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Identification of Normal Blood Pressure in Different Age Group

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Abstract: The concept of using single criterion of normal blood pressure with systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg for all ages is still disputable. The aim of the study is to identify the cutoff value of normotension in different age and sex groups.

Totally, 127,922 (63,724 men and 64,198 women) were enrolled for the analysis. Finally, four fifths of them were randomly selected as the study group and the other one fifths as the validation group. Due the tight relationship with comorbidities from cardiovascular disease (CVD), metabolic syndrome (MetS) was used as a surrogate to replace the actual cardiovascular outcomes in the younger subjects.

For SBP, MetS predicted by our equation had a sensitivity of 55% and specificity of 67% in males and 65%, 83% in females, respectively. At the same time, they are 61%, 73% in males and 73%, 86% in females for DBP, respectively. These sensitivity, specificity, odds ratio, and area under the receiver operating characteristic curve from our equations are all better than those derived from the criteria of 140/90 or 130/85 mmHg in both genders.

By using the presence of MetS as the surrogate of CVD, the regression equations between SBP, DBP, and age were built in both genders. These new criteria are proved to have better sensitivity and specificity for MetS than either 140/90 or 130/85 mmHg. These simple equations should be used in clinical settings for early prevention of CVD.

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Abbreviations: BP = blood pressure, CVD = cardiovascular disease, DBP = diastolic blood pressure, FPG = fasting plasma glucose, JNC = Joint National committee on Detection Evaluation and Treatment of High Blood Pressure, ROC = receiver operating characteristic, MetS = metabolic syndrome, SBP = systolic blood pressure, TG = triglyceride.

INTRODUCTION

It is well-known that high blood pressure (BP) is the fundamental cause for many serious cardiovascular diseases (CVD) such as cerebral vascular disease and coronary artery disease.[1] Several reports have shown that there is a continuous, graded, and strong relationships between BP and the risk CVD.[2,3] The definition of normal BP (systolic blood pressure [SBP] < 140 mmHg and diastolic blood pressure [DBP] < 90 mmHg) was first proposed by the 3rd report of Joint National committee on Detection, Evaluation and Treatment of High Blood Pressure in 1984 (JNC III).[4] However, some of the researchers are still skeptical about this criteria. For example, Domanski et al[5] suggested that the cardiovascular mortality could be avoided by lowering the BP down to 120/80 mmHg in both younger and middle-aged group based on data from a 22 years follow-up cohort (Multiple Intervention Trial cohort). Furthermore, by using logistic splines analytic method, Port et al[6] also suggested that hypertension should be defined according to age- and sex-specific threshold rather than a single value. At the same time, one of the largest meta-analysis including 61 cohorts, 958,074 subjects, and 56,000 cardiovascular deaths also indicated a different value of optimal BP which is 115/75 mmHg.[7] The results of these important studies indicated that the definition of normal BP is still under controversial.

The clustering of hypertension, dyslipidemia, and obesity have been noted early in 2001.[8] As they are highly correlated to future occurring of the CVD and diabetes, the World Health Organization has denoted this phenomenon as metabolic syndrome (MetS) in 1998.[9] Later, a modified and simpler version published by the National Cholesterol Education Program in 2002.[10] By far, this is the most widely accepted and used criteria. It should be stressed that the original purpose to define MetS was trying to early detect subjects with high risk for CVD and diabetes. Till now, compiling results derived either in the cross-sectional or the longitudinal studies all repeatedly validated its predictability. Noticeably, in most of these pivotal studies, actual occurrences of mortality and/or morbidities were often used as the primary endpoints. It is not difficult to postulate that these endpoints are common in the elderly. However, in the younger cohort, these cardiovascular outcomes are much less to be found. To have enough number for an observational study to become statistically significant would take a long time which is difficult for many of the researchers. Unfortunately, the aforementioned definition for normotension derived from older cohort is being applied to all age groups at

present, and it is easily to understand that this is just not reasonable. Ever since the publication of the notion of MetS, there are many longitudinal studies focusing on its predictable CVD.[11–13] These studies unanimously showed positive results and were published in some of the best journals. Thus, MetS could be used as a surrogate to replace the actual cardiovascular outcomes in the younger subjects. Although it is less accurate, by using this method, we could re-evaluate the more logical cutoff points of normotension in the younger population.

