GUIDELINES/CLINICAL TRIALS/META-ANALYSIS (WILLIAM J. KOSTIS, SECTION EDITOR)

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Increased Risk of Hypertension in Young Adults in Southwest China: Impact of the 2017 ACC/AHA High Blood Pressure Guideline

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Abstract

Purpose of Review To examine the impact of the new 2017 ACC/AHA hypertension guideline on the prevalence of hypertension, its constituent ratio, and their associated factors in southwest China.

Recent Findings A total of 14,220 permanent residents ≥ 18 years were enrolled in this survey. According to the 2017 ACC/AHA hypertension guideline, the hypertension prevalence was substantially increased (46.9% vs. 24.5%); consistent across different age and gender groups, while the hypertension awareness (23.8% vs. 45.6%); treatment (18.6% vs. 35.5%); control (2.3% vs. 11.2%); and control among treatment (9.6% vs. 24.0%) patients were decreased in southwest of China. In our cohort, 31.1% participants were newly diagnosed as hypertension. Young adults accounted considerable proportion in this newly diagnosed hypertension population. The proportion of young hypertensive individuals substantially increased, whereas those of the older hypertensive subjects decreased. Among the hypertensive subjects aged ≥ 65 years undergoing treatment, 90% of the elderly subjects were not eligible for hypertension control and 32.5% have systolic blood pressure control at 130–149 mmHg, and thus need to intensify antihypertensive treatment according to 2017 ACC/AHA hypertension guideline. Smoking, drinking, body fat percentage, and body mass index were considered the factors associated with hypertension according to the Chinese hypertension guideline but not in the 2017 ACC/AHA hypertension guideline.

Summary The adoption of the 2017 ACC/AHA hypertension guideline will substantially increase hypertension prevalence in southwest of China. The new definition of hypertension implies that more young adults will likely suffer from high cardiovascular risks, while additional one third of elder hypertensive subjects will likely need intensified antihypertension treatments.

Keywords Hypertension · Prevalence · Control rate · 2017 ACC/AHA hypertension guideline · Chinese hypertension guideline

Introduction

Hypertension is a public health concern affecting one in four adults worldwide, especially among those whose lifetime prevalence exceeds 90% [1]. Furthermore, hypertension is a

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major risk factor of coronary artery disease, stroke, and kidney disease [2–4], and it has accounted for 51% of stroke deaths and 45% of heart disease-related deaths worldwide [5, 6]. Hypertension is also the leading cause of death in China [7, 8]. Many individuals are unaware about hypertension, and most of those affected are insufficiently treated. In China, over 200 million individuals suffer from hypertension but only less than 15% receive proper treatment [6, 9]. A nationally represented survey in China found that hypertension prevalence rate, awareness rate, treatment rate, and control rate were 27.8%, 31.9%, 26.4%, and 9.7% in 2013 and 2014, respectively [10••], which indicated considerable health burden for China.

In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) released an updated guideline detailing the information on the prevention, detection, assessment, and treatment of hypertension among adults [11••]. Relative to that of the Chinese hypertension guideline, the 2017 ACC/AHA hypertension guideline change the definition

of hypertension from ≥ 140/90 to ≥ 130/80 mmHg and having eliminated the prehypertension stage (Table 1). However, the recommendation for adult antihypertensive medication in the updated ACC/AHA guideline has not been changed. Additionally, the new ACC/AHA guideline has recommended antihypertensive medication to adults > 65 years with systolic blood pressure (SBP) of 130–139 mmHg and a new treatment goal (130/80 mmHg) for all adults taking antihypertensive medication. For adults ≥ 65 years, the SBP treatment goal is < 130 mmHg in the 2017 ACC/AHA hypertension guideline as opposed to the target goal of < 150 mmHg in the Chinese guideline.

The changes made to the hypertension criteria have been widely debated since 2017 when the updated ACC/AHA hypertension guideline was launched. The prevalence, control, and treatment rates for hypertension have also changed on the basis of the updated hypertension definition of ACC/AHA. There are 31 million Americans who are considered high blood pressure (BP) because of hypertension definition changes and about 4.2 million of these newly diagnosed patients need antihypertensive drugs [12••]. Furthermore, more than half of the 55 million individuals, currently requiring

medications, need to improve their antihypertensive strategies to meet new targets [12••]. China is a country where hypertension is regarded a huge health burden; thus, analyzing and interpreting the potential impact of the new ACC/AHA guideline in the Chinese setting are imperative. For instance, the lowered threshold for hypertensive diagnosis has increased the proportion of individuals classified as having high BP, and this scenario will likely place China in an enormous public health burden in terms of addressing morbidity, mortality, and health care spending issues.

