Hypertension

STROKE AND BLOOD PRESSURE

Blood Pressure Levels in Young Adulthood and Midlife Stroke Incidence in a Diverse Cohort

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ABSTRACT: We examined the longitudinal association between blood pressure (BP) and stroke incidence in young and middle-aged adults. BP measured during 9 examinations of the CARDIA study (Coronary Artery Risk Development in Young Adults) from 1985-1986 to 2015-2016 was used to classify participants (n=5079) according to the 2017 Hypertension Clinical Practice Guidelines. We used the highest BP obtained through the third examination (1990–1991) to define baseline BP categories; time-dependent categories (accounting for change in BP over time) were determined incorporating follow-up measurements. BP groups at ages 30 and 40 years were also defined. Stroke events were adjudicated until 2018. Mean age at baseline was 29.8 years. Stroke occurred in 100 participants. Stroke incidence (per 100 000 person-years) was higher ($P<0.001$) in Black (120 [95% CI, 95–149]) versus White (29 [95% CI, 18–46]) participants. After adjustment with Cox models for sociodemographic and cardiovascular risk factors, stage 2 hypertension was associated with a higher risk of stroke at baseline (hazard ratio, 3.72 [95% CI, 2.12–6.54]), as a time-dependent variable (hazard ratio, 5.84 [95% CI, 3.43–9.95]), at age 30 (hazard ratio, 4.14 [95% CI, 2.19–7.82]) and at age 40 (hazard ratio, 5.59 [95% CI, 3.35–9.31]), compared with normal BP. Elevated BP and stage 1 hypertension showed more modest increases in risk. As a continuous variable, systolic BP ≥90 mm Hg at age 40 was directly associated with stroke risk. These findings call for primordial prevention strategies to reduce population BP levels among young and middle-aged adults, particularly in Black young adults given ≈4-fold higher stroke incidence, including within values traditionally considered to be normal. **(*Hypertension*. 2021;77:1683–1693. DOI: 10.1161/HYPERTENSIONAHA.120.16535.)** • **Data Supplement**

Key Words: blood pressure ■ cohort studies ■ primary prevention ■ risk factors ■ young adult

Stroke incidence and hospitalization rates have increased among young adults in recent decades.[1–5] Whether this trend is attributable to enhanced case finding, changes in the burden of standard cardiovascular disease (CVD) risk factors, emerging risk factors such as substance abuse, or other causes remains unclear.[6] Regardless of the exact mechanism, the lifetime impact of stroke on young adults is enormous.[7,8]

Hypertension is the single most important risk factor for stroke.[9,10] Blood pressure (BP) moderately increased between 1988 and 2000 among young adults[11] and has plateaued after the turn of the century.[12] The 2017 Hypertension Clinical Practice Guidelines changed the definitions of BP categories by lowering thresholds, resulting in an estimated 2- to 3-fold increase in the prevalence of hypertension among adults aged 20 to 44 years.[13] To date, little is known about the association of hypertension in the newly defined categories with stroke incidence in young and middle-aged adults. Furthermore, the prognostic importance of long-term BP trajectories starting in young adulthood to midlife stroke risk and whether the BP-stroke relationship is age-dependent have yet to be determined. Importantly, compared with White people, Black people tend to have an earlier age of onset, a longer duration, and a greater severity of hypertension.[14] Not only are Black people more likely to have worse BP control but they are also more likely to develop stroke—a disparity that persists throughout the

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The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.120.16535.

For Sources of Funding and Disclosures, see page 1691.

Hypertension is available at www.ahajournals.org/journal/hyp

Novelty and Significance

What Is New?

- We prospectively examined the association between blood pressure (BP) as longitudinally measured over 30 years and incident stroke in over 5000 participants of a population-based cohort study of Black and White young adults from 4 US cities.
- Stroke incidence was 4-fold higher in Black versus White participants.
- The association of high BP categories with stroke incidence varied with age, strengthening from young adulthood to midlife.
- The BP-stroke relationship was dynamic, with the last BP measurement most strongly related to stroke risk.
- At age 40, a stepwise increase in stroke risk was apparent from a systolic BP of 90 mm Hg upward.

What Is Relevant?

- These findings call for more careful management of BP among younger people and particularly Black younger people given ≈4-fold higher incidence of stroke.
- Taking into consideration that the majority of incident strokes in our study occurred in participants whose BP levels have traditionally been considered to be normal, an effort to shift the whole population BP levels down should complement efforts to control high BP.

Summary

BP trajectory beginning in young adulthood was associated with long-term incidence of stroke.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	cardiovascular disease
DBP	diastolic blood pressure
HDL	high-density lipoprotein
HR	hazard ratio
LDL	low-density lipoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
SBP	systolic blood pressure
T-D	time dependent
Y0	year 0
Y2	year 2
Y5	year 5

life span.[15] The CARDIA study (Coronary Artery Risk Development in Young Adults) is uniquely positioned to address these gaps in knowledge with its diverse cohort, longitudinal assessment of BP over decades of follow-up, and rigorous ascertainment of stroke incidence.

METHODS

Anonymized data and materials have been made publicly available at the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/studies/cardia/).

Study Sample

CARDIA is a multicenter population-based prospective cohort study of the development and determinants of CVD in Black and White young adults recruited at 18 to 30 years of age across 4 US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The study design has been described in detail elsewhere.[16] Nine examinations have been completed to date, which were approved by the institutional review boards at all sites and informed consent obtained at every examination. After the first examination (year 0 [Y0], 1985–1986), examinations were conducted at follow-up years 2 (Y2), 5 (Y5), 7, 10, 15, 20, 25, and 30. The present study includes participants with available data on BP measurements at Y0 (n=5113) who did not drop out of the study before Y5 examination date, yielding data on 5079 participants. November 7, 1990 (median examination date), was set as the start date for participants who did not attend the Y5 examination.

