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Progression Rate From New-Onset Pre-Hypertension to Hypertension in Korean Adults

Soo Jeong Kim, PhD; Jakyoung Lee; Chung Mo Nam, PhD; Sun Ha Jee, PhD; Il Soo Park, PhD; Kyung Jong Lee, MD, PhD; Soon Young Lee, MD, PhD

Background: There are limited studies conducted in Asia to investigate the progression rate to hypertension (HTN). This study was done to estimate the progression rate of new-onset pre-HTN (PreHTN) to HTN during an 8-year follow-up period, and to compare the impact of PreHTN on progression to HTN.

Methods and Results: A total of 49,228 participants, aged 30 to 54 years with new-onset PreHTN at baseline (1994–1996) from a biennial national medical exam were enrolled and followed up every 2 years until 2004. The incidence rate recorded at each interval and the cumulative incidence rate of HTN were analyzed. Hazard ratio of high-normal and high blood pressure (BP) in men and women was calculated. The cumulative incidence rate for high-normal BP was 27.6% and 26.4% at 2-year follow-up, increased to respectively 64.1% and 55.8% in men and women at the 8-year follow-up. Compared to optimal BP, hazard ratios for men with high-normal BP across all age groups were 3- to 4-fold higher at 2-year, and 2- to 3-fold higher at 8-year follow-up. Hazard ratios for women were about 6-fold higher at 2-year and around 4-fold higher at 8-year follow-up.

Conclusions: New PreHTN was a significant predisposing factor for future HTN, in young adults and the effect is more prominent in women. (*Circ J* 2011; **75:** 135–140)

Key Words: Epidemiology; Follow-up studies; Hypertension; Population

In the recent JNC-7 report, pre-hypertension (PreHTN), a new category including normal and high-normal blood pressure (BP) were added to the previous JNC-6 because normal or high-normal BP might be another condition related to the development of cardiovascular diseases (CVD) in the future.[1,2] Many researchers in public health and medicine agree to apply more aggressive measures and early lifestyle modification for the population with PreHTN, in order to prevent future CVD and hypertension (HTN). However, the European Society of Hypertension and the European Society of Cardiology do not agree with this idea, because they consider early intervention will unnecessary increase medical care services and send premature warnings to the public. They suggested an intervention would be more effective if it targeted a subset of population with concurrent pre-hypertensive and co-morbid CVD risk factors.[3–5] Although debates on the timing and target population for intervention exist, many studies concluded that the pre-hypertensive status would be likely to progress to HTN.[6–16]

There are several limitations associated with previous studies. First, the results were mostly derived from studies on risk prediction of CVD, and progression to HTN in Western populations. Second, the sample size from the previous studies was not large enough to investigate the natural history of PreHTN in the general population. Third, there are limited number of studies based on Asian and African population.[13,16] Fourth, there are hardly any studies that investigate difference in progression rate to HTN by gender and age. Finally, there were very few studies on the progression rate to HTN in patients newly diagnosed with PreHTN. A study that focuses on the new-onset PreHTN population stands to investigate the role of early detection and intervention.

Two studies in Taiwan and Korea investigated the progression rate to HTN. However, the sample size was too small to investigate the difference in the progression rate by gender or age groups, and to represent the population in each country.[12,15]

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Department of Occupational and Environmental Medicine, Ajou University School of Medicine, Suwon (S.J.K., K.J.L.); Graduate School of Public Health, Yonsei University, Seoul (J.L., S.H.J.); Department of Preventive Medicine, Yonsei University College of Medicine, Seoul (C.M.N.); Institute for Health Promotion, Yonsei University, Seoul (S.H.J); National Health Insurance Policy Research Institute, National Health Insurance Corporation, Seoul (I.S.P.); and Department of Preventive Medicine and Public Health, Ajou University School of Medicine, Suwon (S.Y.L.), Republic of Korea

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Mailing address: Soon Young Lee, MD, PhD, Department of Preventive Medicine and Public Health, Ajou University School of Medicine, San 5, Wonchon-dong, Yeongtong-gu, Suwon, Gyeonggi-do, 443-721, Republic of Korea. E-mail: solee@ajou.ac.kr