This research aimed to examine the impact of the new 2017 ACC/AHA hypertension guideline on the hypertension prevalence, constituent ratio of hypertensive subjects, and associated factors of hypertension in southwest China.

Methods

Study Population

This research represented a subset of a national survey held from October 2012 to December 2013. Participants were

Table 1 Hypertension definition according to 2017 ACC/AHA guideline and Chinese hypertension guideline

	2017 ACC/AHA guidelines	Chinese hypertension guidelines
Guideline definition of hypertension		
SBP, mmHg	≥ 130	≥ 140
DBP, mmHg	≥ 80	≥ 90
Guideline-recommended antihypertensive medication		
SBP, mmHg		
General population	≥ 140	≥ 140
Diabetes or CKD	≥ 130	≥ 130
High cardiovascular disease risk†	≥ 130	*
Age ≥ 65 years	≥ 130	≥ 140
DBP, mmHg		
General population	≥ 90	≥ 90
Diabetes or CKD	≥ 80	≥ 80
High cardiovascular disease risk†	≥ 80	*
Guideline treatment goal		
SBP, mmHg		
General population	< 130	< 140
Diabetes or CKD	< 130	< 130
Age ≥ 65 years	< 130	< 150
DBP, mmHg		
General population	< 80	< 90
Diabetes or CKD	< 80	< 80

ACC/AHA American College of Cardiology/American Heart Association, SBP systolic blood pressure, DBP diastolic blood pressure, CKD chronic kidney diseases

* No specifc BP threshold is provided in the guideline for this population

† High cardiovascular risk is defined as a history of cardiovascular disease or 10-year predicted cardiovascular disease risk ≥10% using the Pooled Cohort risk equations

enrolled by using a stratified multistage cluster sampling design. Of the 38 districts in the municipality of Chongqing, eight were sampled for the survey. The first stage of the sampling involved the random selection of four urban areas (Dadukou District, Qianjiang District, Hechuan District, and Yongchuan District) and four rural areas (Tongnan County, Rongchang County, Bishan County, and Liangping County), and their divisions were set according to the National Civil Administration Bureau's division standard [13]. The second sampling stage involved the random selection of two neighborhoods (urban) or two townships (rural) from each of the selected districts/counties. The third sampling stage involved the random selection of three residential committees (urban) or three villages (rural) from each of the selected neighborhoods/townships. In the final sampling stage involved the random selection of a given number of participants from each of the 14 sex and age groups (male/female aged 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, or 75 years). Individuals aged ≥ 15 years who lived in the local area for more than 6 months at the time of the sampling were eligible to participate. The present work only sampled permanent residents ≥ 18 years old. The total resident samples were 14,220, which accorded with the required population of the new ACC/AHA hypertension guideline. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and all subjects signed informed consent for data collection and analyses prior to participation.

Study Protocol and Data Collection

Data were collected by the investigators trained with questionnaire and physical examination. The questionnaire was used to assess the following: demographic characteristics (name, gender, date of birth, race, education, marital status, and employment); alcohol consumption, smoking, and dietary habits; physical activity level; and disease history. Height, weight, waist circumference, body fat percentage (BFP), visceral adipose index (VAI), and BP were assessed for the physical examination part of the research. BP was measured by using an electronic sphygmomanometer (Omron HEM-1300) after the participants were advised to avoid alcohol consumption, cigarette smoking, and coffee or tea intake. Participants were also instructed to exercise for at least 30 min before their BP measurements and to rest for at least 1 min between each measurement. An average of three measurements was taken for the BP examination.

Evaluation Criteria

The definition of hypertension, presented in this paper, was adopted from two guidelines. According to the Chinese hypertension guideline, hypertension involves an SBP of ≥ 140 mmHg or a diastolic blood pressure (DBP) of ≥ 90 mmHg or a self-reported use of antihypertensive medications in the last 2 weeks irrespective of BP [14]. However, the criteria of prevalent hypertension were changed from ≥ 140/90 to ≥ 130/80 mmHg in the 2017 ACC/AHA hypertension guideline [11••]. Awareness of hypertension can be established when hypertensive patients respond positively to the question, "Have you ever been told by a doctor or other healthcare professional that you had hypertension, also called high blood pressure?" Therefore, the awareness criterion was not comparable between the abovementioned two guidelines.