BP Measurements

The methods of BP measurement have been described previously.[17] In brief, during the year 0 to 15 examinations, trained research staff measured BP 3× in participants' right-arm brachial artery at 1-minute intervals after the participant had been sitting in a quiet room for 5 minutes, using a random-zero sphygmomanometer (Hawksley). The average of the second and third measurements was used for the analysis. The standardized BP measurement techniques using validated equipment in this study met the recommendations by the 2017 Hypertension Clinical Practice Guidelines.[13] An automated oscillometric BP monitor (HEM-907XL; Omron) was used from the year 20 examination; all other aspects of measurement remained the same. To minimize potential misclassification, a calibration study was performed at year 20, and values standardized to the sphygmomanometric measures were used for the year 20, 25, and 30 BP measurements.[18]

BP Group Classification

The 2017 Hypertension Clinical Practice Guidelines defined elevated BP as clinic-measured systolic BP (SBP) of 120 to 129 mm Hg and diastolic BP (DBP) <80 mm Hg and stage 1 hypertension as SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg.[13] Accordingly, participants in the present study

were categorized as having normal BP, elevated BP, stage 1 hypertension, or stage 2 hypertension (see Table S1 in the Data Supplement for definitions). Two main strategies for BP group classification were used: the cumulative method and the dynamic method. The former has been described previously[17] and uses the highest BP measured from the first examination to the examination closest to, but not after, the time point where follow-up begins. In contrast, the dynamic method uses the last examination before the time point where follow-up begins. These 2 strategies served as the basis for different analytical approaches (see Table S2 for detailed description).

Stroke Ascertainment

The primary outcome was fatal and nonfatal stroke events. Stroke was defined as the rapid onset of a headache, meningsmus, or a persistent neurological deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiography or surgery). Deficits resolving in <24 hours accompanied by imaging indicating acute stroke were adjudicated as stroke.[19] For the present investigation, the Trial of ORG 10172 in Acute Stroke Treatment criteria for ischemic stroke were applied.[20] All stroke hospitalizations and deaths identified from study entry to August 2018 were examined. Mortality (other than stroke) was also examined as a competing event. Research staff collected information on hospitalizations and outpatient medical procedures during examinations and annual contacts with participants or designated proxies. Medical records were requested and used to adjudicate stroke events. Semiannual contacts were conducted as well to update participants' contact information and vital status. Vital status was additionally ascertained through periodic searches of the National Death Index. Medical records, death certificates, informant interviews (for outpatient deaths), and autopsy reports, when available, were used to adjudicate stroke events and deaths. Two physician members of the End Points Committee independently reviewed medical records to adjudicate each possible stroke event or underlying cause of death using specific definitions and a detailed manual of operations (http://www.cardia.dopm.uab.edu). If disagreement occurred between the primary reviewers, the case was reviewed by the full committee.[17] Definite or probable stroke events (including deaths) were used in the analysis. The definitions used in the algorithm are available online (http://www.cardia.dopm.uab.edu/images/more/2020/CARDIA_Endpoint_Events_MOO_v10_09_2017_with_reports_instructions.pdf). Brain imaging studies were used to differentiate between ischemic stroke and intracerebral hemorrhage. Transient ischemic attacks were not counted as strokes in this study.

Other Covariates

Standardized protocols for data collection were used across study centers, and measurements have been described previously[16] and are available online (https://www.cardia.dopm.uab.edu). Data from all 9 examinations were used. Participants were asked to fast for at least 12 hours and to avoid smoking and heavy physical activity for at least 2 hours before each examination. Sociodemographic characteristics and lifestyle habits were assessed through questionnaires. Medication use was reported by participants who also brought in medications for verification. Blood was drawn, separated, and plasma frozen to −70 °C before analysis in a central laboratory. Glucose was assayed using the hexokinase method. Total cholesterol and HDL (high-density lipoprotein) cholesterol levels were measured enzymatically by the Northwest Lipid Laboratory. LDL (low-density lipoprotein) cholesterol was calculated using the Friedewald equation. Cigarette smoking was defined as smoking at least 5 cigarettes per week almost every week. If answered yes, the subject was asked whether he or she still smoked regularly, and those who responded no were considered to be past smokers. Measured height and weight were used to calculate body mass index as weight in kilograms divided by the square of height in meters (kg/m^2). Leisure-time physical activity was measured in standardized units based on the duration and intensity reported through a Physical Activity History questionnaire. Excessive alcohol consumption was defined as ≥20 g/day in women and ≥30 g/day in men. Diabetes was defined as fasting plasma glucose ≥126 mg/dL, oral glucose tolerance test ≥200 mg/dL, glycosylated hemoglobin ≥6.5%, or use of medications (when available).

