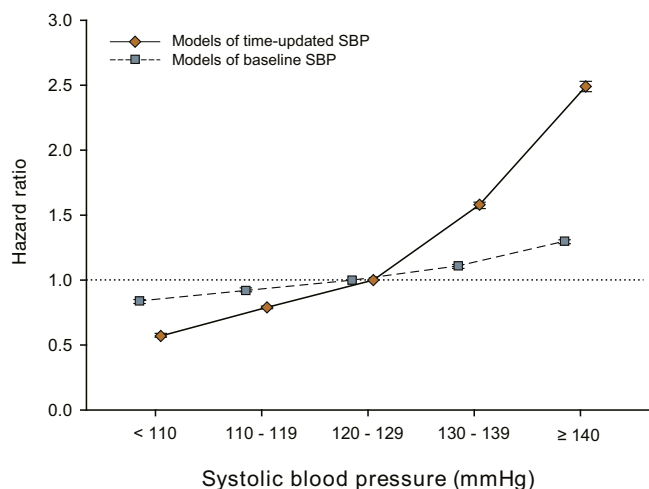
Figure 1. Associations of time-updated and baseline systolic blood pressure (SBP) with risk for incident chronic kidney disease glomerular filtration rate categories 3 to 5 (CKD G3-G5). Time-updated models were analyzed using marginal structural Cox models with mean SBP calculated from all blood pressure readings during the study period. Hazard ratios estimated using marginal structural models with categorical SBP should be interpreted as the risk for incident CKD G3-G5 for individuals assuming their mean SBP across study visits had consistently been in the corresponding SBP category.

Table 2. Multivariate Associations of Time-Updated and Baseline SBP With Incident CKD G3-G5

Model	HR (95% CI)	P
Time-Updated SBP		
Continuous model, per 10 mm Hg increase	1.35 (1.35-1.36)	<0.001
Categorical model		
<110 mm Hg	0.57 (0.56-0.59)	<0.001
110-119 mm Hg	0.79 (0.78-0.80)	<0.001
120-129 mm Hg	1.00 (reference)	
130-139 mm Hg	1.58 (1.55-1.60)	<0.001
≥140 mm Hg	2.49 (2.45-2.53)	<0.001
Baseline SBP		
Continuous model, per 10 mm Hg greater	1.09 (1.09-1.10)	<0.001
Categorical model		
<110 mm Hg	0.84 (0.82-0.85)	<0.001
110-119 mm Hg	0.92 (0.91-0.94)	<0.001
120-129 mm Hg	1.00 (reference)	
130-139 mm Hg	1.11 (1.09-1.12)	<0.001
≥140 mm Hg	1.30 (1.28-1.31)	<0.001

Note: Time-updated models were analyzed using marginal structural Cox models with mean SBP calculated from all blood pressure readings during the study period. HRs estimated using marginal structural models with categorical SBP should be interpreted as the risk for incident CKD G3-G5 for individuals assuming their mean SBP across study visits had consistently been in the corresponding SBP category.
Abbreviations: CI, confidence interval; CKD G3-G5, chronic kidney disease glomerular filtration rate categories 3-5; HR, hazard ratio; SBP, systolic blood pressure.

Strengths of this study are the large sample size; availability of detailed individual-level information including longitudinal sociodemographic, comorbid condition, anthropometric, medication, and laboratory data; and use of rigorous analytic techniques including sophisticated causal inference techniques, namely MSMs, to address time-dependent confounding. These results add to the existing literature on the potential importance of elevated SBP as a modifiable risk factor for prevention of CKD development in individuals with preserved kidney function.

Globally, the estimated number of adults with hypertension has almost doubled from 594 million to 1.13 billion during the last 4 decades.[34] Accordingly, appropriate BP control has long been an important public health concern due to the multitude of hypertension-related complications. However, 2 recent meta-analyses showed that intensive BP control below the current standard did not provide additional benefit for kidney disease outcomes in diabetic and nondiabetic patients, although risk for cardiovascular events and stroke were reduced by lowering BP to <130/80 mm Hg.[17,18] To date, no RCTs have demonstrated that these lower BP targets prevent the development of de novo CKD.