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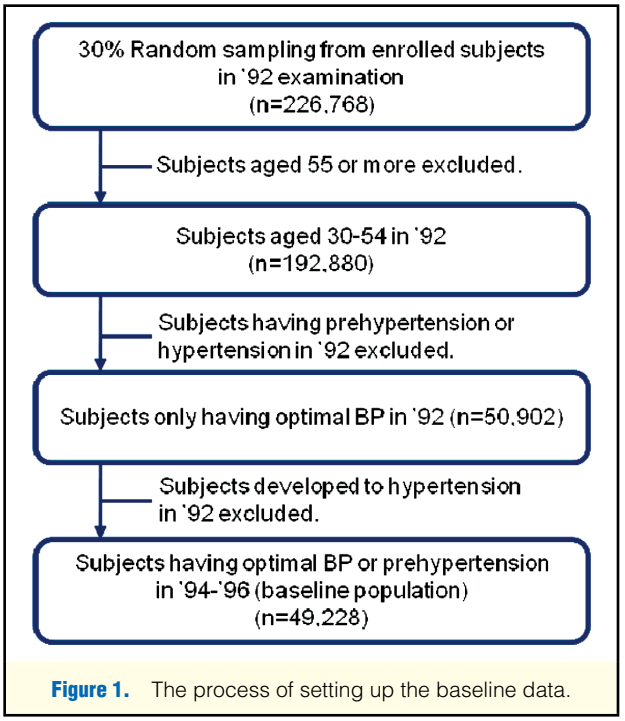


Figure 1. The process of setting up the baseline data.

The purpose of the study was to assess the progression rate of new-onset PreHTN to HTN during the 8-year follow-up period, and to compare the impact of PreHTN on progression to HTN by age and gender.

Methods

Study Population

The National Health Insurance Corporation has provided a biennial medical screening program for Korean adults since the early 1980s. A total of 784,870 adults were enrolled in 1992. Detailed information on the program was described in the previous paper.[22] In this study, 30% (226,768) of the 784,870 participants who received medical examinations in 1992 were randomly selected for enrollment (Figure 1). Individuals over 55 years of age or having high BP (systolic BP (SBP) ≥120 mmHg or diastolic BP (DBP) ≥80 mmHg) were excluded from the first pool of subjects (226,768) in 1992. Among the remaining participants (50,902) with optimal BP in 1992, individuals with optimal BP or PreHTN between 1994 and 1996 were chosen as the final sample for analysis. The final sample comprised of 49,228 adults with optimal BP or PreHTN at baseline (1994–1996), and was followed up every other year until 2004. The study protocol was approved by the Yonsei University College of Medicine ethical committee.

BP Measurements

BP of participants was measured by registered nurses or trained technicians using a standard mercury sphygmomanometer or an automatic manometer. BP was measured once at each year so that potential misclassification of BP status can exist. We used the arithmetic mean value BP of 1994 and 1996 to minimize a misclassification error. The measured BP was classified as optimal (SBP <120 mmHg and DBP <80 mmHg), normal (SBP 120 to 129 mmHg or DBP 80 to 84 mmHg), high-normal (SBP 130–139 mmHg or DBP 85 to 89 mmHg), or HTN (SBP ≥140 mmHg or DBP ≥90 mmHg) based on the JNC-6 criteria.

Other Measurements

Subjects were asked about health behavior and had undergone biochemical measurements in each biennial health examination from 1992 to 2004. Health behavior included smoking, drinking, physical activity and family history of CVD related diseases. For the biochemical measurements, body mass index (BMI), serum glucose and total cholesterol were measured following fasting. The mean value of 1994 and 1996 measurements for BMI, fasting serum glucose (FSG), total serum cholesterol (TC) were used as baseline characteristics.

Statistical Methods

By baseline BP status and gender, the general characteristics of the study population were presented in Table 1. The 2-yearly interval incidence rate and the cumulative incidence

Table 1. General Characteristics of the Study Population According to BP Categories at Baseline