Treatment of hypertension can be determined when hypertensive patients answer affirmatively the question, "Because of your hypertension/high blood pressure, were you taking antihypertensive medications in the previous 2 weeks?" Control of hypertension considered both the SBP and DBP of hypertensive patients and whether the measurement was below the threshold of the standard in the 2017 ACC/AHA hypertension guideline and the Chinese hypertension guideline, respectively. The term control among treatment of hypertension was defined as the BPs of hypertensive patients that have been controlled through treatment. Body mass index (BMI) was calculated as weight in kilograms divided by the square root of height in meters.

Statistical Analysis

Data processing and statistical analysis were performed by using SPSS 20.0 (SPSS Inc., Chicago, USA). All variables were statistically described, measurement dates were reported as mean ± SD (i.e., standard deviation), and counting dates were presented as frequencies and proportions. Analysis of variance and t test were conducted to compare the intergroup differences of measurement dates. Measurement date was compared by using two-sided unpaired Student's t test or Wilcoxon test, and categorical variables were compared by using Pearson's x^2 tests. To explore the factors associated with hypertension prevalence, multivariable logistic regression analysis was also performed. Probability values of $P < 0.05$ were considered statistically significant.

Results

A total of 14,220 permanent residents (male, 7186; 50.5%) aged ≥ 18 years were included in this research. The demographic characteristics and the behavioral risk factors of the population based on the BP data were presented in Table 2. There are 34.0%, 20.2%, 31.1%, and 14.8% of the subjects with SBP/DBP levels of < 120/80 mmHg, 120–129/80 mmHg, 130–139/80–89 mmHg, and ≥ 140/90 mmHg, respectively in our cohort. Adults with higher BP were older and more likely to be female, urban resident, Han national, widowed, and have primary school or lower education level.

Table 2 Characteristics of study population

| Variables	SBP/DBP categories (mmHg)				P value
	< 120/80 (n = 4906)	120–129/< 80 (n = 2906)	130–139/80–89 (n = 4481)	≥ 140/90 (n = 2127)	
Percentage of population(%)	34.0	20.2	31.1	14.8	
Gender					0.000*
Male	55.2	52.0	48.4	37.6	
District					0.000*
Urban	45.7	48.2	49.1	54.7	
Ethnicity					0.212
Han	88.9	89.4	90.0	90.2	
Smoking					0.000*
Yes	23.1	23.0	20.1	16.4	
Drinking					0.734
Yes	59.3	60.1	60.7	57.9	
Marital status					0.001*
Single	10.9	11.2	11.8	9.4	
Married	79.9	78.0	77.3	78.5	
Divorced	2.8	3.0	3.0	2.7	
Widowed	6.5	7.9	7.9	9.3	
Education level					0.000*
Primary school or below	41.6	45.5	45.4	51.5	
Middle school	52.9	48.5	48.1	43.6	
College or above	5.4	6.0	6.5	4.8	
Occupation status					0.008*
Employed	68.1	68.1	68.7	66.3	
Retiree	3.3	4.4	4.4	3.9	
Student	3.4	3.7	4.0	3.5	
Unemployed	25.2	23.8	22.9	26.3	
Age	45.9 ± 17.6	47.1 ± 19.0	47.0 ± 18.9	49.9 ± 19.2	0.000*
Salt intake(g/d)	4.9 ± 4.3	4.8 ± 3.5	4.6 ± 3.3	4.7 ± 3.8	0.001*
BMI	23.2 ± 3.3	23.3 ± 3.4	23.3 ± 3.4	23.1 ± 3.3	0.006*
WC	78.9 ± 9.0	79.3 ± 9.4	79.3 ± 9.3	78.4 ± 9.2	0.006*
BFP	26.5 ± 7.7	27.1 ± 8.0	27.3 ± 7.8	28.2 ± 8.0	0.074
VAI	7.7 ± 4.0	7.9 ± 4.1	7.8 ± 4.1	7.43 ± 3.9	0.279

*$P < 0.001$ compared with different SBP/DBP categories

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *WC* waist circumference, *VAI* visceral adipose index, *BFP* body fat percentage

Meanwhile, those individuals with SBP/DBP of 130–139/80–89 mmHg were more likely to be drinkers and have college or higher education level.

