Atherosclerosis 282 (2019) 188–195

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Increased burden of coronary artery calcium from elevated blood pressure in low-risk young adults

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HIGHLIGHTS

- Coronary artery calcium (CAC) was measured in 96,166 Korean adults.
- Blood pressure (BP) was categorized based on 2017 ACC/AHA guidelines.
- The burden of CAC increased in the elevated BP category.
- This association was observed even in low risk and young adults aged 20–39 years.
- Surveillance and management of high BP is required even in low-risk young adults.

ARTICLE INFO

Keywords:
Blood pressure
Hypertension
Atherosclerosis
Coronary artery calcium
Young adults

ABSTRACT

Background and aims: The relationship between blood pressure (BP) levels given in the new hypertension guidelines by the American College of Cardiology and the American Heart Association (ACC/AHA) and subclinical coronary atherosclerosis in low-risk young adults is unknown. We evaluated the association between the new BP categories and coronary artery calcium (CAC) in low-risk, young and middle-aged adults.

Methods: We performed a cross-sectional study of 96,166 Koreans who underwent a health examination including cardiac tomography estimation of CAC scores in 2012–2017. BP categories were defined according to the 2017 ACC/AHA guidelines. We used Poisson regression models with robust variance to calculate prevalence ratios (PRs) with 95% confidence intervals (CIs) for prevalent CAC > 0.

Results: Overall, higher BP categories were associated with higher CAC scores in both young (aged 20–39) and middle-aged people (aged 40 years or more). After adjusting for possible confounders, including traditional cardiovascular disease (CVD) risk factors, the multivariable-adjusted PRs (95% CI) for prevalent CAC, comparing elevated BP and stage 1 and 2 hypertension to normal BP, were 1.27 (1.08–1.49), 1.45 (1.28–1.63), and 2.02 (1.67–2.43), respectively, among those aged 20–39 years and 1.25 (1.15–1.36), 1.29 (1.23–1.35), and 1.46 (1.36–1.57), respectively, among those aged ≥40 years. This association was also evident in those with a 10-year CVD risk of < 10%.

Conclusions: Higher BP categories were positively associated with prevalent CAC, and that association began in the elevated BP category, even in a young and low-risk population.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; FRS, Framingham risk score; hsCRP, high sensitivity C-reactive protein; HTN, hypertension

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https://doi.org/10.1016/j.atherosclerosis.2018.11.035
Received 1 October 2018; Received in revised form 14 November 2018; Accepted 22 November 2018
Available online 01 December 2018

1. Introduction

High blood pressure (BP) is the most common modifiable risk factor for cardiovascular disease (CVD) and mortality worldwide [1]. Recently, the 2017 American College of Cardiology and the American Heart Association (ACC/AHA) hypertension (HTN) guidelines lowered the cut-off value to 130/80 mmHg [2]. The ACC/AHA guidelines are based on a body of evidence indicating that a gradient of progressively higher risk for CVD and stroke can be observed from elevated BP and stage 1 hypertension [3–6]. Additionally, subclinical target organ damage was found even in prehypertension [7–10]. However, most studies used as the basis for that evidence included middle-aged or older populations [6,11–14]. Thus, the relative prognostic implications of the new BP categories are unclear for low-risk, young adults.

With the introduction of the new BP guidelines, the number of young HTN patients will increase significantly [15–17]. Furthermore, low awareness of HTN and low treatment and control rates for it in young people are another concern because the increase in CVD risk is expected later in their lives [16,18]. Coronary artery calcium (CAC) scoring using computed tomography (CT) is a useful and reliable marker of coronary atherosclerosis [19]. CAC scores reflect the long-term effects of elevated CVD risk factors and are an independent predictor of future CVD events across a wide range of ages, including asymptomatic adults [19,20]. CAC scores have a direct, continuous relation with total coronary plaque burden in histology [21] and the severity of coronary artery disease [22]. No previous studies have demonstrated an association between BP levels in the new guidelines and subclinical atherosclerotic burden, especially in a young population.

Therefore, our aim was to determine the association between the new BP categories and states of HTN management and CAC in a large sample of apparently healthy young Korean adults who participate in a regular health checkup program.

2. Materials and methods

2.1. Study population

This study was performed as part of the Kangbuk Samsung Health Study, a cohort study of South Korean men and women aged 18 years and older who annually or biennially undergo a health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea [23]. Most (> 80%) participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening exams of all employees, offered free of charge. The remaining participants voluntarily had the screening exams at their own expense. This study population consisted of the subsample of Kangbuk Samsung Health Study participants who received a cardiac tomography estimation of their CAC scores as part of their health examination between 2012 and 2017 (N = 115,627). CAC scoring is a common CVD screening test in Korea [24].