Statistical Analysis

Analyses were performed using the R software, version 3.6.1 (R Development Core Team), and IBM SPSS Statistics, version 25 (IBM SPSS, Inc). Characteristics across baseline BP groups are presented as mean (SD) for continuous variables and as frequencies for categorical variables. Total stroke incidence rates with person-time denominators were calculated for the BP groups; CIs were estimated with Fisher exact method. Cox proportional hazards models[21] were constructed to estimate the associations (hazard ratios [HRs] and 95% CIs) between baseline BP groups (based on measurements performed during Y0, Y2, and Y5 examinations) and all-stroke incidence. Follow-up started at Y5 exam (1990–1991) and lasted through 2018. The time-to-event variable was calculated as the difference between the start date and the date of stroke, death, or last contact (whichever came first). An unadjusted analysis was initially conducted. Subsequently, adjustment was made for sociodemographic variables (age, race, sex, study center, and education). Finally, multivariable models additionally adjusted for clinical and behavioral risk factors (smoking, diabetes, LDL cholesterol, HDL cholesterol, body mass index, physical activity, and excessive alcohol use). Data obtained during Y0, Y2, and Y5 examinations were used to assess the covariates; average values were used for body mass index, LDL cholesterol, HDL cholesterol, alcohol consumption, and physical activity (last available information for the remaining covariates). Model covariates were selected a priori if they were well-established stroke risk factors[22,23] or previously shown to be predictive of CVD outcomes in this cohort.[17] BP groups were further handled as time-dependent (T-D) variables in extended Cox regression models incorporating data from year 7, 10, 15, 20, 25, and 30 exams; this approach is suitable for longitudinal studies as it accounts for changes in exposure levels over time.[24] Both the cumulative and dynamic methods (as defined in Table S2) for BP classification were applied.

Cumulative stroke incidence rates across BP groups at ages 30 and 40 years were estimated using the Fine-Gray subdistribution hazard regression model,[25] with death treated as a competing event. We used the Fine-Gray model because standard survival models might produce biased estimates of

stroke incidence in the presence of competing risks.[26] HRs (95% CIs) for incident stroke in BP groups at ages 30 and 40 years were analyzed and compared using the Cox proportional hazards models, with age serving as the time scale.[27] Participants who experienced stroke or died and those lost to follow-up before the specified ages were excluded. Different strategies for BP group classification (Table S2) were applied, and we adjusted for the above-listed covariates (as measured at/last before the specified ages). We used spline methodology to assess and compare the relationship of continuous SBP and DBP levels at age 40 years (or closest before) with subsequent stroke incidence. This was done by adding penalized spline terms for SBP and DBP (separately) to multivariable Cox regression models (as specified above) that also included antihypertensive treatment as a covariate.[28] The proportional hazards assumption was tested using Schoenfeld residuals and was met in all models. Missing values did not exceed 1% in any of the baseline variables considered in the analysis. For missing values of covariates repeatedly assessed during follow-up examinations, the last observation carried forward rule was applied. The Harrell C statistic, which takes into account time to event and censoring, was used as a measure of risk discrimination.[29] $P \leq 0.05$ was considered statistically significant.

RESULTS

We included 5079 participants with mean age of 29.8 (SD, 3.7) years at the Y5 exam, 55% were women, and 52% were Black. The majority of the cohort (82%) participated in all 3 exams (Y0, Y2, and Y5), whereas 13% participated in Y0 and either Y2 or Y5 and 5% in Y0 only. The distribution of BP categories at baseline was 66% normal BP, 10% elevated BP, 18% stage 1 hypertension, and 6% stage 2 hypertension. The mean (SD) SBP and DBP levels were 109 (10) and 68 (8) mm Hg, respectively, and only 102 participants (2%) reported taking antihypertensive medication at any of the 3 exams. On average, higher BP groups were characterized by greater proportions of male and Black participants, higher levels of body mass index, total and LDL cholesterol, and fasting glucose, and lower levels of HDL cholesterol. Excessive alcohol consumption was more prevalent in hypertensive participants compared with those with normal BP (Table 1). Baseline characteristics across BP groups stratified by race are presented in Table S3.

During a mean (SD) follow-up period of 26.1 (3.6) years, 100 individuals experienced fatal/nonfatal incident stroke; 65 were classified as ischemic stroke and 34 as hemorrhagic stroke (1 was unclassified). The median age at stroke occurrence was 49.8 (Q1–Q3, 45.4–54.7) years. The overall incidence of stroke per 100 000 person-years was 76 (95% CI, 62–92), similar between men (71 [95% CI, 51–96]) and women (79 [95% CI, 60–103]; $P=0.61$), but substantially higher in Black (120 [95% CI, 95–149]) versus White (29 [95% CI, 18–46]) participants ($P<0.001$). There was no evidence of race-specific rates differing by sex (28.9 in White women versus 29.7 in White men, $P=0.95$; 123.7 in Black women versus 113.6 in Black men, $P=0.71$). The age- and sex-adjusted cumulative incidence rates of stroke at the end of follow-up, treating death as a competing event, were 3.2% (95% CI, 2.5%–3.9%) in Black versus 0.8% (0.4%–1.2%) in White people (Figure 1).

Stage 2 hypertension, as measured at baseline, was associated with stroke incidence (unadjusted HR, 5.97 [95% CI, 3.64–9.80], compared with normal BP [Table 2]). Multivariable adjustment for sociodemographic, clinical, and behavioral risk factors resulted in a moderate attenuation of the association (HR, 3.72 [95% CI, 2.12–6.54]). Elevated BP and stage 1 hypertension were associated with more modest, nonsignificant increases in risk. Repeated BP measurements were performed among 81% (year 7), 78% (year 10), 73% (year 15), 72% (year 20), 72% (year 25), and 71% (year 30) of the baseline study sample among survivors at each examination. With T-D BP categories, accounting for changes in BP during follow-up, a stronger association was observed between stage 2 hypertension and incident stroke, especially using the dynamic method (multivariable-adjusted HR, 5.84 [95% CI, 3.43–9.95], compared with normal BP [Table 2]). In a sensitivity analysis, using the average (rather than highest) BP measurements during Y0, Y2, and Y5 examinations to define baseline BP groups (restricted to participants with ≥2 measurements; n=4808, 97 incident stroke cases), fewer subjects were classified as having hypertension. Relative to the main analysis (shown in Table 2), this analysis (Table S4) yielded a stronger association with stroke for stage 1 hypertension (multivariable-adjusted HR, 2.15 [95% CI, 1.19–3.91]) and a more moderate association for stage 2 hypertension (multivariable-adjusted HR, 3.18 [95% CI, 1.52–6.64]), compared with normal BP.