The prevalence of hypertension was 46.9% according to the 2017 ACC/AHA hypertension guideline, which was nearly twice the rate in the Chinese hypertension guideline (24.5%). However, the hypertension awareness (23.8% vs. 45.6%) and treatment (18.6% vs. 35.5%) rates according to the ACC/AHA guideline were only half the rates as those in the Chinese guideline. Additionally, the hypertension control and control-among-treatment rates according to the ACC/AHA guideline were 2.3 and 9.6%, respectively, which were significantly lower than the corresponding rates (11.7 and 24.6) in the Chinese guideline ($p < 0.05$) (Fig. 1a). The prevalence of hypertension was also higher in the ACC/AHA guideline compared with those in the Chinese guideline for all age and sex groups (Fig. 1b, c). Subsequent age subgroup analysis showed that hypertension prevalence in the ACC/AHA guideline for subjects aged ≥ 75 years was nearly 80%, which was four times the rate for subjects aged 18–24 years (Fig. 1b). In addition, according to the ACC/AHA guideline, 90% of the elderly subjects were not eligible for hypertension control and 32.5% of the subjects with SBP control at 130–149 mmHg among the hypertensive subjects aged
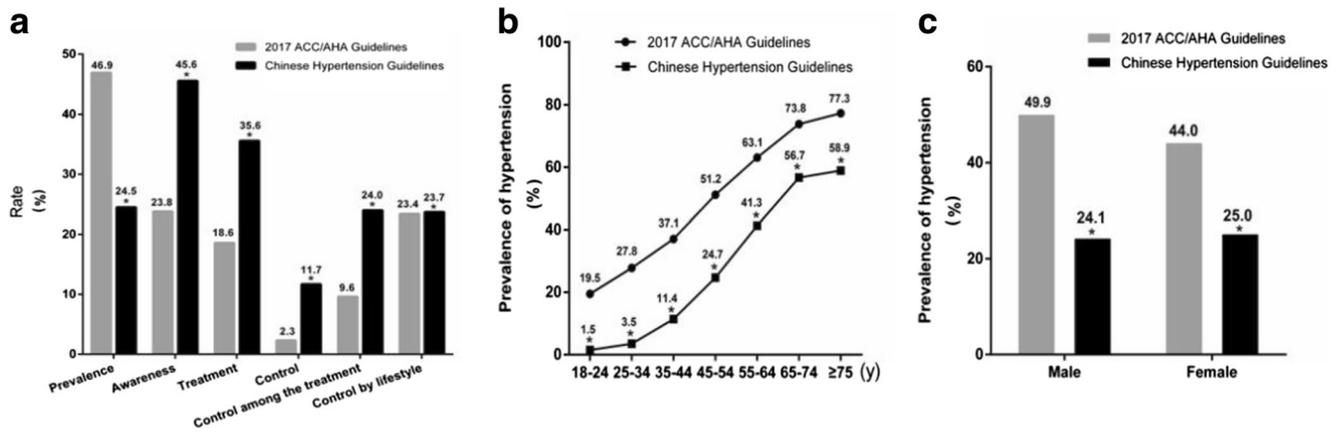
Fig. 1 Comparison of hypertension prevalence, awareness, treatment, control, and control-among-treatment rates as defined by the Chinese hypertension guideline and the 2017 ACC/AHA hypertension guideline. **a** Hypertension prevalence, awareness, treatment, control, and control-among-treatment rate of the overall population. **b** Comparison of hypertension prevalence stratified by age. **c** Comparison of hypertension prevalence stratified by gender. The number shows the percentage of each column. ACC/AHA, American College of Cardiology/American Heart Association

≥ 65 years undergoing treatment required intensified antihypertensive treatment (Fig. 2).