For this analysis, we excluded 19,461 participants for the following reasons: history of CVD (N = 1504); history of malignancy (N = 3229); current use of anti-diabetic medication (N = 3295); current use of anti-hypertensive medication (N = 9271); current use of lipid-lowering agents (N = 5684); and missing data on BP, body mass index (BMI), HOMA-IR, or high sensitivity C-reactive protein (hsCRP) (N = 2974). Some participants met more than one of the exclusion criteria, resulting in a total of 96,166 participants eligible for this study.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent because we used only de-identified data routinely collected as part of health screening exams (IRB No. 2018-05-050).

2.2. Measurements

Data on medical history, medication use, family history, lifestyle factors, and education level were collected through a self-administered questionnaire, and anthropometry, BP, and serum biochemical parameters were measured by trained staff during the health exams. The lifestyle factors we considered were smoking status (never, former, and current smokers), alcohol consumption (none, moderate of ≤ 20 g/day, and high of > 20 g/day) and education level (less than a college graduate and college graduate or more). Physical activity levels were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form [25,26] and were categorized as inactive, minimally active, and health-enhancing physical activity [27]. Usual dietary intake was assessed using a 103-item self-administered food frequency questionnaire that was designed and validated for use in Korea [28].

Anthropometric measurements were conducted by trained nurses. Obesity was defined as BMI ≥ 25 kg/m^2, following Asian-specific criteria [29]. BP was measured using an automated oscillometric device (53000, Welch Allyn, New York, USA) operated by trained nurses while participants were in a sitting position with the arm supported at the heart level. Three consecutive BP readings were obtained after the participants had been resting quietly in a sitting position for 5 min. The average of the second and third BP readings was used in the analysis. BP levels were categorized according to the 2017 ACC/AHA HTN guideline [2]: normal BP (< 120/80 mmHg), elevated BP (120–129/< 80 mmHg), stage 1 HTN (130–139/80–89 mmHg), and stage 2 HTN (≥ 140/90 mm Hg). A history of hypertension was defined as physician-diagnosed hypertension using the following question: “Have you ever been told by a doctor that you had hypertension?” Among participants with a history of HTN, BP states were categorized as treated and strictly controlled HTN (< 130/80 mmHg), controlled HTN (130–139/80–89 mmHg), and uncontrolled HTN (≥ 140/90 mmHg).

The fasting blood measurements we considered were glucose, hemoglobin A1c, uric acid, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hsCRP, and insulin. Insulin resistance was assessed using the HOMA-IR according to the following equation: fasting blood insulin (uU/ml) × fasting serum glucose (mmol/l)/22.5. Diabetes mellitus was defined as fasting serum glucose ≥ 126 mg/dL or a hemoglobin A_1c level≥6.5% because we had already excluded those with self-reported use of insulin or antidiabetic medications.

2.3. Measurement of CAC by multidetector CT

CT scans were performed with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) in both the Seoul and Suwon centers using the standardized scanning protocol: 2.5-mm thickness, 400 ms rotation time, 120 kV tube voltage, and 124 mAS (310 mA*0.4 s) tube current under ECG-gated dose modulation. The CAC Agatston scores were computed by summing the CAC scores of all the foci in the epicardial coronary system [30]. The inter-observer and intra-observer reliabilities for the CAC scores were both excellent (intraclass correlation coefficient of 0.99) [31]. CAC scores were categorized as 0, 1–100, and > 100 [32].

2.4. Statistical analyses

Descriptive statistics were used to summarize the characteristics of participants by the presence of CAC in young (age of < 40 years) and middle-aged (aged 40 or older) adults separately.

To evaluate the association of CAC across BP categories, we used a Poisson regression with robust variance to estimate prevalence ratios (PRs) with 95% confidence intervals (CIs) for prevalent CAC > 0. We used three models with progressive adjustments: Model was initially adjusted for age and sex; model 1 was further adjusted for center, year

of screening exam, smoking status, alcohol intake, physical activity, education level, caloric intake, family history of heart disease, diabetes mellitus, and BMI; model 2 was further adjusted for fasting serum glucose, LDL-C, HDL-C, and triglycerides. To examine whether an association exists between BP categories and CAC in a population with low CVD risk, we performed the same analyses in a low-risk group using the estimated 10-year atherosclerotic CVD (ASCVD) risk based on the ACC/AHA pooled cohort equations (< 10%) or Framingham risk score (< 10%).