Other than this, it is also important to note that both SBP and DBP change as age increases.[14] In other words, age plays a very important role in the regulation of BP. Therefore, we hypothesized that the definition for normal SBP and DBP should vary rather than using the same value in all age-groups.

In this cross-sectional study, we enrolled 127,922 subjects. Four fifths of the subjects were used to build an equation from the logistic regression lines of SBP and DBP to have MetS in different gender. The levels of BP calculated from these curves could detect either CVD or diabetes more precisely and should be regarded as the definition of hypertension in its corresponding age and sex groups. Finally, these equations are further verified and compared with the present standard of normal BP in the remaining one fifths of the subjects.

MATERIALS AND METHODS

Study Population

The study subjects of the present study were enrolled form the data bank of Meei-Jaw (MJ) Health Screening Centers between 1999 and 2008. MJ health screening centers are privately owned chain of outpatient department located throughout the whole Taiwan, which offer routine health check-ups. Therefore, the database contained subjects everywhere in Taiwan. All study subjects were anonymous, and informed consent was obtained from each participant. The study proposal was reviewed by the institutional review board of MJ Health Screening. Totally, 129,680 subjects were enrolled when undergoing routine health checkups. They were between 21 and 65 years old. Since BP was the major variables we evaluated in this study, subjects who taking any medications would influence BP were excluded. Finally, 127,922 (63,724 men and 64,198 women) were eligible for the analysis. Four fifths of them were randomly selected as the study group and the other one fifths as the validation group. Reporting of this study conforms to the STROBE statement along with references to the STROBE statement and the guidelines.

Anthropometric Measurements and General Data

The participant's medical history, including present medications, was acquired by the study nurses using a questionnaire. Detailed physical examinations were done for each subject. An auto-anthropometer Nakamura KN-5000A (Nakamura, Tokyo, Japan) was used to determine body weight and height. Waist circumference was measured at the midpoint between the inferior border of the last rib and the iliac crest in a horizontal level. A computerized auto-mercury-sphygmomanometer, Citizen CH-5000 (Citizen, Tokyo, Japan) was used to measure BP on the right arm of each subject seated, after 5 minutes of rest. BP was measured twice at 10-min intervals. The average value of these 2 records was taken into the analysis.

Laboratory Evaluation

After the 10 hour overnight fast, blood specimens were collected from each subject for further analysis. Plasma was separated from the whole blood within 1 hour and stored at $-70\,^{\circ}C$. Fasting plasma glucose (FPG) and plasma lipid concentrations were measured later. A glucose oxidase method (YSI 203 glucose analyzer; Scientific Division, Yellow Springs Instruments, Yellow Springs, OH) was used to determine FPG levels. The dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan), was used to determine total cholesterol and triglyceride (TG). An enzymatic cholesterol assay following dextran sulfate precipitation was used to determine serum high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels.

Definition of Metabolic Syndrome

We used the newest criteria of MetS in 2009 with some revision.[15] The WC more than or equal to 90 and 80 cm in Taiwanese men and women, respectively.[16] Other 4 criteria were the same: SBP more than or equal to 130 mmHg or DBP more than or equal to 85 mmHg, TG more than or equal to 150 mg/dL, FPG more than or equal to 100 mg/dL, and HDL less than or equal to 40 and 50 mg/dL in men and women or taking related medications.

In the present study, the BP was the independent component. Thus, subjects with any 2 of remaining 4 MetS components were regarded as fulfilling the diagnosis of MetS. Other than the National Cholesterol Education Program hypertension criteria, the JNC VII definition (140/90 mmHg) was also used for the comparison.