Approximately 31.1% participants with SBP/DBP levels of 130–139/80–89 mmHg were newly diagnosed as hypertensive based on the 2017 ACC/AHA hypertension guideline (Table 2). As shown in Fig. 3, young subjects aged 25–34 years accounted the biggest proportion for this newly diagnosed hypertension population (22.4%). Following the 25–34-year-old subgroup, middle-aged crowed in the subgroup 35–45 years and 45–55 years groups account for 16.4 and 15.5% of this population, respectively. Interestingly, old subjects aged > 75 years accounted the smallest proportion (11.0%) relative to the rest of the age groups. Meanwhile, the results of gender analysis indicated that 48.4% males and 51.6% females consisted the newly diagnosed hypertension group based on the ACC/AHA guideline.
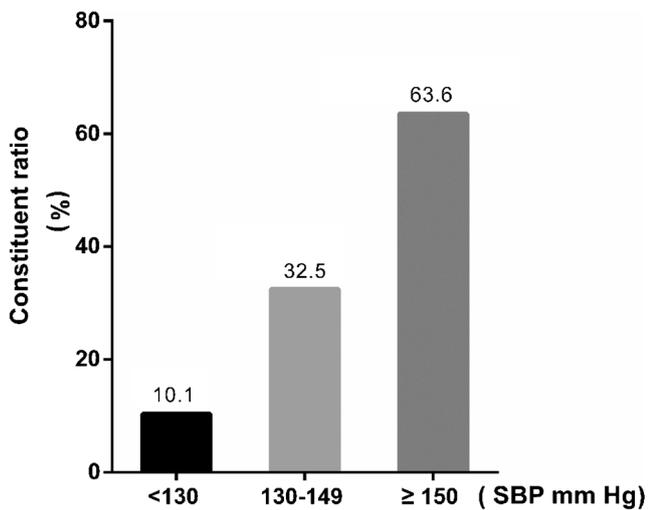

Fig. 2 Constituent ratio of hypertensive subjects aged ≥ 65 years old undergoing treatment. SBP, systolic blood pressure

The proportion of hypertensive subjects stratified by age differed on the basis of the hypertension definitions of the Chinese and ACC/AHA guidelines ($p < 0.001$) (Fig. 4). The elderly (≥ 55 years old) accounted for three fourths of the entire hypertension population based on the Chinese guideline, but they comprised one half as defined by the new ACC/AHA guideline. The proportion of old individuals considered hypertensive in the new ACC/AHA guideline was significantly lower than those in the Chine guideline, especially for the subgroups aged 65–74 years (17.9% vs. 26.3%) and > 74 years (17.6% vs. 25.9%). However, the proportions of the 45–54-year-old hypertensive individuals were similar between the two guidelines. The young subjects aged 35–44, 25–44, and 18–24 years comprised 14.3%, 13.3%, and 4.3%, respectively, according to the new ACC/AHA guideline, and these percentages were much higher than those when the Chinese definition was used (i.e., 8.4%, 3.2%, and 0.7%, respectively) ($p < 0.001$).

Table 3 showed the results of the multivariable logistic regression analyses of factors associated with hypertension prevalence based on the different guidelines. Our results indicated that older rural residents were more likely to have hypertension based on both Chinese and new ACC/AHA definitions. Smoking, drinking, BFP, and BMI were regarded the factors associated with hypertension in the Chinese guideline but not in the 2017 ACC/AHA guideline.

Discussion

To our best knowledge, this study was the first one to explore the potential impact of the 2017 ACC/AHA hypertension guideline on hypertension prevalence, constituent ratio, and associated factors in the southwest China setting. Compared
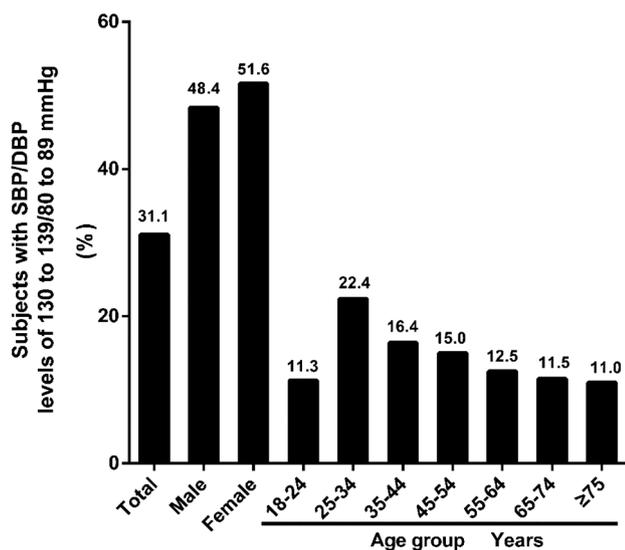
Fig. 3 Newly diagnosed hypertension according to the 2017 ACC/AHA hypertension guideline. Overall, 31.1% of subjects with SBP of 130–139 mmHg or DBP of 80–89 mmHg were newly diagnosed as hypertensive according to the 2017 ACC/AHA hypertension guideline. The number showed the percentage of each column. ACC/AHA, American College of Cardiology/American Heart Association; DBP, diastolic blood pressure; SBP, systolic blood pressure

with the Chinese guideline, the new ACC/AHA guideline has more stringent BP control criteria and treatment goal among those taking antihypertensive medications. For instance, for individuals aged > 65 years, the SBP is < 130 mmHg in the new ACC/AHA guideline versus < 150 mmHg in the Chinese guideline (Table 1).