In a sensitivity analysis, we used a Tobit regression model, an analytic model that fits the distribution of CAC [33], for the natural log (CAC score + 1) with the Huber-White estimation of standard errors [33,34]. We assumed that CAC scores follow a log-normal distribution with left-censored values at 0 Agatston units (non-detectable CAC scores). Tobit models were used to estimate ratios and 95% CIs of the CAC score +1 while comparing BP categories to the normal BP category. We present the estimates of the Tobit models as exponentiated Tobit regression coefficients (CAC score ratios) approximating the relative CAC score increment when comparing BP categories to the reference category (normal BP). For example, a CAC ratio of 1.50 is interpreted as a 50% increase in the CAC score for a specific category compared to the reference category.

As secondary sensitivity analyses, we also used multinomial logistic regression models to estimate the PRs and 95% CIs for CAC scores 1–100 and > 100 while comparing the BP categories to normal BP using participants with CAC 0 as the reference group. Additional subgroup analyses stratified by sex (males vs. females) were performed because the study population consisted mainly of males, and there might be sex-related differences in the effect of BP in the risk of CAC.

Statistical analyses were carried out using STATA version 15.0 (StataCorp LP, College Station, TX, USA). All *p*-values less than 0.05 were considered statistically significant.

3. Results

The average (SD) age of the study participants was 40.4 (7.4) years; 49.1% of the participants were young adults (aged < 40 years), and 75.5% of them were men. Of the 47,199 young subjects (aged 20–39 years), 1721 (3.7%) had a CAC score of 1–100, and 102 (0.2%) had a CAC score > 100; of the 48,967 subjects aged 40 or more, 6690 (13.7%) had a CAC score of 1–100, and 1121 (2.3%) had a CAC score > 100. Among the young adults (Table 1), increasing BP categories were positively associated with age, being male, BMI, current smoking, alcohol intake, diabetes mellitus, glucose, uric acid, total cholesterol, LDL-C, triglycerides, hsCRP, and HOMA-IR and inversely associated with HDL-C in those with and without a history of hypertension. Similarly, in individuals older than 40 (Table 2), increasing BP categories were positively associated with being male, BMI, current smoking, alcohol intake, fasting glucose, uric acid, total cholesterol, LDL-C, triglycerides, hsCRP, and HOMA-IR and inversely associated with HDL-C among those with and without a history of hypertension. In both age groups (< 40 and ≥ 40 years), the presence of CAC (CAC score > 0) was positively associated with age, being male, current smoking, alcohol intake, BMI, BP, fasting glucose, uric acid, total cholesterol, LDL-C, triglycerides, hsCRP, and HOMA-IR and inversely associated with HDL-C (Supplementary Table 1).

Table 3 shows the association between BP categories and the presence of detectable CAC (> 0) by age group (< 40 *vs.* ≥ 40 years). Higher BP categories were significantly associated with a higher presence of CAC in both young and older individuals. For those aged 20–39 years without a history of hypertension, the multivariable-adjusted PRs (95% CI) for prevalent CAC comparing elevated BP and HTN stages 1 and 2 to normal BP (reference category) were 1.27 (1.08–1.49), 1.45 (1.28–1.63), and 2.02 (1.67–2.43), respectively. For those aged 20–39 years with a history of hypertension, the multivariable-adjusted PRs (95% CI) comparing BPs < 130/80, 130–139/80–89, and ≥140/90 mmHg to the normal category were 1.56 (1.19–2.04), 2.07 (1.67–2.58), and 2.97 (2.40–3.67), respectively. Similar findings were observed in those aged ≥40 years, but the magnitude of the association between BP categories and CAC was weaker than in the younger subjects (P for interaction by age group < 0.001). In the Tobit regression analyses (Supplementary Table 2) comparing elevated BP and HTN stages 1 and 2 to normal BP (reference category), those aged 20–39 years without a history of hypertension had multivariable-adjusted CAC score ratios (95% CI) of 1.80 (1.20–2.69), 2.54 (1.87–3.46), and 7.74 (4.53–13.2), respectively. For those aged 20–39 years with a history of hypertension, the multivariable-adjusted CAC score ratios (95% CI) comparing BPs < 130/80, 130–139/80–89, and ≥140/90 mmHg to the normal category were 3.32 (1.63–6.76), 6.79 (3.66–12.59), and 23.96 (12.49–45.96), respectively. Similarly, the positive associations between increased BP categories and CAC scores were observed in the logistic regression models that used CAC scores (0, and > 0) as a binary outcome (Supplementary Table 3) and in multinomial regression models that used categorized CAC scores (0, 1–100, and > 100) as outcomes (Supplementary Table 4).