In contrast to the findings of the previous RCTs, observational cohort studies have shown favorable associations between lower BP with incident CKD or kidney failure in the general population. Hsu et al[19] found that among 316,675 adults from a large US integrated health care system without kidney disease at baseline, risk for the development of kidney failure was significantly higher as BP level increased to >120/80 mm Hg. These findings were corroborated by a prospective study of Chinese participants showing a graded increase in risk for kidney failure from prehypertension to stage 2 hypertension when compared with individuals with normal BPs.[20] Furthermore, among 8,093 men without kidney disease in the Physicians' Health Study, individuals with SBPs of 130 to 139 mm Hg had 1.26-fold higher risk for developing CKD compared with those with SBPs < 120 mm Hg.[21]

These discrepant findings across observational studies and RCTs can partly be explained by differences in underlying characteristics of study participants: although the observational studies largely comprised healthy adults with few to no comorbid conditions, the interventional trials included individuals with higher baseline SBPs (ie, SBPs ≥ 130 mm Hg) who were at higher risk for cardiovascular disease. More than 50% of individuals in the observational studies neither had pre-existing hypertension at baseline nor required antihypertensive medications. Another problem in interpreting the findings from observational studies is that high BP itself can represent underlying disease burden. In addition, lowering BP cannot completely eliminate the risk for high BP–related complications, partly because high BP itself is a marker of disease burden and may increase risk for acute kidney injury in severely ill patients. Moreover, several studies suggest that acute kidney injury events caused by intensive
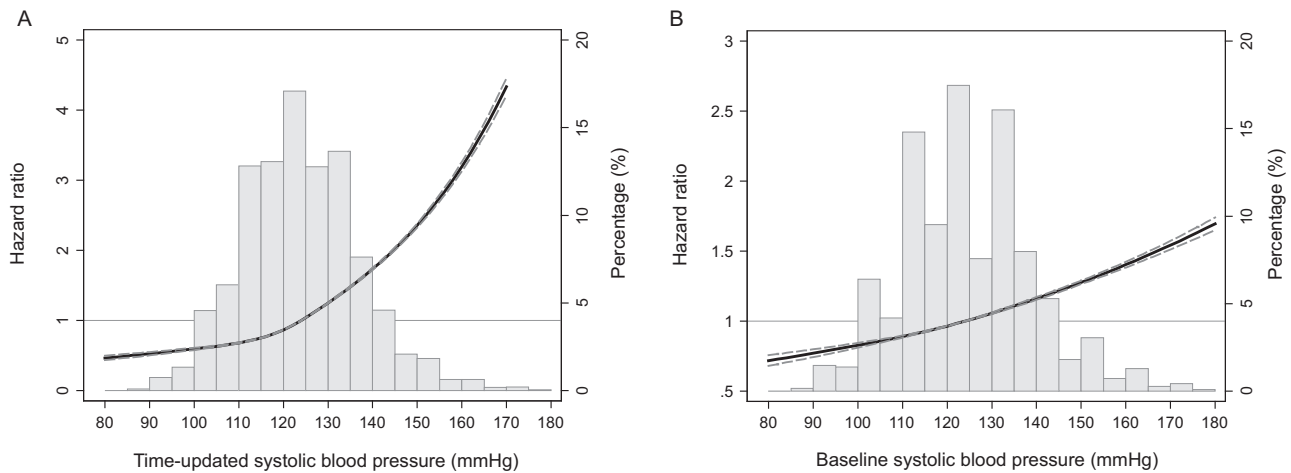
Figure 2. Hazard ratios of incident chronic kidney disease glomerular filtration rate categories 3 to 5 (CKD G3-G5) associated with (A) time-updated and (B) baseline systolic blood pressure. All models were analyzed using restricted cubic splines, adjusted for age, sex, comorbid conditions, smoking status, alcohol intake, physical activity, proteinuria, use of any antihypertensive medications, use of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, use of statins, body mass index, estimated glomerular filtration rate, and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. A histogram of observed systolic blood pressure and a hazard reference ratio of 1 (solid line) is overlaid.

BP control are not associated with intrinsic kidney injury, but predominantly reflect hemodynamic alterations.[35–37] Based on these findings and from a prevention standpoint, it can be argued that "normal" SBPs even <120 mm Hg may be beneficial in healthy adults without underlying hypertension given that mildly elevated BP may result in decreased kidney function and incident CKD in this population.[38,39] Our findings support this point because our study also showed that higher risk for incident CKD G3-G5 was significantly associated with higher SBPs.