Statistical Analysis

Subjects in the study group were stratified by the age interval (every 5-year old) in both men and women. From 21 to 65 years old, 9 age groups were obtained. There are 2 parts of the analysis. The purpose of the 1st one is to build the equations which could be used to identify the cutoff values for MetS. In the study group, whether the participants having MetS or not (0 or 1) was regarded as the dependent variable. At the same time, SBP or DBP was the independent variable. By using the logistic regression and receiver operation curve, cutoff values for SBP and DBP were determined in each age group. Subjects with higher BP than these cutoff values would have a higher chance to have MetS. Then, the cutoff points of each 5-year age group were plotted against age for SBP and DBP in a scatter graph separately (y- and x-axis, respectively). A fitted line was determined by regression analysis and, finally, a corresponding equation was obtained for either SBP or DBP in women and men separately. In the 2nd part, our purpose was to validate the proposed new criteria derived from the equations. Basically, the ages of the participants were put into the equations which are sex-specific and then the estimated criteria for normal BP would be obtained accordingly. Afterwards, we compared the JNC VII (140/90 mmHg) and MetS criteria (130/85 mmHg) against ours for predicting having MetS.[15,17] To fulfill this purpose, in the validation group, subjects were divided into normotensive and hypertensive according to the 3 different definitions. This is regarded as the independent variable. Then, whether having MetS is taken as the dependent variable in logistic regression model. The area under receiver operating characteristic (ROC) curve derived from these 3 models are compared. The larger the area, the more accuracy the model is for predicting having

MetS. In other words, it should be a better definition for hypertension.

All statistical analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL). The data are presented as the mean ± standard deviation unless indicated otherwise. Independent *t*-test was applied to compare the differences between the study and the external validation groups and between subjects with and without MetS. The TG level was not normally distributed and therefore log transformation was performed before analysis. Logistic regression analysis was used to calculate odds ratios (ORs) for an increased risk of having MetS.

RESULTS

The demographic data of the study and validation group for males and females is displayed in Table 1. By the grouping criteria, it could be expected that there were no significant difference in demographic and major MetS components between the 2 groups. However, between subjects with and without MetS, it could be noted that all the components were significantly different which is not surprizing. As it is explained in the method, the cutoff values for proper SBP and DBP were determined by using the logistic regression and ROC curve for each 5-year age group. These results are showed in Table 2. These cutoff points for SBP and DBP in both males and females were plotted against the age and are showed in Figure 1. It could be noted that for both genders the SBP concave down a little bit between 30 and 40 years old. On the other hand, the curves are quite different for DBP. The line for male is a sigmoidal curve. Compared to it, the relationship between age and DBP is a straight line in females. From these lines, equations were built and then were used in the validation groups for predicting MetS. The positive predict value, negative predict value, sensitivity, and specificity of different BP cutoff points are shown in Table 3. For SBP, MetS predicted by our equation had a sensitivity of 55% and specificity of 67% in males and