We also looked for the association between BP categories and CAC in a low-risk population (with a 10-year ASCVD risk of < 10% or a Framingham risk score < 10%) (Table 4 and Supplementary Table 5) and found that it persisted, even in that low-risk group. Additionally, in subgroup analyses stratified by sex (Supplementary Tables 6–7), higher blood pressure categories were associated with a higher presence of coronary calcification even after adjusting for confounders, with no significant interaction by sex (*p* for interaction = 0.394).

4. Discussion

In this large study of young and middle-aged men and women, we identified two major findings. First, we found a graded relationship between BP level and CAC scores in subjects without a history of hypertension. That association persisted even after adjustment for potential confounders, including traditional CVD risk factors, and it started in the elevated BP category. Second, the association between BP levels and the presence of CAC was observed in both young adults (aged 20–39) and a low-risk group (estimated 10-year CVD risk of < 10% or Framingham risk score < 10%). Indeed, the associations were even stronger in the younger group than in the older one. Our study findings indicate that higher BP levels, beginning with the elevated BP category, increase the risk of atherosclerosis in a young, low-risk population and can be an important contributor to coronary artery disease.

Several studies have shown an association among high BP, subclinical atherosclerosis, and alterations in cardiovascular structure and function. Femia et al. reported an increased carotid intima-media thickness in prehypertensive subjects [35]. Another population-based study of Koreans demonstrated an association between prehypertension with arterial stiffness and left ventricular diastolic dysfunction [36].

Only a few studies have evaluated the association between prehypertension and CAC as a marker of atherosclerosis according to the previous BP guideline by the Joint National Committee (JNC VII) [37–40]. In the CARDIA study of young adults, prehypertension (SBP = 120–139 or DBP = 80–89) was associated with the presence of CAC 20 years later [37]. In that study, long intervals between BP assessments and CAC measurements could have introduced misclassification of exposure status because BP levels and other confounders could have changed over time [37]. In the Multi-Ethnic Study of Atherosclerosis, which examined subjects aged 45–84 years at baseline from 4 ethnic groups, systolic BP was positively associated with the presence of CAC within the normal and prehypertension BP levels [39]. In 8238 Korean adults with a mean age of 51.5 years, the prevalence of CAC > 100 gradually increased from the prehypertension stage, but information on antihypertensive medications and lipid-lowering agents was not considered [40]. Whereas the previous studies used prehypertension (120–139/80–89) according to the JNC VII guidelines

Table 1
Baseline characteristics by BP category among adults aged < 40 years.