Characteristics	Men, baseline BP				Women, baseline BP			
	Optimal (n=20,225)	Normal (n=9,657)	High-normal (n=3,251)	P-value for trend*	Optimal (n=12,704)	Normal (n=2,744)	High-normal (n=647)	P-value for trend*
Age (year, 1992) mean±SD**	38.7±6.5	39.1±6.6	40.1±6.8	<0.0001	35.6±5.1	36.8±5.8	38.4±6.5	<0.0001
Body mass index (kg/m^2)	22.5±2.3	23.2±2.4	23.6±2.4	<0.0001	21.2±2.2	21.9±2.4	22.5±2.6	<0.0001
Current smoking (%)	60.6	59.3	56.7	<0.0001	0.14	0.12	0.17	0.9454
Alcohol drinking (%)	75.2	79.8	80.2	<0.0001	17.9	18.0	19.9	0.3540
Regular physical activity (%)	28.7	28.2	29.8	0.6026	14.1	13.7	16.9	0.3323
Family history (%)								
HTN, stroke, heart disease	12.7	13.0	13.9	0.1027	18.4	21.0	20.7	0.0044
Diabetes mellitus	6.4	6.4	5.7	0.3318	10.4	11.8	11.6	0.0544
SBP (mmHg)	108.9±5.5	119.6±4.4	126.5±5.7	<0.0001	106.5±6.3	118.9±4.6	126.0±5.8	<0.0001
DBP (mmHg)	70.2±4.5	78.0±3.5	83.4±3.5	<0.0001	68.5±5.0	77.8±3.8	83.2±3.7	<0.0001
FSG (mg/dl)	88.5±14.4	90.3±16.3	91.7±17.7	<0.0001	84.6±10.0	86.0±12.1	87.8±14.9	<0.0001
TC (mg/dl)	183.8±30.6	188.6±31.2	189.8±31.1	<0.0001	177.6±29.0	182.8±30.3	188.3±31.8	<0.0001

*P-value for trend by ANOVA or Cochran-Armitage test.
**Age in 1992 presented because the data included individuals who participating in health exam in 1992 from the KCPS data.
BP, blood pressure; HTN, hypertension; SBP, systolic BP; DBP, diastolic BP; FSG, fasting serum glucose; TC, total serum cholesterol.

rate were calculated and analyzed by gender and baseline BP status based on the life-table method.

Compared to the optimal BP, the hazard ratio (HR) of high-normal or normal BP in men and women was calculated by the Cox proportional hazard model after adjusting for baseline characteristics such as age, BMI, smoking, alcohol, regular exercise, family history of CVD, FSG and TC. All P-values were 2-tailed, with a P-value of less than 0.05 considered to be of statistical significance. All statistical analyses were conducted using SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA).

Results

Table 1 illustrates the baseline characteristics of the study population. At baseline, the percentage of PreHTN in men was 38.9% (normal 9,657 (29.1%); high-normal 3,251 (9.8%)) and in women was 21.0% (normal 2,744 (17.0%); high-normal 647 (4.0%)). The 3 BP groups by mean age, baseline BMI, FSG, and TC were statistically significant in both men and women (P<0.0001). Smoking and alcohol drinking were statistically significant in all 3 BP groups in men at baseline. In men, smoking rate was lower in high-normal BP group, compared to the optimal BP group while drinking rate was higher in high-normal BP group.

Table 2 showed the 2-yearly interval incidence of HTN in baseline BP in men and women. The 2-year interval incidence rate in men ranged between 9.8 and 12.4%, which was twice as high as in women (5.1–5.9%).

Figure 2 shows a gradual increase in the cumulative incidence rate for each BP status at baseline during the follow-up years in men and women. The cumulative incidence rate of high-normal BP in men and women was 27.6% and 26.4% at 2-year follow-up, and increased to 64.1% and 55.8% at the 8-year follow-up, respectively. The cumulative incidence rate of normal BP in women was closer to that of optimal BP than the rate of high-normal BP, compared to the rate of normal BP in men, which is closer to the rate of high-normal BP.

After adjusting for covariates, Figure 3 presented the results of Cox's proportional HR analysis for each age group and the 3 baseline BP categories at 2-year and 8-year follow-up. In both men and women, the HR and the confidence interval (CI) were reduced and yet statistically significant across all age groups at 8-year follow-up as compared to 2-year follow-up. When compared to optimal BP, HR in men with high-normal BP were 3- to 4-fold higher at 2-year follow-up and 2- to 3-fold higher at 8-year follow-up in each age group. HR in women were about 6-fold higher at 2-year follow-up, and around 4-fold higher at 8-year follow-up.

Discussion

It is a consensus that regular screening is an effective method to detect HTN early in the general public. It was recommended for people with high-normal BP to be screened once a year, and for people with normal BP once every other year.[10] After JNC-7, the attention has been given to PreHTN (normal BP and high-normal) because many studies reported the progression rate to HTN among population with high-normal BP over time was significantly higher than individuals with optimal BP.[6–16] Other studies on PreHTN in the USA also concluded that high-normal BP was associated with an increased risk of CVD.[17–21]