The cumulative incidence curves of total stroke across BP groups at ages 30 and 40 years, with death treated as a competing event and using the last measurements before attaining these ages, are depicted in Figure 2. At age 30, a higher rate of stroke was shown for stage 2 hypertension while the curves for normal BP, elevated BP, and stage 1 hypertension did not differ significantly. A clearer separation of the curves was shown at age 40. Multivariable-adjusted Cox regression models supported these findings (Table 3). High BP groups—as classified using the dynamic method—were more predictive of stroke incidence at age 40 than at age 30. At age 30, the adjusted models revealed a significant association for stage 2 hypertension (HR, 4.14 [95% CI, 2.19–7.82]), while ≈50% (nonsignificant) increases in risk were estimated for elevated BP and stage 1 hypertension, compared with normal BP. A stronger graded relationship was demonstrated at age 40, with significant adjusted associations shown for elevated BP (HR, 3.09 [95% CI, 1.35–7.04]), stage 1 hypertension (HR, 2.34 [95% CI, 1.30–4.23]), and stage 2 hypertension (HR, 5.59 [95% CI, 3.35–9.31]), compared with normal BP. Using the

Table 1. Characteristics of Participants in the CARDIA Study According to the 2017 Hypertension Clinical Practice Guidelines for BP Classification

Characteristics*	Overall (n=5079)	Baseline BP groups†			
		Normal (n=3331)	Elevated (n=516)	Stage 1 HTN (n=934)	Stage 2 HTN (n=298)
Age, y	29.8±3.7	29.6±3.7	29.2±3.7	30.1±3.6	31.3±3.2
Women, n (%)	2778 (54.7)	2190 (65.7)	139 (26.9)	330 (35.3)	119 (39.9)
Black, n (%)	2614 (51.5)	1598 (48.0)	281 (54.5)	535 (57.3)	200 (67.1)
Education, y	14.3±2.7	14.4±2.8	14.0±2.4	14.1±2.5	13.7±2.5
BMI, kg/m^2	25.2±5.3	24.4±4.7	25.9±4.8	26.7±6.0	28.9±7.4
Smoking, n (%)					
Current	1533 (30.2)	1014 (30.5)	172 (33.3)	247 (26.4)	100 (33.7)
Past	706 (13.9)	475 (14.3)	75 (14.5)	130 (13.9)	26 (8.8)
Never	2838 (55.9)	1841 (55.3)	269 (52.1)	557 (59.6)	171 (57.6)
Total cholesterol, mg/dL	177.2±31.1	175.0±30.0	178.2±30.4	181.1±32.1	187.6±37.0
LDL cholesterol, mg/dL	130.4±31.6	127.8±30.5	132.0±31.7	135.2±32.5	141.5±36.7
HDL cholesterol, mg/dL	53.3±12.6	54.3±12.4	51.7±12.6	51.7±13.0	49.6±12.0
SBP, mm Hg	108.9±9.9	103.9±6.5	116.7±4.5	116.7±7.3	126.6±10.3
DBP, mm Hg	68.4±8.3	64.8±5.9	68.6±5.4	76.2±5.0	84.0±8.6
Fasting glucose, mg/dL	82.6±16.4	81.4±13.7	84.3±14.1	84.5±20.6	87.8±27.0
Physical activity, units‡	396.1±256.5	383.9±249.5	470.2±279.1	407.6±260.3	367.8±257.2
Excessive alcohol use, n (%)	673 (13.3)	366 (11.0)	89 (17.2)	158 (16.9)	60 (20.2)
eGFR, mL/min per 1.73 m^2	122.0±22.9	121.2±23.0	124.9±24.3	123.1±22.0	123.3±22.4
No. of clinic visits§	2.8±0.5	2.7±0.6	2.8±0.6	2.8±0.5	2.9±0.5

Data are presented as mean (SD) unless otherwise specified. BMI indicates body mass index; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; SBP, systolic blood pressure; Y0, year 0; Y2, year 2; and Y5, year 5.

*Based on cumulative data obtained during CARDIA clinic visits taken place at Y0, Y2, and Y5; the latter defined the follow-up start date for the main analysis. Average values are presented for BMI, total cholesterol, LDL cholesterol, HDL cholesterol, SBP, DBP, and physical activity (last available information for the other variables presented).

†Classification based on the highest BP measured during CARDIA Y0, Y2, and Y5 clinic visits.

‡As assessed with the CARDIA Physical Activity History questionnaire.

§Number of clinic visits from Y0 (first CARDIA examination) to Y5 (after which follow-up began).

same sets of covariates, the discriminatory power of the model at age 40 was superior to that at age 30 (Table 3). Applying the cumulative method, high BP groups at age 40 were consistently more predictive of stroke incidence than at age 30 (Table S5).