Characteristics	No history of hypertension				History of hypertension			*p* for trend
	SBP < 120 & DBP < 80	SBP 120–129 & DBP < 80	SBP 130–139 or DBP 80-89	SBP ≥ 140 or DBP ≥ 90	SBP < 130 & DBP < 80	SBP 130–139 or DBP 80-89	SBP ≥ 140 or DBP ≥ 90	
Number	33,674	3710	6110	1277	914	901	613	
Age (years)	34.5 (3.4)	33.9 (3.3)	35.0 (3.1)	35.5 (3.1)	33.9 (3.3)	34.3 (3.3)	35.0 (3.3)	< 0.001
Male (%)	71.1	95.3	94.3	93.7	94.6	96.3	96.4	< 0.001
Current smoker (%)	18.0	23.1	22.9	24.2	25.0	27.2	26.3	< 0.001
Alcohol intake (%)[c]	19.0	31.5	34.9	42.5	31.1	38.0	44.2	< 0.001
HEPA (%)[d]	13.0	20.0	12.9	13.4	16.6	15.4	14.9	< 0.001
High education level (%)[e]	88.4	89.2	88.6	88.2	87.1	87.2	88.0	0.335
Family history of CVD (%)	5.8	4.5	5.5	5.0	5.0	6.3	6.7	0.545
Diabetes mellitus (%)	0.8	1.3	1.8	3.2	3.4	5.9	5.2	< 0.001
Obesity (%)[f]	30.5	61.0	57.7	66.0	55.7	66.8	70.2	< 0.001
Body mass index (kg/m^2)	23.6 (3.2)	26.2 (3.4)	26.0 (3.6)	26.8 (3.8)	25.9 (3.6)	26.9 (3.8)	27.4 (4.0)	< 0.001
Glucose (mg/dl)[a]	93.0 (9.7)	96.1 (11.1)	97.8 (13.8)	100.8 (19.4)	95.3 (11.6)	100.7 (22.5)	101.0 (19.6)	< 0.001
Uric acid (mg/dl)[a]	5.7 (1.4)	6.5 (1.3)	6.5 (1.4)	6.7 (1.4)	6.4 (1.4)	6.7 (1.4)	6.8 (1.4)	< 0.001
Total cholesterol (mmol/L)[a]	4.99 (0.85)	5.18 (0.86)	5.31 (0.90)	5.39 (0.88)	5.25 (0.89)	5.35 (0.91)	5.39 (0.90)	< 0.001
LDL-C (mmol/L)[a]	3.20 (0.81)	3.43 (0.81)	3.50 (0.84)	3.54 (0.81)	3.48 (0.83)	3.55 (0.85)	3.51 (0.82)	< 0.001
HDL-C (mmol/L)[a]	1.48 (0.39)	1.37 (0.34)	1.35 (0.35)	1.34 (0.36)	1.36 (0.34)	1.34 (0.34)	1.33 (0.34)	< 0.001
Triglycerides (mmol/L)[b]	1.06 (0.76–1.54)	1.35 (0.94–1.96)	1.52 (1.06–2.18)	1.68 (1.16–2.43)	1.32 (0.91–1.91)	1.54 (1.08–2.27)	1.68 (1.21–2.42)	< 0.001
hsCRP (mg/l)[b]	0.4 (0.3–0.9)	0.6 (0.3–0.1)	0.6 (0.4–1.3)	0.7 (0.4–1.4)	0.6 (0.3–1.2)	0.7 (0.4–1.4)	0.8 (0.4–1.6)	< 0.001
HOMA-IR[b]	1.4 (0.9–2.0)	1.8 (1.2–2.6)	1.9 (1.3–2.8)	2.2 (1.5–3.2)	1.6 (1.1–2.4)	2.0 (1.4–3.0)	2.3 (1.5–3.4)	< 0.001
FRS > 10 (%)	0.2	1.0	1.6	5.6	0.9	2.1	7.3	< 0.001
ASCVD risk > 10 (%)	0.04	0.2	0.3	1.4	0.3	0.6	2.2	< 0.001
CAC > 0 (%)	2.8	4.6	6.3	9.6	5.7	8.8	14.0	< 0.001
CAC score	9 (3–23)	7 (2–20)	10 (3–26)	18 (5–54)	10 (3–33)	8 (3–40)	14 (5–50)	< 0.001
Energy intake (kcal/d)[bg]	1432 (1077–1851)	1540 (1143–1975)	1502 (1144–1900)	1492 (1107–1878)	1600 (1213–2020)	1557 (1174–2000)	1576 (1175–2022)	< 0.001

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; FRS, Framingham risk score; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physical activity; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol.
Data are expressed as follows:

[a] Mean (standard deviation).

[b] Median (interquartile range), or percentage.

[c] 20 g of ethanol per day.

[d] HEPA was defined as physical activity that meets either of two criteria: (i) vigorous intensity activity on three or more days per week accumulating ≥1500 MET min/week; or (ii) seven days of any combination of walking, moderate intensity, or vigorous intensity activities achieving at least 3000 MET min/week.

[e] ≥ college graduate.

[f] BMI ≥25 kg/m^2

[g] Among 33,384 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

Table 2
Baseline characteristics by BP category among adults aged 40 years or more.