TABLE 1. Demographic Data of the Study and Validation Group

	MetS (−)	MetS (+)	*P*
Study group			
Male			
n	34840	14617	
Age, years	46.3 ± 11.4	47.3 ± 9.4	<0.001
Body mass index, kg/m^2	23.6 ± 3.2	23.8 ± 3.0	<0.001
Systolic blood pressure, mmHg	119.9 ± 15.9	122.8 ± 14.1	<0.001
Diastolic blood pressure, mmHg	75.3 ± 10.8	74.3 ± 10.2	<0.001
Fasting plasma glucose, mg/dL	98.4 ± 21.0	94.5 ± 15.6	<0.001
HDL-C, mg/dL	42.4 ± 12.5	43.6 ± 9.3	<0.001
Triglyceride, mg/dL	127.8 ± 73.1	128.0 ± 85.0	<0.001
Female			
n	41265	11598	
Age, years	45.7 ± 11.7	46.3 ± 9.6	<0.001
Body mass index, kg/m^2	22.3 ± 3.4	22.7 ± 3.2	<0.001
Systolic blood pressure, mmHg	115.6 ± 18.3	113.0 ± 14.8	<0.001
Diastolic blood pressure, mmHg	72.1 ± 10.8	67.3 ± 9.8	<0.001
Fasting plasma glucose, mg/dL	95.3 ± 18.7	90.6 ± 13.3	<0.001
HDL-C, mg/dL	50.6 ± 13.3	53.2 ± 11.9	<0.001
Triglyceride, mg/dL	96.3 ± 54.2	94.5 ± 57.1	<0.001
Validation group			
Male			
n	8042	6225	
Age, years	49.0 ± 9.7	50.0 ± 8.8	<0.001
Body mass index, kg/m^2	23.5 ± 2.5	26.5 ± 2.8	<0.001
Systolic blood pressure, mmHg	120.5 ± 13.5	125.7 ± 14.2	<0.001
Diastolic blood pressure, mmHg	72.6 ± 9.8	76.4 ± 10.3	<0.001
Fasting plasma glucose, mg/dL	90.7 ± 10.5	99.0 ± 19.3	<0.001
HDL-C, mg/dL	47.0 ± 9.0	38.7 ± 6.7	<0.001
Triglyceride, mg/dL	102.3 ± 46.5	184.4 ± 100.7	<0.001
Female			
n	8669	2666	
Age, years	47.3 ± 9.5	51.9 ± 8.6	<0.001
Body mass index, kg/m^2	21.7 ± 2.4	25.8 ± 3.4	<0.001
Systolic blood pressure, mmHg	110.6 ± 13.6	120.7 ± 15.4	<0.001
Diastolic blood pressure, mmHg	65.9 ± 9.3	71.6 ± 10.0	<0.001
Fasting plasma glucose, mg/dL	87.6 ± 7.7	99.3 ± 21.1	<0.001
HDL-C, mg/dL	55.7 ± 11.4	44.0 ± 7.6	<0.001
Triglyceride, mg/dL	77.6 ± 33.2	149.7 ± 79.1	<0.001

HDL-C = high density lipoprotein cholesterol.

TABLE 2. Blood Pressure Cutoff Point According to the Age Strata in Study Group

	Age	SBP	DBP
Male			
	21−25	120.5	78.5
	26−30	119.5	76.5
	31−35	114.5	75.5
	36−40	120.5	75.5
	41−45	115.5	78.5
	46−50	119.5	80.5
	51−55	125.5	80.5
	56−60	129.5	79.5
	61−65	143.5	76.5
Female			
	21−25	115.5	70.5
	26−30	113.5	71.5
	31−35	110.5	72.5
	36−40	112.5	74.5
	41−45	116.5	73.5
	46−50	124	78.5
	51−55	122.55	74.5
	56−60	132.5	78.5
	61−65	130.5	77.5

DBP = diastolic blood pressure, SBP = systolic blood pressure.

65%, 83% in females, respectively. At the same time, they are 61%, 73% in males and 73%, 86% in females for DBP, respectively. These sensitivity and specificity are better than those derived from the criteria of 140/90 or 130/85 mmHg. Table 4 shows the ORs derived from the logistic regression of the various criteria of BP predicting MetS. As expected, the ORs estimated by our equations were better than conventional normotension criteria in both genders.

Finally, Figure 2 shows the ROC curves of the 3 different normotension criteria. The areas under ROC from our equations were unanimously the highest one in either SBP or DBP in both genders. All of them reached statistical significance.