We also evaluated and compared the prognostic importance of SBP and DBP (as continuous variables) at age 40 in subsequent development of stroke. Multivariable Cox regression models were fitted, separately for SBP and DBP, with age as the time scale and a penalized spline term added for SBP/DBP. The relationships of SBP and DBP with stroke incidence were generally linear (tests of nonlinear curves were nonsignificant), with a stronger association observed for SBP (multivariable-adjusted HR, 1.84 [95% CI, 1.46–2.31], per 1 SD increase) compared with DBP

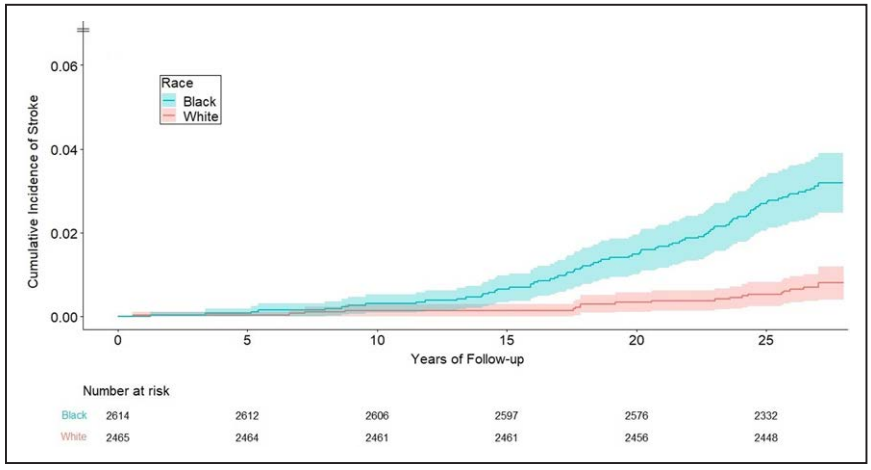

Figure 1. Age- and sex-adjusted cumulative incidence curves for total stroke in Black versus White participants (n=5079 subjects; 100 stroke cases), with death treated as a competing event using the Fine and Gray method (*P*<0.001 for the race comparison).
Colored areas around the curves represent 95% CIs.

Table 2. Association of the 2017 ACC/AHA BP Categories With Subsequent Stroke Incidence Among CARDIA Participants

Exposure definition	BP categories				C statistic (SE)
	Normal BP	Elevated BP	Stage 1 HTN	Stage 2 HTN	
Baseline classification					
No. of participants	3331	516	934	298	...
No. of events	50	10	17	23	...
Incidence rate*	57 (43–75)	74 (36–136)	71 (41–113)	320 (203–480)	...
Unadjusted	1 (ref)	1.32 (0.67–2.61)	1.27 (0.73–2.20)	5.97 (3.64–9.80)	0.613 (0.029)
Model 1†	1 (ref)	1.43 (0.71–2.87)	1.17 (0.67–2.07)	4.45 (2.64–7.49)	0.782 (0.022)
Model 2‡	1 (ref)	1.42 (0.70–2.86)	1.21 (0.68–2.15)	3.72 (2.12–6.54)	0.812 (0.022)
T-D cumulative method					
Unadjusted	1 (ref)	0.99 (0.34–2.82)	1.15 (0.54–2.43)	6.34 (3.74–10.77)	0.714 (0.025)
Model 1†	1 (ref)	0.90 (0.33–2.49)	1.05 (0.50–2.21)	4.65 (2.70–8.01)	0.800 (0.022)
Model 2‡	1 (ref)	0.89 (0.33–2.40)	1.06 (0.50–2.26)	4.30 (2.28–7.49)	0.824 (0.021)
T-D dynamic method					
Unadjusted	1 (ref)	2.08 (0.86–4.99)	2.05 (0.96–4.38)	8.65 (5.19–14.42)	0.732 (0.024)
Model 1†	1 (ref)	1.81 (0.76–4.33)	1.81 (0.85–3.85)	6.34 (3.6–10.68)	0.810 (0.021)
Model 2‡	1 (ref)	1.84 (0.79–4.32)	1.78 (0.83–3.82)	5.84 (3.43–9.95)	0.832 (0.021)

Figures represent HRs (95% CIs) for incident stroke associated with BP groups (unless otherwise specified). The Harrell concordance index (C statistic) is provided for each model as a measure of risk discrimination. The T-D cumulative method defined BP categories according to the highest BP measured up to each follow-up interval; the T-D dynamic method defined BP categories according to the last BP measurement before each follow-up interval. The number of participants at each BP category in the T-D analysis is not presented because it changes during follow-up. ACC indicates American College of Cardiology; AHA, American Heart Association; BMI, body mass index; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; HDL, high-density lipoprotein; HR, hazard ratio; HTN, hypertension; LDL, low-density lipoprotein; ref, reference category; and T-D, time dependent.

*Incidence density per 100 000 person-years (Fisher exact 95% CIs).

†Model 1: adjusted for baseline age, race, sex, study center, and education.

‡Model 2: model 1+smoking, diabetes, LDL cholesterol, HDL cholesterol, BMI, physical activity, and excessive alcohol use (as measured at baseline).

(multivariable-adjusted HR, 1.58 [95% CI, 1.25–1.99], per 1 SD increase); for SBP, a graded association began at ≈90 mm Hg (Figure 3). Restricted to Black participants (n=2543, 74 stroke cases) and analyzed separately, the multivariable-adjusted HRs for stroke at age 40 were 1.87 (95% CI, 1.45–2.40) for SBP and 1.54 (95% CI, 1.20–1.98) for DBP, per 1-SD increases, similar to estimates in the entire cohort. Spline-based HRs are depicted in Figure S1.