Characteristics	No history of hypertension				History of hypertension			*p* for trend
	SBP < 120 & DBP < 80	SBP 120–129 & DBP < 80	SBP 130–139 or DBP 80-89	SBP ≥ 140 or DBP ≥ 90	SBP < 130 & DBP < 80	SBP 130–139 or DBP 80-89	SBP ≥ 140 or DBP ≥ 90	
Number	32,988	2097	9004	2561	589	844	884	
Age (years)	45.7 (5.3)	47.3 (7.5)	46.4 (5.8)	46.6 (5.9)	48.4 (8.3)	47 (6.7)	46.2 (5.5)	< 0.001
Male (%)	66.6	76.5	88.5	88.3	80.0	88.2	92.0	< 0.001
Current smoker (%)	22.8	22.0	28.0	27.6	25.7	28.3	26.0	< 0.001
Alcohol intake (%)[c]	20.5	28.9	37.8	41.7	29.5	37.9	43.5	< 0.001
HEPA (%)	15.8	21.8	15.5	15.3	22.6	17.8	15.3	0.211
High education level (%)[d]	80.5	73.3	79.6	80.5	73.2	75.4	80.1	< 0.001
Family history of CVD (%)	7.1	6.1	6.3	6.2	8.0	7.6	7.0	0.146
Diabetes mellitus (%)	.2	3.6	4.0	5.0	11.2	8.8	8.6	< 0.001
Obesity (%)[e]	28.1	53.1	50.0	58.2	45.3	51.1	58.9	< 0.001
Body mass index (kg/m^2)	23.5 (2.8)	25.4 (3.1)	25.2 (2.9)	25.8 (3.2)	24.8 (2.8)	25.5 (3)	26.0 (3.3)	< 0.001
Glucose (mg/dl)[a]	95.4 (11.6)	99.4 (14.9)	100.6 (15.8)	103.6 (21.7)	99.4 (19.0)	102.3 (21.8)	104.1 (22.7)	< 0.001
Uric acid (mg/dl)[a]	5.4 (1.4)	5.8 (1.4)	6.1 (1.4)	6.2 (1.4)	5.8 (1.4)	6.1 (1.3)	6.4 (1.4)	< 0.001
Total cholesterol (mmol/L)[a]	5.17 (0.85)	5.35 (0.87)	5.41 (0.88)	5.48 (0.88)	5.31 (0.92)	5.41 (0.94)	5.49 (0.91)	< 0.001
LDL-C (mmol/L)[a]	3.36 (0.80)	3.55 (0.82)	3.57 (0.81)	3.59 (0.82)	3.51 (0.86)	3.59 (0.88)	3.64 (0.84)	< 0.001
HDL-C (mmol/L)[a]	1.47 (0.39)	1.41 (0.37)	1.37 (0.35)	1.36 (0.36)	1.41 (0.36)	1.34 (0.36)	1.34 (0.34)	< 0.001
Triglycerides (mmol/L)[b]	1.15 (0.82–1.66)	1.38 (0.97–1.96)	1.52 (1.07–2.19)	1.65 (1.17–2.38)	1.33 (0.95–1.93)	1.52 (1.07–2.27)	1.59 (1.11–2.29)	< 0.001
hsCRP (mg/l)[b]	0.4 (0.3–0.8)	0.6 (0.3–1.1)	0.6 (0.3–1.1)	0.6 (0.4–1.2)	0.6 (0.3–1.1)	0.6 (0.4–1.1)	0.7 (0.4–1.3)	< 0.001
HOMA-IR[b]	1.3 (0.8–1.8)	1.6 (1.1–2.4)	1.7 (1.1–2.5)	1.9 (1.3–2.8)	1.5 (1.0–2.3)	1.7 (1.1–2.5)	1.9 (1.3–2.8)	< 0.001
FRS > 10 (%)	8.3	20.5	24.0	38.4	20.6	31.2	41.3	< 0.001
ASCVD risk > 10 (%)	1.6	7.0	5.7	10.2	7.6	9.4	11.9	< 0.001
CAC > 0 (%)	12.2	20.6	22.0	26.4	28.9	28.8	32.6	< 0.001
CAC score	16 (4–46)	21 (5–59)	21 (6–62)	24 (7–71)	29 (8–113)	21 (6–82)	23 (6–66)	< 0.001
Energy intake (kcal/d)[bf]	1388 (1046–1738)	1390 (1045–1768)	1417 (1092–1750)	1398 (1069–1744)	1464 (1093–1848)	1416 (1073–1770)	1381 (1068–1753)	0.007

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; FRS, Framingham risk score; HDL-C, high-density lipoprotein-cholesterol; HEPA, health-enhancing physical activity; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol.
Data are expressed as follows:
[a] Mean (standard deviation).
[b] Median (interquartile range), or percentage.
[c] 20 g of ethanol per day.
[d] ≥ college graduate.
[e] BMI ≥ 25 kg/m^2
[f] Among 27,449 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

Table 3
Prevalence ratios[a] (95% CI) for coronary artery calcification in relation to BP categories by age group.