There have been short- and long-term studies to investi-

Table 2. Two-Year Interval Incidence Rate of HTN by Baseline BP in Men and Women

BP at baseline	Period 1 (baseline–1998)				Period 2 (1999–2000)				Period 3 (2001–2002)				Period 4 (2003–2004)			
	Total no.	No. of HTN	No. of censored	PR	Total no.	No. of HTN	No. of censored	PR	Total no.	No. of HTN	No. of censored	PR	Total no.	No. of HTN	No. of censored	PR
Men																
Optimal	20,225	1,260	1,161	6.4	17,804	1,528	3,053	9.4	13,223	1,042	2,352	8.6	9,829	714	1,220	7.7
Normal	9,657	1,514	604	16.2	7,539	1,111	1,325	16.2	5,103	716	962	15.5	3,425	427	447	13.3
High-normal	3,251	873	181	27.6	2,197	478	398	23.9	1,321	235	246	19.6	840	148	104	18.8
Total	33,133	3,647	1,946	11.3	27,540	3,117	4,776	12.4	19,647	1,993	3,560	11.2	14,094	1,289	1,771	9.8
Women																
Optimal	12,704	411	595	3.3	11,698	491	1,664	4.5	9,543	441	1,377	5.0	7,725	304	622	4.1
Normal	2,744	286	131	10.7	2,327	223	389	10.5	1,715	145	251	9.1	1,319	123	118	9.8
High-normal	647	167	31	26.4	449	68	79	16.6	302	50	41	17.8	211	25	15	12.3
Total	16,095	864	757	5.5	14,474	782	2,132	5.8	11,560	636	1,669	5.9	9,255	452	755	5.1

PR, progression rate per 100 person. Other abbreviations see in Table 1.

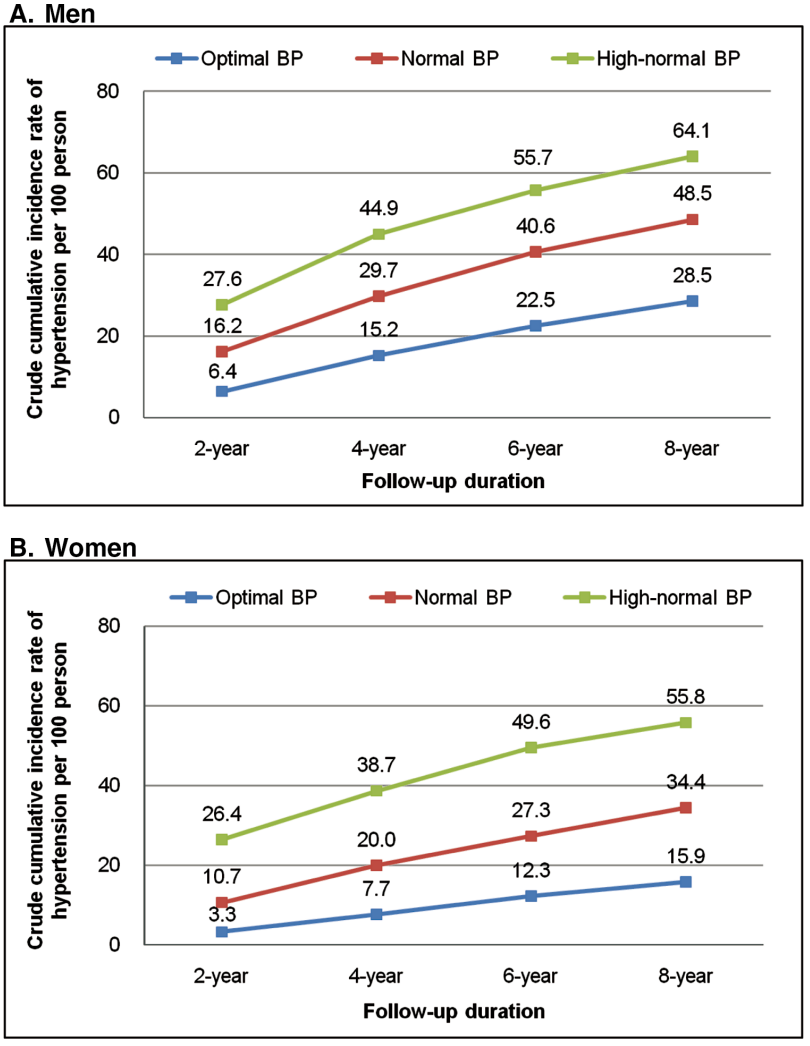


Figure 2. Cumulative incidence rate of hypertenstion (HTN) by baseline blood pressure in (**A**) men and (**B**) women. BP, blood pressure.