DISCUSSION

The present criteria of normal BP was first proposed by JNC III. It was determined according to several large-scale, prospective, and observational studies by using stroke and coronary heart disease as the primary end points. However, the concept of using 1 criterion for all ages is still disputable. For instance, it is hard to be agreed that a 20-year-old subject would under the same CVD risks compared to a 65-year-old subject if they all had a BP of 130/80 mmHg. One may argue about the justifiability to use MetS as an endpoint for determining the cutoff values of BP. However, as mentioned earlier in the introduction, we have several reasons to rationalize this method. First, the traditional definition of normal BP is derived from the older subjects. Caution must be taken when exercise this definition into young adulthoods. Second, it is practically very difficult to follow a person from young to old age. Before further longitudinal study by using CVD as the endpoint in young adults could be done, our results provide a new concept to define ''normal'' BP. Third, Ford[11] had published his milestone study in Diabetes Care by observing all the major longitudinal

studies focusing on the predictability of MetS. Although these studies used different endpoints (coronary heart disease, myocardial infarction, stroke and diabetes, etc.), the results unanimously support the values of MetS. Fourth, it is undoubtable that each component of MetS is independently related to future CVD and diabetes. Thus, the collectively correlations of these components should be better than the single component.

In the present study, equations for SBP and DBP were built separately in men and women. By putting the ages into these equations, the levels of normal SBP and DPB for that age will be calculated. The results of ROC curve showed that our revised criteria have unanimously higher predictive power for MetS than that of the traditional criteria in both genders. In other words, the tradition generalized criteria of hypertension for all ages are challenged.

Most evidences have shown that SBP increases with age. However, DBP increases first before 45 years old and then declines afterwards. The main underlying mechanism of this age-related changes of BP might be caused by the arterial stiffness.[14,18−21] In their longitudinal study, Safar et al[19] found that the relationships between SBP, DBP, and ages are linear and curvilinear, respectively, in a healthy population. Similar to the grouping criteria used in Framingham and Safar's studies, we divided our subjects into 5-year-old subgroups. Four equations were made to define the threshold of BP for having MetS in both genders. Not surprisingly, as age increases, the cutoffs of SBP rise in both sexes. In the same time, this linear relationship was only found in the DBP of females. The curve of DBP in male is an interesting exception which is a sigmoid line and has the lowest values between 31 and 40 years old (75.5 mmHg) and the highest at 46 and 55 (80.5 mmHg). This finding might be attributed to the interference of some risk factors other than the MetS components, such as smoking or low-density lipoprotein cholesterol, which were not analyzed in the present study. Further well-designed research is needed to elucidate this issue.

Pathologically, the mechanisms of increased SBP and DBP in hypertensive patients are not the same. The elevation of SBP is partly caused by the increased cardiac output, reduced large arteries compliance and the rise of peripheral resistance.[22,23] However, in the general population, diseases resulting in increase of the cardiac output, such as anemia, hyperthyroidism aortic regurgitation, and arteriovenous fistula, etc. are relatively few. In other words, age-related arterial rigidity and resistance play the most important role in the ''systolic hypertension.''[18] As age increases or atherosclerosis advances, the elasticity of aorta decreases which followed by the increased SBP and reduced DBP. Interestingly, DBP is considered to be the main target of treatment for the young people while, in the elderly, SBP is the goal.[18,20] In this study, we believed that our criteria are more sensitive for detecting subjects with risks since it is age- and sex-specific.