BP categories	Number	CAC > 0	Prevalence rate (%)	Age and sex-adjusted prevalence ratios (95% CI)	Multivariate-adjusted prevalence ratios (95% CI)	
					Model 1	Model 2
Age < 40						
No history of hypertension						
SBP < 120 & DBP < 80	33,674	932	2.8	1.00 (reference)	1.00 (reference)	1.00 (reference)
SBP 120–129 & DBP < 80	3710	169	4.6	1.46 (1.24–1.71)	1.30 (1.10–1.53)	1.27 (1.08–1.49)
SBP 130–139 or DBP 80-89	6110	382	6.3	1.71 (1.52–1.92)	1.55 (1.37–1.74)	1.45 (1.28–1.63)
SBP≥140 or DBP≥90	1277	123	9.6	2.48 (2.07–2.98)	2.13 (1.76–2.57)	2.02 (1.67–2.43)
History of hypertension						
SBP < 130 & DBP < 80	914	52	5.7	1.83 (1.39–2.39)	1.63 (1.24–2.14)	1.56 (1.19–2.04)
SBP 130–139 or DBP 80-89	901	79	8.8	2.57 (2.07–3.20)	2.17 (1.73–2.71)	2.07 (1.67–2.58)
SBP≥140 or DBP≥90	613	86	14.0	3.75 (3.06–4.60)	3.08 (2.48–3.81)	2.97 (2.40–3.67)
Age ≥40						
No history of hypertension						
SBP < 120 & DBP < 80	32,988	4022	12.2	1.00 (reference)	1.00 (reference)	1.00 (reference)
SBP 120–129 & DBP < 80	2097	431	20.6	1.33 (1.22–1.44)	1.26 (1.15–1.37)	1.25 (1.15–1.36)
SBP 130–139 or DBP 80-89	9004	1981	22.0	1.41 (1.34–1.47)	1.34 (1.27–1.40)	1.29 (1.23–1.35)
SBP≥140 or DBP≥90	2561	676	26.4	1.67 (1.56–1.79)	1.53 (1.43–1.65)	1.46 (1.36–1.57)
History of hypertension						
SBP < 130 & DBP < 80	589	170	28.9	1.66 (1.46–1.88)	1.54 (1.36–1.75)	1.56 (1.38–1.77)
SBP 130–139 or DBP 80-89	844	243	28.8	1.74 (1.56–1.94)	1.61 (1.44–1.80)	1.57 (1.41–1.76)
SBP≥140 or DBP≥90	884	288	32.6	2.12 (1.92–2.34)	1.92 (1.74–2.12)	1.82 (1.65–2.02)

Note: $p < 0.001$ for the overall interaction between age and BP categories for coronary artery calcium score ratios (model 2).

[a] Estimated from Poisson regression with robust variance. Multivariable model 1 was adjusted for age, sex, body mass index, center, year of screening exam, smoking status, alcohol intake, physical activity, educational level, total calorie intake, family history of heart disease, and diabetes mellitus; model 2 was model 1 plus adjustment for LDL-cholesterol, HDL-cholesterol, triglycerides, and glucose.

without differentiating elevated BP (120–129/ < 80) from stage 1 hypertension (130–139/80–89), we were able to apply the new guidelines and found that the risk of CAC increased from the elevated BP category. The mean age of our population was 40.4 years, with almost half of participants aged 20–39, much younger than the populations in former studies. In low-risk and young adults aged 20–39 years without a history of hypertension, the association between BP category and CAC was observed consistently. In young adults with a history of hypertension, higher BP was significantly associated with much higher CAC scores compared to the normal BP category, beginning from stage 1 hypertension, reaffirming the necessity of lowering the target for BP control to 130/80 mmHg. Previous studies have reported low awareness, treatment, and control rates for HTN in young populations [16,18]. The lower prevalence of treatment among young adults with hypertension is not fully understood, but it might result, in part, from healthcare providers' uncertainty and concern about the long-term benefits and adverse effects of early pharmacological intervention in this age group or from patient reluctance [16].In our study, higher BP categories were strongly associated with higher CAC scores, even in young (aged 20–39) and low-risk adults, underscoring the importance

Table 4
Prevalence ratios[a] (95% CI) for coronary artery calcification in relation to BP categories in low-risk group (10-year CVD risk of < 10% or Framingham risk score < 10%).

BP categories	Number	CAC > 0	Prevalence rate (%)	Age and sex-adjusted prevalence ratios (95% CI)	Multivariate-adjusted prevalence ratios (95% CI)	
					Model 1	Model 2
10-year ASCVD risk < 10%						
No history of hypertension						
SBP < 120 & DBP < 80	63,769	4484	7.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
SBP 120–129 & DBP < 80	5494	488	8.9	1.34 (1.22–1.48)	1.27 (1.15–1.39)	1.26 (1.14–1.39)
SBP 130–139 or DBP 80-89	14,145	2025	14.3	1.49 (1.41–1.58)	1.41 (1.34–1.50)	1.38 (1.30–1.46)
SBP≥140 or DBP≥90	3436	644	18.7	1.88 (1.71–2.07)	1.74 (1.58–1.92)	1.75 (1.59–1.92)
History of hypertension						
SBP < 130 & DBP < 80	1416	181	12.8	1.74 (1.50–2.02)	1.64 (1.41–1.90)	1.65 (1.43–1.91)
SBP 130–139 or DBP 80-89	1621	281	17.3	2.08 (1.83–2.36)	1.92 (1.69–2.18)	1.90 (1.67–2.15)
SBP≥140 or DBP≥90	1347	298	22.1	2.53 (2.23–2.88)	2.33 (2.05–2.65)	2.34 (2.06–2.66)
Framingham risk score < 10%						
No history of hypertension						
SBP < 120 & DBP < 80	61,626	3840	6.2	1.00 (reference)	1.00 (reference)	1.00 (reference)
SBP 120–129 & DBP < 80	5197	402	7.7	1.31 (1.20–1.43)	1.25 (1.14–1.36)	1.23 (1.13–1.34)
SBP 130–139 or DBP 80-89	12,485	1495	12.0	1.50 (1.43–1.57)	1.41 (1.35–1.48)	1.36 (1.29–1.43)
SBP≥140 or DBP≥90	2694	396	14.7	1.86 (1.73–2.00)	1.70 (1.58–1.84)	1.65 (1.53–1.78)
History of hypertension						
SBP < 130 & DBP < 80	1339	148	11.1	1.66 (1.45–1.89)	1.57 (1.37–1.79)	1.58 (1.38–1.80)
SBP 130–139 or DBP 80-89	1431	206	14.4	2.04 (1.83–2.27)	1.87 (1.68–2.08)	1.81 (1.63–2.02)
SBP≥140 or DBP≥90	1064	200	18.8	2.41 (2.17–2.67)	2.16 (1.95–2.39)	2.12 (1.91–2.35)