DISCUSSION

We examined prospectively the association between BP and incident stroke in over 5000 participants of a population-based cohort study of Black and White young adults from 4 US cities. With up to 9 BP measurements between 1985-1986 and 2015-2016, and stroke events identified through 2018, incidence rate of stroke, per 100 000 person-years, was similar between women and men but 4-fold higher in Black versus White participants. Using the 2017 Hypertension Clinical Practice Guideline classifications, stage 2 hypertension in young and later adulthood (up to age 40) was strongly and significantly associated with stroke risk compared with participants with normal BP. Elevated BP and stage 1 hypertension were associated with more modest increases in risk. In a T-D analysis, the last BP measurement before each follow-up interval was more strongly related to stroke risk than the highest measurement up to that point. Analyzed separately, SBP and DBP at age 40 were both linearly associated with adjusted stroke risk throughout the entire range, with SBP showing a stronger and more graded association than DBP.

Approximately 10% to 15% of all strokes occur in adults aged 18 to 50 years.[30,31] A temporal increase in stroke incidence in younger age groups is concerning. Data from the US Nationwide Inpatient Sample reveal that although hospitalization rates for acute ischemic stroke decreased by 18.4% between 2000 and 2010, trends diverged by age categories. Thus, the decrease observed in individuals aged 65 to 84 years (−28.5%) and ≥85 years (−22.1%) contrasted with a substantial increase in individuals aged 25 to 44 years (+43.8%).[3] An analysis of the Greater Cincinnati Northern Kentucky Stroke Study suggested that between 1993-1994 and 2005, the mean age at stroke decreased by 2 years, while the proportion of stroke contributed by patients aged 20 to 54 years increased from 12.9% to 18.6%. This increase was significant among both Black and White people and was primarily seen in ischemic stroke.[32]

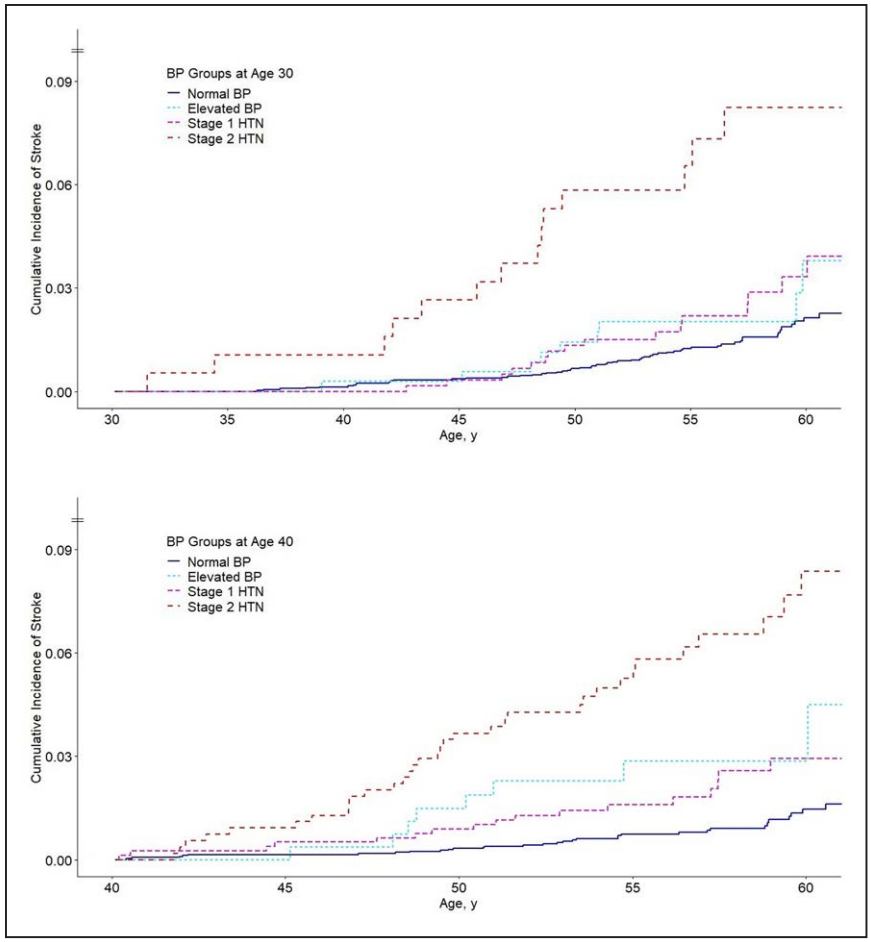

Figure 2. Cumulative incidence curves for total stroke according to blood pressure (BP) group. Incidence is presented at age 30 (top), based on 5084 subjects and 99 stroke events, and at age 40 (bottom), based on 4977 subjects and 91 stroke events.

BP groups were determined according to the last examination before attaining 30 and 40 y of age, as appropriate (dynamic method). The cumulative incidence was calculated as a function of age, with death treated as a competing event using the Fine and Gray method ($P<0.001$ between BP categories by log-rank test in both panels). HTN indicates hypertension.