Consistent with previous results [15•, 16•], our results demonstrated that the 2017 ACC/AHA hypertension guideline
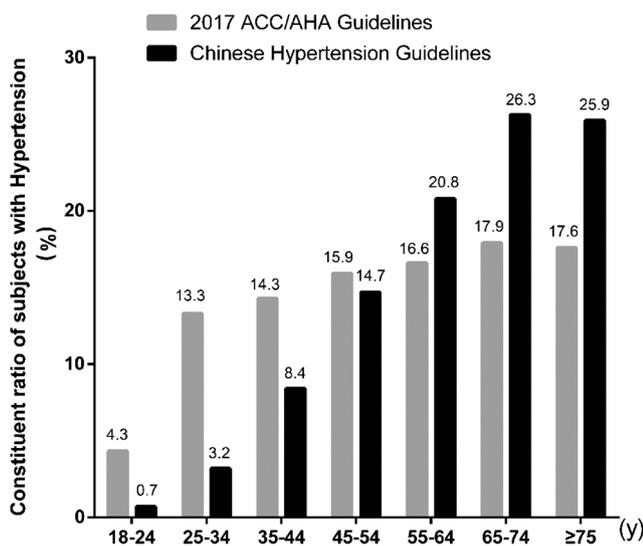
Fig. 4 Comparison of constituent ratio of hypertensive subjects stratified by age as defined by the Chinese hypertension guideline and the 2017 ACC/AHA hypertension guideline. The number showed the percentage of each column. ACC/AHA, American College of Cardiology/American Heart Association

substantial increased in hypertension prevalence, which was consistent across different age and gender groups, and the decrease in hypertension awareness, treatment, control, and control-among-treatment rates in the southwestern Chinese population. Our study also showed that, among the hypertensive subjects aged ≥ 65 years undergoing treatment, 90% of the subjects have poor BP control and 32.5% of the subjects with SBP at 130–149 mmHg, who required intensified antihypertensive treatment according to 2017 ACC/AHA hypertension guideline. In the overall population, approximately 31.1% of the participants with SBP/DBP levels of 130–139/80–89 mmHg were newly diagnosed as hypertensive according to the 2017 ACC/AHA hypertension guideline. The proportion of elderly individuals in the overall hypertension population was substantially lower while the proportion of younger individuals was higher in the new ACC/AHA guideline compared with those in the Chinese guideline. The associated factors of hypertension prevalence also varied between the two guidelines.

The 2017 ACC/AHA hypertension guideline has set 130/80 mmHg as the BP goal for the overall population regardless of age. On the basis, nearly one third of the subjects controlled SBP at 130–149 mmHg among the hypertensive individuals aged ≥ 65 years undergoing treatment which has been met the treatment goal on the basis of the Chinese guideline but not with the new ACC/AHA guideline. Optimal BP control targets for certain age groups have been a topic of debate and controversy, and such concern may be attributed to the proportion of benefits gained and risks of injuries obtained on the basis of BP levels and goals that vary with age [17–19], especially among the elderly [20]. Although several studies on cardiovascular diseases (CVDs) have evaluated the potential risk-reduction benefits of BP goals lower than those in the Chinese hypertension guideline (i.e., 140/90 mmHg), BP is a less-powerful risk factor when correlated with age [21–23, 24••]. General knowledge dictates that BP increases with age. The elevation of BP among the elderly may be a compensatory mechanism to guarantee normal blood circulation to the heart, brain, and kidneys. Interestingly, high BP has instigated fears among susceptible patients. For elderly patients, especially those with isolated systolic hypertension and poor vascular compliance, BP levels of < 130/80 mmHg may not be achieved; furthermore, individuals will likely experience dizziness and cognitive failure when SBP is < 140 mmHg [25••, 26, 27]. Among elderly hypertensive patients, the beneficial target should be to focus on SBP reduction, and treatments beyond this target may be detrimental to their health [28–30]. China, currently, has the world's largest population of 1.4 billion, comprising 19.13% of the world's population, and is rapidly transforming into an aging nation [31]. The optional BP goal for older individuals should be taken seriously, and further investigations are warranted.