It is well-recognized that gender differences in BP starts since adolescence.[24] After puberty, females generally have lower BP than males. This difference might be caused by the higher androgen secretion in males. This hypothesis could be supported by either the human or the animal studies. For example, in females with polycystic ovary syndrome, the BP increases.[25] On the other hand, in castration male rats which have decreased androgen, the BP parallels with the change of the hormone.[26] Results of observational studies in human beings also suggest the protection role of estrogen against hypertension since higher BP is noted after menopause.[25] However, some reports showed that there was no significant
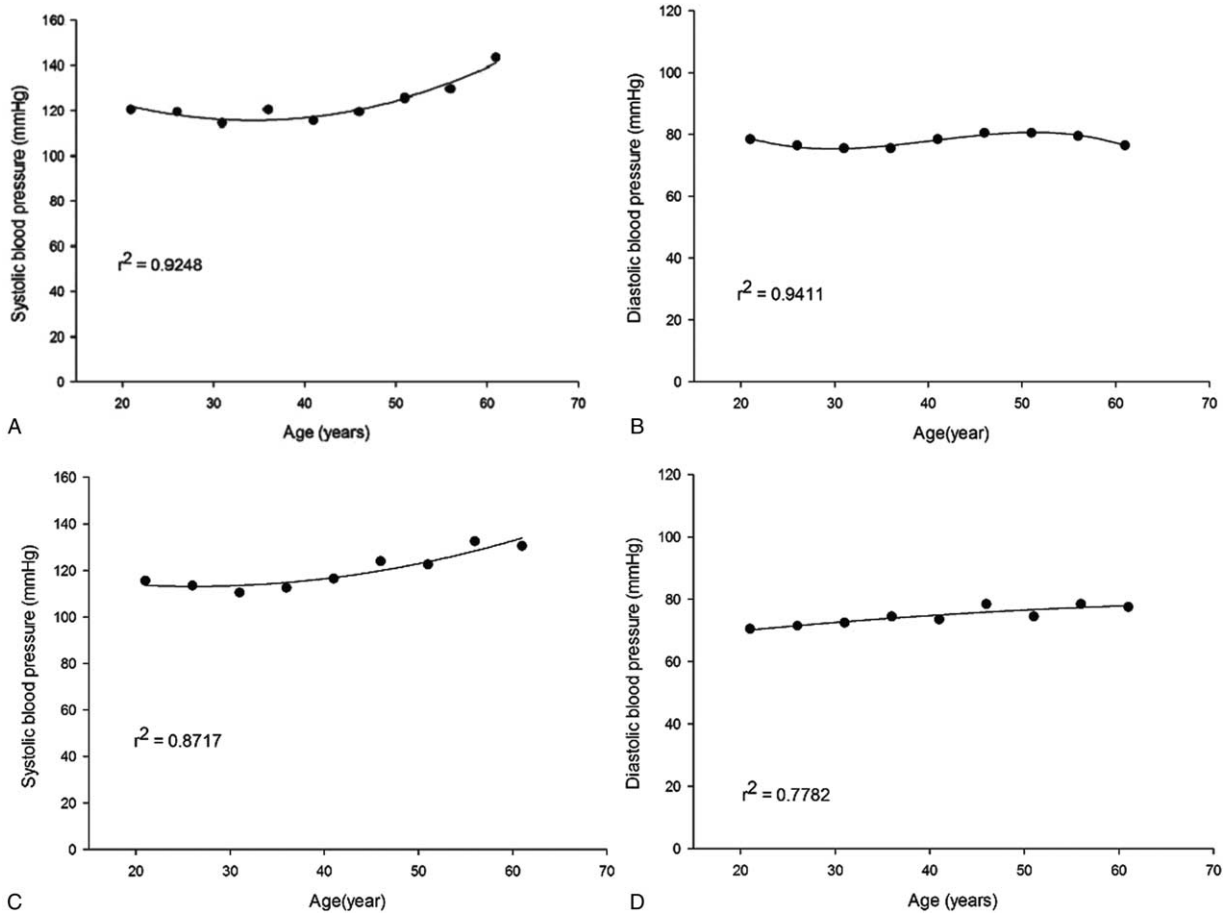
FIGURE 1. Equation of the blood pressure according to the cutoff point in different age strata in study group. (**A**) Male systolic blood pressure; (**B**) male diastolic blood pressure; (**C**) female systolic blood pressure; and (**D**) female diastolic blood pressure.