Higher stroke incidence rates have been documented in Black versus White people at every age, with the greatest relative risks seen in younger age groups[33–35]—a finding supported by our data. About two-thirds of stroke events in our study were classified as ischemic and one-third as hemorrhagic. This partition is also in line with the literature, showing that among young stroke victims, a greater proportion (≈40%) is due to subarachnoid hemorrhage and intracranial hemorrhage, compared with the general stroke population (≈20%).[31]

Previous studies have demonstrated increases in traditional stroke risk factors among younger stroke patients.[1,31,32,36] Hypertension is particularly prevalent among the latter.[32,37] Moreover, it was recently suggested that young adults have lower awareness, treatment, and control of hypertension compared with adults >40 years of age.[12] Our findings highlight the importance of BP control, ideally maintaining normal levels, in primary prevention of stroke in young and middle-aged adults. Hypertension was strongly associated with stroke risk in our study, yet the relationship was dynamic; high BP categories at age 40 were more predictive of stroke risk than the same categories at age 30. Furthermore, our T-D analysis demonstrated that the most recent BP measurement was most strongly associated with stroke. Rather than being a fixed exposure that remains unchanged after a single assessment, BP is a dynamic risk factor that changes over time, for better or for worse. Beyond temporal changes in BP levels, the duration of hypertension also plays a contributory role. Indeed, among ≈240 000 patients with atrial fibrillation from the Republic of Korea, longer duration of hypertension before atrial fibrillation diagnosis was associated with higher risk of subsequent ischemic stroke regardless of baseline SBP levels.[38] In support of this concept, it was recently shown that using long-term measures of cumulative BP may improve CVD risk prediction over a single measurement.[39] In CARDIA, cumulative BP in young adults (determined by summing the product of average mm Hg and the years between each 2 consecutive clinic visits from years 0 to 15) was associated with subsequent CVD risk and improved risk discrimination compared with single BP assessments or changes in BP.[40] Previously, data from the MESA (Multi-Ethnic Study of Atherosclerosis) and CARDIA studies were used to examine whether effective treatment of hypertension can reduce CVD risk to that seen in individuals who have always had ideal BP levels. It was found that participants with well-controlled hypertension on antihypertensive medication still constituted a high-risk group for CVD, possibly attributable to a longer period of prior exposure to higher BP levels.[41] Hypertension is thought to drive cerebrovascular disease in young adults

Table 3. Association of the 2017 ACC/AHA BP Categories at Different Ages With Subsequent Stroke Incidence Among CARDIA Participants

Age at start of follow-up, y	BP groups (dynamic method)				C statistic (SE)
	Normal BP	Elevated BP	Stage 1 HTN	Stage 2 HTN	
Age, 30 y					
No. of subjects	3942	353	601	188	...
No. of events	60	9	16	14	...
Incidence rate*	59 (45–75)	99 (45–187)	104 (60–170)	309 (169–519)	...
Unadjusted	1 (ref)	1.67 (0.83–3.37)	1.80 (1.04–3.12)	5.50 (3.05–9.90)	0.606 (0.028)
Model 1†	1 (ref)	1.56 (0.74–3.29)	1.65 (0.93–2.94)	4.40 (2.40–8.09)	0.783 (0.022)
Model 2‡	1 (ref)	1.47 (0.70–3.09)	1.55 (0.86–2.81)	4.14 (2.19–7.82)	0.803 (0.023)
Age, 40 y					
No. of subjects	3367	271	794	545	...
No. of events	32	8	17	34	...
Incidence rate*	58 (40–82)	188 (81–371)	130 (76–208)	408 (283–570)	...
Unadjusted	1 (ref)	3.33 (1.54–7.21)	2.24 (1.24–4.03)	7.27 (4.49–11.77)	0.712 (0.029)
Model 1†	1 (ref)	2.98 (1.34–6.64)	2.12 (1.18–3.80)	5.23 (3.16–8.66)	0.811 (0.023)
Model 2‡	1 (ref)	3.09 (1.35–7.04)	2.34 (1.30–4.23)	5.59 (3.35–9.31)	0.840 (0.022)

Figures represent HRs (95% CIs) for incident stroke associated with BP groups (unless otherwise specified). The Harrell concordance index (C statistic) is provided for each model as a measure of risk discrimination. BP groups at ages 30 and 40 y were determined according to the last examination before participants attained that specified age (dynamic method). ACC indicates American College of Cardiology; AHA, American Heart Association; BMI, body mass index; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; HDL, high-density lipoprotein; HR, hazard ratio; HTN, hypertension; LDL, low-density lipoprotein; and ref, reference category.

*Incidence density per 100 000 person-years (Fisher exact 95% CIs).

†Model 1: adjusted for race, sex, study center, and education.

‡Model 2: model 1+smoking, diabetes, LDL cholesterol, HDL cholesterol, BMI, physical activity, and excessive alcohol use (as measured at/last before ages 30 or 40 y, as appropriate).

through mechanisms involving endothelial dysfunction and oxidative stress,[42,43] left atrial structure and function,[44] and coronary artery calcification.[45]

Importantly, in MESA (n=1457; mean baseline age, 58.1 years), beginning with an SBP level of 90 mm Hg, there was a stepwise increase in the prevalence of classic