Table 3 Associated factors for hypertension according to two guidelines

Variables	Chinese hypertension guidelines		2017 ACC/AHA guidelines	
	OR (95% CI)	P vale	OR (95% CI)	P vale
District		0.005		< 0.001
Urban	1.000 (reference)		1.000 (reference)	
Rural	1.280 (1.077, 1.520)		1.487 (1.286, 1.718)	
Ethnicity		0.001		0.003
Han	1.000 (reference)		1.000 (reference)	
Other	0.548 (0.388, 0.773)		0.664 (0.505, 0.874)	
Smoking		0.021		NA
No	1.000 (reference)		1.000 (reference)	
Yes	1.218 (1.030, 1.520)		NA	
Drinking		< 0.001		NA
No	1.000 (reference)		1.000 (reference)	
Yes	1.503 (1.257, 1.798)		NA	
Salt intake(g/d)		NA		NA
< 6 g/d	1.000 (reference)		1.000 (reference)	
≧ 6 g/d	NA		NA	
Age (years)		< 0.001		< 0.001
18–44	1.000 (reference)		1.000 (reference)	
45–64	3.762 (3.023, 4.683)		2.285 (1.954, 2.672)	
> 65	8.985 (6.998, 11.536)		5.042 (4.144, 6.135)	
VAI	1.093 (1.071, 1.116)	< 0.001	1.093 (1.068, 1.118)	< 0.001
BFP	1.031 (1.018, 1.045)	< 0.001	NA	NA
BMI	NA	NA	NA	NA
WC	NA	NA	1.017 (1.007, 1.028)	< 0.001

VAI visceral adipose index, *BFP* body fat percentage, *BMI* body mass index, *WC* waist circumference, *NA* not applicable, *CI* confidence interval, *OR* odds ratio

A number of randomized trials demonstrated that the CVD mortality risk reduction was associated with BP treatment goals, which are lower in the 2017 ACC/AHA guideline than those recommended in the Chinese guideline. Here, 3228 subjects (22.4%) were newly diagnosed as having hypertension and added 255 subjects (32.5%) involved older hypertensive subjects undergoing treatment who need intensified treatment according to the 2017 ACC/AHA guideline. Hypertension treatment and control rates were dramatically decreased from 35.6 and 11.2% to 18.6 and 2.3%, respectively. This change indicates an increase in the number of individuals who were previously healthy and now considered unhealthy, and an increase in those who need intensified antihypertension treatment, which further demonstrate an enormous public health burden in terms of morbidity, mortality, and health care expending in the coming decades. Individuals, medical care system handlers, and the government should pay more attention to the potential increased proportion of hypertension according to the updated guideline.

The findings also indicated that the young, drinkers, and those individuals with college or higher education level were more likely to have BPs of 130–140 mmHg/80–90 mmHg

(Table 2). The proportion of newly diagnosed young individuals according to the 2017 ACC/AHA hypertension guideline significantly increased (Fig. 4), especially for subgroup aged 25–34 years (Fig. 3). The young generation of China usually suffers from considerable work-life pressure, unhealthy lifestyle, and lack of physical exercise, which altogether contribute to high cardiovascular risks among young adults. The subjects from this subgroup should therefore pay more attention to their health, while policymakers should tailor effective intervention strategies for this specific population. However, smoking, drinking, BFP, and BMI were the factors found to be associated with hypertension according to the Chinese hypertension guideline but not in the 2017 ACC/AHA hypertension guideline, hence the need to further investigate the underlying reasons for the deviation.

Conclusion

Hypertension prevalence substantially increases and hypertension treatment and control rates decrease on the basis of the 2017 ACC/AHA hypertension guideline. The new

definition of hypertension implies that more young adults will likely suffer from high cardiovascular risks, while additional one third of elder hypertensive subjects will likely need intensified antihypertension treatments. The applicability of the 2017 ACC/AHA hypertension guideline to the Chinese population should be further evaluated.

Compliance with Ethical Standards

Conflict of Interest   This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and all subjects signed informed consent for data collection and analyses prior to participation.

Dan Li, Xiaofang Zeng, Yi Huang, Han Lei, Ge Li, Nan Zhang, and Wei Huang declare that they no conflicts of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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