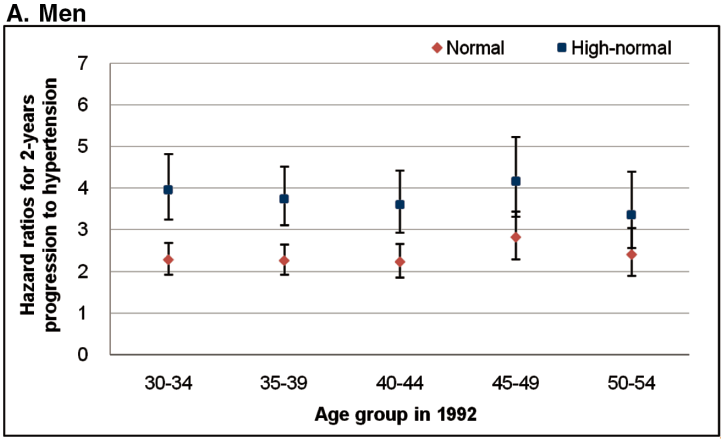
gate the patterns of progression rate to HTN among different population in the West. The Framingham Heart Study, one of the first long-term studies, reported that people with normal or high-normal BP were 2 to 3 times more likely to develop HTN than people with optimal BP in 26 years of follow-up.[9] In a rather short-term follow-up study of 4 years, the progression rate among people with high-normal BP was reported to be increased by 11.6% in 35–64 age groups, and only 5.5% increase in the 65–94 age groups.[10]

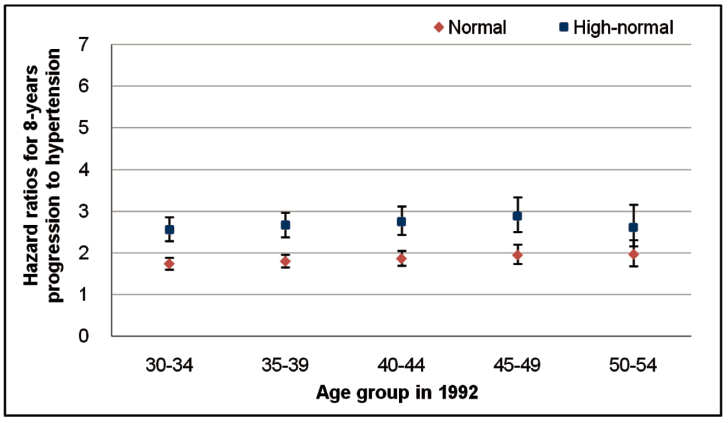
In a study using Health and Lifestyle Surveys in the UK, researchers analyzed 2 sets of data measured 7 years apart.[11] The result of the study showed 4.3 times higher progression rate in people with high-normal BP in a 7-year follow-up period, and higher HR in people with high-normal BP among younger age group (34–44 year olds). In another study in Europe, Zhang and others[12] reconfirmed that a stepwise increase in the incidence of HTN across 3 non-hypertensive BP categories showed similar outcomes to the Framingham Heart study. The risk of CVD among people progressed to PreHTN, researchers from the MONICA cohort study in Copenhagen reported that the 10-year crude progression rates to HTN from optimal, normal and high-normal BP were 10.4%, 37.3% and 58.1%, respectively.[13] The authors of the MONICA cohort study suggested that people progressed from optimal or normal BP to high-normal BP or HTN had almost the same CVD risk as those with sustained high-normal BP or HTN from baseline (1982–1984) to the follow-up (1993–1994). Studies in Western populations concluded that PreHTN was one of the main contributors to HTN, and possibly to the future development of CVD, although there were differences in the progression rate of PreHTN to HTN depending on the length of follow-up.

There have also been more attention on PreHTN and progression rates among Asian population in recent years. There were 2 studies from Taiwan and Korea on the progression rate of PreHTN to HTN. In the Chin-Shan Community Cardiovascular Cohort study in Taiwan, the adjusted cumulative HTN incidence probability among ethnic adult Chinese was higher in PreHTN participants (0.59) than (0.27) in normotensive participants during an 8-year follow-up period.[14] In Korea, Kim et al also reported the incidence rates in individuals with high-normal BP at baseline were 2 or 5 times higher than those with optimal BP in a 2-year follow-up.[15] In these studies, researchers validated results from the Framingham study, although the sample size in these studies was too small to represent the general population in Taiwan or Korea.