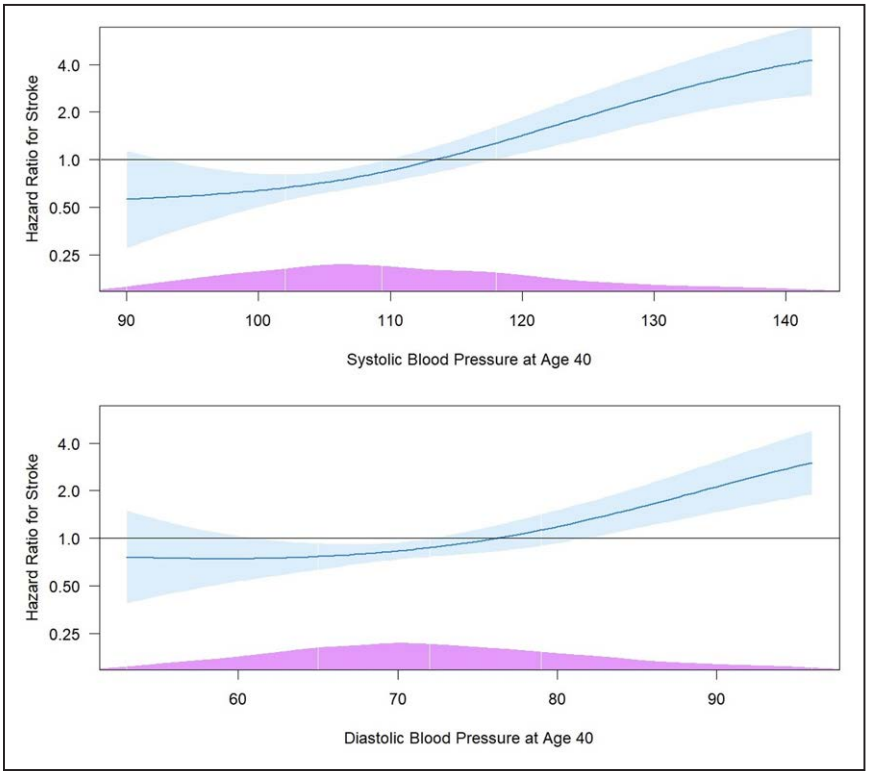

Figure 3. Spline-based hazard ratios (95% CIs) for stroke incidence associated with blood pressure levels. Estimates are presented for systolic blood pressure (top) and diastolic blood pressure (bottom), in mm Hg, as measured at age 40 or last before.

The curves are based on multivariable Cox models adjusted for covariates assessed at age 40 or last before, including race, sex, study center, education, antihypertensive medications, smoking, diabetes, LDL (low-density lipoprotein) cholesterol, HDL (high-density lipoprotein) cholesterol, body mass index, physical activity, and excessive alcohol use. The reference points are 114 and 76 mm Hg (65th percentile) for systolic and diastolic blood pressure, respectively. The histograms at the **bottom** (purple) show the distribution of blood pressure in the sample. The highest and lowest 2.5% of blood pressure values have been winsorized for visualization purposes.

CVD risk factors, coronary artery calcium, and HRs for CVD events over a 15-year follow-up.[46] In CARDIA, cumulative exposure to BP in the prehypertension range (SBP of 120 to 139 mm Hg or DBP of 80 to 89 mm Hg) during young adulthood (up to age 35) was associated with coronary calcium later in life.[47] Among 1.3 million adults in a general outpatient population from Kaiser Permanente Northern California (median age [interquartile range], 53 [40–64] years), both systolic and diastolic hypertension independently influenced the risk of CVD events, with a linear relationship seen for SBP and a J curve for DBP.[48] The present findings regarding SBP at age 40 extend these results to stroke incidence in middle-aged adults by demonstrating a positive graded association that begins at an SBP level as low as 90 mm Hg. Taking into consideration that the vast majority of incident strokes in our study occurred in the normotensive category, these results highlight the importance of primordial prevention to maintain optimal BP levels, including within values traditionally considered to be normal.[13]

Strengths and Limitations

The findings of this study should be interpreted in the context of several potential limitations. As stroke in young and middle-aged adults is relatively uncommon,[49] despite the large biracial population-based cohort and long-term follow-up being used, the small number of incident strokes resulted in reduced statistical precision. This imprecision may explain the greater risk observed for elevated BP compared with stage 1 hypertension in some analyses; indeed, as a continuous variable, the adjusted association with stroke of SBP at age 40 appeared linear. Power considerations also limited subgroup analysis and interaction testing. It remains unclear how BP measurements in this study, collected in a highly controlled research setting, correspond to BP measurements commonly obtained in a typical clinic setting. In addition, research participation effects may have contributed to changes in behaviors or health care provided.[50] Also, missing data on variables repeatedly assessed during follow-up may have resulted in an attenuation of regression coefficients caused by infrequent updating. This study also has notable strengths, including the large, diverse, and well-characterized cohort, adjudication of suspected stroke events by a panel of physicians using detailed evaluation criteria, high retention rates, and the standardized data collection protocols and rigorous quality control. The young age of participants included in the CARDIA study means that all strokes in this analysis should be considered premature events. BP was repeatedly measured during 9 examinations, allowing assessment of long-term changes. These multiple time point assessments over a period of 3 decades provide a more accurate picture of true exposure than would be possible from evaluating single points. Furthermore, inclusion of BP categories as T-D variables in the survival models ensures appropriate analysis of these categories as recently defined by the 2017 Hypertension Clinical Practice Guidelines.[13]

Conclusions

In conclusion, the association of high BP with stroke incidence in CARDIA varies with age, strengthening from young adulthood to midlife. The BP-stroke relationship is dynamic, with the last measurement most strongly related to risk. These findings call for primordial prevention strategies to reduce population BP levels among young and middle-aged adults, particularly in Black young adults given ≈4-fold higher stroke incidence, including within values traditionally considered to be normal.

Perspectives

The association between high BP and stroke is well known. Our results demonstrate the remarkable increase in stroke risk in Black versus White young adults and highlight the importance of primordial prevention of stroke by maintaining optimal BP levels in young adulthood, including within values traditionally considered to be normal.

ARTICLE INFORMATION

Received October 16, 2020; accepted February 8, 2021.

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Sources of Funding

The CARDIA study (Coronary Artery Risk Development in Young Adults) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201800005I and HHSN268201800007I), Northwestern University (HHSN268201800003I), University of Minnesota (HHSN268201800006I), and Kaiser Foundation Research Institute (HHSN268201800004I). This article has been reviewed by CARDIA for scientific content. The views expressed in this article are those of the authors and do not necessarily represent the views of the NHLBI, the National Institutes of Health, or the US Department of Health and Human Services.

Disclosures

None.

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