TABLE 3. Positive Predict Value, Negative Predict Value, Sensitivity, and Specificity of Different Blood Pressure Cut Point in Validation Group

	PPV, %	NPV, %	Sensitivity, %	Specificity, %
Male				
SBP cut point by equation	56	66	55	67
SBP cut point of 130 mmHg	55	61	37	76
SBP cut point of 140 mmHg	60	58	15	92
DBP cut point by equation	64	71	61	73
DBP cut point of 85 mmHg	59	59	20	89
DBP cut point of 80 mmHg	63	58	11	95
Female				
SBP cut point by equation	54	89	65	83
SBP cut point of 130 mmHg	47	80	27	91
SBP cut point of 140 mmHg	47	78	10	96
DBP cut point by equation	62	91	73	86
DBP cut point of 85 mmHg	57	78	11	98
DBP cut point of 80 mmHg	53	77	5	99

DBP = diastolic blood pressure, SBP = systolic blood pressure.

TABLE 4. Odds Ratio of Different Blood Pressure Cut Point in Validation Group

	Odds Ratio (95% Confidence Interval)		P Value
Male			
SBP cut point by equation	2.350	(2.197−2.514)	<0.001
SBP cut point of 130 mmHg	1.897	(1.766−2.038)	<0.001
SBP cut point of 140 mmHg	2.109	(1.895−2.346)	<0.001
DBP cut point by equation	4.042	(3.769−4.334)	<0.001
DBP cut point of 85 mmHg	2.038	(1.860−2.234)	<0.001
DBP cut point of 80 mmHg	2.315	(2.037−2.630)	<0.001
Female			
SBP cut point by equation	8.720	(7.923−9.598)	<0.001
SBP cut point of 130 mmHg	3.605	(3.229−4.025)	<0.001
SBP cut point of 140 mmHg	4.745	(3.956−5.690)	<0.001
DBP cut point by equation	15.927	(14.367−17.656)	<0.001
DBP cut point of 85 mmHg	3.105	(2.626−3.671)	<0.001
DBP cut point of 80 mmHg	3.879	(2.986−5.039)	<0.001