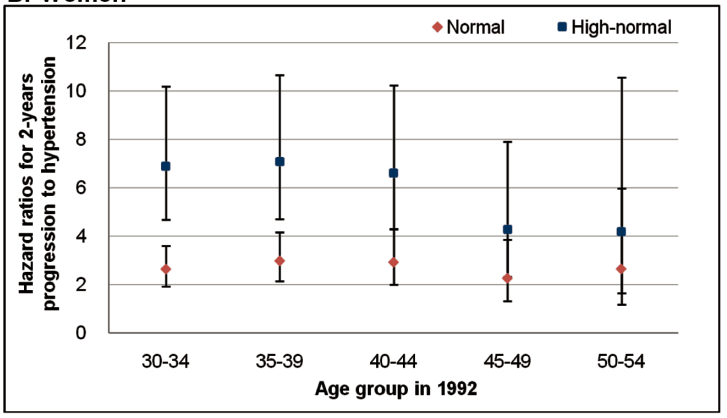
In this study, we reconfirmed a stepwise increase in the incidence of HTN in 3 populations with non-hypertensive

A. Men





B. Women



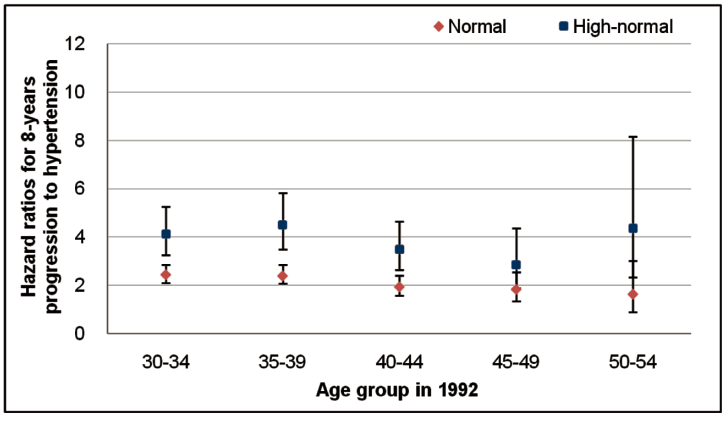


Figure 3. Hazard ratios for 2-years and 8-years progression to hypertension by baseline blood pressure and age in (**A**) men and (**B**) women. Adjusted for baseline characteristics such as age, smoking status, alcohol drinking, regular physical activity, family history of cardiovascular disease, body mass index, fasting serum glucose, and total serum cholesterol.

BP, and the incidence rate of HTN in men was twice that of women. These results were consistent with that of previous studies. However, the results of HR at 2- and 8-year follow-up showed that women seemed to have higher risks of developing HTN from new-onset PreHTN than men in most of the age groups, after controlling for other variables such as age and smoking. In addition, we could not find significant differences in the HR of PreHTN progresses to HTN among age groups. The strength of the study was the presentation of short- and long-term progression rates of PreHTN by age and sex based on a large sample size. Unlike other studies, another strength was that the progression rate was in participants with new-onset PreHTN.

There were several limitations due to the characteristics of the population and the measurement of indices of the study. First of all, we used the national health screening data, which was conducted in numerous clinic settings. BP was measured once in each period. There was not a unified protocol about rest time, position, and sphygmomanometer. There was no information on whether BP was measured by a mercury sphygmomanometer or not. We could not compare the data between a mercury sphygmomanometer and an automatic manometer. Second, although this study included a large population, study participants were comprised of government employees, private school teachers and their dependents who might be categorized as middle class, who might be healthier than the general population in Korea. Therefore, the study could have underestimated the incidence of HTN and the prevalence of CVD risk factors. In addition, study data were collected from individuals under 65 years of age and hence analyses were not performed in people over 65 years of age. Fourth, another limitation of study is the lack of information on the use of antihypertensive medication, which could led to underestimation of PreHTN and HTN. One would question the possibility of misclassification bias due to measurement error, because biennial health examination was carried out at different hospitals throughout the country. The medical institute responsible for the national screening program has been under internal and external quality control. Mean BP in 1994 and 1996 defined based on JNC-6 criteria were used to minimize bias in categorizing the BP at baseline. Lastly, the regression to the means phenomenon might exist in any populations because we first excluded the participants with PreHTN in 1992.

In conclusion, it was clear that PreHTN was a strong indicator to progression to HTN in adulthood and the impact is more pronounced in women. Although European scientists recommended that intervention and treatment should be focused on people with PreHTN with CVD risk factors, our study supported that identification of new-onset PreHTN, even in young adults, would be important and a more aggressive and early clinical and lifestyle intervention in people with new-onset PreHTN should be given more attention.

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