Multivariable model 1 was adjusted for age, sex, body mass index, center, year of screening exam, smoking status, alcohol intake, physical activity, educational level, total calorie intake, family history of heart disease, and diabetes mellitus; model 2 was model 1 plus adjustment for LDL-cholesterol, HDL-cholesterol, triglycerides, and glucose.

[a] Estimated from Poisson regression with robust variance.

of controlling BP in young people to prevent CVD. This finding is in line with the fact that uncontrolled hypertension, even among young adults from the CARDIA study, was associated with an increased risk of future cardiovascular events [18].

Like previous study findings, our study found that conventional risk factors are more frequently observed in higher BP categories [41]. However, even after adjusting for traditional CVD risk factors, we still observed a graded, positive association between BP categories and CAC scores. Furthermore, in our study, the association between BP categories and CAC scores persisted even among participants with CVD risk scores < 10%. Some experimental and clinical studies have suggested that prehypertension is associated with oxidative stress, systemic and local inflammation, and endothelial dysfunction [42–44]. Slightly high BP categories that do not generally require anti-hypertensive agents have been reported to be associated with impaired endothelial repair capacity in early endothelial progenitor cells, which leads to atherosclerosis [44–46].

Several limitations of our study need to be considered. First, the cross-sectional design limits the possibility of establishing causal inferences; we cannot rule out reverse causation or residual confounding. However, we examined the association in individuals free of CVD and use of antihypertensives, lipid-lowering agents, and antidiabetics and used CAC, a marker of subclinical disease not recognized by study participants, as the outcome, thereby minimizing the possibility of reverse causation. Second, the determination of BP was based on a single-day measurement, although three readings were taken. Twenty-four hour ambulatory blood pressure monitoring was not available in this study. However, if participants with white coat hypertension were classified as those with hypertension or if those with masked hypertension were classified as those with normal BP, this type of misclassification of blood pressure categories would have underestimated the true associations BP categories and CAC. Third, behavioral factors such as smoking and alcohol use were assessed via the standard self-administered structured questionnaire used in health checkup programs in Korea as part of the National Health Insurance plan [47]. Measurement errors for those variables could introduce some degree of residual confounding, similar to most epidemiologic studies. Finally, our study population consisted of relatively highly educated, mostly male, young to middle-aged Korean adults. Thus, these findings might not be generalizable to older groups, other race/ethnicity groups, or populations with different demographics. Epidemiologic studies indicate that the prevalence and severity of coronary artery disease vary depending on ethnicity [48,49]. Specifically, Asian populations have been reported to have a lower burden of coronary artery disease and CAC than Western populations, despite similar conventional risk factors [49,50]. Though the issue remains controversial, no major difference in the predictive value of CAC for incident coronary artery disease has been reported to exist among racial and ethnic groups [51]. Additionally, in a young population, even low CAC scores appear to predict CVD events and mortality [52]. Further studies are needed to confirm our findings in different populations.

In this large study of young and middle-aged men and women, the BP categories in the 2017 ACC/AHA guidelines were independently associated with subclinical atherosclerosis beginning with the elevated BP category. This association was observed even in a low-risk population and young adults, reaffirming the importance of early surveillance and proper management of high BP to prevent atherosclerosis and its associated consequences in a young population.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Jeonggyu Kang: drafting of the manuscript and critical revision of the manuscript.

Yoosoo Chang: study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, and critical revision of the manuscript.

Seolhye Kim: acquisition of data, interpretation of data, and critical revision of the manuscript.

Ki-Chul Sung: technical and material support and study supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.11.035.

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