DBP = diastolic blood pressure, SBP = systolic blood pressure.
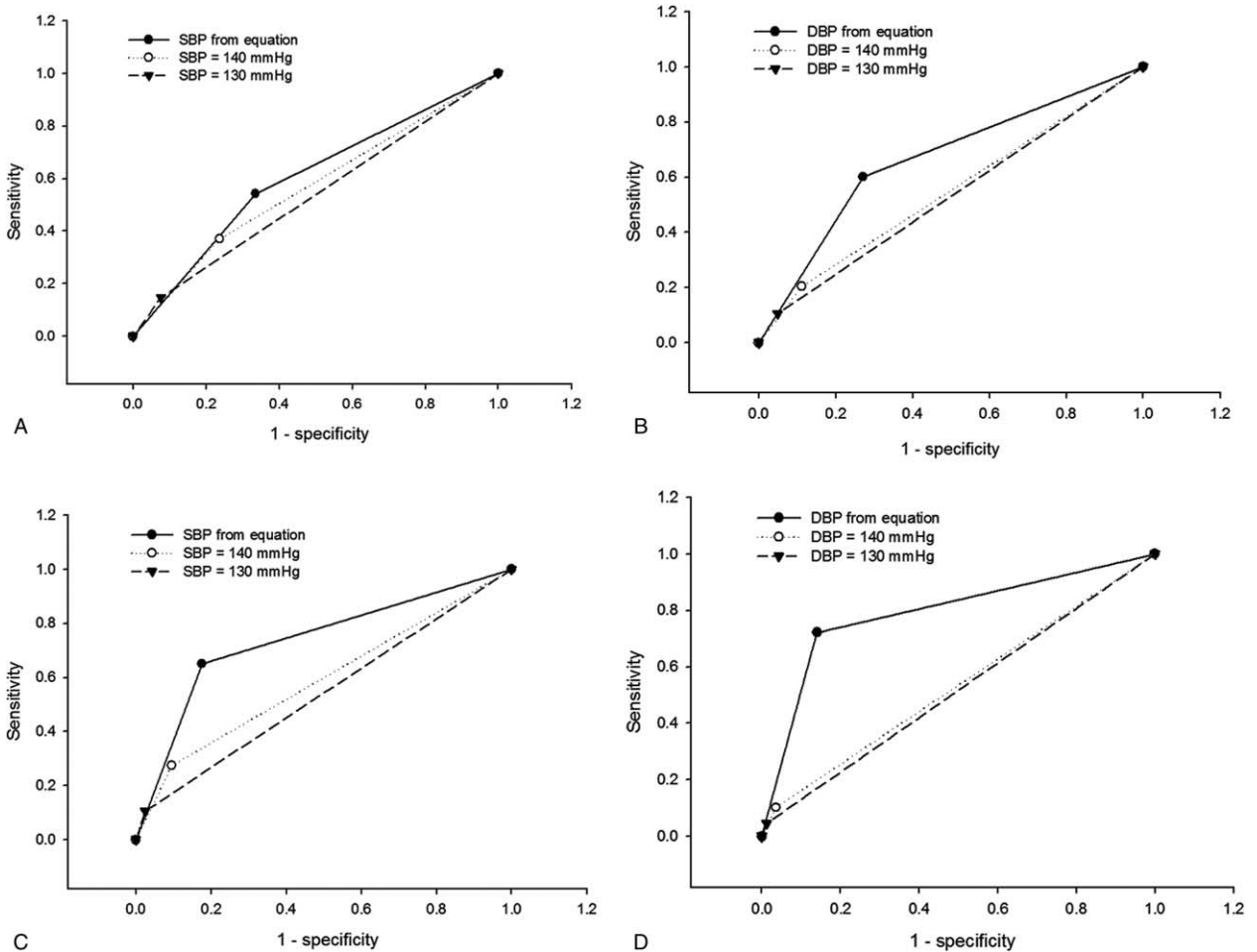

FIGURE 2. Receiver operating characteristic curve of different blood pressure criteria in predicting subjects with 2 or more metabolic syndrome components in validation group. (**A**) Male systolic blood pressure; (**B**) male diastolic blood pressure; (**C**) female systolic blood pressure; and (**D**) female diastolic blood pressure.

reduction of BP after replacement of estrogen in the menopause females.[27,28] The discrepancy might be explained by the possibility that the abrupt decline of estrogen in menopause women might not be the only component responsible for increase of BP.[27,28] For instance, other than the drop of the estrogen, a mild decrease of androgen secretion was also noted which could modulate BP through the rennin-angiotensin-aldosterone system and oxidative stress.[29] Because of these aforementioned reasons, our data highly suggest that the definition of normal BP should be gender-specific.

To our knowledge, this is the 1st study trying to define normotension criteria in subjects with different age and genders. However, there are still some limitations in our study. First, this is a cross-sectional study which is less powerful. A longitudinal study may yield more conclusive results. Second, it should be noted that only Chinese were enrolled in this study. In other words, it should be exercised with caution when being extrapolated to other ethnic groups.[30] Third, some important confounding factors were not available in the data bank such as exercise and smoking status and thus could not be adjusted. This would reduce the reliability of our results. However, because of the number of cohort is quite substantial, this drawback could be justified.

In conclusion, by using the presence of MetS as the surrogate of CVD and diabetes outcomes, the regression equations between SBP, DBP, and age were built, respectively, in males and females. All the regression lines are straight except for the DBP in males. From these equations, cutoff values for normotension are redefined. By using ROC curves, these new criteria are proved to have better sensitivity and specificity for MetS compared to either 140/90 or 130/85 mmHg. We believe that these simple equations should be used in clinical settings for early detection of and prevention of CVD.

ACKNOWLEDGMENTS

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