However, it is possible that lowering SBP to <130 mm Hg may not be associated with additional "renoprotection" with respect to the development of CKD. The potential benefits of intensive BP control will need to be weighed against the growing concern regarding the detrimental effects of aggressive BP management, particularly with respect to kidney disease outcomes. Several RCTs have found that reduction of SBP to <120 mm Hg caused more adverse renal events such as decline in eGFR and other hypotension-related symptoms.[15,40] However, in our study with low-risk people, we observed a graded association between lower SBP and lower risk for incident CKD G3-G5, such that those with SBPs < 110 mm Hg demonstrated lower risk when compared with the reference group, and this is consistent with other studies.[19–21] Moreover, use of different time-updated SBP models with rigorous adjustment for concurrent covariates showed a consistent and robust association between elevated SBP and incident CKD. These findings suggest that appropriate levels of BP for primary prevention of CKD may be different depending on risk burden.

In this study, the proportions of people who received antihypertensive drugs were low. In general, most people

are reluctant to start pharmacotherapy when they are first diagnosed with hypertension. Interestingly, suboptimal adherence to antihypertensive drug treatment is common worldwide. Adherence with pharmacotherapy for hypertension 1 year after initiation is typically reported at <50%.[41,42] This phenomenon is also observed in Korea. According to a 2018 fact sheet by the Korean Society of Hypertension Epidemiology Research Working Group, only 64% of all hypertensive patients were consistently being treated with antihypertensive drugs in 2016.[43] Thus, untreated hypertension among people with SBPs > 140 mm Hg might result in prominent association of higher SBP with risk for incident CKD. Notably, people are often not aware of the importance of BP control and seeking other measures to lower BP such as lifestyle modification. And although some diets and aerobic exercises have been proven in lowering BP by well-conducted studies, it is not easy to implement such measures in the real world. The odds of success with diet and behavioral modification can be maximized when clear explanations and supports are provided together. Therefore, in clinical practice, we believe it is very important to establish a referral system from a medical health checkup to the individual's physician to confirm the presence of hypertension and provide proper management.

Several limitations of our study bear mention. First, as with all observational studies, our findings cannot prove a causal association between SBP and incident CKD G3-G5, and we cannot exclude the possibility of residual bias due to potential unmeasured confounders. Second, BP was measured annually or biennially, which may not represent overall BP status. In addition, BP was measured only once at each visit (unless measured BP was >120/80 mm Hg)

using different devices, which could result in to inaccurate BP values. However, it is required that the instruments used for BP measurement receive quality assessment every 3 years in all health examination institutions. Furthermore, we used the time-updated mean SBP calculated from all BP readings during the study period. These approaches might partly compensate for the shortcomings of BP measurements. The use of office BP is another limitation because it cannot accurately detect diverse BP patterns such as white coat hypertension, variability of BP, and reverse dipping pattern, etc.[44]

Third, records on comorbid conditions entirely relied on ICD-10 codes, which might not precisely capture disease burden. Fourth, given that our cohort comprised relatively healthy adults with few comorbid conditions and included only individuals who had at least 3 eGFR assessments during follow-up, we cannot rule out the possibility of selection bias. The incidence of CKD in our cohort was much lower than in other countries.[3,45] Thus, our findings may not be generalizable to those at high risk for cardiovascular events or CKD.

Finally, our study specifically focused on the outcome of incident CKD G3-G5 and did not examine other end points such as mortality. Several studies have shown favorable associations between low SBP and lower risk for CKD yet higher mortality.[46,47] Hence, further studies are needed to clarify the impact of SBP and non-CKD end points in healthy adults.

In conclusion, in this large national study of healthy Korean adults, we found that incrementally higher SBPs are associated with increasingly higher risk for incident CKD G3-G5. At this time, further studies are needed to define optimal BP targets and management strategies with respect to CKD and non-CKD outcomes based on each individuals' unique characteristics, including underlying comorbid condition status and cardiovascular risk.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart of study cohort construction.

Item S1: Analyses of time-updated systolic blood pressure.

Table S1: Multivariate associations between time-updated SBP and incident CKD G3-G5 in individuals in the same SBP category at all study visits.

Table S2: Competing-risk analyses between baseline SBP and incident CKD G3-G5.

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